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Studies towards the inhibition of Adipose Triglyceride Lipase (ATGL)

DISSERTATION

zur Erlangung des akademischen Grades

DOKTOR RERUM NATURALIUM

(Dr. rer. nat.)

an der

Technischen Universität Graz

unter der Betreuung von

Univ.-Prof. Dipl.-Ing. Dr.rer.nat. R. Breinbauer

27.01.2012

Deutsche Fassung:
Beschluss der Curricula-Kommission für Bachelor-, Master- und Diplomstudien vom 10.11.2008
Genehmigung des Senates am 1.12.2008

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Abstract

The biochemical pathway lipolysis is responsible for the catabolism of triacylglycerol (TAG) stored in cellular lipid droplets. Three enzymes play a major role. The *Adipose Triglyceride Lipase* (ATGL) cleaves triglycerides (TG) and generates diglycerides (DG) which in turn get hydrolyzed by the *Hormone-sensitive Lipase* (HSL). The *Monoglyceride Lipase* (MGL) is responsible for the hydrolysis of the resulting monoglycerides (MG). During this process, fatty acids (FA) are released and glycerol (G) is generated (Fig. 1).

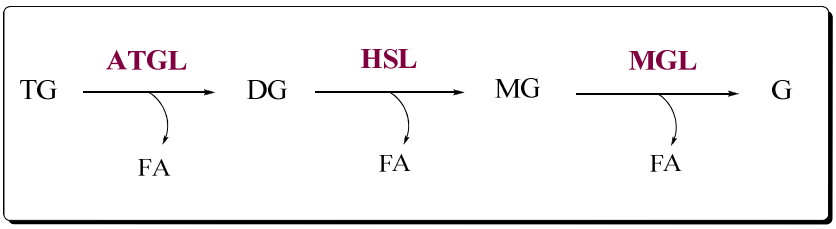


Fig. 1: Scheme of the lipolytic cascade

Lipolysis is dependent on the presence of ATGL activity. The absence of ATGL, i.e. reduced release of fatty acids, exhibit increased insulin sensitivity and resistance to cachexia.

In this thesis studies towards the inhibition of ATGL are presented. Two lead structures were identified and optimized regarding binding affinity to the enzyme and inhibition effect (*in vitro* screening).

A great number of compounds were successfully synthesized, which inhibit ATGL- one of them with 100 % selectivity towards ATGL. Another compound reached full inhibition of ATGL *in vitro* applying at a considerably decreased inhibitor concentration. By “scaffold hopping” cell toxicity could be removed completely leading to first *in vivo* studies in mice. Two compounds achieved inhibition of lipolysis in adipose tissue comparable to ATGL knockout mice. Additionally, it was possible to establish first structure-activity-relationships for the studied chemotypes.

Kurzfassung

Der “biochemische Reaktionsweg“ Lipolyse ist für den Abbau von Triacylglycerol (TAG), welches in Lipid Droplets gespeichert wird, verantwortlich. Dabei spielen drei Enzyme eine wichtige Rolle. Die *“Adipose Triglyceride Lipase“* (ATGL) spaltet Triglyceride (TG) und generiert Diglyceride (DG), welche wiederum von der *“Hormon-sensitiven Lipase“* (HSL) hydrolysiert werden. Die *“MonoglycerideLipase“* (MGL) ist veranwortlich für die Hydrolyse der dabei entstehenden Monoglyceride (MG). Während des Prozesses werden Fettsäuren (FA) freigesetzt und Glycerol (G) wird generiert (Fig. 2).

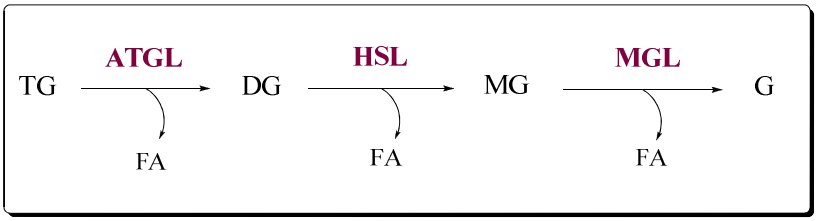


Fig. 2: Schematische Darstellung des lipolytischen Prozesses

Lipolyse ist abhängig vom Vorhandensein der ATGL-Aktivität. ATGL-Mangel, d.h. verringerte Freisetzung von Fettsäuren, ruft erhöhte Insulinsensitivität und Resistenz gegenüber Kachexie hervor.

In dieser Arbeit werden erste Untersuchungen zur Inhibierung der ATGL vorgestellt. Zwei Leitstrukturen wurden identifiziert und hinsichtlich der inhibitorischen Wirkung und Bindungsaffinität zum Enzym (*in vitro* Screeening) optimiert.

Eine Vielzahl von Verbindungen konnte erfolgreich synthetisiert werden, welche die ATGL inhibieren- eine sogar mit 100 %iger ATGL-Selektivität. Eine andere Verbindung erreicht *in vitro* vollständige Inhibierung des Enzyms bei wesentlich verringerter Inhibitorkonzentration. Die Zelltoxizität konnte vollständig entfernt werden, was zu ersten *in vivo* Experimenten in Mäusen führte. Zwei Verbindungen erreichten eine Inhibierung der Lipolyse in Fettgewebe vergleichbar zu ATGL-knockout Mäusen. Zusätzlich war es möglich erste Struktur-Aktivitäts-Beziehungen für die untersuchten Chemotypen aufzustellen.

1. Introduction

The development of organic synthesis methodology during the last fifty years has been truly impressive. There are practically no limits on what can be synthesized in a laboratory. Presently, medicinal chemists have an incredible portfolio of reactions and analytical apparatus at their disposal to design new drugs to meet society`s demands.[1]

Medicinal chemistry is the science that deals with the discovery and design of new therapeutic chemicals and their development into useful pharmaceuticals. It may involve isolation of compounds from nature or the synthesis of new molecules, followed by the investigation of the relationships between the structure of natural and/or synthetic compounds and their biological activities.

Medicinal chemistry, in its crudest sense, has been practiced for several thousand years.[2] However, over the last two decades, the drug discovery process has changed dramatically, making use of different technologies such as high-throughput screening and combinatorial chemistry (Fig. 3).[1] These new technologies and the continuous increase of interest in new and improved drugs have changed pharmaceutical research.

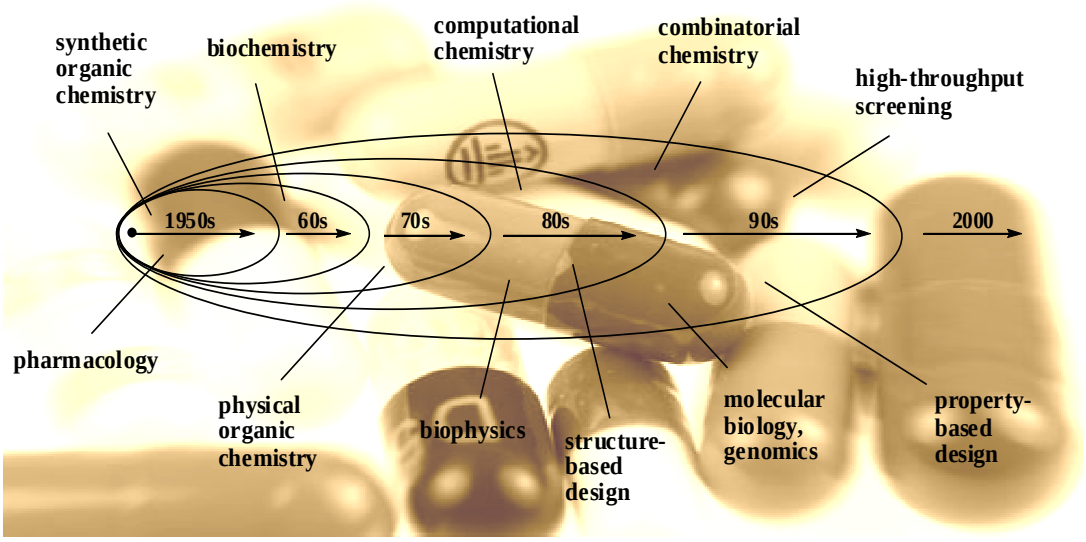


Fig. 3: Historical development of medicinal chemistry. [3] (Picture taken from ref.[4])

For a candidate therapeutic drug to be of clinical benefit, its metabolism and pharmacokinetic properties must be understood to ensure that it has a reliable activity.[5]

About one century ago organic compounds were already synthesized and optimized systematically to fulfill the requirements with a new pharmaceutical.[6] As a starting point for such chemical modifications of a chemical structure in order to improve potency, selectivity or pharmacokinetic parameters, compounds with pharmacological and biological activity are

taken which are called lead compounds. Today they are often found in high-throughput screenings or are secondary metabolites from natural sources. A lead compound may have undesireable side effects, characteristics that limit its bioavailability, or structural features which adversely influence its metabolism.[7]

For many years, the discovery of new drugs was achieved by starting from a lead structure and derive in iterating cycles of new compound synthesis with biological testing of these compounds and a structure-activity relationship related to some measure of therapeutic efficacy.[8] If the structure of the target protein is available, an alternative approach is possible: "Structure-based screening" integrates several biophysical techniques for the identification and optimization of small molecules based on lead structures with the goal to identify tool compounds with improved drug profiles.[9] But with the improvements in experimental techniques of X-ray crystallography and NMR, the amount of information concerning 3-D structures of biomolecular targets has increased dramatically.[10] By utilizing the essential structural properties of the target macromolecule, a variety of methods now exist for suggesting potential ligand molecules either by screening large chemical databases or by assembling molecular fragments inside the binding site.[11]

Due to the still unsolved and unpublished 3-D structure of the enzyme Adipose Triglyceride Lipase (ATGL), the goal of this thesis is to synthesize a large number of small molecular compounds to create a small compound library and establish a structure-activity relationship (SAR). The synthesized compounds will be screened for biological activity at the *Institute of Molecular Biosciences, University of Graz, Austria*. The first step is an *in-vitro* screening to determine the inhibition effect and binding affinity to the enzyme, followed by testing the promising compounds in an *ex-vivo* assay in isolated fat pads for selectivity and cell permeability and at last, investigating the *in-vivo* effect of selected compounds in mice.

2. Theoretical background

Metabolic pathways organize chemical reactions that happen in living organisms. In this process one chemical is transformed through a series of steps into another chemical, by a sequence of enzymes, which often require dietary minerals, vitamins and other cofactors. Metabolism is usually divided into two categories. Catabolism consumes organic substances to produce energy, anabolism uses energy to build up components of cells such as proteins and nucleic acids.[12]

Glycolysis was the first discovered metabolic pathway which results in the breakdown of glucose, but a lot of reactions in the glycolysis pathway are reversible and participate in the re-synthesis of glucose (gluconeogenesis).[13] Lipolysis describes the hydrolysis of triglycerides, esterification of the generated fatty acids with glycerol is called lipogenesis.[14-15]

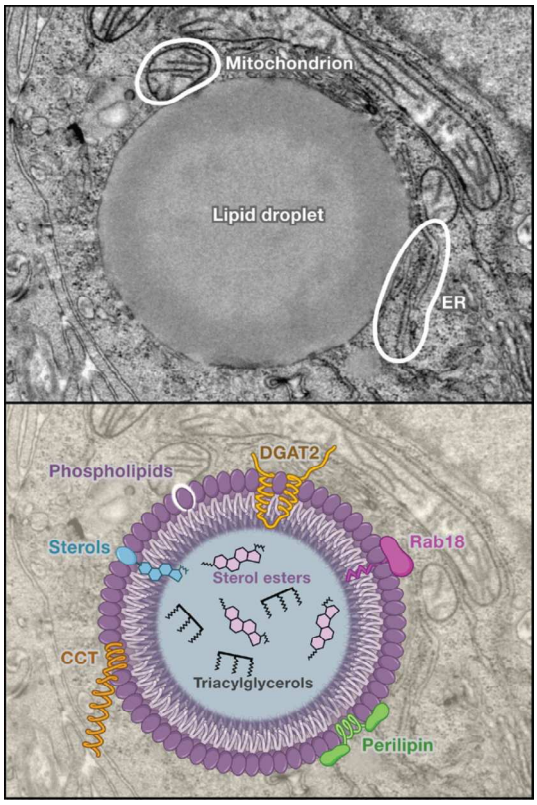
2.1. Triacylglycerol (TAG)

Triacylglycerols are triesters of fatty acids with glycerol and function as the most important energy storage in human organisms.[16] During food intake, excess of dietary non-esterified fatty acids (NEFAs) are esterified to the relatively chemical inert TAGs which are subsequently stored in cytosolic lipid droplets (LDs) of adipocytes.[17] Adipocytes are cells that primarily compose adipose tissue which can be distinguished into two types, the white adipose tissue (WAT) and brown adipose tissue (BAT). The fat stored in WAT is released as energy while BAT combust fatty acids (FAs) by itself to generate heat - a process known as adaptive thermogenesis.[18] BAT is darkly colored due to the high density of mitochondria.

2.2. Lipid droplets

Lipid droplets are ubiquitous triglyceride and sterol ester storage organelles found in most eukaryotic cells required for energy storage homeostasis and biosynthesis.[19-20] Free cholesterol and retinol ester, and xenobiotic hydrophobic compounds such as polycyclic aromatic hydrocarbons, are also found in the droplet core.[21] The stored lipids can also be used as substrates for the synthesis of other important cellular molecules, such as membrane

phospholipids and eicosanoids.[22] LDs vary greatly in size (diameter < 1-100 µm), and each consists of a phospholipid monolayer that surrounds a core of neutral lipids, such as sterol esters or triacylglycerols. On the bottom of Fig. 4 the structural features of a LD are shown. Polar surface lipids of the monolayer (e.g. phospholipids and sterols), the nonpolar lipids of the core (e.g. sterol esters and triacylglycerols) and a variety of proteins decorating the surface of the droplet are visible. One protein is perilipin which plays an important role in lipolysis. Under basal, non-hormone stimulated conditions, perilipin protects the LD from lipolysis, whereas in stimulated cells phosphorylated perilipin facilitates lipid degradation.[23]



There are diseases of excess triacylglycerol storage where LDs play an important role like obesity, diabetes, fatty liver disease and atherosclerosis, all characterized by accumulation of excessive LDs in different types of cells and tissues. The concentration of LDs can be a sign for cell degradation.[24]

Fig. 4: (Top) An electron micrograph of a lipid droplet in a cultured hepatoma cell. (Bottom) The structural features of a lipid droplet. (Picture taken from ref.[23])

2.3. Lipolysis

The definition of lipolysis is deduced from the greek words *lipos* (= fat) and *lysis* (= dissolving) and it describes the biochemical pathway responsible for the catabolism of triacylglycerol stored in cellular lipid droplets.[25] The hydrolytic cleavage of TAG generates non-esterified fatty acids and glycerol (Fig. 5).

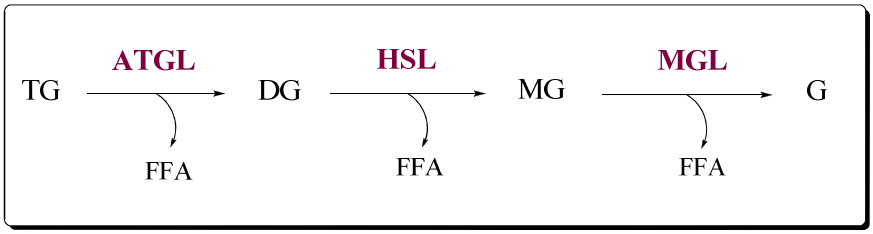


Fig. 5: Scheme of the lipolytic cascade.

Three enzymes play a major role. The Adipose Triglyceride Lipase (ATGL) cleaves triglycerides (TG) and generates diglycerides (DG) which in turn get hydrolyzed by the Hormone-sensitive Lipase (HSL). The Monoglyceride Lipase (MGL) is responsible for the hydrolysis of the resulting monoglycerides (MG).[26]

2.3.1. Monoglyceride lipase (MGL)

In the year 1976, two scientists, H. TORNQVIST and P. BELFRAGE,[27] from the University of Lund in Sweden described the enzyme for the first time. They describe it as the "monoacyl-glyceride-hydrolysing" enzyme which could be isolated in 85 % purity from the fat tissue of rats. Additionally, they determined that the enzyme hydrolyses 1(3)- and 2-monooleoyl – glycerol at equal rates (Fig. 6), but it did not catalyze the hydrolysis of triacyl- and diacylglycerole.

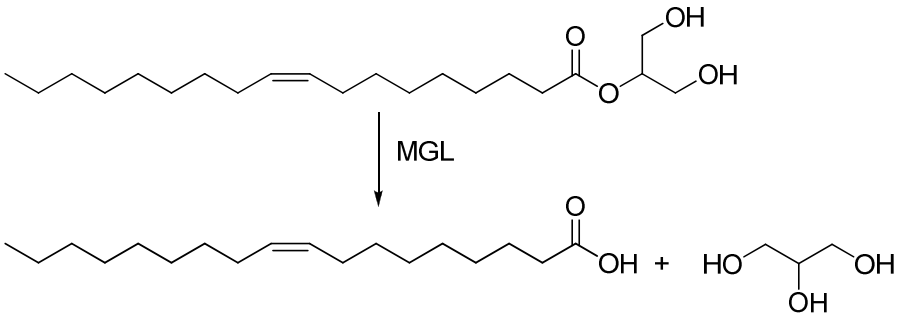


Fig. 6: Hydrolysis of monooleoylglycerol to oleic acid and glycerol

MGL codes for a protein of 303 residues with a molecular weight of ~33 kDa and in January 2010 LAMBERT *et al.* presented the 3-D crystal structure of the human MGL as a dimer (Fig. 7).[28]

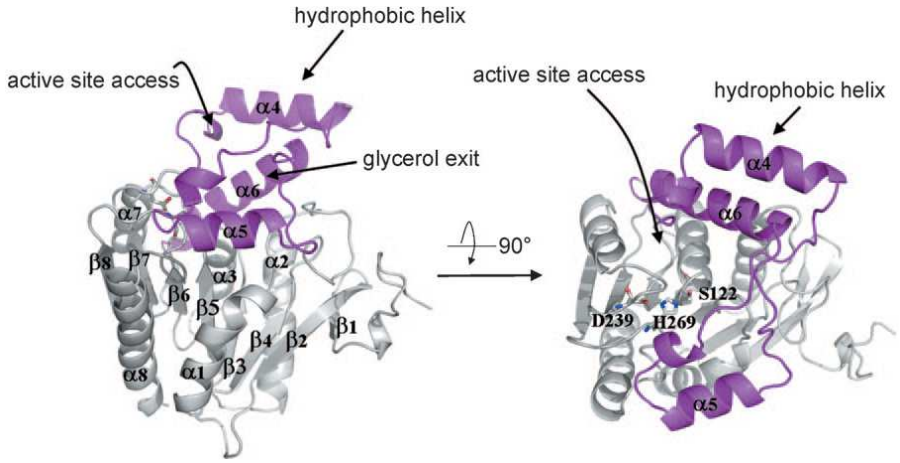


Fig. 7: 3-D structure of MGL. (Picture taken from ref.[28])

They describe the α/β-hydrolase fold, which consists of a central β-sheet, already mentioned by KARLSSON *et al.*,[29] surrounded by a variable number of α-helices. The catalytic triade is composed by Ser122, Asp239 and His269.

The investigation of the role of MGL in endocanabinoid metabolism and regulation of appetite, pain sensation and mood control is currently actively studied by using mouse models that lack or overexpress MGL, and by MGL-selective small molecule inhibitors.[17]

2.3.2. Hormone-sensitive lipase (HSL)

For more than four decades the HSL was considered to be the only and consequently the rate limiting enzyme for lipolytic catabolism.[25] It was assumed to be the enzyme responsible for the hydrolysis of triacylglycerol from the lipid droplet of adipocytes into glycerol and non-esterified fatty acids.[30-31]

BELFRAGE *et al.*[32] could show that the HSL is a multifunctional enzyme with a mass of 84 kDa that in addition to its activity against triglycerides also shows significant activity against diacylglycerol, monoacylglycerol and against long chain esters of cholesterol. Fourteen years later they could demonstrate a ~10-fold higher specific activity of the enzyme for DG compared with TG, MG or CE when analyzed in *in vitro* assay systems, suggesting a specific role of the enzyme in DG catabolism.[33]

HSL activation occurs by phosphorylation of the enzyme. YEAMAN *et al.*[34] presented in 1994 two possibilities for HSL polypeptide phosphorylation *in vitro* and *in vivo*. Site 1, the regulatory site, is responsible for the activation of HSL which occurs in response to lipolytic stimuli by hormones or adrenaline. At the second site or the basal site phosphorylation takes place within adipocytes under basal conditions of lipolysis. The cyclic-GMP-dependent protein kinase and the cyclic-AMP-dependent protein kinase (PKA) phosphorylate exclusively the regulatory site, while the AMP-activated protein kinase is the most likely and physiologically most important kinase phosphorylating site 2. Phosphorylation at site 2 has no direct effect on the HSL activity. But due to interactions between the kinases themselves site 2 phosphorylation prevents activation at site 1.[35-36]

2.3.2.1. HSL knockout mice

YAMADA *et al.*[37] generated HSL knockout mice by homologous recombination in embryonic stem cells to clarify the precise role of HSL in the development of different diseases like obesity and steroidogenesis. In this process they determined by examination of weight and morphology of BAT and WAT that these HSL knockout mice were not obese and as cold sensitive as wild-type mice. Based on this knowledge ZECHNER *et al.*[38] studied HSL-deficient mice in detail by taking lipid extracts from BAT and WAT from fasted control and HSL-ko mice to investigate whether HSL deficiency affects the lipid composition in adipose tissue *in vivo* and analyzed them by TLC (Fig. 8).

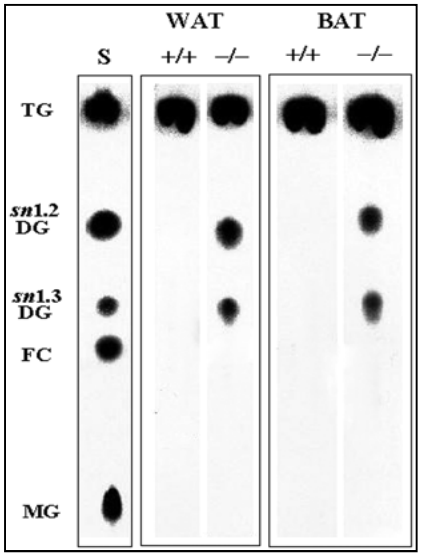


Fig. 8: Lipid analysis of WAT and BAT by TLC. (Picture taken from ref.[38])

Strong signals at R_f-values typical for 1.2-DG and 1.3-DG were detected in HSL-deficient WAT and BAT which are not present in WAT and BAT of wild-type mice.

These results were confirmed by analysis of WAT lipid extracts by ESI mass spectroscopy (Fig. 9). Compared with WAT from control mice that essentially lacked DG in relation to the TG content (less than 1 %), WAT from HSL-ko mice exhibits 8 % DG of the total fat mass. These two observations provided evidence that there is DG accumulation in adipose tissue suggesting that HSL is not essential for TG mobilization but rather is the rate-limiting enzyme for DG catabolism and consequently at least one additional TG hydrolase must exist.[38]

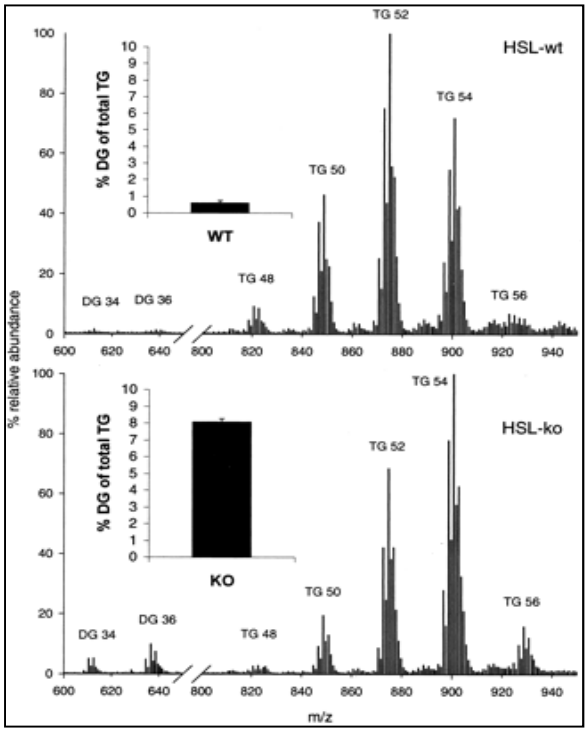


Fig. 9: Lipid and fatty acid analysis by mass spectrometry. (Picture taken from ref.[38])

In addition, *in vitro* lipolysis experiments were performed using isolated WAT fat pads from control and HSL-deficient mice to specify further the defect of hydrolysis in HSL-deficient adipose tissue (Fig. 10).

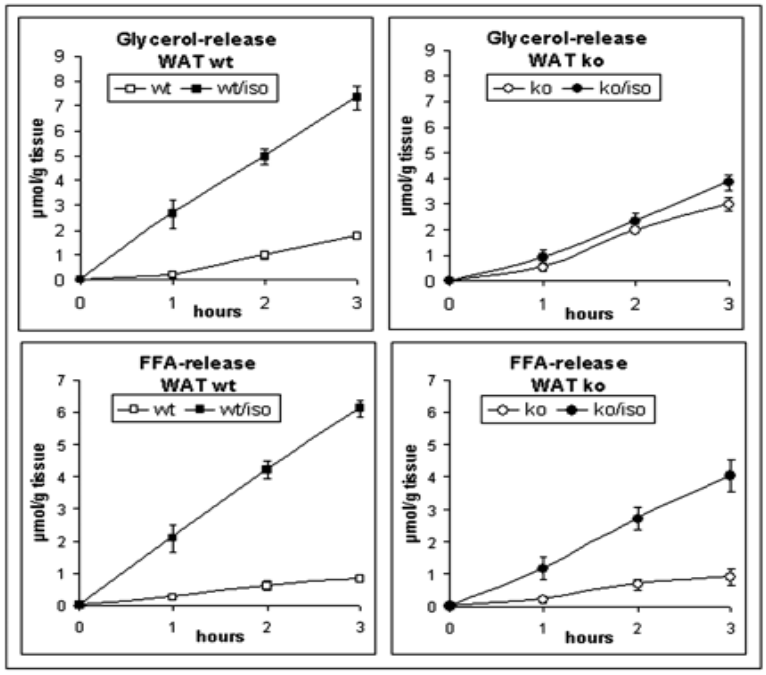


Fig. 10: *In vitro* analysis from isolated epididymal WAT of wt-mice and HSL-ko mice (Picture taken from ref.[38])

Fig. 10 demonstrates that 3 h after stimulation with isoproterenol the release of glycerol from HSL-ko WAT was only marginally enhanced, in contrast to the release of glycerol from wild-type WAT which was increased 4.3-fold. The net release of free fatty acids (FFA) was reduced relative to control. In addition, it was determined that hormone stimulation caused an additional 88 % increase in the tissue DG content in HSL-deficient fat pads.[38]

In summary, all these results show that there must exist at least one alternative or additional TG hydrolase to HSL to compensate for the breakdown of stored TG in the absence of HSL.

2.3.3. Adipose Triglyceride Lipase (ATGL)

In 2004, three groups independently reported a new enzyme able to hydrolyze TG, named adipose triglyceride lipase,[39] desnutrin[40] or calcium-independent phospholipase A2ξ.[41-42] The murine gene for ATGL encodes a 486-amino acid protein with a calculated molecular mass of 54 kDa, the human ATGL gene encodes a 504-amino acid protein with 86 % amino acid identity to the mouse enzyme. The 3-D structure of ATGL is not available to date but by studying sequence similarities of the human and the murine ATGL it can be predicted that the *N*-terminal half of ATGL is an α/β-fold protein which belongs to the superfamily of patatin-like phospholipases and it is assumed that the enzyme also acts through a catalytic dyad (Fig. 11). The *C*-terminal region contains a putative lipid-binding domain rich in hydrophobic amino acids.[17]

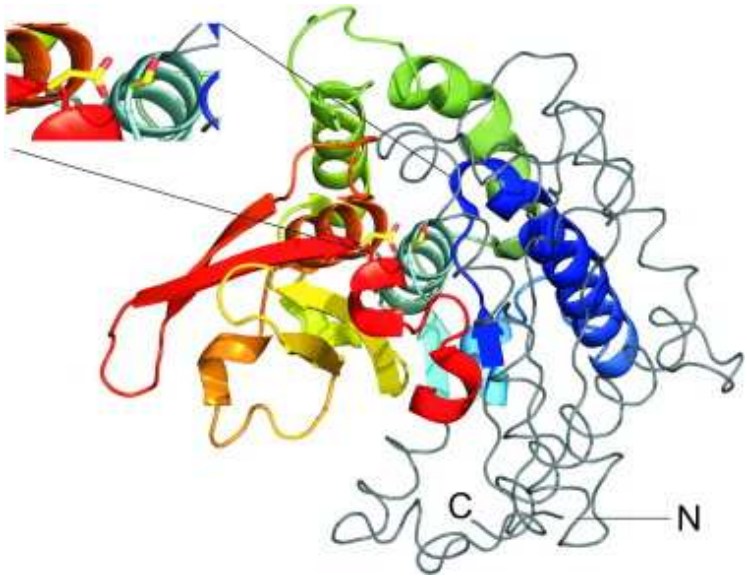


Fig. 11: 3-D structure of Pat17 depicting sequence similarities with human ATGL. The insert shows the catalytic dyad of Pat17 with the catalytic residues Ser77 and Asp215 which correspond to Ser47 and Asp166 in human ATGL (Picture taken from ref.[17])

As described above it is known that HSL hydrolyzes TGs and DGs even though its specific activity against DGs is 10 times than for TGs. In comparison, ATGL exhibits a very strong activity against a radiolabeled TG substrate in contrast to the DG substrate (Fig. 12A).

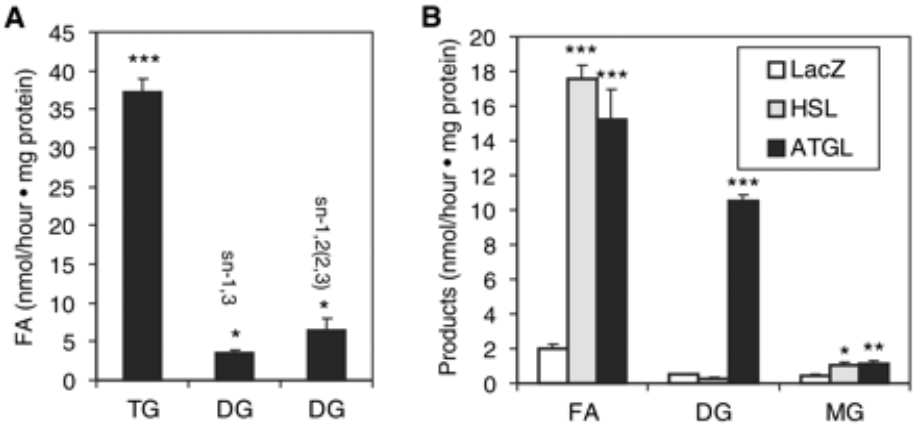


Fig. 12: Role of ATGL within the TG hydrolysis cascade. (A) ATGL activity against TG- and DG-substrate. (B) Accumulation of reaction products during ATGL- and HSL-mediated lipolysis. (Picture taken from ref.[39])

By measuring the relative abundance of lipolytic reaction products (Fig. 12B) the low DG-hydrolase activity was confirmed. The acyl-hydrolase activity of extracts from ATGL and HSL-transfected cells is higher compared to control extracts of LacZ-transfected COS-7 cells. The accumulation of DGs was increased 21-fold in the presence of ATGL which indicates its predominant hydrolysis effect to TGs, in contrast to the lipolysis assay from HSL-transfected cells which shows no DG accumulation. It was calculated that ~90 % of the FA molecules released by the action of ATGL originate from the hydrolysis of TGs in the first ester bond, in comparison to HSL, where most of the FA originate from all three ester bonds leading to glycerol formation. These observations support the assumption that ATGL and HSL have different substrate-specificities, which hypothesizes their coordinate action in the catabolism of TGs.[39]

2.3.3.1. ATGL activation

In 2006, ZIMMERMANN *et al.*[43] predicted that ATGL is no target for activation by phosphorylation and accordingly not activated by translocation to the lipid substrate as described for HSL. Instead, ATGL activity is regulated by an activator protein annotated as α/β-fold domain-containing protein 5 (ABHD5), also known as comparative gene identification 58 (CGI-58).

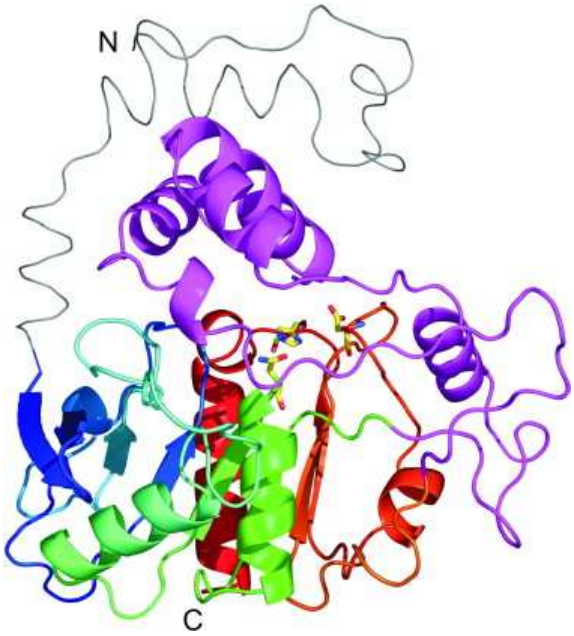


Fig. 13: 3-D structure and domain organization of CGI-58. (Picture taken from ref.[17])

As displayed in Fig. 13 the model of mouse CGI-58 shows that the compact core provides a three-layer (αβα) sandwich containing the α/β-hydrolase core. The human CGI-58 consists of 349 amino acids, the murine CGI-58 is established by 351 amino acids and both display 94 % sequence identity. ATGL activation by CGI-58 is in mice ten-fold higher as in humans (Fig. 14).

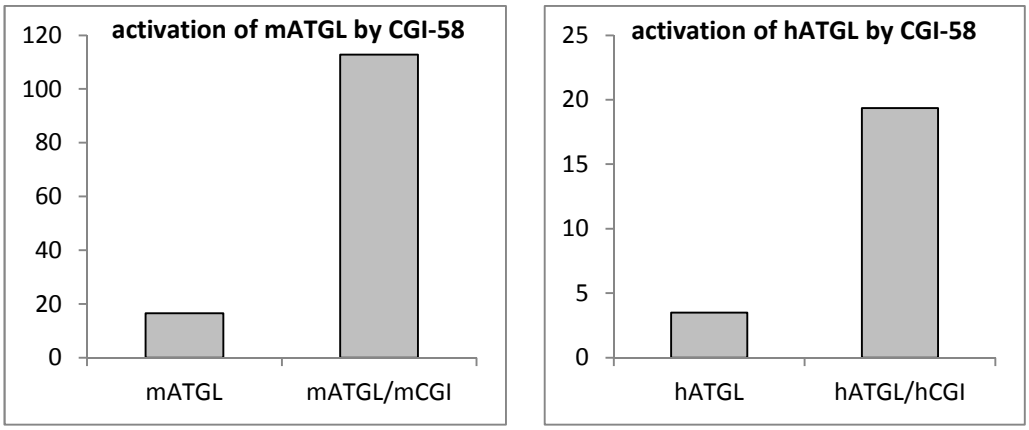


Fig. 14: ATGL activation in mATGL and hATGL by CGI-58.

That suggests that activation of ATGL by CGI-58 depends on the amino acid sequence present within the patatin domain in the *N*-terminal half of ATGL which could be confirmed by mutation studies.[17]

Analysis by northern blotting revealed that ATGL mRNA levels are highest in adipose tissue followed by testis, cardiac muscle and skeletal muscle, in comparison to CGI-58 which is most abundant in testis followed by adipose tissue, liver and muscle (Fig. 15).[44]

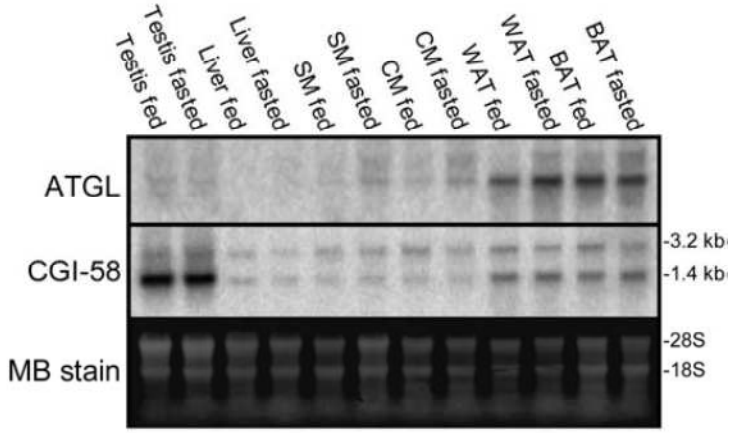


Fig. 15: Expression of ATGL and CGI-58 in different tissues analyzed by Northern blotting. (Picture taken from ref.[44])

In an experiment where CGI-58 was added to wild-type cytosol, it was determined that endogenously produced CGI-58 is not sufficient to obtain maximum ATGL activity because the addition increased TG hydrolase activity in a dose-dependent manner up to ~100 % (Fig. 16A).

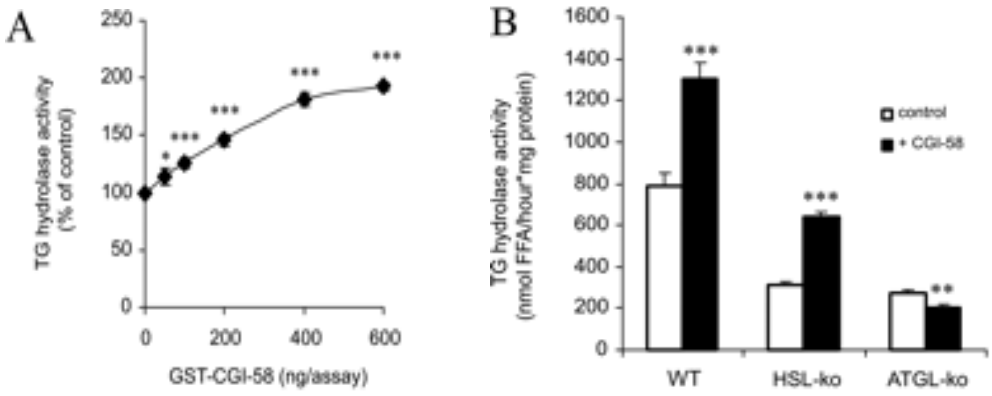


Fig. 16: ATGL is the major target enzyme for CGI-58-mediated activation of lipolysis in WAT. (A) Dose-dependent effect of CGI-58 on TG hydrolase activities. (B) TG hydrolase activities in WAT of wt, HSL-ko and ATGL-ko mice. (Picture taken from ref.[43])

Fig. 16B demonstrates that CGI-58 increased TG hydrolase activity in wild-type and HSL-ko mice by 1.7- and 2.1-fold, respectively, but was not able to stimulate the activity in ATGL-ko WAT. These results confirm the assumption that ATGL is the sole target for CGI-58-mediated activation of adipose lipolysis.[43]

2.3.4. Molecular mechanisms regulating lipolysis

2.3.4.1. Perilipin

The PAT family includes 5 members of proteins, one is perilipin. The sequence of all PAT proteins is similar and they are able to bind intracellular lipid droplets. Perilipin is closely associated with the periphery of lipid storage droplets in cultured adipocytes and phosphorylated/activated by PKA or in response to signals that stimulate breakdown of triacylglycerol. It interacts with other proteins, like CGI-58 and ATGL, via protein-protein interactions and functions to control both basal and stimulated lipolysis.[45-47]

2.3.4.2. Molecular mechanism of lipolysis

Perilipin regulates the ATGL and HSL activity by binding CGI-58. As pictured in Fig. 17, in the basal state CGI-58 is bound to perilipin which protects the LD from lipolysis and HSL is predominantly cytosolic resulting in low ATGL (present in the cytosol and on LD) and HSL activity. In the activated state phosphorylation of perilipin leads to the release of CGI-58 which becomes available for ATGL activation leading to diglyceride generation. HSL is phosphorylated by PKA and perilipin promotes the translocation[48] of the enzyme from the cytoplasm to the surface of lipid droplets leading to diglyceride hydrolysis. The last step is the hydrolysis of the monoglycerides by cytosolic MGL generating glycerol and free fatty acids.[24][47]

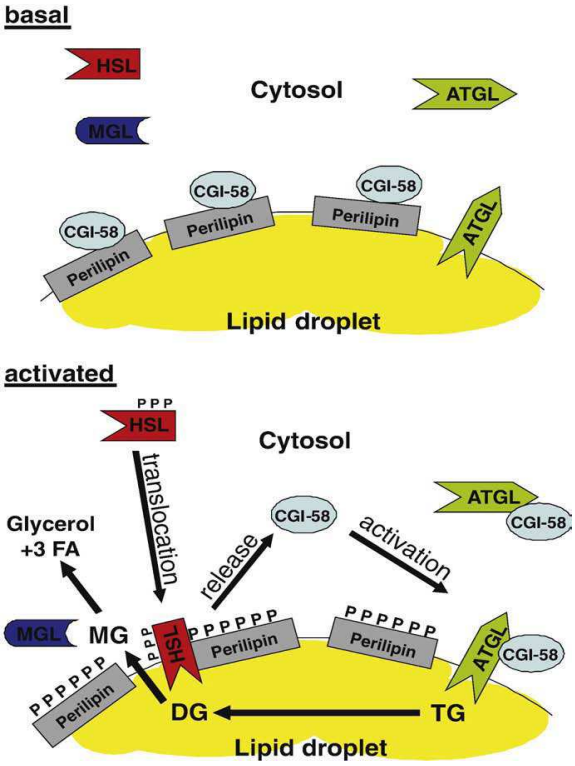


Fig. 17: Molecular mechanism of lipolysis. (Picture taken from ref.[24])

2.3.5. ATGL knockout mice

For analyzing the parameters of lipid and energy metabolism *in vivo* the ATGL gene in mice was inactivated by replacing the first exon resulting in so called ATGL-ko mice. It was observed that ATGL-ko mice, in contrast to HSL-ko mice, are extremely cold-sensitive because upon fasting they reduce their oxygen consumption and drop their body temperature. Additionally, they show a twofold increase in whole body fat mass, exhibit enlarged adipose fat depots and the TG hydrolase activity was reduced by ~80 % (Fig. 18).

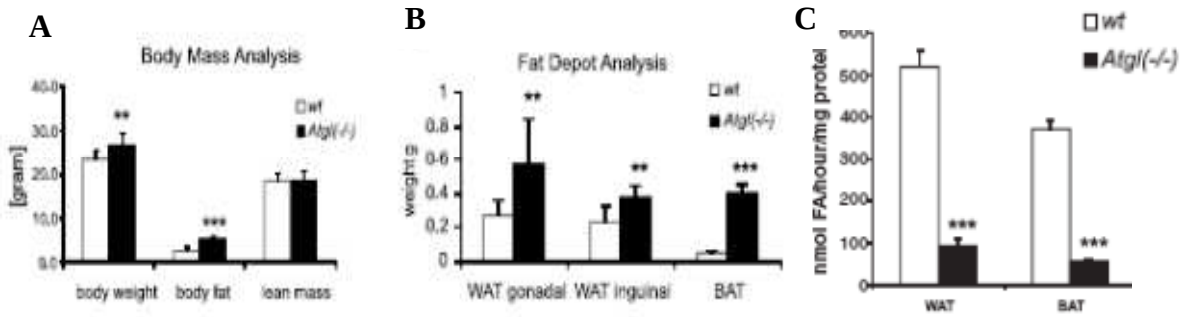


Fig. 18: (A) Body mass analysis from wt- and ATGL-ko mice. (B) Fat depot analysis from wt- and ATGL-ko mice. (C) TG-hydrolase activities in WAT and BAT. (Picture taken from ref.[49])

In response to isoproterenol treatment the release of FA from ATGL-deficient WAT was decreased by ~70 % and the release of glycerol by ~78 % which accordingly resulted in reduced plasma FA levels in ATGL-ko mice (Fig. 19).[49]

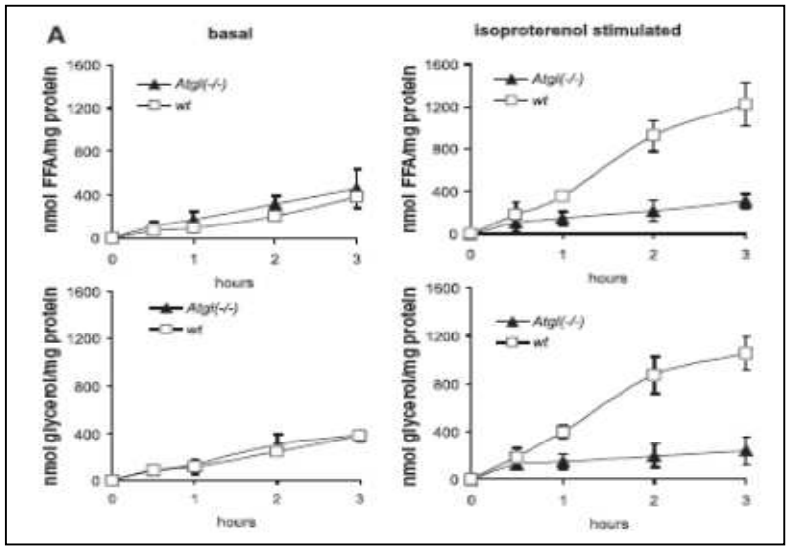


Fig. 19: Basal and isoproterenol-stimulated increase of FFA and glycerol release in gonadal WAT from female wt- and ATGL-ko mice. (Picture taken from ref.[49])

2.3.6. Diseases related to ATGL-deficiency

The absence of ATGL causes not only TG accumulation in adiose tissue but also in almost all tissues of the body, such as cardiac and skeletal muscle, testis, kidney and pancreas.[24] At the age of 12 weeks, the TG content in cardiac muscle of ATGL-ko mice was more than 20 times higher than in wild-type mice, leading to a 1.4-fold increase in heart weight (Fig. 20).

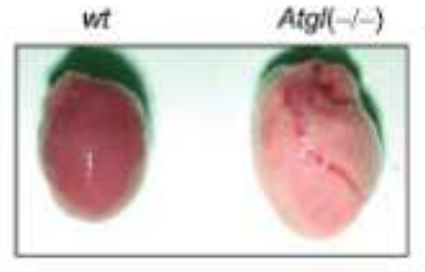


Fig. 20: Photographs of hearts from 14-week-old wt- and ATGL-ko mice. (Picture taken from ref.[49])

The first ATGL-ko mice died 12 weeks after birth, 50 % of the male mice died after 16 weeks and 50 % of the female mice died after 20 weeks.[49]

In humans, ATGL deficiency and mutation in the gene for CGI-58 are associated with a rare inherited disorder annotated as **neutral lipid storage disease (NLSD)**[50] where TGs accumulate in leukocytes, originally observed by JORDANS *et al.* and named Jordans` anomaly.[51] In the 1970`s, DORFMAN *et al.*[52] and CHANARIN *et al.*[53] reported additional cases of NLSD with ichthyosis and lipid accumulation in leukocytes which was subsequently named Chanarin-Dorfman syndrome (CDS). In 1997, IGAL *et al.*[54] published examination results from 44 patients with NLSD, where they discriminated between two groups. 26 patients were affected with ichthyosis and 18 patients were not. And they could show that all patients without ichthyosis suffered from cardiomyopathy, whereas this condition was uncommon in NLSD patients with ichthyosis, which leads to the suggestion that the underlying mutations might affect two different genes. LEFEVRE *et al.*[55] examined 150 proteins and identified mutations in one of these 150, the CGI-58, as causative for NLSD with ichthyosis. In 2007, FISCHER *et al.*[56] reported a NLSD subgroup characterized by mild myopathy, absence of ichthyosis, mutations in ATGL but without mutations in CGI-58. The demonstrated mutations do not alter the N-terminal region of ATGL containing the patatin domain and the catalytic site, whereas the C-terminal region is altered and deleted by mutations. This could explain the low activity of the LD-associated lipase and the defect in

TG catabolism. They proposed **NLSDI** as a name for NLSD with ichthyosis due to mutations in CGI-58 and **NLSDM** as a name for NLSD with myopathy due to mutations in ATGL.

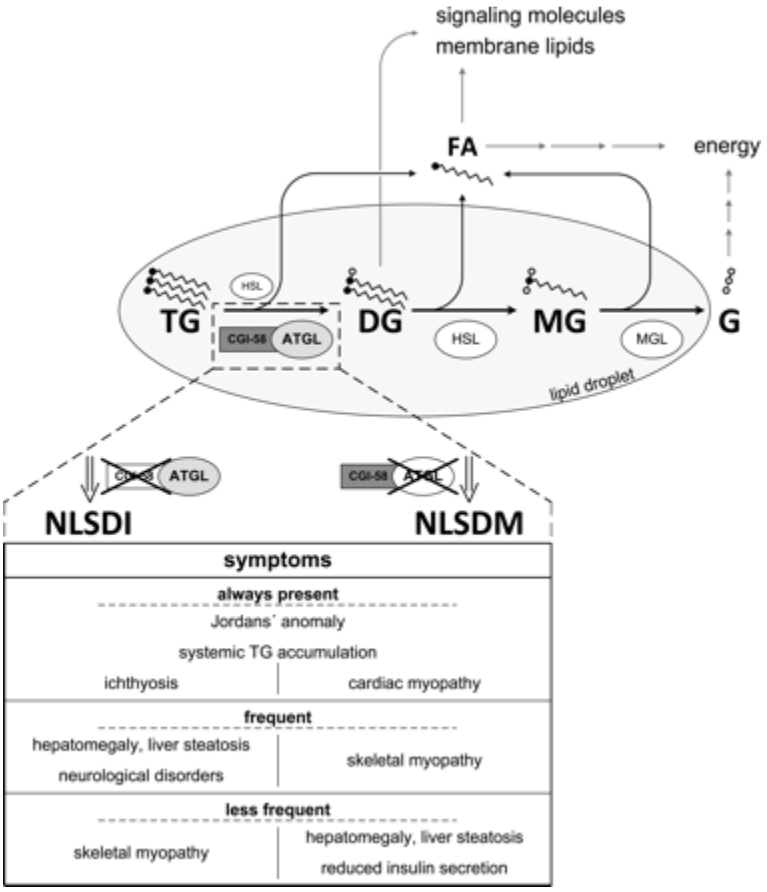


Fig. 21: Scheme of the lypolytic pathway and the clinical features observed in NLSDM and NLSDI. (Picture taken from ref.[57])

In a review ZECHNER *et al.*[57] summarized several symptoms, observed in patients suffering from NLSDM and NLSDI, which vary in frequency (Fig. 21). Surprisingly, patients with NLSDI and NLSDM are not obese, in contrast to ATGL-ko mice which develop obesity. These observations in species-specific differences may suggest that ATGL is more important as TG hydrolase in murine adipose tissue than in human adipose tissue.

One third of the patients suffering from NLSDM also develop **diabetes**, suggesting an interesting connection between lipid and carbohydrate metabolism because the reduced availability of FA, which are normaly generated during lipolysis, for energy production is accompanied by an increased usage of carbohydrates as energy source which leads to improved glucose tolerance and insulin sensitivity.

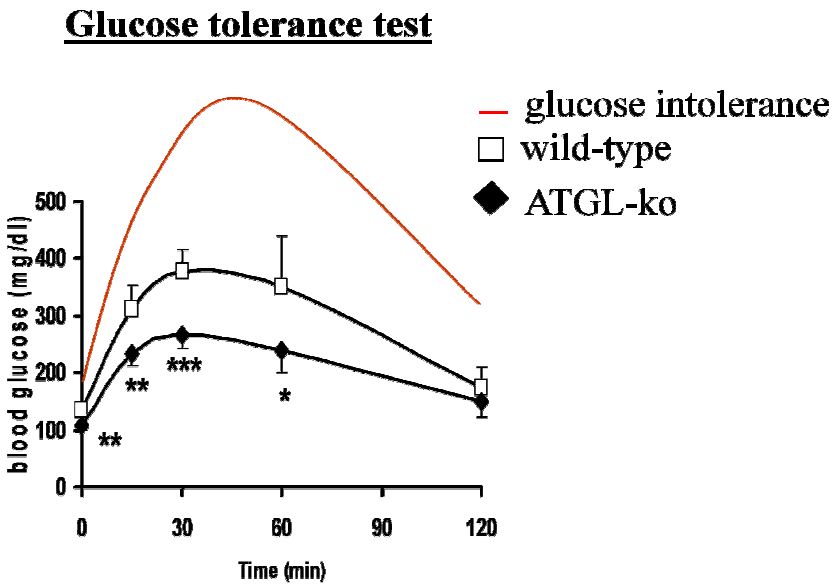


Fig. 22: Results of a glucose tolerance test from wt-and ATGL ko mice.

In glucose tolerance tests fasted ATGL-ko mice exhibited significantly lower basal glucose values and displayed a markedly improved glucose tolerance compared to wild-type mice (Fig. 22).[49] Therefore, the inhibition of ATGL could offer the opportunity to treat **Type 2 diabetes** which is characterized by insulin resistance and high insulin levels.[58]

In 2011, HOEFLER *et al.*[59] published investigations about the relationship of lipases in adipose tissue and **Cancer-associated Cachexia**. The uncontrolled loss of body weight due to depletion of adipose tissue and skeletal muscle characterizes the wasting disorder most common in patients with cancer, known as cachexia (Fig. 23).

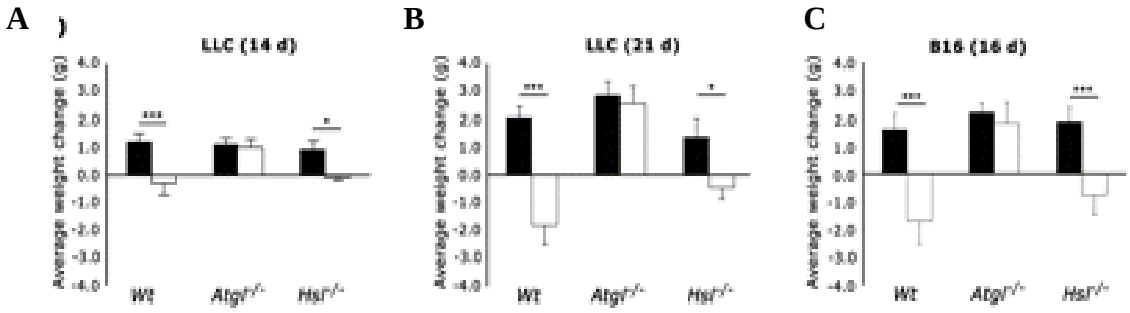


Fig. 23: Average weight change after injection of LLC and B16 tumor cells. (A, B, C) Wt mice significantly lost weight with tumor progression compared to ATGL- or HSL-ko mice. (Picture taken from ref.[59])

The researchers studied the cachexia effect of lung carcinoma (LLC) or melanoma (B16) in mice and observed that in wild-type mice the growth of these tumors caused increased rates of lipolysis, loss of fat mass and reduction of skeletal muscle volume.

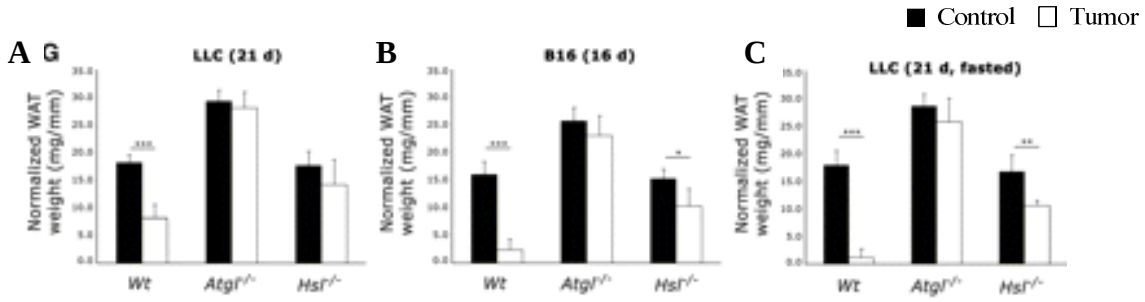


Fig. 24: (A, B, C) Normalized gonadal and epididymal WAT was reduced by 55 % in wt mice compared to ATGL- or HSL-ko mice. (Picture taken from ref.[59])

In contrast, ATGL or HSL deficient mice were resistant to the cachexia effects of the tumors, in which the protective effect was strongest in ATGL-ko mice (Fig. 24). They also observed upregulated lipase activity in adipose tissue of human cachexia patients. It was suggested that there could be a correlation with the increased circulating concentrations of fatty acids and glycerol observed in patients which leads to the speculation if drugs or small molecules inhibiting the lipases could represent a powerful strategy to prevent cancer cachexia and its devastating effects.

2.4. Drug Design

Modern drug discovery research requires the continual application of strategies to increase efficiency, implement new technologies and increase candidate quality. For a long time the most consistently successful source of drug leads were natural products. But with the evolution of new technologies such as high-throughput screening (HTS), combinatorial chemistry and technologies based on genomics, the role natural products have historically had in lead generation, has started to diminish.[60] Current strategies view discovery in terms of four stages: `hit` selection, lead selection, lead optimization and development selection (Fig. 25).[61]

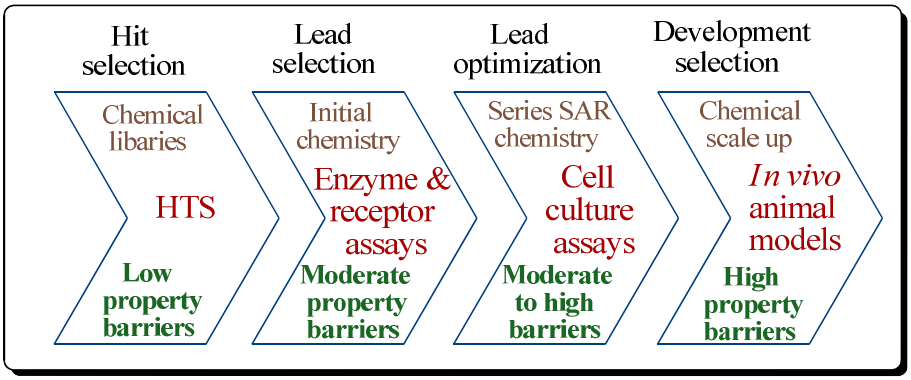


Fig. 25: Stages of the drug discovery process and their associated chemical synthesis (brown) and biological testing (red) activities. (Picture taken from ref.[61])

Advances in molecular biology have had a dramatic impact on the drug discovery process because the ability to produce significant quantities of pure protein has facilitated the possibility to determine the structure of many of these biologically relevant targets which provides a new tool in the drug design process.[62]

There are two major types of drug design, the first is referred to as ligand-based drug design. The second, structure-based drug design, relies on the knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy.[63] By knowing the structure of the biological target candidate drugs that are predicted to bind with high affinity and selectivity to the target may be designed using the knowledge of medicinal chemists, interactive graphics or automated computational procedures to suggest new drug candidates.

The ligand-based drug design relies on the knowledge of lead structures or lead compounds which already exhibits a desired biological effect but lack several properties important for usage in therapeutic application. These molecules may be analyzed to derive a pharmacophore model which defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target.[64] The chemical variation of such pharmacophores is terminated by the introduction of additional substituents can effect increased affinity and biological activity. In addition, improved hydrophilicity of the molecule can have a positive influence on the bioavailability in a biological system.[65]

2.4.1. Lead structure optimization

In the last centuries different approaches were pursued to search for a lead structure. At the beginning the therapeutic potential of a drug was tested under *in vivo* conditions with human patients, which was not ethical. In addition, lead structures were obtained by isolation of

herbal natural products, animal toxins and ingredients and microorganisms. Also dyes and intermediates could lead to pharmaceuticals.[66] Today, with new technologies (HTS, combinatorial chemistry) lead structures are identified and can be modified in order to improve the desired pharmacological properties using approaches described below.

2.4.1.1. Functional group modification

In 1868, Crum-Brown and Fraser recognized a relationship between the molecular structure of a compound and its physiological action which today is reflected in so called structure-activity relationships (SARs).

Almost all drugs act at specific sites, such as a receptor or an enzyme, and their activity and potency are very susceptible to small changes in chemical structure. Molecules with common structural features tend to have similar biological activities.[67] Often molecules exhibit undesirable side effects and characteristics which influence the metabolism. Small modifications of these compounds can lead to safer and more clinically effective agents, e.g. by introduction or removal of heteroatoms, changing the ring size or chain length, variation of substituents at the aromatic- or heteroaromatic ring to change the hydrophilicity or electronic effects or introducing chiral centers.[7]

2.4.1.2. Bioisosterism

Bioisosterism is understood as the variation of the lead structure to get more effective or better compatible drugs by replacing an atom or a group of atoms with other atoms or groups of atoms having similar steric and electronic properties. The most important aims of bioisosterism are less side effects, decreased toxicity, greater selectivity and increased stability which should be achieved by optimizing especially the physicochemical parameters such as polarity, electron density distribution and solubility.[68-69]

Many pharmaceutical examples illustrate the possibilities of bioisosteric exchange. One example is the benzene/thiophene-bioisosterism (Fig. 26).

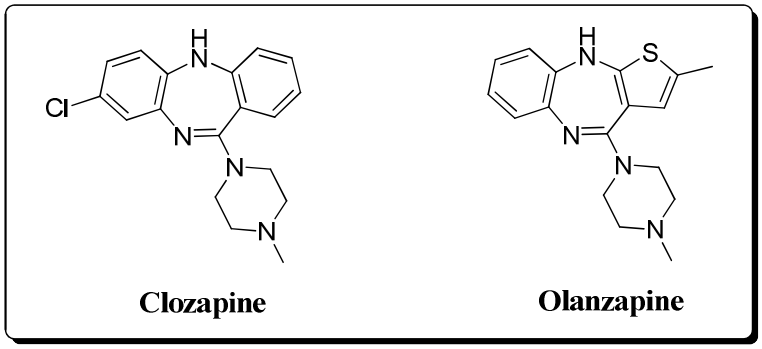


Fig. 26: Benzene/thiophene-bioisosterism.

The benzene ring in Clozapine is substituted by a methylthiophene in Olanzapine, which led to a reduced risk of death by agranulozytose. Another example is the nitrogen/methane-bioisosterism (Fig. 27).

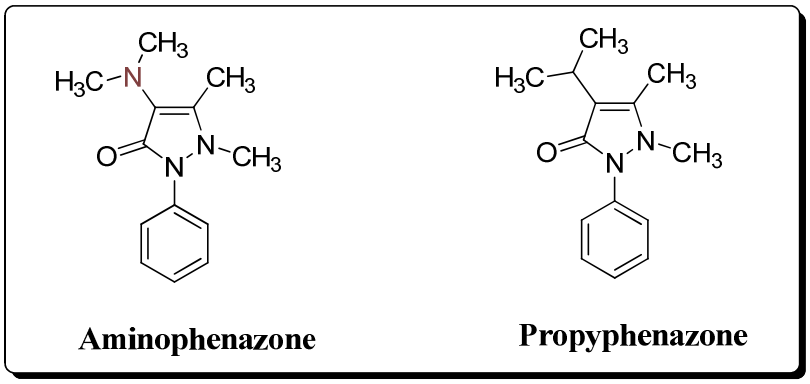


Fig. 27: Nitrogen/methane-bioisosterism.

Both compounds act analgetic and antipyretic, but Aminophenazone is carcinogenic because the reaction with $NaNO_2$ leads to the formation of nitrosoamines.[68]

The replacement of a trichloromethyl moiety with a *tert*-butyl group results in diminished persistence of the pesticide DDT (Fig. 28). DDT tends to accumulate for long periods of time in adipose tissue whereas the methyl substituents provide a site which is susceptible to metabolic degradation.[70]

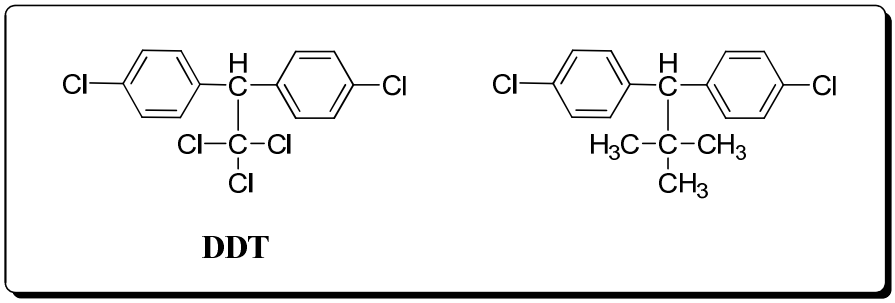


Fig. 28: Replacement of a trichloromethyl moiety by a *tert*-butyl group.

2.4.1.3. Water solubility

The conversion of water-insoluble drugs into water-soluble ones can be realized by attaching covalently an appropriate solubilizing side chain without losing its potency (Fig. 29).[71]

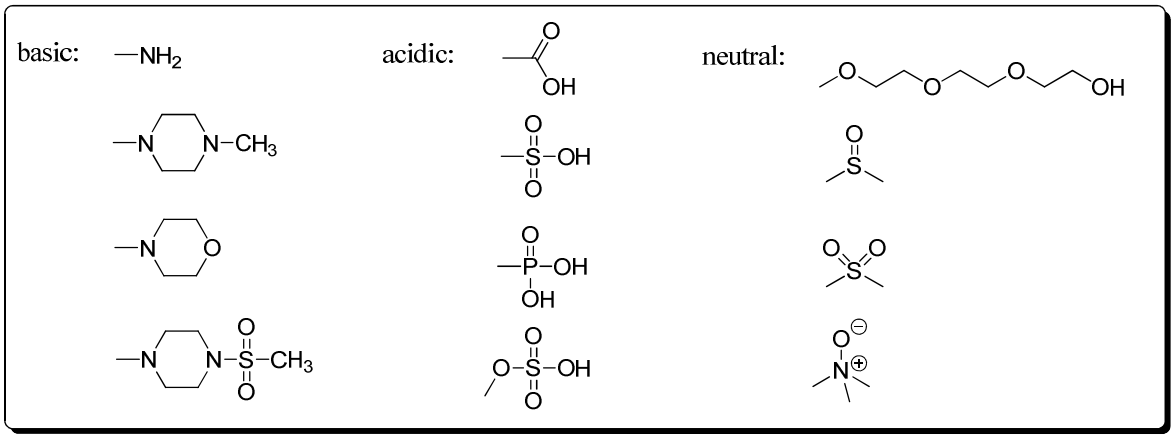


Fig. 29: Functional groups which are known to mediate water solubility in small molecules.

The solubility and permeability of drug compounds is strongly influencing their bioavailability. Bioavailable compounds are defined as the part which is freely available to cross an organism`s cellular membrane from the medium the cell inhabits at a given time. Once transfer across the membrane has occurred, storage, transformation, assimilation, or degradation can take place within the organism.[72] Poor oral bioavailability can result in variable exposure to active drugs. Lipinski *et al.*[73-74] defined a set of rules relating to the importance of lipophilicity (octanol-water partition), molecular weight and the number of hydrogen bond donors and acceptors.[75]

2.4.1.4. Combinatorial chemistry

Combinatorial chemistry is not only used for identification of lead compounds but also for lead optimization. It is defined by techniques to synthesize in parallel more than one compound. To be correct, one should perform at least one combinatorial step in the synthesis; one step in which the number of processed compartments (reaction vessels) is lower than the number of prepared compounds (Fig. 30).[76]

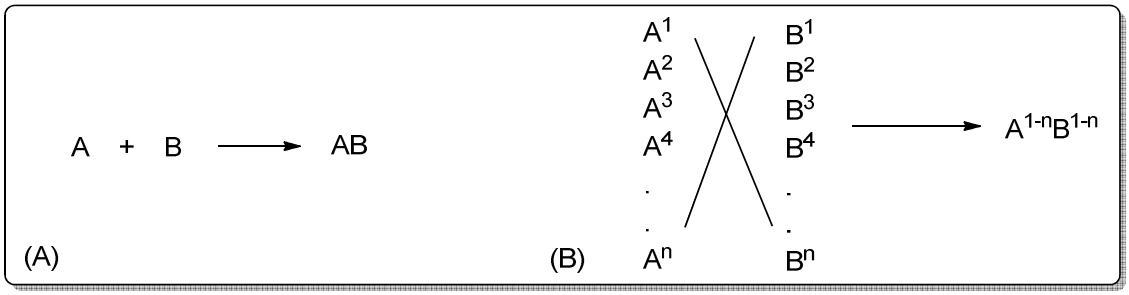


Fig. 30: (A) Conventional synthesis. (B) General scheme of a combinatorial synthesis. (Picture taken from ref.[77])

In a combinatorial synthesis different building blocks A are treated simultaneously with different building blocks B according to combinatorial principles resulting in a combinatorial library which can be analyzed by various techniques to search for biologically potent compounds.

2.4.1.5. Diversity-oriented synthesis (DOS)

According to BURKE and SCHREIBER,[78] DOS describes an efficient and three-to five step approach to a collective of small molecules with high stereochemical diversity and diversity of the molecular scaffold. In comparison to TOS (target-oriented synthesis) which characterizes the synthesis of one proposed structure with common or predicted properties and combinatorial chemistry which describes the synthesis of a collective of analogues of a proposed structure with common or predicted properties, DOS aims at the synthesis of complex and diverse structures with unidentified properties in the unknown area of the chemical space (Fig. 31).

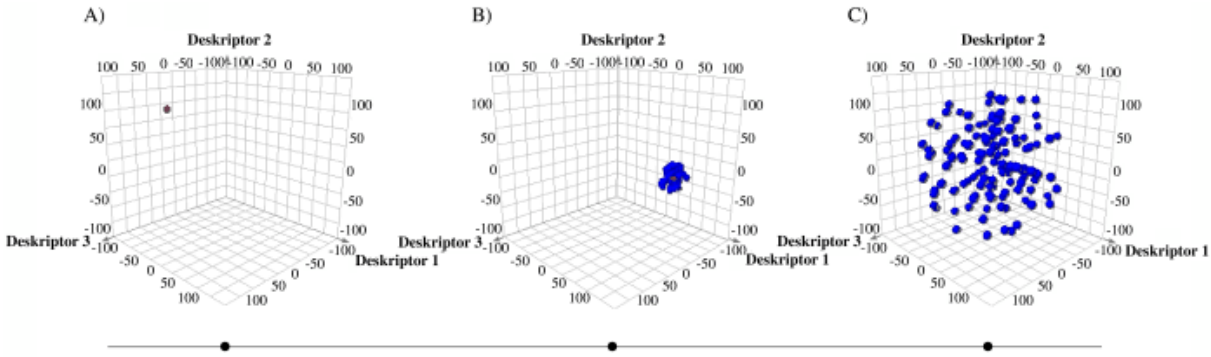


Fig. 31: Comparison of TOS (A), combinatorial chemistry (B) and DOS (C). (Picture taken from ref.[78])

With DOS, branched and divergent ways of synthesis are pursued which have to be planned in the direction of the synthesis aim. One discriminates between three components of diversity: substituents-, stereochemical- and molecular scaffold diversity.

2.4.1.6. Prodrugs

The “carrier-prodrug principle” consists of the `attachment of a carrier group to the active drug to alter its physiochemical properties and then the subsequent enzyme attack to release the active drug moiety`.[79] Taxol e.g. is a potent microtubule-stabilizing agent which is used in cancer treatment. But its aqueous insolubility hampers its clinical application which led NICOLAOU *et al.*[80-81] to design and synthesis of taxol prodrugs with improve water solubility (Fig. 32).

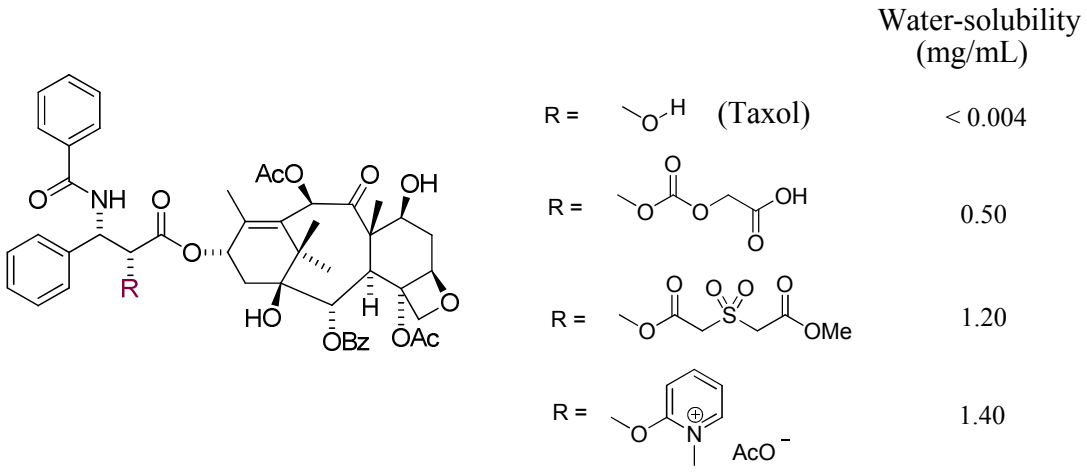


Fig. 32: Taxol and its prodrugs mediating water solubility. (Picture taken from ref.[79])

After absorption the carbonate ester decomposes *in vivo* spontaneously after abstraction of one of the activated protons or of an acidic proton or in the case of the pyridinium prodrug the release of taxol is presumed to be the result of a nucleophilic attack by water or another nucleophile.

2.5. Small molecule inhibitors in lipid metabolism

Naturally occurring small molecules such as neutral fatty acid esters, phospholipids, lipid amides, fat-soluble vitamins, triglycerides and cholesteryl esters are substrates for metabolic serine hydrolases (SHs) which consist of >200 enzymes in humans characterized by the presence of an active site serine. Intracellular triglycerides in adipose tissue are hydrolyzed by SHs, including ATGL, HSL, MGL and diacylglycerol lipase α and β (DAGLα and DAGLβ).[82] The development of inhibitors for these enzymes can open the door to the treatment of several diseases as inhibitors could target a human enzyme and aim to correct a pathological condition.

2.5.1. Monoglyceride lipase (MGL) inhibitors

As described above MGL is an enzyme which is capable to hydrolyze monoglycerides into free fatty acids and glycerol. One monoglyceride is the endocannabinoid 2-arachidonoyl-glycerol (2-AG), a ligand for the cannabinoid receptors CB1 and CB2 (Fig. 33).

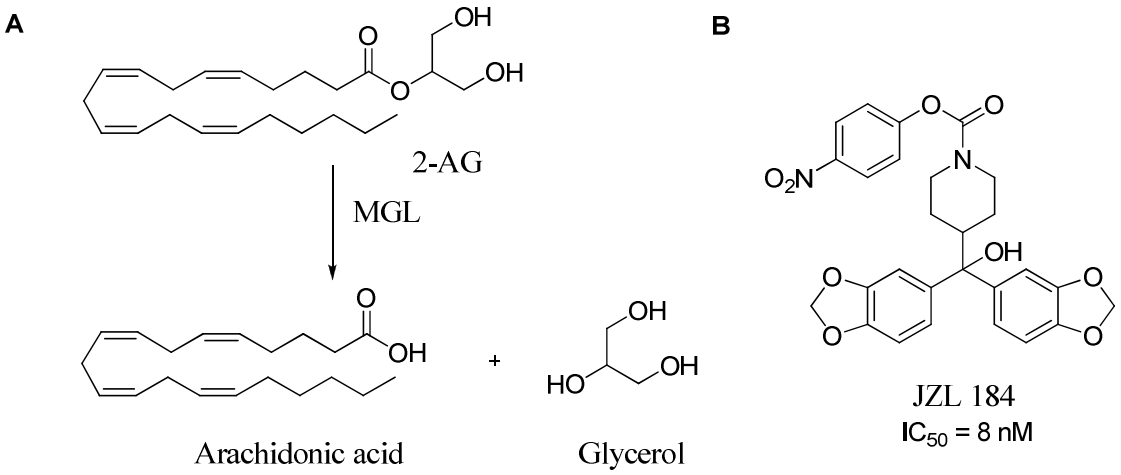


Fig. 33: (A) Hydrolysis of endocannabinoid 2-AG by MGL generating arachidonic acid and glycerol. (B) Structure of the MGL-selective inhibitor JZL 184. (Picture taken from ref.[82])

In 2009, CRAVATT *et al*.[83-84] reported a piperidine carbamate, JZL 184, that inhibits MGL with high potency and selectivity. It binds covalently to MGL and inactivates the enzyme by carbamoylation of the enzyme`s catalytic serine nucleophile leading to decreased MG hydrolysis activity, reduced intracellular fatty acids and reduced pathogenicity when aggressive cancer cells are treated with JZL 184.

2.5.2. Hormone-sensitive lipase (HSL) inhibitors

HSL hydrolyzes TGs, DGs and MGs with ~10-fold higher activity for DGs over TGs and MGs. Elevated levels of free fatty acids, which are formed during lipolysis, have been shown to be associated with increased insulin resistance and increased risk for type 2 diabetes. There are several chemical classes of HSL inhibitors mentioned in the literature. A few examples are depicted in Fig. 34, such as a series of 3-phenyl-5-alkoxy-1,3,4-oxadiazol-2-ones (general formula 1) which are described by SCHOENAFINGER *et al.*[85] or (3,4-dihydro-1*H*-isoquinolin-2-yl)-carbamates (general formula 2) published by BELTRANDELRIO *et al.*[86] In 2003, SLEE *et al.*[87] reported a novel series of pyrrolopyrazinediones (general formula 3) that demonstrate submicromolar activity against HSL.

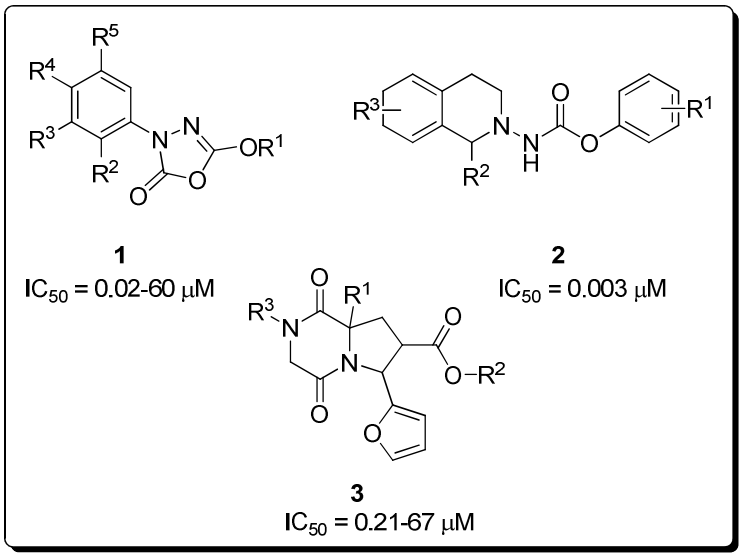


Fig. 34: Literature known HSL inhibitors.

2.5.3. Diacylglycerol lipase α and β (DAGLα and DAGLβ) inhibitors

DAGLα/β are two key enzymes which play an important role in regulating 2-AG biosynthesis in neurons. Two small molecule inhibitors are known, tetrahydrolipstatin (THL, also called orlistat or Xenical, which is produced by ROCHE®) and RHC80267, which inhibit the two enzymes nonselectively (Fig. 35). In 2008, selectivity studies of both inhibitors were performed by CRAVATT *et al.* applying activity-based protein profiling.[88]

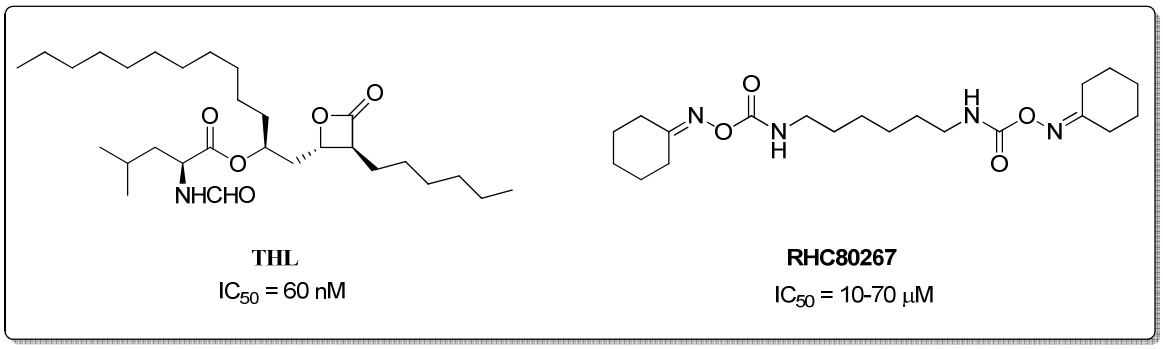


Fig. 35: Nonselective inhibitors of DAGLα/β.

The inhibition of the enzymes suggest that the DAGL enzymes regulate different forms of endocannabinoid-mediated retrograde signalling in the nervous system.[89]

3. Aims of the dissertation

Medicinal Chemistry attempts to correlate molecular structure with biological activity with a focus on the relationships of chemistry to biological activity. In the past most drugs have been discovered either by identifying the active ingredient from traditional remedies or by serendipitous discovery - the so called random approach to drug discovery. More recently, a new approach tries to understand how disease and infection are controlled at the molecular and physiological level and to target specific entities based on this knowledge.[2]

Adipose Triglyceride Lipase (ATGL) is known to play an important role in lipolysis and it is one of the major acylglycerol hydrolases in adipose tissue. ATGL removes the first fatty acid from the triglyceride molecule and generates diglycerides. In experiments with mutant mice and observations in humans, increased adipose tissue lipolysis has been identified to be responsible for at least two unfavorable metabolic conditions: (i) insulin resistance and (ii) cachexia. Mice lacking ATGL exhibit increased insulin sensitivity and are resistant to tumor induced cachexia. Thus, inhibition of ATGL could improve systemic insulin sensitivity and counteract tumor-induced cachexia.

To date there are no selective inhibitors of ATGL described in literature. But in preliminary studies, several small-molecule compounds were identified capable of inhibiting ATGL (Fig. 36). These compounds originate from a high-throughput screen performed by *Novo Nordisk (Denmark)* with the intention to identify HSL inhibitors.[26]

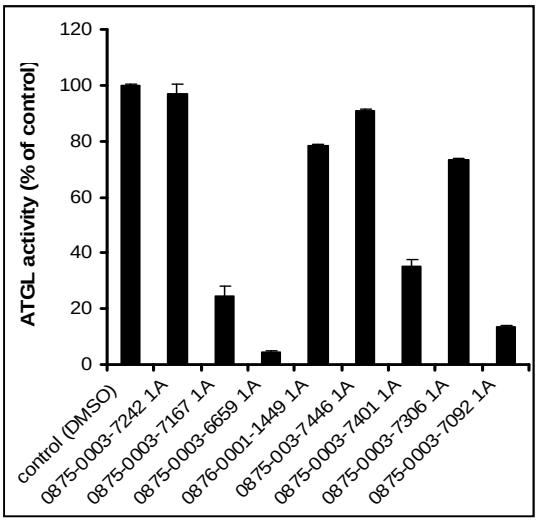


Fig. 36: Compounds inhibiting ATGL activity *in vitro.* (Picture taken from ref.[26])

This screening effort resulted in two promising compounds as lead compounds to find more potent inhibitors of the enzyme, compound 0875-0003-6659-1A and compound 0875-0003-7092-1A (Fig. 37). As no 3-D structure of the enzyme is available until now it was necessary to use a classic Medicinal Chemistry structure-based approach to establish a structure-activity relationship (SAR).

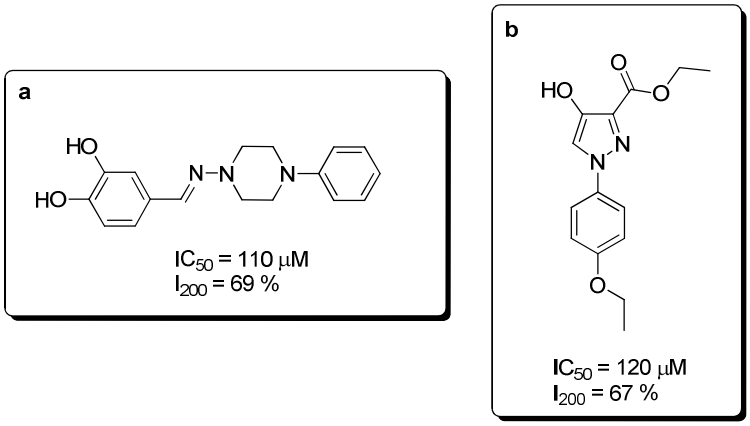


Fig. 37: (a) Lead compound 1. (b) Lead compound 2.

These two compounds provide a good starting point to synthesize structural analogues which on the one hand should show higher potency in relation to affinity and inhibition effect (*in vitro)* and on the other hand show all the properties required for *in vivo* use such as selectivity, no cell toxicity, bioavailability, metabolic stability, and solubility.

The two compounds are composed of four different main structural elements in lead structure 1 and three main structural features for structure 2 (Fig. 38).

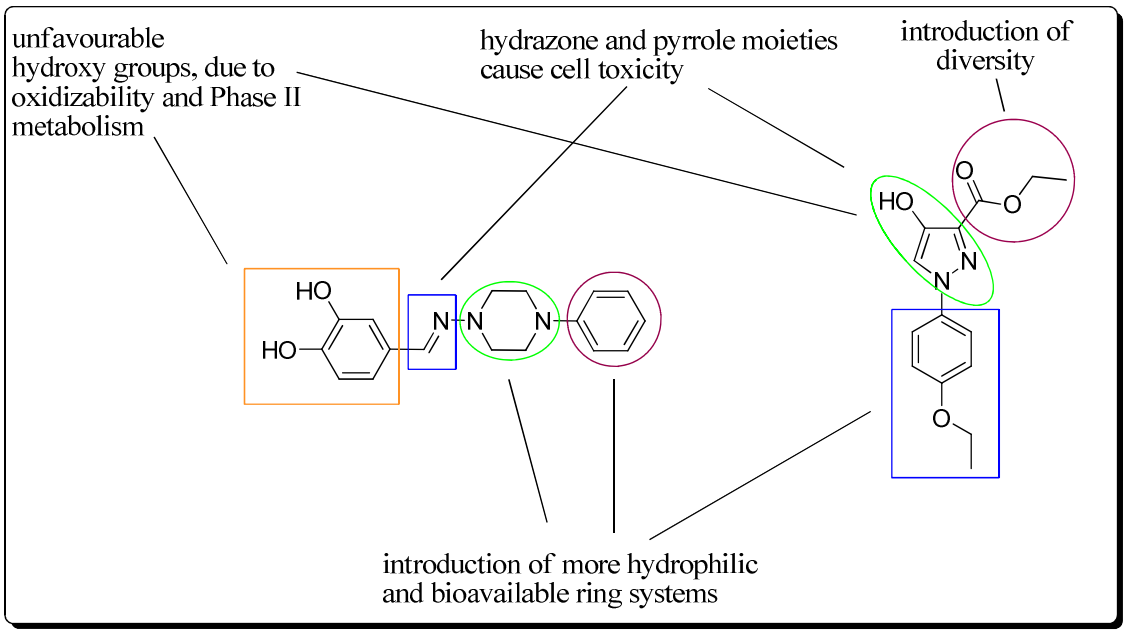


Fig. 38: Structural properties and design considerations for both lead compounds.

The biological screenings, determination of blood and plasma parameters and glucose and insulin tolerance tests were performed by the group of Prof. Dr. Rudolf Zechner and Priv.-Doz. Dr. Robert Zimmermann from the *Institute of Molecular Biosciences, University of Graz, Austria*. This screening process will be performed at three different levels of increasing complexity (Fig. 39). An exact description can be found in chapter 6.1.2.

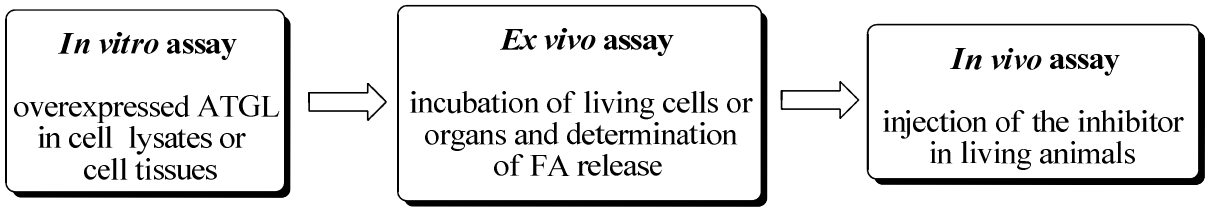
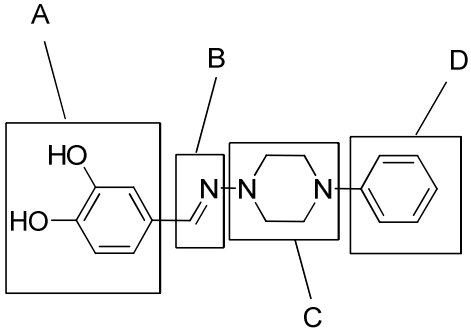


Fig. 39: Flow chart of the biological screening

In the first step all synthesized compounds will undergo an *in vitro* screening in a TG hydrolase assay, in which triolein is used as the TG substrate. Cell lysates (COS7 cells – a cell line derived from kidney cells of the African green monkey) are incubated with radiolabeled triolein in the presence or in the absence of inhibitors and the FFA release is determined by radioactivity measurements. On the second level promising compounds with high biological activity (inhibition effect and binding affinity) are tested for cell permeability and selectivity in an *ex vivo* assay. Therefore, tissue pieces of gonatal fat are incubated either in the presence or absence of inhibitors. Lipolysis is activated by hormones (isoproterenol or forskolin) and FFA release is determined. Enzyme selective compounds, which inhibit lipolysis with high affinity and show no cell toxicity, will finally be injected in mice to determine the influence on plasma fat cells in adipose tissue of a living organism.

4. Results and discussion

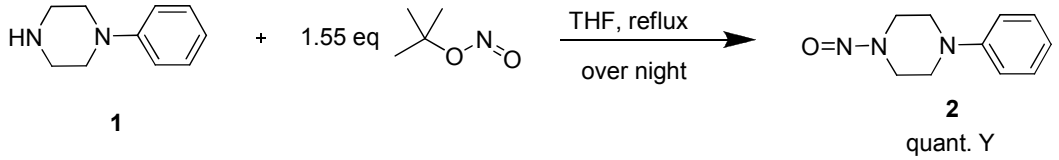
4.1. Lead structure 1



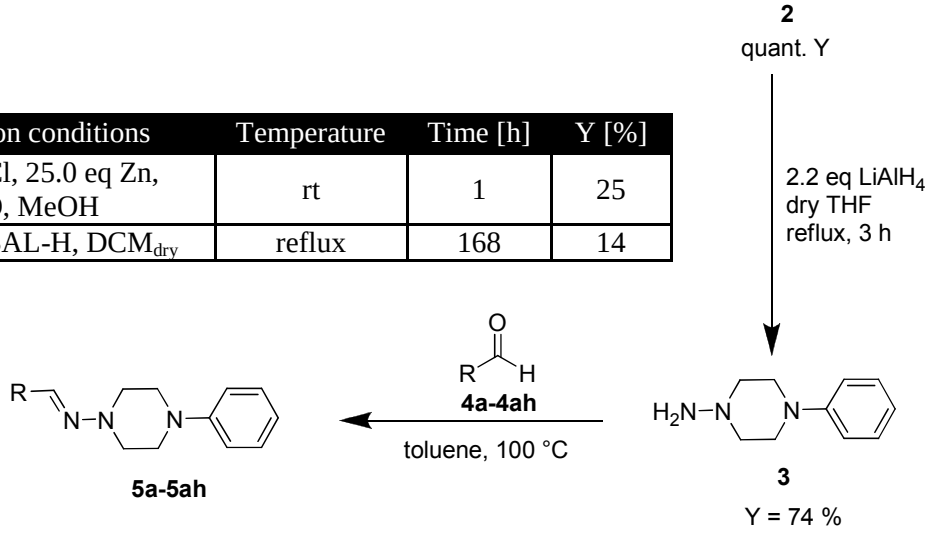
Lead structure 1 resulting from the HTS can be formally described as a composition of four main building blocks. The structure is characterized by a hydrophobic side chain (building block D), a probably water-solubility mediating piperazine ring, a hydrophilic ring system (building block A) and the hydrazine function as linking element which is known to introduce high toxicity in a molecule. The IC_{50}-value of lead structure 1 is 110 µM and it inhibits the enzyme using a concentration of 200 µM inhibitor by 69 %.

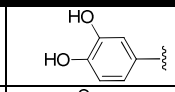
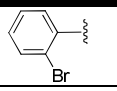
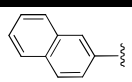
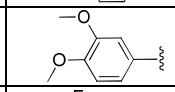
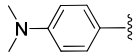
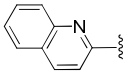
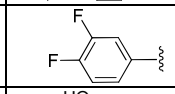
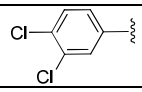
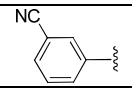
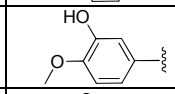
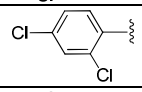
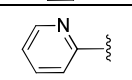
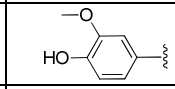
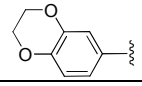
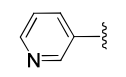
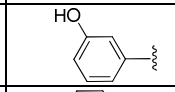
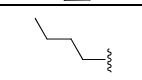
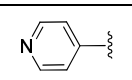
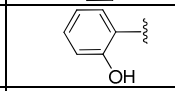
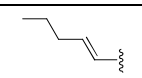
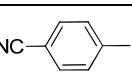
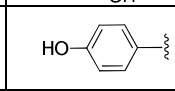
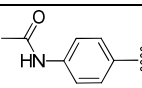
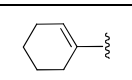
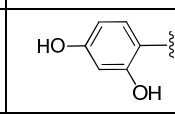
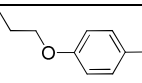
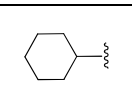
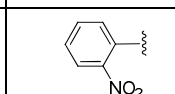
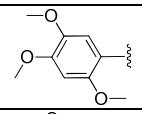
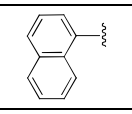
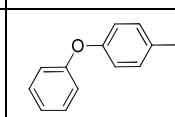
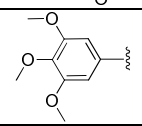
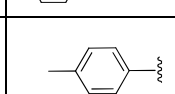
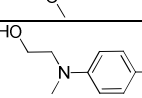
4.1.1. Synthesis of different hydrazones using several aldehydes

The first step was to synthesize the lead compound to be sure that the data known from the HTS-screening can be reproduced. In addition, a series of compounds was synthesized in which building block A was replaced because it is well known that phenols are easy to oxidize and to transform into water soluble derivatives in human metabolism. Therefore, different aromatic and aliphatic aldehydes were be used to combine them in a hydrazone formation reaction. It was necessary to synthesize sufficient quantities of hydrazine **3**. In the first reaction 1-nitroso-4-phenylpiperazine **(2)** could be isolated in quantitative yields by using an excess of *tert*.-butylnitrite.[90] For the reduction of the nitroso to an amine group we applied the method by ENDERS *et al.*[90] (DIBAL-H as reducing agent) and FRANZBLAU *et al.*[91] (zinc and conc. HCL), but both approaches led to disappointingly low yields (insert of Scheme 1). Fortunately, with 2.2 eq $LiAlH_4$,[92] refluxing for 2 h, hydrolysis by n,n,3n-method and a short silica filtration 74 % pure 4-phenylpiperazin-1-amine **(3)** could be isolated. In the last step, structurally different aldehydes **4a-4ah** had to undergo a reaction with the hydrazine **3** in toluene at 100 °C according to a procedure published by HITCHCOCK *et al.*[93] to furnish the hydrazone compounds **5a-5ah** (Table of Scheme 1).



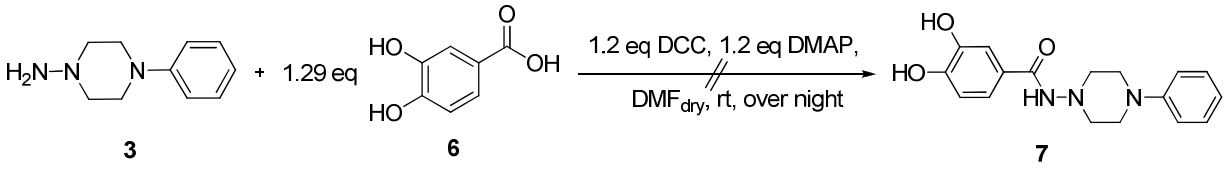
Reduction conditions	Temperature	Time [h]	Y [%]
conc. HCl, 25.0 eq Zn, H_2O, MeOH	rt	1	25
3.0 eq DIBAL-H, DCM_{dry}	reflux	168	14



No.	R	Y [%]	No.	R	Y [%]	No.	R	Y [%]
5a		92	**5m**		89	**5y**		82
5b		> 99	**5n**		61	**5z**		83
5c		90	**5o**		90	**5aa**		99
5d		> 99	**5p**		95	**5ab**		87
5e		68	**5q**		95	**5ac**		99
5f		50	**5r**		94	**5ad**		99
5g		99	**5s**		> 99	**5ae**		92
5h		> 99	**5t**		96	**5af**		94
5i		> 99	**5u**		71	**5ag**		98
5j		97	**5v**		83	**5ah**		98
5k		94	**5w**		44			
5l		99	**5x**		84			

Scheme 1: Hydrazone formation and yields depending on the used aldehyde.

Not every hydrazone could be synthesized by performing a simple condensation reaction. It was planned to synthesize 3,4-dihydroxy-*N*-4-phenylpiperazin-1-yl)benzamide **(7)** (Scheme 2) by an amide coupling using DCC and DMAP in dry DMF combining the procedures of IGUCHI *et al.*[94] and ORTIZ DE MONTELLANO *et al.*[95]. DMF was chosen as solvent because of solubility issues.



Scheme 2: Planned synthesis of compound X containing an amide bond instead of the hydrazone.

Against expectations not the desired product was observed but the hydrazone **5ai** could be isolated in 50 % yield (Fig. 40). DMF seemed to function as aldehyde species leading to imine formation catalyzed by the 3,4-dihydroxybenzoic acid **(6)**.

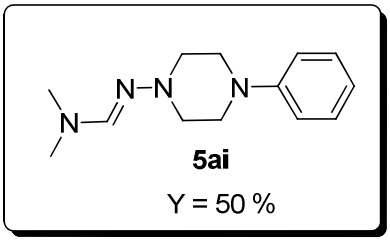
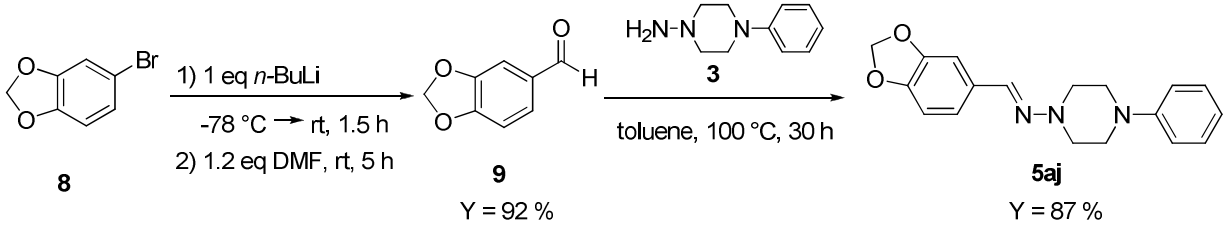


Fig. 40: Dimethylamine substituted hydrazone **5ai**.

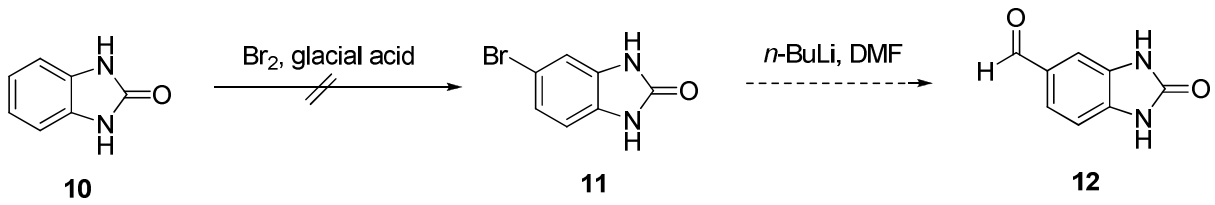
The compound could be characterized by GC-MS analysis and NMR-spectroscopy.

One further hydrazine was synthesized using 5-bromobenzo[*d*][1,3]dioxole **(8)** as starting material. According to a procedure published by SUTTER *et al.*[96] lithiation by *n*-BuLi and formylation by reaction with DMF led to the desired aldehyde **9** in 92 % yield. Condensation reaction with hydrazine **3** in toluene at 100 °C[93] gave the product **5aj** in 87 % yield (Scheme 3).



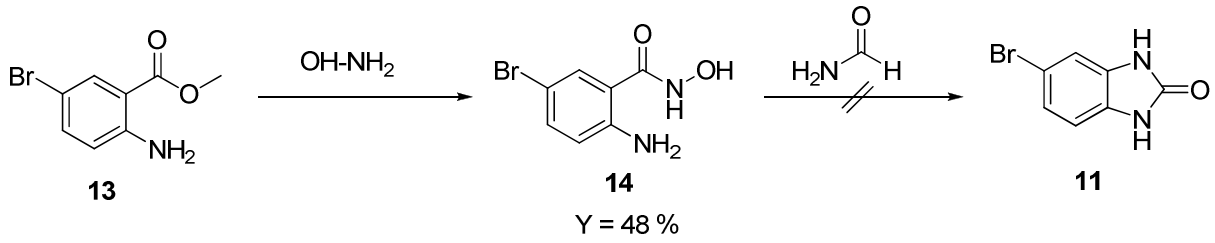
Scheme 3: Two-step synthesis of hydrazone **5aj** starting from 5-bromobenzo[*d*][1,3]dioxole **8**.

With another interesting hydrazone compound we wanted to introduce an urea functionality especially to improve or keeping perhaps the hydrophilicity of the hydroxy groups. For this reaction a lot of optimization work was done by Michaela Melcher (bachelor student, August 2009). The big challenge was to synthesize the aldehyde species **12** by starting from commercially available material. The direct bromination of 2-hydroxybenzimidazole **(10)** followed by formylation with DMF was not successful (Scheme 4).



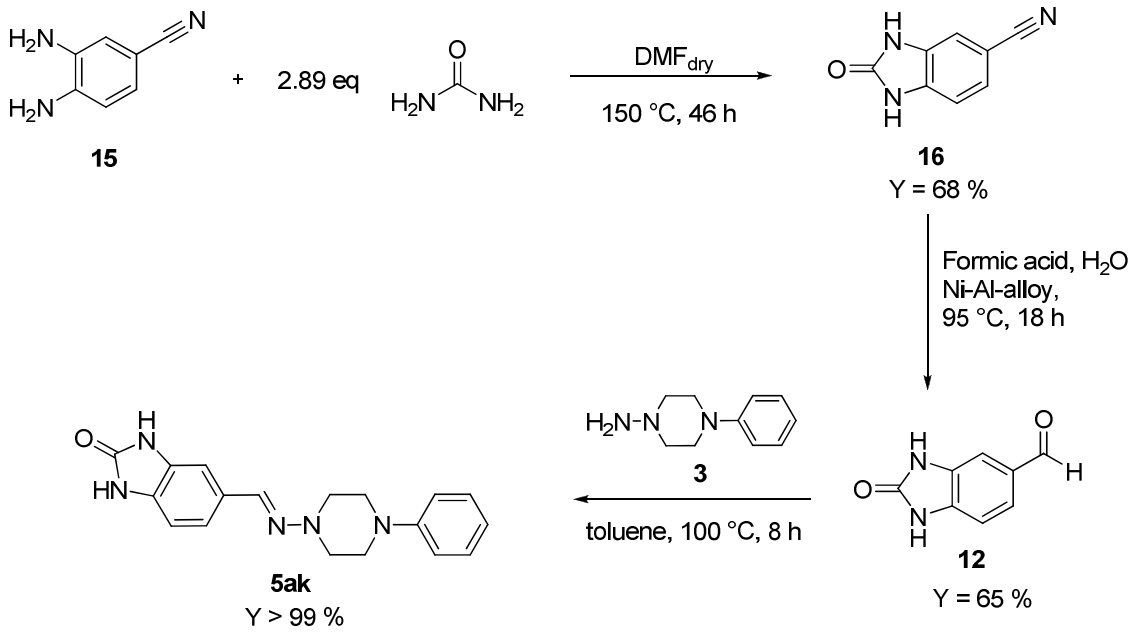
Scheme 4: Failed attempt to synthesize aldehyde **12** by bromination and formylation.

The failure of the bromination of **10** could be explained by the electron deficiency of 2-hydroxybenzimidazole **(10)**. The electrophilic aromatic substitution is known to work better with electron rich systems. Therefore, we decided to try a reaction published by LIPCZYNSKA-KOCHANY *et al.*(Scheme 5).[97] Methyl 2-amino-5-bromobenzoate **(13)** was converted with hydroxylamine in a substitution reaction to the hydroxamic acid **14** in 48 % isolated yield. Unfortunately, the following Lossen rearrangement stirring in hot (130 → 150 °C) formamide led only to the recovery of starting material **13**.



Scheme 5: Failed synthesis of the bromine derivative **11** trying to use Lossen rearrangement.

Following the procedure published by LAVOIE *et al.*[98] we finally produced the desired aldehyde species **12** directly via a ring closing reaction between 3,4-diaminobenzonitrile **(15)** with urea in DMF obtaining 5-cyano-2-hydroxybenzimidazole **(16)** in 68 % yield, which was subsequently reduced by Ni-Al-alloy in formic acid to yield 65 % 5-formyl-2-hydroxybenzimidazole **(12)** after basic work up in adequate purity (Scheme 6). The final hydrazone formation worked in quantitative yield.[93]



Scheme 6: Successful three-step synthesis yielding the desired hydrazone **5ak**.

4.1.1.1. Screening results and discussion

All synthesized hydrazones were screened *in vitro* to determine the IC_{50}-value and the inhibition effect in a dose-dependent manner. The results are summarized in Table 1. The IC_{50}-values (half maximal inhibitory concentration of a substance) and the inhibition of the enzyme using an inhibitor concentration of 200 µM are listed.

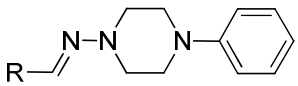
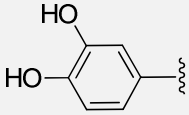
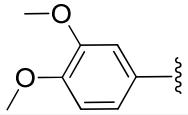
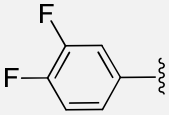
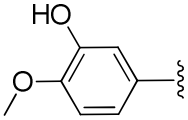
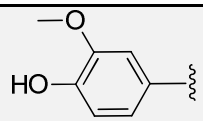
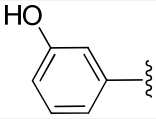
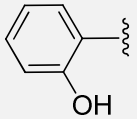
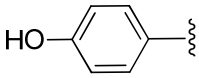
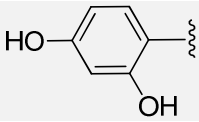
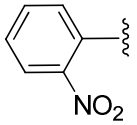
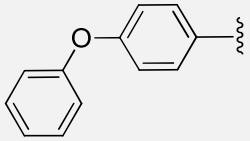
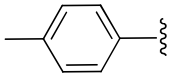
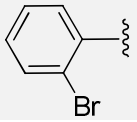
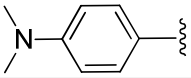
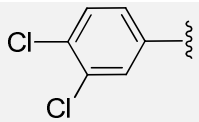
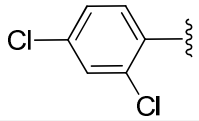
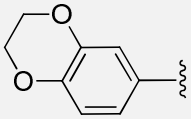
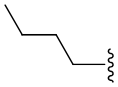
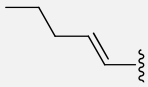
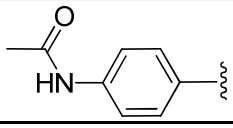
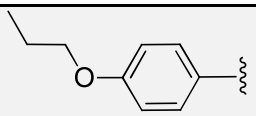
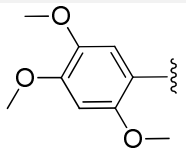
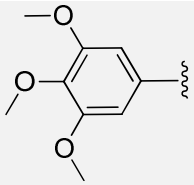
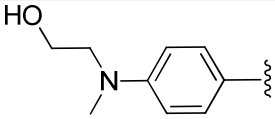
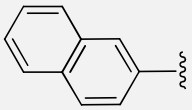
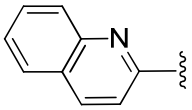
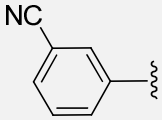
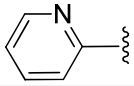
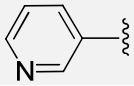
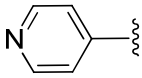
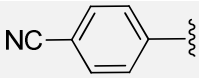
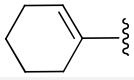
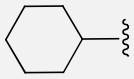
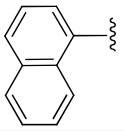
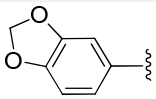
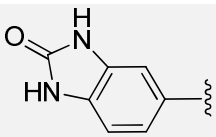


Table 1: IC_{50}-values and *in vitro* inhibition of the enzyme using an inhibitor concentration of 200 µM

Entry	No.	R	IC_{50} [µM]	I_{200} [%]
1	5a		110	69
2	5b		100	65
3	5c		75	67
4	5d		80	56

5	**5e**		**60**	**82**
6	**5f**		**70**	**71**
7	**5g**		**75**	**64**
8	**5h**		**50**	**85**
9	**5i**		**10**	**94**
10	**5j**		180	60
11	**5k**		➢ 200	24
12	**5l**		➢ 200	22
13	**5m**		➢ 150	73
14	**5n**		➢ 200	5
15	**5o**		➢ 200	20
16	**5p**		➢ 200	42
17	**5q**		➢ 200	27
18	**5r**		➢ 200	12
19	**5s**		➢ 200	12
20	**5t**		➢ 200	14

21	**5u**		➢ 200	14
22	**5v**		➢ 200	43
23	**5w**		➢ 200	41
24	**5x**		➢ 200	5
25	**5y**		➢ 200	<1
26	**5z**		➢ 200	8
27	**5aa**		120	60
28	**5ab**		➢ 200	16
29	**5ac**		➢ 200	46
30	**5ad**		140	60
31	**5ae**		**50**	**76**
32	**5af**		130	58
33	**5ag**		200	49
34	**5ah**		200	49
35	**5ai**		150	94
36	**5aj**		➢ 200	64
37	**5ak**		➢ 200	16

The biological data of the lead substance (entry 1) could compared to the results of the high-throughput screening performed by *Novo Nordisk, Denmark* and confirmed the identity of the compound of the original assay. Because phenols are known to oxidize and metabolize very fast in human organisms, the first idea was to replace the hydroxy groups. Either both hydroxy groups were replaced by methoxy groups (entry 2) or fluorines (entry 3) or only one hydroxy group was replaced by a methoxy group (entries 4 and 5). In three other cases the phenyl ring was substituted with only one hydroxy group in different positions (entries 6 - 8), which resulted in an improvement of the IC_{50}-value (50 µM) and inhibition effect (85 %) in the case of entry 8. With these compounds the biological activity concerning affinity and inhibition effect could be slightly increased or were consistent compared to the lead compound. But the best result was achieved with a hydrazone substituted with the 2,4-dihydroxyphenylic system (entry 9) instead of the 3,4-dihydroxy substitution (entry 1). The IC_{50}-value could be increased by one order of magnitude to 10 µM with 94 % inhibition. The results of the best compounds are depicted in Fig. 41.

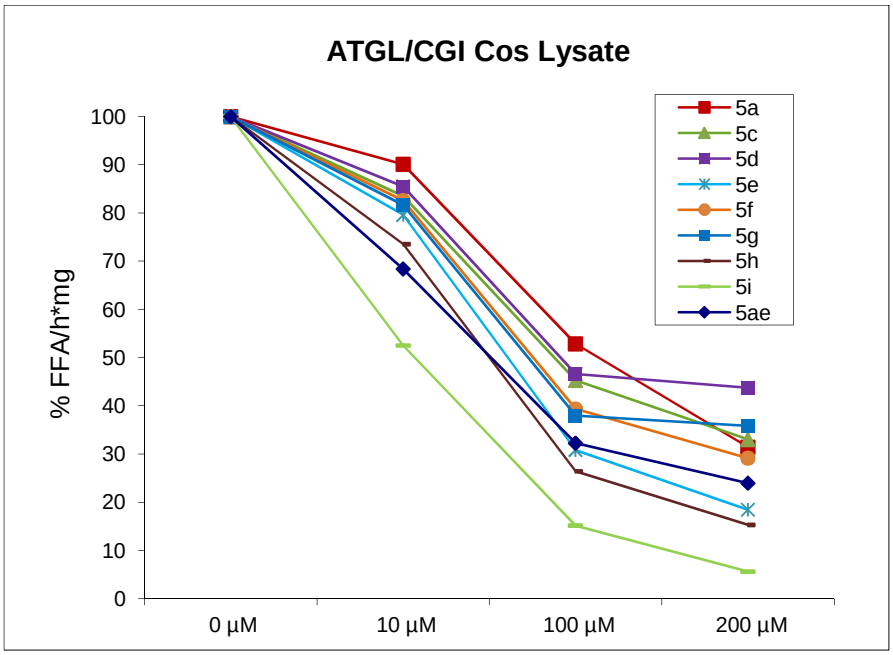


Fig. 41: Dose-dependent inhibition of ATGL activity *in vitro*.

Sterically more challenging (entries 11, 17, 25, 26, 36 and 37) or aliphatic substituents (entry 18 and 19) led to the loss of biological activity just as chlorine substituents (entries 15 and 16), which are normally known to be promising isosteres for hydroxy groups.

Lead compound **5a** and compound **5i** were tested for ATGL- and HSL-selectivity by incubating fat pads of wild-type, ATGL-ko and HSL-ko mice with different inhibitor concentrations (Fig. 42).

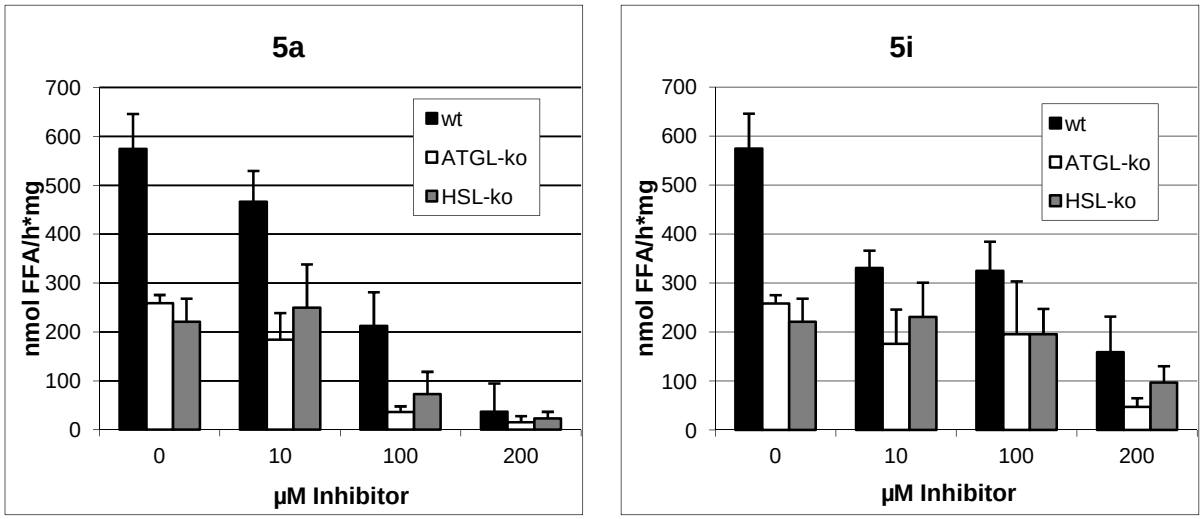


Fig. 42: Selectivity test of **5a** and **5i**.

Both compounds are not selective to ATGL or HSL but the selectivity could be improved using compound **5i**, in which **5i** shows a slightly higher selectivity towards HSL.

In further tests it was determined that compound **5i** does not inhibit MGL, phospholipase (PLP) and lipoprotein lipase (LPL) (both enzymes are commercially available). But a great disadvantage was determined by performing a toxicity test (Tox 4-test). Therefore, living cells were incubated with the inhibitor. After addition of a detection reagent (neutral red solution) living cells showed red color, death cells were colorless. The optic density was measured photometrically at 540 nm and the higher the optic density the less cell toxic is the inhibitor.

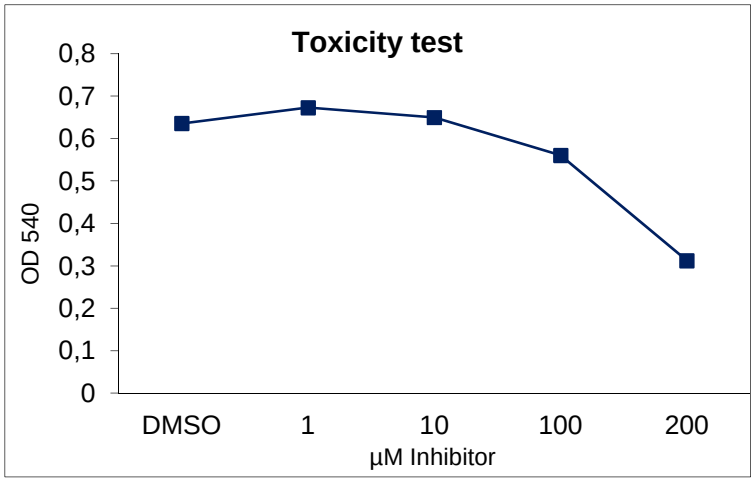
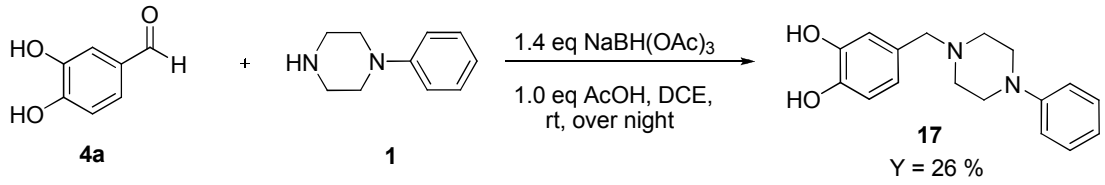


Fig. 43: Toxicity test of inhibitor **5i**.

Fig. 43 shows the decrease of the optic density with increasing inhibitor concentration which can be explained by rising cell death pointing out high cell toxicity of **5i**.

4.1.2. Replacement of the hydrazone functionality

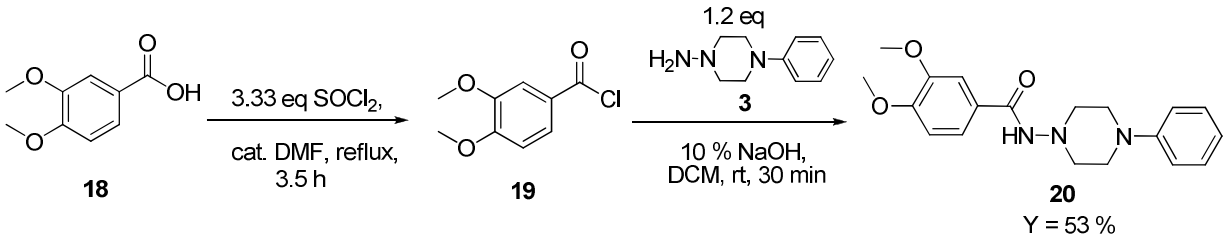
Because of the known cell toxicity of the hydrazone linkage system the next goal was to replace it by other functionalities such as amine, amide, urea or carbamate. The hydoxygroups of our best compound can be troublesome under different reaction conditions. In order to compare the biological data of new compounds with already known ones it was necessary to maintain the building block A with known and unreactive substitution patterns like methoxygroups and fluorine substituents. For the first compound it was possible to keep the two hydroxygroups. To synthesize the 1,2.diol **17** with the amino functionality as bridging element a reductive amination could be applied according to the procedure of ABDEL-MAGID *et al.*[99] (Scheme 7).



Scheme 7: Replacement of the hydrazone functionality by an amine moiety applying reductive amination.

Sodium triacetoxyborohydride was used as reducing agent in excess in the presence of acetic acid. The yield is very low which could be explained by the aqueous work up where some of the product could be retained in the water phase.

In our effort to replace the hydrazone moiety we wanted to test an analogue with a hydrazide function to eliminate the toxicity and possibly introduce higher hydrophilicity in the molecule.

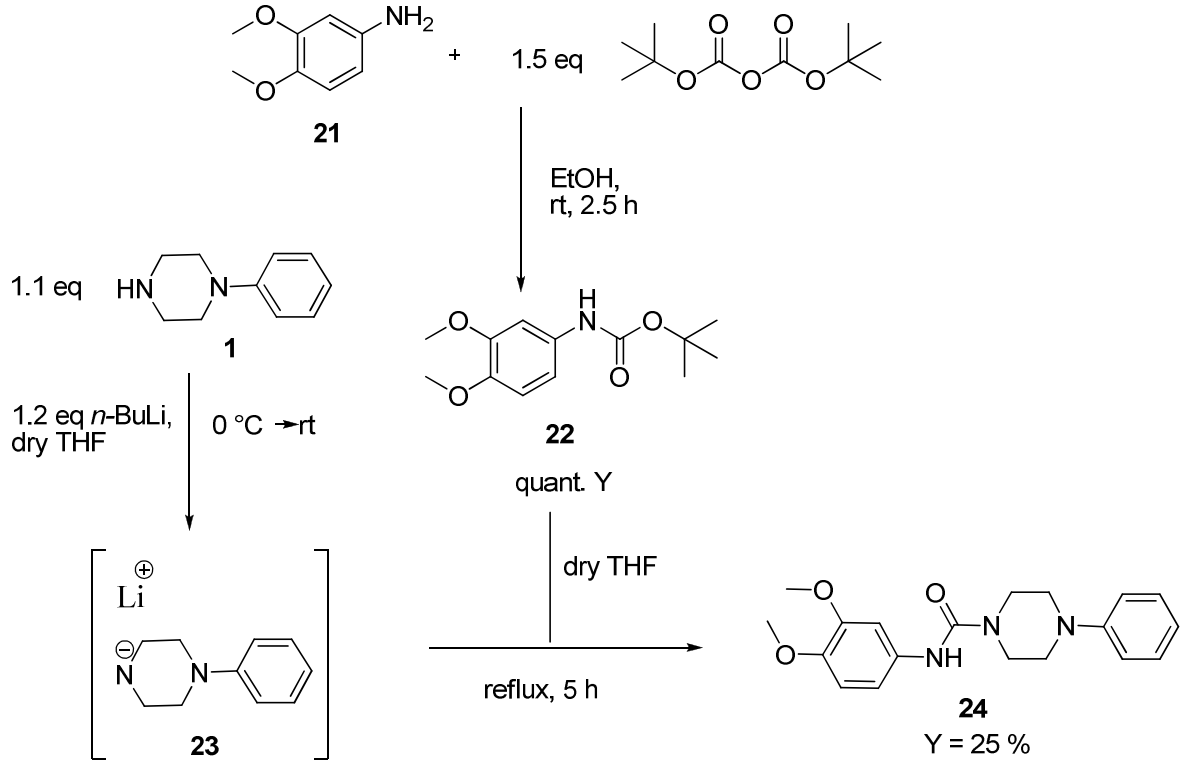


Scheme 8: Replacement of the hydrazone functionality by a hydrazide moiety leading to compound **20.**

In Scheme 8 the synthesis of 3,4-dimethoxy-*N*-(4-phenylpiperazin-1-yl)benzamide **(20)** is depicted, where the two hydroxy groups are replaced by methoxy groups because these are not so troublesome under the chosen reaction conditions which were performed according to a procedure published by NARASIMHAN *et al.*[100] The synthesis of the acid chloride was

performed in an excess of thionylchloride **19** using one drop of DMF as catalyst to accelerate the conversion.[101] The amide formation was accomblished in DCM as a solvent.

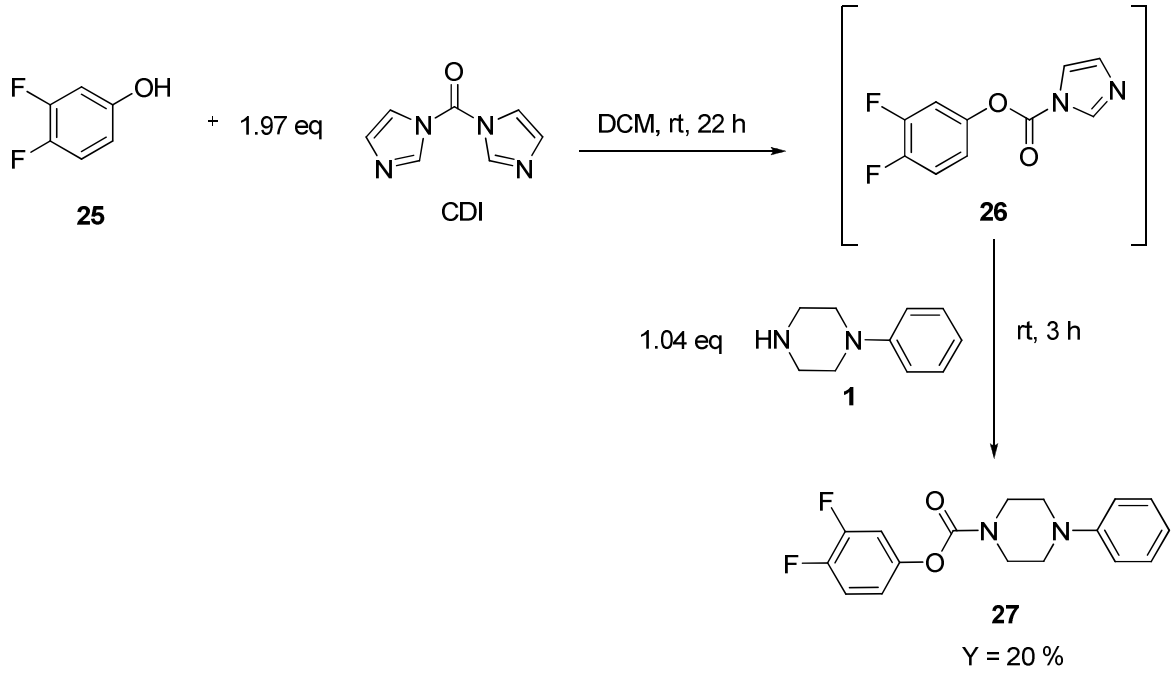
As a third possible alternative to the hydrazone an urea functionality should be introduced (Scheme 9).



Scheme 9: Replacement of the hydrazone functionality by an urea moiety applying substitution reaction.

For this purpose, 3,4-dimethoxyaniline **(21)** was reacted with 1.5 eq Boc-anhydride in EtOH to produce carbamate **22** in full conversion.[102] The removal of excess Boc-anhydride was not trivial, perhaps for repetition its sufficient to use stoichiometric amounts of it. In the next step 1-phenylpiperazine **(1)** was deprotonated by *n*-BuLi in THF at 0 °C according to LAMOTHE *et al.*[103] The carbamate **22** was dissolved in THF and added slowly to the solution of deprotonated phenylpiperazine **23** at rt undergoing a condensation reaction resulting in the desired urea **24**. There are two important issues which could explain the low product yield. The first one is the difficult reaction control regarding the deprotonation rate, and the second explaination could be the possibility for carbamate deprotonation applying the deprotonated phenylpiperazine **23**.

The last interesting linking functionality replacing the hydrazone and introducing hydrophilicity was the carbamate with two fluorine substituents. The reaction was done according to IWASAKI *et al.*[104] by preparing *in situ* the alkyloxycarbonylimidazol **26** using 3,4-difluorophenol **25** and *N*,*N*`-carbonyldiimidazole (CDI) (Scheme 10).



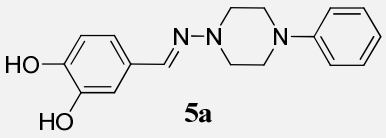
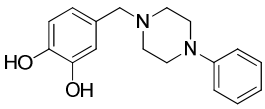
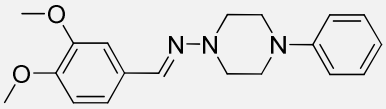
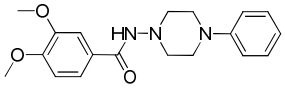
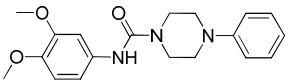
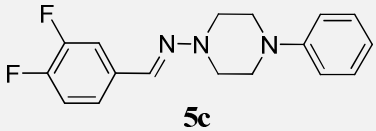
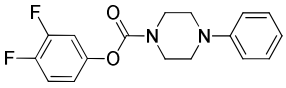
Scheme 10: Replacement of the hydrazone functionality by a carbamate moiety applying CDI activation.

In the last step 1-phenylpiperazine **(1)** was added in a slight excess to the *in situ* prepared solution to obtain the final carbamate **27** in 20 % yield after silica gel filtration and washing with 2 M NaOH solution. To improve the yield it is perhaps necessary to isolate the alkyloxycarbonylimidazol **26** by washing with water to remove the imidazole which is released upon the activation reaction.

4.1.2.1. Screening results and discussion

All four compounds were screened *in vitro* and the results are listed in Table 2 assigning the new synthesized compounds to the analogous hydrazones.

Table 2: IC_{50}-values and *in vitro* inhibition of the enzyme using an inhibitor concentration of 200 µM

Entry	No.	Compound	IC_{50} [µM]	I_{200} [%]
		 **5a**		
1	**17**		➢ 200	20
		 **5b**		
2	**20**		➢ 200	38
3	**24**		➢ 200	40
		 **5c**		
4	**27**		110	57

The biological activity of all compounds could not be improved, only compound **27** could show comparable data to **5c**. **17**, **20** and **24** showed no significant IC_{50}-values and the inhibition is strongly decreased, which is also visible in the three diagrams depicted in Fig. 44.

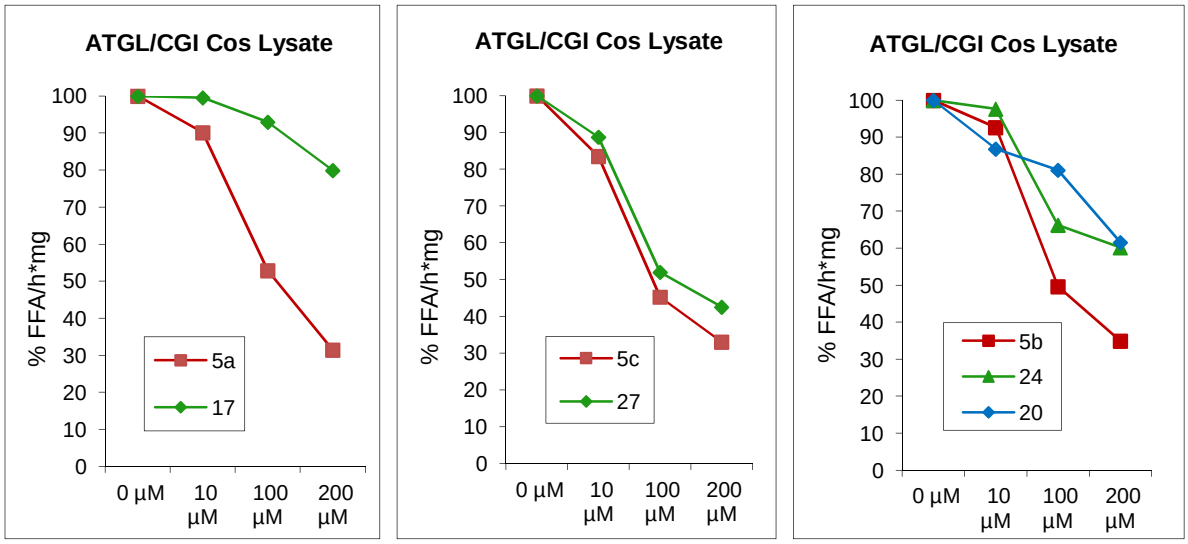
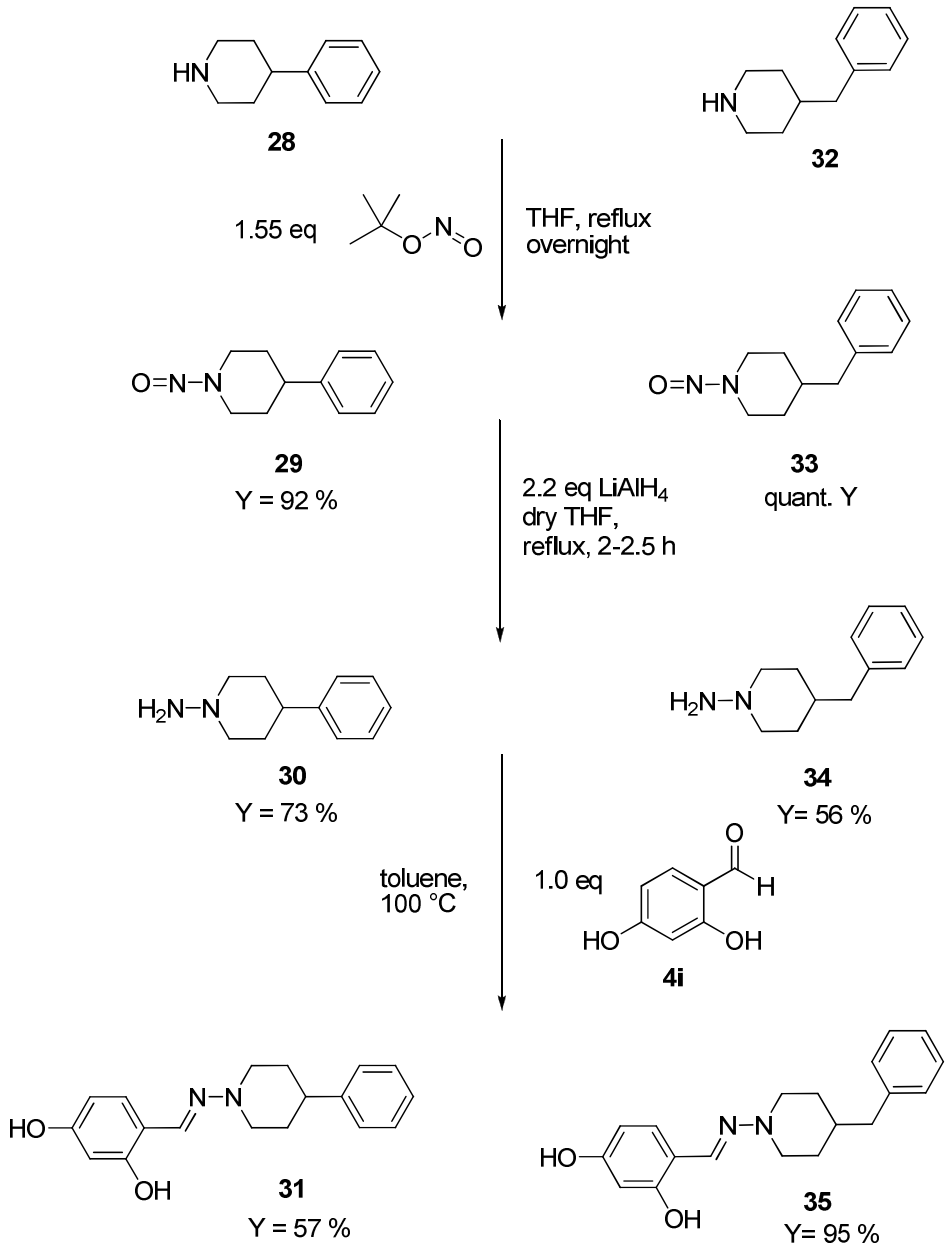


Fig. 44: Dose-dependent inhibition of ATGL activity *in vitro*.

In conclusion, the hydrazone **5i** is still the best compound. Although it is cell toxic we used the optimized moieties of the compound to improve the biological activity *in vitro* as the convenient hydrazone formation could give us fast access to series of derivatives for SAR-studies.

4.1.3. Replacement of the piperazine ring system

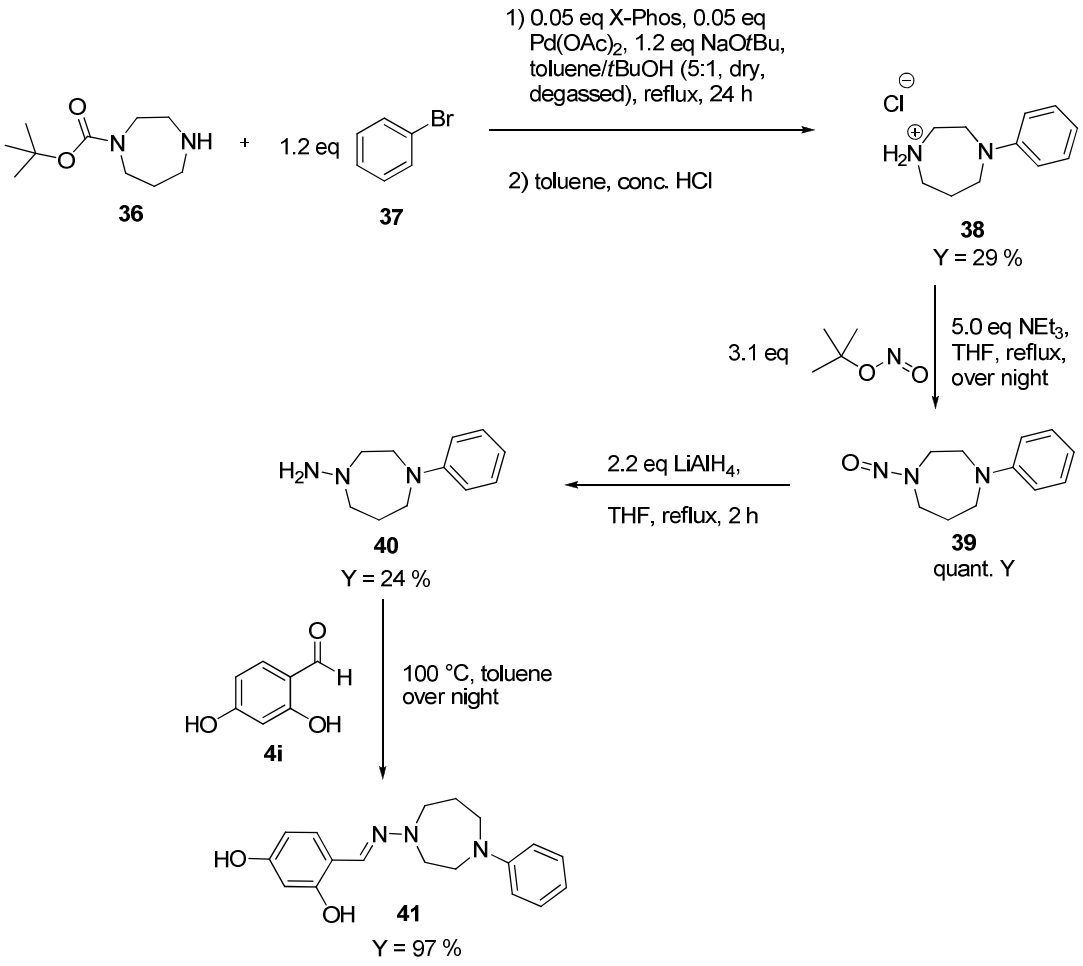
In the next part we put our focus on the piperazine function by replacing the piperazine through a piperidine, homopiperazine and an elongation between the building block C and building block D (Scheme 11). The to date best substitution pattern of building block A containing the 2,4.dihydroxyphenylic system was kept constant in these studies.



Scheme 11: Synthesis of piperidine containing compounds **31** and **35** with a CH_2-elongation in **35**.

According to the publications [90,92-93] described for the reactions in Scheme 11, 4-phenylpiperidine **(28)** and 4-benzylpiperidine **(32)** were nitrosylated in 92 % and quantitative yield, respectively. After reduction with $LiAlH_4$ the obtained hydrazines **30** and **34** were reacted with the 2,4-dihydroxybenzaldehyde **(4i)** obtaining the desired hydrazone compounds in 57 % and 95 % yield, respectively.

To introduce the homopiperazine moiety it was necessary to synthesize the starting material based on a Pd(0)-catalyzed Buchwald-Hartwig protocol applied to the *N*-arylation of Boc-protected homopiperazine **36** with bromobenzene **(37)**. SCHOEN *et al.*[105] described a procedure exactly for our desired molecule using $Pd(OAc)_2$ as Pd-species and X-Phos as ligand. Additionally, NaO*t*Bu was applied as base in a mixture of degassed toluene and *t*-BuOH. For the subsequent synthetic step it was necessary to have the Boc-deprotected homopiperazine isolated as a hydrochloride salt **38** in 29 % yield (Scheme 12).



Scheme 12: Four-step synthesis of the homopiperazine containing compound **41** .

To nitrosylate the 1-phenylhomopiperazine hydrochloride salt **(38)** addition of 5.0 eq triethylamine was required. The conversion by reduction[92] and condensation[93] with 2,4-dihydroxybenzaldehyde **(4i)** led to the desired product **41** in 97 % yield.

4.1.3.1. Screening results and discussion

The results of the *in vitro* screening of all three compounds, which are mentioned in Table 3, were very surprising.

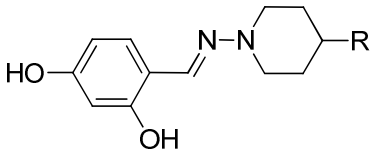
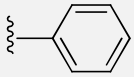
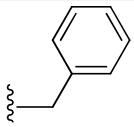
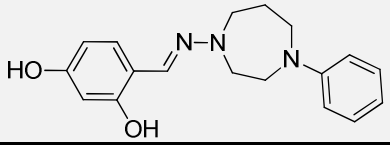


Table 3: IC_{50}-values and *in vitro* inhibition of the enzyme using an inhibitor concentration of 200 µM

Entry	No.	R	IC_{50} [µM]	I_{200} [%]
1	**31**		**40**	**81**
2	**35**		➢ 200	26

Entry	No.	Compound	IC_{50} [µM]	I_{200} [%]
3	**41**		➢ 200	87

By replacing the piperazine ring with a piperidine ring (entry 1) the IC_{50}-value could be improved from 50 µM to 40 µM but the inhibition was slightly worse, which is also depicted in Fig. 45. The elongation by a CH_2-group (entry 2) showed no improvement of the biological activity. The homopiperazine (entry 3), that means the increase of the ring size by one carbon, indeed inhibits the enzyme with 87 % but the IC_{50}-value is >200µM.

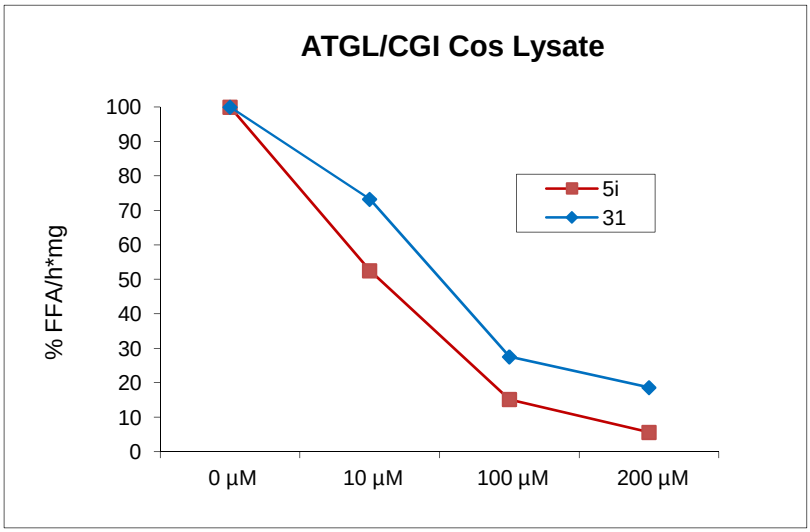


Fig. 45: Dose-dependent inhibition of ATGL activity *in vitro*.

Similar to **5i** compound **31** does also not inhibit PLP. Surprisingly, we could observe less cell toxicity of **31** compared to **5i**, which is depicted in Fig. 46.

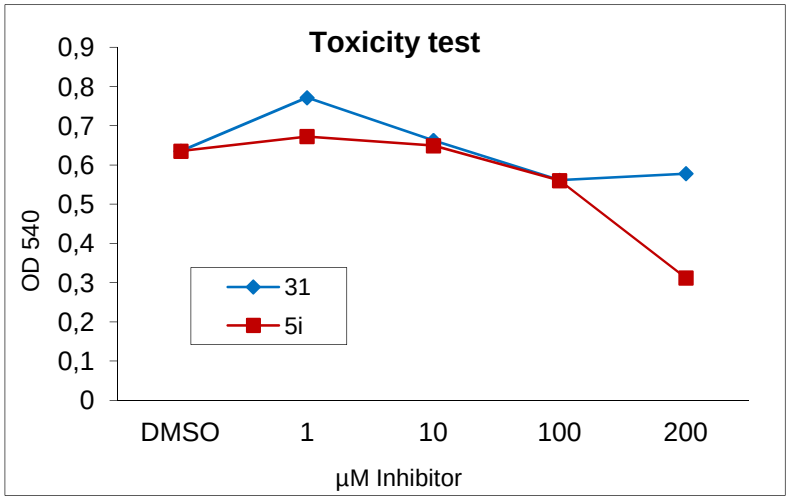
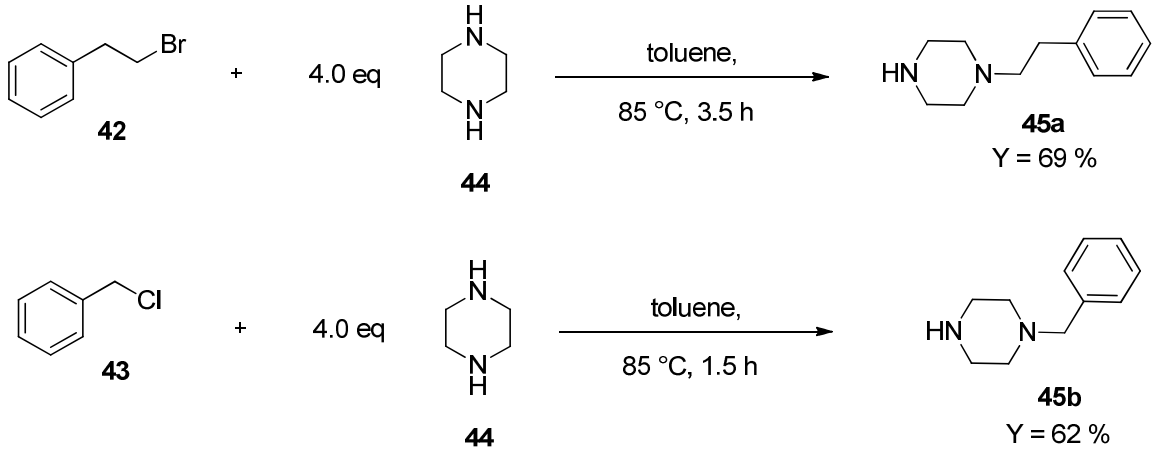


Fig. 46: Toxicity test of **31** compared with **5i**.

The decrease of the optic density after incubation with inhibitor **31** is less compared with **5i**, but the compound is still cell toxic and cannot be used in living organisms.

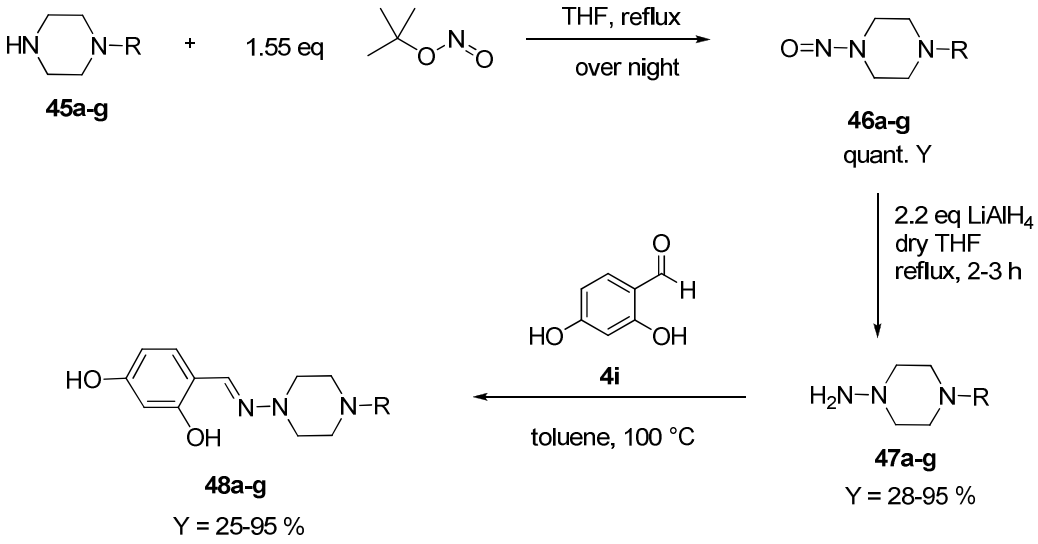
4.1.4. Diversification of building block D using different arylpiperazines

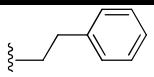
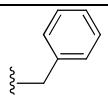
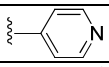
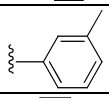
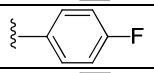
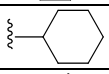
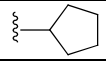
In this section we focused on the variation of building block D. We wanted to investigate the hydrophobic influence of the benzene ring by replacing it with a pyridine or saturated ring systems. In addition, we wanted to explore the space and steric requirements and limitations. Almost all arylpiperazines which we planned to convert were commercially available. Only the two piperazines which are extended between the two ringsystems had to be synthesized by a substitution reaction following procedures published by CAPUANO *et al.*[106] and PIKE *et al.*[107] (Scheme 13). Piperazine **(44)** was used in excess because on the one hand it additionally functions as a base to quench HBr and HCl, respectively, which are formed during the reactions, and on the other hand dialkylation can occur. However, the two desired arylpiperazines **45a** and **45b** could be obtained in moderate yields after purification by vacuum distillation and column chromatography, respectively.



Scheme 13: Synthesis of the starting materials **45a** and **45b** with bond elongation.

The commercially available arylpiperazines **45c-g** and the two ones synthesized by ourselves underwent than the well known reaction steps depicted in Scheme 14, showing the results for the nitrosylation, reduction and hydrazone formation.[90,92-93]



R	No.	Y [%] (NH_2)	No.	Y [%] (C=N)
	**47a**	56	**48a**	95
	**47b**	73	**48b**	95
	**47c**	95	**48c**	74
	**47d**	28	**48d**	58
	**47e**	45	**48e**	25
	**47f**	46	**48f**	66
	**47g**	65	**48g**	76

Scheme 14: Yields for hydrazine formation and subsequent hydrazone condensation for the various piperazine substrates.

4.1.4.1. Screening results and discussion

The screening results of the diversification on building block D are listed in Table 4.

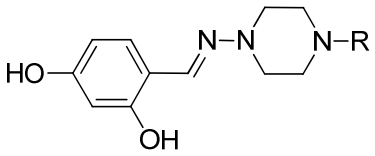
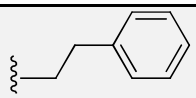
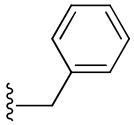
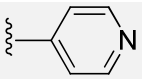
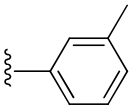
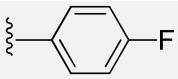
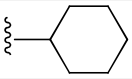
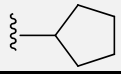


Table 4: IC_{50}-values and *in vitro* inhibition of the enzyme using an inhibitor concentration of 200 µM

Entry	No.	R	IC_{50} [µM]	I_{200} [%]
1	**48a**		➢ 200	14
2	**48b**		➢ 200	48
3	**48c**		➢ 200	19
4	**48d**		➢ 200	44
5	**48e**		**50**	**78**
6	**48f**		➢ 200	25
7	**48g**		➢ 200	36

The phenylring was replaced by pyridine (entry 3) and saturated ring systems (entries 6 and 7) and the chain between the piperazine and the phenyl ring was extended (entries 1 and 2). But all synthesized compounds did not show improved biological activity. The data direct to the following insights regarding SAR:

- The space in the binding pocket seems to be limited as by introduction of non-planarity in the case of cyclohexyl and cyclopentyl ring systems the activity gets lost and the hydrophobic π-π-interaction of an aromatic ring is required.
- Electron poor aromatic rings (fluorine substituent, entry 5) are better than electron rich ones (entry 4), but the IC_{50}-value and inhibition effect of the fluorine substituted ring are not improved compared to the non-substituted aromatic ring. (Fig. 47)

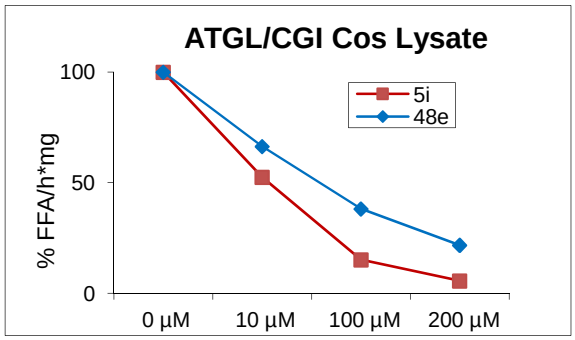
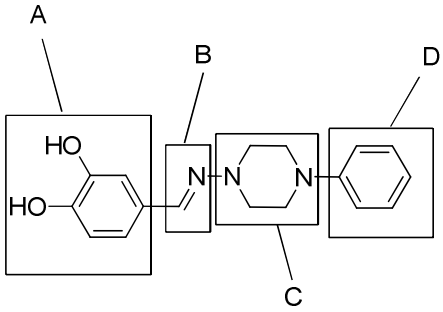


Fig. 47: Dose-dependent inhibition of ATGL activity *in vitro*.

- Chain elongation between the rings increased the flexibility of the residue but decreased the biological activity in a great manner.

4.1.5. Summary of the improvement efforts of lead structure 1



Lead structure 1 is a composition of four main building blocks, which were synthetically varied in this thesis. The IC_{50}-value of lead structure 1 is 110 µM and it inhibits the enzyme using a concentration of 200 µM inhibitor by 69 %. In the first chapter we reacted 4-phenylpiperazin-1-amine **(3)** with different aldehydes **(4a-4ah)** to hydrazones **(5a-5ah)**. (Fig. 48)

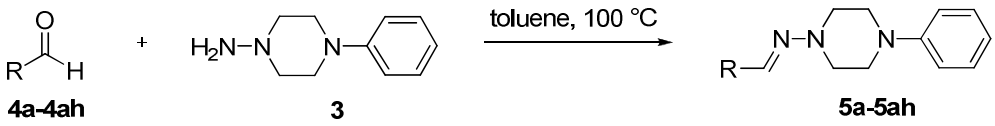


Fig. 48: General scheme for the hydrazone synthesis replacing building block A.

It was planned to replace the hydroxygroups because phenols are easy to oxidize and metabolize. By introducing methoxy groups or fluorine the biological activity indeed could be improved but by substituting the phenyl ring with hydroxyl groups in 2- and 4-position instead of 3- and 4- position the biological activity could be dramatically improved (IC_{50} = 10 µM, 94 % inhibition). (Fig. 49)

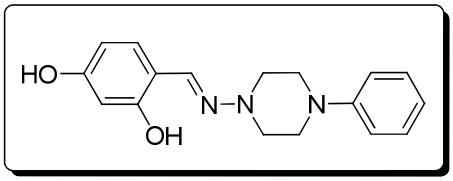


Fig. 49: Improved compound **5i**.

The selectivity could also be improved towards ATGL but it is still activity towards HSL observable. A big throwback was the still maintained toxicity, which is introduced by hydrazones. We tried to replace the hydrazone bond with other functionalities, such as a amine, amide, urea or carbamate but their biological activity was disappointing. Only the carbamate could function as a competetive replacement for the hydrazine linkage. Also the replacement of the piperazine ring by piperidine and homopiperazine or chain elongation

between the piperidine and phenyl ring did not improve the biological activity. By introducing the piperidine ring at least the toxicity could be reduced. (Fig. 50)

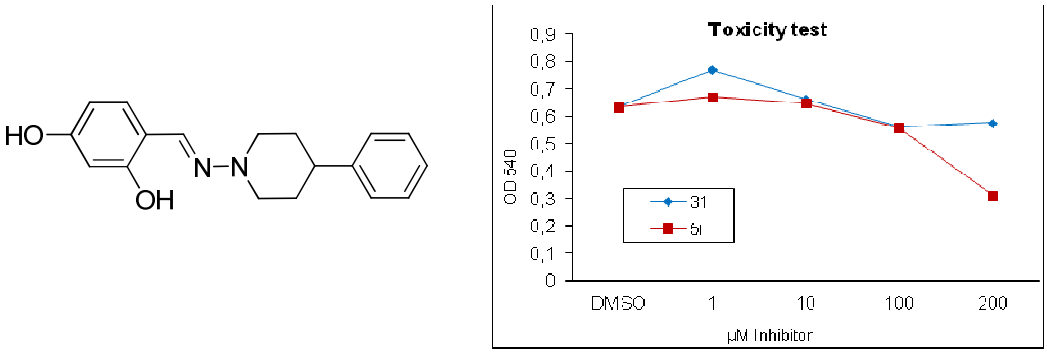
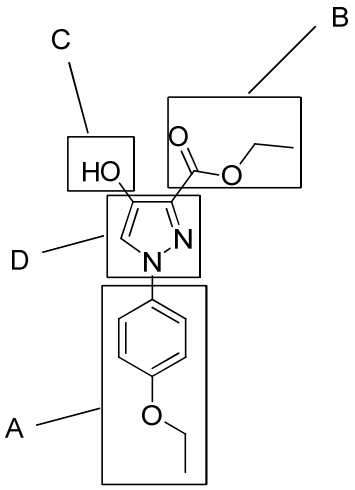


Fig. 50: Compound **31** and the reduced toxicity.

The diversification of building block D with pyridine-, cyclohexyl- or cyclopentyl rings while keeping the piperazine ring showed almost no biological activity. Elongation of the chain between the piperazine and phenyl ring led to the same effect. Only the fluorine substituent in 4-position of the phenyl ring resulted in a similar but slightly worse biological activity.

To summarize the optimization of lead structure 1 we were successful in improving the biological activity (10 µM vs. 110 µM, 94 % inhibition vs. 69 % inhibition) impressively. We could improve the selectivity towards ATGL but could not reach a 100 % selectivity. Unfortunately, we did not succeed in removing the cell toxicity but we decreased the toxicity. Because of this results and the limited possibilities for further optimization steps we decided to explore a second lead structure.

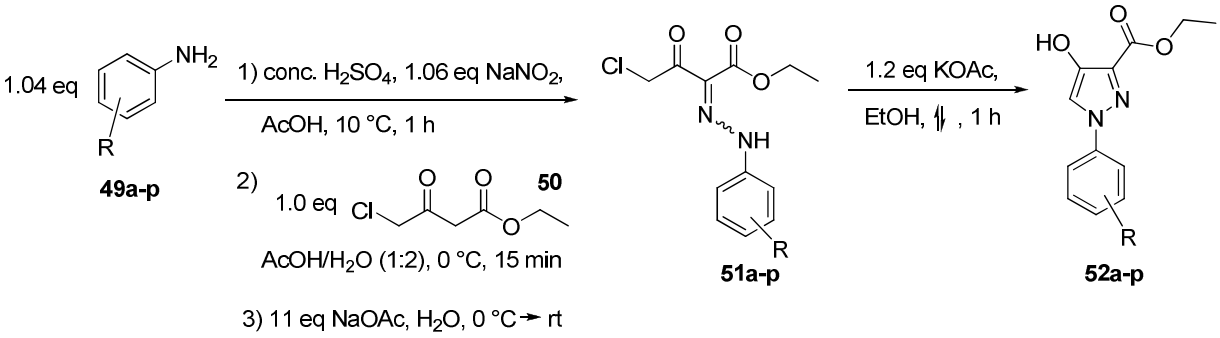
4.2. Lead structure 2

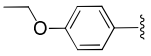
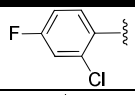
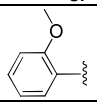
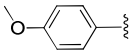
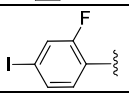
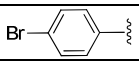
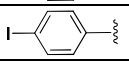
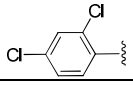
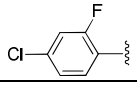
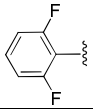
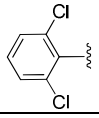
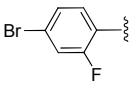
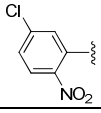


Lead structure 2 also results from the HTS performed by *Novo Nordisk Denmark*. It is formally composed of four main building blocks. The structure is characterized by a relativly hydrophobic side chain surely depending on the substitution (building block A), a pyrazole function (building block D), which is hydroxy-substituted (building block C) plus an ethyl ester functionality as a side chain (building block B). The IC_{50}-value of lead structure 2 is 120 µM and it inhibits the enzyme using a concentration of 200 µM inhibitor by 67 %.

4.2.1. Synthesis of different 4-hydroxypyrazoles using different arene substituted systems

For the synthesis of the lead compound and other pyrazoles differing in the substitution on building block A a patent published by LI *et al.*[108] was used. Starting from different anilines **49a-p** diazonium salts were synthesized by using conc. H_2SO_4 and $NaNO_2$. The salt was then reacted with 4-chloro-3-oxobutanoate **(50)** to obtain compounds **51a-p** as *cis-/trans*-isomers in a JAAP-KLINGEMANN-reaction (Scheme 15).



No.	R	51 [%]	52 [%]	No.	R	51 [%]	52 [%]
a		55	97	**i**		80	95
b		69	83	**j**		77	98
c		60	99	**k**		99	76
d		56	93	**l**		78	90
e		75	93	**m**		75	97
f		55	98	**n**		78	96
g		92	91	**o**		69	99
h		86	93	**p**		77	41

Scheme 15: Synthesis of different 4-hydroxypyrazoles **(52a-p)** and the yields of the isolated oxobutanoates **(51)** and pyrazoles **(52)**.

The *cis-/trans*-ratio depends on the substitution at the aniline and the product is isolated as a mixture of both isomers. It was not possible to assign the signals in the ^{1}H- and ^{13}C-NMR using NOE-spectroscopy or HSQC and HMBC. However, the question of the isomeric purity is probably of little relevance, since for the acid induced cyclization reaction using KOAc the isomeric mixture was converted to the desired pyrazoles **52a-p** in good yields. Pyrazole **52p** had to be purified by column chromatography.

4.2.1.1. Screening results and discussion

All synthesized 4-hydroxypyrazoles **52a-p** were screened *in vitro* and the results are listed in Table 5.

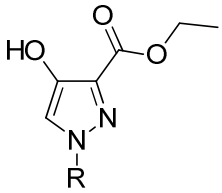
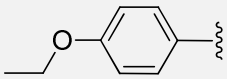
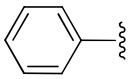
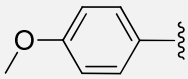
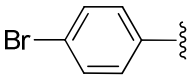
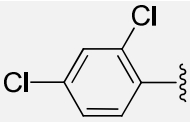
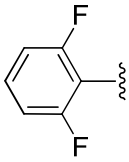
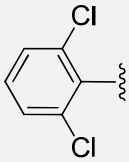
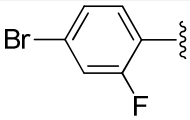
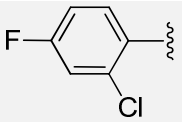
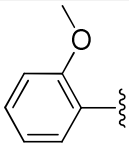
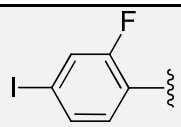
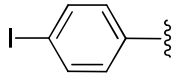
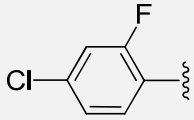
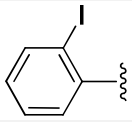
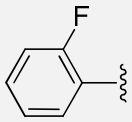
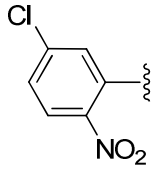


Table 5: IC_{50}-values and *in vitro* inhibition of the enzyme using an inhibitor concentration of 200 µM

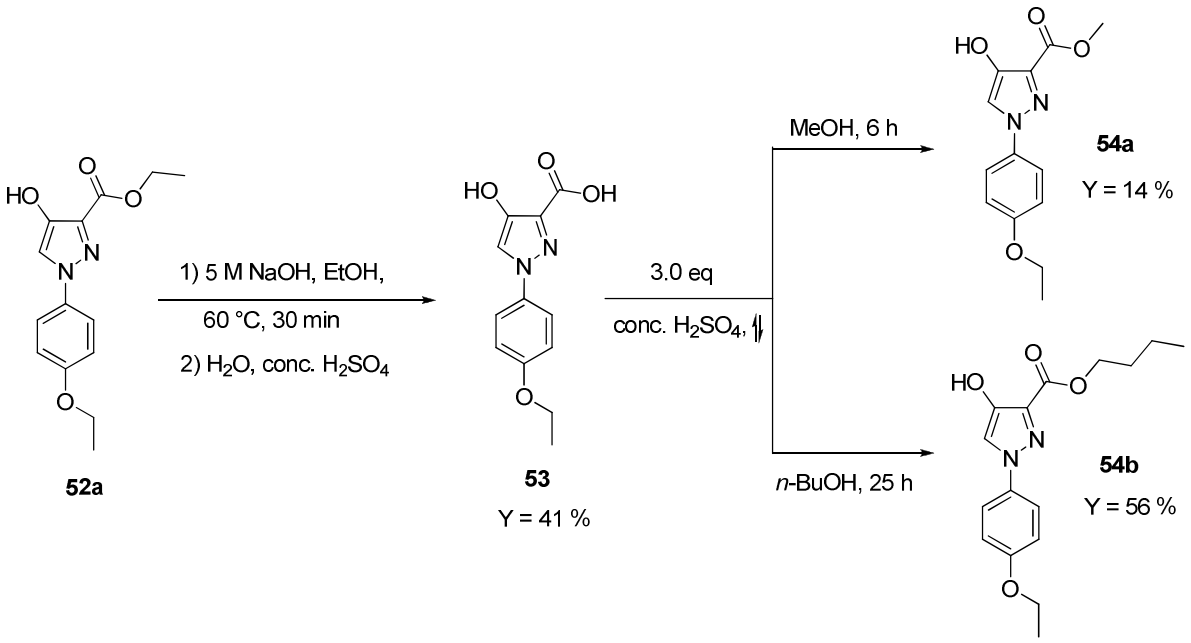
Entry	No.	R	IC_{50} [µM]	I_{200} [%]
1	**52a**		120	67
2	**52b**		200	51
3	**52c**		200	49
4	**52d**		120	60
5	**52e**		➢ 200	44
6	**52f**		➢ 200	30
7	**52g**		➢ 200	19
8	**52h**		➢ 200	31
9	**52i**		➢ 200	30
10	**52j**		➢ 200	23

11	**52k**		➢ 200	29
12	**52l**		120	61
13	**52m**		➢ 200	38
14	**52n**		➢ 200	16
15	**52o**		➢ 200	25
16	**52p**		➢ 200	30

The biological data of the resynthesized lead substance (entry 1) confirmed the results of the high-throughput screening performed by *Novo Nordisk, Denmark*. The diversification of the phenyl ring by introduction of different electron donating and electron withdrawing substituents did not lead to the improvement of the biological activity. Only the replacement of the ethoxy group in *para* position by halogens (entries 4 and 12) induced consistent IC_{50}-values and inhibition effects. Once substituents were introduced in *ortho* or *meta* position on the ring (entries 5-11 and entries 13-16) the steric hindrance seemed to be too high and the biologcal activity decreased.

4.2.2. Variation of the ester side chain

By changing the ester functionality we wanted to find out how important the ethyl ester is for the binding affinity to the enzyme and if it plays a special role in the inhibition effect. Therefore, the hydrolysis of the pyrazole **52a** was attempted under the conditions of LI *et al*.[108] With **53** in hand it was possible to synthesize the methyl and *n*-butyl ester by a simple acid-catalyzed esterification working either in MeOH or *n*-BuOH applying the conditions of BÜNZLI *et al.*(Scheme 16).[109]



Scheme 16: Variation of the ethyl ester by synthesizing the *n*-butyl-and methylester substituted pyrazoles **54a** and **54b**.

4.2.2.1. Screening results and discussion

The variation of the ethyl ester functionality on the pyrazole ring led to the results listed in Table 6

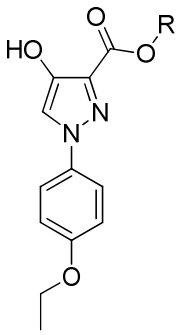


Table 6: IC_{50}-values and *in vitro* inhibition of the enzyme using an inhibitor concentration of 200 µM

Entry	No.	R	IC_{50} [µM]	I_{200} [%]
1	**53**	H	➢ 200	15
2	**54a**	Methyl	130	64
3	**54b**	*n*-Butyl	100	74

The free carboxylic acid group of compound **53** (entry 1) decreased the biological activity of the lead compound dramatically, which is also depicted in Fig. 51.

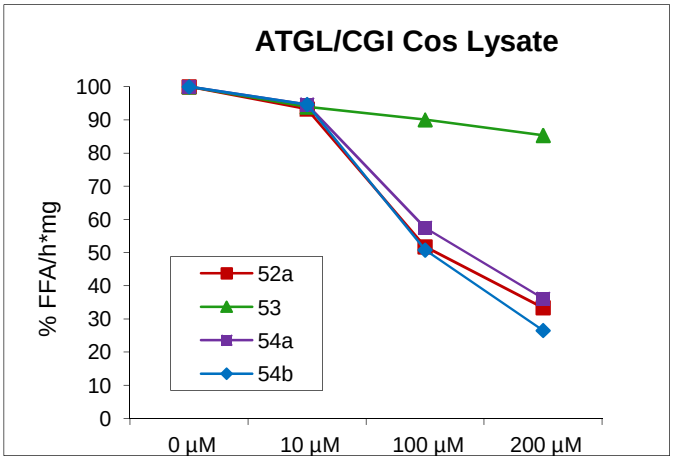
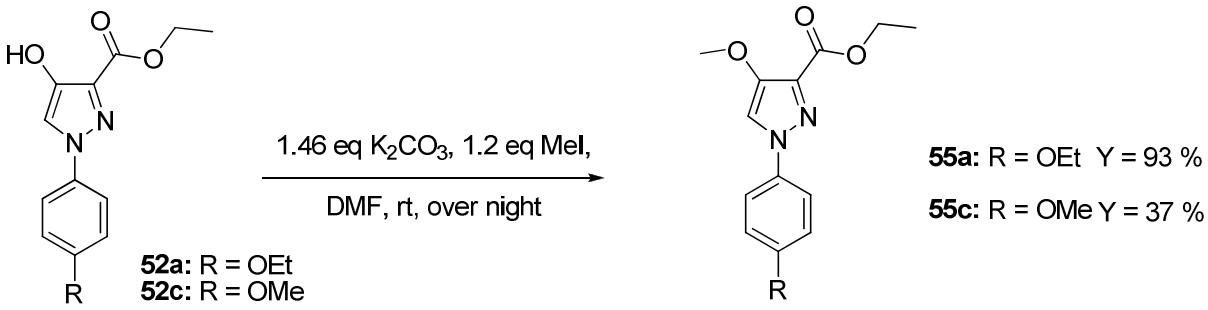


Fig. 51: Dose-dependent inhibition of ATGL activity *in vitro*.

Almost no inhibition of the enzyme could be observed, in contrast to the methyl and butyl esters (entries 2 and 3). They showed data comparable to the methyl ester functionality and slightly improved biological activity for the butyl ester concerning both, the IC_{50}-value and the inhibition effect. The butyl ester indeed delivered a slightly improved inhibitor compound but because of the limited number of suitable commercially available building blocks, we maintained the ethyl ester side chain for further lead structure optimization.

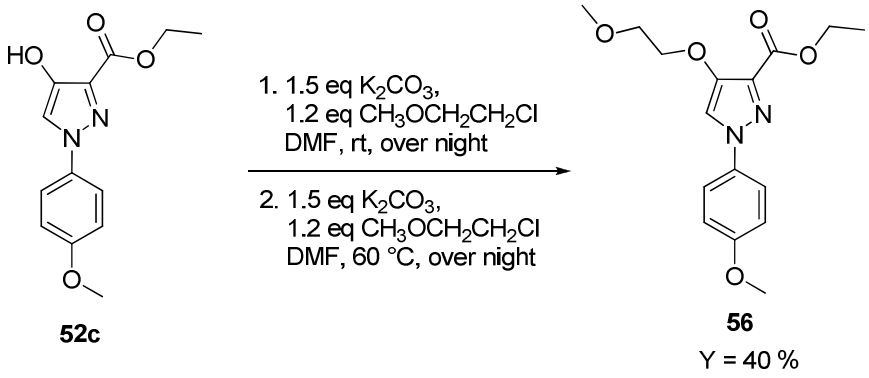
4.2.3. Synthesis of different arylpyrazoles replacing the hydroxy group

To resolve the question if the hydroxy group is essential for the inhibtition of the enzyme, we decided to alkylate it to produce perhaps a more metabolic stable compound.



Scheme 17: Alkylation of the hydroxy group using methyl iodide.

The methylation could be realized in good to acceptable yields according to LI *et al.*[108] using potassium carbonate as base and methyl iodide as alkylation reagent (Scheme 17). The alkylation of hydroxypyrazole **52c** using 1-chloro-2-methoxyethane as alkylating species was also done to explore the available space in the binding pocket (Scheme 18).



Scheme 18: Alkylation of the hydroxy group using 1-chloro-2-methoxyethane.

After stirring at rt over night no conversion of the starting material could be monitored by TLC and GC-MS. But the increase of the temperature to 60 °C led to full conversion and successful isolation of the pyrazole **56**.

4.2.3.1. Screening results and discussion

All three synthesized alkylated pyrazoles were screened *in vitro* obtaining results, which are listed in Table 7.

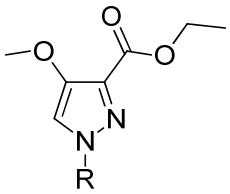
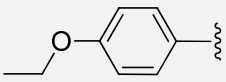
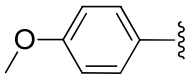
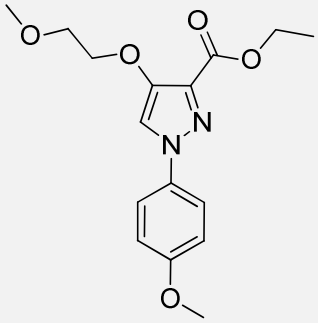


Table 7: IC_{50}-values and *in vitro* inhibition of the enzyme using an inhibitor concentration of 200 µM

Entry	No.	R	IC_{50} [µM]	I_{200} [%]
1	**55a**		**90**	**63**
2	**55c**		140	58

Entry	No.	Compound	IC_{50} [µM]	I_{200} [%]
3	**56**		➢ 200	37

The methylation of the hydroxy group of compound **52a** led to the improvement of the IC_{50}-value from 120 µM to 90 µM by a consistent inhibition effect (entry 1). Similar results were obtained for the methoxy substituted 1-phenylpyrazole (entry 2). The results are also shown in Fig. 52.

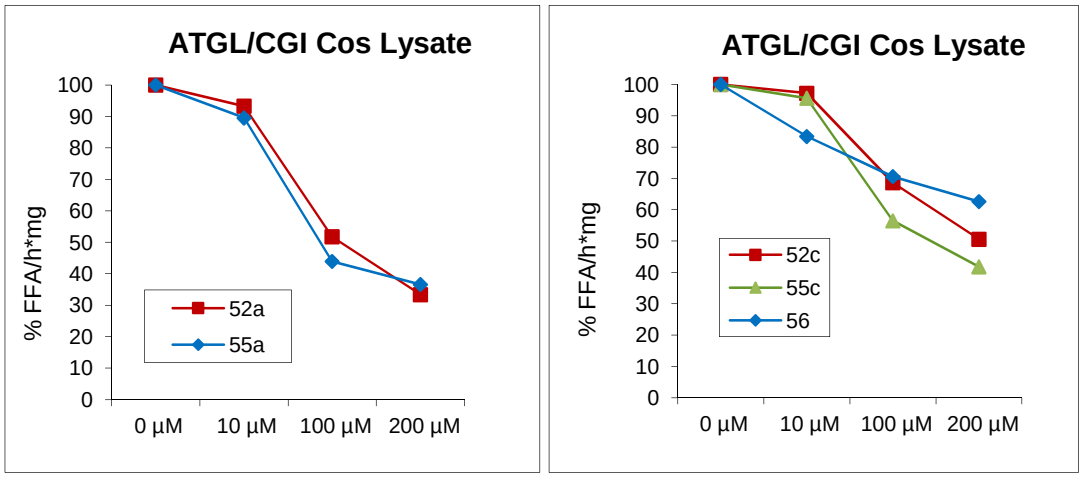
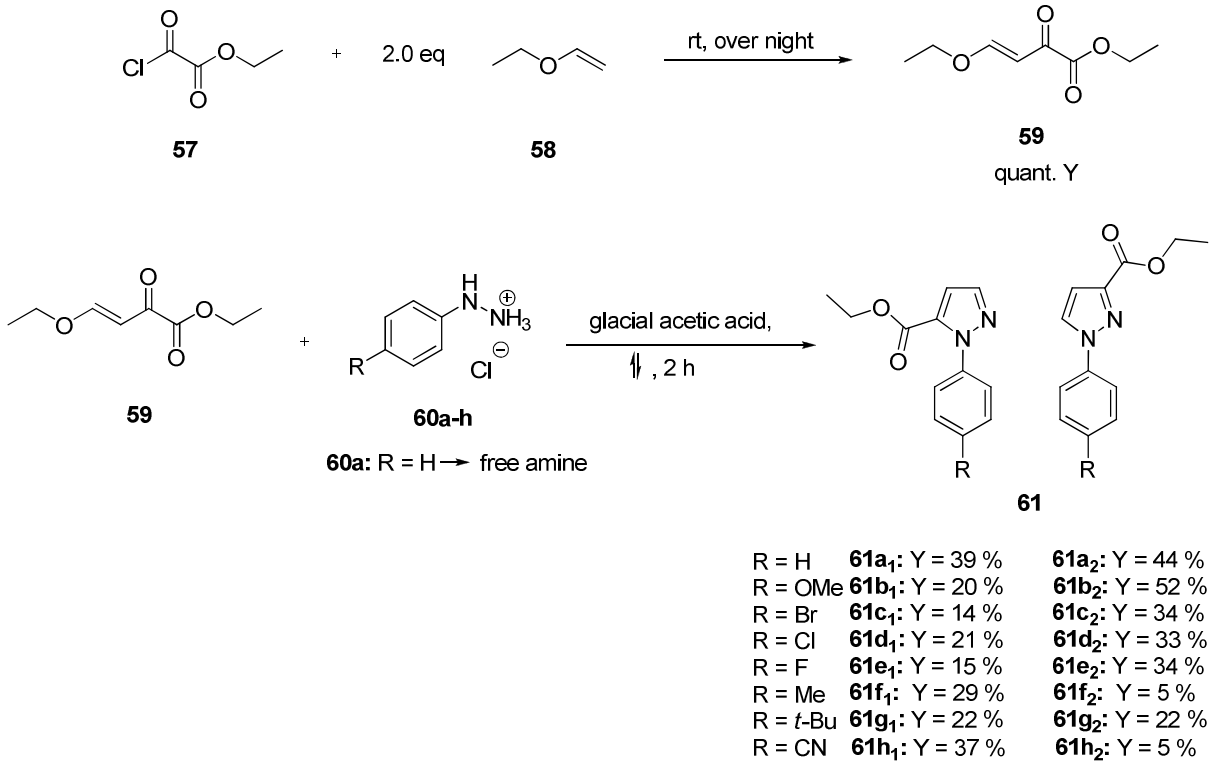


Fig. 52: Dose-dependent inhibition of ATGL activity *in vitro*.

In contrast, by introducing a longer alkyl chain (entry 3) the biological activity was immediately decreased, probably pointing out the space in the binding pocket of the target protein.

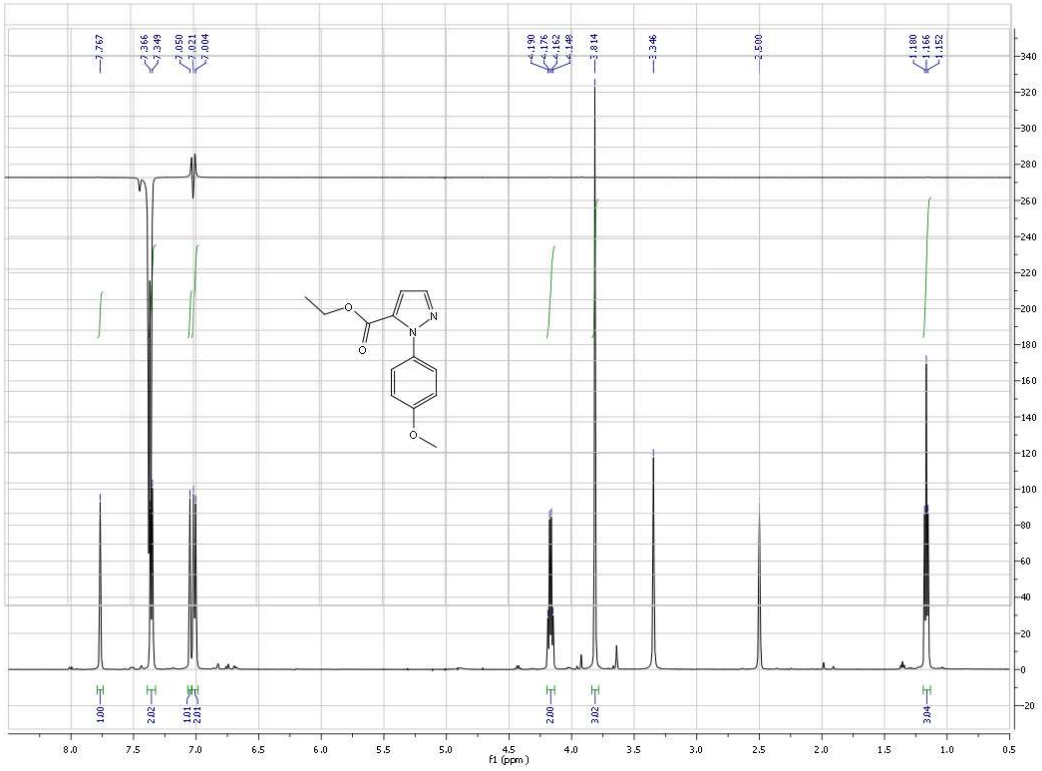
4.2.4. Synthesis of various arylpyrazoles without hydroxy group

As the alkylated hydroxy group of the pyrazole seemed to improve the biological properties of our substances we were interested if there is generally a substitution necessary at this position of the pyrazole ring. For the synthesis of the pyrazoles without the hydroxy group a very interesting procedure was published in a patent by SOHN *et al.* in 1990.[110]



Scheme 19: Synthesis of pyrazoles **61** without hydroxy group yielding 3-and 5-substituted products.

With this procedure it was possible to synthesize first the pyruvate **59** in quantitative yield at a bigger scale and convert it then in a ring closing reaction in glacial acetic acid by attaching different phenylhydrazine hydrochlorides **60b-h** or the free phenylhydrazine **60a** (Scheme 19). In this pyrazole formation two different isomers are formed. The ester group can be oriented in 3- or 5-position of the pyrazole ring. The product ratio depends on the substitution at the phenyl ring. We were successful in separating both compounds from each other via column chromatography. Both products exhibit different retention times in GC-MS and different NMR-spectra. The structure of both isomers could be unambiguously assigned by NOE-spectroscopy (Nuclear Overhauser-Effect) (Fig. 53). In the bottom spectra there is not only a NOE-effect of the phenylic protons visible but also an additional effect between the 2`-phenylic proton and the proton in 5-position at the pyrazole ring.



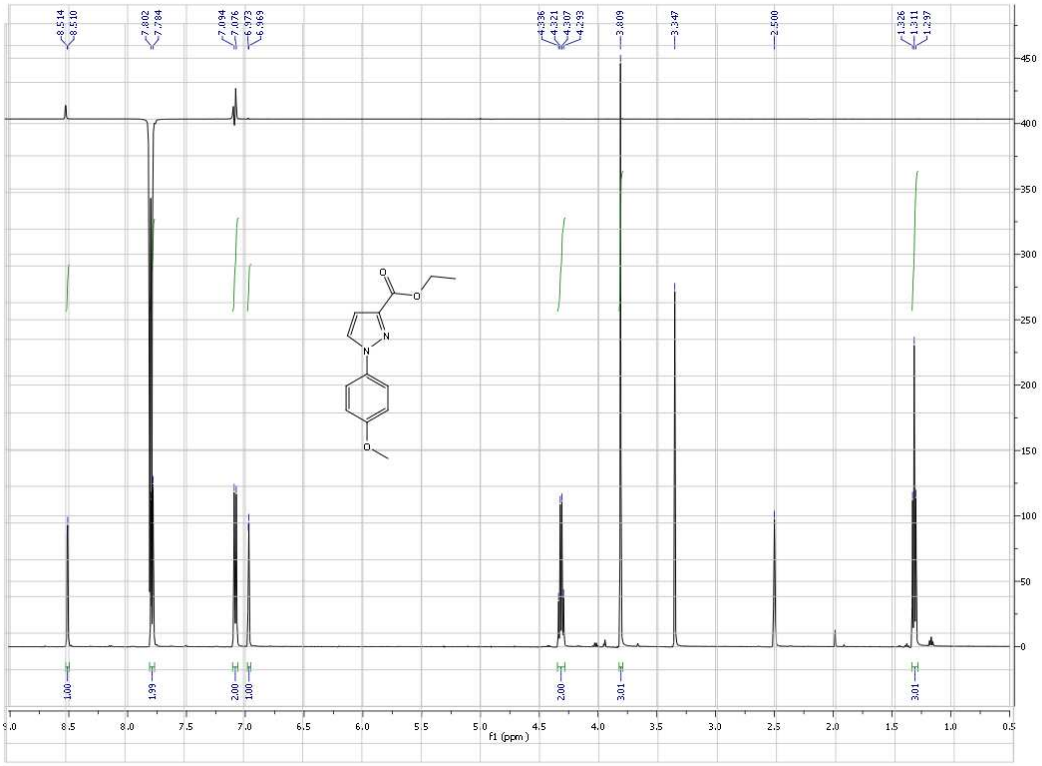
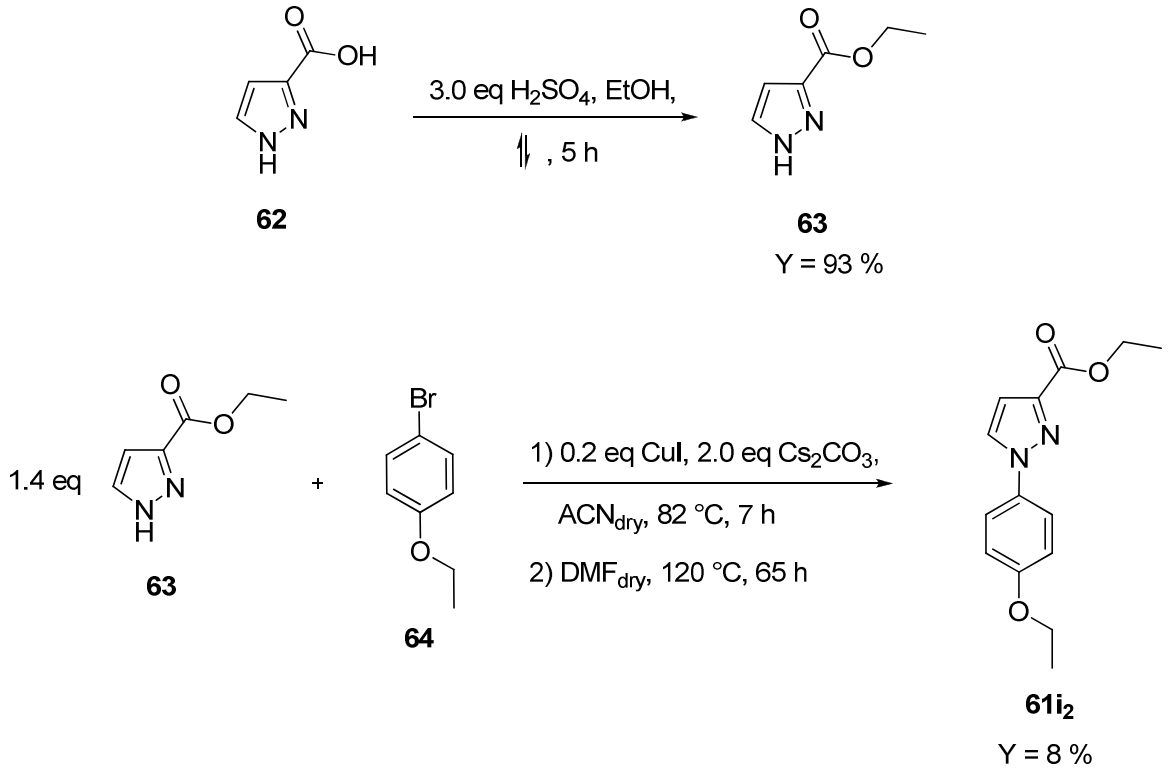


Fig. 53: Spectra showing the NOE-effect which led to the assignment of the products.

4-Ethoxyphenylhydrazine was not commercially available. As this compound would have been essential for comparing the biological data of the corresponding pyrazole **61i$_2$** with the lead structure 2, an alternative synthesis route to **61i$_2$** was developed (Scheme 20). According to BÜNZLI *et al.*[109] the pyrazole-3-carboxylic acid **(62)** was converted to ethyl 3-pyrazolecarboxylate **(63)** by a simple acid-catalyzed esterification in EtOH.



Scheme 20: Alternative synthesis of pyrazole **61i$_2$**.

For the CuI-catalyzed *N*-arylation of 3-pyrazolecarboxylate **(63)** and *p*-bromophenetole **(64)** two different procedures were combined. In the first one by TAILLEFER *et al.*[111] the reaction takes place in acetonitrile but because of solubility issues it was necessary to add DMF as was mentioned in a procedure by YOU *et al.*[112]. Full conversion of the starting material was achieved but the low isolated yield remains unexplainable. After full conversion of the pyrazole **63** a lot of bromophenetole **64** was remaining. However, the product **61i$_2$** was 98 % pure and the most important objective was to test it in biological screenings, for which we had sufficient material.

4.2.4.1. Screening results and discussion

As described in the reaction discussion the substitution of the ester group can take place in 3- or 5-position of the pyrazole ring. It was our intention to analyze which isomer exhibit the higher biological activity in the *in vitro* screening. Both isomers of compound **61a** and **61b** were tested and the results are listed in Table 8 and Table 9 (entries 1 and 2).

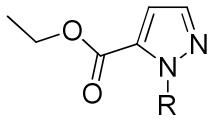
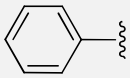
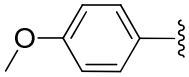


Table 8: IC_{50}-values and *in vitro* inhibition of the enzyme using an inhibitor concentration of 200 µM

Entry	No.	R	IC_{50} [µM]	I_{200} [%]
1	**61a$_1$**		➢ 200	24
2	**61b$_1$**		170	56

In both cases the pyrazole with the ethylester functionality oriented in 3-position of the pyrazole ring showed higher biological activity than the pyrazole with the ester in 5-position, which is also depicted in Fig. 54.

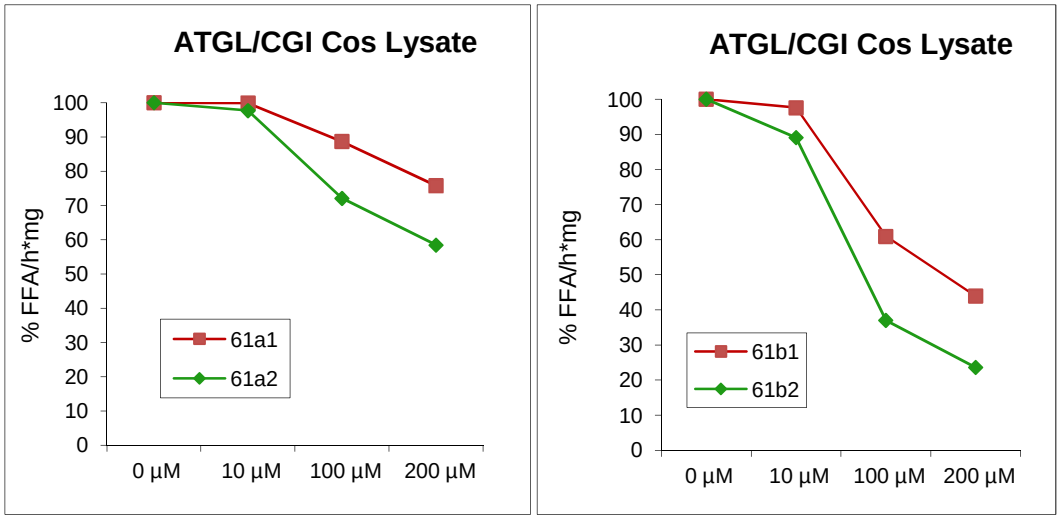


Fig. 54: Dose-dependent inhibition of ATGL activity *in vitro*.

As a consequence of these results only the 3-substituted isomers of the newly synthesized pyrazoles were screened *in vitro* and the results are listed in Table 9.

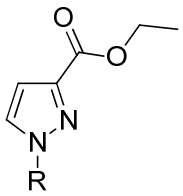
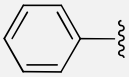
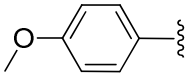
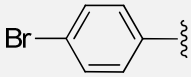
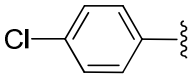
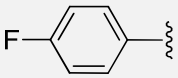
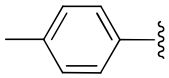
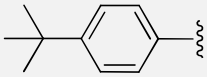
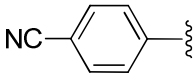
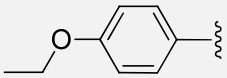


Table 9: IC_{50}-values and *in vitro* inhibition of the enzyme using an inhibitor concentration of 200 µM

Entry	No.	R	IC_{50} [µM]	I_{200} [%]
1	**61a$_2$**		➢ 200	42
2	**61b$_2$**		**80**	**76**
3	**61c$_2$**		120	65
4	**61d$_2$**		100	66
5	**61e$_2$**		200	48
6	**61f$_2$**		**80**	**72**
7	**61g$_2$**		100	64
8	**61h$_2$**		➢ 200	31
9	**61i$_2$**		**40**	**89**

The so far best compounds were **52a** (IC_{50} = 120 µM, 67 % inhibition) and **55a** (IC_{50} = 90 µM, 63 % inhibition) (Fig. 55). By removing the hydroxy group from the pyrazole ring (entry 9) the IC_{50}-value could be improved to 40 µM with 89 % inhibition of the enzyme. Also the methoxy- (entry 2) and methyl- (entry 6) substituents exhibit enhanced biological activity.

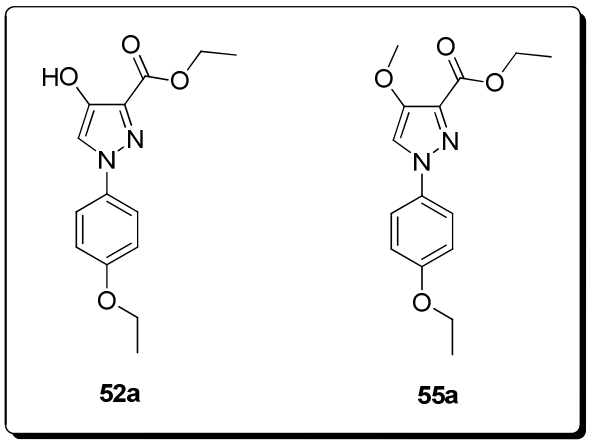


Fig. 55: Structures of **52a** and **55a**

The dose-dependent curves of the *in vitro* screenings of lead structure 2 and the optimized compounds are depicted graphically in Fig. 56.

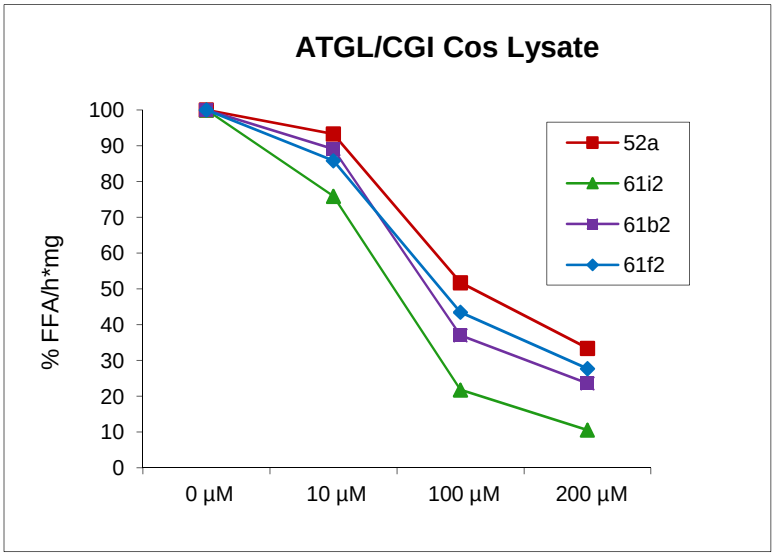


Fig. 56: Dose-dependent inhibition of ATGL activity *in vitro*.

Unfortunately, compound **61i$_2$** is not ATGL selective as demonstrated in Fig. 57. It shows also high MGL activity.

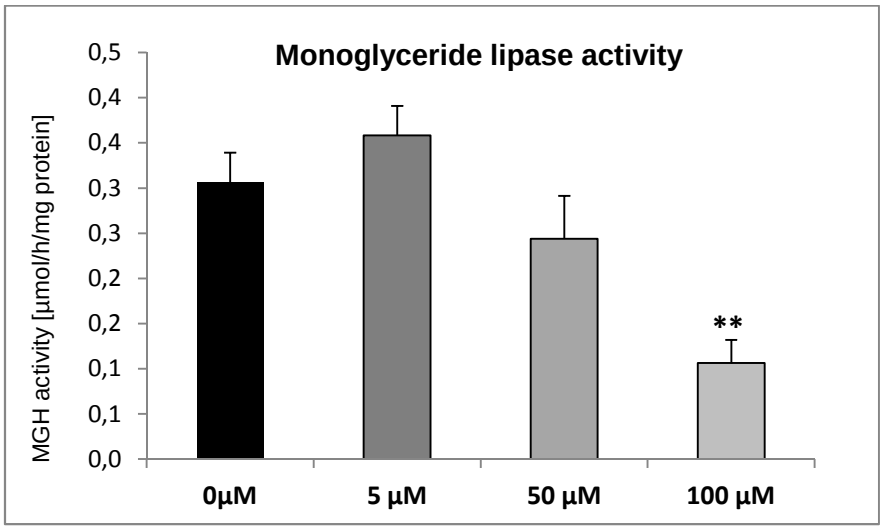


Fig. 57: MGL activity test of compound **61i$_2$**.

To summarize the results of the last four chapters we can say that the methylation of the 4-hydroxypyrazoles **52a** and **52c** increased the biological activity slightly but fortunately, the elimination of the hydroxy substituent improved the IC_{50}- value and inhibition effect towards ATGL even more.

4.2.5. Replacement of the pyrazole ring keeping the ethylester functionality

As it was discussed in the chapters before the biological activity could be improved impressively but the optimized compound showed not the desired specificity towards ATGL. Additionally, we were aiming for an enzyme affinity in a nanomolar range. Therefore, we wanted to replace the pyrazole fragment by other cyclic structures. The Pd-catalyzed Suzuki crosscoupling reaction pointed out to be an attractive type of reaction, which connects two aromatic systems by reacting organoboron compounds with arylhalides using palladium catalysts. These reactions can be described by a catalytic cycle shown in Fig. 58.[113]

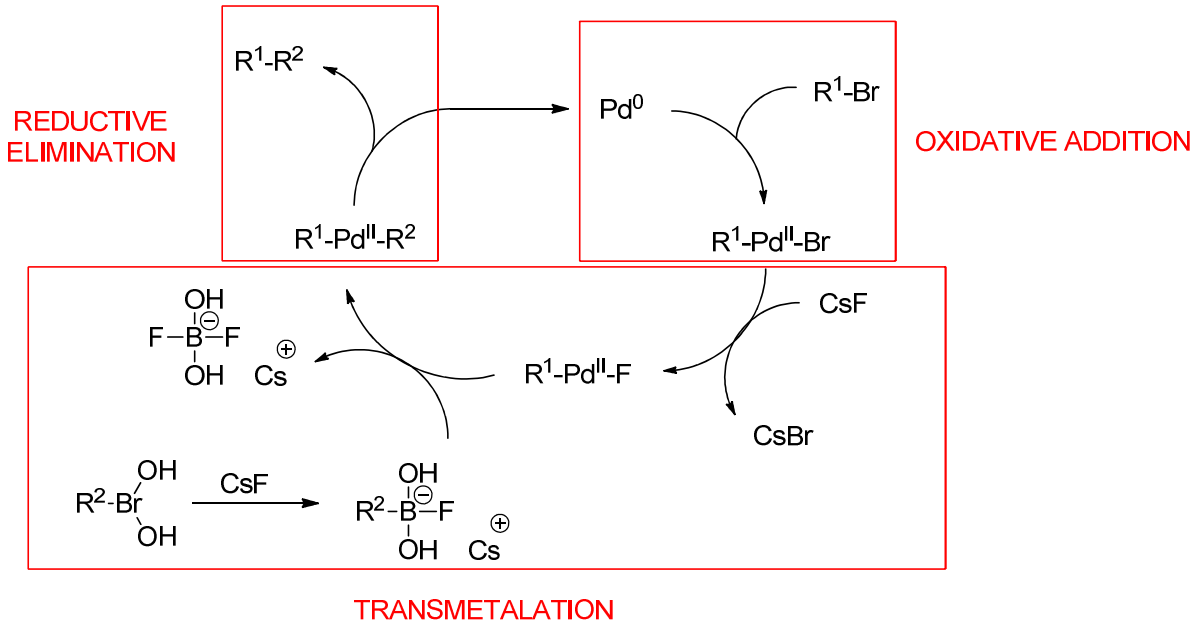
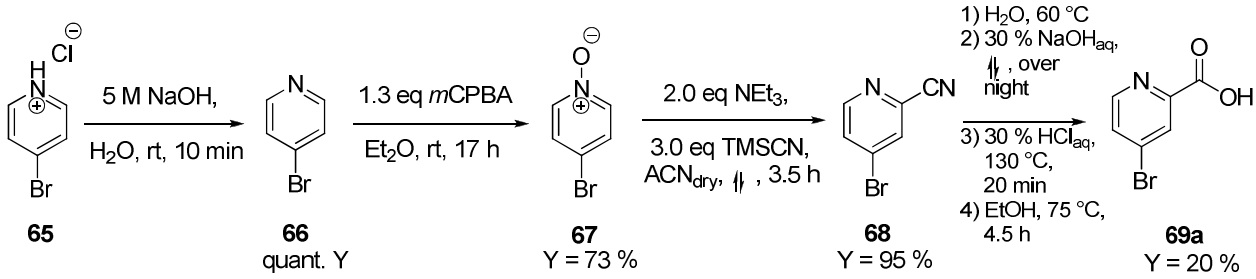


Fig. 58: Catalytic cycle of the Suzuki coupling reaction.

In our case we used arylboronic acids and arylbromides which add to the Pd(0)-complex by an oxidative addition resulting in an organo-Pd-halogenide. The next step is the transmetalation for which a base is essential especially in the Suzuki coupling. As depicted one equivalent is needed for activating the boronate where boron acts as a Lewis acid and a tetravalent boron is generated. The second equivalent base is used to facilitate the transmetalation because of improving the electrophilicity of the Pd-complex. By a reductive elimination of the diorgano-Pd-complex the biarylic product is released and the Pd(0)-complex is recycled.[114]

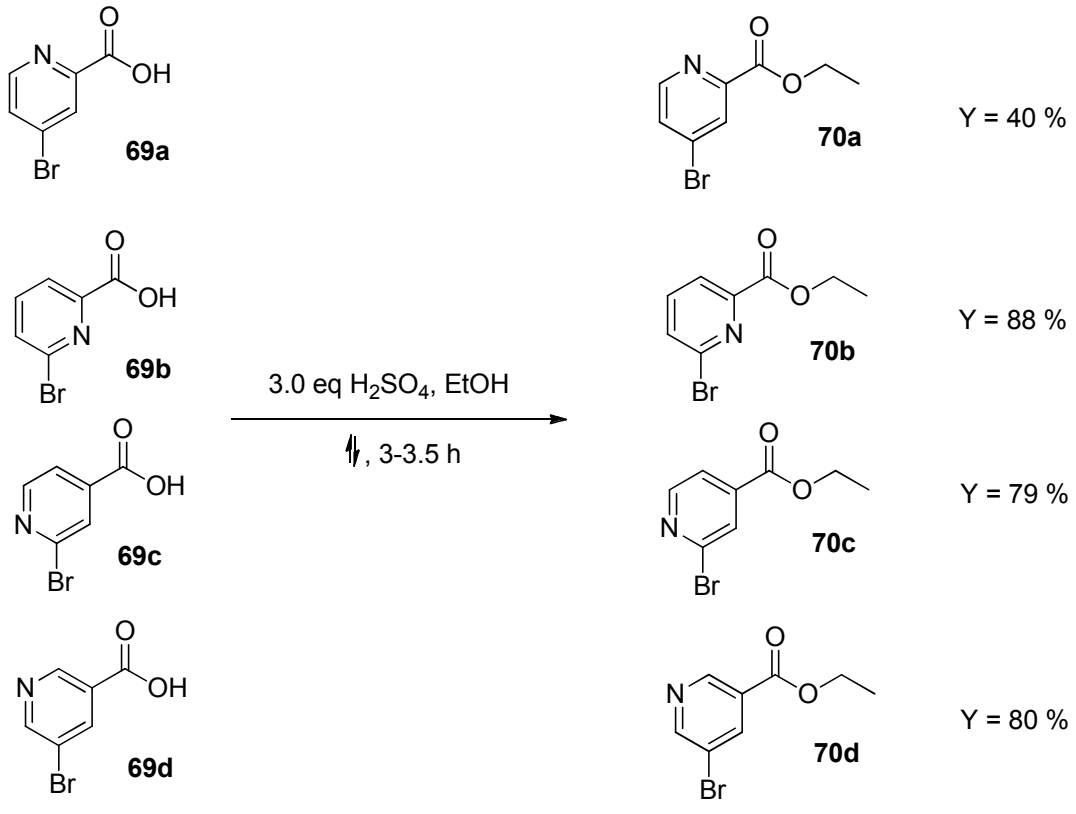
A few arylbromides **70e-g** were commercially available. In case of the pyridine derivatives **70a-d** the pyridine acids **69a-d** first had to be esterified by the acid-catalyzed reaction in

EtOH according to BÜNZLI *et al.* (Scheme 22).[109] The bromopicolinic acid **(69a)** even had to be synthesized by the reaction sequence shown in Scheme 21.



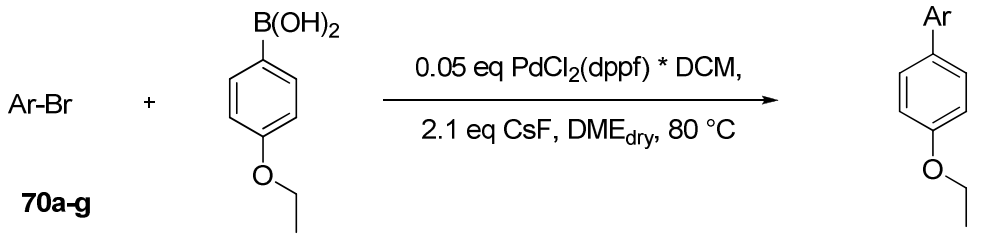
Scheme 21: Four-step synthesis of bromopicolinic acid (X).

The first four steps were done according to a patent by CLEMENTS *et al.*[115] The 4-bromopyridine hydrochloride **(65)** was stirred in aqueous NaOH solution to obtain the free pyridine **66** which was then oxidized by *m*-chloroperbenzoic acid in Et_2O from which the *N*-oxide **67** precipitates. The carbonitrile **68** was generated by adding trimethylsilyl cyanide to the solution of the *N*-oxide **67** in acetonitrile. The basic work up has to be done with caution because HCN can be generated. In the last step the carbonitrile **68** underwent hydrolysis in aqueous NaOH solution to obtain the free acid **69a** which could be esterified similar to the other pyridine acids **69a-d** (Scheme 22).

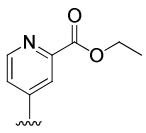
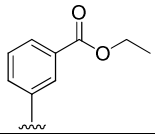
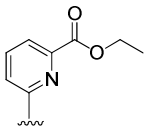
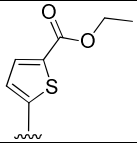
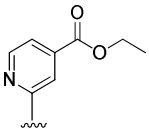
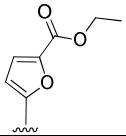
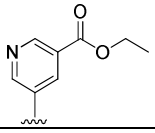


Scheme 22: Esterification of four pyridine acids **69a-d** to the ethylesters **70a-d**.

These synthesized arylbromides X-Y and the commercially available ones (listed in the table of Scheme 23) were then coupled with 4-ethoxyphenylboronic acid (X) in a Suzuki coupling reaction using CsF as base, $PdCl_2$(dppf)*DCM as catalyst and DME as solvent applying a procedure which is based on the first experiments and publications from HAO *et al.* and which was improved in our laboratories.[116]



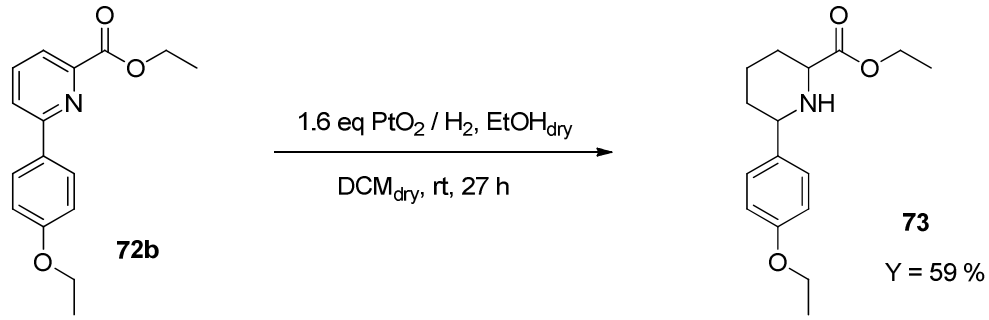
70a-g **71** **72a-g**

No.	Ar	t [h]	Y [%]	No.	Ar	t [h]	Y [%]
a		24	47	**e**		7	93
b		4.5	81	**f**		14	40
c		4.5	91	**g**		24	18
d		4.5	92				

Scheme 23: Suzuki coupling of different arylbromides **70a-g** and the reaction times and yields.

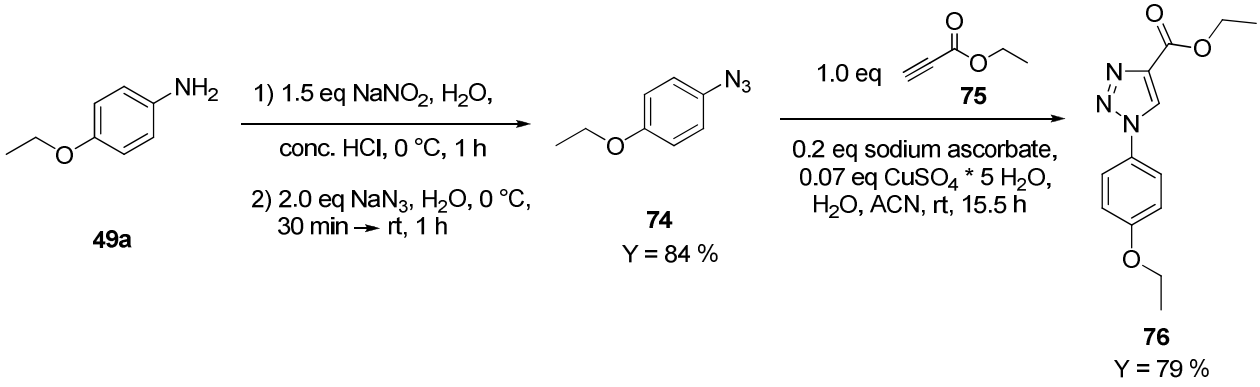
The low yields for compounds **72f** and **72g** can be explained by the initial unexperience of the student, but they could be improved during the thesis synthesizing other biarylic systems.

Afterwards we destroyed the planarity in the upper ring by hydrogenating the aromatic system of the biphenyl **72b** to a piperidine ring applying PtO_2 and hydrogen according to a procedure by STARK *et al.* (Scheme 24).[117] A mistake was made in the calculation of the amount of catalyst and it is likely that catalytic amounts will be sufficient for this transformation.



Scheme 24: Hydrogenation of the pyridine ring into a piperidine ring.

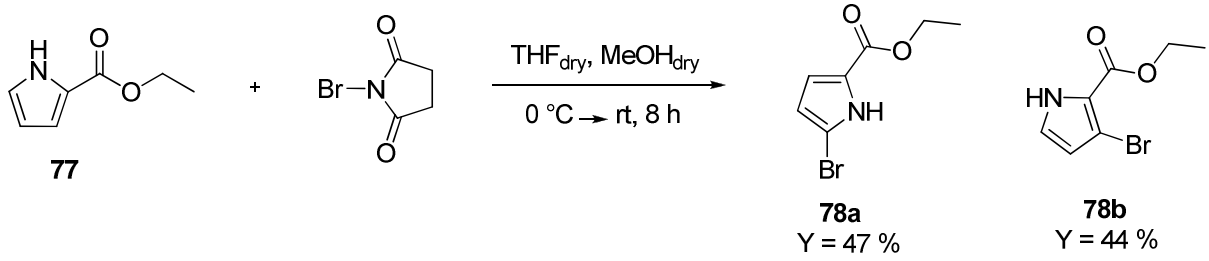
Triazoles are a well known structural element in drug compounds to improve the hydrophilicity of a molecule because biphenyls are characterized by high hydrophobicity, whose hydrophilicity can only be improved by introducing various water-mediating substituents. As depicted in Scheme 25 the azide **74** was obtained by generating the diazonium salt with $NaNO_2$ in conc. HCl and afterwards applying a Sandmeyer-type reaction using NaN_3 according to a procedure by PHILLIPS *et al.*[118] The synthesized azide **74**, which could be obtained in good yield, underwent the well known "Click reaction". For this Cu(I)-catalyzed azide-alkyne 1,3-dipolar cycloaddition the azide **74** was reacted with ethyl propiolate **(75)** in presence of sodium ascorbate and $CuSO_4$ in acetonitrile and water. Stirring at rt and in air resulted in the formation of the desired triazole **76** also in good yield.[119]



Scheme 25: Two-step synthesis of the triazole containing biaryl **76**.

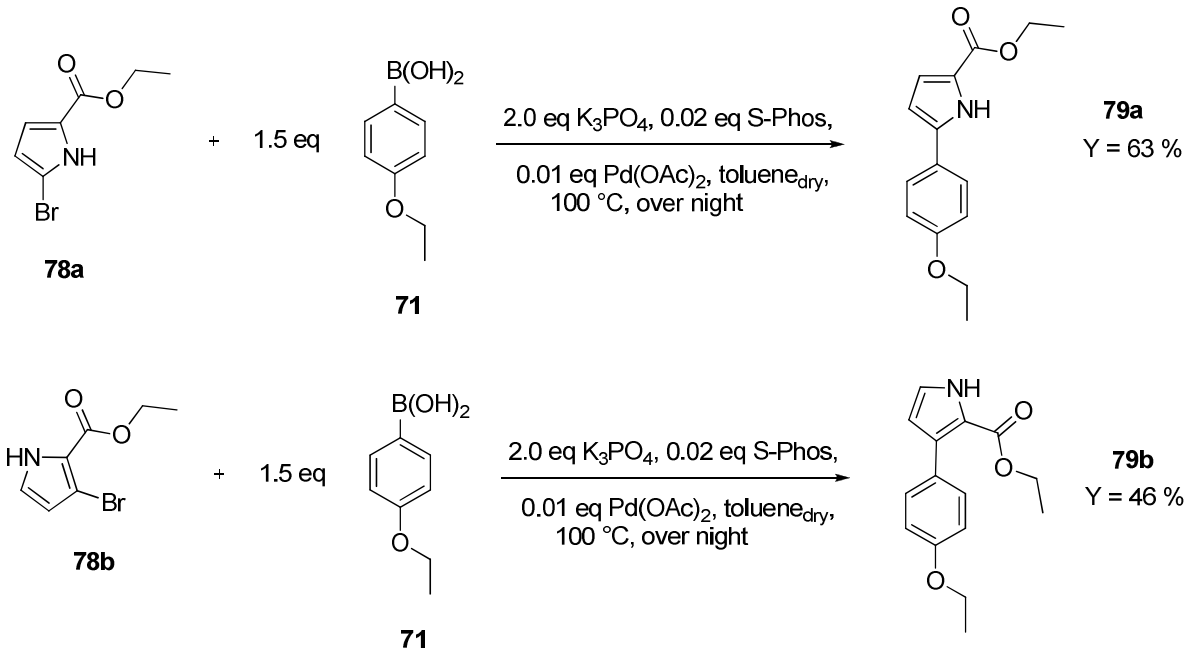
In the last synthesis of this chapter the pyrazole unit should be replaced by a pyrrole functionality. The bromopyrrole **78a** which is necessary to establish the biarylic system by Suzuki-coupling could not be purchased commercially. We brominated ethyl 1*H*-pyrrole-2-carboxylate **(77)** with NBS.[120] Unfortunately, GC-MS analysis indicated the formation of

three products, the two pyrroles **78a** and **78b** shown in Scheme 26 and the dibrominated pyrrole.



Scheme 26: Bromination of 1*H*-pyrrole2-carboxylate **(77)** yielding 3 different products in varying yields.

Pyrroles **78a** and **78b** could be isolated in good yields by column chromatography but it was not possible to assign their structure at this stage by COSY, NOESY, HSQC and HMBC. We decided to run two Suzuki reactions in parallel, one with the pyrrole **78a** and one with pyrrole **78b**, and attempted the assignment at the biaryl stage. For this Suzuki reaction the previous conditions were not suited because nitrogen heterocycles represent a challenge for Pd-coupling reactions as they can coordinate competitively to palladium and pyrroles are electron-rich substrates. BUCHWALD *et al.*[121-123] published highly active catalytic systems which allow a smooth reaction of heteroaryl compounds, with the S-Phos/Pd(OAc)$_2$-system as one of the best. In our case, potassium phosphate was used instead of CsF, S-Phos as ligand and Pd(OAc)$_2$ as Pd-source. The catalyst was formed *in situ* while the reaction was running in toluene and at 100 °C (Scheme 27). These conditions were already used and improved successfully in our laboratory for the Suzuki-coupling with electron-rich indole compounds.[124]



Scheme 27: Suzuki coupling of the two monobrominated substrates **78a** and **78b** using the S-Phos/$Pd(OAc)_2$-catalyst system.

In the two reactions depicted in Scheme 27 the biaryls **79a** and **79b** are formed over night and could be isolated by simple filtration through a silica pad and purification by column chromatography starting from the two electron rich pyrroles. Thankfully, at this time an assignment of the two isomers was possible applying NOE-spectroscopy (Fig. 59). For both compounds there are the same NOE effects for the arylic protons visible as expected but only in the spectra for compound **79a** a NOE effect between the protons from the lower ring and the NH from the pyrrazole ring was detectable.

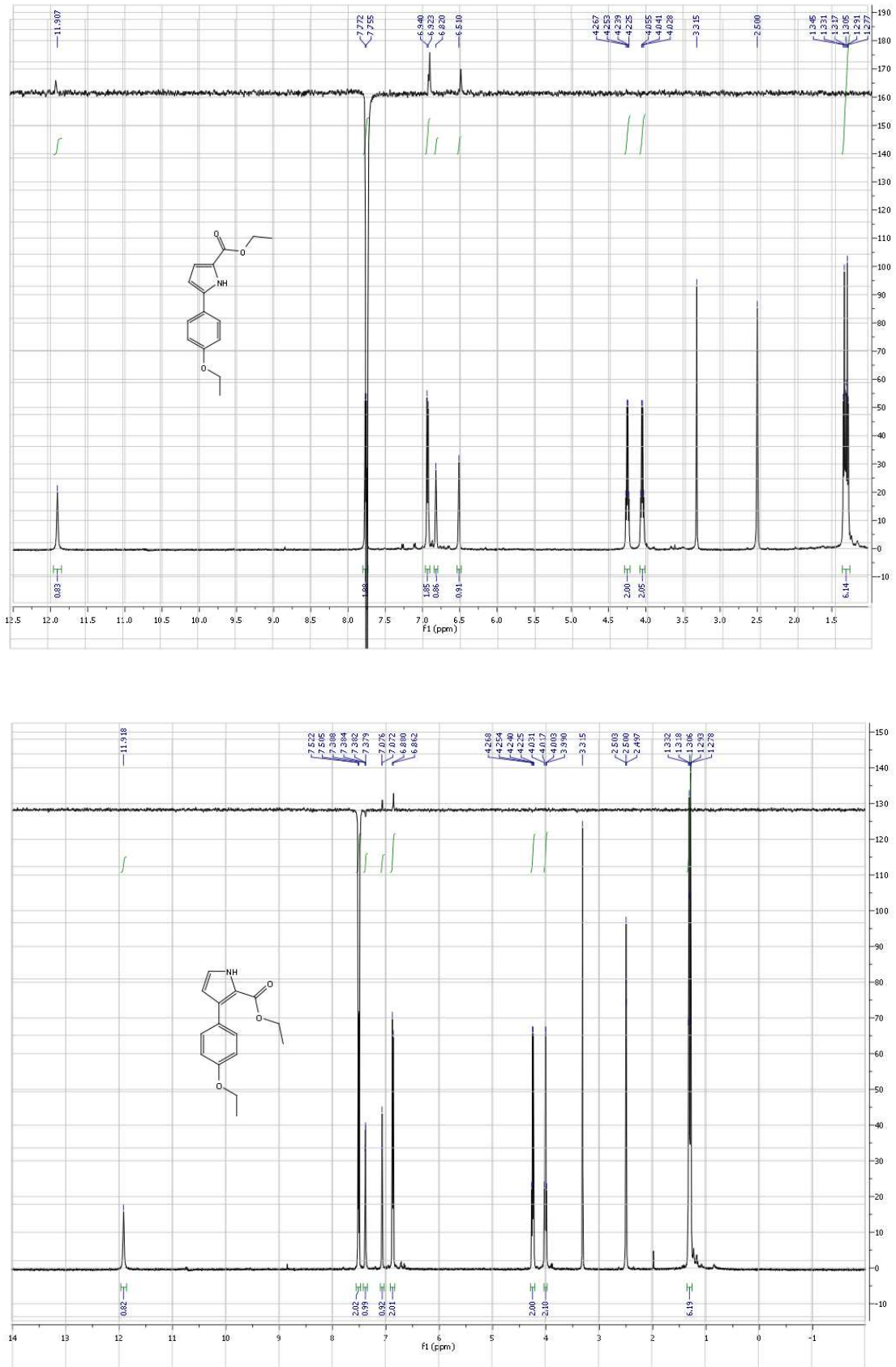


Fig. 59: NOE-spectra of both products **79a** and **79b** leading to assignment of the structures.

4.2.5.1. Screening results and discussion

The pyrazole ring was replaced by several different ring systems in an attempt to improve the selectivity. The biological data of the *in vitro* screening is mentioned in Table 10.

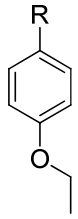
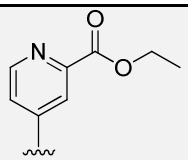
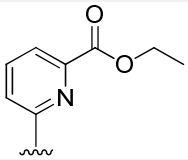
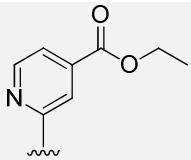
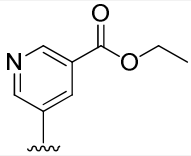
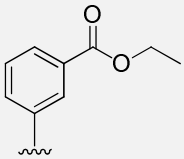
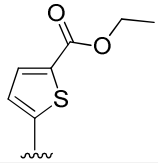
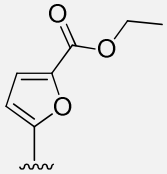
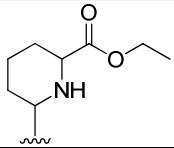
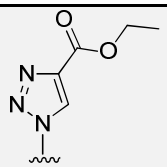
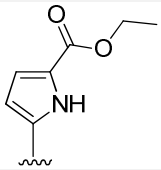
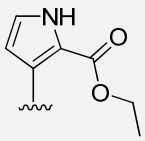


Table 10: IC_{50}-values and *in vitro* inhibition of the enzyme using an inhibitor concentration of 200 µM

Entry	No.	R	IC_{50} [µM]	I_{200} [%]
1	**72a**		105	72
2	**72b**		**60**	**79**
3	**72c**		**80**	**87**
4	**72d**		130	70
5	**72e**		**50**	**87**
6	**72f**		**70**	**81**
7	**72g**		**50**	**93**
8	**73**		➢ 200	48

9	**76**		➢ 200	43
10	**79a**		➢ 200	44
11	**79b**		➢ 200	30

The results were remarkable. Replacing the pyrazole ring with a phenyl ring (entry 5) resulted in a similar IC_{50}-value (50 µM) and inhibition effect (87 %). Also the pyridine ring with the nitrogen in 2-position (entry 2) and the furan ring (entry 7) showed comparably impressive results, which are also summarized in Fig. 60.

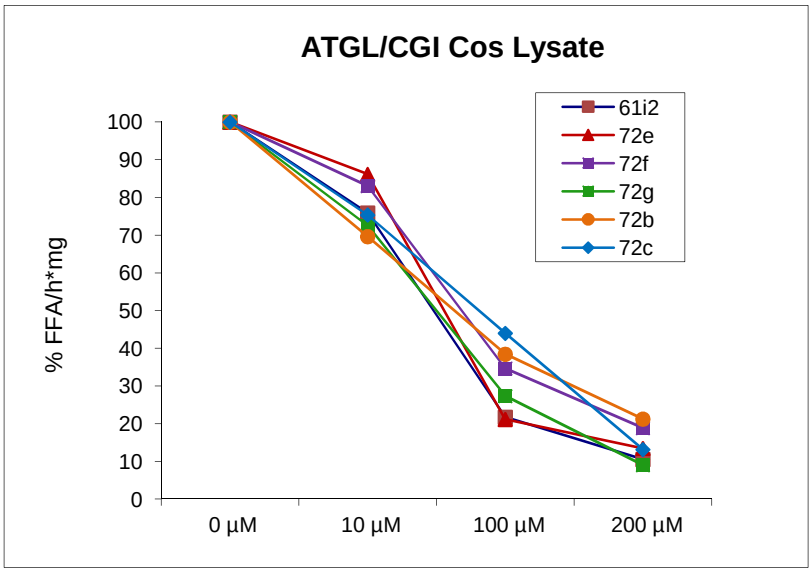


Fig. 60: Dose-dependent inhibition of ATGL activity *in vitro*.

As we assumed before inhibitor compound **72e** exhibited no cell toxicity compared to the hydrazone compounds because in the Tox 4-toxicity assay the optic density increased with increasing inhibitor concentration. (Fig. 61)

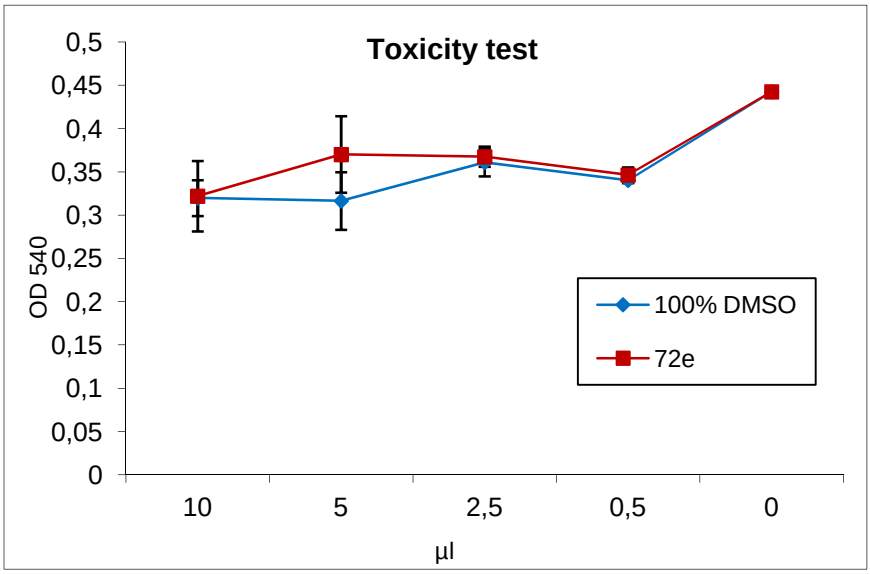


Fig. 61: Toxicity test of compound **72e**

A selectivity test for compound **72e** and **72f** was performed in an *ex vivo* assay by taking tissue pieces of gonatal fat and incubate them with the inhibitor compounds. As depicted in Fig. 62 both compounds show no decrease in FFA release in the ATGL-ko mice compared to the basal conditions which indicates good cell permeability and 100 % selectivity towards ATGL.

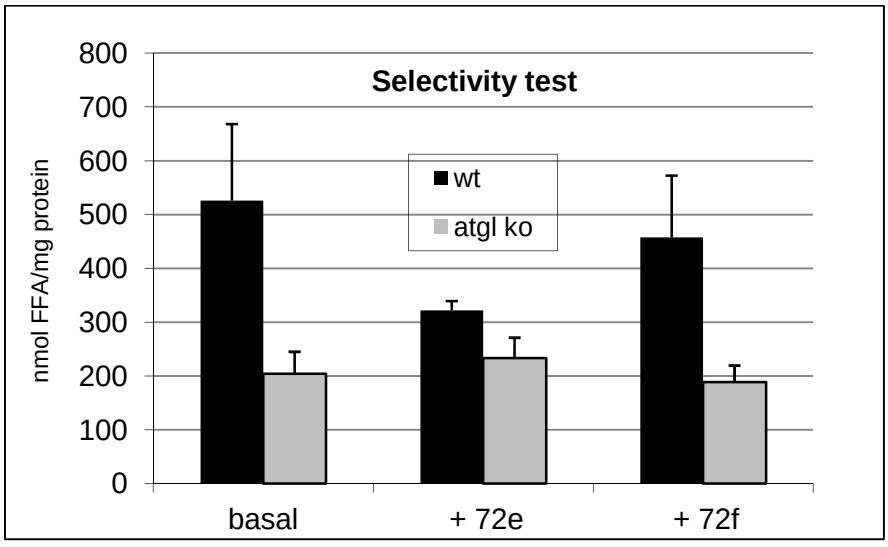


Fig. 62: Selectivity test of **72e** and **72f**.

These promising results of non–toxicity and ATGL selectivity of inhibitor compound **72e** led to the first experiments in mice. Therefore, inhibitor **72e** was injected in different concentrations in mice and 24 h after injection a blood sample was taken and fat was isolated to measure lipolysis in the fat pads of the mice.

As pictured in Fig. 63 the mice with inhibitor showed a decreased release of FFA in blood compared to the mice without inhibitor, which suggested reduced lipolysis in fat tissue.

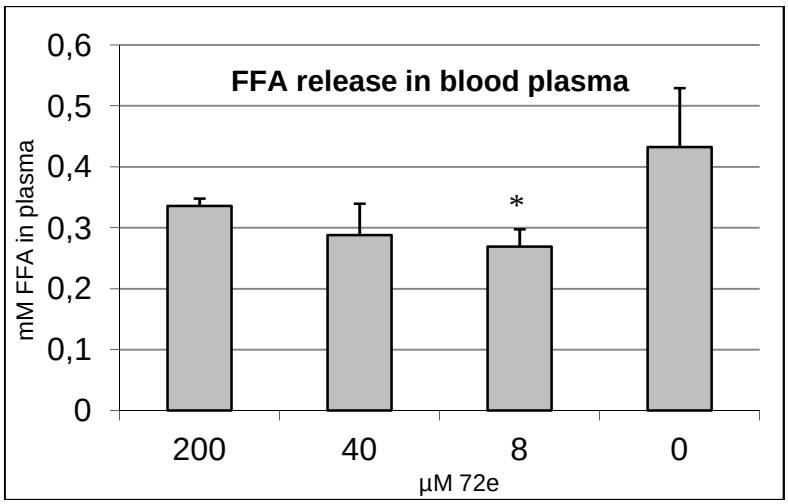


Fig. 63: FA release in blood plasma after injection of **72e** in mice.

After taking blood samples from the mice fat was isolated to determine the FA release, which was decreased by 27 % with the injection of the inhibitor **72e**. (Fig. 64)

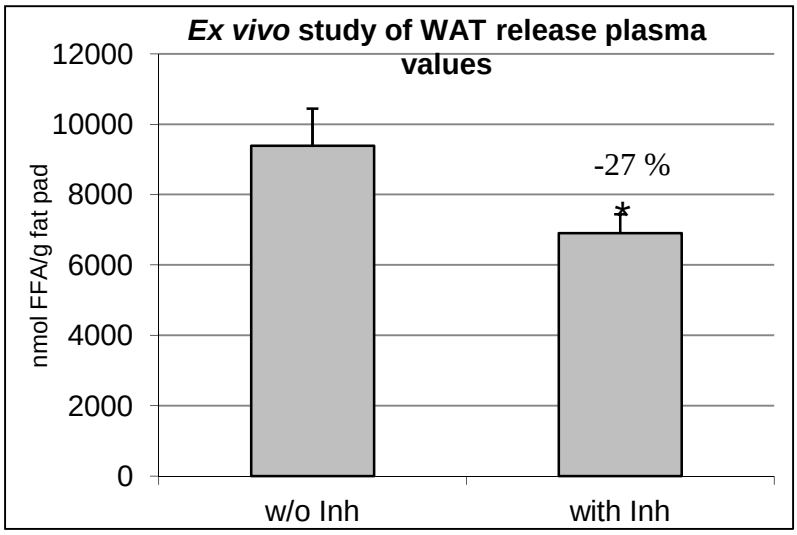
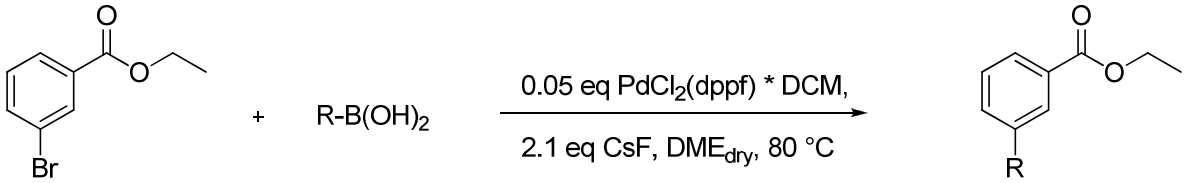


Fig. 64: FA release in isolated fat pads after injection of **72e** in mice.

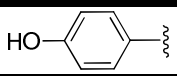
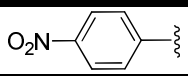
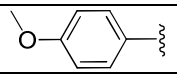
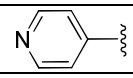
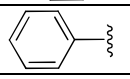
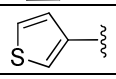
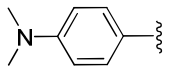
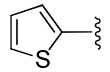
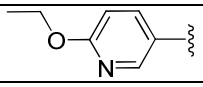
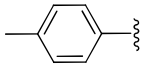
This were excellent results for the first *in vivo* studies. But the reduction of the FA release was not in the range we expected after the *in vitro* screening related to the presumably decreased bioavailability of the biphenylic system compared to the pyrazole.

4.2.6. Synthesis of several biarylic systems with different electronic effects

These successful and surprising results with the biarylic systems showed almost similar biological activity as pyrazole **61i$_2$** but increased the selectivity towards ATGL. Unfortunately, the hydrophilicity was reduced considerably, which might result in a poor bioavailability. We decided to synthesize different biarylic systems by employing once more the Suzuki cross coupling reaction and vary the lower ring by keeping the ethylester functionality constant. As reported above for different Suzuki reactions CsF was used as base, $PdCl_2$(dppf)*DCM as catalyst and DME as solvent at 80 °C (Scheme 28).



80 **81a-j** **82a-j**

No.	Ar	t [h]	Y [%]	No.	Ar	t [h]	Y [%]
a		5	22	**f**		4	73
b		5.5	66	**g**		24	87
c		4.5	50	**h**		5	90
d		26	77	**i**		8.5	85
e		5	51	**j**		4	84

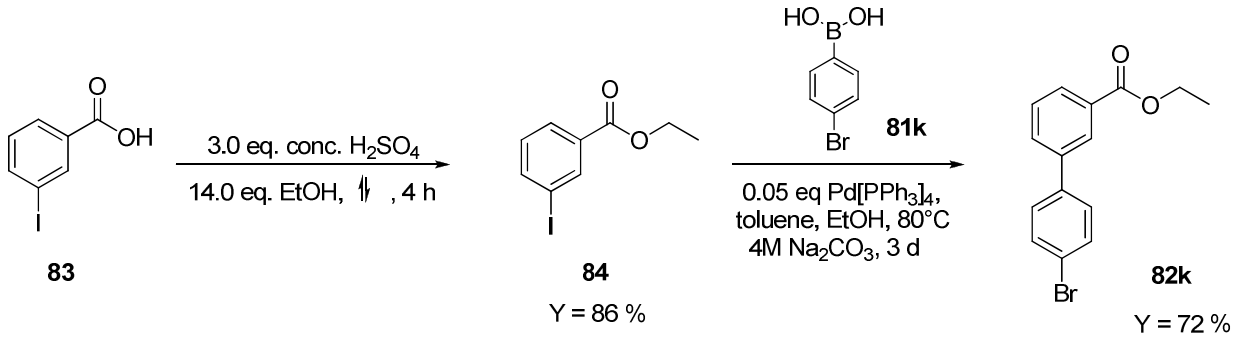
Scheme 28: Suzuki coupling and yields for different arylboronic acids **81a-j**.

In dependence of the different electronic effects imposed by the ring substituents the reactions worked in acceptable time ranges and with full conversions. The biaryls **82a-j** could be isolated in good yields and high purity after filtration through a silica pad and column chromatography.

In Medicinal Chemistry several groups are known which improve the water-solubility of compounds. One representative group are amines which often increase the polarity to a great extent. In the next reactions the water-solubility of the biphenylic system should be improved by attaching different cyclic or aliphatic amines.

At the beginning biphenyls, which are directly linked to the amine functionality should be synthesized using the Buchwald-Hartwig amination. It was necessary to synthesize a

sufficient amount of ethyl 4`-bromophenyl-3-carboxylate **(82k)** which could be realized by an acid-catalyzed esterification of 3-iodobenzoic acid **(83)**[109] generating ethyl 3-iodobenzoate **(84)** in good yield followed by Suzuki reaction using 4-bromophenylboronic acid **(81k)**, $Pd[PPh_3]_4$ as catalyst and 4 M aqueous Na_2CO_3 solution in toluene and EtOH according to WHITEHOUSE *et al.*[125] yielding the pure brominated biphenyl **82k** in good yield (Scheme 29).



Scheme 29: Synthesis of biphenyl **82k** using $Pd[PPh_3]$ as catalyst.

This successfully synthesized 4`-bromophenyl-3-carboxylate **(82k)** underwent Buchwald-Hartwig amination using pyrrolidine and piperidine as amine species. The Buchwald-Hartwig amination describes the coupling of arylbromides with amines in a catalytic cycle (Fig. 65).[126]

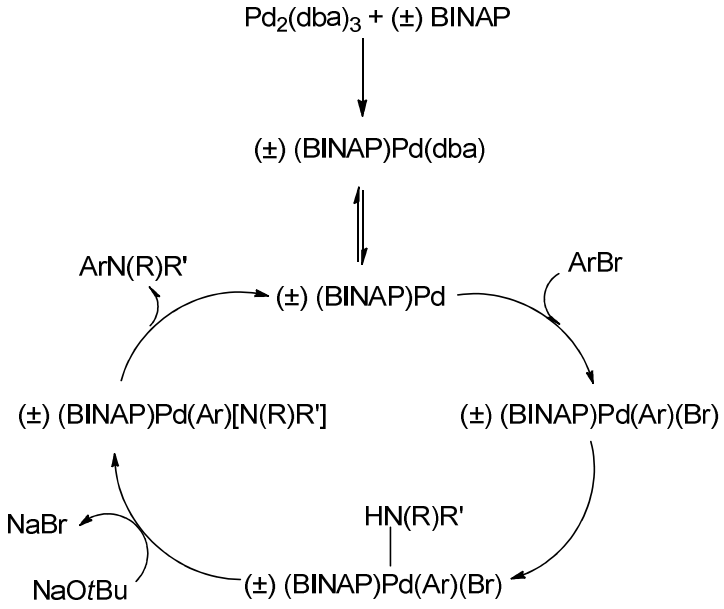
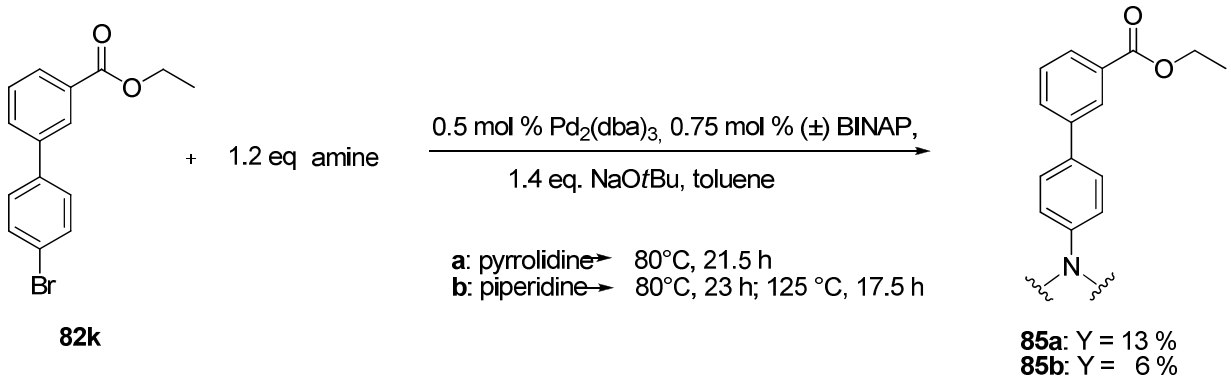


Fig. 65: Catalytic cycle of the Buchwald-Hartwig amination.

Eveline Brodl (Bachelor student, February 2011) did a lot of optimization work. She tested $Pd_2(dba)_3$ and $Pd(OAc)_2$ as Pd-species and (±)-BINAP, S-Phos and XantPhos as ligands in different combinations. Additionally, the solvent was varied (toluene, DME, 1,4-dioxane) and different bases were applied (NaO*t*Bu, Cs_2CO_3, CsF) because the strong base NaO*t*Bu is known to be problematic in reactions with compounds carrying sensitive groups like ethyl ester functionality. Cesium carbonate is a weaker base which should be compatible with the ester.[127] However, the best results and successful isolations of the products were achieved according to BUCHWALD *et al.*[128] using 1.2 eq of the amine, 0.5 mol % of $Pd_2(dba)_3$, 0.75 mol % (±)-BINAP as ligand and 1.4 eq NaO*t*Bu in toluene (Scheme 30).

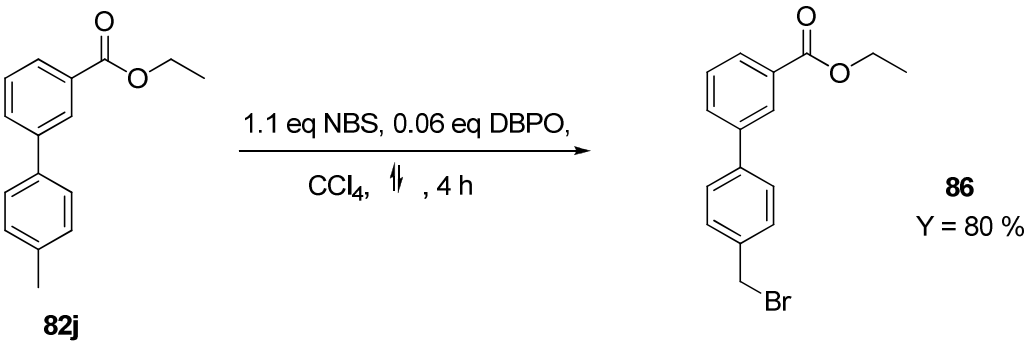


Scheme 30: Optimized Buchwald-Hartwig amination using the $Pd_2(dba)_3$/(±) BINAP catalyst system.

The reactions proceeded very slowly and after full conversion of the starting material, work-up and purification both biphenyls **85a** and **85b** were obtained only in low yields. Because there are so much possibilities to influence this type of reaction a lot of more optimization work is necessary to get this reaction running satisfyingly.

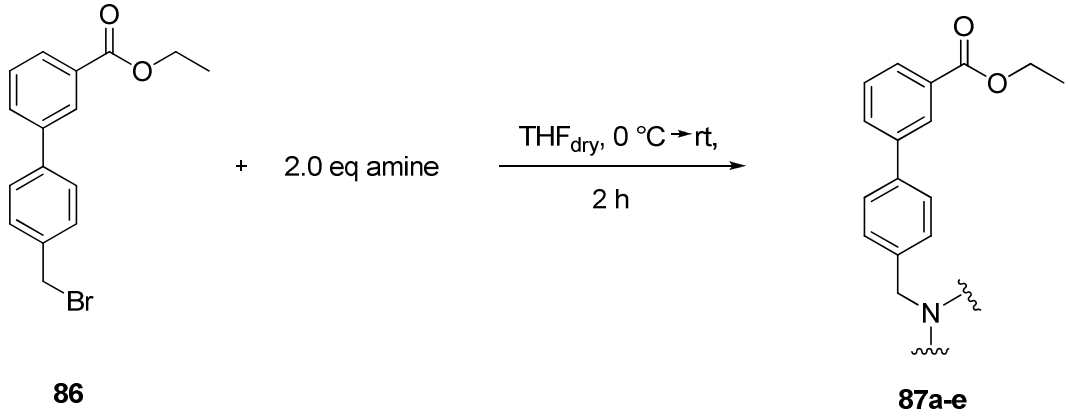
As the direct coupling of the biphenyl and amine was so problematic, a linkage between the biaryl and the amine seemed to be an alternative way although we were fully aware that this change might lead to different screening data. In comparison to the fixed amine-coupled biphenyl the new compounds are more flexible because of the rotation around the CH_2 group. Nevertheless the strategy sounded very promising and hopefully the compounds should give us more information about the binding effects to the enzyme.

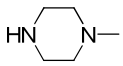
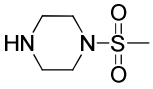
In the first step the previously synthesized ethyl 4`-methylbiphenyl-3-carboxylate **(82j)** was brominated using NBS in $CCl_4$ and DBPO as activator according to CUSHMAN *et al.*[129] After 4 h at reflux ethyl 4`-(bromomethyl)biphenyl-3-carboxylate **(86)** could be obtained by simple filtration and purification by column chromatography (Scheme 31).



Scheme 31: Bromination of 4`-methylbiphenyl-3-carboxylate **(82j)** using NBS and DBPO.

Afterwards, the biphenyl **86** could be converted according to HORIUCHI *et al.*[130] obtaining the desired products **87a-e** using 2 eq of the amine species, 1 eq for catching the generated HBr (Scheme 32).



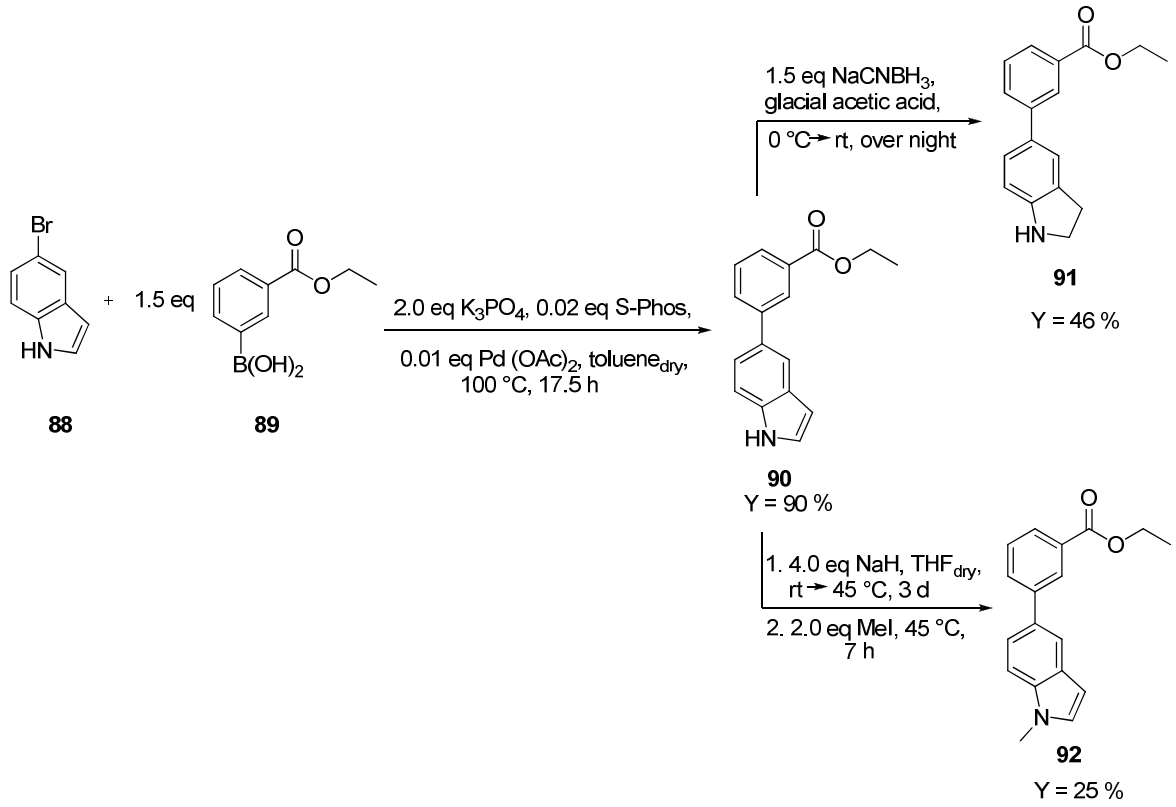
No.	amine	Y [%]
87a		28
87b		53
87c		26
87d		61
87e		48

Scheme 32: Substitution reaction and yields using different amines.

Column chromatography should be done using EtOH instead of MeOH because a transesterification can occur due to the acidic properties of the silica gel.

We were also interested to introduce an indole functionality into the compound to create more electron rich aryl systems. As already explained before indoles are electron-rich *N*-heterocycles which can be converted in a Suzuki coupling using the S-Phos/$Pd(OAc)_2$-catalyst system. The reaction of 5-bromoindole **(88)** and 3-ethoxycarbonylphenylboronic acid **(89)** yielded after 17.5 h stirring at 100 °C the coupled indole **90** in 90 % isolated yield (Scheme 33).

In literature it has been reported that small variations in the structure quite often can lead to an extreme improvement in the biological properties. Following this rationale, we planned to reduce the douple bond of the indole and methylate the free amine. According to GRIBBLE *et al.*[131] the reduction of the indole **90** to indoline **91** occurs by using sodium cyanoborohydride in glacial acetic acid over night and 46 % indoline **91** could be isolated after column chromatography. As discussed in literature, typically the reduction is complete in less than five minutes but the reaction time increases with decreased basicity. GRIBBLE *et al.* also observed air-sensitivity of some indoles, reverting part of the product to the starting material which also happened in our case.

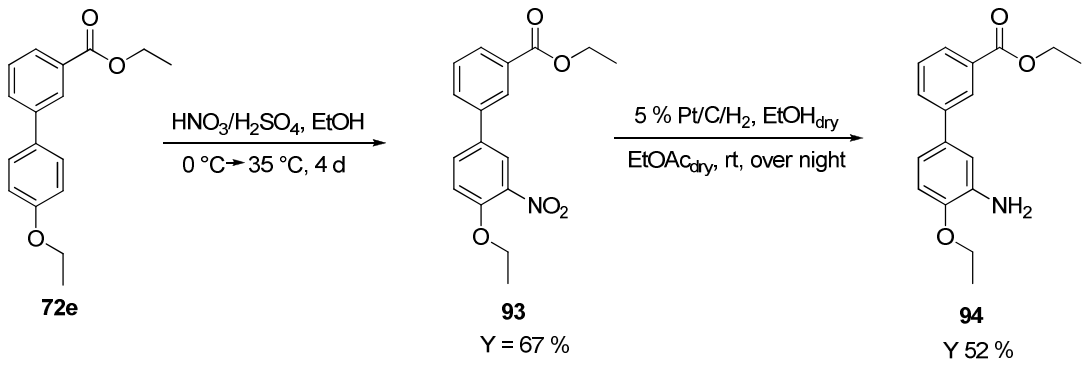


Scheme 33: Synthesis of indol containing biphenyl **90** with subsequent reduction to **91** and methylation to **92**.

The *N*-methylation was considerably more complicated than expected and a lot of optimization was done by Michael Tuechler (bachelor student, February 2011). According to

ZHENG *et al.*[132] the deprotonation was first carried out in DMF using 1.5 eq sodium hydride and stirring at rt for 1 h. This was done two times. The first time with a 60 % dispersion in mineral oil and the second time with hexane-washed sodium hydride. Afterwards, 2.0 eq iodomethane were added and the mixture was stirred over night at rt. But on the next day GC-MS analysis showed only the indole **90** in both cases. That means the deprotonation did not take place. In further approaches DMF was replaced by THF according to LISKAMP *et al.*[133] because DMF sometimes can be problematic when using it together with amines. The reaction temperature was also increased to 45 °C. Another problem is the deprotonation with sodium hydride. Normally it is sufficiently reactive using it as a dispersion in mineral oil but because of the failed deprotonation it was also washed in hexane to increase the reactivity. But the bigger problem is thought to be the complicated reaction control. There is no possibility to monitor the deprotonation by TLC or GC-MS. We decided one time after 3 d deprotonation with 4.0 eq sodium hydride at 45 °C to divide the reaction mixture and added to one half the calculated amount of iodomethane. After 7 h methylation GC-MS analysis indicated 98 % conversion to the methylindole **92**. Because of this success we added iodomethane to the other half but after 2 h stirring GC-MS analysis indicated no product formation and no starting material. In conclusion we were one time successful in isolating the desired product **92** after purification by column chromatography but the reproducibility is not yet achieved.

To investigate the steric effect of the inhibitor a nitro group should be introduced in the lower ring at the position *ortho* to the ethoxy group. Therefore, it was necessary to nitrate the previously synthesized ethyl 4`-ethoxybiphenyl-3-carboxylate **(72e)** according to TIETZE *et al.* (Scheme 34).[134]



Scheme 34: Nitration of ethyl 4`-ethoxybiphenyl-3-carboxylate **(72e)** and reduction to the amine **94**.

In their procedure they used nitric acid in excess as reagent and solvent at 15 °C. These conditions seemed to be too harsh for our case as the starting material decomposed. Changing the conditions by using EtOH as solvent, nitric acid only as reagent and increasing the temperature to 35 °C resulted in the full conversion of the starting material to the nitrated biphenyl **93** in 67 % yield after purification by column chromatography. The reduction of the nitro group to the amino group using 5 % Pt/C and hydrogen stream at rt over night led to the formation of the amino substituted biphenyl **94** in 52 % yield.

We felt confident that the nitration could only take place at the lower ring because of the deactivation of the upper ring by the ethylester substituent. NOE-spectroscopy of the amino substituted biphenyl **94** confirmed that the amino functionality is placed in *ortho*-position to the ethoxy group because a NOE-effect between the isolated aromatic proton signals of both rings could be detected (Fig. 66).

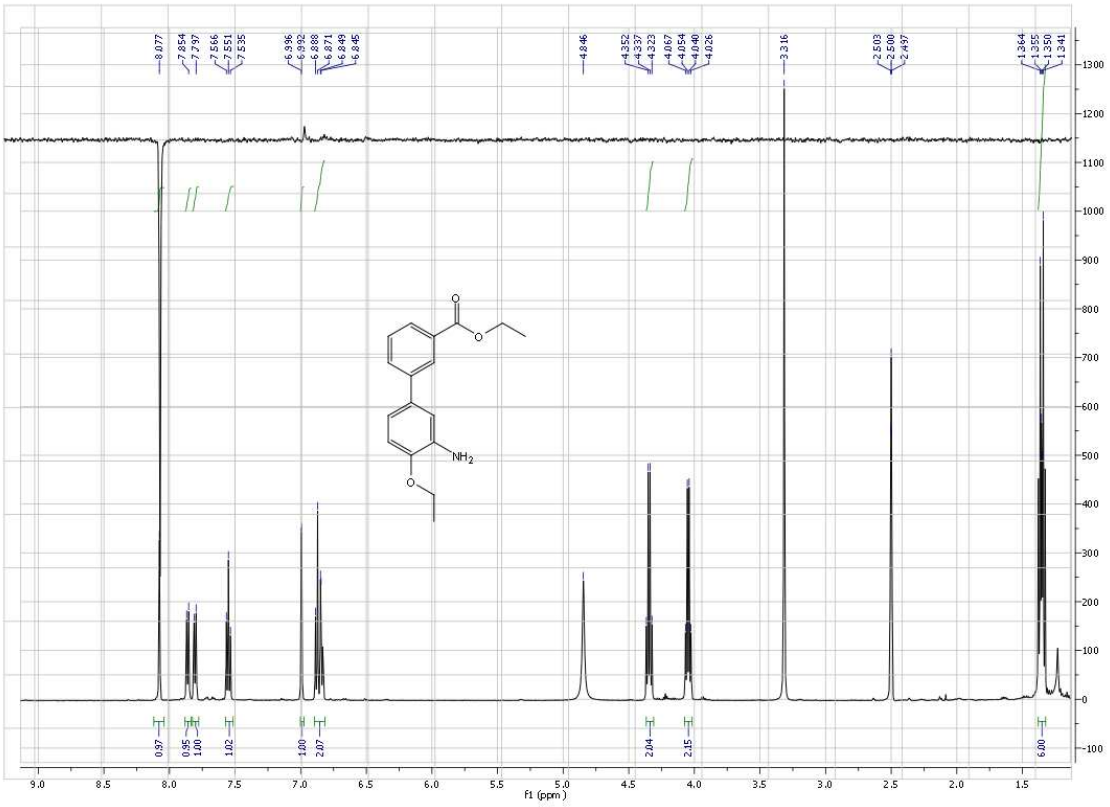
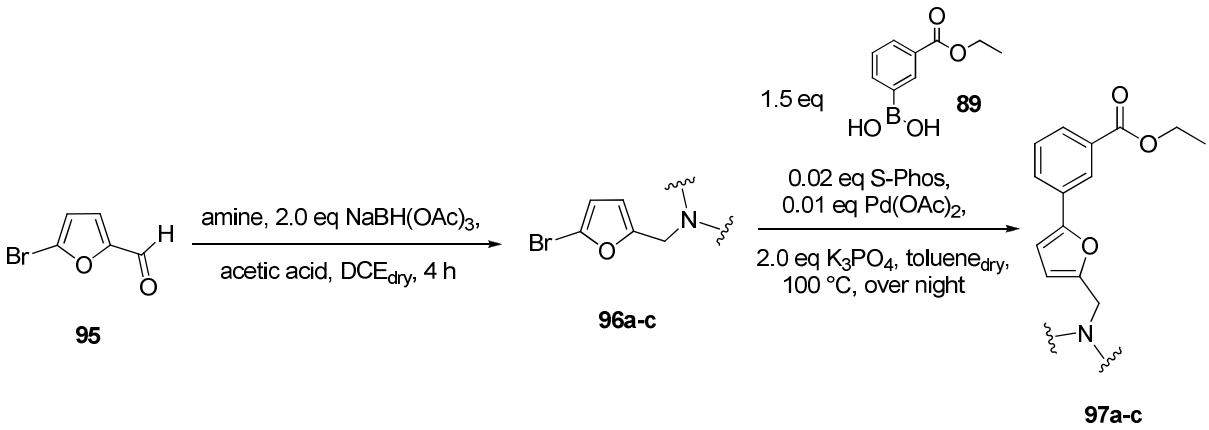
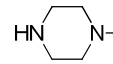
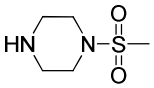


Fig. 66: NOE-spectra of ethyl 3`-amino-4`-ethoxybiphenyl-3-carboxylate **(94)**.

The next syntheses should provide compounds which introduce hydrophilicity in the molecule, on the one side by replacing the lower phenyl ring with a furane and on the other hand by making once more use of the CH_2-bridged amines. According to DEVASAGAYARAJ *et al.*[135] 5-bromofuran-2-carbaldehyde **(95)** had to be converted to the amines **96a-c** by reductive amination. With 2.0 eq amine and 2.0 eq sodium

triacetoxyborohydride in the first approaches we faced the problem to remove the excess amine in the purification. Consequently, the amount of amine was decreased to 1 eq reaching also full conversion of the starting material after 4 h. The three amines **96a-c** were isolated in good to excellent yields and used in the next reaction step without further purification (Scheme 35).

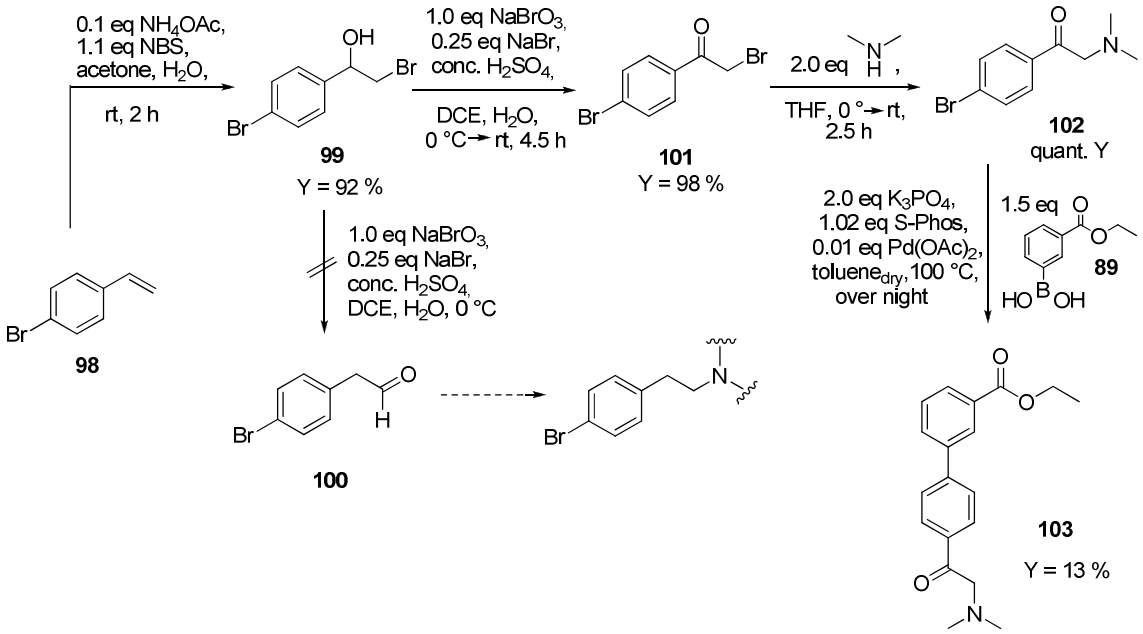


amine	No.	Y [%]	No.	Y [%]
	**96a**	75	**97a**	68
	**96b**	92	**97b**	44
	**96c**	97	**97c**	74

Scheme 35: Suzuki coupling of different furanes X-Y synthesized by reductive amination of 5-bromo-2-carbaldehyde (X) using different amines.

The Suzuki coupling between the arylbromides **96a-c** and 3-ethoxycarbonylphenylboronic acid **(89)** with the already known S-Phos/$Pd(OAc)_2$-catalyst system led to the formation of the desired biarylic compounds **97a-c** in good yields after purification by column chromatography.

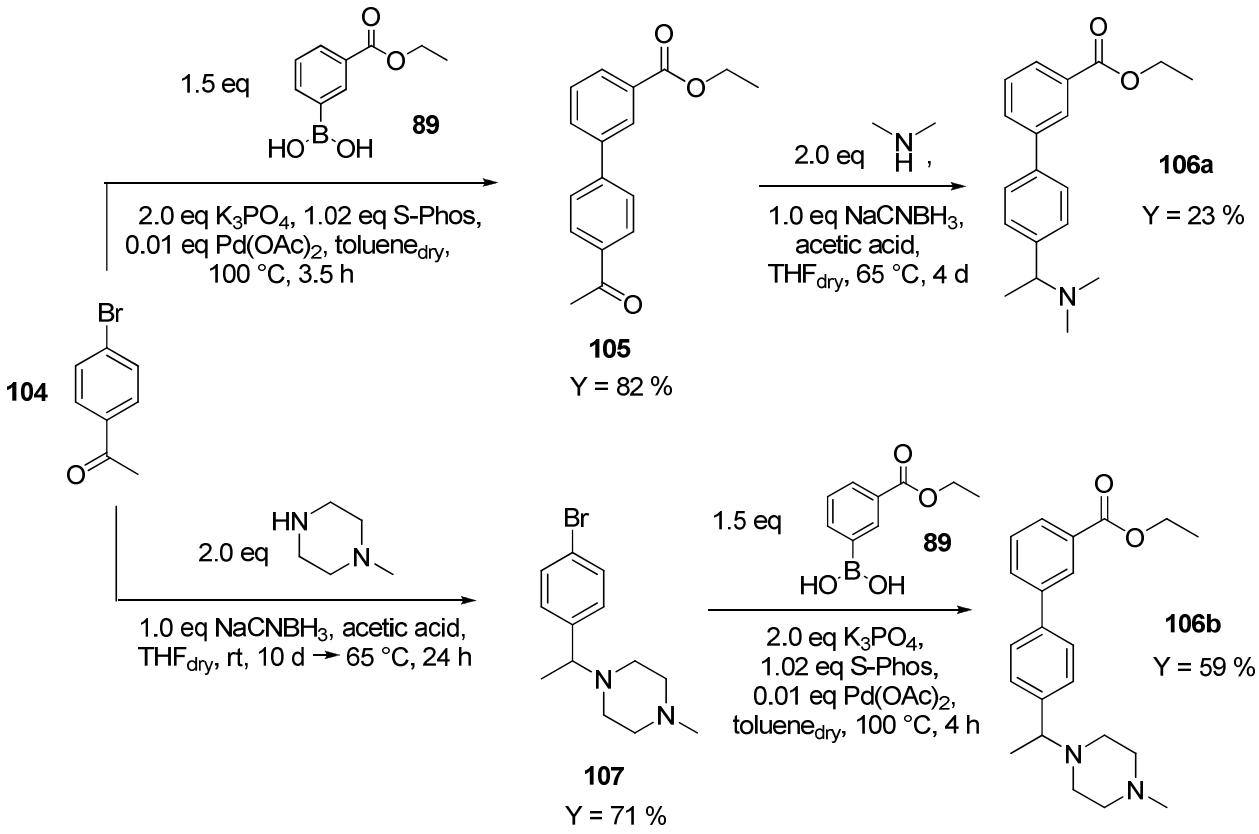
The following product could be formed by a 4-step reaction sequence (Scheme 36). In the first step 4-bromostyrene **(98)** was converted in a hydroxyhalogenation reaction according to DAS *et al.*[136] using NBS as brominating agent and ammonium acetate in catalytic amounts. The reaction works in short times because NBS and ammonium acetate are known to produce AcOH and HBr which can polarize the N-Br bond of NBS and facilitate the bromination reaction of olefins.



Scheme 36: Four-step reaction sequence yielding biphenyl **103**.

The bromohydrine **99** could be obtained in 92 % yield and should be directly converted to 4-bromophenylacetaldehyde **(100)** according to GHOSH *et al.*[137] using $NaBrO_3$, NaBr and conc. H_2SO_4 at 0 °C. The goal was to elongate the chain between the biphenylic system and the water-mediating amine. Unfortunately, the reaction was not performed at 0 °C but at rt and it was not possible to isolate the desired product **100**. Also after repetition of the reaction at 0 °C phenylacetaldehyde formation could not be observed which perhaps can be caused from the instability of the aldehyde. Nevertheless, the reaction performed at rt led to the oxidation of the bromohydrine **99** obtaining 98 % of isolated phenylethanone **101**. As we were substrate interested in different types of functionalities and structures, we took advantage of this and converted the ethanone **101** into dimethylamino-1-phenylethanone **102** according to HORIUCHI *et al.*[130] The product **102** was contaminated with BHT, the stabilizer of the THF, which was used for the work-up. It did not disrupt the next reaction and could be removed making a column chromatography of the final biphenylic system **103** which could be achieved by Suzuki coupling reaction applying the S-Phos/$Pd(OAc)_2$-catalyst system obtaining 13 % yield of biphenyl **103**.

With the last type of structure in this optimization section once more the steric effect of an additional methyl group should be tested. Therefore, the reductive amination of a ketone is the reaction of choice. For our planned synthesis their were two possible pathways to achieve the product formation. Either first the Suzuki-coupling between the arylbromide and boronic acid and afterwards the reductive amination or the other way around (Scheme 37).



Scheme 37: Synthesis of two biphenyls **106a** and **106b** applying two different approaches.

To construct first the biphenylic system and convert it then with different amines is more flexible and saves time making more reactions instead of synthesizing first the 1-phenylethanamines and convert each product to the final biphenyl.

Nevertheless with both strategies it was possible to achieve product formation with two different amines. The biphenyl **106a** was formed by coupling first 4-bromoacetophenone **(104)** with 3-ethoxycarbonylphenylboronic acid **(89)** by Suzuki reaction applying the S-Phos/$Pd(OAc)_2$-catalyst system and performing afterwards the reductive amination using 2.0 eq dimethylamine and 1.0 eq sodium cyanoborohydride, according to AMSTUTZ *et al.*[138] Using sodium triacetoxyborohydride as reducing agent the reaction did not work and also the addition of acetic acid is essential to activate the ketone. The second biphenyl **106b** was synthesized the other way around. First, 4-bromoacetophenone **(104)** was converted in a reductive amination using 2.0 eq 1-methylpiperazine and 1.0 eq sodium cyanoborohydride to obtain 71 % 1-(1-(4-bromophenyl)ethyl)-4-methylpiperazine **(107)** which was directly coupled in the Suzuki reaction applying once more the S-Phos/$Pd(OAc)_2$-catalyst system to deliver 59 % biphenyl **106b**.

4.2.6.1. Screening and discussion

In this part of the thesis we especially wanted to introduce increased hydrophilicity combined with improved bioavailability compared to the biphenyl **72e**. In addition, we wanted to analyze the electronic effects at the ring system to learn more about the SAR. The behaviour of the synthesized compounds in the *in vitro* screening is listed in Table 11. In comparison to the screenings done prior to this chapter, in some cases Cos7 cell lysates were replaced by Coli lysates (signed with *), in which 90 % ATGL is overexpressed. The motivation is to switch completely to Coli lysates during our investigations because there are several advantages regarding to purity, reproducability and decreased costs compared to the Cos7 lysates.

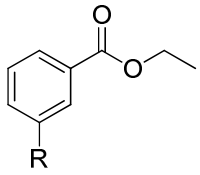
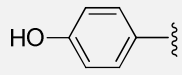
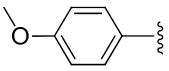
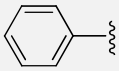
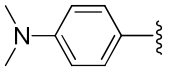
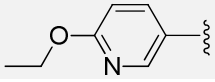
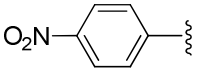
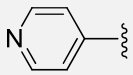
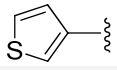
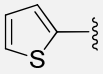
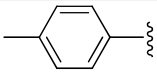
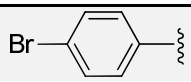
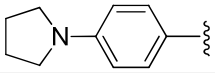
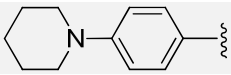
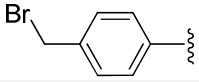
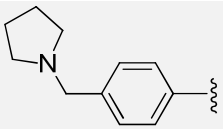
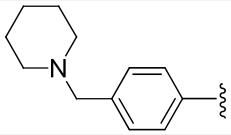
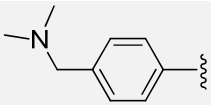
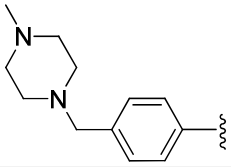
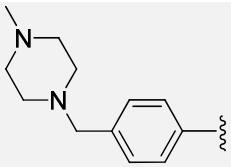
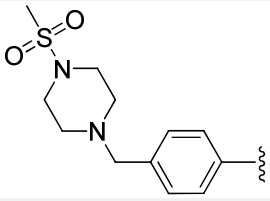
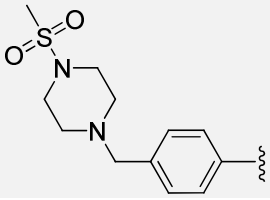
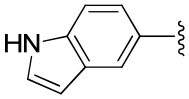
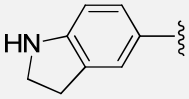
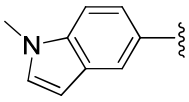
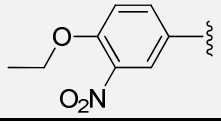
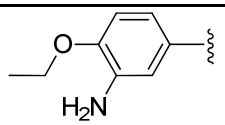
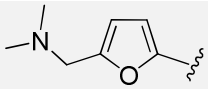
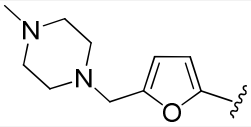
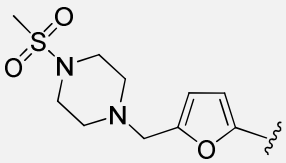
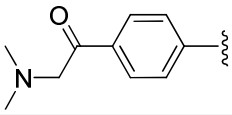
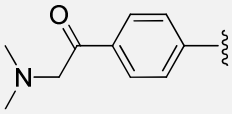
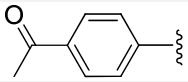
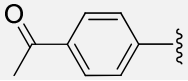
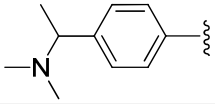
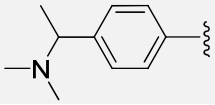
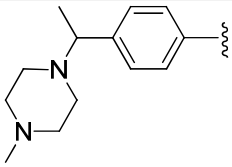
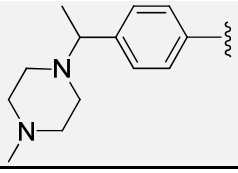


Table 11: IC_{50}-values and *in vitro* inhibition of the enzyme using an inhibitor concentration of 200 µM

Entry	No.	R	IC_{50} [µM]	I_{200} [%]
1	**82a**		100	77
2	**82b**		80	77
3	**82c**		200	52
4	**82d**		**40**	**87**
5	**82e**		130	68
6	**82f**		95	63
7	**82g**		➢ 200	40
8	**82h**		75	67
9	**82i**		90	55
10	**82j**		140	63

11	**82k**		➢ 200	34
12	**85a**		200	45
13	**85b**		**8**	**76**
14	**86**		**40**	**99**
15	**87a**		➢ 200	33
16	**87b**		75	68
17	**87c**		150	67
18	**87d**		➢ 200	26
19	**87d***		➢ 200	32
20	**87e**		100	68
21	**87e***		200	54
22	**90**		**60**	**80**
23	**91**		120	66
24	**92**		**75**	**84**
25	**93**		➢ 200	44

26	**94**		140	59
27	**97a**		190	53
28	**97b**		120	67
29	**97c**		100	66
30	**103a**		➢ 200	20
31	**103***		➢ 200	4
32	**105**		➢ 200	36
33	**105***		➢ 200	17
34	**106a**		➢ 200	50
35	**106a***		➢ 200	9
36	**106b**		90	69
37	**106b***		➢ 200	30

* values meassured with Coli-lysate

The *in vitro* screening offered valueable clues to the electronic properties which are desired for the inhibitor compound. With improved knowledge about improved inhibitor strutures the number of negative screening results could be decreased and specific optimizations could be done. As can be concluded from Table 11 and Fig. 67 only electron-rich biarylic systems with electron donating substituents, such as dimethylamine (entry 4), piperidine (entry 13) and indoles (entries 22 and 24) showed high biological activity.

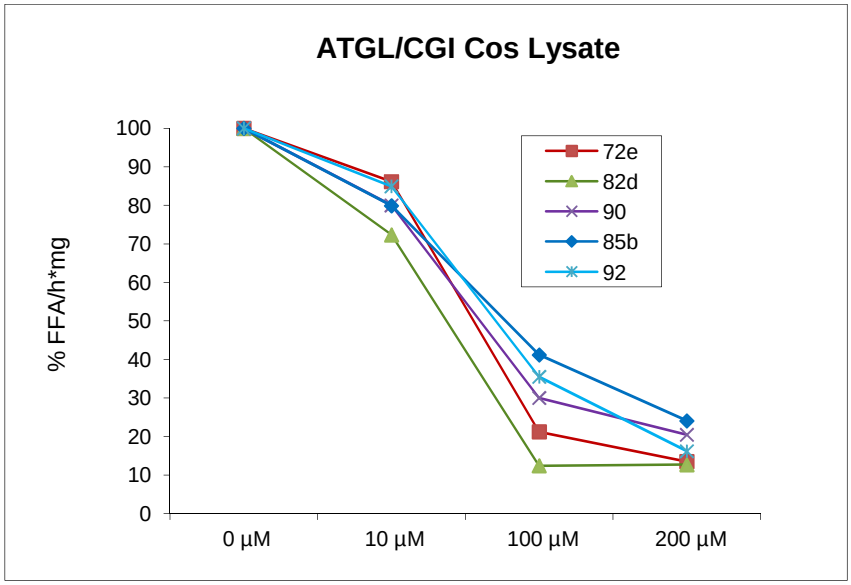


Fig. 67: Dose-dependent inhibition of ATGL activity *in vitro*.

By introducing substituents bridged with a CH_2-group to the biphenyl (entries 15, 16, 17, 18, and 20) or keto- (entries 30 and 32) and methine-moieties (entries 34 and 36) the biological activity was decreased suggesting the flexibility by possible rotation as one reason. The best results were achieved by **82d** (entry 4), **85b** (entry 13) and **90** (entry 22) with IC_{50}-values from 8-60 µM and good to acceptable inhibition effects. Also entry 14 seems to show significant biological activity but we fear several covalent side reactions when applying this compound due to its high electrophilicity. For further biological tests the synthesis of bigger amounts of the substances was necessary. As described before the synthesis of **85b** did not work out in good yields because of the still not optimized reaction conditions. We concentrated on compound **82d** and determined their ATGL and HSL activity by using isolated fat pads from mice. As it is depicted in Fig. 68 the inhibition of ATGL is higher than for HSL, concluding that although no ATGL specificity of 100 % is reached improved selectivity compared to **61i$_2$** was achieved.

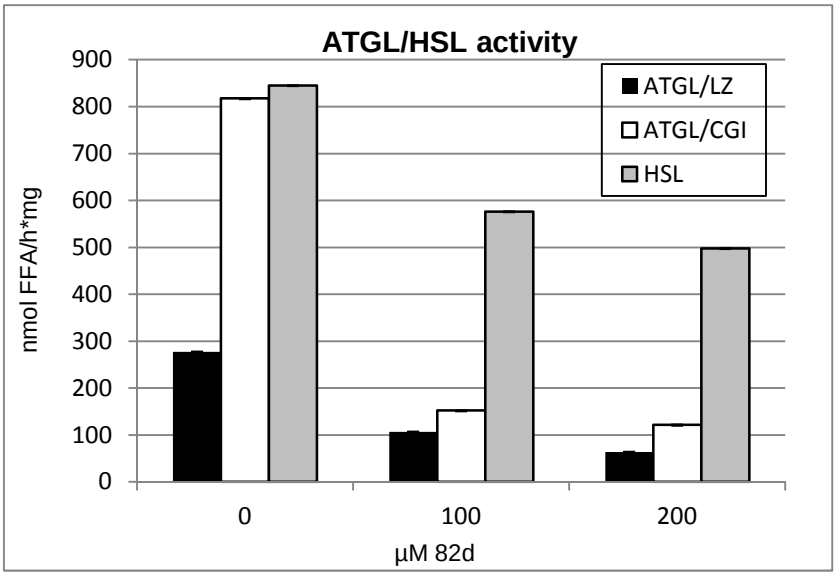


Fig. 68: ATGL- and HSL activity of inhibitor compound **82d**.

A further experiment was an inhibitor study with **82d** and **72e** in cell cultures (3T3 cells). The 3T3 cells were incubated with the respective inhibitors in a concentration of 200 µM to determine the FA release (Fig. 69).

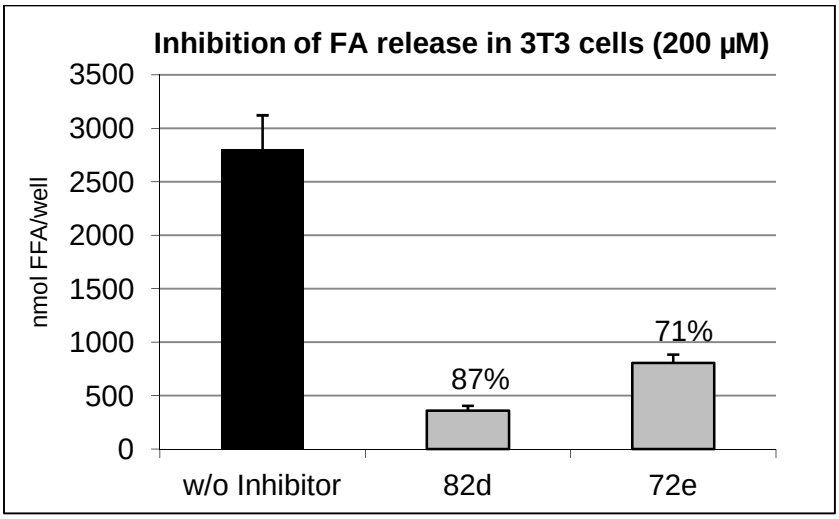


Fig. 69: Cell culture experiment in 3T3 cells.

Fortunately, both compounds inhibited the lipolysis suggesting a very good cell permeability for both, **82d** even more than **72e**, connected with desired and improved bioavailability. Almost full inhibition of the lipolysis in cell cultures and non-toxicity of both compounds mediated their use in an insulin tolerance test (Fig. 70).

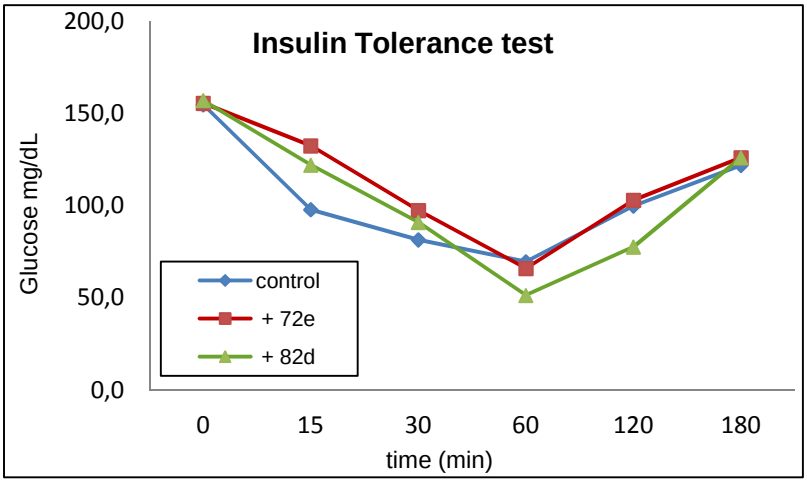


Fig. 70: Insuline tolerance test of **82d** and **72e**.

Therefore, the inhibitors (200 µM) were injected in mice. On the next day the mice were fasted for 4 h and 0.75 international Units/kg body weight insulin were injected intraperitoneal. Blood was taken after 0, 15, 30, 60, 120 and 180 min and the glucose levels (mg/dL) were determined. Fig. 71 shows that all mice had the same blood glucose values at the beginning. By the use of insulin the glucose level decreased rapidly and increased slowly back into the blood when insulin stopped to function. Insulin seemed to appear longer in the mice with **82d** which means they would be more insulin sensitive than control mice or mice injected with **72e**.

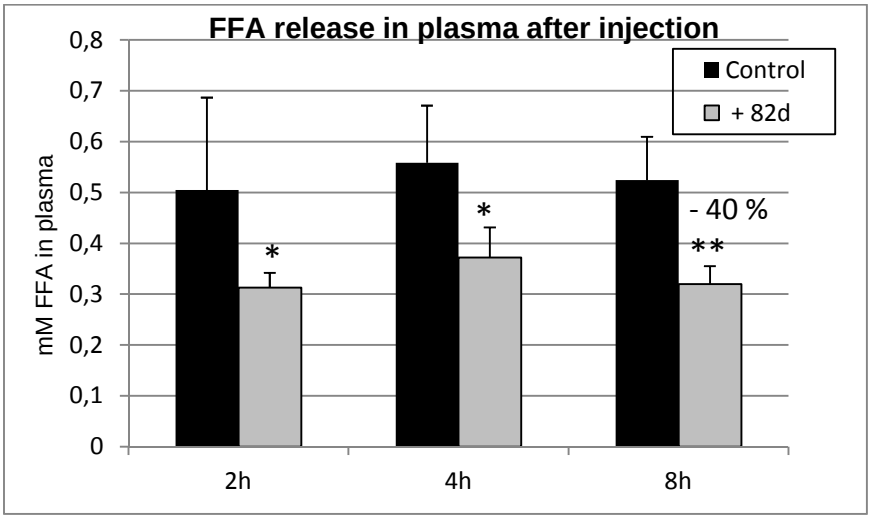


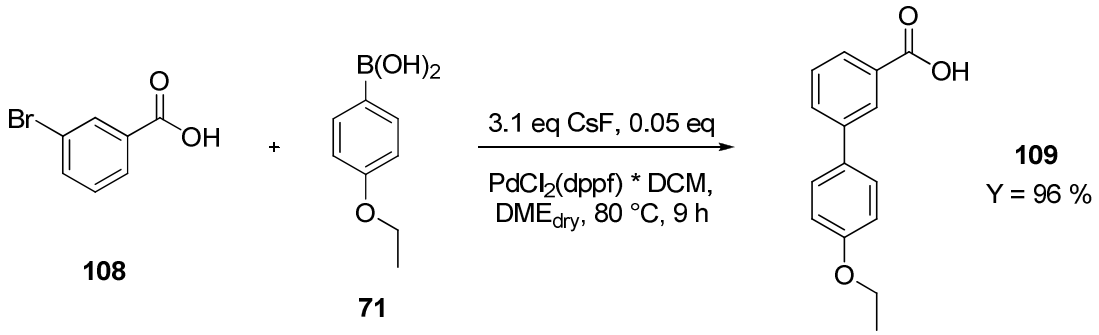
Fig. 71: FA release in isolated fat pads after injection of **82d** in mice.

As done for compound **72e**, **82d** was also injected in mice and mice fat was isolated after 2, 4 and 8 h to determine the release of FA, which was decreased by 40 % 8 h after inhibitor injection. In summary, the inhibition of lipolysis by the use of **82d** could be increased from 27

to 40 % in mice, which is a phenomenal result considering the maximum inhibition of lipolysis by ~60 % applying ATGL-ko mice.

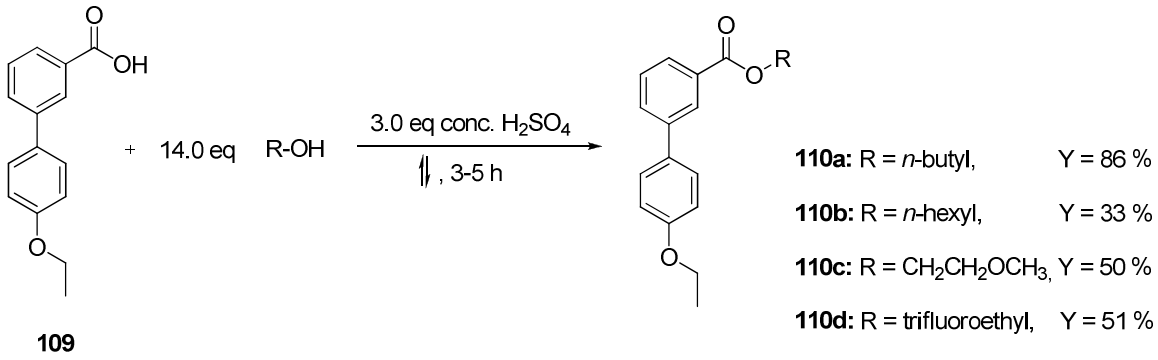
4.2.7. Diversification of the ethylester functionality at the biphenylic system

In the final part concerning optimization of lead structure we were interested how the diversification of the ethyl ester functionality at the biphenylic system would influence the biological activity. This work was done by three bachelor students (Eveline Brodl and Michael Tuechler, February 2011, Bettina Grumm, August 2011). At first 4`-ethoxybiphenyl-3-carboxylic acid **(109)** had to be synthesized by Suzuki coupling reaction of 3-bromobenzoic acid **(108)** and 4-ethoxyphenylboronic acid **(71)** applying the $PdCl_2$(dppf)*DCM catalyst and CsF as base which led to the isolation of 96 % product **109** after column chromatography (Scheme 38).



Scheme 38: Suzuki coupling of 3-bromobenzoic acid **(108)** and 4-ethoxyphenylboronic acid **(71)**.

The pure 4`-ethoxybiphenyl-3-carboxylic acid **(109)** was then converted with different alcohols in an acid-catalyzed esterification according to BÜNZLI *et al.* (Scheme 39).[109]

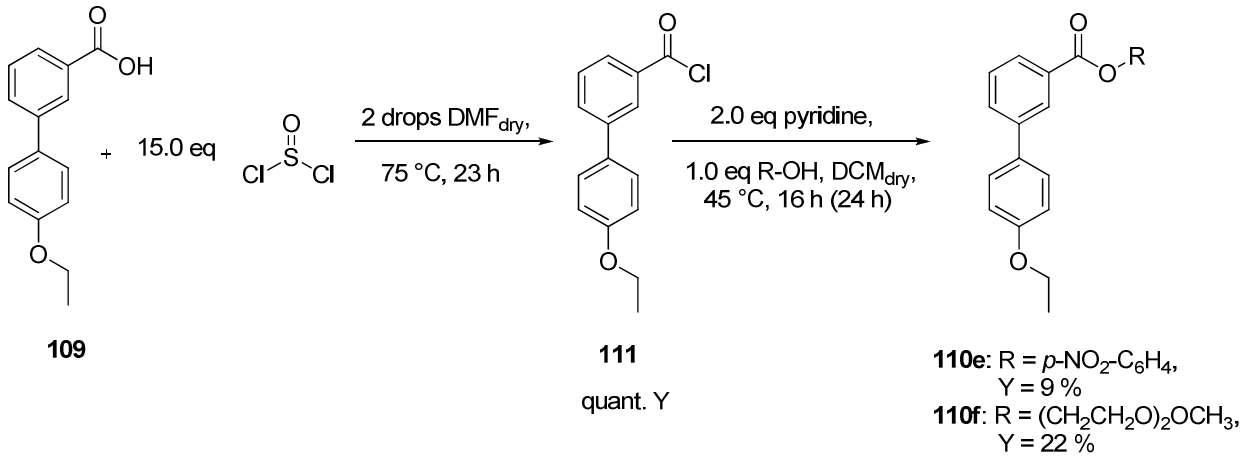


Scheme 39: Esterification of 4`-ethoxybiphenyl-3-carboxylic acid **(109)**.

n-BuOH, *n*-hexanol, 2-methoxyethanol and trifluoroethanol were used as reagent and solvent and product formation occurred in 3-5 h. In the case of the esterification with *n*-hexanol it was difficult to remove the excess solvent even at high vacuum because of the high boiling point. Consequently, in the future approaches it would be better to decrease the amount of *n*-hexanol.

The two following products were synthesized on the one hand to replace the aliphatic side chains by an aromatic one applying *p*-nitrophenol and on the other hand to increase the hydrophilicity of the molecule by attaching a PEG group. The nitrophenol was chosen because it is already known to be a reactive side chain in the JZL 184 inhibitor of the monoglyceride lipase[83-84] and it would be interesting if the aromatic system influences the binding properties.

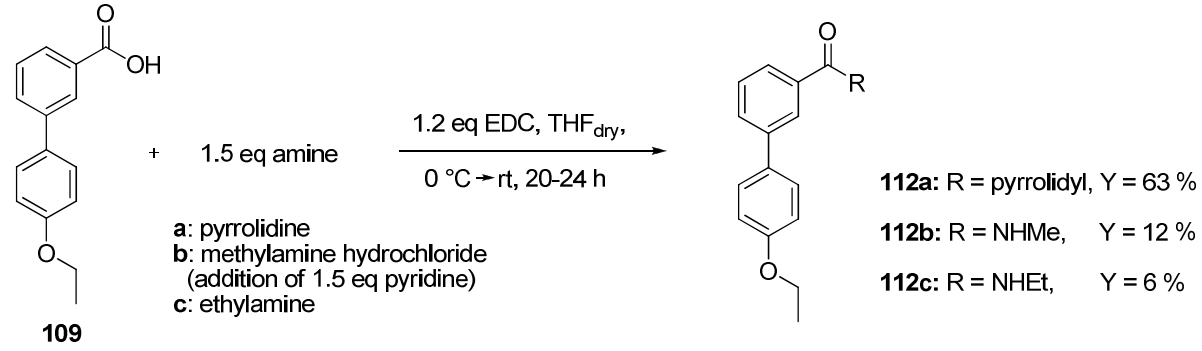
For the synthesis of both compounds it was necessary to convert the acid **109** *in situ* into an acid chloride **111** using thionylchloride in excess and catalytic amounts of DMF according to ZHAO *et al.*[139] After full conversion the excess thionylchloride was removed and the acid chloride **111** was directly used in the second step without further purification (Scheme 40).



Scheme 40: Synthesis of two ester functionalities reacting the acid **109** *in situ* to the acid chloride **111**.

The acid chloride **111** was then converted using 2.0 eq pyridine, DCM as solvent and either *p*-nitrophenol or 2-(2-methoxyethoxy)ethanol for the esterification.[140] In both cases full conversion of the acid chloride **111** could be achieved as monitored by TLC analysis but after column chromatography only very low yields of both final biphenyls **110e** and **110f** were obtained.

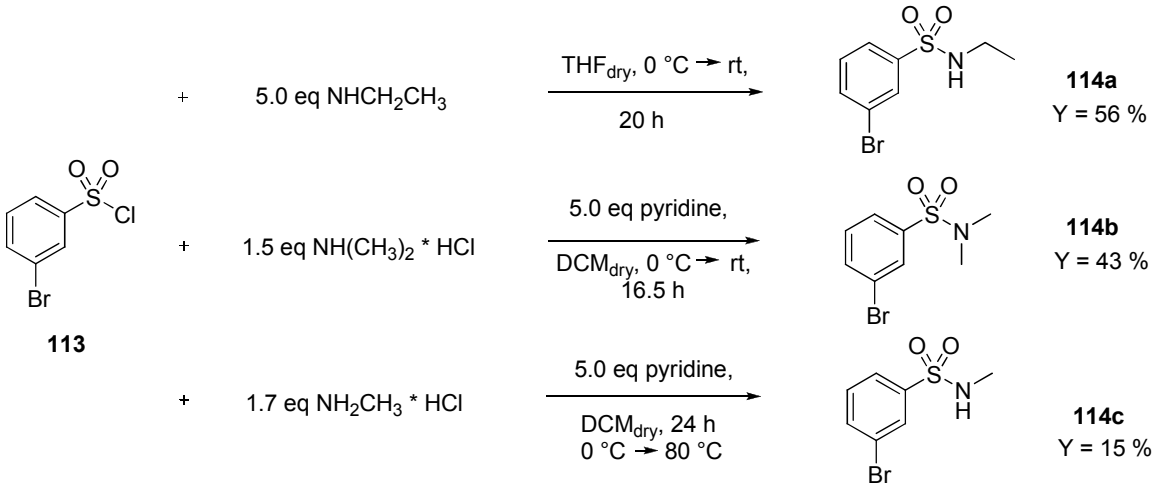
For the amide coupling EDC was used as it allows the removal of the urea side product by simple washing with water. To replace the ethylester functionality 4`-ethoxybiphenyl-3-carboxylic acid **(109)** was converted to the biphenylic amides **112a-c** using 1.5 eq of amine and 1.2 eq of EDC in THF instead of DCM (solubility issues) according to HAMMOCK *et al.*[141] In the case of methylamine addition of 1.5 eq pyridine was necessary to react the free amine (Scheme 41).



Scheme 41: Amide formation to biphenyls **112a**, **112b** and **112c** using the EDC coupling method.

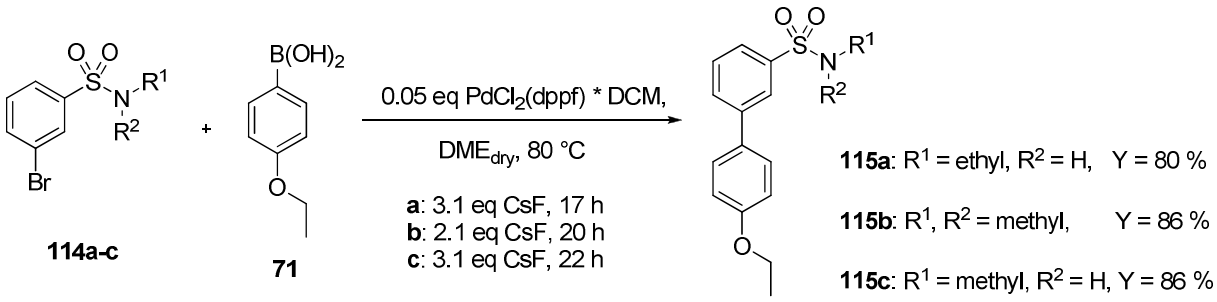
After 20-24 h stirring at rt full conversion was determined but the amides **112a-112c** could only be obtained in strongly varying yields after purification by column chromatography.

Sulfonamides are also well known to mediate water solubility into a molecule. In addition, they are transition state analoga for ester and amide hydrolysis. The synthesis of biphenyls carrying a sulfonamide side chain seemed to be very interesting tool compounds. Commercially available 3-bromobenzenesulfonylchloride **(113)** was reacted with amines in a substitution reaction to obtain the three bromobenzenesulfonamides **114a-c** (Scheme 42).



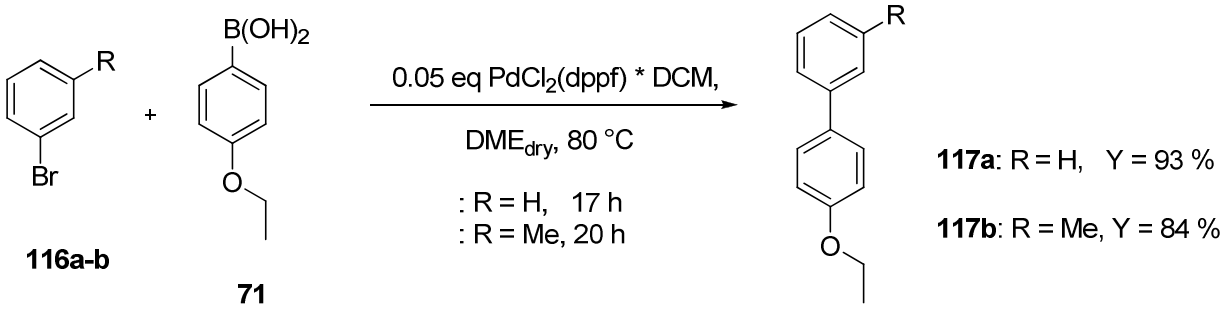
Scheme 42: Synthesis of the substrates **114a-c** containing a sulfonamide functionality.

Sulfonamide **114a** was synthesized according to RIEDL *et al*.,[142] the other two sulfonamides **114b** and **114c** according to BARROW *et al.*[143] using additionally 5.0 eq pyridine to react the free amines. These 3 sulfonamides were finally converted to the biphenylic sulfonamides **115a-115c** via Suzuki reaction with $PdCl_2$(dppf)*DCM catalyst (Scheme 43).



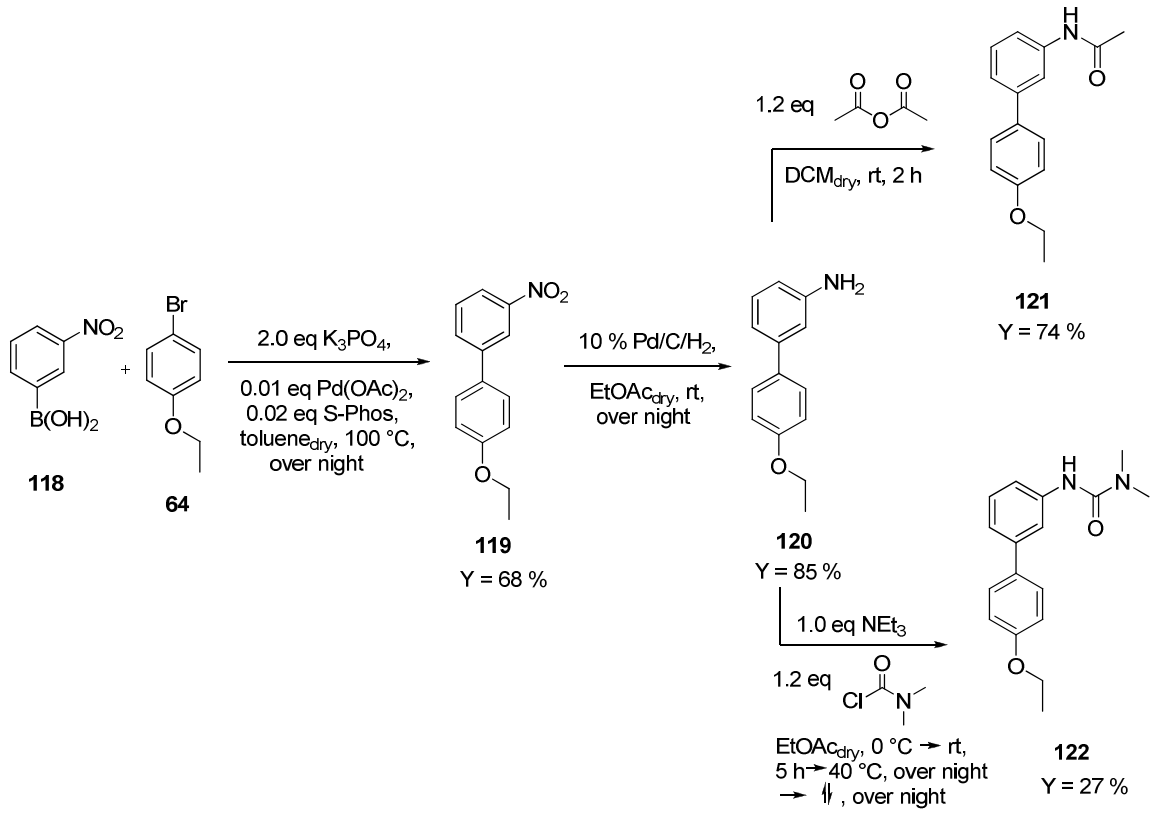
Scheme 43: Conversion of the sulfonamide substrates **114a-114c** in a Suzuki coupling reaction.

With the same conditions of the coupling reaction it was possible to synthesize two additional biphenyls **117a** and **117b** in good isolated yields (Scheme 44).



Scheme 44: Suzuki coupling of two different arylbromides **116a** and **116b** with 4-ethoxyphenylboronic acid **(71)**.

The last two interesting compounds synthesized in this optimization part are an acetanilide and an urea derivative well known to mediate hydrophilicity in a molecule without introducing cell toxicity. 3-Nitrophenylboronic acid **(118)** was converted with *p*-bromophenetole **(64)** in a Suzuki coupling reaction using the S-Phos/$Pd(OAc)_2$-catalyst system to generate 4`-ethoxy-3-nitrobiphenyl **(119)** which could be isolated in 68 % yield. The nitro group was reduced by catalytic hydrogenation with 10 % Pd/C and hydrogen stream according to HALBERT *et al.* over night furnishing 85 % 4`-ethoxybiphenyl-3-amine **(120)** (Scheme 45).[144]



Scheme 45: Synthesis of two different biphenyls **121** and **122** containing an acetanilide and urea moiety

The amine **120** was used in the final steps without further purification. One half of it was transformed to the acetanilide **121** using 1.2 eq acetanhydride in DCM according to STUART *et al.*[145] After 2 h stirring at rt and purification by column chromatography 74 % acetanilide **121** could be obtained. The second half of the amine was converted to an urea using 1.2 eq dimethylcarbamoyl chloride in EtOAc with addition of 1.0 eq triethylamine according to KUHN *et al.*[146] In accordance with the literature the reaction was first stirred at rt for 5 h but no conversion of the starting material could be observed. Therefore, the temperature was increased to 40 °C for one night. At the next day conversion to the product was detectable but to reach full conversion the temperature was once more increased to reflux. After a further night the conversion was completed and 27 % 1,1-dimethyl-3-biphenylurea **122** could be isolated after column chromatography.

4.2.7.1. Screening results and discussion

All synthesized compounds underwent an *in vitro* screening and the results are listed in Table 12.

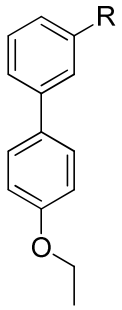
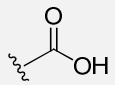
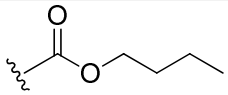
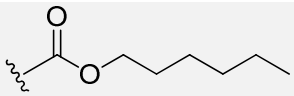
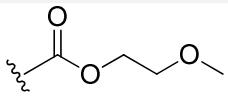
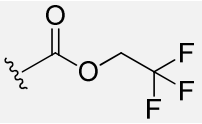
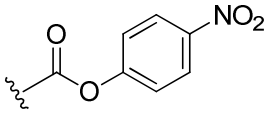
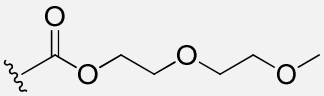
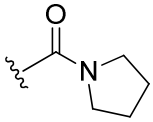
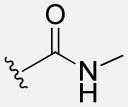
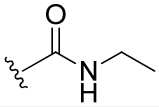
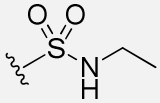
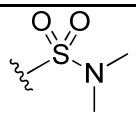
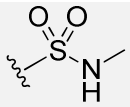
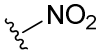
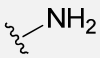
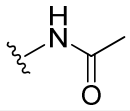
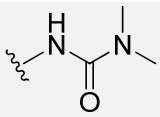
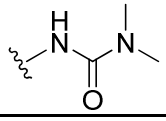


Table 12: IC_{50}-values and *in vitro* inhibition of the enzyme using an inhibitor concentration of 200 µM

Entry	No.	R	IC_{50} [µM]	I_{200} [%]
1	**109**		➢ 200	23
2	**110a**		100	61
3	**110b**		➢ 200	48
4	**110c**		**80**	**89**
5	**110d**		120	71
6	**110e**		150	56
7	**110f**		➢ 200	43
8	**112a**		160	53
9	**112b**		➢ 200	40
10	**112c**		90	62
11	**115a**		200	46

12	**115b**		110	63
13	**115c**		200	47
14	**117a**		➢ 200	35
15	**117b**		70	54
16	**119**		➢ 200	35
17	**120**		100	65
18	**121**		200	52
19	**122**		**70**	**68**
20	**122***		**9**	**83**

* values meassured with Coli-lysate

A large number of compounds was synthesized with the intention to replace the ethyl ester functionality to improve the hydrophilicity and bioavailability of the biphenylic system. The biological activities of the amides (entries 8, 9 and 10) and sulfonamides (entries 11, 12 and 13) did not meet our expectations, in comparison to different ester functionalities. By introducing ethyloxy groups (entries 4 and 7) we expected increased water solubility. But as it is shown in Table 12 only the shorter methoxyethoxy side chain (entry 4) with an IC_{50}-value of 80 µM and 89 % inhibition shows similar biological activity compared to the compounds discussed in the chapters before. The longer PEG side chain seemed to be sterically too challenging. Surprisingly, the urea moiety (entries 19 and 20) produced very good results with an IC_{50}-value of 9 µM and 83 % enzyme inhibition. Unfortunately, the results of entry 19, using Cos7 lysates, and Entry 20, using Coli lysates varied strongly from each other, which can be explained by the initial unexperience with the experiments. The results of the best compounds are also depicted in Fig. 72.

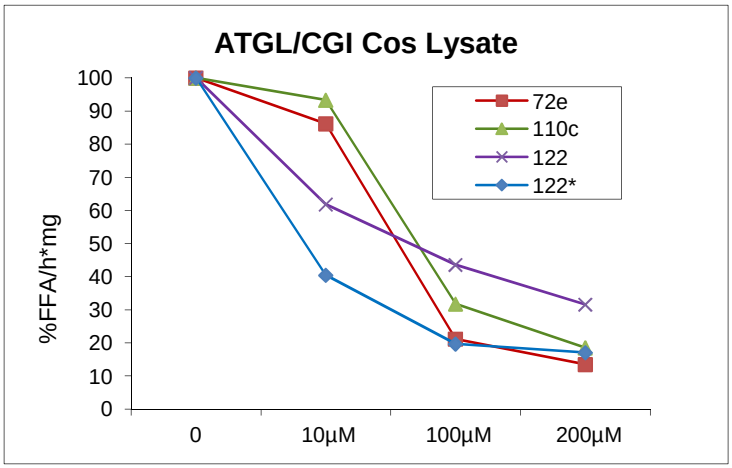
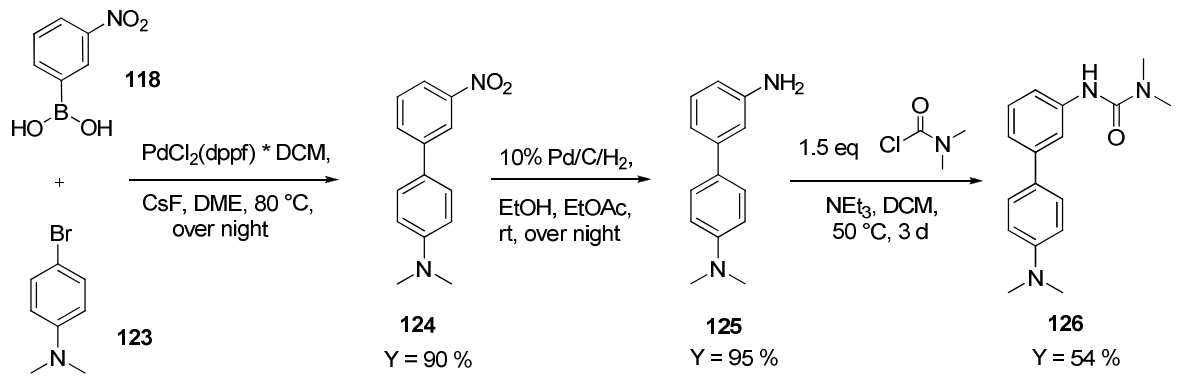


Fig. 72: Dose-dependent inhibition of ATGL activity *in vitro*.

Although we could not be sure which result we should believe (entries 19 and 20) we notified the positive trend in the polarity combined with increased bioavailability of the inhibitor compound. This motivated us to synthesize a final inhibitor structure combining the best optimized features.

4.2.8. Synthesis and screening results of the optimized inhibitor compound

At the end the combination of the best functionalities received from all optimization steps led us to the structure pictured in Scheme 46, 3-(4`-dimethylamino)biphenyl-3-yl)-1,1-dimethylurea **(126)**. The structure is composed of a biphenylic scaffold with an urea functionality instead of the ethylester and a dimethylamine substituent in contrast to the former ethoxygroup.



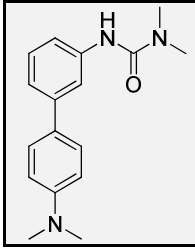
Scheme 46: Three-step synthesis of the optimized inhibitor compound X.

The synthesis of this final compound starts with the known Suzuki coupling reaction between 3-nitrophenylboronic acid **(118)** and 4-bromo-*N*,*N*-dimethylaniline **(123)** using

$PdCl_2$(dppf)*DCM catalyst and CsF in DME. After one night the biphenyl **124** could be isolated in 90 % yield after purification by column chromatography. The nitro group was reduced by hydrogenation with 10 % Pd/C and hydrogen stream according to HALBERT *et al.*[144] over night furnishing 95 % 4`-(1,1-dimethylamino)biphenyl-3-amine **(125)**. The amine **125** was directly converted to the urea without further purification. It was reacted with 1.5 eq dimethylcarbamoyl chloride and 1.0 eq triethylamine in DCM according to KUHN *et al.*[146] at 50 °C for 5 d. After reaching full conversion the final inhibitor compound could be isolated and purified by column chromatography yielding 54 % urea **126**.

The results of the *in vitro* screnning of compound **126** were amazing and comparable in both lysates, Cos7-and Coli-lysates. (Table 13) With an IC_{50}-value of 5 µM we could achieve up to 98 % inhibition of the enzyme by applying an inhibitor concentration of 100 µM instead of 200 µM as for all compounds before.

Table 13: IC_{50}-values and *in vitro* inhibition of the enzyme using an inhibitor concentration of 200 µM (Cos- and Coli-lysate)

compound	No.	I (Coli)	IC_{50} (Coli)	I (Cos)	IC_{50} (Cos)
	**126**	98 96 (100 µM)	5	92 90 (100 µM)	5

The *in vitro* behavior of the best inhibitor compounds by optimizing lead structure 2 are summarized and illustrated in Fig. 73.

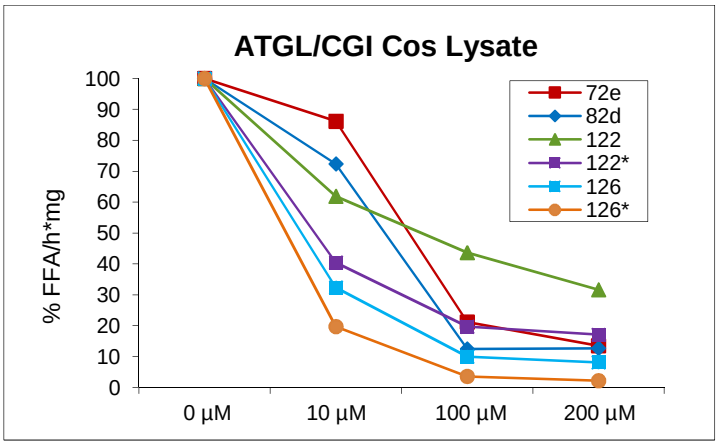


Fig. 73: Dose-dependent inhibition of ATGL activity *in vitro*. (* values measured with Coli lysates)

Because of the fantastic biological activity determined for **126** it was tested in an *ex vivo* screening isolating the gonatal fat of normal wild-type mice and incubate them with different concentrations of the inhibitor. (Fig. 74)

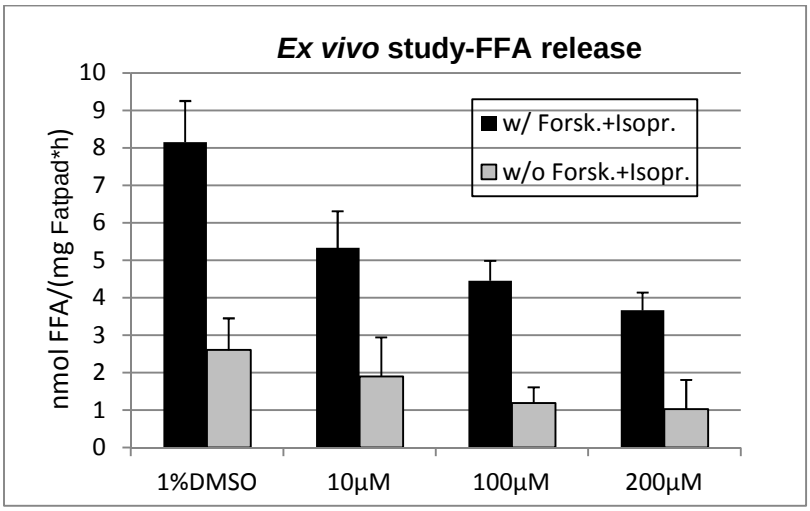


Fig. 74: Results of the *ex vivo* screening of **126** with and without hormone stimulated lipolysis.

The black bar represent the fat pads, which were stimulated by forskolin and isoproterenol and the grey bar stands for the basal lipolysis, which means the normal degradation of triglycerides and release of FFA without hormone stimulation. The inhibitor exhibited the capability to reduce the lipolysis as a function of the concentration in both cases, basal (40 % inhibition) as well as hormone stimulated lipolysis (55 % inhibition).

Inhibitor **126** (200 µM) was also injected in mice and mice fat was isolated after 8 h. (Fig. 75)

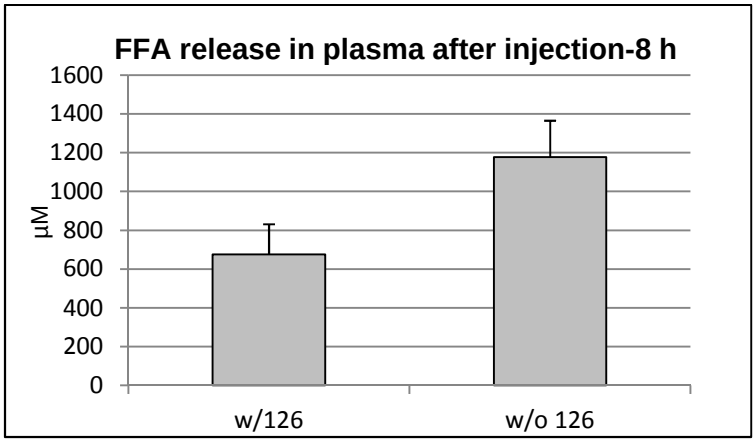
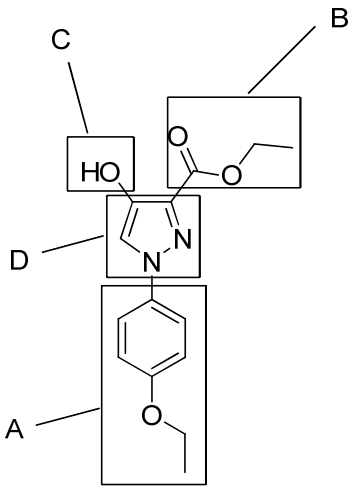


Fig. 75: FA release in isolated fat pads after injection of **126** in mice.

The release of FFA was determined, which was decreased by 43 % after injection of the inhibitor indicating a slight improvement compared to **82d**.

4.2.9. Summary of the improvement of lead structure 2



Lead structure 2 is structurally composed of four main building blocks, which should be diverisified during the thesis. The IC_{50}-value of lead structure 2 is 120 µM and it inhibits the enzyme using a concentration of 200 µM inhibitor by 67 %.

By removing the hydroxy group the affinity could be improved to 40 µM and the inhibition effect to 89 %. Unfortunately the compound inhibits also the MGL in a great manner. By introducing a phenyl ring instead the pyrazole ring the biological activity differed only marginal (50 µM, 87 % inhibition) but with this compound we reached 100 % selectivity towards ATGL and in first experiments in mice an inhibition of lipolysis by 27 % was observed. (Fig. 76)

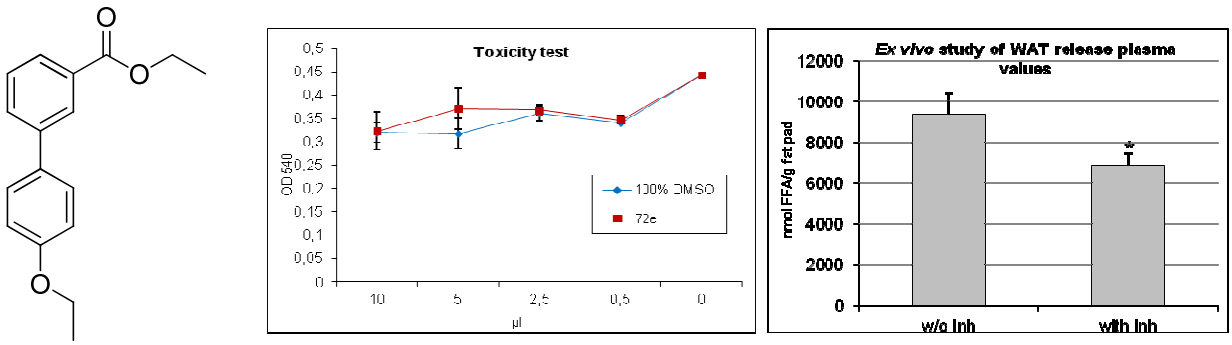


Fig. 76: Toxicity test and *in vivo* data of compound **72e**.

A big problem was the increased hydrophobicity, which is mediated by the biphenylic system directing us to the the idea to introduce more polar and water soluble substituents at the biphenylic system. By replacing the ethoxy group by a dimethylamino moiety the affinity could be improved to 40 µM with the same inhibition effect. In addition, we could determine

enhanced cell permeability compared to **72e** connected with increased *in vivo* inhibition of lipolysis by 40 %. First studies checking the insulin tolerance of both compounds indicated a higher insulin sensitivity for compound **82d** compared to **72e**. Unfortunately, the selectivity towards ATGL was degraded marginally and it also inhibits MGL slightly. (Fig. 77)

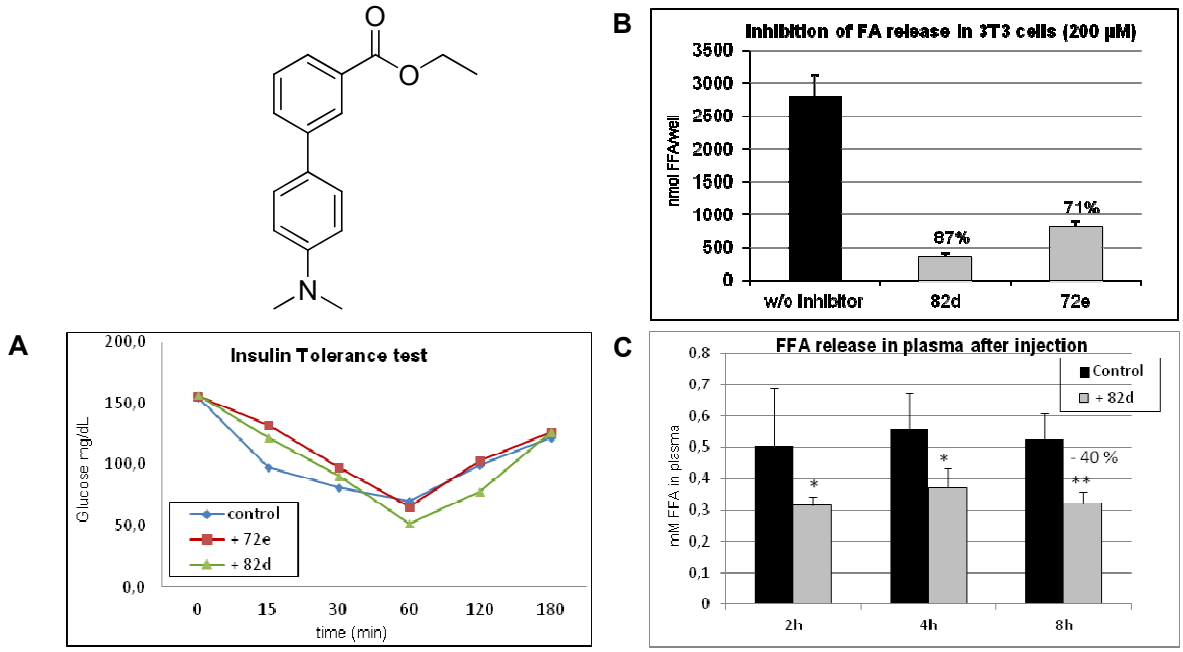


Fig. 77: Summary of the screening results for compound **82d**: (A) insulin tolerance test, (B) test for cell permeability, (C) inhibition of lipolysis *in vivo* in mice.

By replacing the ethyl ester functionality by an urea moiety maintaining the dimethylamino substituent the biological activity could be once more enhanced dramatically with an IC_{50}-value of 5 µM and an almost full inhibition effect between 92 % and 98 %, depending on the applied lysates. Inhibitor compound **126** is able to inhibit the basal lipolysis as well as the hormone stimulated lipolysis (*ex vivo*) and after injection in mice lipolysis was inhibited by 43 %. (Fig. 78)

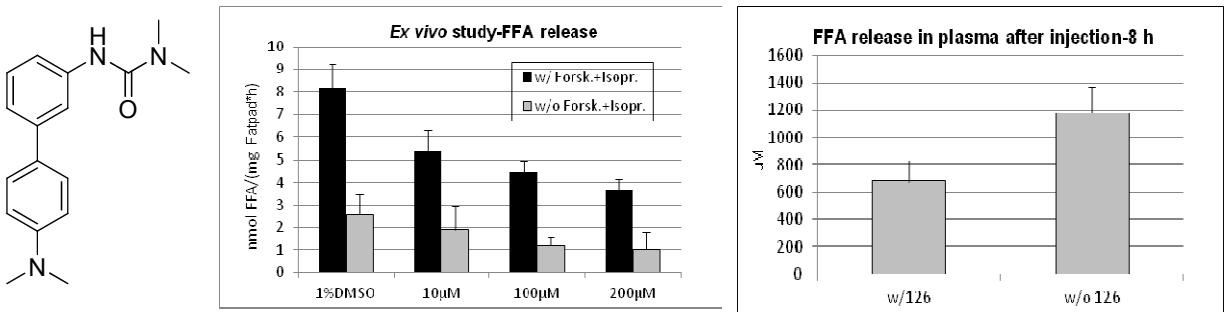


Fig. 78: Results of the *ex vivo* and *in vivo* screening for compound **126**.

All optimized structures based on lead structure 2 are depicted in Fig. 79 differentiated in applied lysates.

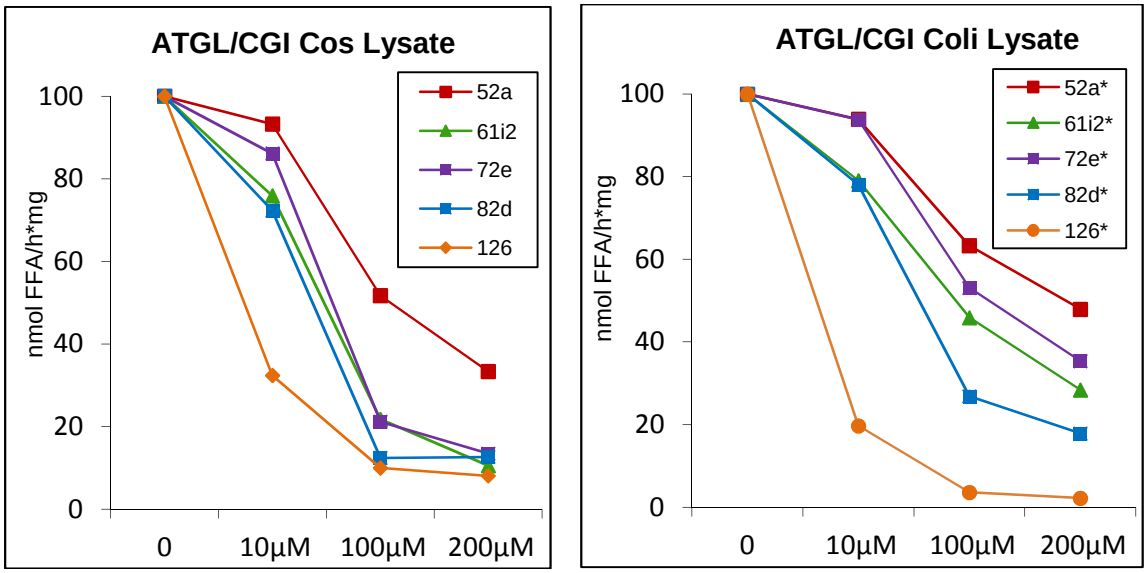


Fig. 79: Results of the *in vitro* screening applying Cos7 lysates and the results using Coli lysates.

Although the results vary slightly depending on the applied lysates the overall trends are visible in both graphs. The three non-toxic compounds (**72e**, **82d** and **126**) with the best biological activity optimized during this thesis were once more measured in an *in vitro* assay (incubation at 37 °C) applying also smaller inhibitor concentrations to determine more precise IC_{50}-values. (Fig. 80)

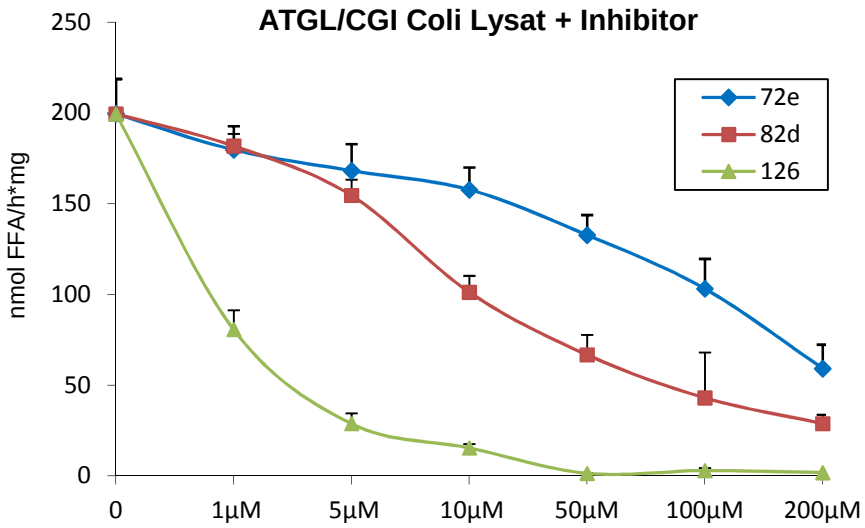


Fig. 80: Dose-dependent inhibition of ATGL activity *in vitro* applying smaller inhibitor concentrations. (Coli lysate)

This graph shows the impressive optimization work we succeeded in this thesis and precis IC_{50}- values of 900 nM for **126** and 10 µM for **82d** could be determined.

In summary, we were successful in improving the IC_{50}-value from 120 µM to 900 nM and the inhibition effect from 67 % (200 µM inhibitor concentration) to 99 % (50 µM inhibitor concentration). Additionally, we succeeded in improving the selectivity towards ATGL, in the case of compound **72e** we even reached 100 % selectivity. First studies in mice with inhibitor compound **126** indicated an inhibition of lipolysis by 43 % after injection of an inhibitor concentration of 200 µM, which is an enormous result considering the maximum inhibition of lipolysis by ~60 % applying ATGL-ko mice.

5. Summary and future work

The aim of this thesis was to synthesize small molecule inhibitors for the enzyme Adipose Triglyceride Lipase (ATGL), which is responsible for the hydrolysis of TG in the lipolysis pathway. Increased adipose tissue lipolysis has been identified to be responsible for at least two unfavorable metabolic conditions: (i) insulin resistance and (ii) cachexia. Mice lacking ATGL exhibit increased insulin sensitivity and are resistant to tumor induced cachexia. Thus, inhibition of ATGL could improve systemic insulin sensitivity and counteract tumor-induced cachexia. The synthesis of the inhibitors should be performed based on two lead structures by applying a classic structure-variation approach due to the unavailable 3-D structure of the enzyme.

The optimization based on the first lead structure were not satisfying. Indeed, we were successful in improving the enzyme affinity from 110 µM to 10 µM and the inhibition effect from 69 % to 94 % in the case of compound **5i** but we could not replace the hydrazone functionality to remove the cell toxicity by maintaining the biological activity. (Fig. 81)

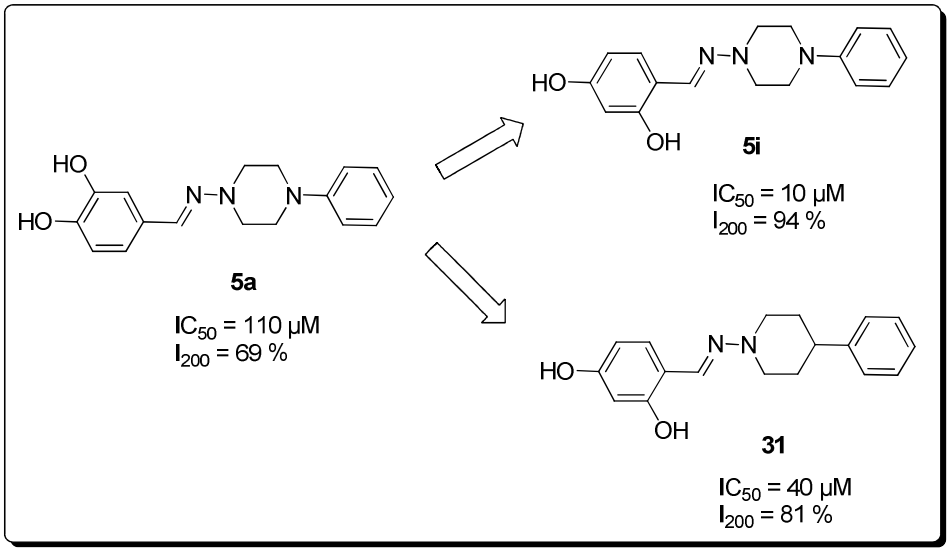


Fig. 81: Optimized inhibitor compounds based on lead structure 1.

By replacing the piperazine ring by a piperidine ring we could decrease the toxicity but slightly diminished the biological activity.

The second chemotype lead structure 2 offered several opportunities for optimization work. We were very successful by changing different functionalities to improve the biological activity as well as removing cell toxicity completely leading us to first experiments in mice. The synthetical optimization of the inhibitor structure is shown in Fig. 82.

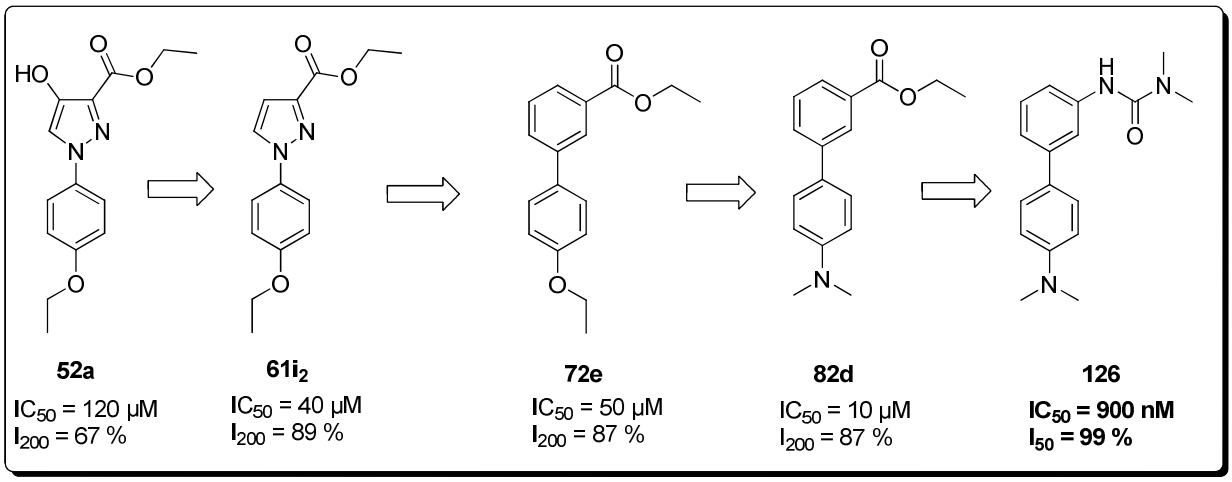


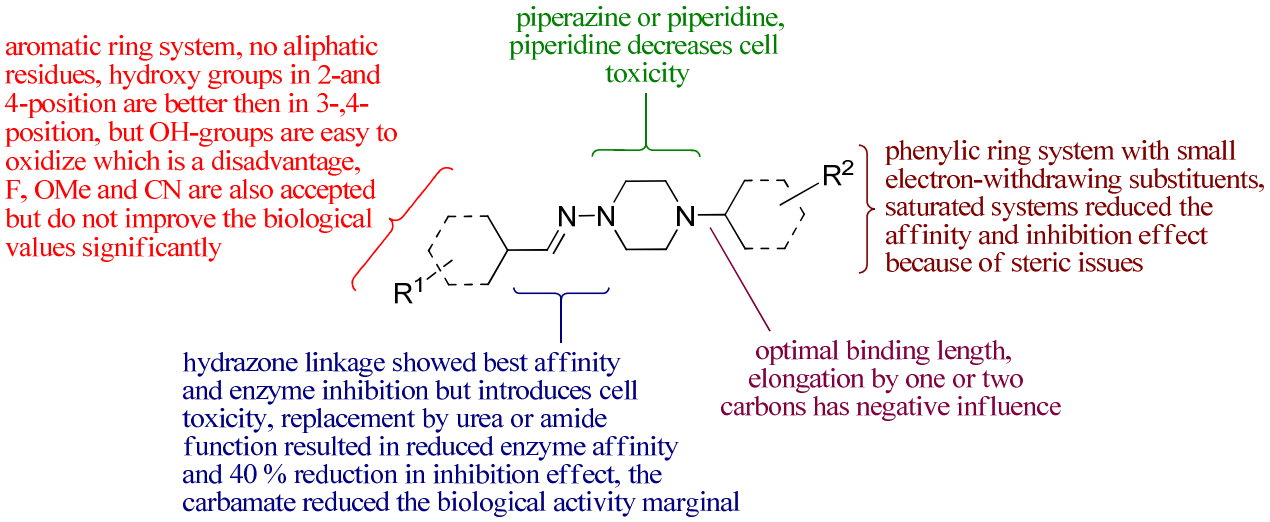
Fig. 82: Flow scheme of the synthetic optimization of the inhibitor compound with corresponding biological activities.

The removal of the hydroxyl group led to highly improved biological activity and by replacing the pyrazole ring by a phenyl ring the biological activity could be nearly maintained but compound **72e** was 100 % ATGL selective and first *in vivo* studies in mice resulted in a 27 % inhibition of lipolysis in adipose tissue (200 µM inhibitor concentration). By replacing the ethoxy group by a dimethylamino group (**82d**) we wanted to induce higher polarity in the molecule which resulted in increased enzyme affinity, increased cell permeability and better inhibition of lipolysis in mice (40 %, 200 µM inhibitor concentration) compared to **72e**. Unfortunately, **82d** is not completely ATGL selective but also inhibits MGL slightly depending on the inhibitor concentration. The replacement of the ethyloxy by a dimethylamino urea functionality in compound **126** led once more to improvement of the IC_{50}-value to 900 nM and an inhibition of the enzyme by 99 % even at an lower inhibitor concentration of 50 µM instead of 200 µM, which had to be normally used to reach acceptable to almost full enzyme inhibition. The inhibition of lipolysis in *in vivo* experiments could also slightly increased to 43 % using an inhibitor concentration of 200 µM.

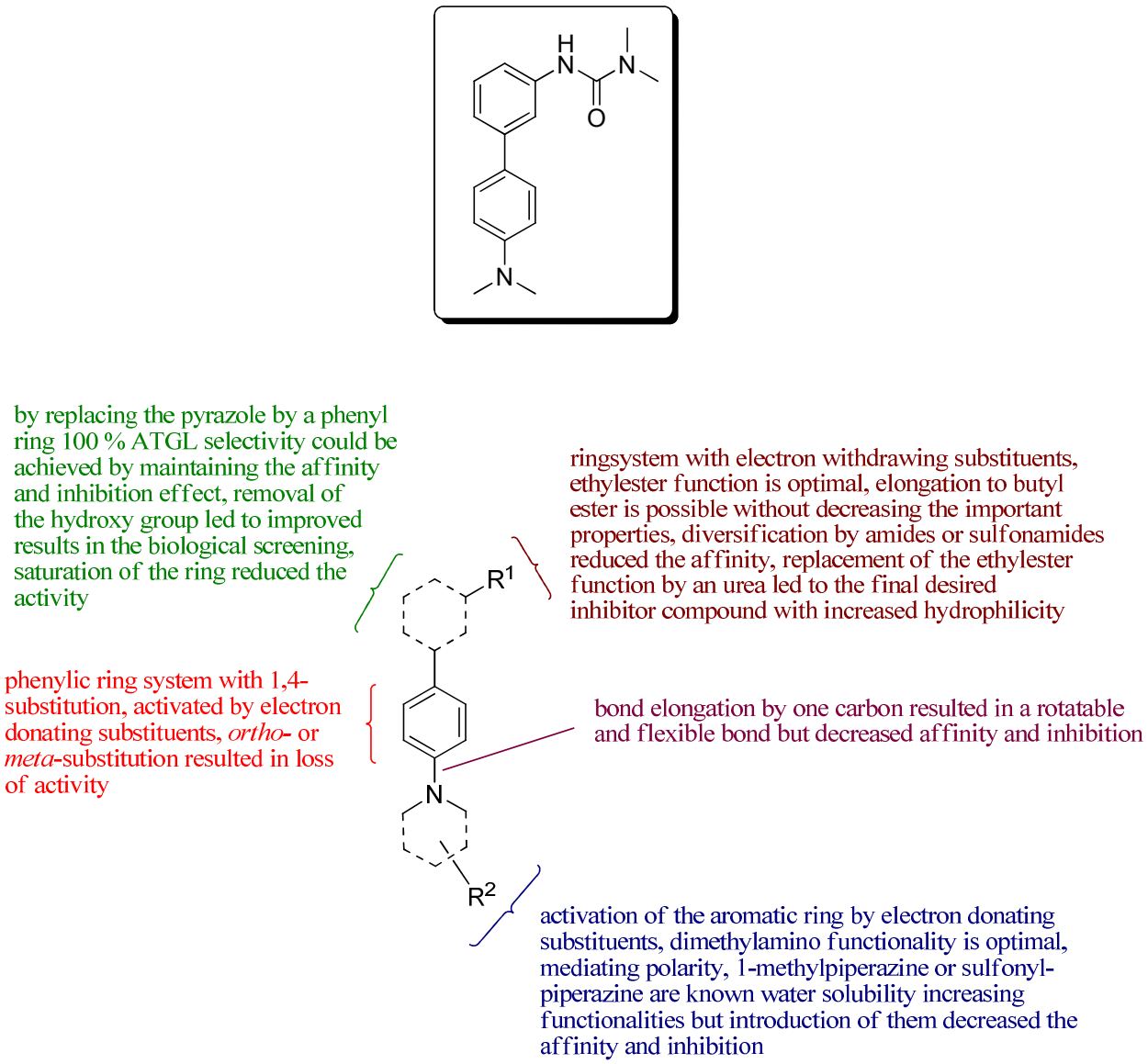
5.1. Structure-Activity Relationship (SAR)

The structure-activity relationship plays a key role in the aspect of drug design and describes the relationship between a chemical structure of a molecule and its biological activity, which can be influenced by solubility, permeability or stability. These parameters can be optimized towards a special enzyme by changing structural properties of a presumable drug candidate. Structure modifications at different moieties in the molecule can affect the biological activity. [147]

It was a major aim of this thesis to establish a first structure-activity relationship by taking two different lead compounds and optimize them by replacing or changing structural features. All synthesized compounds were tested *in vitro* to determine a correlation between the structural properties and biological activity. In the next two schemes (Scheme 47, Scheme 48) the SAR for both lead structures is discussed and structural features and their influence on the biological activity towards the ATGL is specified.



Scheme 47: SAR of lead structure 1.



Scheme 48: SAR of lead structure 2.

5.2. Future work

In contrast to ATGL-knockout mice, which completely lack the enzyme ATGL, small molecule inhibitors are synthesized to have the possibility for studying inhibition effects and signalling mechanisms by partial inhibition of the lipase. In this thesis the synthesis of potent inhibitors for the enzyme ATGL based on lead structure optimization was successfully demonstrated. However, there is definitely still great potential concerning the structural properties and the different biological requirements. Four possibilities for diversification based on the optimized inhibitor compound **126** are illustrated in Fig. 83.

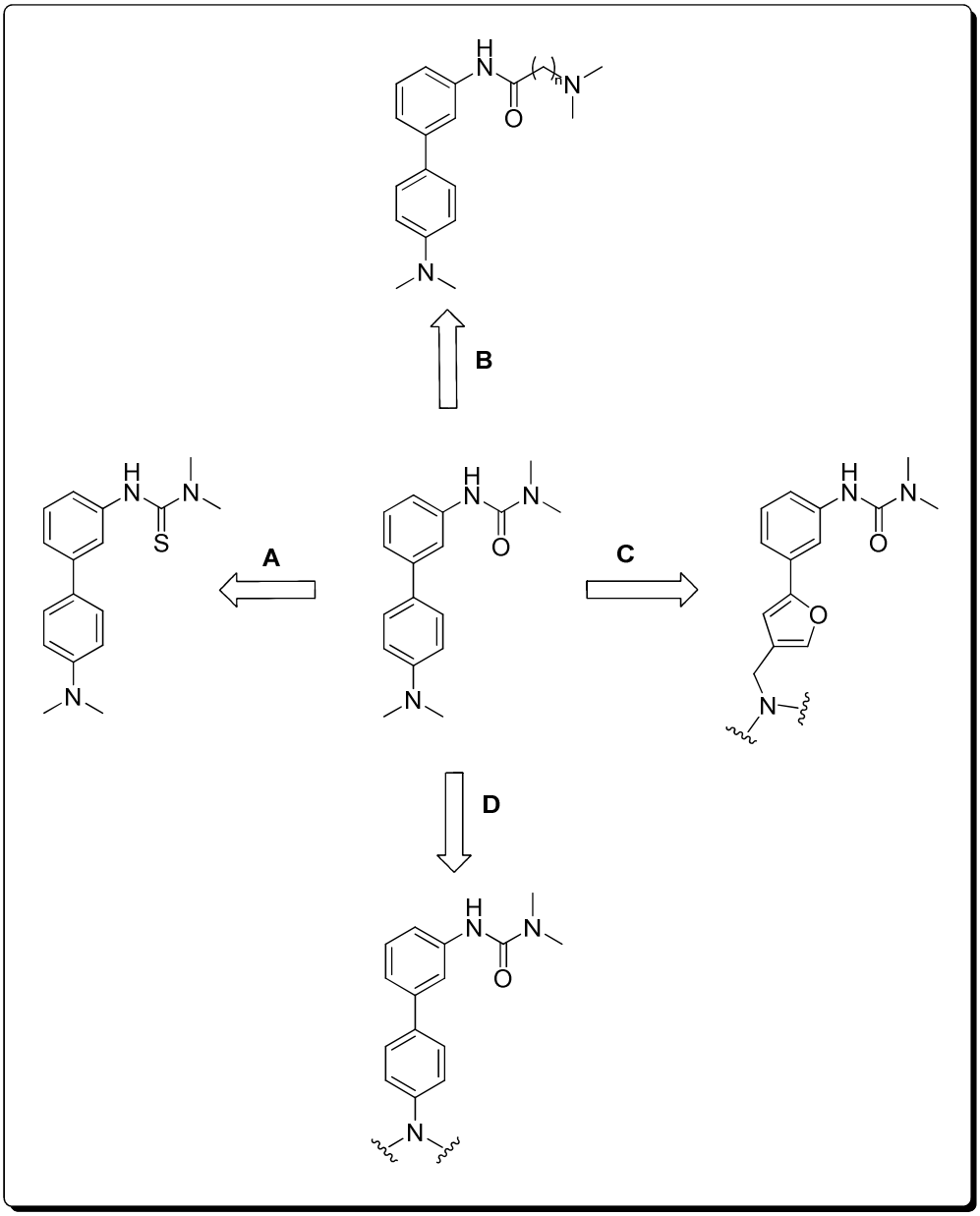
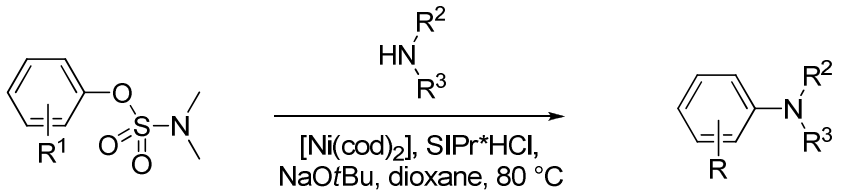


Fig. 83: Diversification possibilities based on the optimized inhibitor compound.

The introduction of a thiourea functionality (way A) would be not advisable concerning the biological application because of its metabolic instability, but on the other hand we could explore the steric requirements of the binding pocket because of the different length of the C=S bond compared to the C=O bond. The same motivation is pursued by elongating the chain length between the carbonyl group and the dimethylamino group of the urea (way B) to determine the maximum sterical requirements. The idea of introducing a furane ring instead the upper phenyl ring is no innovation and was done during this thesis. But we expected the decreased biological activity could be arised from the changed angles and conformations introduced by a five-membered ring instead a six-membered ring. Additionally, the furane was substituted with the amine moiety in the 2-position. Now it would be interesting to

synthesize a furane substituted with an amine in 3-position (way C) starting from 5-bromo-3-furancarboxaldehyde and the corresponding amine performing the reductive amination. Finally, it would be interesting and very important to optimize the Buchwald-Hartwig amination or to apply a totally other type of reaction to synthesize the biaryls directly coupled to water solubility mediating amines (way D). One new idea is to couple aryl O-sulfamates with amines using a nickel catalyst, which was published by GARG *et al.* (Scheme 49).[148]



Scheme 49: Nickel-catalyzed amination of aryl sulfamates.

They applied catalytic amounts of [Ni(cod)$_2$], SIPr*HCl as *N*-heterocyclic carbene ligand, NaO*t*Bu as base and a great variety of amines, such as morpholine, piperidine, pyrrolidine and aliphatic amines and reached acceptable to excellent yields.

Besides the structural diversifications of the inhibitor compound we have to avoid the solubility issues for injection in mice. Because the organic solvent DMSO is no adequate solvent for medication of the inhibitor in mice it would be perfect to assure that the inhibitor is soluble in water or aqueous buffer systems. Therefore, in pharmaceutical chemistry a few possibilities are known to increase the polarity (Fig. 84).

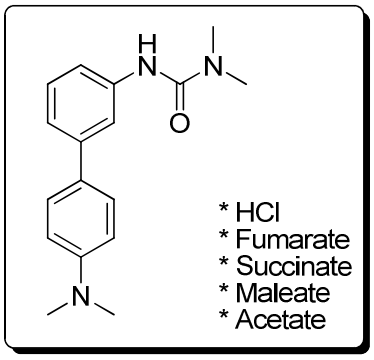


Fig. 84: Possible salt formations for inhibitor compound **126**.

By transformation of the synthesized inhibitor **126** in a hydrochloride, fumarate, succinate, maleate or acetate depending on the pKa-value of the compound it would be possible to increase the polarity and remove the solubility issues in water.

Concerning the biological screenings the next step will be the performance of glucose and insulin tolerance tests *in vivo* in mice. Additionally, the respiratory quotient of high-fat diet mice (insulin resistence is induced) shall be determined. The quotient of normal mice is 1. Diabetic mice exhibit a huge FA and glucose storage and the quotient decreases to 0.7. After injection of the inhibitor the release of FAs should be reduced, which should be accompanied with an increased usage of carbohydrates as energy source leading to an increase of the respiratory quotient indicating improved glucose tolerance and insulin sensitivity.

6. Experimental section

6.1. General aspects, materials and methods

6.1.1. Chemistry section

Reactions under inert atmosphere were carried out with standard Schlenk techniques. The solvents utilized in this thesis were distilled before use and stored under argon atmosphere. The syntheses which are sensitive against oxidation were accomplished under nitrogen or argon atmosphere and absolute and degassed solvents (when its necessary) were applied. Degassing of reaction mixtures or solvents was performed by subjecting the accordant vessel to vacuum and refilling with an inert gas. This procedure was repeated at least five times, depending on the solvent volume ("vacuum/gas cycles").
Alternatively, degassing is carried out by passing a stream of inert gas through the solvent using a balloon filled with inert gas which is placed on a canula plunged through a septum. The vessel is then placed in an ultrasonic bath for at least twenty minutes, depending on the solvent volume.
Molecular sieves were activated by heating at 200 °C in a heating mantle under high vacuum for 2 days and stored at rt under argon atmosphere.
Hydrogenation reactions had to be performed under special safety precautions. During the work-up the catalyst was filtrated through an inverse filter funnel under argon atmosphere and catalyst storage under wet conditions was necessary.

6.1.1.1. Solvents

The solvents listed below were used as absolute solvents in the reactions carried out in this thesis.

Acetonitrile: Acetonitrile was purchased from ACROS Organics in 99.9 % purity without any stabilizer and stored over 3 Å molecular sieves in a brown 1 L Schlenk bottle under argon atmosphere.

***tert.*-Butanol:** *Tert.*-butanol was purchased from Sigma Aldrich as anhydrous solvent with ≥ 99.5 % purity and stored under argon in a 1 L Schlenk flask under light exclusion.

1,2-Dichloroethane: 1,2-Dichloroethane was purchased from ACROS Organics as extra dry solvent (99.8 %, AcroSeal®) and directly used in the reactions.

Dichloromethane: Dichloromethane was first distilled over phosphorus pentoxide and then over calciumhydride under argon atmosphere and stored over 4 Å molecular sieves in a brown 1 L Schlenk bottle under argon atmosphere.

1,2-Dimethoxyethane: 1,2-Dimethoxyethane was purchased from Sigma Aldrich as absolute solvent ($H_2O \leq 0.005$ %) and directly used in the reactions.

***N,N*-Dimethylformamide:** *N,N*-Dimethylformamide was purchased from ACROS Organics as extra dry solvent (99.8 %, over 3 Å molecular sieves, AcroSeal®) and directly used in the reactions.

Dimethylsulfoxide: Dimethylsulfoxide was purchased from ACROS Organics and stored over 4 Å molecular sieve in a brown 1 L Schlenk bottle.

Ethanol: Ethanol was distilled over sodium and stored over 3 Å molecular sieves under argon atmosphere in a brown 1 L Schlenk bottle.

Ethylacetate: Ethylacetate was purchased from ACROS Organics as extra dry solvent (99.9 %, AcroSeal®, over molecular sieves) and directly used in the reactions.

Methanol: Methanol was dried over magnesium turnings and iodine, distilled under argon atmosphere and stored over 3 Å molecular sieves in a brown 1 L Schlenk bottle under argon atmosphere.

Tetrachloromethane: Tetrachloromethane was purchased from Riedel de Haën (99.8 %) and directly used in the reaction.

Tetrahydrofuran: Tetrahydrofuran was dried at reflux temperature under argon atmosphere over sodium until benzophenone indicated dryness by a deep blue color. The dried THF was stored over 4 Å molecular sieves in a brown 1 L Schlenk bottle under argon atmosphere.
Toluene: Toluene was purchased from Sigma Aldrich (99.7 %), dried in an aluminium oxide column under inert conditions and filled in a brown 1 L Schlenk bottle over 4 Å molecular sieves under argon atmosphere.

For reactions which could be performed in air, for work-ups and purification steps different solvents listed below were applied.

Cyclohexane, dichloromethane, ethylacetate and methanol were purchased from Fisher Scientific as analytical grade (99.99 %) and directly used in the reactions.

Diethylether and tetrahydrofuran were distilled and stored over KOH pellets in a brown 1 L bottle.

Ethanol: Ethanol was purchased from Merck (1 % ethylmethylketone as stabilizer) and directly used in the reactions.

Toluene: Toluene was purchased from Sigma Aldrich (99.7 %) and directly used in the reactions.

6.1.1.2. Reagents

All used chemicals and reagents were purchased from the companies Aldrich, Sigma Aldrich, Fluka, Merck, ABCR, Alfa Aesar, Fisher Scientific and ACROS Organics. They were used without further purification, unless otherwise stated.

***n*-Butyllithium:** *n*-Butyllithium was purchased from ACROS Organics as a 2.5 M solution in hexane. Before starting a reaction with *n*-BuLi the exact concentration of the solution was determined by a titration method from W.G. KOFRON and L.M. BACLAWSK.[149] A 100 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged with 250.0 mg diphenylacetic acid and 10 mL absolute THF. To this solution *n*-BuLi was added dropwise by using a syringe until the color of the solution turned from colorless to yellow. The added

amount of *n*-BuLi corresponds to the weighed amount of diphenylacetic acid. This procedure was repeated twice and the average was used to calculate the exact concentration of *n*-BuLi.

Thionylchloride: Before using thionylchloride in a reaction it was freshly distilled under inert conditions and stored in the fridge under argon atmosphere and light exclusion.

***N*-Bromosuccinimide:** *N*-Bromosuccinimide was purchased from Merck and recrystallized from water before using it in a reaction (50 g in 400 mL water).

S-Phos-ligand: The S-Phos ligand was synthesized by a former PhD student of our group, Matthias Mentel (Leipzig, 2007). A procedure published by BUCHWALD *et al*.[150] was used.

1-(Methylsulfonyl)-piperazine: The piperazine was synthesized by a former bachelor student of our group, Jens Schmidt (Leipzig, 2007), applying a procedure published by LEE.[151]

6.1.1.3. Analytical methods

Nuclear magnetic resonance spectroscopy

The described and attached nuclear resonance spectra were recorded with the following equipment:

• Bruker AVANCE III: 300.36 MHz-1H-NMR, 75.5 MHz-13C-NMR

Chemical shifts δ are referenced to residual protonated solvent signals as internal standard. Signal multiplicities *J* are abbreviated as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quadruplet), sext (sextet) and m (multiplet). Additionally, quarternary carbon atoms are demonstrated as $\mathbf{C}_q$, arylic carbon atoms as $\mathbf{C}H_{Ar}$ and aromatic protons as Ar-H. For differentiation of the carbon atoms APT spectra were recorded if necessary.

Gas chromatography

Analytical gas chromatography was performed on two different machines.

- **Hewlett Packard GC-system "HP 6890 series"** with a HP-5MS column (30 m x 250 µm x 0.25 µm); injection occured by an autosampler "7683B injector" used in split mode; carrier gas: helium 5.0; EI ionisation source with a potential of E = 70 eV; mass selective detector

Temperature programs:

HS_50_S2/ NM_50_S2: 50 °C 1 min, ramp 40 °C/min linear to 300 °C, 5 min
HS_100_L/ NM_100_L: 100 °C 1 min, ramp 40 °C/min linear to 300 °C, 15 min

- **Agilent Technologies 5975C inert MSD with Triple Axis Detector** with a HP-5MS column (30 m x 250 µm x 0.25 µm); injection occured by an autosampler "7683B injector" used in split mode; carrier gas: helium 5.0; EI ionisation source with a potential of E = 70 eV; mass selective detector

Temperature programs:

NM-50-S2/ NM_50_S2: 50 °C 1 min, ramp 40 °C/min linear to 300 °C, 5 min
NM-100-L/ NM_100_L: 100 °C 1 min, ramp 40 °C/min linear to 300 °C, 15 min

Infrared spectroscopy

IR spectra were recorded on a **Bruker Tensor 37** with ATR analyzer with integrated ATR support. The background "air" was automatically subtracted from the recorded spectra of the products.

Mass spectroscopy

Electron impact (EI, 70 eV) HRMS spectra were recorded with a **Waters GCT Premier** equipped with direct insertion (DI) and GC (HP GC7890A).

Thin layer chromatography

Analytical thin layer chromatography was performed using TLC-plates from Merck (TLC aluminium foil, silica gel 60 F_{254}). Generally, the spots were visualized using a UV lamp (λ = 254, 366 nm) or by treatment with different reagents (listed below) followed by heating.

- **CAM-solution:** 2.0 g cer(IV)-sulfate, 50.0 g ammonium molybdate and 50 mL conc. H_2SO_4 in 400 mL water
- **Ninhydrin:** 250.0 mg ninhydrin, 5 mL pyridine and 95 mL MeOH
- **Potassium permanganate:** 3.0 g potassium permanganate, 20.0 g K_2CO_3, 300 mL of a 5 % aqueous NaOH solution

The used solvent mixtures and R_f -values are stated in the experimental procedures.

Column chromatography

Preparative column chromatography was performed using silica gel 60 from ACROS Organics (35-70 µm particle size). The mass of silica gel used was generally 30-100 x (w/w) the amount of dry crude product, depending on the separation problem. Appropriatly sized columns and solvent mixtures were used and the exact data are given in the experimental procedures.

Determination of the melting point

Melting points are uncorrected and were determined with the apparatus “Mel-Temp®“ from **Electrothermal** with an integrated microscopical support. The temperature was measured with a mercury-in-glass thermometer.

6.1.2. Biology section

TG hydrolase assays

For the determination of TG hydrolase activity cell lysates or tissue lysates are incubated with a radiolabeled triolein substrate in the presence or in the absence of inhibitors. Tissues/Cells are homogenized on ice in lysis buffer (0.25 M sucrose, 1 mM EDTA, 1 mM dithiothreitol, 20 µg/mL leupetine, 2 µg/mL antipain, 1 µg/mL pepstatin, pH 7.0) using an ultra turax (IKA, Janke & Kunkel, Germany). The TG substrate is prepared by emulsifying 330 µM triolein (40,000 cpm/nmol) (GE Healthcare) and 45 µM phosphatidylcholine/phosphatidylinositol (3/1) (Sigma) in 100 mM potassium phosphate buffer (pH 7.0) by sonication (Virsonic 475, Virtis) and is adjusted to 5% (w/v) fatty acid free bovine serum albumine (BSA, Sigma). For determination of tissue TG hydrolase activity the final triolein concentration is 1.67 mM (8,000 cpm of [9,10-3H]triolein/nmol). 100 µL cell lysate is incubated with 100 µL substrate in a water bath for one hour at 37 °C. After incubation, the reaction is terminated by adding 3.25 mL of methanol/chloroform/heptane (10/9/7) and 1 mL of 0.1 M potassium carbonate, 0.1 M boric acid (pH 10.5). After centrifugation (800 g, 15 min), the radioactivity in 1 mL of the upper phase is determined by liquid scintillation counting.[26]

Lipolysis in fat pads and adipocyte cell lines

Tissue pieces of gonatal fat (~20 mg) or cultured differentiated adipocytes (3T3-L1, SGBS) are preincubated in DMEM (GIBCO) containing 2 % (w/v) fatty acid-free BSA (Sigma) either in the presence or in the absence of inhibitors at 37 °C for 1 h. Thereafter, fat pads are transferred into an identical, fresh medium and lipolysis is activated by the addition of isoproterenol or forskolin (10 µM). After 1 h at 37 °C, aliquots of the medium are collected and analyzed for FFA and glycerol content using commercial kits (Wako Chemicals, Neuss, Germany; Sigma).[26]

Blood and plasma parameters

Blood samples are collected by retro-orbital puncture from isoflurane anesthetized animals in the fed and fasted state. Plasma levels of glycerol, TG, FFA, total cholesterol, and high density lipoprotein-cholesterol are determined using commercial kits (Thermo Electron,

Thebarton, Australia; Wako Chemicals, Neuss, Germany; Sigma, St. Louis, MO; and Roche Diagnostics, Vienna, Austria). Plasma glucose concentrations are determined using a commercial kit from Merck (Darmstadt, Germany). For glucose and insulin tolerance tests, blood glucose is monitored using blood glucose strips and the Accu-Check glucometer (Roche Diagnostics, Vienna, Austria). Plasma insulin is measured using commercial ELISA kits from Crystal Chem (Downers Grove, IL).[26]

Glucose and insulin tolerance tests

Prior to glucose tolerance, mice are fasted for 6 h and then injected i.p. with 3 g glucose per kg of body weight. Glucose levels are monitored before and 15, 30, 60, and 120 min after injection. For insulin sensitivity, mice are fasted for 4 h and injected i.p. with human insulin, resulting in a final concentration of 1 U/kg of body weight. Blood is collected before injection and 15, 30, 60, 120, and 180 min after injection and glucose levels are determined as described above.[26]

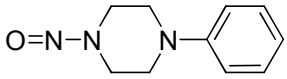
Animals

Mice are maintained on a regular light-dark cycle (14 h light, 10 h dark) and kept on a standard laboratory chow diet (4.5 % w/w fat; Sniff, Germany) under SPF conditions. They are set on a high-fat diet (30 % w/w fat; Sniff, Germany) to induce insulin resistence. ATGL-deficient mice are generated by targeted homologous recombination as described and backcrossed at least 5 times to the C57BL/6J background. Experiments are authorized by the Austrian ethics committee, and are in accordance with the council of Europe Convention (ETS 123).[26]

6.2. Experimental procedures and analytical data for lead structure 1 optimization

6.2.1. Hydrazone synthesis I (building block A)

1-Nitroso-4-phenylpiperazin (2)

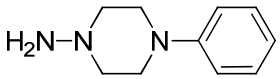


A 100 mL Schlenk tube was charged with 1.00 g (940 µL, 6.17 mmol, 1.00 eq) 1-phenyl piperazine **(1)**, 50 mL THF and 1.15 mL (9.57 mmol, 1.55 eq) *tert*. butylnitrite. The mixture was refluxed over night. GC-MS analysis indicated full conversion of the starting material. The orange solution was transferred to a one-neck round bottom flask and concentrated in vacuum at a temperature of 30 °C. The crude product was used in the next reaction without further purification.

$C_{10}H_{13}ON_3$ [191.0]

yield:	1.32 g (> 99 %), brown solid
R_f (MeOH)	0.76
GC-MS (HS_50_S2):	t_R = 6.696 min (m/z = 191.1, 99 % M^+, BP: 56.1).

4-Phenylpiperazin-1-amine (3)



A 250 mL three-neck round bottom flask with dropping funnel and reflux condenser was dried under vacuum, filled with nitrogen and charged with 516 mg (13.6 mmol, 2.20 eq) $LiAlH_4$ and 25 mL absolute THF. The grey suspension was heated to reflux and a solution of 1.18 g (6.18 mmol, 1.00 eq) 1-nitroso-4-phenylpiperazine **(2)** in 10 mL absolute THF was added dropwise to the boiling suspension. After complete addition the suspension was

refluxed for further 3 h. GC-MS analysis showed full conversion of the starting material. The suspension was hydrolyzed according to the n,n,3n-method (1 mL water, 1 mL 15 % aqueous NaOH and 3 mL water) upon which the color turned to yellow. The mixture was filtrated through a fritted funnel, the filter cake was washed with 10 mL THF and the filtrate was concentrated under reduced pressure. Final purification by silica gel filtration (MeOH) yielded the pure product.

$C_{10}H_{15}N_3$ [177.0]

yield:	813.0 mg (74 %), light brown solid
R_f (MeOH/DCM 1:1)	0.55
^{1}H-NMR (300 MHz, MeOD):	δ (ppm) = 7.25-7.20 (m, 2H, Ar-H), 6.96 (d, ^3J = 7.8 Hz, 2H, Ar-H), 6.84 (t, ^3J = 7.2 Hz, 1H, Ar-H), 3.22 (bs, 4H, 2 CH_2), 2.82 (bs, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, MeOD):	δ (ppm) = 152.3 (**C**$_q$), 130.1 (2 **C**H$_{Ar}$), 121.2 (**C**H$_{Ar}$), 117.6 (2 **C**H$_{Ar}$), 59.2 (2 **C**H$_2$), 50.1 (2 **C**H$_2$).
M.p.:	36-38°C
GC-MS (HS_50_S2):	t_R = 6.333 min (m/z = 177.0, 99 % M^+, BP: 77.0).

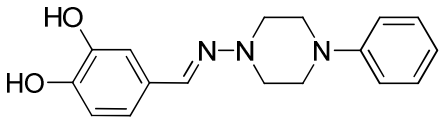
Synthesis of different hydrazones 5a-5ak starting with 4-Phenylpiperazin-1-amine (3)

Fig. 85: Picture of the apparatus used for hydrazone synthesis

General Procedure (GP-1):

A reaction block was placed on a hotplate stirrer as depicted in Fig. 85. A brown 10 mL reaction vessel was charged consecutively with 1.00 eq 4-phenylpiperazin-1-amine **(3)**, toluene (1.0 mL/50 mg amine), 1.00 eq aldehyde and a magnetic stirring bar. The vessel was crimped with a cap, placed in the preheated (100 °C) reaction block and stirred vigorously at 100 °C. GC-MS analysis indicated full conversion of the starting material. After cooling to rt the cap was removed, the reaction mixture was transferred into a one-neck round bottom flask and concentrated under reduced pressure to yield the product.

(*E*)-4-((4-Phenylpiperazin-1-ylimino)methyl)benzene-1,2-diol (5a)



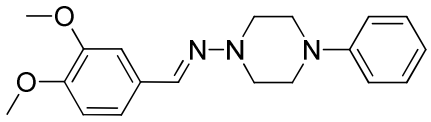
according to GP-1:

50.0 mg (282 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 39.0 mg (282 µmol, 1.00 eq) 3,4- dihydroxybenzaldehyde **(4a)**, 1.0 mL toluene, stirring for 2.5 h.

$C_{17}H_{19}O_2N_3$ [297.0]

yield:	77.0 mg (92 %), brown solid
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 7.58 (s, 1H, CH=N), 7.26-7.21 (m, 2H, Ar-H), 7.10 (d, ^4J = 1.8 Hz, 1H, Ar-H), 7.00 (t, ^3J = 8.1 Hz, 2H, Ar-H), 6.83-6.78 (m, 2H, Ar-H), 6.72 (d, ^3J = 8.1 Hz, 1H, Ar-H), 3.30-3.28 (m, 4H, 2 CH_2), 3.17-3.14 (m, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 150.6 (**C**$_q$), 146.0 (**C**$_q$-OH), 145.3 (**C**$_q$-OH), 137.4 (**C**H=N), 128.9 (2 **C**H$_{Ar}$), 127.7 (**C**$_q$), 119.1 (**C**H$_{Ar}$), 118.6 (**C**H$_{Ar}$), 115.8 (2 **C**H$_{Ar}$), 115.3 (**C**H$_{Ar}$), 112.1 (**C**H$_{Ar}$), 51.0 (2 **C**H$_2$), 47.8 (2 **C**H$_2$).
M.p.:	180 °C

(*E*)-*N*-(3,4-Dimethoxybenzylidene)-4-phenylpiperazin-1-amine (5b)



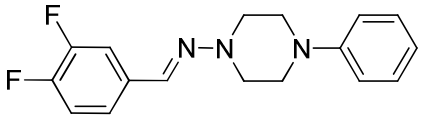
according to GP-1:

10.0 mg (56.0 µmol, 1.20 eq) 4-phenylpiperazin-1-amine **(3)**, 7.80 mg (47.0 µmol, 1.00 eq) 3,4- dimethoxybenzaldehyde **(4b)**, 0.5 mL toluene, stirring for 4 h.

$C_{19}H_{23}O_2N_3$ [297.0]

yield:	15.3 mg (> 99 %), yellow-brown solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.62 (bs, 1H, CH=N), 7.36-7.27 (m, 3H, Ar-H), 7.05-6.98 (m, 3H, Ar-H), 6.93-6.84 (m, 2H, Ar-H), 3.94 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.40-3.38 (m, 4H, 2 CH_2), 3.34-3.32 (m, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 150.9 (2 **C**$_q$-OCH_3), 149.6 (**C**$_q$), 149.3 (**C**$_q$), 137.3 (**C**H=N), 129.2 (2 **C**H_{Ar}), 120.4 (**C**H_{Ar}), 120.2 (**C**H_{Ar}), 116.5 (2 **C**H_{Ar}), 110.7 (**C**H_{Ar}), 107.5 (**C**H_{Ar}), 55.9 (O**C**H_3), 55.8 (O**C**H_3), 51.4 (2 **C**H_2), 48.9 (2 **C**H_2).
M.p.:	153-154 °C
GC-MS (HS_50_S2):	t_R = 11.05 min (m/z = 325.1, 97 % M^+, BP: 56.1).

(*E*)-*N*-(3,4-Difluorobenzylidene)-4-phenylpiperazin-1-amine (5c)



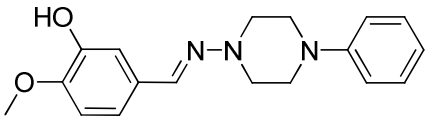
according to GP-1:

250 mg (1.41 mmol, 2.00 eq) 4-phenylpiperazin-1-amine **(3)**, 100 mg (78.0 µL, 706 µmol, 1.00 eq) 3,4- difluorobenzaldehyde **(4c)**, 3.0 mL toluene, stirring over night.

$C_{17}H_{17}N_3F_2$ [301.0]

yield:	189.8 g (90 %), yellow solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.52-7.43 (m, 2H, CH=N, Ar-H), 7.31-7.24 (m, 3H, Ar-H), 7.16-7.07 (m, 1H, Ar-H), 6.98 (d, ^3J = 7.8 Hz, 2H, Ar-H), 6.90 (t, ^3J = 7.2 Hz, 1H, Ar-H), 3.37-3.36-3.34 (m, 8H, 4 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 152.4, 152.2 ($^3J_{C-F}$ = 16.5 Hz, **C**$_q$), 151.8, 149.1 ($^1J_{C-F}$ = 203.2 Hz, **C**$_q$-F), 150.8, 148.7 ($^1J_{C-F}$ = 161.2 Hz, **C**$_q$-F), 133.6 (**C**H=N), 133.5 (**C**$_q$), 129.2 (2 **C**H$_{Ar}$), 122.5, 122.4, 122.4, 122.3 ($^3J_{C-F}$ = 6.2 Hz, $^4J_{C-F}$ = 3.2 Hz, **C**H$_{Ar}$), 120.4 (**C**H$_{Ar}$), 117.3, 117.1 ($^2J_{C-F}$ = 17.6 Hz, **C**H$_{Ar}$), 116.6 (2 **C**H$_{Ar}$), 114.2, 114.0 ($^2J_{C-F}$ = 18.2 Hz, **C**H$_{Ar}$), 51.0 (2 **C**H$_2$), 48.9 (2 **C**H$_2$).
M.p.:	152-154 °C
GC-MS (HS_50_S2):	t_R = 8.59 min (m/z = 301.0, 98 % M^+, BP: 160.3).
HRMS (EI^+):	*m/z*: calcd for $C_{17}H_{17}N_3F_2$ $[M]^+$: 301.1391; found 301.1395.

(*E*)-2-Methoxy-5-((4-phenylpiperazin-1-ylimino)methyl)phenol (5d)



according to GP-1:

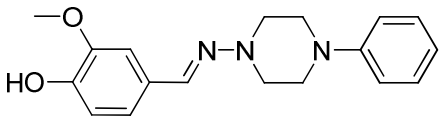
10.0 mg (56.0 µmol, 1.10 eq) 4-phenylpiperazin-1-amine **(3)**, 7.80 mg (51 µmol, 1.00 eq) 3-hydroxyanisaldehyde **(4d)**, 0.5 mL toluene, stirring for 4.5 h.

$C_{18}H_{21}O_2N_3$ [311.0]

yield:	16.0 mg (> 99 %), yellow solid
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 9.06 (s, 1H, OH), 7.62 (s, 1H, CH=N), 7.26-7.21 (m, 2H, Ar-H), 7.12 (d, ^4J = 1.5 Hz, 1H, Ar-H),

	7.02-6.79 (m, 5H, Ar-H), 3.77 (s, 3H, OCH_3), 3.31-3.29 (m, 4H, 2 CH_2), 3.20-3.18 (m, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 150.6 (**C**$_q$), 148.0 (**C**$_q$-OCH_3), 146.5 (**C**$_q$-OH), 136.7 (**C**H=N), 129.2 (**C**$_q$), 128.9 (2 **C**H_{Ar}), 119.1 (**C**H_{Ar}), 118.3 (**C**H_{Ar}), 115.8 (2 **C**H_{Ar}), 111.8 (**C**H_{Ar}), 111.7 (**C**H_{Ar}) 55.5 (O**C**H_3), 50.9 (2 **C**H_2), 47.8 (2 **C**H_2).
M.p.:	180 °C (decomposition)

(*E*)-2-Methoxy-4-((4-phenylpiperazin-1-ylimino)methyl)phenol (5e)



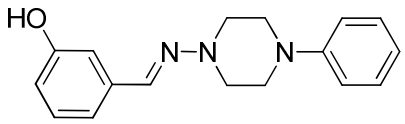
according to GP-1:

44.0 mg (249 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 31.3 mg (205 µmol, 1.00 eq) vanillin **(4e)**, 1.0 mL toluene, stirring over night, recrystallization from 2.5 mL toluene.

$C_{18}H_{21}O_2N_3$ [311.0]

yield:	48.0 mg (68 %), brown oil
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 9.18 (s, 1H, OH), 7.66 (s, 1H, CH=N), 7.26-7.16 (m, 3H, Ar-H), 7.02-6.97 (m, 3H, Ar-H), 6.83-6.75 (m, 2H, Ar-H), 3.78 (s, 3H, OCH_3), 3.31-3.19 (m, 8H, 4 CH_2).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 150.6 (**C**$_q$), 147.7 (**C**$_q$-OCH_3), 147.0 (**C**$_q$-OH), 137.2 (**C**H=N), 128.9 (2 **C**H_{Ar}), 128.1 (**C**$_q$), 127.7 (**C**H_{Ar}), 119.9 (**C**H_{Ar}), 115.8 (2 **C**H_{Ar}), 115.3 (**C**H_{Ar}), 108.6 (**C**H_{Ar}), 55.4 (O**C**H_3), 51.0 (2 **C**H_2), 47.8 (2 **C**H_2)

(*E*)-3-((4-Phenylpiperazin-1-ylimino)methyl)phenol (5f)



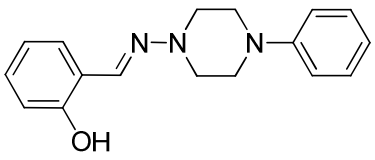
according to GP-1:

40.0 mg (226 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 27.6 mg (226 µmol, 1.00 eq) 3-hydroxybenzaldehyde **(4f)**, 1.0 mL toluene, stirring over night.

$C_{17}H_{19}ON_3$ [281.0]

yield:	32.0 mg (50 %), yellow solid
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 9.41 (s, 1H, OH), 7.64 (s, 1H, CH=N), 7.27-7.21 (m, 2H, Ar-H), 7.15 (t, ^3J = 7.8 Hz, 1H, Ar-H), 7.06-6.99 (m, 4H, Ar-H), 6.81 (t, ^3J = 7.2 Hz, 1H, Ar-H), 6.68 (dd, ^4J = 1.5 Hz, ^3J = 7.8 Hz, 1H, Ar-H), 3.32-3.30 (m, 4H, 2 CH_2), 3.24-3.23 (m, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 157.4 (**C**$_q$-OH), 150.6 (**C**$_q$), 137.4 (**C**$_q$), 136.1 (**C**H=N), 129.3 (**C**H$_{Ar}$), 128.9 (2 **C**H$_{Ar}$), 119.1 (**C**H$_{Ar}$), 117.3 (**C**H$_{Ar}$), 115.8 (2 **C**H$_{Ar}$), 115.2 (**C**H$_{Ar}$), 111.7 (**C**H$_{Ar}$) 50.6 (2 **C**H$_2$), 47.7 (2 **C**H$_2$).
M.p.:	190°C (decomposition)
GC-MS (HS_50_S2):	t_R = 10.61 min (m/z = 281.1, 98 % M^+, BP: 56.0).

(*E*)-2-((4-Phenylpiperazin-1-ylimino)methyl)phenol (5g)



according to GP-1:

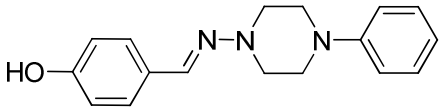
40.0 mg (226 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 27.6 mg (24.0 µL, 226 µmol, 1.00 eq) 3-hydroxybenzaldehyde **(4g)**, 1.0 mL toluene, stirring over night. Addition of 14.0

mg (79.0 µmol, 0.35 eq) 4-phenylpiperazin-1-amine **(3)** after 15 h to reach full conversion of the starting material after further 6 h stirring.

$C_{17}H_{19}ON_3$ [281.0]

yield:	84.0 mg (99 %), yellow solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 11.54 (s, 1H, OH), 7.80 (s, 1H, CH=N), 7.35-7.16 (m, 4H, Ar-H), 7.06-6.88 (m, 5H, Ar-H), 3.41-3.38 (m, 8H, 4 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 157.7 (**C**$_q$-OH), 141.6 (**C**H=N), 129.8 (**C**H$_{Ar}$), 129.7 (2 **C**H$_{Ar}$), 129.2 (2 **C**H$_{Ar}$), 129.0 (**C**$_q$), 120.6 (**C**$_q$), 119.1 (**C**H$_{Ar}$), 118.9 (**C**H$_{Ar}$), 116.7 (**C**H$_{Ar}$), 116.6 (**C**H$_{Ar}$) 51.3 (2 **C**H_2), 48.7 (2 **C**H_2).
M.p.:	138-142°C
GC-MS (HS_50_S2):	t_R = 9.90 min (m/z = 281.1, 99 % M^+, BP: 56.0).

(*E*)-4-((4-Phenylpiperazin-1-ylimino)methyl)phenol (5h)



according to GP-1:

40.0 mg (226 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 27.6 mg (226 µmol, 1.00 eq) 4-hydroxybenzaldehyde **(4h)**, 1.0 mL toluene, stirring over night.

$C_{17}H_{19}ON_3$ [281.0]

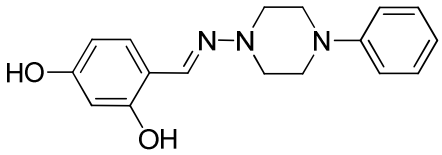
yield:	63.5 mg (> 99 %), beige solid
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 9.59 (s, 1H, OH), 7.66 (s, 1H, CH=N), 7.42 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.25-7.20 (m, 2H, Ar-H), 7.00 (d, ^3J = 8.1 Hz, 2H, Ar-H), 6.83-6.74 (m, 3H, Ar-H), 3.30-3.28 (m, 4H, 2 CH_2), 3.18-3.16 (m, 4H, 2 CH_2).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 157.6 (**C**$_q$-OH), 150.6 (**C**$_q$), 137.1 (**C**H=N), 128.9 (2 **C**H$_{Ar}$), 127.3 (2 **C**H$_{Ar}$), 127.2 (**C**$_q$), 119.1 (**C**H$_{Ar}$), 115.7 (2 **C**H$_{Ar}$), 115.3 (2 **C**H$_{Ar}$), 51.0 (2 **C**H$_2$), 47.8 (2 **C**H$_2$).

M.p.: 192°C (decomposition)

GC-MS (HS_50_S2): t_R = 10.59 min (m/z = 281.1, 98 % M^+, BP: 56.0).

(*E*)-4-(4-Phenylpiperazin-1-ylimino)methylbenzene-1,3-diol (5i)



according to GP-1:

30.0 mg (169 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 23.4 mg (169 µmol, 1.00 eq) 2,4-dihydroxybenzaldehyde **(4i)**, 1.0 mL toluene, stirring for 2 h.

$C_{17}H_{19}O_2N_3$ [297.0]

yield: 51.0 mg (> 99 %), brown solid

R_f (MeOH): 0.62

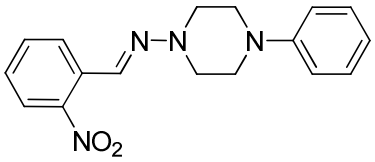
^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) = 11.60 (s, 1H, OH), 9.72 (bs, 1H, OH), 7.95 (s, 1H, CH=N), 7.26-7.16 (m, 3H, Ar-H), 7.00 (d, ^3J = 8.1 Hz, 2H, Ar-H), 6.81 (t, ^3J = 7.2 Hz, 1H, Ar-H), 6.32 (dd, ^3J = 8.1 Hz, ^4J = 2.1 Hz, 1H, Ar-H), 6.25 (d, ^4J = 2.1 Hz, 1H, Ar-H), 3.33-3.30 (m, 4H, 2 CH_2), 3.18-3.15 (m, 4H, 2 CH_2).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 159.0 (**C**$_q$-OH), 158.6 (**C**$_q$-OH), 150.5 (**C**$_q$), 142.3 (**C**H=N), 130.7 (**C**H$_{Ar}$), 128.9 (2 **C**H$_{Ar}$), 119.2 (**C**H$_{Ar}$), 115.8 (2 **C**H$_{Ar}$), 111.4 (**C**$_q$), 107.0 (**C**H$_{Ar}$), 102.4 (**C**H$_{Ar}$), 51.1 (2 **C**H$_2$), 47.5 (2 **C**H$_2$).

M.p.: 183-184 °C

GC-MS (HS_50_S2): t_R = 12.08 min (m/z = 297.1, 95 % M^+, BP: 56.0).

(*E*)-*N*-(2-nitrobenzylidene)-4-phenylpiperazin-1-amine (5j)



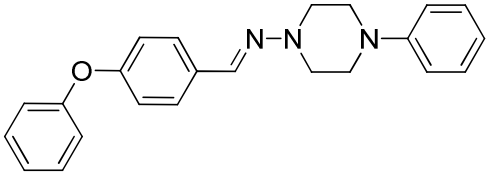
according to GP-1:

40.0 mg (226 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 26.2 mg (226 µmol, 1.00 eq) 2-nitrobenzaldehyde **(4j)**, 1.0 mL toluene, stirring over night. Addition of 3.40 mg (22.0 µmol, 0.10 eq) 2-nitrobenzaldehyde **(4j)** after 20 h to reach full conversion of the starting material after further 3 h stirring.

$C_{17}H_{18}O_2N_4$ [310.0]

yield:	60.0 mg (97 %), yellow-brown solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.15-8.13 (m, 1H, Ar-H), 8.10 (s, 1H, CH=N), 8.00 (d, ^3J = 8.1 Hz, 1H, Ar-H), 7.58 (t, ^3J = 7.8 Hz, 1H, Ar-H), 7.41-7.28 (m, 3H, Ar-H), 7.01 (d, ^3J = 7.8 Hz, 2H, Ar-H), 6.92 (t, ^3J = 7.2 Hz, 1H, Ar-H), 3.45-3.39 (m, 8H, 4 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 150.8 (**C**$_q$), 147.3 (**C**$_q$-NO_2), 133.0 (**C**H=N), 131.1 (**C**$_q$), 130.2 (**C**H$_{Ar}$), 129.2 (2 **C**H$_{Ar}$), 127.9 (**C**H$_{Ar}$), 127.5 (**C**H$_{Ar}$), 124.6 (**C**H$_{Ar}$), 120.4 (**C**H$_{Ar}$), 116.6 (2 **C**H$_{Ar}$), 50.8 (2 **C**H_2), 48.8 (2 **C**H_2).
M.p.:	103-106 °C
GC-MS (HS_50_S2):	t_R = 10.96 min (m/z = 310.1, 97 % M^+, BP: 56.0).

(*E*)-*N*-(4-Phenoxybenzylidene)-4-phenylpiperazin-1-amine (5k)



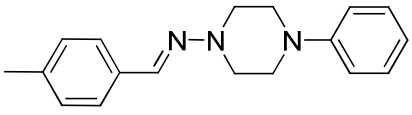
according to GP-1:

40.0 mg (226 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 44.7 mg (226 µmol, 1.00 eq) 4-phenoxybenzaldehyde **(4k)**, 1.0 mL toluene, stirring over night.

$C_{23}H_{23}ON_3$ [357.0]

yield:	76.0 mg (94 %), yellow-brown solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.66 (s, 1H, CH=N), 7.61 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.38-7.28 (m, 4H, Ar-H), 7.12 (t, ^3J = 7.2 Hz, 1H, Ar-H), 7.02 (m, 6H, Ar-H), 6.92 (t, ^3J = 7.2 Hz, 1H, Ar-H), 3.41-3.34 (m, 8H, 4 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 157.6 (**C**$_q$), 156.9 (**C**$_q$), 150.9 (**C**$_q$), 136.4 (**C**H=N), 131.2 (**C**$_q$), 129.8 (2 **C**H$_{Ar}$), 129.2 (2 **C**H$_{Ar}$), 127.7 (2 **C**H$_{Ar}$), 123.4 (2 **C**H$_{Ar}$), 120.3 (**C**H$_{Ar}$), 119.0 (2 **C**H$_{Ar}$), 118.8 (2 **C**H$_{Ar}$), 116.6 (**C**H$_{Ar}$), 51.3 (2 **C**H$_2$), 48.9 (2 **C**H$_2$).
M.p.:	161-164 °C
GC-MS (HS_100_L):	t_R = 15.47 min (m/z = 357.1, 96 % M^+, BP: 56.0).
HRMS (EI^+):	*m/z*: calcd for $C_{23}H_{23}ON_3$ $[M]^+$: 357.1841; found 357.1844.

(*E*)-*N*-(4-Methylbenzylidene)-4-phenylpiperazin-1-amine (5l)



according to GP-1:

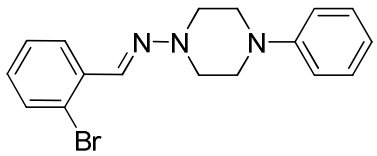
40.0 mg (226 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 27.0 mg (27.0 µL, 226 µmol, 1.00 eq) *p*-tolylbenzaldehyde **(4l)**, 1.0 mL toluene, stirring over night.

$C_{18}H_{21}N_3$ [279.0]

yield:	64.0 mg (99 %), light yellow solid

^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.66 (s, 1H, CH=N), 7.53 (d, ^{3}J = 8.1 Hz, 2H, Ar-H), 7.30 (dd, ^{3}J = 8.4 Hz, ^{3}J = 7.5 Hz, 2H, Ar-H), 7.17 (d, ^{3}J = 7.8 Hz, 2H, Ar-H), 7.00 (d, ^{3}J = 8.1 Hz, 2H, Ar-H), 6.91 (t, ^{3}J = 7.5 Hz, 1H, Ar-H), 3.41-3.34 (m, 8H, 4 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 150.9 (**C**$_q$), 138.4 (**C**-CH_3), 137.3 (**C**H=N), 133.2 (**C**$_q$), 129.3 (2 **C**H_{Ar}), 129.2 (2 **C**H_{Ar}), 126.2 (2 **C**H_{Ar}), 120.3 (**C**H_{Ar}), 116.6 (2 **C**H_{Ar}), 51.3 (2 **C**H_2), 48.9 (2 **C**H_2), 21.3 (**C**H_3).
M.p.:	184-186 °C
GC-MS (HS_50_S2):	t_R = 9.42 min (m/z = 279.1, >99 % M^+, BP: 56.0).

(*E*)-*N*-(2-Bromobenzylidene)-4-phenylpiperazin-1-amine (5m)



according to GP-1:

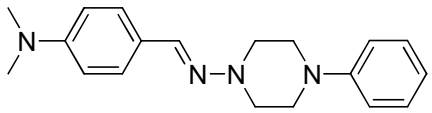
40.0 mg (226 µmol, 1.20 eq) 4-phenylpiperazin-1-amine **(3)**, 34.8 mg (22.0 µL, 118 µmol, 1.00 eq) 2-bromobenzaldehyde **(4m)**, 1.0 mL toluene, stirring over night.

$C_{17}H_{18}N_3Br$ [344.0]

yield:	69.0 mg (89 %), yellow-orange solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.95 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.5 Hz, 1H, Ar-H), 7.90 (s, 1H, CH=N), 7.53 (dd, ^{3}J = 8.1 Hz, ^{4}J = 0.9 Hz, 1H, Ar-H), 7.33-7.28 (m, 3H, Ar-H), 7.16-7.10 (m, 1H, Ar-H), 7.00 (d, ^{3}J = 7.8 Hz, 2H, Ar-H), 6.92 (t, ^{3}J = 7.5 Hz, 1H, Ar-H), 3.41 (s, 8H, 4 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 150.9 (**C**$_q$), 135.0 (**C**H=N), 134.8 (**C**$_q$), 132.8 (**C**H_{Ar}), 129.3 (**C**H_{Ar}), 129.2 (2 **C**H_{Ar}), 127.5 (**C**H_{Ar}),

	126.7 (**C**H_{Ar}), 123.2(**C**$_q$-Br), 120.3 (**C**H_{Ar}), 116.6 (2 **C**H_{Ar}), 51.0 (2 **C**H_2), 48.9 (2 **C**H_2).
M.p.:	88-90 °C
GC-MS (HS_100_L):	t_R = 9.04 min (m/z = 344.1, 99 % M^+, BP: 56.0).

(*E*)-*N*-(4-(dimethylamino)benzylidene)-4-phenylpiperazin-1-amine (5n)



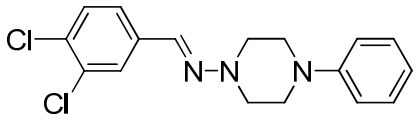
according to GP-1:

40.0 mg (226 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 34.0 mg (226 µmol, 1.00 eq) 4-dimethylaminobenzaldehyde **(4n)**, 1.0 mL toluene, stirring over night. Addition of another 4.00 mg (23.0 µmol, 0.10 eq) 4-phenylpiperazin-1-amine **(3)** after 18 h to reach full conversion of the starting material after further 2 h stirring.

$C_{19}H_{24}N_4$ [308.0]

yield:	43.0 mg (61 %), light yellow solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.68 (bs, 1H, CH=N), 7.53 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.33-7.28 (m, 2H, Ar-H), 7.00 (d, ^3J = 8.1 Hz, 2H, Ar-H), 6.90 (t, ^3J = 7.2 Hz, 1H, Ar-H), 6.71 (d, ^3J = 8.7 Hz, 2H, Ar-H), 3.40-3.38 (m, 4H, 2 CH_2), 3.31-3.29 (m, 4H, 2 CH_2), 2.99 (s, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 151.0 (**C**$_q$-N), 150.8 (**C**$_q$), 139.5 (**C**H=N), 129.1 (2 **C**H_{Ar}), 127.6 (2 **C**H_{Ar}), 124.2 (**C**$_q$), 120.0 (**C**H_{Ar}), 116.4 (2 **C**H_{Ar}), 112.1 (2 **C**H_{Ar}), 51.8 (2 **C**H_2), 48.9 (2 **C**H_2), 40.4 (2 **C**H_3).
M.p.:	190 °C (decomposition)
GC-MS (HS_100_L):	t_R = 10.90 min (m/z = 308.2, 98 % M^+, BP: 56.0).

(*E*)-*N*-(3,4-Dichlorobenzylidene)-4-phenylpiperazin-1-amine (5o)



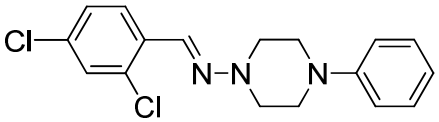
according to GP-1:

50.0 mg (282 µmol, 2.00 eq) 4-phenylpiperazin-1-amine **(3)**, 25.0 mg (141 µmol, 1.00 eq) 3,4-dichlorobenzaldehyde **(4o)**, 1.0 mL toluene, stirring over night. Addition of another 14.0 mg (80.0 µmol, 0.60 eq) 4-phenylpiperazin-1-amine **(3)** after 16 h to reach full conversion of the starting material after further stirring over a second night.

$C_{17}H_{17}N_3Cl_2$ [333.9]

yield:	67.0 mg (90 %), light yellow solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.73 (s, 1H, CH=N), 7.47 (s, 1H, Ar-H), 7.42 (s, 2H, Ar-H), 7.34-7.28 (m, 2H, Ar-H), 7.00 (d, ^3J = 8.1 Hz, 2H, Ar-H), 6.95-6.90 (m, 1H, Ar-H), 3.38 (s, 8H, 4 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 150.7 (**C**$_q$), 136.3 (**C**H=N), 133.0 (**C**$_q$-Cl), 132.8 (**C**$_q$), 131.6 (**C**$_q$-Cl), 130.4 (**C**H_{Ar}), 129.2 (2 **C**H_{Ar}), 127.5 (**C**H_{Ar}), 125.2 (**C**H_{Ar}), 120.5 (**C**H_{Ar}), 116.7 (2 **C**H_{Ar}), 50.8 (2 **C**H_2), 49.0 (2 **C**H_2).
M.p.:	176-178 °C
GC-MS (HS_50_S2):	t_R = 11.68 min (m/z = 334.1, 97 % M^+, BP: 161.1).

(*E*)-*N*-(2,4-Dichlorobenzylidene)-4-phenylpiperazin-1-amine (5p)



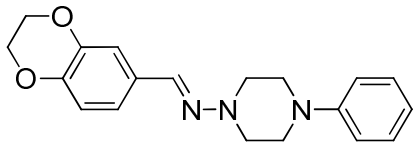
according to GP-1:

50.0 mg (282 µmol, 2.00 eq) 4-phenylpiperazin-1-amine **(3)**, 25.0 mg (141 µmol, 1.00 eq) 2,4-dichlorobenzaldehyde **(4p)**, 1.0 mL toluene, stirring over night. Addition of another 14.0 mg (80.0 µmol, 0.60 eq) 4-phenylpiperazin-1-amine **(3)** after 16 h to reach full conversion of the starting material after further stirring over a second night.

$C_{17}H_{17}N_3Cl_2$ [333.9]

yield:	71.0 mg (95 %), yellow solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.85 (d, ^3J = 8.7 Hz, 1H, Ar-H), 7.77 (s, 1H, CH=N), 7.29 (d, ^4J = 2.1 Hz, 1H, Ar-H), 7.25-7.13 (m, 3H, Ar-H), 6.94-6.91 (m, 2H, Ar-H), 6.85 (t, ^4J = 7.2 Hz, 1H, Ar-H), 3.33 (s, 8H, 4 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 150.8 (**C**$_q$), 133.9 (**C**$_q$-Cl), 133.1 (**C**$_q$), 132.1 (**C**$_q$-Cl), 130.9 (**C**H=N), 129.3 (**C**H$_{Ar}$), 129.2 (2 **C**H$_{Ar}$), 127.3 (**C**H$_{Ar}$), 127.1 (**C**H$_{Ar}$), 120.4 (**C**H$_{Ar}$), 116.7 (2 **C**H$_{Ar}$), 50.9 (2 **C**H$_2$), 48.9 (2 **C**H$_2$).
M.p.:	113-115 °C
GC-MS (HS_50_S2):	t_R = 11.89 min (m/z = 334.1, 98 % M^+, BP: 161.1).

(*E*)-*N*-((2,3-Dihydrobenzol[b][1,4]dioxin-6-yl)methylen)-4-phenylpiperazin-1-amine (5q)



according to GP-1:

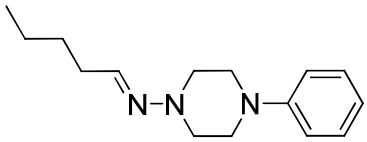
50.0 mg (282 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 46.0 mg (282 µmol, 1.00 eq) 1,4-benzodioxan-6-carboxaldehyde **(4q)**, 1.0 mL toluene, stirring over night.

$C_{19}H_{21}O_2N_3$ [323.0]

yield:	87.0 mg (95 %), light brown solid

^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 7.63 (s, 1H, CH=N), 7.26-7.21 (m, 2H, Ar-H), 7.09-7.06 (m, 2H, Ar-H), 7.01-6.98 (m, 2H, Ar-H), 6.86-6.79 (m, 2H, Ar-H), 4.24 (s, 4H, 2 CH_2), 3.32-3.29 (m, 4H, 2 CH_2), 3.21-3.17 (s, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 150.6 (**C**$_q$-O), 143.5 (**C**$_q$), 143.3 (**C**$_q$-O), 135.9 (**C**H=N), 129.7 (**C**$_q$), 128.8 (2 **C**H$_{Ar}$), 119.1 (**C**H$_{Ar}$), 117.0 (**C**H$_{Ar}$), 115.8 (2 **C**H$_{Ar}$), 114.0 (**C**H$_{Ar}$), 64.0 (2 **C**H$_2$), 50.8 (2 **C**H$_2$), 47.7 (2 **C**H$_2$).
M.p.:	186-187 °C
GC-MS (HS_100_L):	t_R = 11.91 min (m/z = 323.1, 97 % M^+, BP: 160.1).
HRMS (EI$^+$):	*m/z*: calcd for $C_{19}H_{21}O_2N_3$ $[M]^+$: 323.1634; found 323.1644.

(*E*)-*N*-Pentyliden-4-phenylpiperazin-1-amine (5r)



according to GP-1:

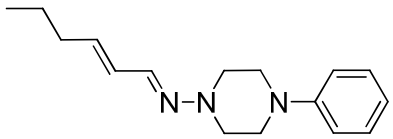
50.0 mg (282 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 24.3 mg (30.0 µL, 282 µmol, 1.00 eq) valeraldehyde **(4r)**, 1.0 mL toluene, stirring over night.

$C_{15}H_{23}N_3$ [245.0]

yield:	65.0 mg (94 %), orange oil
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.31-7.25 (m, 2H, Ar-H), 7.05 (t, ^3J = 5.4 Hz, 1H, CH=N), 6.96 (d, ^3J = 7.8 Hz, 2H, Ar-H), 6.88 (t, ^3J = 7.2 Hz, 1H, Ar-H), 3.34 (t, ^3J = 5.1 Hz, 4H, 2 CH_2), 3.12 (t, ^3J = 5.1 Hz, 4H, 2 CH_2), 2.28 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.55-1.32 (m, 4H, 2 CH_2), 0.93 (t, ^3J = 7.2 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 150.9 (**C**H=N), 143.5 (**C**$_q$), 129.1 (2 **C**H$_{Ar}$), 120.1 (**C**H$_{Ar}$), 116.4 (2 **C**H$_{Ar}$), 51.9 (2 **C**H$_2$), 48.8 (2 **C**H$_2$), 32.8 (**C**H$_2$), 29.5 (**C**H$_2$), 22.3 (**C**H$_2$), 13.9 (**C**H$_3$).
GC-MS (HS_50_S2):	t_R = 7.54 min (m/z = 245.2, 99 % M^+, BP: 161.1).
HRMS (EI$^+$):	*m/z*: calcd for $C_{15}H_{23}N_3$ $[M]^+$: 245.1892; found 245.1885.

(*E*)-*N*-((*E*)-Hex-2-enyliden)-4-phenylpiperazin-1-amine (5s)



according to GP-1:

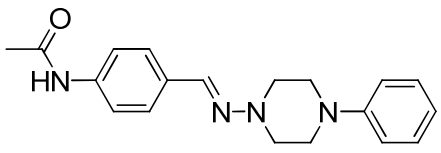
51.1 mg (289 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 28.3 mg (30.0 µL, 289 µmol, 1.00 eq) *trans*-2-hexen-1-al **(4s)**, 3.0 mL toluene, stirring for 3 h.

$C_{16}H_{23}N_3$ [257.0]

yield:	74.3 mg (> 99 %), brown solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.38 (d, ^3J = 8.7 Hz, 1H, CH=N), 7.31-7.27 (m, 2H, Ar-H), 6.98 (d, ^3J = 7.8 Hz, 2H, Ar-H), 6.89 (t, ^3J = 7.2 Hz, 1H, Ar-H), 6.28-6.20 (m, 1H, CH), 5.99-5.89 (m, 1H, CH), 3.36-3.33 (m, 4H, 2 CH_2), 3.22-3.19 (m, 4H, 2 CH_2), 2.20-2.12 (m, 2H, CH_2), 1.47 (sext, ^3J = 7.2 Hz, ^3J = 7.5 Hz, 2H, CH_2), 0.93 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 150.9 (**C**$_q$), 140.6 (**C**H), 138.4 (**C**H=N), 129.1 (2 **C**H$_{Ar}$), 128.7 (**C**H), 120.1 (**C**H$_{Ar}$), 116.5 (2 **C**H$_{Ar}$), 51.3 (2 **C**H$_2$), 48.8 (2 **C**H$_2$), 34.7 (**C**H$_2$), 22.1 (**C**H$_2$), 13.6 (**C**H$_3$).
M.p.:	48 °C
GC-MS (HS_50_S2):	t_R = 8.11 min (m/z = 257.1, 97 % M^+, BP: 161.1).

HRMS (EI^+): *m/z*: calcd for $C_{16}H_{23}N_3$ $[M]^+$: 257.1892; found 257.1898.

(*E*)-*N*-(4-((4-Phenylpiperazin-1-ylimino)methyl)phenyl)acetamide (5t)



according to GP-1:

30.0 mg (169 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 27.5 mg (169 µmol, 1.00 eq) 4-acetamidobenzaldehyde **(4t)**, 1.0 mL toluene, stirring over night.

$C_{19}H_{22}ON_4$ [322.0]

yield: 54.0 mg (96 %), yellow solid

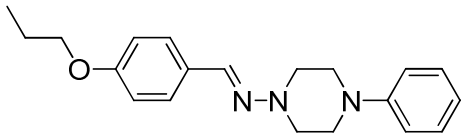
^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) = 10.00 (s, 1H, NH), 7.68 (s, 1H, CH=N), 7.61-7.50 (m, 4H, Ar-H), 7.26-7.21 (m, 2H, Ar-H), 7.00 (d, ^3J = 8.1 Hz, 2H, Ar-H), 6.81 (t, ^3J = 7.2 Hz, 1H, Ar-H), 3.32-3.30 (m, 4H, 2 CH_2), 3.23-3.21 (m, 4H, 2 CH_2), 2.05 (s, 3H, CH_3).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 168.1 (**C**=O), 150.6 (**C**$_q$), 139.1 (**C**$_q$-NH), 136.0 (**C**H=N), 130.9 (**C**$_q$), 128.8 (2 **C**H$_{Ar}$), 126.2 (2 **C**H$_{Ar}$), 119.1 (**C**H$_{Ar}$), 118.8 (2 **C**H$_{Ar}$), 115.8 (2 **C**H$_{Ar}$), 50.7 (2 **C**H_2), 47.7 (2 **C**H_2), 23.9 (**C**H_3).

M.p.: 229-232 °C

HRMS (EI^+): *m/z*: calcd for $C_{19}H_{22}ON_4$ $[M]^+$: 322.1794; found 322.1795.

(*E*)-4-Phenyl-*N*-(4-propoxybenzylidene)piperazin-1-amine (5u)



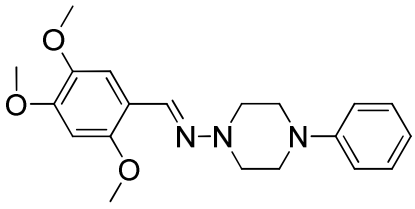
according to GP-1:

30.0 mg (169 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 27.7 mg (27.0 µL, 169 µmol, 1.00 eq) 4-propoxybenzaldehyde **(4u)**, 1.0 mL toluene, stirring over night.

$C_{20}H_{25}ON_3$ [323.0]

yield:	40.0 mg (71 %), light yellow solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.65 (s, 1H, CH=N), 7.57 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.33-7.28 (m, 2H, Ar-H), 6.99 (d, ^3J = 8.1 Hz, 2H, Ar-H), 6.93-6.88 (m, 3H, Ar-H), 3.94 (t, ^3J = 6.6 Hz, 2H, OCH_2), 3.41-3.38 (m, 4H, 2 CH_2), 3.33-3.30 (m, 4H, 2 CH_2), 1.82 (sext, ^3J = 6.9 Hz, ^3J = 7.2 Hz, 2H, CH_2), 1.05 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 159.6 (**C**$_q$-OCH_2), 150.9 (**C**$_q$), 137.7 (**C**H=N), 129.2 (2 **C**H_{Ar}), 128.6 (**C**$_q$), 127.6 (2 **C**H_{Ar}), 120.2 (**C**H_{Ar}), 116.5 (2 **C**H_{Ar}), 114.6 (2 **C**H_{Ar}), 69.5 (O**C**H_2), 51.5 (2 **C**H_2), 48.9 (2 **C**H_2), 22.6 (**C**H_2), 10.5 (**C**H_3).
M.p.:	184-185 °C
GC-MS (HS_50_S2):	t_R = 11.42 min (m/z = 323.1, 99 % M^+, BP: 160.1).

(*E*)-4-Phenyl-*N*-(2,4,5-trimethoxybenzyliden)piperazin-1-amine (5v)



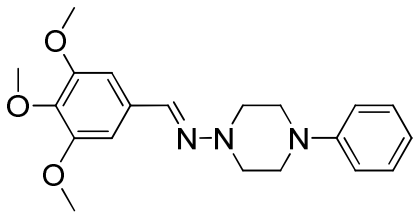
according to GP-1:

30.0 mg (169 µmol, 2.00 eq) 4-phenylpiperazin-1-amine **(3)**, 33.1 mg (169 µmol, 1.00 eq) 2,4,5-trimethoxybenzaldehyde **(4v)**, 1.0 mL toluene, stirring over night. Addition of 3.0 mg (15.0 µmol, 0.09 eq) 4-phenylpiperazin-1-amine **(3)** after 18 h to reach full conversion of the starting material after further stirring over a second night.

$C_{20}H_{25}O_3N_3$ [355.0]

yield:	55.0 mg (83 %), yellow-orange solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.00 (bs, 1H, CH=N), 7.46 (s, 1H, Ar-H), 7.34-7.27 (m, 3H, Ar-H), 6.99 (d, ^3J = 7.8 Hz, 2H, Ar-H), 6.50 (s, 1H, arom.H), 3.91 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.41-3.38 (m, 4H, 2 CH_2), 3.34-3.31 (m, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 152.1 (**C**$_q$-OCH_3), 151.0 (**C**$_q$-OCH_3), 150.3 (**C**$_q$-OCH_3), 143.7 (**C**H=N), 129.1 (2 **C**H$_{Ar}$), 128.2 (**C**$_q$), 120.1 (**C**H$_{Ar}$), 116.6 (**C**$_q$), 116.5 (2 **C**H$_{Ar}$), 107.9 (**C**H$_{Ar}$), 97.3 (**C**H$_{Ar}$), 56.7 (O**C**H$_3$), 56.2 (O**C**H$_3$), 56.0 (O**C**H$_3$), 51.5 (2 **C**H$_2$), 48.9 (2 **C**H$_2$).
M.p.:	153-156 °C
GC-MS (HS_100_L):	t_R = 11.82 min (m/z = 355.2, 96 % M^+, BP: 160.1).

(*E*)-4-Phenyl-*N*-(3,4,5-trimethoxybenzylidene)piperazin-1-amine (5w)



according to GP-1:

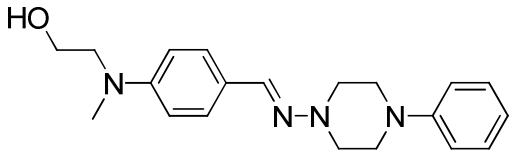
30.0 mg (169 µmol, 2.00 eq) 4-phenylpiperazin-1-amine **(3)**, 33.1 mg (169 µmol, 1.00 eq) 3,4,5-trimethoxybenzaldehyde **(4w)**, 1.0 mL toluene, stirring over night. Addition of 2.00 mg

(10.0 µmol, 0.06 eq) 4-phenylpiperazin-1-amine **(3)** after 18 h to reach full conversion of the starting material after further stirring over a second night.

$C_{20}H_{25}O_3N_3$ [355.0]

yield:	28.0 mg (44 %), yellow solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.93 (s, 1H, CH=N), 7.70-7.64 (m, 3H, Ar-H), 7.37 (d, ^3J = 8.1 Hz, 2H, Ar-H), 7.33-7.28 (m, 2H, Ar-H), 4.28 (s, 6H, 2 OCH_3), 4.24 (s, 3H, OCH_3), 3.78-3.71 (m, 8H, 4 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 153.4 (2 **C**$_q$-OCH_3), 150.9 (**C**$_q$-OCH_3), 138.5 (**C**$_q$), 136.4 (**C**H=N), 131.7 (**C**$_q$), 129.2 (2 **C**H_{Ar}), 120.3 (**C**H_{Ar}), 116.6 (2 **C**H_{Ar}), 103.2 (**C**H_{Ar}), 60.9 (O**C**H_3), 56.1 (2 O**C**H_3), 51.2 (2 **C**H_2), 48.9 (2 **C**H_2).
M.p.:	93-98 °C
GC-MS (HS_100_L):	t_R = 11.84 min (m/z = 355.2, 96 % M^+, BP: 160.2).

(*E*)-2-(Methyl(4-((4-phenylpiperazin-1-ylimino)methyl)phenyl)amino)ethanol (5x)



according to GP-1:

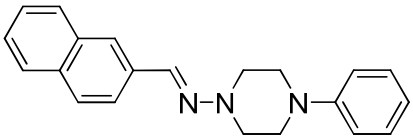
30.0 mg (169 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 30.3 mg (169 µmol, 1.00 eq) *N*-methyl-*N*-(2-hydroxyethyl)-4-aminobenzaldehyde **(4x)**, 1.0 mL toluene, stirring over night.

$C_{20}H_{26}ON_4$ [338.0]

yield:	48.0 mg (84 %), light yellow solid
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 7.66 (s, 1H, CH=N), 7.42 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.23 (t, ^3J = 8.1 Hz, 2H, Ar-H), 6.99 (d, ^3J = 8.1 Hz, 2H, Ar-H), 6.81 (t, ^3J = 7.2 Hz, 1H, Ar-H), 6.68 (d,

	^{3}J = 9.0 Hz, 2H, Ar-H), 4.68 (t, ^{3}J = 5.1 Hz, OH), 3.58-3.52 (m, 2H, CH_2), 3.43-3.39 (m, 2H, CH_2), 3.32-3.38 (m, 4H, 2 CH_2), 3.17-3.14 (m, 4H, 2 CH_2), 2.95 (s, 3H, N-CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 150.6 (**C**$_q$-N), 149.2 (**C**$_q$), 138.0 (**C**H=N), 128.8 (2 **C**H$_{Ar}$), 127.1 (2 **C**H$_{Ar}$), 123.4 (**C**$_q$), 119.0 (**C**H$_{Ar}$), 115.7 (2 **C**H$_{Ar}$), 111.3 (2 **C**H$_{Ar}$), 58.0 (N-**C**H$_2$), 54.0 (O-**C**H$_2$), 51.2 (2 **C**H$_2$), 47.8 (2 **C**H$_2$), 38.5 (N-**C**H$_3$).
M.p.:	202-204 °C
HRMS (EI$^+$):	*m/z*: calcd for $C_{20}H_{26}ON_4$ [M]$^+$: 338.2107; found 338.2117.

(*E*)-*N*-(Naphthalene-2-ylmethylen)-4-phenylpiperazin-1-amine (5y)



according to GP-1:

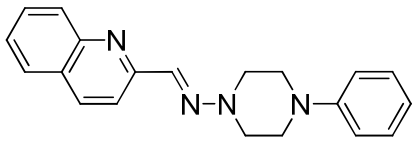
40.0 mg (226 µmol, 2.00 eq) 4-phenylpiperazin-1-amine **(3)**, 35.3 mg (226 µmol, 1.00 eq) 2-naphthaldehyde **(4y)**, 1.0 mL toluene, stirring over night. Addition of 2.0 mg (13.0 µmol, 0.06 eq) 4-phenylpiperazin-1-amine **(3)** after 18 h to reach full conversion of the starting material after further stirring for 6 h.

$C_{21}H_{21}N_3$ [315.0]

yield:	61.0 mg (82 %), yellow solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.98-7.96 (m, 1H, Ar-H), 7.88 (s, 1H, CH=N), 7.84-7.80 (m, 4H, Ar-H), 7.48-7.46 (m, 2H, Ar-H), 7.34-7.29 (m, 2H, Ar-H), 7.02 (d, ^{3}J = 8.1 Hz, 2H, Ar-H), 6.95-6.90 (m, 1H, Ar-H), 3.42 (s, 8H, 4 CH_2).

^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 150.9 (**C**$_q$), 136.6 (**C**H=N), 133.8 (**C**$_q$), 133.5 (**C**$_q$), 133.4 (**C**$_q$), 129.2 (2 **C**H$_{Ar}$), 128.3 (**C**H$_{Ar}$), 128.0 (**C**H$_{Ar}$), 127.8 (**C**H$_{Ar}$), 126.6 (**C**H$_{Ar}$), 126.2 (**C**H$_{Ar}$), 126.0 (**C**H$_{Ar}$), 123.1 (**C**H$_{Ar}$), 120.3 (**C**H$_{Ar}$), 116.6 (2 **C**H$_{Ar}$), 51.2 (2 **C**H$_2$), 49.0 (2 **C**H$_2$).
M.p.:	195-198 °C (decomposition)
GC-MS (HS_100_L):	t_R = 12.48 min (m/z = 315.3, 97 % M^+, BP: 160.2).
HRMS (EI^+):	*m/z*: calcd for $C_{21}H_{21}N_3$ $[M]^+$: 315.1736; found 315.1738.

(*E*)-4-Phenyl-*N*-(chinoline-2-yl-(*E*)-4-phenyl-*N*-(chinoline-2-ylmethylen)-piperazin-1-amine (5z)



according to GP-1:

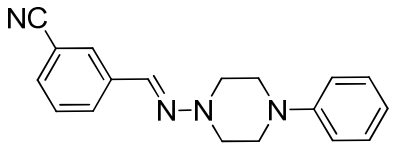
40.0 mg (226 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 35.5 mg (226 µmol, 1.00 eq) 2-quinolinecarboxaldehyde **(4z)**, 1.0 mL toluene, stirring for 5.5 h.

$C_{20}H_{20}N_4$ [316.0]

yield:	59.0 mg (83 %), dark yellow solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.09 (s, 2H, Ar-H), 8.05 (d, ^3J = 8.4 Hz, 1H, Ar-H), 7.86 (s, 1H, CH=N), 7.78 (dd, ^3J = 8.1 Hz, ^4J = 0.6 Hz, 1H, Ar-H), 7.72-7.67 (m, 1H, Ar-H), 7.52-7.47 (m, 1H, Ar-H), 7.33-7.28 (m, 2H, Ar-H), 7.00 (d, ^3J = 7.8 Hz, 2H, Ar-H), 6.92 (t, ^3J = 7.2 Hz, 1H, Ar-H), 3.52-3.49 (m, 4H, 2 CH_2), 3.43-3.39 (m, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 155.6 (**C**$_q$), 150.8 (**C**$_q$), 147.7 (**C**$_q$), 136.1 (**C**H=N), 135.7 (**C**$_q$), 129.6 (**C**H$_{Ar}$), 129.2 (2 **C**H$_{Ar}$), 128.7 (**C**H$_{Ar}$), 127.7 (**C**H$_{Ar}$), 127.6 (**C**H$_{Ar}$), 126.2 (**C**H$_{Ar}$),

	120.4 (**C**CH_{Ar}), 117.5 (**C**CH_{Ar}), 116.7 (2 **C**CH_{Ar}), 50.7 (2 **C**H_2), 48.9 (2 **C**H_2).
M.p.:	210-212 °C
GC-MS (HS_100_L):	t_R = 12.46 min (m/z = 316.1, 97 % M^+, BP: 161.1).
HRMS (EI^+):	*m/z*: calcd for $C_{20}H_{20}N_4$ $[M]^+$: 316.1688; found 316.1696.

(*E*)-3-((4-Phenylpiperazin-1-ylimino)methyl)benzonitrile (5aa)



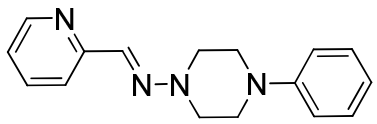
according to GP-1:

40.0 mg (226 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 30.0 mg (226 µmol, 1.00 eq) 3-formylbenzonitrile **(4aa)**, 1.0 mL toluene, stirring for 6 h.

$C_{18}H_{18}N_4$ [290.0]

yield:	67.0 mg (99 %), yellow solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.91 (s, 1H, CH=N), 7.82 (dd, ^3J = 7.8 Hz, ^4J = 1.2 Hz, 1H, Ar-H), 7.55-7.52 (m, 2H, Ar-H), 7.44 (t, ^3J = 7.8 Hz, 1H, Ar-H), 7.33-7.28 (m, 2H, Ar-H), 7.99 (d, ^3J = 7.8 Hz, 2H, Ar-H), 6.92 (t, ^3J = 7.2 Hz, 1H, Ar-H), 3.39 (s, 8H, 4 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 150.8 (**C**$_q$), 137.5 (**C**H=N), 132.6 (**C**H_{Ar}), 131.0 (**C**$_q$), 130.0 (**C**H_{Ar}), 129.4 (**C**H_{Ar}), 129.3 (**C**H_{Ar}), 129.2 (2 **C**H_{Ar}), 120.4 (**C**H_{Ar}), 118.8 (**C**N), 116.7 (2 **C**H_{Ar}), 112.7 (**C**$_q$-CN), 50.8 (2 **C**H_2), 48.9 (2 **C**H_2).
M.p.:	140-142 °C
GC-MS (HS_50_S2):	t_R = 10.86 min (m/z = 290.1, 98 % M^+, BP: 161.1).
HRMS (EI^+):	*m/z*: calcd for $C_{18}H_{18}N_4$ $[M]^+$: 290.1531; found 290.1539.

(*E*)-4-Phenyl-*N*-(pyridine-2-ylmethylen)piperazin-1-amine (5ab)



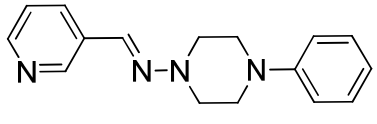
according to GP-1:

50.0 mg (282 µmol, 2.00 eq) 4-phenylpiperazin-1-amine **(3)**, 30.2 mg (27.0 µL, 282 µmol, 1.00 eq) 2-pyridinecarboxaldehyde **(4ab)**, 1.0 mL toluene, stirring for 4.5 h. Addition of 3.0 mg (28.0 µmol, 0.10 eq) 2-pyridinecarboxaldehyde **(4ab)** to reach full conversion of the starting material after further stirring over night.

$C_{16}H_{18}N_4$ [266.0]

yield:	65.0 mg (87 %), brown solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.38-8.36 (m, 1H, Ar-H), 7.71-7.69 (m, 1H, Ar-H), 7.51 (s, 1H, CH=N), 7.15-7.08 (m, 3H, Ar-H), 7.00-6.97 (m, 1H, Ar-H), 6.81 (d, ^3J = 7.8 Hz, 2H, Ar-H), 6.73 (t, ^3J = 7.2 Hz, 1H, Ar-H), 3.23-3.20 (m, 8H, 4 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 155.2 (**C**$_q$), 150.9 (**C**$_q$), 149.0 (**C**H$_{Ar}$), 136.3 (**C**H=N), 135.9 (**C**H$_{Ar}$), 129.2 (2 **C**H$_{Ar}$), 122.4 (**C**H$_{Ar}$), 120.3 (**C**H$_{Ar}$), 119.3 (**C**H$_{Ar}$), 116.6 (2 **C**H$_{Ar}$), 50.7 (2 **C**H$_2$), 48.9 (2 **C**H$_2$).
M.p.:	117-119 °C
GC-MS (HS_50_S2):	t_R = 9.08 min (m/z = 266.1, 98 % M^+, BP: 161.1).

(*E*)-4-Phenyl-*N*-(pyridine-3-ylmethylen)piperazin-1-amine (5ac)



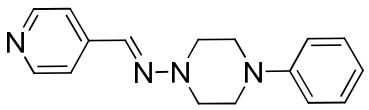
according to GP-1:

50.0 mg (282 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 30.2 mg (26.5 µL, 282 µmol, 1.00 eq) 3-pyridinecarboxaldehyde **(4ac)**, 1.0 mL toluene, stirring for 5 h.

$C_{16}H_{18}N_4$ [266.0]

yield:	75.0 mg (99 %), red-brown solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.75 (d, ^4J = 1.8 Hz, 1H, Ar-H), 8.51-8.49 (m, 1H, Ar-H), 8.02-7.98 (m, 1H, Ar-H), 7.56 (s, 1H, CH=N), 7.33-7.25 (m, 3H, Ar-H), 6.99 (d, ^3J = 8.1 Hz, 2H, Ar-H), 6.91 (t, ^3J = 7.2 Hz, 1H, Ar-H), 3.39 (s, 8H, 4 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 150.8 (**C**$_q$), 149.0 (**C**H$_{Ar}$), 148.2 (**C**H$_{Ar}$), 132.3 (**C**H=N), 132.2 (**C**H$_{Ar}$), 132.0 (**C**$_q$), 129.2 (2 **C**H$_{Ar}$), 123.5 (**C**H$_{Ar}$), 120.4 (**C**H$_{Ar}$), 116.6 (2 **C**H$_{Ar}$), 50.8 (2 **C**H$_2$), 48.9 (2 **C**H$_2$).
M.p.:	111-113 °C
GC-MS (HS_50_S2):	t_R = 9.37 min (m/z = 266.1, 97 % M^+, BP: 161.1).

(*E*)-4-Phenyl-*N*-(pyridine-4-ylmethylen)piperazin-1-amine (5ad)



according to GP-1:

50.0 mg (282 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 30.2 mg (26.5 µL, 282 µmol, 1.00 eq) 4-pyridinecarboxaldehyde **(4ad)**, 1.0 mL toluene, stirring for 5 h.

$C_{16}H_{18}N_4$ [266.0]

yield:	75.0 mg (99 %), orange solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.55 (d, ^3J = 6.0 Hz, 2H, Ar-H), 7.46 (d, ^3J = 6.0 Hz, 2H, Ar-H), 7.43 (s, 1H, CH=N), 7.33-7.27 (m,

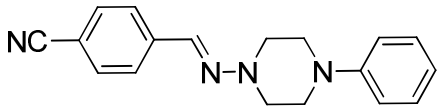
2H, Ar-H), 6.98 (d, ^{3}J = 7.8 Hz, 2H, Ar-H), 6.92 (t, ^{3}J = 7.2 Hz, 1H, Ar-H), 3.41-3.40 (m, 8H, 4 CH_2).

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 150.8 (**C**$_q$), 149.8 (2 **C**H$_{Ar}$), 143.6 (**C**$_q$), 131.6 (**C**H=N), 129.2 (2 **C**H$_{Ar}$), 120.5 (**C**H$_{Ar}$), 120.1 (2 **C**H$_{Ar}$), 116.7 (2 **C**H$_{Ar}$), 50.6 (2 **C**H$_2$), 48.9 (2 **C**H$_2$).

M.p.: 156-158 °C

GC-MS (HS_50_S2): t_R = 9.48 min (m/z = 266.1, 99 % M^+, BP: 161.1).

(*E*)-4-((4-Phenylpiperazin-1-ylimino)methyl)benzonitrile (5ae)



according to GP-1:

40.0 mg (226 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 29.6 mg (226 µmol, 1.00 eq) 4-formylbenzonitrile **(4ae)**, 1.0 mL toluene, stirring over night.

$C_{18}H_{18}N_4$ [290.0]

yield: 60.0 mg (92 %), yellow-orange solid

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.69 (d, ^{3}J = 8.4 Hz, 2H, Ar-H), 7.61 (d, ^{3}J = 8.4 Hz, 2H, Ar-H), 7.52 (s, 1H, CH=N), 7.33-7.28 (m, 2H, Ar-H), 6.99 (d, ^{3}J = 7.8 Hz, 2H, Ar-H), 6.92 (t, ^{3}J = 7.2 Hz, 1H, Ar-H), 3.40 (s, 8H, 4 CH_2).

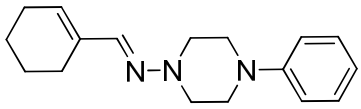
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 150.8 (**C**$_q$), 140.6 (**C**$_q$), 132.5 (**C**H=N), 132.3 (2 **C**H$_{Ar}$), 129.2 (2 **C**H$_{Ar}$), 126.2 (2 **C**H$_{Ar}$), 120.5 (**C**H$_{Ar}$), 119.1 (**C**N),116.7 (2 **C**H$_{Ar}$), 110.8 (**C**$_q$-CN), 50.7 (2 **C**H$_2$), 48.9 (2 **C**H$_2$).

M.p.: 165-169 °C

GC-MS (HS_50_S2): t_R = 11.85 min (m/z = 290.1, 97 % M^+, BP: 161.1).

HRMS (EI$^+$): *m/z*: calcd for $C_{18}H_{18}N_4$ $[M]^+$: 290.1531; found 290.1519.

(*E*)-*N*-(Cyclohexenylmethylen)-4-phenylpiperazin-1-amine (5af)



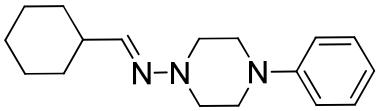
according to GP-1:

40.0 mg (226 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 24.9 mg (25.8 µL, 226 µmol, 1.00 eq) 1-cyclohexene-1-carboxaldehyde **(4af)**, 1.0 mL toluene, stirring for 4 h.

$C_{17}H_{23}N_3$ [269.0]

yield:	57.0 mg (94 %), yellow-brown solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.34 (s, 1H, CH=N), 7.31-7.26 (m, 2H, Ar-H), 6.97 (d, ^3J = 8.1 Hz, 2H, Ar-H), 6.88 (t, ^3J = 7.2 Hz, 1H, Ar-H), 5.92 (t, ^3J = 3.9 Hz, 1H, CH), 3.36-3.33 (m, 4H, 2 CH_2), 3.20-3.17 (m, 4H, 2 CH_2), 2.31 (bs, 2H, CH_2), 2.19 (bs, 2H, CH_2), 1.67-1.65 (m, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 151.9 (**C**$_q$), 142.5 (**C**H=N), 136.3 (**C**$_q$), 132.3 (**C**H), 129.1 (2 **C**H_{Ar}), 120.0 (**C**H_{Ar}), 116.4 (2 **C**H_{Ar}), 51.5 (2 **C**H_2), 48.9 (2 **C**H_2), 25.9 (**C**H_2), 23.8 (**C**H_2), 22.7 (**C**H_2), 22.2 (**C**H_2).
M.p.:	118-120 °C
GC-MS (HS_50_S2):	t_R = 8.83 min (m/z = 269.1, 99 % M^+, BP: 160.1).
HRMS (EI^+):	*m/z*: calcd for $C_{17}H_{23}N_3$ $[M]^+$: 269.1892; found 269.1899.

(*E*)-*N*-(Cyclohexylmethylen)-4-phenylpiperazin-1-amine (5ag)



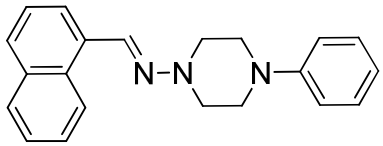
according to GP-1:

40.0 mg (226 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 25.1 mg (27.1 µL, 226 µmol, 1.00 eq) cyclohexanecarboxaldehyde **(4ag)**, 1.0 mL toluene, stirring for 4 h.

$C_{17}H_{25}N_3$ [271.0]

yield:	60.0 mg (98 %), yellow-brown solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.31-7.24 (m, 3H, Ar-H, CH=N), 6.96 (d, ^3J = 8.1 Hz, 2H, Ar-H), 6.90-6.86 (m, 1H, Ar-H), 3.35-3.32 (m, 4H, 2 CH_2), 3.12-3.08 (m, 4H, 2 CH_2), 2.25-2.21 (m, 1H, CH), 1.82-1.66 (m, 5H, CH_2, CH), 1.35-1.16 (m, 5H, CH_2, CH).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 150.9 (**C**H=N), 147.4 (**C**$_q$), 129.1 (2 **C**H_{Ar}), 120.0 (**C**H_{Ar}), 116.4 (2 **C**H_{Ar}), 51.8 (2 **C**H_2), 48.8 (2 **C**H_2), 41.4 (**C**H), 31.0 (2 **C**H_2), 26.0 (**C**H_2), 25.6 (2 **C**H_2).
M.p.:	69-71 °C
GC-MS (HS_50_S2):	t_R = 8.43 min (m/z = 271.1, 99 % M^+, BP: 161.1).
HRMS (EI$^+$):	*m/z*: calcd for $C_{17}H_{25}N_3$ $[M]^+$: 271.2048; found 271.2058.

(*E*)-*N*-(Naphthalene-1-methylen)-4-phenylpiperazin-1-amine (5ah)



according to GP-1:

50.9 mg (288 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 44.9 mg (39.0 µL, 288 µmol, 1.00 eq) 1-naphthaldehyde **(4ah)**, 3.0 mL toluene, stirring for 4 h.

$C_{21}H_{21}N_3$ [315.0]

yield:	88.6 mg (98 %), brown solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.60 (d, ^3J = 8.1 Hz, 1H, Ar-H), 8.33 (s, 1H, CH=N), 7.91-7.87 (m, 2H, Ar-H), 7.83 (d, ^3J = 8.1 Hz, 1H, Ar-H), 7.59-7.48 (m, 3H, Ar-H), 7.36-7.30 (m, 2H,

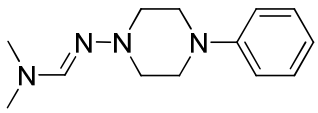
Ar-H), 7.03 (d, ^{3}J = 7.8 Hz, 2H, Ar-H), 6.94 (t, ^{3}J = 7.2 Hz, 1H, Ar-H), 3.47 (s, 8H, 4 CH_2).

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 150.9 (**C**$_q$), 135.7 (**C**H=N), 133.9 (**C**$_q$), 131.5 (**C**$_q$), 130.7 (**C**$_q$), 129.2 (2 **C**H_{Ar}), 128.8 (**C**H_{Ar}), 128.7 (**C**H_{Ar}), 126.3 (**C**H_{Ar}), 125.7 (**C**H_{Ar}), 125.5 (**C**H_{Ar}), 125.3 (**C**H_{Ar}), 123.8 (**C**H_{Ar}), 120.3 (**C**H_{Ar}), 116.6 (2 **C**H_{Ar}), 51.3 (2 **C**H_2), 49.0 (2 **C**H_2).

M.p.: 118 °C

GC-MS (NM_100_L): t_R = 11.44 min (m/z = 315.3, 99 % M^+, BP: 160.2).

(*E*)-*N*,*N*-Dimethyl-*N*`-(4-phenylpiperazin-1-yl)formimidamide (5ai)



A 15 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged consecutively with 40.0 mg (226 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 35.0 mg (226 µmol, 1.00 eq) 3,4-dihydroxybenzoic acid **(6)**, 4.0 mL anhydrous DMF, 33.0 mg (271 µmol, 1.20 eq) DMAP and 56.0 mg (271 µmol, 1.20 eq) DCC. The light brown solution was stirred at rt for 6 h. Because GC-MS analysis showed no full conversion of the starting material, additional 10.0 mg (65.0 µmol, 0.29 eq) 3,4-dihydroxybenzoic acid **(6)** were added and the solution was stirred at rt for further 13 h. The mixture was diluted with 5 mL DCM and filtrated through a pad of celite which afterwards was rinsed with DCM. The filtrate was concentrated under reduced pressure. The residue was triturated with 15 mL DCM and then purified by column chromatography (DCM/MeOH 8:1, size: 13.5 x 2.5 cm, 17 g silica gel) to yield the pure product.

$C_{13}H_{20}N_4$ [232.0]

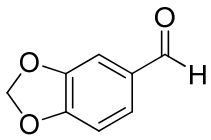
yield: 35.0 mg (50 %), light yellow solid

R_f (DCM/MeOH 8:1): 0.32

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.82 (s, 1H, CH=N), 7.28-7.22 (m, 2H, Ar-H), 6.92 (d, ^{3}J = 8.1 Hz, 2H, Ar-H), 6.84 (t, ^{3}J = 7.2 Hz, 1H,

	Ar-H), 3.32-3.29 (m, 4H, 2 CH_2), 2.94-2.91 (m, 4H, 2 CH_2), 2.87 (s, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 158.0 (**C**H=N), 150.9 (**C**$_q$), 129.0 (2 **C**H_{Ar}), 119.5 (**C**H_{Ar}), 115.8 (2 **C**H_{Ar}), 57.0 (2 **C**H_2), 48.4 (2 **C**H_2), 38.0 (2 **C**H_3).
M.p.:	84-88 °C
GC-MS (HS_50_S2):	t_R = 7.36 min (m/z = 232.1, >99 % M^+, BP: 56.0).

Benzo[*d*][1,3]-dioxol-5-carbaldehyde (9)



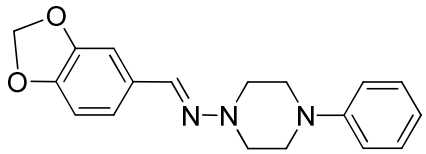
A 25 mL Schlenk tube was dried under vacuum, filled with argon and charged with 500 mg (0.30 mL, 2.49 mmol, 1.00 eq) 1-bromo-3,4-methylenedioxybenzene **(8)** and 7.5 mL absolute THF. The reaction mixture was cooled to -78 °C (dry ice, acetone) and 157 mg (1.25 mL, 2.46 mmol, 1.00 eq) *n*-butyllithium was added dropwise. The colorless suspension was stirred at this temperature for 2 h and 218 mg (229 µL, 2.98 mmol, 1.20 eq) anhydrous DMF were added. The colorless solution was warmed to rt and stirred for 4 h. TLC analysis indicated full conversion of the starting material. The mixture was hydrolyzed with 5 mL water and concentrated under reduced pressure to remove the THF. The obtained yellow oil was dissolved in 5 mL DCM and washed with 10 mL water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Final purification by column chromatography (CH/EtOAc 20:1, size: 11.0 x 4.0 cm, 53 g silica gel) yielded the pure product.

$C_8H_6O_3$ [150.1]

yield:	345.0 mg (92 %), colorless solid
R_f (CH/ EtOAc 20:1):	0.19

^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 9.80 (s, 1H, CHO), 7.41-7.38 (dd, ^3J = 7.8 Hz, ^4J = 1.2 Hz, 1H, Ar-H), 7.32-7.31 (m, 1H, Ar-H), 6.92 (d, ^3J = 7.8 Hz, 1H, Ar-H), 6.06 (s, 2H, CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 190.2 (**C**HO), 153.1 (**C**$_q$), 148.7 (**C**$_q$), 131.9 (**C**$_q$), 128.6 (**C**H$_{Ar}$), 108.3 (**C**H$_{Ar}$), 106.9 (**C**H$_{Ar}$) 102.1 (**C**H_2).
M.p.:	125-127°C
GC-MS (NM_50_S2):	t_R = 5.21 min (m/z = 150.0, 99 % M^+, BP: 149.0).

***(E)-N*-(benzo[*d*][1,3]dioxol-5-ylmethylen)-4-phenylpiperazin-1-amine (5aj)**



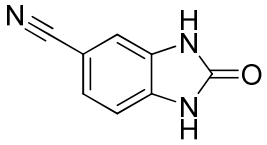
A reaction block was placed on a hotplate stirrer as depicted in Fig. 85. A brown 10 mL reaction vessel was charged consecutively with 38.0 mg (215 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 1.0 mL toluene, 32.2 mg (215 µmol, 1.00 eq) benzo[*d*][1,3]-dioxol-5-carbaldehyde **(9)** and a magnetic stirring bar. The vessel was crimped with a cap, placed in the preheated (100 °C) reaction block and stirred vigorously at 100 °C for 4 h. GC-MS analysis indicated full conversion of the starting material. After cooling to rt the cap was removed, the reaction mixture was transferred into a one-neck round bottom flask and concentrated under reduced pressure. Final purification by recrystallization from 1.0 mL toluene yielded the pure product.

$C_{18}H_{19}N_3O_2$ [309.1]

yield:	40.0 mg (67 %), orange-brown solid
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 7.67 (s, 1H, CH=N), 7.26-7.21 (m, 2H, Ar-H), 7.18-7.17 (m, 1H, Ar-H), 7.05-6.99 (m, 3H, Ar-H), 6.92-6.90 (m, 1H, Ar-H), 6.83-6.79 (m, 1H, Ar-H), 6.03 (s, 2H, CH_2), 3.31 (m, 4H, 2 CH_2), 3.21 (m, 4H, 2 CH_2).

^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 150.6 (**C**$_q$), 147.6 (**C**$_q$), 147.2 (**C**$_q$), 136.1 (**C**H=N), 130.7 (**C**$_q$), 128.8 (2 **C**H$_{Ar}$), 121.0 (**C**H$_{Ar}$), 119.1 (**C**H$_{Ar}$), 115.8 (2 **C**H$_{Ar}$), 108.1 (**C**H$_{Ar}$), 104.3 (**C**H$_{Ar}$), 101.0 (**C**H$_2$), 50.8 (2 **C**H$_2$), 47.7 (2 **C**H$_2$).
M.p.:	125°C-129°C
GC-MS (HS_100_L):	t_R = 9.87 min (m/z = 309.1, 99 % M^+, BP: 56.0).

2-Oxo-2,3-dihydro-1*H*-benzimidazol-5-carbonitrile (16) [98]



A 15 mL Schlenk tube was filled with nitrogen and charged consecutively with 500 mg (3.79 mmol, 1.00 eq) 3,4-diaminobenzonitrile **(15)**, 245 mg (4.09 mmol, 1.10 eq) urea and 4.5 mL anhydrous DMF. The dark purple solution was stirred at 150 °C for 1 h. To reach full conversion (TLC analysis) of the starting material another 406 mg (6.76 mmol, 1.80 eq) urea were added and the solution was stirred over night. The mixture was transferred into a one-neck round bottom flask with DCM during which a rose-red solid precipitated. The suspension was filtrated through a fritted funnel, the filtrate was concentrated under reduced pressure and purified by silica gel filtration (EtOAc, EtOAc/THF 1:1) to yield the pure product.

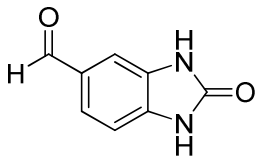
$C_8H_5ON_3$ [159.0]

yield:	404.2 mg (68 %), light brown solid
R_f (THF):	0.7
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 11.14 (bs, 2H, 2 NH), 7.41-7.38 (m, 1H, Ar-H), 7.40 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H, Ar-H), 7.31 (d, ^4J = 1.5 Hz, 1H, Ar-H), 7.07 (d, ^3J = 8.1 Hz, 1H, Ar-H).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 155.0 (**C**=O), 133.6 (**C**$_q$), 129.9 (**C**$_q$), 125.7 (**C**H$_{Ar}$) 119.7 (**C**N), 111.3 (**C**H$_{Ar}$), 109.4 (**C**H$_{Ar}$), 102.2 (**C**$_q$-CN).

M.p.: 286– 289°C

2-Oxo-2,3-dihydro-1*H*-benzimidazol-5-carbaldehyde (12) [98]



A 100 mL Schlenk tube was filled with argon and charged with 200 mg (1.26 mmol, 1.00 eq) 2-oxo-2,3-dihydro-1*H*-benzimidazol-5-carbonitrile **(16)**, 15 mL formic acid and 4 mL water. After addition of 1.13 g nickel-aluminium alloy the black suspension was stirred at 95 °C for 17.5 h. TLC analysis (EtOAc) indicated full conversion of the starting material. The catalyst was filtered through a pad of celite and the pad was rinsed with MeOH. The solution of the filtrate was concentrated under reduced pressure and the residue was alkalized with 92 mL 2 M aqueous NaOH solution to pH 8. The aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Drying under high vacuum yielded the pure product.

$C_8H_6O_2N_2$ [162.1]

yield: 133.2 mg (65 %), colorless solid

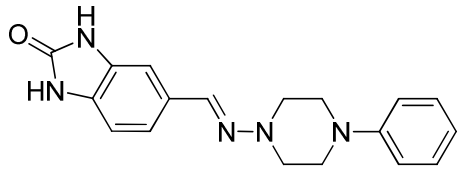
R_f (EtOAc /MeOH 20:1): 0.67

^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) = 11.17 (bs, 1H, 1 NH), 11.00 (bs, 1H, NH), 9,85 (s, 1H, CHO) 7.58-7.55 (m, 1H, Ar-H), 7.39 (s, 1H, Ar-H), 7.10 (d, ^3J = 8.1 Hz, 1H, Ar-H).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 191.8 (**C**HO), 155.3 (**C**=O), 135.3 (**C**$_q$), 130.1 (**C**$_q$), 129.8 (**C**$_q$), 125.1 (**C**H$_{Ar}$), 108.4 (**C**H$_{Ar}$), 107.8 (**C**H$_{Ar}$).

M.p.: 292– 299°C (decomposition)

***(E)*-5-((4-phenylpiperazin-1-ylimino)methyl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one (5ak)**



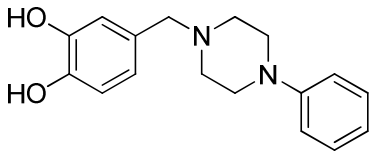
A reaction block was placed on a hotplate stirrer as depicted in Fig. 85. A brown 10 mL reaction vessel was charged consecutively with 65.6 mg (370 µmol, 1.00 eq) 4-phenylpiperazin-1-amine **(3)**, 1.0 mL toluene, 60.0 mg (370 µmol, 1.00 eq) 2-oxo-2,3-dihydro-1*H*-benzimidazol-5-carbaldehyde **(12)** and a magnetic stirring bar. The vessel was crimped with a cap, placed in the preheated (100 °C) reaction block and stirred vigorously at 100 °C for 5 h. Because TLC analysis indicated no full conversion of the aldehyde another 6.10 mg (34.0 µmol, 0.09 eq) 4-phenylpiperazin-1-amine **(3)** were added and the reaction mixture was stirred for additional 3 h. After cooling to rt the cap was removed, the reaction mixture was transferred into a one-neck round bottom flask and concentrated under reduced pressure to yield the pure product.

$C_{18}H_{19}ON_5$ [321.1]

yield:	119.0 mg (99 %), colorless solid
R_f (EtOAc /MeOH 30:1):	0.27
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 10.64 (bs, 2H, 2 NH), 7.73 (s, 1H, CH=N) 7.26-7.21 (m, 3H, Ar-H), 7.18-7.14 (m, 1H, Ar-H), 7.01 (d, ^3J = 8.1 Hz, 2H, Ar-CH), 6.90 (d, ^3J = 8.1 Hz, 1H, Ar-H), 6.81 (t, ^3J = 7.2 Hz, 1H, Ar-H), 3.33-3.30 (m, 4H, 2 CH_2), 3.22-3.20 (m, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 155.4 (**C**=O), 150.6 ($\mathbf{C}_q$), 137.4 (**C**H=N), 130.0 ($\mathbf{C}_q$), 129.1 ($\mathbf{C}_q$), 128.9 (2 $\mathbf{C}H_{Ar}$), 119.9 ($\mathbf{C}H_{Ar}$), 119.1 ($\mathbf{C}H_{Ar}$), 115.8 (2 $\mathbf{C}H_{Ar}$), 115.3 ($\mathbf{C}_q$), 108.2 ($\mathbf{C}H_{Ar}$), 104.9 ($\mathbf{C}H_{Ar}$), 50.9 (2 $\mathbf{C}H_2$), 47.8 (2 $\mathbf{C}H_2$).
M.p.:	320- 330°C (decomposition)
HRMS (EI$^+$):	*m/z*: calcd for $C_{18}H_{19}ON_5$ $[M]^+$: 321.1590; found 321.1606.

6.2.2. Replacement of the hydrazone functionality (building block B)

4-((4-Phenylpiperazin-1-yl)methyl)benzene-1,2-diol (17)



A 25 mL Schlenk tube was flushed with argon and charged with 250 mg (1.81 mmol, 1.00 eq) 3,4-dihydroxybenzaldehyde **(4a)**, 7.0 mL anhydrous DCE and 294 mg (0.28 mL, 1.81 mmol, 1.00 eq) 1-phenylpiperazine **(1)**. To the orange solution 538 mg (2.54 mmol, 1.40 eq) sodium triacetoxyborhydride and 100 µmL (1.81 mmol, 1.00 eq) acetic acid were added. The colorless suspension was stirred at rt over night, during which the color of the suspension turned bright yellow. GC-MS analysis and TLC analysis indicated full conversion of the starting material. The mixture was hydrolyzed by addition of 10 mL saturated $NaHCO_3$ solution and concentrated under reduced pressure. The residue was dissolved in 30 mL EtOAc and 30 mL water and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers were washed with 25 mL brine, dried over $MgSO_4$ and concentrated under reduced pressure. Final purification by silica gel filtration (DCM/MeOH 19:1, R_f = 0.38) yielded the pure product.

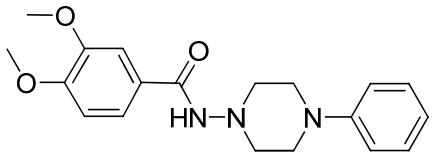
$C_{17}H_{20}O_2N_2$ [284.3]

yield:	135.9 mg (26 %), brown solid
R_f (MeOH)	0.63
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.87 (bs, 2H, 2 OH), 7.19 (t, ^3J = 7.8 Hz, 2H, Ar-H), 6.90 (d, ^3J = 8.1 Hz, 2H, Ar-H), 6.78-6.73 (m, 2H, Ar-H), 6.68-6.65 (m, 1H, Ar-H), 6.56-6.53 (m, 1H, Ar-H), 3.32 (s, 2H, CH_2), 3.10 (bs, 4H, 2 CH_2), 2.47-2.46 (m, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 150.9 (**C**$_q$), 144.9 (**C**$_q$-OH), 144.1 (**C**$_q$-OH), 128.8 (2 **C**H$_{Ar}$), 128.6 (**C**$_q$), 119.7 (**C**H$_{Ar}$), 118.6 (**C**H$_{Ar}$), 116.2 (**C**H$_{Ar}$), 115.2 (2 **C**H$_{Ar}$), 115.0 (**C**H$_{Ar}$), 61.8 (**C**H$_2$), 52.4 (2 **C**H$_2$), 48.1 (2 **C**H$_2$).

M.p.: 100-102 °C

HRMS (EI^+): *m/z*: calcd for $C_{17}H_{20}O_2N_2$ $[M]^+$: 284.1525; found 284.1540

3,4-Dimethoxy-*N*-(4-phenylpiperazin-1-yl)benzamide (20)



A 25 mL Schlenk tube was charged with 100 mg (549 µmol, 1.00 eq) 3,4-dimethoxybenzoic acid **(18)**, 218 mg (140 µL, 1.83 mmol, 3.33 eq) thionylchloride and one catalytic drop anhydrous DMF. The light yellow suspension was refluxed for 3.5 h. The excess thionylchloride was removed under high vacuum over a cooling trap to obtain a light yellow solid (acid chloride).

A 25 mL one-neck round bottom flask was charged with 117 mg (659 µmol, 1.20 eq) 4-phenylpiperazin-1-amine **(3)** and 2.0 mL 10 % aqueous NaOH solution. The solution was cooled to 0 °C and the acid chloride (synthesized before), dissolved in 1 mL absolute DCM, was added. The mixture was stirred at rt for 30 min, during which a colorless solid precipitated. The solid was collected by filtration, washed with DCM and dried under vacuum. Final purification by recrystallization from 25 mL EtOH yielded the pure product.

$C_{19}H_{23}O_3N_3$ [341.0]

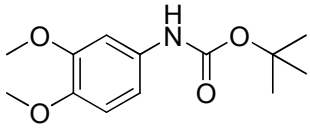
yield: 98.0 mg (53 %), colorless solid

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.40 (bs, 1H, NH), 7.31-7.27 (m, 3H, Ar-H), 6.98-6.84 (m, 5H, Ar-H), 3.93-3.92 (m, 6H, 2 OCH_3), 3.40 (m, 4H, 2 CH_2), 3.12 (m, 4H, 2 CH_2).

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 165.2 (**C**=O), 151.9 (**C**$_q$-OCH_3), 150.9 (**C**$_q$-OCH_3), 149.1 (**C**$_q$), 129.2 (2 **C**H_{Ar}), 126.2 (**C**$_q$), 120.3 (**C**H_{Ar}), 119.4 (**C**H_{Ar}), 116.5 (2 **C**H_{Ar}), 110.8 (**C**H_{Ar}), 110.2 (**C**H_{Ar}), 56.0 (2 **C**H_2), 55.4 (2 O**C**H_3), 48.9 (2 **C**H_2).

M.p.:	219-221 °C
GC-MS (HS_50_S2):	t_R = 7.95 min (m/z = 341.1, 99 % M^+, BP: 91.0).
HRMS (EI^+):	*m/z*: calcd for $C_{19}H_{23}O_3N_3$ $[M]^+$: 341.1740; found 341.1754.

***Tert*-Butyl-3,4-dimethoxyphenylcarbamate (22)**

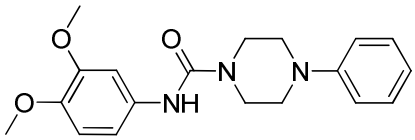


A 25 mL Schlenk tube was dried under vacuum, filled with argon and charged with 500 mg (3.26 mmol, 1.00 eq) 3,4-dimethoxyaniline **(3)** amd 6.1 mL absolute EtOH. 1.07 g (4.90 mmol, 1.50 eq) di-*tert*-butyl dicarbonate were added slowly and the suspension was stirred at rt for 2.5 h. GC-MS analysis indicated full conversion of the starting material. The mixture was transferred to a one-neck round bottom flask and concentrated under reduced pressure. Drying under high vacuum over night yielded the product which was used in the next reaction without further purification.

$C_{13}H_{19}O_4N$ [253.2]

yield:	906.0 mg (>99 %), grey solid
R_f (CH/ EtOAc 1:1):	0.72
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.16 (bs, 1H, NH), 6.78 – 6.69 (m, 2H, Ar-H), 6.43 (s, 1H, Ar-H), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3) 1.50 (s, 9H, 3 CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 153.0 (**C**=O), 149.2 ($\mathbf{C}_q$-OCH_3), 145.0 ($\mathbf{C}_q$-OCH_3), 132.0 ($\mathbf{C}_q$), 111.6 ($\mathbf{C}H_{Ar}$), 110.4 ($\mathbf{C}H_{Ar}$), 103.8 ($\mathbf{C}H_{Ar}$), 80.2 ($\mathbf{C}_q$), 56.2 (O**C**H_3), 55.8 (O**C**H_3), 28.3 (3 **C**H_3).
M.p.:	74°C
GC-MS (HS_50_S2):	t_R = 7.04 min (m/z = 253.2, 87 % M^+, BP: 197.0, 13 % Boc_2O).

***N*-(3,4-dimethoxyphenyl)-4-phenylpiperazin-1-carboxamide (24)**

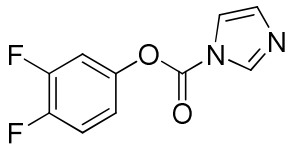


A 15 mL Schlenk tube was dried under vacuum, filled with argon and charged with 176 mg (166 µL, 1.09 mmol, 1.10 eq) 1-phenylpiperazine **(1)** and 2.0 mL absolute THF. The yellow solution was cooled to 0 °C and 76.0 mg (474 µL, 1.18 mmol, 1.20 eq) *n*-butyllithium were added. The mixture was warmed to rt and a solution of 250 mg (987 µmol, 1.00 eq) *tert*-butyl-3,4-dimethoxyphenylcarbamate **(22)** in 2.0 mL absolute THF was added dropwise. The green-brown solution was refluxed for 5 h. TLC analysis indicated full conversion and the mixture was hydrolyzed with 5 mL 5 % aqueous HCL solution. The aqueous layer was extracted with DCM (3 x 5 mL) and the combined organic layers were washed with 5 mL saturated aqueous $NaHCO_3$ solution, 5 mL water and 5 mL brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Final purification by column chromatography (CH/EtOAc, size: 18.5 x 2.5 cm, 30 g silica gel) yielded the pure product.

$C_{19}H_{23}O_3N_3$ [341.0]

yield:	81.0 mg (25 %), yellow-orange solid
R_f (CH/ EtOAc 1:1):	0.19
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.44 (b, 1H, NH), 7.26 - 7.17 (m, 3H, Ar-H), 7.00-6.97 (m, 3H, Ar-H), 6.84-6.79 (m, 2H, Ar-H), 3.71 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.59-3.56 (m, 4H, 2 CH_2), 3.17-3.13 (m, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 155.0 (**C**=O), 150.8 ($\mathbf{C}_q$-OCH_3), 148.3 ($\mathbf{C}_q$-OCH_3), 143.9 ($\mathbf{C}_q$), 133.9 ($\mathbf{C}_q$), 128.8 (2 **C**H_{Ar}), 119.1 (**C**H_{Ar}), 115.7 (2 **C**H_{Ar}), 112.0 (**C**H_{Ar}), 111.5 (**C**H_{Ar}), 105.3 (**C**H_{Ar}), 55.7 (O**C**H_3), 55.2 (O**C**H_3), 48.3 (2 **C**H_2), 43.5 (2 **C**H_2).
M.p.:	122°C -125°C

3,4-Difluorophenyl-1*H*-imidazol-1-carboxylate (26)

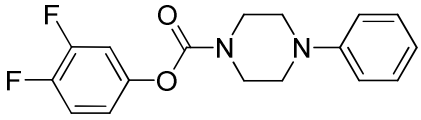


A 15 mL Schlenk tube was dried under vacuum, filled with argon and charged with 500 mg (3.84 mmol, 1.00 eq) 3,4-difluorophenol **(25)**, 2.0 mL absolute DCM and 624 mg (3.84 mmol, 1.00 eq) 1,1`-carbonyldiimidazole. The yellow mixture was stirred at rt for 1.5 h. To reach full conversion of the starting material (GC-MS analysis) 605 mg (3.72 mmol, 0.97 eq) 1,1`-carbonyldiimidazol, dissolved in 1 mL DCM, were added and the mixture was stirred at rt for further 20 h. The product solution was used in the next reaction without work up or any purification step.

$C_{10}H_6O_2N_2F_2$ [224.1]

GC–MS (HS_50_S2): t_R = 5.96 min (m/z = 223.9, 90 % M^+, BP: 130.0).

3,4-Difluorophenyl-4-phenylpiperazin-1-carboxylate (27)



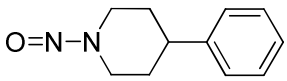
623 mg (590 µL, 3.84 mmol, 1.00 eq) 1-phenylpiperazine **(1)** were added to the product mixture of 3,4-difluorophenyl-1*H*-imidazol-1-carboxylate **(26)**. After 1 h stirring at rt once more 25.0 mg (20 µL, 150 µmol, 0.04 eq) 1-phenylpiperazine **(1)** were added to reach full conversion (GC-MS analysis). The mixture was stirred at rt for 2 h and washed with water (2 x 5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. As the obtained solid was not pure enough, even after silica gel filtration (CH/EtOAc 5:1, R_f = 0.18), it was dissolved in 5 mL DCM and washed with 5 mL 2 M aqueous NaOH solution. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and dried under high vacuum to yield the pure product.

$C_{17}H_{16}O_2N_2F_2$ [318.3]

yield:	246.0 mg (20 %), light yellow solid
R_f (DCM):	0.49
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.34-7.29 (m, 2H, Ar-H), 7.15 (q, ^3J = 9.0 Hz, Ar-H), 7.07-6.86 (m, 5H, Ar-H), 3.82-3.75 (m, 4H, 2 CH_2), 3.25 (t, ^3J = 5.4 Hz, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 153.0 (**C**=O), 151.7, 151.5, 148.4, 148.2 ($^1J_{C-F}$ = 249.5 Hz, $^2J_{C-F}$ = 13.9 Hz,**C**$_q$-F), 149.7, 149.6, 146.5, 146.3 ($^1J_{C-F}$ = 245.7 Hz, $^2J_{C-F}$ = 12.5 Hz, **C**$_q$-F), 147.0, 146.9, 146.8, ($^3J_{C-F}$ = *8*.8 Hz, $^4J_{C-F}$ = 3.2 Hz, **C**$_q$), 129.3 (2 **C**H$_{Ar}$), 120.9 (**C**H$_{Ar}$), 117.7, 117.6, 117.5 (**C**H$_{Ar}$), 117.2 (**C**$_q$), 116.9 (2 **C**H$_{Ar}$), 111.9, 111.6 ($^2J_{C-F}$ = 19.9 Hz, **C**H$_{Ar}$), 49.6 (2 **C**H$_2$), 43.9 (2 **C**H$_2$).
M.p.:	94-96°C
GC-MS (HS_50_S2):	t_R = 8.72 min (m/z = 318.2, 99 % M^+, BP: 189.0).
HRMS (EI^+):	*m/z*: calcd for $C_{17}H_{16}O_2N_2F_2$ $[M]^+$: 318.1180; found 318.1182.

6.2.3. Replacement of the piperazine ring (building block C)

1-Nitroso-4-phenylpiperidine (29)

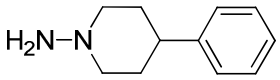


A 100 mL Schlenk tube was charged with 250 mg (1.55 mmol, 1.00 eq) phenylpiperidine **(28)**, 13 mL THF and 0.29 mL (2.40 mmol, 1.55 eq) *tert*. butylnitrite. The mixture was refluxed for 18 h. GC-MS analysis indicated full conversion of the starting material. The solution was transferred to a one-neck round bottom flask and concentrated in vacuum at a temperature of 30 °C. The crude product was used in the next reaction without further purification.

$C_{11}H_{14}ON_2$ [190.2]

yield:	272.0 mg (92 %), yellow-orange oil
R_f (DCM):	0.55
GC-MS (HS_50_S2):	t_R = 6.78 min (m/z = 190.2, 98 % M^+, BP: 56.1).

4-Phenylpiperidine-1-amine (30)

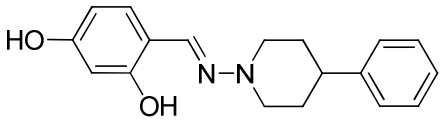


A 100 mL three-neck round bottom flask with dropping funnel and reflux condenser was dried under vacuum, filled with nitrogen and charged with 119 mg (3.16 mmol, 2.20 eq) $LiAlH_4$ and 5.8 mL absolute THF. The grey suspension was heated to reflux and a solution of 273 mg (1.44 mmol, 1.00 eq) 1-Nitroso-4-phenylpiperidine **(29)** in 2.3 mL absolute THF was added dropwise to the boiling suspension. After complete addition the suspension was refluxed for further 2.5 h. GC-MS analysis showed full conversion of the starting material. The suspension was hydrolyzed according to the n,n,3n- method (0.5 mL water, 0.5 mL 15 % aqueous NaOH and 1.5 mL water). The mixture was filtrated, the filter cake was washed with 10 mL THF and concentrated under reduced pressure. Final purification by silica gel filtration (MeOH) yielded the pure product.

$C_{11}H_{16}N_2$ [176.1]

yield:	184.0 mg (73 %), colorless solid
R_f (MeOH):	0.45
^{1}H-NMR (300 MHz, MeOD):	δ (ppm) = 7.30-7.16 (m, 5H, Ar-H), 3.24-3.20 (m, 2H, CH_2), 2.54-2.48 (m, 1H, CH), 2.40-2.31 (m, 2H, CH_2), 1.88-1.80 (m, 4H, 2 CH_2).
M.p.:	56 – 59°C
GC-MS (HS_50_S2):	t_R = 6.08 min (m/z = 176.2, 92 % M^+, BP: 71.2).

***(E)*-4-((4-Phenylpiperidine-1-ylimino)methyl)benzene-1,3-diol (31)**

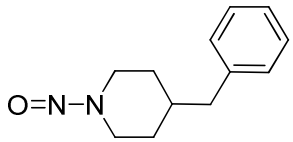


A reaction block was placed on a hotplate stirrer as depicted in Fig. 85. A brown 10 mL reaction vessel was charged consecutively with 50.0 mg (284 µmol, 1.00 eq) 4-phenylpiperidine-1-amine **(30)**, 1.0 mL toluene, 39.0 mg (284 µmol, 1.00 eq) 2,4-dihydroxybenzaldehyde **(4i)** and a magnetic stirring bar. The vessel was crimped with a cap, placed in the preheated (100 °C) reaction block and stirred vigorously at 100 °C for 2.5 h. GC-MS analysis indicated full conversion of the starting material. After cooling to rt the cap was removed, the reaction mixture was transferred into a one-neck round bottom flask and concentrated under reduced pressure. Final purification by recrystallization from 2.0 mL toluene yielded the pure product.

$C_{18}H_{20}O_2N_2$ [296.1]

yield:	48.0 mg (57 %), yellow crystals
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 11.77 (s, 1H, OH), 9.66 (bs, 1H, OH), 7.89 (s, 1H, CH=N), 7.34-7.27 (m, 4H, Ar-H), 7.23-7.20 (m, 1H, Ar-H), 7.14 (d, ^3J = 8.4 Hz; 1H, Ar-H), 6.29 (dd, ^3J = 8.4 Hz, ^4J = 2.4 Hz, 1H, Ar-H), 6.23 (d, ^4J = 2.4 Hz, 1H, Ar-H) 3.74-3.70 (m, 2H, CH_2), 2.67-2.59 (m, 3H, CH, CH_2), 1.88-1.80 (m, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 158.7 (**C**$_q$-OH), 158.5 (**C**$_q$-OH), 145.5 (**C**$_q$), 141.1 (**C**H=N), 130.6 (**C**H$_{Ar}$), 128.3 (2 **C**H$_{Ar}$), 126.6 (2 **C**H$_{Ar}$), 126.1 (**C**H$_{Ar}$), 111.7 (**C**$_q$), 106.8 (**C**H$_{Ar}$) 102.3 (**C**H$_{Ar}$), 51.6 (2 **C**H$_2$), 41.0 (**C**H), 31.7 (2 **C**H$_2$).
M.p.:	139°C-142°C
HRMS (EI$^+$):	*m/z*: calcd for $C_{18}H_{20}O_2N_2$ $[M]^+$: 296.1525; found 296.1530.

4-Benzyl-1-nitrosopiperidine (33)

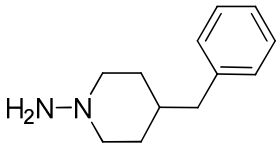


A 100 mL Schlenk tube was charged with 500 mg (500 µL, 2.85 mmol, 1.00 eq) 4-benzylpiperidine **(32)**, 20 mL THF and 590 µL (4.91 mmol, 1.72 eq) *tert*. butylnitrite. The mixture was refluxed 48 h. TLC analysis indicated full conversion of the starting material. The orange solution was transferred to a one-neck round bottom flask and concentrated in vacuum at a temperature of 30 °C. The crude product was used in the next reaction without further purification.

$C_{12}H_{16}ON_2$ [204.0]

yield:	601.0 mg (> 99 %), orange oil
R_f (DCM):	0.58
GC-MS (HS_50_S2):	t_R = 7.05 min (m/z = 204.1, 95 % M^+, BP: 174.1).

4-Benzylpiperidine-1-amine (34)



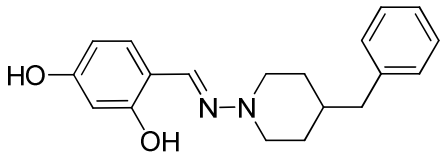
A 100 mL three-neck round bottom flask with dropping funnel and reflux condenser was dried under vacuum, filled with nitrogen and charged with 238 mg (6.28 mmol, 2.20 eq) $LiAlH_4$ and 15 mL absolute THF. The grey suspension was heated to reflux and a solution of 582 mg (2.85 mmol, 1.00 eq) 4-benzyl-1-nitrosopiperidine **(33)** in 5 mL absolute THF was added dropwise to the boiling suspension. After complete addition the suspension was refluxed for further 2 h. GC-MS analysis showed full conversion of the starting material. The suspension was hydrolyzed according to the n,n,3n- method (0.5 mL water, 0.5 mL 15 % aqueous NaOH and 1.5 mL water) upon which the color turned to orange. The mixture was

filtrated, the filter cake was washed with 10 mL THF and concentrated under reduced pressure. Final purification by silica gel filtration (MeOH) yielded the product with 96 % purity.

$C_{12}H_{18}N_2$ [190.0]

yield:	304.5 mg (56 %), light yellow solid
R_f (MeOH):	0.44
^{1}H-NMR (300 MHz, MeOD):	δ (ppm) = 7.28-7.23 (m, 2H Ar-H), 7.18-7.13 (m, 3H, Ar-H), 3.07 (d, ^3J = 11.1 Hz, 2H, CH_2), 2.53 (d, ^3J = 6.9 Hz, 2H, CH_2), 2.15 (t, ^3J = 11.1 Hz, 2H, CH_2), 1.68-1.50 (m, 3H, CH_2, CH), 1.40-1.32 (m, 2H, CH_2).
^{13}C-NMR (75.5 MHz, MeOD):	δ (ppm) = 141.7 (**C**$_q$), 130.1 (2 **C**H$_{Ar}$), 129.3 (2 **C**H$_{Ar}$), 127.0 (**C**H$_{Ar}$), 60.0 (2 **C**H$_2$), 43.5 (**C**H$_2$), 38.1 (**C**H), 32.8 (2 **C**H$_2$).
M.p.:	43-47 °C
GC-MS (HS_50_S2):	t_R = 6.36 min (m/z = 190.1, 96 % M^+, BP).

***(E)*-4-((4-benzylpiperidine-1-ylimino)methyl)benzene-1,3-diol (35)**

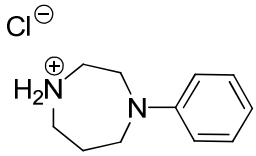


A reaction block was placed on a hotplate stirrer as depicted in Fig. 85. A brown 10 mL reaction vessel was charged consecutively with 86.0 mg (453 µmol, 1.00 eq, 96 % purity) 4-benzylpiperidine-1-amine **(34)**, 2.0 mL toluene, 60.1 mg (435 µmol, 1.0 eq) 2,4-dihydroxybenzaldehyde **(4i)** and a magnetic stirring bar. The vessel was crimped with a cap, placed in the preheated (100 °C) reaction block and stirred vigorously at 100 °C over night. GC-MS analysis indicated full conversion of the starting material. After cooling to rt the cap was removed, the reaction mixture was transferred into a one-neck round bottom flask, concentrated under reduced pressure and dried under high vacuum yielding the pure product.

$C_{19}H_{22}O_2N_2$ [310.0]

yield:	134.0 mg (95 %), yellow-brown solid
^{1}H-NMR (300 MHz, MeOD):	δ (ppm) = 7.82 (s, 1H, CH=N), 7.29-7.24 (m, 2H, Ar-H), 7.19-7.16 (m, 3H, Ar-H), 7.04 (d, ^3J = 8.4 Hz, 1H, Ar-H), 6.30 (dd, ^3J = 8.4 Hz, ^4J = 2.4 Hz, 1H, Ar-H), 6.25 (d, ^4J = 2.4 Hz, 1H, Ar-H), 3.61-3.57 (m, 2H, CH_2), 2.58 (d, ^3J = 6.9 Hz, 2H, CH_2), 2.54-2.46 (m, 2H, CH_2), 1.79-1.75 (m, 2H, CH_2), 1.71-1.63 (m, 1H, CH), 1.50-1.41 (m, 2H, CH_2).
^{13}C-NMR (75.5 MHz, MeOD):	δ (ppm) = 160.6 (**C**$_q$-OH), 160.5 (**C**$_q$-OH), 144.5 (**C**H=N), 141.6 (**C**$_q$), 132.3 (**C**H$_{Ar}$), 130.2 (2 **C**H$_{Ar}$), 129.3 (2 **C**H$_{Ar}$), 127.0 (**C**H$_{Ar}$), 113.4 (**C**$_q$), 108.1 (**C**H$_{Ar}$), 103.7 (**C**H$_{Ar}$), 53.3 (2 **C**H$_2$), 43.7 (**C**H$_2$), 38.8 (**C**H), 32.1 (2 **C**H$_2$).
M.p.:	138-141 °C
GC-MS (HS_100_L):	t_R = 11.10 min (m/z = 310.1, 98 % M^+, BP).
HRMS (EI$^+$):	*m/z*: calcd for $C_{19}H_{22}O_2N_2$ $[M]^+$: 310.1681; found 310.1683.

4-Phenyl-1,4-diazepane hydrochloride (38) [105]



A 250 mL Schlenk tube, filled with argon, was charged with 500 mg (416 µL, 2.50 mmol, 1.00 eq) *tert*.-butyl-1-homopiperazine **(36)**, 470 mg (315 µL, 3.00 mmol, 1.20 eq) bromobenzene **(37)** and 50 mL toluene/*tert*.-BuOH (5:1, absolute, degassed). A colorless solution was obtained (**reaction mixture A**). A second 250 mL Schlenk tube was dried under vacuum, filled with argon and charged consecutively with 59.5 mg (125 µmol, 0.05 eq) **X-Phos**, 28.0 mg (125 µmol, 0.05 eq) $Pd(OAc)_2$, 240 mg (2.50 mmol, 1.20 eq) sodium *tert*-butoxide and 100 mL toluene/*tert*.-BuOH (5:1, absolute, degassed). A yellow suspension was obtained (**reaction mixture B**). The **reaction mixture A** was added to **B** under an argon

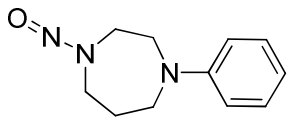
stream and the gained yellow suspension was refluxed for 24 h. GC-MS analysis and TLC analysis (MeOH, R_f = 0.89) indicated full conversion of the starting material. The reaction mixture was filtered through a pad of celite, which was then rinsed with EtOAc. The yellow filtrate was concentrated under reduced pressure and the obtained brown oil was purified by column chromatography (CH/EtOAc 20:1 → 15:1, R_f = 0.11(free homopiperazine), size: 22.5 x 3.5 cm, 75 g silica gel) to yield 196 mg (28 %) *tert*.-butyl-4-phenyl-1,4-diazepane-1-carboxylate as a yellow oil, which was dissolved in 8 mL toluene. Afterwards 1.5 mL conc. HCl were added. The mixture was stirred at rt for 3 h and was than extracted with 10 mL water. The aqueous layer was dried at the lyophilisator to obtain the pure product.

$C_{11}H_{17}N_2Cl$ [212.7]

yield: 153.7 mg (29 %), yellow-orange solid

^{1}H-NMR (300 MHz, D_2O): δ (ppm) = 7.53-7.48 (m, 2H, Ar-H), 7.38-7.31 (m, 3H, Ar-H), 4.04-4.03 (m, 2H, CH_2), 3.83-3.79 (m, 2H, CH_2), 3.72-3.58 (m, 4H, 2 CH_2), 3.52-3.49 (m, 2H, CH_2), 2.37-2.34 (m, 2H, NH_2).

1-Nitroso-4-phenyl-1,4-diazepan (39)

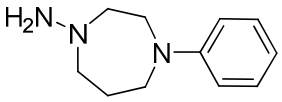


A 25 mL Schlenk tube was charged with 154 mg (723 µmol, 1.00 eq) 4-phenyl-1,4-diazepane hydrochloride **(38)**, 5.0 mL THF and 503 µL (365 mg, 3.61 mmol, 5.00 eq) triethylamine. To this yellow-orange suspension 134 µL (116 mg, 1.12 mmol, 1.55 eq) *tert*. butylnitrite were added. The yellow suspension was refluxed over night. Because GC-MS analysis and TLC analysis (MeOH, R_f = 0.80) indicated no full conversion of the starting material another 134 µL (116 mg, 1.12 mmol, 1.55 eq) *tert*. butylnitrite were added and the mixture was refluxed for further 2 h. The orange solution was transferred to a one-neck round bottom flask and concentrated in vacuum at a temperature of 30 °C. The crude product was used in the next reaction without further purification.

$C_{11}H_{15}N_3O$ [205.2]

yield:	254.6 mg (>99 %), brown oil
R_f (DCM):	0.34
GC-MS (HS_50_S2):	t_R = 7.29 min, (m/z = 205.1, 97 % M^+, BP: 132.1).

4-Phenyl-1,4-diazepane-1-amine (40)

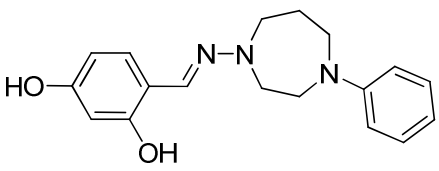


A 25 mL Schlenk tube was dried under vacuum, filled with argon and charged with 60.4 mg (1.59 mmol, 2.20 eq) $LiAlH_4$ and 3.0 mL absolute THF. The grey suspension was heated to reflux and a solution of 148 mg (723 µmol, 1.00 eq) 1-nitroso-4-phenyl-1,4-diazepane **(39)** in 1.3 mL absolute THF was added dropwise to the boiling suspension. After complete addition the brown suspension was refluxed for 2 h. GC-MS analysis showed full conversion of the starting material. The suspension was hydrolyzed according to the n,n,3n- method (0.5 mL water, 0.5 mL 15 % aqueous NaOH and 1.5 mL water). The mixture was filtrated, the filter cake was washed with 10 mL THF, dried over $MgSO_4$ and concentrated under reduced pressure. Final purification by column chromatography (MeOH, size: 14.0 x 2.5 cm, 17 g silica gel) yielded the pure product.

$C_{11}H_{17}N_3$ [191.2]

yield:	32.7 mg (24 %) orange oil
R_f (MeOH):	0.37
GC-MS (HS_50_S2):	t_R = 6.82 min (m/z = 191.1, 97 % M^+, BP: 132.1).

***(E)*-4-((4-Phenyl-1,4-diazepan-1-ylimino)methyl)benzene-1,3-diol (41)**



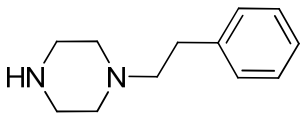
A reaction block was placed on a hotplate stirrer as depicted in Fig. 85. A brown 10 mL reaction vessel was charged consecutively with 31.7 mg (166 µmol, 1.00 eq) 4-phenyl-1,4-diazepane-1-amine **(40)**, 1.0 mL toluene, 21.9 mg (166 µmol, 1.00 eq) 2,4-dihydroxybenzaldehyde **(4i)** and a magnetic stirring bar. The vessel was crimped with a cap, placed in the preheated (100 °C) reaction block and stirred vigorously at 100 °C over night. TLC analysis indicated full conversion of the starting material. After cooling to rt the cap was removed, the reaction mixture was transferred in a one-neck round bottom flask and concentrated under reduced pressure. Drying under high vacuum yielded the pure product.

$C_{18}H_{21}O_2N_3$ [311.3]

yield:	50.0 mg (97 %), brown-red oil
R_f (CH/ EtOAc 3:1):	0.75
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 11.39 (s, 1H, CH), 9.51 (bs, 1H, OH), 7.54 (s, 1H, OH), 7.18-7.12 (m, 2H, Ar-H), 7.06 (d, ^3J = 8.4 Hz, 1 H, Ar-H), 6.75 (d, ^3J = 8.4 Hz, 1 H, Ar-H), 6.58 (t, ^3J = 7.2 Hz, 1H, Ar-H), 6.25 (dd, ^3J = 8.4 Hz, ^4J = 2.1 Hz, 1H, Ar-H), 6.19 (d, ^4J = 2.1 Hz, 1H, Ar-H), 3.63-3.62 (m, 2H, CH_2), 3.52-3.50 (m, 2H, CH_2), 3.43-3.37 (m, 4H, 2 CH_2), 1.99-1.95 (m, 2H, CH_2).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 157.8 (**C**$_q$-OH), 157.5 (**C**$_q$-OH), 147.1 (**C**H=N), 135.5 (**C**$_q$), 129.4 (**C**H$_{Ar}$), 129.2 (2 **C**H$_{Ar}$), 115.5 (**C**H$_{Ar}$), 112.5 (**C**$_q$), 111.4 (2 **C**H$_{Ar}$), 106.7 (**C**H$_{Ar}$), 102.3 (**C**H$_{Ar}$), 51.7 (**C**H$_2$), 49.6 (**C**H$_2$), 47.3 (**C**H$_2$), 47.2 (**C**H$_2$), 23.2 (**C**H$_2$).
HRMS (EI$^+$):	*m/z*: calcd for $C_{18}H_{21}O_2N_3$ $[M]^+$: 311.1634; found 311.1616.

6.2.4. Hydrazone synthesis II (building block D) [106]

1-Phenethylpiperazin (45a)

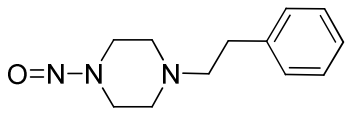


A 100 mL Schlenk tube was charged with 1.00 g (730 µL, 5.41 mmol, 1.00 eq) 2-phenethylbromide **(42)**, 20 mL toluene and 2.33 g (27.0 mmol, 4.00 eq) piperazine **(44)**. The colorless suspension was stirred at 85 °C for 3.5 h. GC-MS analysis showed full conversion of the starting material. The mixture was filtrated and concentrated under reduced pressure. The generated colorless solid was suspended in 6 mL 5 % aqueous HCl and extracted with DCM (3 x 6 mL). The aqueous phase was alkalized with solid NaOH and extracted with DCM (3 x 10 mL). The combined orgenic layers were washed with water (2 x 10 mL) and 10 mL brine, dried over $MgSO_4$ and concentrated under reduced pressure. Final purification by vacuum destillation yielded the product with 95 % purity.

$C_{12}H_{18}N_2$ [190.0]

yield:	710.1 mg (69 %), colorless liquid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.30-7.25 (m, 2H, Ar-H), 7.20-7.18 (m, 3H, Ar-H), 2.92 (t, ^3J = 5.1 Hz, 4H, 2 CH_2), 2.83-2.77 (m, 2H, CH_2), 2.60-2.54 (m, 2H, CH_2), 2.49 (bs, 4H, 2 CH_2), 1.82 (s, 1H, NH).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 140.3 (**C**$_q$), 128.6 (2 **C**H$_{Ar}$), 128.3 (2 **C**H$_{Ar}$), 125.9 (**C**H$_{Ar}$), 61.1 (**C**H$_2$), 54.5 (2 **C**H$_2$), 46.0 (2 **C**H$_2$), 33.3 (**C**H$_2$).
bp.:	85-90 °C (0.35-0.37 mbar)
GC-MS (HS_50_S2):	t_R = 6.21 min (m/z = 190.1, 95 % M^+, BP: 99.0, 5 % dialkylated product).

1-Nitroso-4-phenethylpiperazin (46a)



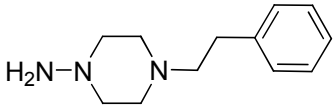
A 100 mL Schlenk tube was charged with 680 mg (3.58 mmol, 1.00 eq) 1-phenethylpiperazine **(45a)**, 25 mL THF and 670 µL (5.55 mmol, 1.55 eq) *tert*. butylnitrite. The mixture was refluxed over night. GC-MS analysis indicated full conversion of the starting material. The brown solution was transferred to a one-neck round bottom flask and

concentrated in vacuum at a temperature of 30 °C. The crude product was used in the next reaction without further purification.

$C_{12}H_{17}ON_3$ [219.0]

yield:	830.0 mg (> 99 %), brown solid
GC-MS (HS_50_S2):	t_R = 7.22 min (m/z = 218.9, 95 % M^+, BP: 128.0).

4-Phenethylpiperazin-1-amine (47a)



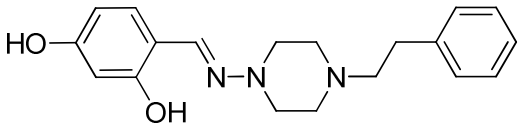
A 100 mL three-neck round bottom flask with dropping funnel and reflux condenser was dried under vacuum, filled with nitrogen and charged with 299 mg (7.87 mmol, 2.20 eq) $LiAlH_4$ and 15 mL absolute THF. The grey suspension was heated to reflux and a solution of 784 mg (3.58 mmol, 1.00 eq) 1-nitroso-4-phenethylpiperazine **(46a)** in 5 mL absolute THF was added dropwise to the boiling suspension. After complete addition the suspension was refluxed for further 2.5 h. GC-MS analysis showed full conversion of the starting material. The suspension was hydrolyzed according to the n,n,3n-method (0.5 mL water, 0.5 mL 15 % aqueous NaOH and 1.5 mL water) upon which the color turned to orange. The mixture was filtrated, the filter cake was washed with 10 mL THF and the filtrate was concentrated under reduced pressure. Final purification by column chromatography (MeOH, size: 23.5 x 2.0 cm, 30 g silica gel) yielded the product with 90 % purity.

$C_{12}H_{19}N_3$ [205.0]

yield:	580.2 mg (79 %), light brown solid
R_f (MeOH):	0.27
^{1}H-NMR (300 MHz, MeOD):	δ (ppm) = 7.29-7.17 (m, 5H, Ar-H), 2.82-2.56 (m, 12H, 6 CH_2).

^{13}C-NMR (75.5 MHz, MeOD):	δ (ppm) = 131.6 (**C**$_q$), 120.1 (2 **C**H$_{Ar}$), 119.9 (2 **C**H$_{Ar}$), 117.6 (**C**H$_{Ar}$), 51.4 (**C**H$_2$), 49.3 (2 **C**H$_2$), 44.0 (2 **C**H$_2$), 24.7 (**C**H$_2$).
M.p.:	rt (22 °C)
GC-MS (HS_50_S2):	t_R = 6.63 min (m/z = 205.2, 90 % M^+, BP: 114.1).

***(E)*-4-((4-Phenethylpiperazin-1-ylimino)methyl)benzene-1,3-diol (48a)**



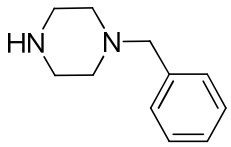
A reaction block was placed on a hotplate stirrer as depicted in Fig. 85. A brown 10 mL reaction vessel was charged consecutively with 100 mg (488 µmol, 1.00 eq, 90 % purity) 4-phenethylpiperazin-1-amine **(47a)**, 2.0 mL toluene, 60.7 mg (439 µmol, 1.00 eq) 2,4-dihydroxybenzaldehyde **(4i)** and a magnetic stirring bar. The vessel was crimped with a cap, placed in the preheated (100 °C) reaction block and stirred vigorously at 100 °C over night. GC-MS analysis indicated full conversion of the starting material. After cooling to rt the cap was removed, the reaction mixture was transferred into a one-neck round bottom flask and concentrated under reduced pressure. Final purification by recrystallization from 20.0 mL toluene yielded the pure product.

$C_{19}H_{23}O_2N_3$ [325.0]

yield:	148.5 mg (94 %), orange-brown solid
^{1}H-NMR (300 MHz, DMSO-d$_6$):	δ (ppm) = 11.83 (bs, 1H, OH), 9.88 (bs, 1H, OH), 8.05 (s, 1H, CH=N), 7.51-7.32 (m, 6H, Ar-H), 6.50 (dd, ^3J = 8.4 Hz, ^4J = 1.8 Hz, 1H, Ar-H), 6.43 (d, ^4J = 1.8 Hz, 1H, Ar-H), 3.23 (bs, 2H, CH$_2$), 2.98-2.93 (m, 2H, CH$_2$), 2.83-2.70 (m, 8H, 4 CH$_2$).
^{13}C-NMR (75.5 MHz, DMSO-d$_6$):	δ (ppm) = 158.8 (**C**$_q$-OH), 158.5 (**C**$_q$-OH), 141.3 (**C**H=N), 140.2 (**C**$_q$), 130.6 (**C**H$_{Ar}$), 128.6 (2 **C**H$_{Ar}$), 128.1 (2 **C**H$_{Ar}$), 125.8 (**C**H$_{Ar}$), 111.5 (**C**$_q$), 106.9 (**C**H$_{Ar}$),

	102.3 (**C**CH_{Ar}), 59.2 (**C**H_2), 51.6 (2 **C**H_2), 51.1 (2 **C**H_2), 32.8 (**C**H_2).
M.p.:	211-214 °C
HRMS (EI^+):	*m/z*: calcd for $C_{19}H_{23}O_2N_3$ $[M]^+$: 325.1790; found 325.1799.

1-Benzylpiperazin (45b) [107]

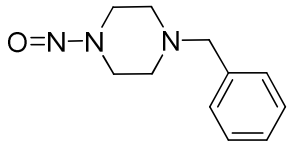


A 100 mL Schlenk tube was dried under vacuum, filled with argon and charged with 5.44 g (63.2 mmol, 4.00 eq) piperazine **(44)**, 50 mL absolute toluene and 2.00 g (1.82 mL, 15.8 mmol, 1.00 eq) benzylchloride **(43)**. The colorless suspension was stirred at 85 °C for 1.5 h. GC-MS analysis indicated full conversion of the starting material. The mixture was filtrated, washed with 5 mL toluene and concentrated under reduced pressure. The residue was dissolved in 10 mL DCM and extracted with 10 mL 2 M aqueous HCl solution. The aqueous layer was alkalyzed by adding 1.0 g solid NaOH and extracted with DCM (2 x 25 mL). The combined organic layers were washed with 30 mL brine and 30 mL water, dried over $MgSO_4$ and concentrated under reduced pressure. Final purification by silica gel filtration (MeOH) yielded the pure product.

$C_{11}H_{16}N_2$ [176.1]

yield:	1.715g (62 %), colorless oil
R_f (MeOH):	0.12
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.32-7.24 (m, 5H, Ar-H), 3.49 (s, 2H, CH_2), 2.88 (t, ^3J = 7.8 Hz, 4H, 2 CH_2), 2.41 (bs, 4H, 2 CH_2), 1.86 (s, 1H, NH).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 138.1 (**C**$_q$), 129.2 (2 **C**H_{Ar}), 128.1 (2 **C**H_{Ar}), 127.0 (**C**H_{Ar}), 63.7 (**C**H_2), 54.4 (2 **C**H_2), 46.1 (2 **C**H_2).
GC-MS (HS_50_S2):	t_R = 5.84 min (m/z = 176.1, 99 % M^+, BP: 91.0).

1-Benzyl-4-nitrosopiperazine (46b)

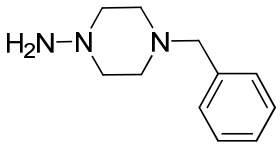


A 100 mL Schlenk tube was charged with 1.68 g (9.57 mmol, 1.00 eq) 1-benzylpiperazine **(45b)**, 50 mL THF and 1.78 mL (14.8 mmol, 1.55 eq) *tert*. butylnitrite. The mixture was refluxed over night. GC-MS analysis indicated full conversion of the starting material. The solution was transferred to a one-neck round bottom flask and concentrated in vacuum at a temperature of 30 °C. The crude product was used in the next reaction without further purification.

$C_{11}H_{15}N_3O$ [205.1]

yield: 1.99 g (>99 %), brownish oil
GC – MS (HS_50_S2): t_R = 6.90 min (m/z = 205.1, 97 % M^+, BP: 91.0).

4-Benzylpiperazin-1-amine (47b)

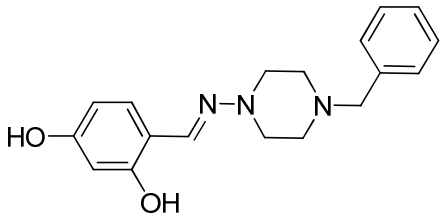


A 250 mL three-neck round bottom flask with dropping funnel and reflux condenser was dried under vacuum, filled with nitrogen and charged with 802 mg (21.1 mmol, 2.20 eq) $LiAlH_4$ and 40 mL absolute THF. The grey suspension was heated to reflux and a solution of 1.96 g (9.57 mmol, 1.00 eq) 1-benzyl-4-nitrosopiperazine **(46b)** in 17 mL absolute THF was added dropwise to the boiling suspension. After complete addition the suspension was refluxed for further 2 h. GC-MS analysis showed full conversion of the starting material. The suspension was hydrolyzed according to the n,n,3n-method (0.8 mL water, 0.8 mL 15 % aqueous NaOH and 2.4 mL water). The mixture was filtrated, the filter cake was washed with

10 mL THF and the filtrate was concentrated under reduced pressure. Final purification by silica gel filtration (MeOH, size: 17.5 x 3.0 cm, 80 g silica gel) yielded the pure product.
$C_{11}H_{16}N_2$ [191.1]

yield:	1.37 g (73%), yellow solid
R_f (MeOH):	0.27
^{1}H-NMR (300 MHz, MeOD):	δ (ppm) = 7.32-7.25 (m, 5H, Ar-H), 3.51 (s, 2H, CH_2), 2.69-2.53 (m, 8H, 4 CH_2).
^{13}C-NMR (75.5 MHz, MeOD):	δ (ppm) = 138.6 (**C**$_q$), 130.6 (2 **C**H$_{Ar}$), 129.4 (2 **C**H$_{Ar}$), 128.5 (**C**H$_{Ar}$), 63.5 (**C**H_2), 59.0 (2 **C**H_2), 53.5 (2 **C**H_2).
M.p.:	31°C - 34°C
GC–MS (HS_50_S2):	t_R = 6.27 min (m/z = 191.1, 97 % M^+, BP: 91.0).

***(E)*-4-((4-Benzylpiperazin-1-ylimino)methyl)benzene-1,3-diol (48b)**



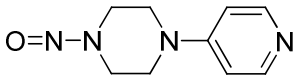
A reaction block was placed on a hotplate stirrer as depicted in Fig. 85. A brown 10 mL reaction vessel was charged consecutively with 150 mg (785 µmol, 1.00 eq) 4-benzylpiperazin-1-amine **(47b)**, 2.0 mL toluene, 108 mg (785 µmol, 1.00 eq) 2,4-dihydroxybenzaldehyde **(4i)** and a magnetic stirring bar. The vessel was crimped with a cap, placed in the preheated (100 °C) reaction block and stirred vigorously at 100 °C for 2 h. GC-MS analysis indicated full conversion of the starting material. After cooling to rt the cap was removed, the reaction mixture was transferred into a one-neck round bottom flask and concentrated under reduced pressure. Final purification by recrystallization from 4.0 mL toluene yielded the pure product.

$C_{18}H_{21}O_2N_3$ [311.3]

yield:	134.0 mg (95 %), beige solid

^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 11.61 (bs, 1H, OH), 9.67 (bs, 1H, OH), 7.83 (s, 1H, CH), 7.33-7.25 (m, 5H, Ar-H), 7.12 (d, ^{3}J = 8.4 Hz, 1H, Ar-H), 6.30 (dd, ^{3}J = 8.4 Hz, ^{4}J = 2.1 Hz, 1H, Ar-H), 6.23 (d, ^{4}J = 2.1 Hz, 1H, Ar-H), 3.52 (s, 2H, CH_2), 3.03 (s, 4H, 2 CH_2), 2.53 (s, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 158.8 (**C**$_q$-OH), 158.5 (**C**$_q$-OH), 141.3 (**C**H=N), 137.9 (**C**$_q$), 130.6 (**C**H$_{Ar}$), 128.7 (2 **C**H$_{Ar}$), 128.1 (2 **C**H$_{Ar}$), 126.9 (**C**H$_{Ar}$), 111.5 (**C**$_q$), 106.9 (**C**H$_{Ar}$), 102.3 (**C**H$_{Ar}$), 61.6 (**C**H$_2$), 51.4 (2 **C**H$_2$), 51.1 (2 **C**H$_2$).
M.p.:	225– 228°C
HRMS (EI$^+$):	*m/z*: calcd for $C_{18}H_{21}O_2N_3$ $[M]^+$: 311.1634; found 311.1656.

1-Nitroso-4-(pyridin-4-yl)piperazine (46c)

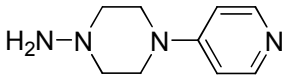


A 100 mL Schlenk tube was charged with 1.00 g (6.13 mmol, 1.00 eq) 1-(4-pyridinyl)-piperazin **(45c)**, 40 mL THF and 1.20 mL (9.80 mmol, 1.55 eq) *tert*. butylnitrite. The mixture was refluxed over night. GC-MS analysis and TLC analysis indicated full conversion of the starting material. The brown solution was transferred to a one-neck round bottom flask and concentrated in vacuum at a temperature of 30 °C. The crude product was used in the next reaction without further purification.

$C_9H_{12}ON_4$ [192.2]

yield:	1.60 g (> 99 %), brown oil
R_f (DCM/MeOH 8:1):	0.47
GC-MS (HS_50_S2):	t_R = 7.35 min (m/z = 192.8, 98 % M^+, BP: 121.0).

4-(Pyridine-4-yl)piperazine-1-amine (47c)

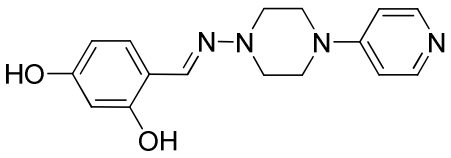


A 500 mL three-neck round bottom flask with dropping funnel and reflux condenser was dried under vacuum, filled with nitrogen and charged with 510 mg (13.5 mmol, 2.20 eq) $LiAlH_4$ and 26 mL absolute THF. The grey suspension was heated to reflux and a solution of 1.18 g (6.14 mmol, 1.00 eq) 1-nitroso-4-(pyridin-4-yl)piperazine **(46c)** in 7 mL absolute THF was added dropwise to the boiling suspension. After complete addition the suspension was refluxed for further 2 h. GC-MS analysis and TLC analysis showed full conversion of the starting material. The suspension was hydrolyzed according to the n,n,3n-method (1.0 mL water, 1.0 mL 15 % aqueous NaOH and 3.0 mL water). The mixture was filtrated, the filter cake was washed with 10 mL THF and the filtrate was concentrated under reduced pressure. Final purification by column chromatography (MeOH, R_f = 0.12, size: 27.5 x 4.5 cm, 250 g silica gel) yielded the pure product.

$C_9H_{12}N_4$ [178.2]

yield:	1.04 g (95 %), yellow solid
R_f (DCM/MeOH 3:1):	0.21
^{1}H-NMR (300 MHz, MeOD):	δ (ppm) = 8.12 (d, ^3J = 6.6 Hz, 2H, Ar-H), 6.84 (d, ^3J = 6.9 Hz, 2H, Ar-H), 3.45 (bs, 4H, 2 CH_2), 2.78-2.75 (m, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, MeOD):	δ (ppm) = 156.7 (**C**$_q$), 150.2 (2 **C**H$_{Ar}$), 109.7 (2 **C**H$_{Ar}$), 58.6 (2 **C**H_2), 46.5 (2 **C**H_2).
M.p.:	95-96 °C
GC-MS (NM_50_S2):	t_R = 6.82 min (m/z = 178.1, 96 % M^+, BP: 56.0).

(*E*)-4-((4-(Pyridine-4-yl)piperazin-1-ylimino)methyl)benzene-1,3-diol (48c)

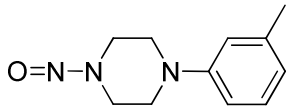


A reaction block was placed on a hotplate stirrer as depicted in Fig. 85. A brown 10 mL reaction vessel was charged consecutively with 250 mg (1.40 mmol, 1.00 eq) 4-(pyridine-4-yl)piperazine-1-amine **(47c)**, 4.0 mL toluene, 190 mg (1.40 mmol, 1.00 eq) 2,4-dihydroxybenzaldehyde **(4i)** and a magnetic stirring bar. The vessel was crimped with a cap, placed in the preheated (100 °C) reaction block and stirred vigorously at 100 °C for 2 h. GC-MS analysis and TLC analysis indicated full conversion of the starting material. After cooling to rt the cap was removed, the reaction mixture was transferred into a one-neck round bottom flask, concentrated under reduced pressure and dried under high vacuum. Trituration with 15 mL hot toluene yielded the pure product.

$C_{16}H_{18}O_2N_4$ [298.3]

yield:	310.0 mg (74 %), brown solid
R_f (MeOH):	0.30
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 11.52 (bs, 1H, OH), 9.90 (bs, 1H, OH), 8.19 (bs, 2H, Ar-H), 7.97 (s, 1H, CH=N), 7.17 (d, ^3J = 8.4 Hz, 1H, Ar-H), 6.88 (d, ^3J = 6.0 Hz, 2H, Ar-H), 6.31 (dd, ^3J = 8.4 Hz, ^4J = 2.1 Hz, 1H, Ar-H), 6.24 (d, ^4J = 2.1 Hz, 1H, Ar-H), 3.53-3.49 (m, 4H, 2 CH_2), 3.15-3.12 (m, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 159.1 (**C**$_q$-OH), 158.6 (**C**$_q$-OH), 154.1 (**C**$_q$), 149.8 (2 **C**H$_{Ar}$), 142.7 (**C**H=N), 130.8 (**C**H$_{Ar}$), 111.4 (**C**$_q$), 108.6 (2 **C**H$_{Ar}$), 107.0 (**C**H$_{Ar}$), 102.4 (**C**H$_{Ar}$), 50.7 (2 **C**H_2), 44.6 (2 **C**H_2).
M.p.:	270-273 °C (decomposition)
HRMS (EI$^+$):	*m/z*: calcd for $C_{16}H_{18}O_2N_4$ $[M]^+$: 298.1430; found 298.1447.

1-Nitroso-4-*m*-tolylpiperazine (46d)

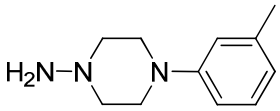


A 100 mL Schlenk tube was charged with 1.00 g (5.68 mmol, 1.00 eq) 1-(3-methylphenyl)-piperazin **(45d)**, 30 mL THF and 1.05 mL (8.80 mmol, 1.55 eq) *tert*. butylnitrite. The mixture was refluxed over night. GC-MS analysis and TLC analysis indicated full conversion of the starting material. The brown solution was transferred to a one-neck round bottom flask and concentrated in vacuum at a temperature of 30 °C. The crude product was used in the next reaction without further purification.

$C_{11}H_{15}ON_3$ [205.2]

yield:	1.23 g (> 99 %), brown oil
R_f (DCM):	0.55
GC-MS (HS_50_S2):	t_R = 7.11 min (m/z = 205.1, 95 % M^+, BP: 134.1).

4-*m*-Tolylpiperazine-1-amine (47d)

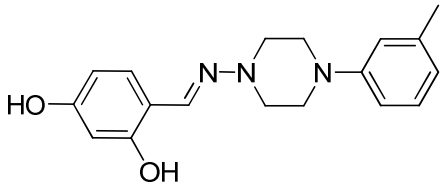


A 250 mL three-neck round bottom flask with dropping funnel and reflux condenser was dried under vacuum, filled with nitrogen and charged with 500 mg (13.2 mmol, 2.20 eq) $LiAlH_4$ and 25 mL absolute THF. The grey suspension was heated to reflux and a solution of 1.16 g (5.68 mmol, 1.00 eq) 1-nitroso-4-*m*-tolylpiperazine **(46d)** in 7 mL absolute THF was added dropwise to the boiling suspension. After complete addition the suspension was refluxed for further 2 h. GC-MS analysis and TLC analysis showed full conversion of the starting material. The suspension was hydrolyzed according to the n,n,3n-method (1.0 mL water, 1.0 mL 15 % aqueous NaOH and 3.0 mL water). The mixture was filtrated, the filter cake was washed with 10 mL THF and the filtrate was concentrated under reduced pressure. Final purification by column chromatography (MeOH, size: 26.0 x 4.0 cm, 200 g silica gel) yielded the pure product.

$C_{11}H_{17}N_3$ [191.2]

yield:	323.0 mg (28 %), brown oil
R_f (MeOH):	0.37
^{1}H-NMR (300 MHz, MeOD):	δ (ppm) = 7.10 (t, ^3J = 7.8 Hz, 1H, Ar-H), 6.78-6.74 (m, 2H, Ar-H), 6.67 (d, ^3J = 7.5 Hz, 1H, Ar-H), 3.20 (bs, 4H, 2 CH_2), 2.81 (bs, 4H, 2 CH_2), 2.28 (s, 3H, CH_3).
^{13}C-NMR (75.5 MHz, MeOD):	δ (ppm) = 152.3 (**C**$_q$), 139.8 (**C**$_q$), 130.0 (**C**H$_{Ar}$), 122.1 (**C**H$_{Ar}$), 118.3 (**C**H$_{Ar}$), 114.8 (**C**H$_{Ar}$), 59.3 (2 **C**H$_2$), 50.2 (2 **C**H$_2$), 21.8 (**C**H$_3$).
GC-MS (NM_50_S2):	t_R = 6.52 min (m/z = 191.1, 95 % M^+, BP: 134.1).

(*E*)-4-((4-*m*-Tolylpiperazin-1-ylimino)methyl)benzene-1,3-diol (48d)



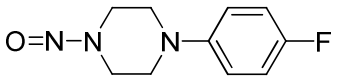
A reaction block was placed on a hotplate stirrer as depicted in Fig. 85. A brown 10 mL reaction vessel was charged consecutively with 150 mg (731 µmol, 1.00 eq) 4-*m*-tolylpiperazine-1-amine **(47d)**, 2.0 mL toluene, 101 mg (731 µmol, 1.00 eq) 2,4-dihydroxybenzaldehyde **(4i)** and a magnetic stirring bar. The vessel was crimped with a cap, placed in the preheated (100 °C) reaction block and stirred vigorously at 100 °C for 2 h. GC-MS analysis and TLC analysis indicated full conversion of the starting material. After cooling to rt the cap was removed, the reaction mixture was transferred into a one-neck round bottom flask, concentrated under reduced pressure and dried under high vacuum. Recrystallization from 2 mL toluene yielded the pure product.

$C_{18}H_{21}O_2N_3$ [311.3]

yield:	141.8 mg (58 %), brown solid
R_f (MeOH):	0.65

^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 11.60 (s, 1H, OH), 9.75 (bs, 1H, OH), 7.95 (s, 1H, CH=N), 7.18-7.09 (m, 2H, Ar-H), 6.82-6.78 (m, 2H, Ar-H), 6.64 (d, ^{3}J = 7.2 Hz, 1H, Ar-H), 6.31 (dd, ^{3}J = 8.1, ^{4}J = 2.1 Hz, 1H, Ar-H), 6.25 (d, ^{4}J = 2.1 Hz, 1H, Ar-H), 3.31-3.28 (m, 4H, 2 CH_2), 3.17-3.15 (m, 4H, 2 CH_2), 2.26 (s, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 159.0 (**C**$_q$-OH), 158.6 (**C**$_q$-OH), 150.5 (**C**$_q$), 142.3 (**C**H=N), 138.0 (**C**$_q$-CH_3), 130.7 (**C**H$_{Ar}$), 128.7 (**C**H$_{Ar}$), 120.0 (**C**H$_{Ar}$), 116.4 (**C**H$_{Ar}$), 113.0 (**C**H$_{Ar}$), 111.4 (**C**$_q$), 107.0 (**C**H$_{Ar}$), 102.4 (**C**H$_{Ar}$), 51.1 (2 **C**H_2), 47.6 (2 **C**H_2), 21.3 (**C**H_3).
M.p.:	135-139 °C
HRMS (EI$^+$):	*m/z*: calcd for $C_{18}H_{21}O_2N_3$ [M]$^+$: 311.1654; found 311.1634.

1-(4-Fluorophenyl)-4-nitrosopiperazine (46e)

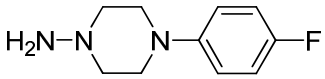


A 100 mL Schlenk tube was charged with 1.00 g (5.55 mmol, 1.00 eq) 1-(4-fluorophenyl)-piperazine **(45e)**, 30 mL THF and 1.15 mL (8.59 mmol, 1.55 eq) *tert*. butylnitrite. The mixture was refluxed over night. GC-MS analysis and TLC analysis indicated full conversion of the starting material. The brown solution was transferred to a one-neck round bottom flask and concentrated in vacuum at a temperature of 30 °C. The crude product was used in the next reaction without further purification.

$C_{10}H_{12}ON_3F$ [209.2]

yield:	1.25 g (> 99 %), brown oil
R_f (DCM):	0.47
GC-MS (NM_50_S2):	t_R = 6.75 min (m/z = 209.0, 99 % M$^+$, BP: 120.1).

4-(4-Fluorophenyl)piperazine-1-amine (47e)

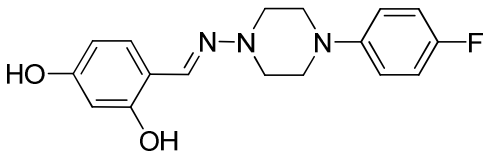


A 500 mL three-neck round bottom flask with dropping funnel and reflux condenser was dried under vacuum, filled with nitrogen and charged with 460 mg (12.21 mmol, 2.20 eq) $LiAlH_4$ and 23 mL absolute THF. The grey suspension was heated to reflux and a solution of 1.16 g (5.55 mmol, 1.00 eq) 1-(4-fluorophenyl)-4-nitrosopiperazine **(46e)** in 8 mL absolute THF was added dropwise to the boiling suspension. After complete addition the suspension was refluxed for further 2 h. GC-MS analysis and TLC analysis showed full conversion of the starting material. The suspension was hydrolyzed according to the n,n,3n-method (1.0 mL water, 1.0 mL 15 % aqueous NaOH and 3.0 mL water). The mixture was filtrated, the filter cake was washed with 10 mL THF and the filtrate was concentrated under reduced pressure. Final purification by column chromatography (MeOH, size: 24.0 x 3.5 cm, 180 g silica gel) yielded the pure product.

$C_{10}H_{14}N_3F$ [195.2]

yield:	0.49 g (45 %), light yellow solid
R_f (MeOH):	0.46
^{1}H-NMR (300 MHz, MeOD):	δ (ppm) = 6.97-6.95 (m, 4H, Ar-H), 3.16 (bs, 4H, 2 CH_2), 2.82 (bs, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, MeOD):	δ (ppm) = 160.4, 157.2 ($^1J_{C-F}$ = 237.6 Hz, $\mathbf{C}_q$-F), 149.0 ($\mathbf{C}_q$), 119.4, 119.3 ($^3J_{C-F}$ = 7.7 Hz, 2 $\mathbf{C}H_{Ar}$), 116.5, 116.2 ($^2J_{C-F}$ = 22.3 Hz, 2 $\mathbf{C}H_{Ar}$), 59.2 (2 $\mathbf{C}H_2$), 50.9 (2 $\mathbf{C}H_2$).
M.p.:	67 °C
GC-MS (NM_50_S2):	t_R = 6.21 min (m/z = 195.2, 99 % M^+, BP: 138.1).

(*E*)-4-((4-(4-Fluorophenyl)piperazin-1-ylimino)methyl)benzene-1,3-diol (48e)

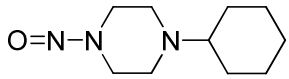


A reaction block was placed on a hotplate stirrer as depicted in Fig. 85. A brown 10 mL reaction vessel was charged consecutively with 150 mg (768 µmol, 1.00 eq) 4-(4-fluorophenyl)piperazine-1-amine **(47e)**, 2.0 mL toluene, 110 mg (768 µmol, 1.00 eq) 2,4-dihydroxybenzaldehyde **(4i)** and a magnetic stirring bar. The vessel was crimped with a cap, placed in the preheated (100 °C) reaction block and stirred vigorously at 100 °C for 2 h. GC-MS analysis and TLC analysis indicated full conversion of the starting material. After cooling to rt the cap was removed, the reaction mixture was transferred into a one-neck round bottom flask, concentrated under reduced pressure and dried under high vacuum. Recrystallization from 7 mL toluene yielded the pure product.

$C_{17}H_{18}O_2N_3F$ [315.3]

yield:	67.8 mg (25 %), brown solid
R_f (MeOH):	0.64
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 11.59 (bs, 1H, OH), 9.72 (bs, 1H, OH), 7.95 (s, 1H, CH=N), 7.17 (d, ^3J = 8.4 Hz, 1H, Ar-H), 7.10-6.99 (m, 4H, Ar-H), 6.31 (dd, ^3J = 8.4 Hz, ^4J = 2.4 Hz, 1H, Ar-H), 6.25 (d, ^4J = 2.4 Hz, 1H, Ar-H), 3.26-3.25 (m, 4H, 2 CH_2), 3.18-3.16 (m, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 159.0 (**C**$_q$-OH), 158.6 (**C**$_q$-OH), 157.7, 154.6 ($^1J_{C\text{-}F}$ = 236.0 Hz, **C**$_q$-F), 147.4, 147.3 ($^4J_{C\text{-}F}$ = 2.0 Hz, **C**$_q$), 142.3 (**C**H=N), 130.7 (**C**H$_{Ar}$), 117.7, 117.6 ($^3J_{C\text{-}F}$ = 7.6 Hz, 2 **C**H$_{Ar}$), 115.4, 115.1 ($^2J_{C\text{-}F}$ = 21.9 Hz, 2 **C**H$_{Ar}$), 111.4 (**C**$_q$), 107.0 (**C**H$_{Ar}$), 102.4 (**C**H$_{Ar}$), 51.1 (2 **C**H$_2$), 48.3 (2 **C**H$_2$).
M.p.:	176-178 °C
GC-MS (HS_100_L):	t_R = 10.63 min (m/z = 315.1, BP: 56.0).

1-Cyclohexyl-4-nitrosopiperazine (46f)

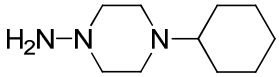


A 100 mL Schlenk tube was charged with 1.00 g (5.95 mmol, 1.00 eq) 1-cyclohexylpiperazine **(45f)**, 35 mL THF and 1.10 mL (9.22 mmol, 1.55 eq) *tert*. butylnitrite. The mixture was refluxed over night. GC-MS analysis and TLC analysis indicated full conversion of the starting material. The brown solution was transferred to a one-neck round bottom flask and concentrated in vacuum at a temperature of 30 °C. The crude product was used in the next reaction without further purification.

$C_{10}H_{19}ON_3$ [197.2]

yield:	1.41 g (> 99 %), red-brown oil
R_f (DCM/MeOH 8:1):	0.82
GC-MS (NM_50_S2):	t_R = 6.63 min (m/z = 197.2, 99 % M^+, BP: 167.2).

4-Cyclohexylpiperazine-1-amine (47f)

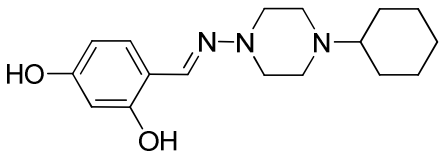


A 500 mL three-neck round bottom flask with dropping funnel and reflux condenser was dried under vacuum, filled with nitrogen and charged with 500 mg (13.1 mmol, 2.20 eq) $LiAlH_4$ and 23 mL absolute THF. The grey suspension was heated to reflux and a solution of 1.17 g (5.93 mmol, 1.00 eq) 1-cyclohexyl-4-nitrosopiperazine **(46f)** in 8 mL absolute THF was added dropwise to the boiling suspension. After complete addition the suspension was refluxed for further 2 h. GC-MS analysis and TLC analysis showed full conversion of the starting material. The suspension was hydrolyzed according to the n,n,3n-method (1.0 mL water, 1.0 mL 15 % aqueous NaOH and 3.0 mL water). The mixture was filtrated, the filter cake was washed with 10 mL THF and the filtrate was concentrated under reduced pressure. Final purification by column chromatography (MeOH, size: 22.0 x 3.5 cm, 180 g silica gel) yielded the pure product.

$C_{10}H_{21}N_3$ [183.3]

yield:	0.5 g (46 %), orange-brown solid
R_f (MeOH):	0.33
^{1}H-NMR (300 MHz, MeOD):	δ (ppm) = 2.72-2.66 (m, 8H, 4 CH_2), 2.30-2.22 (m, 1H, CH), 1.93-1.80 (m, 4H, CH_2), 1.67-1.63 (m, 1H, CH), 1.31-1.12 (m, 5H, CH, CH_2).
^{13}C-NMR (75.5 MHz, MeOD):	δ (ppm) = 64.6 (**C**H), 59.3 (2 **C**H_2), 49.4 (2 **C**H_2), 29.9 (2 **C**H_2), 27.3 (**C**H_2), 26.9 (2 **C**H_2).
M.p.:	36-37 °C
GC-MS (NM_50_S2):	t_R = 5.95 min (m/z = 183.2, 99 % M^+, BP: 167.2).

(*E*)-4-((4-Cyclohexylpiperazin-1-ylimino)methyl)benzene-1,3-diol (48f)



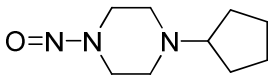
A reaction block was placed on a hotplate stirrer as depicted in Fig. 85. A brown 10 mL reaction vessel was charged consecutively with 150 mg (818 µmol, 1.00 eq) 4-cyclohexylpiperazine-1-amine **(47f)**, 2.0 mL toluene, 113 mg (818 µmol, 1.00 eq) 2,4-dihydroxybenzaldehyde **(4i)** and a magnetic stirring bar. The vessel was crimped with a cap, placed in the preheated (100 °C) reaction block and stirred vigorously at 100 °C for 2 h. GC-MS analysis and TLC analysis indicated full conversion of the starting material. After cooling to rt the cap was removed, the reaction mixture was transferred into a one-neck round bottom flask, concentrated under reduced pressure and dried under high vacuum. Trituration with 16 mL hot toluene yielded the pure product.

$C_{17}H_{25}O_2N_3$ [303.4]

yield:	110.0 mg (66 %), brown solid
R_f (MeOH):	0.55

^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 11.65 (s, 1H, OH), 9.69 (bs, 1H, OH), 7.82 (s, 1H, CH=N), 7.11 (d, ^{3}J = 8.4 Hz, 1H, Ar-H), 6.28 (dd, ^{3}J = 8.4 Hz, ^{4}J = 2.1 Hz, 1H, Ar-H), 6.21 (d, ^{4}J = 2.1 Hz, 1H, Ar-H), 2.99 (bs, 4H, 2 CH_2), 2.65 (bs, 4H, 2 CH_2), 2.30-2.27 (m, 1H, CH), 1.75-1.73 (m, 4H, 2 CH_2), 1.59-1.56 (m, 1H, CH), 1.19-1.05 (m, 5H, 2 CH_2, CH).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 158.8 (**C**$_q$-OH), 158.5 (**C**$_q$-OH), 141.1 (**C**H=N), 130.6 (**C**H_{Ar}), 111.5 (**C**$_q$), 106.9 (**C**H_{Ar}), 102.3 (**C**H_{Ar}), 62.2 (**C**H), 51.6 (2 **C**H_2), 47.4 (2 **C**H_2), 28.3 (2 **C**H_2), 25.8 (**C**H_2), 25.2 (2 **C**H_2).
M.p.:	247-249 °C (decomposition)
GC-MS (HS_100_L):	t_R = 10.06 min (m/z = 303.1, 95 % M^+, BP: 166.1).
HRMS (EI^+):	*m/z*: calcd for $C_{17}H_{25}O_2N_3$ $[M]^+$: 303.1947; found 303.1942.

1-Cyclopentyl-4-nitrosopiperazine (46g)

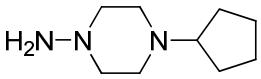


A 100 mL Schlenk tube was charged with 980 mg (6.48 mmol, 1.00 eq) 1-cyclopentylpiperazine **(45g)**, 30 mL THF and 1.34 mL (10.0 mmol, 1.55 eq) *tert*. butylnitrite. The mixture was refluxed over night. GC-MS analysis and TLC analysis indicated full conversion of the starting material. The brown solution was transferred to a one-neck round bottom flask and concentrated in vacuum at a temperature of 30 °C. The crude product was used in the next reaction without further purification.

$C_9H_{17}ON_3$ [183.2]

yield:	1.44 g (> 99 %), brown oil
GC-MS (NM_50_S2):	t_R = 6.25 min (m/z = 183.2, 99 % M^+, BP: 153.2).

4-Cyclopentylpiperazine-1-amine (47g)

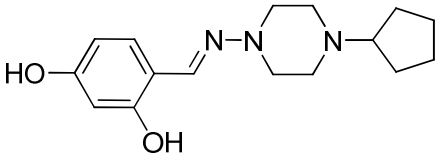


A 500 mL three-neck round bottom flask with dropping funnel and reflux condenser was dried under vacuum, filled with nitrogen and charged with 560 mg (17.3 mmol, 2.20 eq) $LiAlH_4$ and 27 mL absolute THF. The grey suspension was heated to reflux and a solution of 1.18 g (6.44 mmol, 1.00 eq) 1-cyclopentyl-4-nitrosopiperazine **(46g)** in 8 mL absolute THF was added dropwise to the boiling suspension. After complete addition the suspension was refluxed for further 2 h. GC-MS analysis and TLC analysis showed full conversion of the starting material. The suspension was hydrolyzed according to the n,n,3n-method (1.0 mL water, 1.0 ml 15 % aqueous NaOH and 3.0 mL water). The mixture was filtrated, the filter cake was washed with 10 mL THF and the filtrate was concentrated under reduced pressure. Final purification by column chromatography (MeOH, size: 26.0 x 3.5 cm, 200 g silica gel) yielded the pure product.

$C_9H_{19}N_3$ [169.2]

yield:	0.67 g (65 %), yellow solid
R_f (MeOH):	0.25
^{1}H-NMR (300 MHz, MeOD):	δ (ppm) = 3.10-2.30 (m, 9H, 4 CH_2, CH), 1.94-1.85 (m, 2H, CH_2), 1.71-1.56 (m, 4H, 2 CH_2), 1.45-1.36 (m, 2H, CH_2).
^{13}C-NMR (75.5 MHz, MeOD):	δ (ppm) = 68.5 (**C**H), 58.9 (2 **C**H_2), 52.9 (2 **C**H_2), 31.3 (**C**H_2), 25.1 (**C**H_2).
M.p.:	32 °C
GC-MS (NM_50_S2):	t_R = 5.56 min (m/z = 169.2, 98 % M^+, BP: 153.2).

(*E*)-4-((4-Cyclopentylpiperazin-1-ylimino)methyl)benzene-1,3-diol (48g)



A reaction block was placed on a hotplate stirrer as depicted in Fig. 85. A brown 10 mL reaction vessel was charged consecutively with 150 mg (887 µmol, 1.00 eq) 4-cyclopentylpiperazine-1-amine **(47g)**, 2.0 mL toluene, 123 mg (887 µmol, 1.00 eq) 2,4-dihydroxybenzaldehyde **(4i)** and a magnetic stirring bar. The vessel was crimped with a cap, placed in the preheated (100 °C) reaction block and stirred vigorously at 100 °C for 2 h. GC-MS analysis and TLC analysis indicated full conversion of the starting material. After cooling to rt the cap was removed, the reaction mixture was transferred into a one-neck round bottom flask, concentrated under reduced pressure and dried under high vacuum. Trituration with 16 mL hot toluene yielded the pure product.

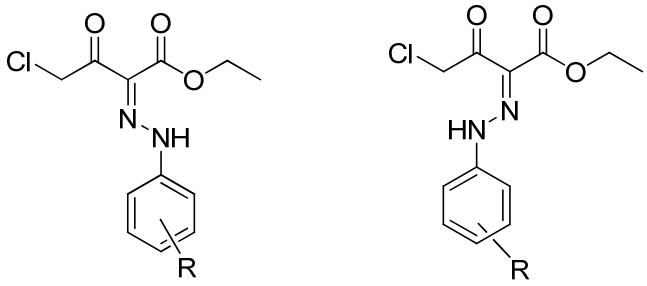
$C_{16}H_{23}O_2N_3$ [289.3]

yield:	186.1mg (76 %), beige solid
R_f (MeOH):	0.57
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 11.63 (s, 1H, OH), 9.69 (bs, 1H, OH), 7.82 (s, 1H, CH=N), 7.12 (d, ^3J = 8.4 Hz, 1H, Ar-H), 6.28 (dd, ^3J = 8.4 Hz, ^4J = 2.1 Hz, 1H, Ar-H), 6.22 (d, ^4J = 2.1 Hz, 1H, Ar-H), 3.00 (bs, 4H, 2 CH_2), 2.58-2.49 (m, 4H, 2 CH_2), 2.46-2.44 (m, 1H, CH), 1.81-1.78 (m, 2H, CH_2), 1.63-1.47 (m, 4H, 2 CH_2), 1.36-1.30 (m, 2H, CH_2).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 158.8 (**C**$_q$-OH), 158.5 (**C**$_q$-OH), 141.2 (**C**H=N), 130.6 (**C**H$_{Ar}$), 111.5 (**C**$_q$), 106.9 (**C**H$_{Ar}$), 102.3 (**C**H$_{Ar}$), 66.3 (**C**H), 51.2 (2 **C**H$_2$), 50.6 (2 **C**H$_2$), 29.9 (2 **C**H$_2$), 23.6 (2 **C**H$_2$).
M.p.:	237-239 °C (decomposition)
GC-MS (HS_100_L):	t_R = 9.13 min (m/z = 289.0, 95 % M^+, BP: 206.9).
HRMS (EI$^+$):	*m/z*: calcd for $C_{16}H_{23}O_2N_3$ $[M]^+$: 289.1790; found 289.1795.

6.3. Experimental procedures and analytical data for lead structure 2 optimization

6.3.1. Synthesis of 4-hydroxy-1*H*-pyrazole-3-carboxylates 52

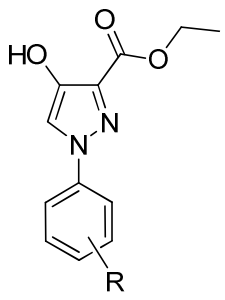
Butanoatderivative:



General procedure (GP-2):

A 10 mL one-neck round-bottom flask was charged with 1.04 eq aniline **49** which was dissolved in acetic acid at 10 °C (ice bath). To this cooled solution 1.06 eq $NaNO_2$, dissolved in conc. H_2SO_4, was added and the reaction mixture was stirred at 10 °C for 1 h. In a second 25 mL one-neck round-bottom flask 1.00 eq ethyl-4-chloro-3-oxobutanoate **(50)** was dissolved in a mixture of acetic acid and water (v/v 1:2) and cooled to 0 °C (ice bath + NaCl). After 1 h stirring at 10 °C the generated solution of the diazonium salt was added to the second solution at 0 °C and stirred for further 15 min at this temperature. An aqueous solution of 11.0 eq NaOAc (3.00 mL water/20.0 mmol NaOAc) was added to the reaction mixture at 0 °C and the product precipitated. After stirring at rt over night, the product was collected by filtration, washed with a small amount of water and dried under high pressure. The crude product was used in the next reaction step without further purification.

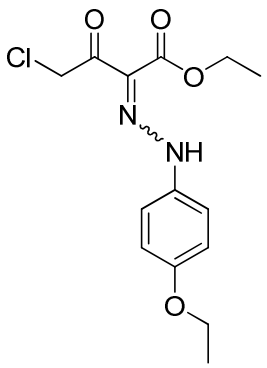
4-Hydroxypyrazolderivative:



General procedure (GP-3):

A 25 mL Schlenk tube was flushed with nitrogen and charged with 1.00 eq of synthesized oxobutanoate **51** (see above), which was suspended in EtOH. After adding 1.20 eq KOAc the suspension was heated under reflux (100 °C) for 1.5-2 h, during which the suspension dissolved. TLC analysis (CH/EtOAc 3:1) indicated full conversion of the starting material.
After cooling to rt the mixture was transferred to a flask and the volatiles were removed using a rotary evaporator. The residue was dissolved in 20 mL EtOAc and washed with water (2 x 15 mL) and 15 mL brine, dried over $MgSO_4$ and concentrated at the rotary evaporator. Drying at high vacuum yielded the pure product without further purification.

Ethyl-4-chloro-2-((4-ethoxyphenyl)diazenyl)-3-oxobutanoate (51a)



according to GP-2:

250 mg (240 µL, 1.83 mmol) 4-ethoxyaniline **(49a)** in 3.1 mL acetic acid and 128 mg (1.86 mmol) $NaNO_2$ in 0.5 mL conc. H_2SO_4 were combined at 10 °C resulting in a red-purple solution, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 289 mg (240 µL, 1.76 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 1.3 mL acetic acid and 2.6 mL water. Addition of 1.58 g (19.3 mmol) NaOAc in 3.0 mL water precipitated the title compound.

$C_{14}H_{17}O_4N_2Cl$ [312.5]

yield: 301.3 mg (55 %), yellow-brown solid

^{1}H-NMR (300 MHz, DMSO-d_6): **Isomer I (25 %):** δ (ppm) = **14.39 (s, 1H, NH)**, 7.57-

7.35 (m, 2H, Ar-H), 7.98-7.95 (m, 2H, Ar-H), 4.95-4.92 (m, 2H, Cl-CH_2), 4.31-4.27 (m, 2H, CH_2), 4.03-3.98 (m, 4H, 2 CH_2), 1.34-1.27 (m, 6H, 2 CH_3).

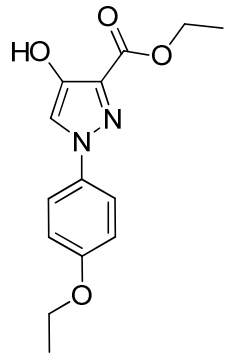
Isomer II (75 %): δ (ppm) = **12.35 (s, 1H, NH)**, 7.57-7.35 (m, 2H, Ar-H), 6.98-6.95 (m, 2H, Ar-H), 4.95-4.92 (m, 2H, Cl-CH_2), 4.31-4.27 (m, 2H, CH_2), 4.03-3.98 (m, 4H, 2 CH_2), 1.34-1.27 (m, 6H, 2 CH_3).

^{13}C-NMR (75.5 MHz, DMSO-d_6): **Isomer I:** δ (ppm) = **187.6 (C=O)**, **164.0 (C=O)**, **156.9 (C_q)**, 135.2 (**C**=N), 125.1 (C_q), **118.1 (2 CH_{Ar})**, **115.2 (2 CH_{Ar})**, 63.2 (O**C**H_2), **60.3 (Cl-CH_2)**, **49.6 (CH_2)**, **14.1 (CH_3)**, 13.9 (**C**H_3).

Isomer II: δ (ppm) = **185.7 (C=O)**, **162.0 (C=O)**, **156.0 (C_q)**, 135.2 (**C**=N), 125.1 (C_q), **117.4 (2 CH_{Ar})**, **115.1 (2 CH_{Ar})**, 63.2 (O**C**H_2), **60.8 (Cl-CH_2)**, **46.9 (CH_2)**, **14.5 (CH_3),** 13.9 (**C**H_3).

M.p.: 106-110 °C

Ethyl 1-(4-ethoxyphenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate (52a)



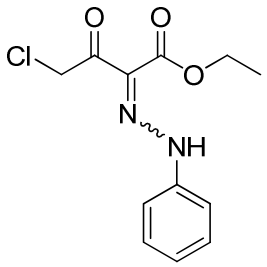
according to GP-3:

271 mg (866 µmol) (*Z*)-ethyl-4-chloro-2-((4-ethoxyphenyl)diazenyl)-3-oxobutanoate **(51a)** were suspended in 4 mL EtOH. 102 mg (1.04 mmol) KOAc were added.

$C_{14}H_{16}O_4N_2$ [276.0]

yield:	232.4 mg (97 %), dark red-brown solid
R_f (CH/ EtOAc 3:1):	0.35
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 9.07 (s, 1H, OH), 7.96 (s, 1H, Ar-H), 7.70 (d, ^3J = 9.0 Hz, 2H, Ar-H), 7.03 (d, ^3J = 9.0 Hz, 2H, Ar-H), 4.28 (q, ^3J = 6.9 Hz, 2H, CH_2), 4.06 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.36-1.27 (m, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 161.6 (**C**=O), 157.3 (**C**$_q$), 145.0 (**C**$_q$-OH), 132.8 (**C**$_q$), 131.1 (**C**$_q$), 120.0 (2 **C**H$_{Ar}$), 114.9 (2 **C**H$_{Ar}$), 114.8 (**C**H$_{Ar}$), 63.3 (**C**H$_2$), 59.7 (**C**H$_2$), 14.5 (**C**H$_3$), 14.2 (**C**H$_3$).
M.p.:	96-98 °C
GC-MS (NM_50_S2):	t_R = 8.07 min (m/z = 276.1, 99.0 % M^+, BP).

Ethyl-4-chloro-3-oxo-2-(phenyldiazenyl)butanoate (51b)



according to GP-2:

250 mg (250 µL, 2.69 mmol) aniline **(49b)** in 4.6 mL acetic acid and 189 mg (2.74 mmol) $NaNO_2$ in 0.7 mL conc. H_2SO_4 were combined at 10 °C resulting in a dark brown solution, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 425 mg (350 µL, 2.58 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 1.9 mL acetic acid and 3.8 mL water. Addition of 2.33 g (28.4 mmol) NaOAc in 3.8 mL water precipitated the title compound.

$C_{12}H_{13}O_3N_2Cl$ [268.5]

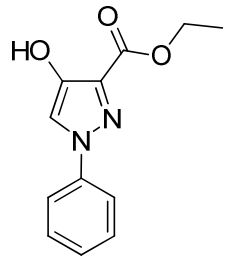
yield:	478.2 mg (69 %), brown solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 13.10 (bs, 1H, NH), 7.44-7.39 (m, 2H, Ar-H), 7.35-7.33 (m, 2H, Ar-H), 7.22-7.18 (m, 1H, Ar-H), 4.73

(s, 2H, Cl-CH_2), 4.38 (q, ^3J = 7.2 Hz, CH_2), 1.41 (t, ^3J = 7.2 Hz, CH_3).

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 186.3 (**C**=O), 163.6 (**C**=O), 141.1 ($\mathbf{C}_q$), 129.7 (2 $\mathbf{C}H_{Ar}$), 125.7 ($\mathbf{C}H_{Ar}$), 124.7 (**C**=N), 115.8 (2 $\mathbf{C}H_{Ar}$), 61.6 (Cl-$\mathbf{C}H_2$), 46.6 ($\mathbf{C}H_2$), 14.0 ($\mathbf{C}H_3$).

M.p.: 82-84 °C

Ethyl 4-hydroxy-1-phenyl-1*H*-pyrazole-3-carboxylate (52b)



according to GP-3:

250 mg (931 µmol) (*Z*)-ethyl-4-chloro-3-oxo-2-(phenyldiazenyl)butanoate **(51b)** were suspended in 4 mL EtOH. 110 mg (1.12 mmol) KOAc were added.

$C_{12}H_{12}O_3N_2$ [232.2]

yield: 178.3 mg (83 %), orange solid

R_f (CH/ EtOAc 5:1): 0.34

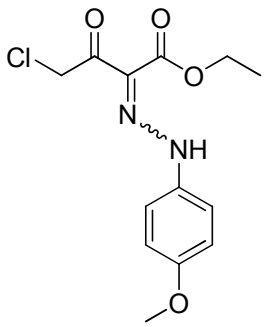
^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) = 9.19 (s, 1H, OH), 8.08 (s, 1H, Ar-H), 7.83-7.80 (m, 2H, Ar-H), 7.53-7.48 (m, 2H, Ar-H), 7.37-7.32 (m, 1H, Ar-H), 4.30 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.31 (t, ^3J = 7.2 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 161.5 (**C**=O), 145.1 ($\mathbf{C}_q$-OH), 139.2 ($\mathbf{C}_q$), 131.9 ($\mathbf{C}_q$), 129.4 (2 $\mathbf{C}H_{Ar}$), 126.9 ($\mathbf{C}H_{Ar}$), 118.4 (2 $\mathbf{C}H_{Ar}$), 114.9 ($\mathbf{C}H_{Ar}$), 59.8 ($\mathbf{C}H_2$), 14.2 ($\mathbf{C}H_3$).

M.p.: 81-83 °C

GC-MS (NM_50_S2): t_R = 7.15 min (m/z = 232.0, 98.0 % M^+, BP: 104.0).

Ethyl-4-chloro-2-((4-methoxyphenyl)diazenyl)-3-oxobutanoate (51c)



according to GP-2:

250 mg (2.03 mmol) 4-methoxyaniline **(49c)** in 3.5 mL acetic acid and 143 mg (2.07 mmol) $NaNO_2$ in 0.5 mL conc. H_2SO_4 were combined at 10 °C resulting in a dark purple solution, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 321 mg (260 µL, 1.95 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 1.4 mL acetic acid and 2.8 mL water. Addition of 1.76 g (21.5 mmol) NaOAc in 3.0 mL water precipitated the title compound.

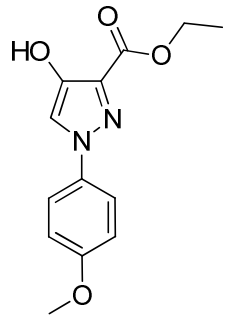
$C_{13}H_{15}O_4N_2Cl$ [298.5]

yield:	352.0 mg (60 %), orange-brown solid
^{1}H-NMR (300 MHz, DMSO-d_6):	**Isomer I (23 %):** δ (ppm) = **14.39 (s, 1H, NH)**, **7.57 (d, ^3J = 9.0 Hz, 2H, Ar-H)**, 7.04-6.97 (m, 2H, Ar-H), **4.95 (s, 2H, Cl-CH_2)**, 4.34-4.27 (m, 2H, CH_2), 3.76 (s, 3H, OCH_3), 1.32-1.27 (m, 3H, CH_3). **Isomer II (77 %):** δ (ppm) = **12.34 (s, 1H, NH)**, **7.51 (d, ^3J = 9.0 Hz, 2H, Ar-H)**, 7.04-6.97 (m, 2H, Ar-H), **4.93 (s, 2H, Cl-CH_2)**, 4.34-4.27 (m, 2H, CH_2), 3.76 (s, 3H, OCH_3), 1.32-1.27 (m, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	**Isomer I:** δ (ppm) = **188.8 (C=O)**, **164.8 (C=O)**, **158.6 (C_q)**, 134.8 (**C**=N), 123.7 (C_q), **118.2 (2 CH_{Ar})**, 115.0 (2 **C**H_{Ar}), **61.0 (Cl-CH_2)**, 55.6 (O**C**H_3), **49.5 (CH_2)**, **14.1 (CH_3)**. **Isomer II:** δ (ppm) = **186.2 (C=O)**, **163.9 (C=O)**, **157.9 (C_q)**, 134.7 (**C**=N), 122.8 (C_q), **117.2 (2 CH_{Ar})**, 115.0

(2 **C**CH_{Ar}), **61.4 (Cl-CH_2)**, 55.6 (O**C**CH_3), **46.6 (CH_2)**, **14.3 (CH_3)**.

M.p.: 84-87 °C

Ethyl 4-hydroxy-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (52c)



according to GP-3:

175 mg (586 µmol) (*Z*)-ethyl-4-chloro-2-((4-methoxyphenyl)diazenyl)-3-oxobutanoate **(51c)** were suspended in 3 mL EtOH. 69.1 mg (704 µmol) KOAc were added.

$C_{14}H_{16}O_4N_2$ [262.2]

yield: 152.4 mg (99 %), red-brown solid

R_f (CH/ EtOAc 3:1): 0.30

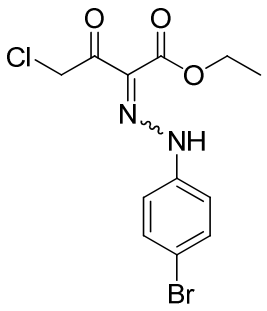
^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) = 9.09 (s, 1H, OH), 7.97 (s, 1H, Ar-H), 7.73 (d, ^3J = 9.0 Hz, 2H, Ar-H), 7.05 (d, ^3J = 9.0 Hz, 2H, Ar-H), 4.28 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 1.30 (t, ^3J = 7.2 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 161.6 (**C**=O), 158.1 ($\mathbf{C}_q$), 145.0 ($\mathbf{C}_q$-OH), 132.9 ($\mathbf{C}_q$), 131.1 ($\mathbf{C}_q$), 120.1 (2 **C**H_{Ar}), 114.9 (**C**H_{Ar}), 114.5 (2 **C**H_{Ar}), 59.7 (**C**H_2), 55.4 (O**C**H_3), 14.2 (**C**H_3).

M.p.: 109-111 °C

GC-MS (NM_50_S2): t_R = 7.86 min (m/z = 262.1, 99.0 % M^+, BP).

Ethyl-4-chloro-2-((4-bromophenyl)diazenyl)-3-oxobutanoate (51d)



according to GP-2:

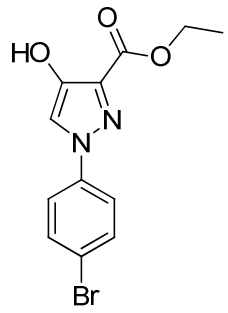
250 mg (1.45 mmol) 4-bromoaniline **(49d)** in 2.5 mL acetic acid and 102 mg (1.48 mmol) $NaNO_2$ in 0.4 mL conc. H_2SO_4 were combined at 10 °C resulting in a dark brown solution, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 229 mg (190 µL, 1.40 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 1.0 mL acetic acid and 2.1 mL water. Addition of 1.26 g (15.4 mmol) NaOAc in 2.1 mL water precipitated the title compound.

$C_{12}H_{12}O_3N_2BrCl$ [347.5]

yield:	270.0 mg (56 %), terracotta solid
^{1}H-NMR (300 MHz, $CDCl_3$):	**Isomer I (35 %):** δ (ppm) = **14.65 (s, 1H, NH)**, 7.54-7.51 (m, 2H, Ar-H), **7.34-7.31 (m, 2H, Ar-H)**, **4.85 (s, 2H, Cl-CH_2)**, 4.39-4.33 (m, 2H, CH_2), 1.40 (t, ^3J = 7.2 Hz, 3H, CH_3) **Isomer II (65 %):** δ (ppm) = **13.06 (s, 1H, NH)**, 7.54-7.51 (m, 2H, Ar-H), **7.23-7.20 (m, 2H, Ar-H)**, **4.70 (s, 2H, Cl-CH_2)**, 4.39-4.33 (m, 2H, CH_2), 1.40 (t, ^3J = 7.2 Hz, 3H, CH_3)
^{13}C-NMR (75.5 MHz, $CDCl_3$):	**Isomer I:** δ (ppm) = **189.6 (C=O)**, **164.4 (C=O)**, 140.3 (**C_q**), 132.7 (2 **C**H_{Ar}), 125.3 (**C**=N), 118.5 (**C_q**-Br), **118.2 (2 CH_{Ar})**, **61.4 (Cl-CH_2)**, **49.5 (CH_2)**, **14.3 (CH_3)**. **Isomer II:** δ (ppm) = **186.3 (C=O)**, **163.5 (C=O)**, 140.2 (**C_q**), 132.7 (2 **C**H_{Ar}), 125.3 (**C**=N), 118.5 (**C_q**-Br), **117.3 (2 CH_{Ar})**, **61.8 (Cl-CH_2)**, **46.5 (CH_2)**, **14.0 (CH_3)**.

M.p.: 89-91 °C

MM-48: **Ethyl 1-(4-bromphenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate**



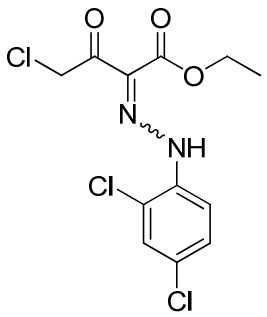
according to GP-3:

150 mg (432 µmol) (*Z*)-ethyl-4-chloro-2-((4-bromophenyl)diazenyl)-3-oxobutanoate **(51d)** were suspended in 2.8 mL EtOH. 50.8 mg (518 µmol) KOAc were added.

$C_{12}H_{11}O_3N_2Br$ [311.1]

yield:	125.2 mg (93 %), orange-red oil
R_f (CH/ EtOAc 3:1):	0.68
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 9.27 (s, 1H, OH), 8.09 (s, 1H, Ar-H), 7.80 (d, ^3J = 9.0 Hz, 2H, Ar-H), 7.69 (d, ^3J = 9.0 Hz, 2H, Ar-H), 4.29 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.30 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 161.3 (**C**=O), 145.1 (**C**$_q$-OH), 138.5 (**C**$_q$), 132.3 (2 **C**H$_{Ar}$), 132.1 (**C**H$_{Ar}$), 120.3 (2 **C**H$_{Ar}$), 119.3 (**C**$_q$), 114.9 (**C**$_q$-Br), 59.9 (**C**H_2), 14.2 (**C**H_3).
M.p.:	111-113 °C
GC-MS (NM_50_S2):	t_R = 7.95 min (m/z = 310.9, 97.0 % M^+, BP: 181.9).

Ethyl-4-chloro-2-((2,4-dichlorophenyl)diazenyl)-3-oxobutanoate (51e)



according to GP-2:

250 mg (1.54 mmol) 2,4-dichloroaniline **(49e)** in 2.6 mL acetic acid and 109 mg (1.57 mmol) $NaNO_2$ in 0.4 mL conc. H_2SO_4 were combined at 10 °C resulting in a light brown solution, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 244 mg (200 µL, 1.49 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 1.0 mL acetic acid and 2.2 mL water. Addition of 1.34 g (16.3 mmol) NaOAc in 2.7 mL water precipitated the title compound.

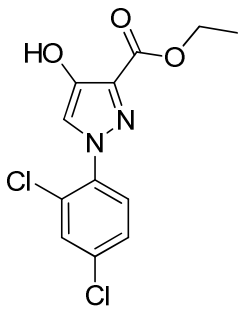
$C_{12}H_{11}O_3N_2Cl_3$ [337.4]

yield:	376.0 mg (75 %), yellow solid
^{1}H-NMR (300 MHz, $CDCl_3$):	**Isomer I (26 %):** δ (ppm) = **14.73 (bs, 1H, NH)**, **7.80 (d, ^3J = 8.7 Hz; 1H, Ar-H)**, 7.44-7.42 (m, 1H, Ar-H), 7.34-7.30 (m, 1H, Ar-H), **4.86 (s, 2H, Cl-CH_2),** 4.45-4.35 (m, 2H, CH_2), 1.41 (t, ^3J = 7.2 Hz, CH_3)
	Isomer II (74 %): δ (ppm) = **13.30 (bs, 1H, NH)**, **7.60 (d, ^3J = 8.7 Hz; 1H, Ar-H)**, 7.44-7.42 (m, 1H, Ar-H), 7.34-7.30 (m, 1H, Ar-H), **4.69 (s, 2H, Cl-CH_2),** 4.45-4.35 (m, 2H, CH_2), 1.41 (t, ^3J = 7.2 Hz, CH_3)
^{13}C-NMR (75.5 MHz, $CDCl_3$):	**Isomer I:** δ (ppm) = 186.4 (**C**=O), 163.1 (**C**=O), **136.9 (C_q)**, 130.4 (C_q-Cl), **129.9 (CH_{Ar})**, **128.1 (CH_{Ar})**, 126.9 (**C**=N), 122.1 (C_q-Cl), **118.0 (CH_{Ar})**, **61.6 (Cl-CH_2)**, **49.5 (CH_2)**, **14.3 (CH_3)**.
	Isomer II: δ (ppm) = 186.4 (**C**=O), 163.1 (**C**=O), **136.7 (C_q)**, 130.4 (C_q-Cl), **129.6 (CH_{Ar})**, **128.6 (CH_{Ar})**, 126.9

(**C**=N), 122.1 (**C**$_q$-Cl), **116.8 (CH$_{Ar}$)**, **62.1 (Cl-CH$_2$)**, **46.5 (CH$_2$)**, **14.1 (CH$_3$)**.

M.p.: 84-86 °C

Ethyl 1-(2,4-dichlorophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate (52e)



according to GP-3:

200 mg (593 µmol) (*Z*)-ethyl-4-chloro-2-((2,4-dichlorophenyl)diazenyl)-3-oxobutanoate **(51e)** were suspended in 3.9 mL EtOH. 69.8 mg (711 µmol) KOAc were added.

$C_{12}H_{10}O_3N_2Cl_2$ [301.1]

yield: 165.0 mg (93 %), orange solid

R_f (CH/ EtOAc 3:1): 0.48

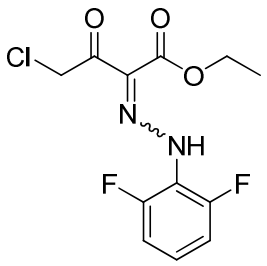
^{1}H-NMR (300 MHz, DMSO-d$_6$): δ (ppm) = 9.23 (s, 1H, OH), 7.88 (d, ^4J = 1.5 Hz, 1H, Ar-H), 7.73 (s, 1H, Ar-H), 7.62-7.60 (m, 2H, Ar-H), 4.28 (q, ^3J = 7.2 Hz, 2H, CH$_2$), 1.28 (t, ^3J = 7.2 Hz, 3H, CH$_3$).

^{13}C-NMR (75.5 MHz, DMSO-d$_6$): δ (ppm) = 161.3 (**C**=O), 144.0 (**C**$_q$-OH), 136.6 (**C**$_q$), 134.0 (**C**$_q$), 132.3 (**C**$_q$-Cl), 129.9 (**C**H$_{Ar}$), 129.4 (**C**H$_{Ar}$), 129.2 (**C**$_q$-Cl), 128.3 (**C**H$_{Ar}$), 119.3 (**C**H$_{Ar}$), 59.9 (**C**H$_2$), 14.2 (**C**H$_3$).

M.p.: 140-142 °C

GC-MS (NM_50_S2): t_R = 7.86 min (m/z = 300.9, 97.0 % M$^+$, BP: 171.9)

Ethyl-4-chloro-2-((2,6-difluorophenyl)diazenyl)-3-oxobutanoate (51f)



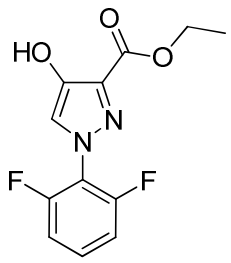
according to GP-2:

250 mg (210 µL, 1.94 mmol) 2,6-difluoroaniline **(49f)** in 3.3 mL acetic acid and 136 mg (1.97 mmol) $NaNO_2$ in 0.5 mL conc. H_2SO_4 were combined at 10 °C resulting in a orange-brown solution, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 305 mg (250 µL, 1.86 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 1.3 mL acetic acid and 2.8 mL water. Addition of 1.68 g (20.5 mmol) NaOAc in 2.8 mL water precipitated the title compound.

$C_{12}H_{11}O_3N_2F_2Cl$ [304.6]

yield:	310.1 mg (55 %), orange solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 12.85 (bs, 1H, NH), 7.13-6.97 (m, 3H, Ar-H), 4.70 (s, 2H, Cl-CH_2), 4.39 (d, ^3J = 7.2 Hz, 2H, CH_2), 1.40 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 186.4 (**C**=O), 162.8 (**C**=O), 155.4, 155.4, 152.1, 152.0 ($^1J_{C\text{-}F}$ = 251.6 Hz, $^3J_{C\text{-}F}$ = 4.2 Hz, 2 $\mathbf{C}_q$-F), 127.2 (**C**=N), 125.3, 125.2, 125.1 ($^3J_{C\text{-}F}$ = 9.5 Hz, $\mathbf{C}H_{Ar}$), 119.5, 119.3, 119.2 ($^2J_{C\text{-}F}$ = 10.9 Hz, $\mathbf{C}_q$), 112.7, 112.6, 112.5, 112.4 ($^2J_{C\text{-}F}$ = 23.1 Hz, $^4J_{C\text{-}F}$ = 6.6 Hz, 2 $\mathbf{C}H_{Ar}$), 61.9 (Cl-$\mathbf{C}H_2$), 46.8 ($\mathbf{C}H_2$), 14.0 ($\mathbf{C}H_3$)
M.p.:	146-149 °C

Ethyl 1-(2,6-difluorophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate (52f)



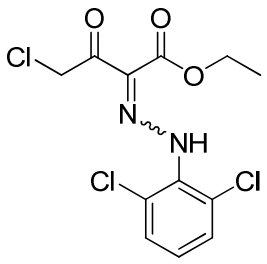
according to GP-3:

200 mg (656 µmol) (*Z*)-ethyl-4-chloro-2-((2,6-difluorophenyl)diazenyl)-3-oxobutanoate **(51f)** were suspended in 4.3 mL EtOH. 77.3 mg (788 µmol) KOAc were added.

$C_{12}H_{10}O_3N_2F_2$ [268.2]

yield:	171.4 mg (98 %), brown solid
R_f (CH/ EtOAc 3:1):	0.40
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 9.26 (s, 1H, OH), 7.74 (s, 1H, Ar-H), 7.66-7.61 (m, 1H, Ar-H), 7.38 (t, ^3J = 8.7 Hz, 2H, Ar-H), 4.28 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.28 (t, ^3J= 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 161.3 (**C**=O), 158.7, 155.4 ($^1J_{C-F}$ = 252.6 Hz, 2 **C**$_q$-F), 144.0 (**C**$_q$-OH), 133.0 (**C**$_q$), 131.5 ($^3J_{C-F}$ = 10.0 Hz, **C**H$_{Ar}$), 120.5 (**C**H$_{Ar}$), 117.8, 117.6 ($^2J_{C-F}$ = 15.5 Hz, **C**$_q$), 112.8, 112.5 ($^2J_{C-F}$ = 20.2 Hz, 2 **C**H$_{Ar}$), 60.0 (**C**H$_2$), 14.2 (**C**H$_3$).
M.p.:	70-73 °C
GC-MS (NM_50_S2):	t_R = 6.90 min (m/z = 267.9, 97.0 % M^+, BP:139.9).
HRMS (EI$^+$):	*m/z*: calcd for $C_{12}H_{10}O_3N_2F_2$ $[M]^+$: 268.0659; found 268.0672.

Ethyl-4-chloro-2-((2,6-dichlorophenyl)diazenyl)-3-oxobutanoate (51g)



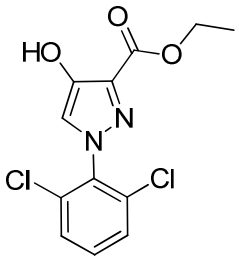
according to GP-2:

250 mg (1.54 mmol) 2,6-dichloroaniline **(49g)** in 2.7 mL acetic acid and 108 mg (1.57 mmol) $NaNO_2$ in 0.4 mL conc. H_2SO_4 were combined at 10 °C resulting in a white solution, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 243 mg (200 µL, 1.48 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 1.1 mL acetic acid and 2.2 mL water. Addition of 1.34 g (16.3 mmol) NaOAc in 2.2 mL water precipitated the title compound.

$C_{12}H_{11}O_3N_2Cl_3$ [337.6]

yield:	460.3 mg (92 %), yellow solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 12.95 (bs, 1H, NH), 7.39 (d, , ^3J = 8.1 Hz, 2H, Ar-H), 7.14-7.09 (m, 1H, Ar-H), 4.72 (s, 2H, Cl-CH_2), 4.40 (q, ^3J = 7.2 Hz, CH_2), 1.41 (t, ^3J = 7.2 Hz, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 186.4 (**C**=O), 162.7 (**C**=O), 134.9 ($\mathbf{C}_q$), 129.7 (2 $\mathbf{C}H_{Ar}$), 127.2 (2 $\mathbf{C}_q$-Cl), 126.9 (**C**=N), 126.7 ($\mathbf{C}H_{Ar}$), 61.9 ($\mathbf{C}H_2$), 47.1 ($\mathbf{C}H_2$), 14.0 ($\mathbf{C}H_3$).
M.p.:	125-126 °C

Ethyl 1-(2, 6-dichlorophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate (52g)



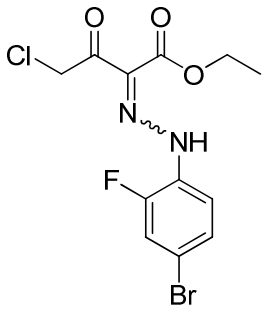
according to GP-3:

200 mg (592 µmol) (*Z*)-ethyl-4-chloro-2-((2,6-dichlorophenyl)diazenyl)-3-oxobutanoate **(51g)** were suspended in 3.8 mL EtOH. 69.8 mg (711 µmol) KOAc were added.

$C_{12}H_{10}O_3N_2Cl_2$ [301.1]

yield:	168.2 mg (91 %), orange solid
R_f (CH/ EtOAc 3:1):	0.38
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 9.19 (s, 1H, OH), 7.72-7.58 (m, 4H, Ar-H), 4.27 (q, ^3J= 7.2 Hz, 2H, CH_2), 1.28 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 161.3 (**C**=O), 143.9 (**C**$_q$-OH), 135.6 (**C**$_q$), 133.2 (2 **C**$_q$-Cl), 132.2 (**C**$_q$), 132.0 (**C**H$_{Ar}$), 128.9 (2 **C**H$_{Ar}$), 119.7 (**C**H$_{Ar}$), 59.9 (**C**H$_2$), 14.1 (**C**H$_3$).
M.p.:	135-137 °C
GC-MS (NM_50_S2):	t_R = 7.69 min (m/z = 300.9, 99.0 % M^+, BP: 171.9).
HRMS (EI$^+$):	*m/z*: calcd for $C_{12}H_{10}O_3N_2Cl_2$ $[M]^+$: 300.0068; found 300.0072.

Ethyl-4-chloro-2-((4-bromo-2-fluorophenyl)diazenyl)-3-oxobutanoate (51h)



according to GP-2:

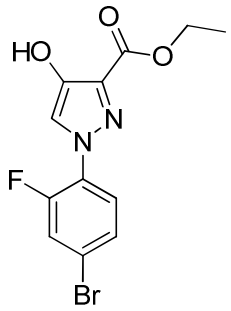
250 mg (1.32 mmol) 4-bromo-2-fluoroaniline **(49h)** in 2.3 mL acetic acid and 92.5 mg (1.34 mmol) $NaNO_2$ in 0.33 mL conc. H_2SO_4 were combined at 10 °C resulting in a yellow solution, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 207 mg

(170 µL, 1.27 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 0.9 mL acetic acid and 1.9 mL water. Addition of 1.14 g (13.9 mmol) NaOAc in 2.0 mL water precipitated the title compound.

$C_{12}H_{11}O_3N_2BrFCl$ [365.6]

yield:	396.0 mg (86 %), yellow solid
^{1}H-NMR (300 MHz, $CDCl_3$):	**Isomer I (30 %):** δ (ppm) = **14.55 (bs, 1H, NH)**, **7.73-7.68 (m, 1H, Ar-H)**, 7.36-7.32 (m, 2H, Ar-H), **4.85 (s, 2H, CH_2)**, 4.43-4.32 (m, 2H, CH_2), 1.40 (t, ^3J = 7.2 Hz, 3H, CH_3). **Isomer II (70 %):** δ (ppm) = **13.07 (bs, 1H, NH)**, **7.54-7.49 (m, 1H, Ar-H)**, 7.36-7.32 (m, 2H;, Ar-H), **4.68 (s, 2H, CH_2)**, 4.43-4.32 (m, 2H, CH_2), 1.40 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	**Isomer I:** δ (ppm) = **189.6 (C=O)**, **164.1 (C=O)**, **153.3 (C_q-F)**, **129.1 (C_q)**, 128.6, 128.5 (**C**H_{Ar}), 126.9 (**C**=N), 119.6,119.3 ($^2J_{C-F}$ = 20.7 Hz, **C**H_{Ar}), 118.2 (**C**$_q$-Br), 117.3, 117.2, 117.1 (**C**H_{Ar}), **61.5 (Cl-CH_2)**, **49.4 (CH_2)**, **14.2 (CH_3)**. **Isomer II:** δ (ppm) = **186.3 (C=O)**, **163.1 (C=O)**, **153.0, 149.7 ($^1J_{C-F}$ = 250.6 Hz, C_q-F)**, **129.0 (C_q)**, 128.6, 128.5 (**C**H_{Ar}), 126.9 (**C**=N), 119.7, 119.4 ($^2J_{C-F}$ = 20.9 Hz, **C**H_{Ar}), 118.2 (**C**$_q$-Br), 117.3, 117.2, 117.1 (**C**H_{Ar}), **62.0 (Cl-CH_2)**, **46.4 (CH_2)**, **14.0 (CH_3)**.
M.p.:	139-141 °C

Ethyl 1-(4-bromo-2-fluorophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate (52h)



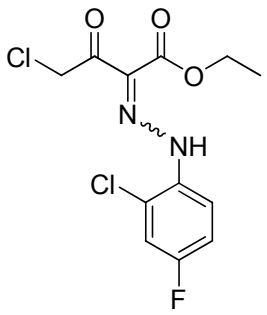
according to GP-3:

150 mg (410 µmol) (*Z*)-ethyl-4-chloro-2-((4-bromo-2-fluorophenyl)diazenyl)-3-oxobutanoate **(51h)** were suspended in 2.7 mL EtOH. 48.3 mg (492 µmol) KOAc were added.

$C_{12}H_{10}O_3N_2FBr$ [329.1]

yield:	125.2 mg (93 %), orange-beige solid
R_f (CH/ EtOAc 3:1):	0.45
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 9.34 (s, 1H, OH), 7.87-7.71 (m, 3H, Ar-H), 7.59-7.56 (m, 1H, Ar-H), 4.29 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.29 (t, ^3J = 6.9 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 161.1 (**C**=O), 154.9, 151.5 ($^1J_{C-F}$ = 253.9 Hz, **C**$_q$-F), 144.5 (**C**$_q$-OH), 132.5 (**C**$_q$), 128.5, 128.4 ($^4J_{C-F}$ = 3.4 Hz, **C**H$_{Ar}$), 127.2, 127.1 ($^3J_{C-F}$ = 9.4 Hz, **C**H$_{Ar}$), 126.0 (**C**H$_{Ar}$), 120.5, 120.2 ($^2J_{C-F}$ = 17.4 Hz, **C**$_q$), 120.4, 120.2 ($^2J_{C-F}$ = 15.4 Hz, **C**H$_{Ar}$), 118.4, 118.3 ($^3J_{C-F}$ = 7.8 Hz, **C**$_q$-Br), 60.0 (**C**H$_2$), 14.2 (**C**H$_3$).
M.p.:	131-133 °C
GC-MS (NM_50_S2):	t_R = 7.69 min (m/z = 328.9, 98.0 % M^+, BP: 199.8).
HRMS (EI$^+$):	*m/z*: calcd for $C_{12}H_{10}O_3N_2FBr$ $[M]^+$: 327.9859; found 327.9864.

Ethyl-4-chloro-2-((2-chloro-4-fluorophenyl)diazenyl)-3-oxobutanoate (51i)



according to GP-2:

250 mg (210 µL, 1.72 mmol) 2-chloro-4-fluoroaniline **(49i)** in 3.0 mL acetic acid and 121 mg (1.75 mmol) $NaNO_2$ in 0.4 mL conc. H_2SO_4 were combined at 10 °C resulting in a yellow suspension, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 272 mg (220 µL, 1.65 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 1.1 mL acetic acid and 2.5 mL water. Addition of 1.49 g (18.2 mmol) NaOAc in 2.8 mL water precipitated the title compound.

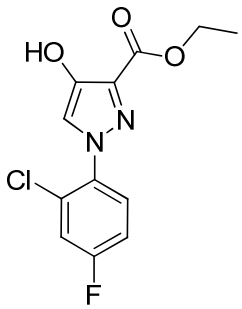
$C_{12}H_{11}O_3N_2FCl_2$ [320.9]

yield:	422.2 mg (80 %), dark yellow solid
^{1}H-NMR (300 MHz, $CDCl_3$):	**Isomer I (9 %):** δ (ppm) = **14.81 (bs, 1H, NH)**, 7.67-7.62 (m, 1H, Ar-H), 7.19-7.16 (m, 1H, Ar-H), 7.12-7.06 (m, 1H, Ar-H), **4.86 (s, 2H, Cl-CH_2),** 4.44-4.34 (m, 2H, CH_2), 1.41 (t, ^3J = 7.2 Hz, CH_3) **Isomer II (91 %):** δ (ppm) = **13.33 (bs, 1H, NH)**, 7.67-7.62 (m, 1H, Ar-H), 7.19-7.16 (m, 1H, Ar-H), 7.12-7.06 (m, 1H, Ar-H), **4.69 (s, 2H, Cl-CH_2),** 4.44-4.34 (m, 2H, CH_2), 1.41 (t, ^3J = 7.2 Hz, CH_3)
^{13}C-NMR (75.5 MHz, $CDCl_3$):	**Isomer I:** δ (ppm) = **189.3 (C=O), 164.2 (C=O),** 161.0, 157.7 ($^1J_{C-F}$ = 248.6 Hz, **C**$_q$-F), **134.5 (C$_q$)**, 126.4 (**C**=N), 122.1, 122.0 ($^3J_{C-F}$ = 10.3 Hz, **C**$_q$-Cl), 117.2, 116.9 (**$^2J_{C-F}$** = 21.3 Hz, **C**H_{Ar}**)**, 117.1, 116.9 (**$^3J_{C-F}$** = 13.5 Hz, **C**H_{Ar}**)**, 115.8, 115.5 (**$^2J_{C-F}$** = 22.8 Hz **C**H_{Ar}**)**, **61.4 (Cl-CH_2)**, **49.4 (CH_2)**, **14.2 (CH_3)**.

Isomer II: δ (ppm) = **186.3 (C=O), 163.1 (C=O),** 161.0, 157.7 ($^{1}J_{C-F}$ = 248.6 Hz, **C**$_q$-F), **134.6 (C$_q$)**, 126.4 (**C**=N), 122.1, 122.0 ($^{3}J_{C-F}$ = 10.3 Hz, **C**$_q$-Cl), 117.2, 116.9 ($^{2}J_{C-F}$ = 21.3 Hz, **C**H$_{Ar}$), 117.1, 116.9 ($^{3}J_{C-F}$ = 13.5 Hz, **C**H$_{Ar}$), 115.8, 115.5 ($^{2}J_{C-F}$ = 22.8 Hz, **C**H$_{Ar}$), **62.0 (Cl-CH$_2$)**, **46.4 (CH$_2$)**, **14.0 (CH$_3$)**.

M.p.: 77-79 °C

Ethyl 1-(2-chlor-4-fluorophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate (52i)



according to GP-3:

150 mg (467 µmol) (*Z*)-ethyl-4-chloro-2-((2-chloro-4-fluorophenyl)diazenyl)-3-oxobutanoate **(51i)** were suspended in 3.0 mL EtOH. 55.0 mg (561 µmol) KOAc were added.

$C_{12}H_{10}O_3N_2F_2Cl$ [284.7]

yield: 126.0 mg (95 %), orange solid

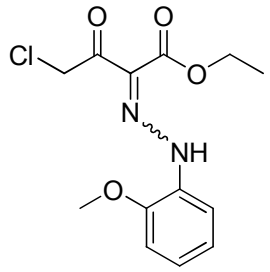
R_f (CH/ EtOAc 3:1): 0.48

^{1}H-NMR (300 MHz, DMSO-d$_6$): δ (ppm) = 9.19 (s, 1H, OH), 7.76-7.64 (m, 3H, Ar-H), 7.44-7.37 (m, 1H, Ar-H), 4.27 (q, ^{3}J = 7.2 Hz, 2H, CH$_2$), 1.28 (t, ^{3}J = 7.2 Hz, 3H, CH$_3$).

^{13}C-NMR (75.5 MHz, DMSO-d$_6$): δ (ppm) = 161.4 (**C**=O), 163.1, 159.7 ($^{1}J_{C-F}$ = 249.9 Hz, **C**$_q$-F), 143.9 (**C**$_q$-OH), 134.5, 134.4 ($^{4}J_{C-F}$ = 3.5 Hz, **C**$_q$), 132.0 (**C**$_q$), 130.0, 129.9 ($^{3}J_{C-F}$ = 9.4 Hz, **C**$_q$-Cl), 129.9, 129.7 (**C**H$_{Ar}$), 119.5, (**C**H$_{Ar}$), 117.7, 117.4 ($^{2}J_{C-F}$ = 26.5 Hz, **C**H$_{Ar}$), 115.4, 115.1 ($^{2}J_{C-F}$ = 22.7 Hz, **C**H$_{Ar}$), 59.8 (**C**H$_2$), 14.2 (**C**H$_3$).

M.p.:	117-119 °C
GC-MS (NM_50_S2):	t_R = 7.24 min (m/z = 284.9, 98.0 % M^+, BP: 155.9).
HRMS (EI^+):	*m/z*: calcd for $C_{12}H_{10}O_3N_2F_2Cl$ $[M]^+$: 284.0364; found 284.0378.

Ethyl-4-chloro-2-((2-methoxyphenyl)diazenyl)-3-oxobutanoate (51j)



according to GP-2:

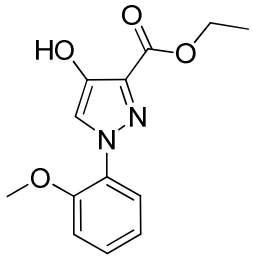
250 mg (230 µL, 2.03 mmol) 2-methoxyaniline **(49j)** in 3.5 mL acetic acid and 143 mg (2.07 mmol) $NaNO_2$ in 0.5 mL conc. H_2SO_4 were combined at 10 °C resulting in a dark brown solution, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 321 mg (270 µL, 1.95 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 1.3 mL acetic acid and 3.0 mL water. Addition of 1.76 g (21.5 mmol) NaOAc in 3.3 mL water precipitated the title compound.

$C_{13}H_{15}O_4N_2Cl$ [298.4]

yield:	452.0 mg (77 %), orange-brown solid
^{1}H-NMR (300 MHz, $CDCl_3$):	**Isomer I (31 %):** δ (ppm) = **14.79 (bs, 1H, NH)**, **7.80 (d, ^3J = 7.8 Hz, 1H, Ar-H)**, 7.18-7.13 (m, 1H, Ar-H), 7.05-6.94 (m, 1H, Ar-H), **4.87 (s, 2H, Cl-CH_2),** 4.42-4.43 (m, 2H, CH_2), 3.95 (s, 3H, OCH_3), 1.41 (t, ^3J = 7.2 Hz, CH_3) **Isomer II (67 %):** δ (ppm) = **13.23 (bs, 1H, NH)**, **7.59 (d, ^3J = 7.8 Hz; 1H, Ar-H)**, 7.18-7.13 (m, 1H, Ar-H), 7.05-6.94 (m, 1H, Ar-H), **4.74 (s, 2H, Cl-CH_2),** 4.42-

	4.43 (m, 2H, CH_2), 3.95 (s, 3H, OCH_3), 1.41 (t, ^3J = 7.2 Hz, CH_3)
^{13}C-NMR (75.5 MHz, $CDCl_3$):	**Isomer I:** δ (ppm) = 188.4 (**C**=O), 164.9 (**C**=O), **148.7 (C_q-OCH_3)**, **130.4 (C_q)**, 126.8 (**C**=N), **125.1 (CH_{Ar})**, 121.5 (**C**H_{Ar}), **116.0 (CH_{Ar})**, **111.0 (CH_{Ar})**, **61.1 (Cl-CH_2)**, **55.9 (OCH_3)**, **49.6 (CH_2)**, **14.3 (CH_3)**.
	Isomer II: δ (ppm) = 186.4 (**C**=O), 163.3 (**C**=O), **148.3 (C_q-OCH_3)**, **130.4 (C_q)**, 126.8 (**C**=N), **125.8 (CH_{Ar})**, 121.5 (**C**H_{Ar}), **114.8 (CH_{Ar})**, **111.1 (CH_{Ar})**, **61.4 (Cl-CH_2)**, **55.9 (OCH_3)**, **46.8 (CH_2)**, **14.1 (CH_3)**.
M.p.:	138-140 °C

Ethyl 1-(2-methoxyphenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate (52j)



according to GP-3:

150 mg (503 µmol) (*Z*)-ethyl-4-chloro-2-((2-methoxyphenyl)diazenyl)-3-oxobutanoate **(51j)** were suspended in 3.3 mL EtOH. 59.0 mg (603 µmol) KOAc were added.

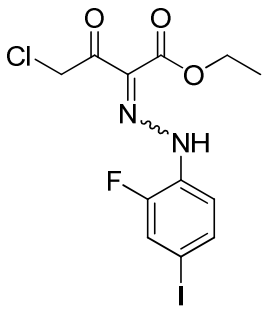
$C_{13}H_{14}O_4N_2$ [262.2]

yield:	128.6 mg (98 %), dark red oil
R_f (CH/ EtOAc 3:1):	0.45
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 9.02 (s, 1H, OH), 7.72 (s, 1H, Ar-H), 7.57 (dd, ^3J = 7.8 Hz , ^4J = 1.5 Hz, 1H, Ar-H), 7.44-7.38 (m, 1H, Ar-H), 7.26-7.23 (m, 1H, Ar-H), 7.11-7.05 (m, 1H, Ar-H), 4.28 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.29 (t, ^3J = 7.2 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 161.6 (**C**=O), 151.3 (**C**$_q$), 143.7 (**C**$_q$-OH), 130.9 (**C**$_q$-OCH$_3$), 129.1 (**C**H$_{Ar}$), 128.8 (**C**$_q$), 125.0 (**C**H$_{Ar}$), 120.8 (**C**H$_{Ar}$), 119.2 (**C**H$_{Ar}$), 112.9 (**C**H$_{Ar}$), 59.7 (**C**H$_2$), 56.0 (O**C**H$_3$), 14.2 (**C**H$_3$).

GC-MS (NM_50_S2): t_R = 7.59 min (m/z = 262.1, 99.0 % M^+, BP: 134.1).

Ethyl-4-chloro-2-((2-fluoro-4-iodophenyl)diazenyl)-3-oxobutanoate (51k)



according to GP-2:

250 mg (1.055 mmol) 2-fluoro-4-iodoaniline **(49k)** in 1.8 mL acetic acid and 74.0 mg (1.08 mmol) $NaNO_2$ in 0.3 mL conc. H_2SO_4 were combined at 10 °C resulting in a yellow-orange suspension, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 166 mg (140 µL, 1.01 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 0.7 mL acetic acid and 1.5 mL water. Addition of 910 mg (11.2 mmol) NaOAc in 1.5 mL water precipitated the title compound.

$C_{12}H_{11}O_3N_2FICl$ [412.6]

yield: 414.8 mg (99 %), yellow solid

^{1}H-NMR (300 MHz, $CDCl_3$): **Isomer I (28 %):** δ (ppm) = **14.53 (bs, 1H, NH)**, 7.54-7.49 (m, 2H, Ar-H), 7.40-7.34 (m, 1H, Ar-H), **4.84 (s, 2H, Cl-CH$_2$),** 4.43-4.34 (m, 2H, CH$_2$), 1.40 (t, ^3J = 7.2 Hz, CH$_3$)

Isomer II (72 %): δ (ppm) = **13.06 (bs, 1H, NH)**, 7.54-7.49 (m, 2H, Ar-H), 7.40-7.34 (m, 1H, Ar-H), **4.68 (s,**

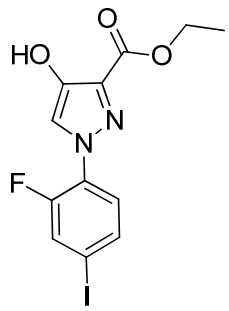
2H, Cl-CH_2), 4.43-4.34 (m, 2H, CH_2), 1.40 (t, ^3J = 7.2 Hz, CH_3)

^{13}C-NMR (75.5 MHz, $CDCl_3$): **Isomer I:** δ (ppm) = **189.6 (C=O)**, **164.1 (C=O)**, **153.1 (C_q-F)**, 134.5, 134.4 (**C**H_{Ar}), **129.8 (C_q)**, 127.0 (**C**=N), 125.2,125.0 ($^2J_{C-F}$ = 20.2 Hz, **C**H_{Ar}), **118.5 (CH_{Ar})**, **88.3, 88.2 ($^3J_{C-F}$ = 7.3 Hz, C_q-I)**, **61.5 (Cl-CH_2)**, **49.4 (CH_2)**, **14.2 (CH_3)**.

Isomer II: δ (ppm) = **186.3 (C=O)**, **163.1 (C=O)**, **152.9, 149.5 ($^1J_{C-F}$ = 251.4 Hz, C_q-F)**, 134.5, 134.4 (**C**H_{Ar}), **129.7 (C_q)**, 127.0 (**C**=N), 125.2, 125.0 ($^2J_{C-F}$ = 20.2 Hz, **C**H_{Ar}), **117.5 (CH_{Ar})**, **86.9, 86.8 ($^3J_{C-F}$ = 7.2 Hz, C_q-I)**, **62.1 (Cl-CH_2)**, **46.4 (CH_2)**, **14.0 (CH_3)**.

M.p.: 109-111 °C

Ethyl 1-(2-fluor-4-iodophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate (52k)



according to GP-3:

150 mg (364 µmol) (*Z*)-ethyl-4-chloro-2-((2-fluoro-4-iodophenyl)diazenyl)-3-oxobutanoate **(51k)** were suspended in 2.4 mL EtOH. 42.9 mg (437 µmol) KOAc were added.

$C_{12}H_{10}O_3N_2FI$ [376.1]

yield: 103.6 mg (76 %), orange solid

R_f (CH/ EtOAc 3:1): 0.52

^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) = 9.51 (s, 1H, OH), 7.89-7.86 (m, 1H, Ar-H), 7.75-7.69 (m, 2H, Ar-H), 7.53 (t, ^3J = 8.4 Hz, 1H, Ar-H),

4.27 (q, ^{3}J = 6.9 Hz, 2H, CH_2), 1.27 (t, ^{3}J = 6.9 Hz, 3H, CH_3).

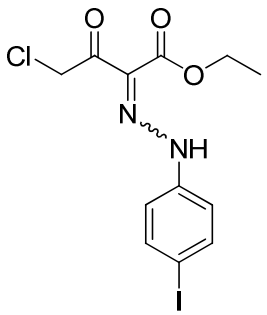
^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 161.5 (**C**=O), 154.9, 151.5 ($^{1}J_{C-F}$ = 254.6 Hz, $\mathbf{C}_q$-F), 144.7 ($\mathbf{C}_q$-OH), 134.6, 134.5 ($^{4}J_{C-F}$ = 3.6 Hz, $\mathbf{C}H_{Ar}$), 132.7 ($\mathbf{C}_q$), 127.8, 127.7 ($^{3}J_{C-F}$ = 9.4 Hz, $\mathbf{C}H_{Ar}$), 126.3 ($\mathbf{C}H_{Ar}$), 126.1, 125.8 ($^{2}J_{C-F}$ = 22.4 Hz, $\mathbf{C}_q$), 118.6, 118.5 ($^{3}J_{C-F}$ = 7.9 Hz, $\mathbf{C}H_{Ar}$), 93.1, 93.0 ($^{3}J_{C-F}$ = 7.4 Hz, $\mathbf{C}_q$-I), 60.4 ($\mathbf{C}H_2$), 14.4 ($\mathbf{C}H_3$).

M.p.: 118-119 °C

GC-MS (NM_50_S2): t_R = 8.10 min (m/z = 375.9, 95.0 % M^+, BP: 247.9).

HRMS (EI^+): *m/z*: calcd for $C_{12}H_{10}O_3N_2FI$ $[M]^+$: 375.9720; found 375.9739.

Ethyl-4-chloro-2-((4-iodophenyl)diazenyl)-3-oxobutanoate (51l)



according to GP-2:

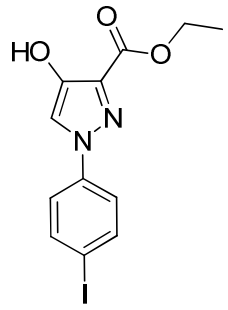
250 mg (1.14 mmol) 4-iodoaniline **(49l)** in 2.0 mL acetic acid and 80.2 mg (1.16 mmol) $NaNO_2$ in 0.3 mL conc. H_2SO_4 were combined at 10 °C resulting in a beige suspension, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 180 mg (150 µL, 1.10 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 0.8 mL acetic acid and 1.6 mL water. Addition of 990 mg (12.1 mmol) NaOAc in 1.6 mL water precipitated the title compound.

$C_{12}H_{12}O_3N_2ICl$ [394.6]

yield: 337.8 mg (78 %), yellow solid

^{1}H-NMR (300 MHz, $CDCl_3$):	**Isomer I (10 %):** δ (ppm) = **14.61 (bs, 1H, NH)**, 7.70 (d, ^{3}J = 8.7 Hz, 2H, Ar-H), 7.21-7.08 (m, 2H, Ar-H), **4.85 (s, 2H, CH_2),** 4.37 (q, ^{3}J = 7.2 Hz, 2H, CH_2), 1.40 (t, ^{3}J = 7.2 Hz, 3H, CH_3).
	Isomer II (90%): δ (ppm) = **13.02 (bs, 1H, NH)**, 7.70 (d, ^{3}J = 8.7 Hz, 2H, Ar-H), 7.21-7.08 (m, 2H, Ar-H), **4.69 (s, 2H, CH_2),** 4.37 (q, ^{3}J = 7.2 Hz, 2H, CH_2), 1.40 (t, ^{3}J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	**Isomer I:** δ (ppm) = 186.3 (**C**=O), 164.3 (**C**=O), 140.9 ($\mathbf{C}_q$), 138.6 (2 **C**H_{Ar}), 125.3 (**C**=N), **118.4 (2 $\mathbf{CH_{Ar}}$)**, **90.3 ($\mathbf{C_q}$-I)**, **61.8 (Cl-$\mathbf{CH_2}$)**, **49.5 ($\mathbf{CH_2}$)**, **14.3 ($\mathbf{CH_3}$)**.
	Isomer II: δ (ppm) = 186.3 (**C**=O), 164.3 (**C**=O), 140.9 ($\mathbf{C}_q$), 138.6 (2 **C**H_{Ar}), 125.3 (**C**=N), **117.6 (2 $\mathbf{CH_{Ar}}$)**, **89.0 ($\mathbf{C_q}$-I)**, **61.4 (Cl-$\mathbf{CH_2}$)**, **46.5 ($\mathbf{CH_2}$)**, **14.0 ($\mathbf{CH_3}$)**.
M.p.:	118-120 °C

Ethyl 1-(4-iodophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate (52l)



according to GP-3:

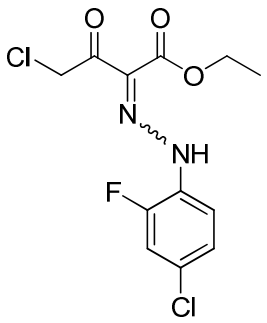
150 mg (381 µmol) (*Z*)-ethyl-4-chloro-2-((4-iodophenyl)diazenyl)-3-oxobutanoate **(51l)** were suspended in 2.5 mL EtOH. 44.8 mg (457 µmol) KOAc were added.

$C_{12}H_{11}O_3N_2I$ [358.1]

yield:	122.0 mg (90 %), orange solid
R_f (CH/ EtOAc 3:1):	0.42

^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 9.26 (s, 1H, OH), 8.08 (s, 1H, Ar-H), 7.84 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.65 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.29 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.30 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 161.3 (**C**=O), 145.1 ($\mathbf{C}_q$-OH), 138.9 ($\mathbf{C}_q$), 138.1 (2 **C**H_{Ar}), 132.3 ($\mathbf{C}_q$), 120.4 (2 **C**H_{Ar}), 114.8 (**C**H_{Ar}), 91.9 ($\mathbf{C}_q$-I), 59.9 (**C**H_2), 14.2 (**C**H_3).
M.p.:	108-112 °C (decomposition)
GC-MS (NM_50_S2):	t_R = 8.38 min (m/z = 357.9, 95.0 % M^+, BP).
HRMS (EI$^+$):	*m/z*: calcd for $C_{12}H_{11}O_3N_2I$ $[M]^+$: 357.9814; found 357.9844.

Ethyl-4-chloro-2-((4-chloro-2-fluorophenyl)diazenyl)-3-oxobutanoate (51m)



according to GP-2:

250 mg (190 µL, 1.72 mmol) 4-chloro-2-fluoroaniline **(49m)** in 3.0 mL acetic acid and 121 mg (1.75 mmol) $NaNO_2$ in 0.4 mL conc. H_2SO_4 were combined at 10 °C resulting in a dark brown solution, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 272 mg (220 µL, 1.65 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 1.1 mL acetic acid and 2.5 mL water. Addition of 1.49 g (18.2 mmol) NaOAc in 3.0 mL water precipitated the title compound.

$C_{12}H_{11}O_3N_2FCl_2$ [320.9]

yield:	398.0 mg (75 %), yellow-brown solid
^{1}H-NMR (300 MHz, $CDCl_3$):	**Isomer I (94 %):** δ (ppm) = **14.57 (bs, 1H, NH)**, **7.79-7.73 (m, 1H, Ar-H),** 7.21-7.16 (m, 2H, Ar-H), **4.85**

(s, 2H, Cl-CH_2), 4.41-4.32 (m, 2H, CH_2), 1.40 (t, ^3J = 7.2 Hz, CH_3)

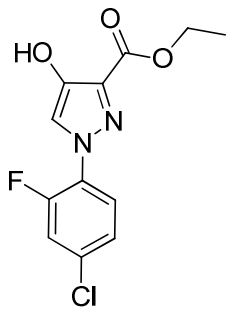
Isomer II (6 %): δ (ppm) = **13.08 (bs, 1H, NH)**, **7.63-7.57 (m, 1H, Ar-H),** 7.21-7.16 (m, 2H, Ar-H), **4.68 (s, 2H, Cl-CH_2),** 4.41-4.32 (m, 2H, CH_2), 1.40 (t, ^3J = 7.2 Hz, CH_3)

^{13}C-NMR (75.5 MHz, $CDCl_3$): **Isomer I:** δ (ppm) = **189.6 (C=O)**, **164.1 (C=O)**, 153.2, 149.9 (**$^1J_{C-F}$** = 251.0 Hz, **C_q**-F), 131.4, 131.2 (**$^3J_{C-F}$** = 9.3 Hz, **C_q**), 128.7, 128.6 (**$^3J_{C-F}$** = 9.0 Hz, **C_q**-Cl**)**, 125.7,125.6 (**$^3J_{C-F}$** = 3.7 Hz, **C**H_{Ar}), 125.4 (**C**=N), 117.9, 117.8 (**$^4J_{C-F}$** = 1.6 Hz, **C**H_{Ar}), **116.8, 116.5 (*$^2J_{C-F}$* = 21.1 Hz, CH_{Ar}), 61.5 (Cl-CH_2)**, **49.4 (CH_2)**, **14.2 (CH_3)**.

Isomer II: δ (ppm) = **186.3 (C=O)**, **163.1 (C=O)**, 153.2, 149.9 (**$^1J_{C-F}$** = 251.0 Hz, **C_q**-F), 131.4, 131.2 (**$^3J_{C-F}$** = 9.3 Hz, **C_q**), 128.7, 128.6 (**$^3J_{C-F}$** = 9.0 Hz, **C_q**-Cl**)**, 125.7,125.6 (**$^3J_{C-F}$** = 3.7 Hz, **C**H_{Ar}), 125.4 (**C**=N), 117.9, 117.8 (**$^4J_{C-F}$** = 1.6 Hz, **C**H_{Ar}), **116.9, 116.6 (*$^2J_{C-F}$* = 21.1 Hz, CH_{Ar}), 62.0 (Cl-CH_2)**, **46.4 (CH_2)**, **14.0 (CH_3)**.

M.p.: 123-124 °C

Ethyl 1-(4-chlor-2-fluorophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate (52m)



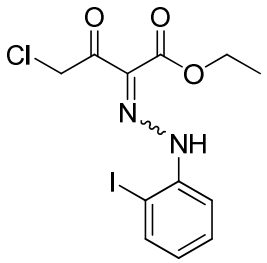
according to GP-3:

150 mg (467 µmol) (*Z*)-ethyl-4-chloro-2-((4-chloro-2-fluorophenyl)diazenyl)-3-oxo-butanoate **(51m)** were suspended in 3.0 mL EtOH. 55.0 mg (561 µmol) KOAc were added.

$C_{12}H_{10}O_3N_2FCl$ [284.6]

yield:	128.5 mg (97 %), brown solid
R_f (CH/ EtOAc 3:1):	0.52
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 9.51 (s, 1H, OH), 7.80-7.74 (m, 2H, Ar-H), 7.70-7.65 (m, 1H, Ar-H), 7.44-7.41 (m, 1H, Ar-H), 4.27 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.27 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 161.5 (**C**=O), 155.2, 151.8 ($^1J_{C-F}$ = 252.9 Hz, $\mathbf{C}_q$-F), 144.7 ($\mathbf{C}_q$-OH), 132.9, 132.8 ($^3J_{C-F}$ = 10.0 Hz, $\mathbf{C}_q$-Cl), 132.7 ($\mathbf{C}_q$), 127.0, 126.9 ($^3J_{C-F}$ = 9.7 Hz, $\mathbf{C}_q$), 126.1 (**C**H_{Ar}), 125.8, 125.7 ($^4J_{C-F}$ = 3.6 Hz, **C**H_{Ar}), 118.7, 118.6 ($^3J_{C-F}$ = 7.6 Hz, **C**H_{Ar}), 117.9, 117.6 ($^2J_{C-F}$ = 23.9 Hz, **C**H_{Ar}), 60.4 (**C**H_2), 14.4 (**C**H_3).
M.p.:	114-116 °C
GC-MS (NM_50_S2):	t_R = 7.39 min (m/z = 283.9, 98.0 % M^+, BP: 155.9).
HRMS (EI$^+$):	*m/z*: calcd for $C_{12}H_{10}O_3N_2FCl$ $[M]^+$: 284.0364; found 284.0354.

Ethyl-4-chloro-2-((2-iodophenyl)diazenyl)-3-oxobutanoate (51n)



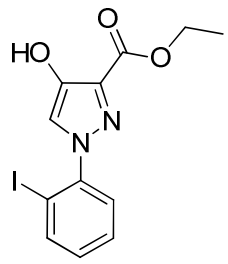
according to GP-2:

250 mg (1.14 mmol) 2-iodoaniline **(49n)** in 2.0 mL acetic acid and 80.3 mg (1.16 mmol) $NaNO_2$ in 0.3 mL conc. H_2SO_4 were combined at 10 °C resulting in a dark brown solution, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 181 mg (150 µL, 1.10 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 0.8 mL acetic acid and 1.6 mL water. Addition of 990 mg (12.1 mmol) NaOAc in 2.0 mL water precipitated the title compound.

$C_{12}H_{12}O_3N_2ICl$ [394.5]

yield:	336.5 mg (78 %), yellow-green solid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 13.19 (bs, 1H, NH), 7.80 (dd, ^3J = 7.8 Hz, ^4J = 0.9 Hz, 1H, Ar-H), 7.60-7.57 (m, 1H, Ar-H), 7.42 (t, ^3J = 7.8 Hz, 1H, Ar-H), 6.95-6.90 (m, 1H, Ar-H), 4.72 (s, 2H, Cl-CH_2), 4.43 (q, ^3J = 7.2 Hz, CH_2), 1.42 (t, ^3J = 7.2 Hz, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 186.4 (**C**=O), 162.9 (**C**=O), 141.5 ($\mathbf{C}_q$), 139.5 ($\mathbf{C}H_{Ar}$), 129.6 ($\mathbf{C}H_{Ar}$), 126.7 ($\mathbf{C}H_{Ar}$), 126.2 (**C**=N), 116.4 ($\mathbf{C}H_{Ar}$), 85.0 ($\mathbf{C}_q$-**I**), 61.9 (Cl-$\mathbf{C}H_2$), 46.6 ($\mathbf{C}H_2$), 14.1 ($\mathbf{C}H_3$).
M.p.:	111-114 °C

Ethyl 1-(2-iodophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate (52n)



according to GP-3:

200 mg (507 µmol) (*Z*)-ethyl-4-chloro-2-((2-iodophenyl)diazenyl)-3-oxobutanoate **(51n)** were suspended in 2.2 mL EtOH. 59.7 mg (608 µmol) KOAc were added.

$C_{12}H_{11}O_3N_2I$ [358.1]

yield:	174.2 mg (96 %), dark brown solid
R_f (CH/ EtOAc 3:1):	0.38
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 9.13 (s, 1H, OH), 8.03-8.01 (m, 1H, Ar-H), 7.61 (s, 1H, Ar-H), 7.55-7.52 (m, 1H, Ar-H), 7.48-7.45

(m,1H, Ar-H), 7.31- 7.29 (m, 1H, Ar-H), 4.27 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.28 (t, ^3J = 7.2 Hz, 3H, CH_3).

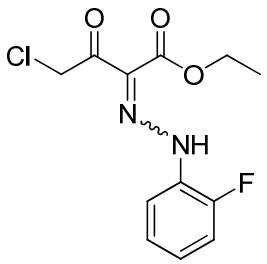
^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 161.6 (**C**=O), 143.9 ($\mathbf{C}_q$-OH), 142.9 ($\mathbf{C}_q$), 139.5 ($\mathbf{C}H_{Ar}$), 131.4 ($\mathbf{C}_q$), 130.9 ($\mathbf{C}H_{Ar}$), 129.1 ($\mathbf{C}H_{Ar}$), 128.0 ($\mathbf{C}H_{Ar}$), 119.1 ($\mathbf{C}H_{Ar}$), 95.2 ($\mathbf{C}_q$-I), 59.7 ($\mathbf{C}H_2$), 14.2 ($\mathbf{C}H_3$).

M.p.: 58-61 °C

GC-MS (NM_50_S2): t_R = 7.96 min (m/z = 357.9, 99.0 % M^+, BP).

HRMS (EI^+): *m/z*: calcd for $C_{12}H_{11}O_3N_2I$ $[M]^+$: 357.9814; found 357.9846.

Ethyl-4-chloro-2-((2-fluorophenyl)diazenyl)-3-oxobutanoate (51o) [108]



according to GP-2:

1.00 g (860 µL, 9.00 mmol) 2-fluoroaniline **(49o)** in 15.1 mL acetic acid and 630 mg (9.13 mmol) $NaNO_2$ in 3.0 mL conc. H_2SO_4 and 2 mL acetic acid were combined at 10 °C resulting in a brown solution, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 1.42 g (1.17 mL, 8.63 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 6.6 mL acetic acid and 13.2 mL water. Addition of 7.81 g (95.2 mmol) NaOAc in 13.8 mL water precipitated the title compound.

$C_{12}H_{12}O_3N_2FCl$ [286.5]

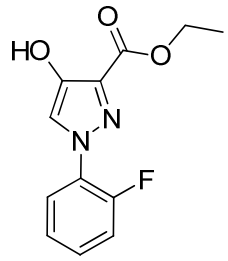
yield: 425.7 mg (69 %), orange solid

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 13.26 (bs, 1H, NH), 7.76 (t, ^3J = 7.8 Hz, 1H, Ar-H), 7.38-7.25 (m, 3H, Ar-H), 4.84 (s, 2H, CH_2), 4.52 (q, ^3J = 7.2 Hz; 2H, CH_2), 1.53 (t, ^3J = 7.2 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 186.4 (**C**=O), 163.2 (**C**=O), 153.6, 150.3 ($^{1}J_{C-F}$ = 246.3 Hz, $\mathbf{C}_q$-F), 129.8, 129.7 ($^{2}J_{C-F}$ = 9.6 Hz, $\mathbf{C}_q$), 126.4 (**C**=N), 125.8, 125.7 ($^{2}J_{C-F}$ = 7.2 Hz, $\mathbf{C}H_{Ar}$), 125.3, 125.2 ($^{3}J_{C-F}$ = 3.6 Hz, $\mathbf{C}H_{Ar}$), 116.1 ($\mathbf{C}H_{Ar}$), 115.9 ($\mathbf{C}H_{Ar}$), 61.9 (Cl-$\mathbf{C}H_2$), 46.6 ($\mathbf{C}H_2$), 14.1 ($\mathbf{C}H_3$).

M.p.: 122-124 °C

Ethyl 1-(2-fluorophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate (52o) [108]



according to GP-3:

1.60 g (5.58 mmol) (*Z*)-ethyl-4-chloro-2-((2-fluorophenyl)diazenyl)-3-oxobutanoate **(51o)** were suspended in 17.5 mL EtOH. 660 mg (6.72 mmol) KOAc were added.

$C_{12}H_{11}O_3N_2F$ [250.2]

yield: 1.38 g (99 %), brown solid

R_f (CH/ EtOAc 3:1): 0.43

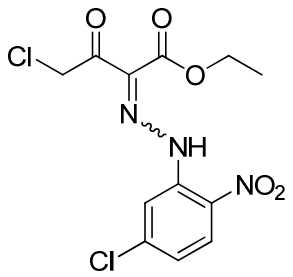
^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) = 9.28 (s, 1H, OH), 7.79-7.74 (m, 2H, Ar-H), 7.49-7.45 (m, 2H, Ar-H), 7.39-7.33 (m, 1H, Ar-H), 4.29 (q, ^{3}J = 7.2 Hz, 2H, CH_2), 1.29 (t, ^{3}J = 7.2 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 161.3 (**C**=O), 155.2, 151.9 ($^{1}J_{C-F}$ = 249.1 Hz, $\mathbf{C}_q$-F), 144.4 ($\mathbf{C}_q$-OH), 132.2 ($\mathbf{C}_q$), 129.4, 129.3 ($^{3}J_{C-F}$ = 7.9 Hz, $\mathbf{C}H_{Ar}$), 127.7, 127.6 ($^{2}J_{C-F}$ = 9.6 Hz, $\mathbf{C}_q$), 125.3, 125.2 ($^{4}J_{C-F}$ = 3.6 Hz, $\mathbf{C}H_{Ar}$), 124.8 ($\mathbf{C}H_{Ar}$), 118.5, 118.4 ($^{3}J_{C-F}$ = 7.3 Hz, $\mathbf{C}H_{Ar}$), 117.1, 116.8 ($^{2}J_{C-F}$ = 20.0 Hz, $\mathbf{C}H_{Ar}$), 59.9 ($\mathbf{C}H_2$), 14.2 ($\mathbf{C}H_3$).

M.p.: 63-65 °C

GC-MS (NM_50_S2): t_R = 7.02 min (m/z = 250.0, 99.0 % M^+, BP: 122.0).

Ethyl-4-chloro-2-((5-chloro-2-nitrophenyl)diazenyl)-3-oxo-butanoate (51p)



according to GP-2:

750 mg (4.35 mmol) 5-chloro-2 nitroaniline **(49p)** in 11.3 mL acetic acid and 300 mg (4.43 mmol) $NaNO_2$ in 2.3 mL conc. H_2SO_4 were combined at 10 °C resulting in a orange solution, which was added after 1 h stirring at 10 °C to the cooled (0 °C) solution of 910 mg (750 µL, 4.18 mmol) ethyl-4-chloro-3-oxobutanoate **(50)** in a mixture of 3.2 mL acetic acid and 6.4 mL water. Addition of 3.17 g (46.0 mmol) NaOAc in 8.2 mL water precipitated the title compound.

$C_{12}H_{11}O_5N_3Cl_2$ [362.1]

yield: 1.16 g (77 %), yellow solid

^{1}H-NMR (300 MHz, $CDCl_3$): **Isomer I (7 %):** δ (ppm) = **15.28 (bs, 1H, NH)**, **8.05 (d, ^3J = 9.0 Hz, 1H, Ar-H)**, **8.15 (s, 1H, Ar-H), 6.65 (d, ^3J = 9.0 Hz, 1H, Ar-H), 4.80 (s, 2H, Cl-CH_2),** 4.50-4.37 (m, 2H, CH_2), 1.42 (t, ^3J =7.2 Hz, CH_3)

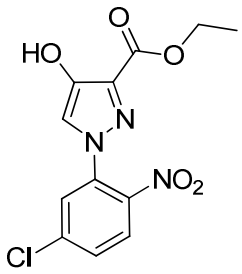
Isomer II (74 %): δ (ppm) = **14.25 (bs, 1H, NH)**, **8.23 (d, ^3J = 9.0 Hz, 1H, Ar-H)**, **8.05 (d, ^3J = 9.0 Hz, 1H, Ar-H)**, **7.18 (d, ^3J = 9.0 Hz, 1H, Ar-H)**, **4.72 (s, 2H, Cl-CH_2),** 4.50-4.37 (m, 2H, CH_2), 1.42 (t, ^3J = 7.2 Hz, CH_3)

^{13}C-NMR (75.5 MHz, $CDCl_3$): **Isomer I:** δ (ppm) = 186.6 (**C**=O), 161.2 (**C**=O), 142.9 ($\mathbf{C}_q$), 138.8 ($\mathbf{C}_q$-Cl), 133.5 (**C**=N),130.7 ($\mathbf{C}_q$-NO_2), 127.6 (**C**H_{Ar}), 123.8 (**C**H_{Ar}), **117.7 (C$\mathbf{H}_{Ar}$)**, 62.7 (Cl-**C**H_2), 46.5 (**C**H_2), 14.0 (**C**H_3).

Isomer II: δ (ppm) = 186.6 (**C**=O), 161.2 (**C**=O), 142.9 (**C**$_q$), 138.8 (**C**$_q$-Cl), 133.5 (**C**=N),130.7 (**C**$_q$-NO$_2$), 127.6 (**C**H$_{Ar}$), 123.8 (**C**H$_{Ar}$), **116.6 (CH$_{Ar}$)**, 62.7 (Cl-**C**H$_2$), 46.5 (**C**H$_2$), 14.0 (**C**H$_3$).

M.p.: 144-147 °C

Ethyl 1-(5-chloro-2-nitrophenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate (52p)



according to GP-3:

1.16 g (3.20 mmol) (*Z*)-ethyl-4-chloro-2-((5-chloro-2-nitrophenyl)diazenyl)-3-oxobutanoate **(51p)** were suspended in 12.5 mL EtOH. 380 mg (3.84 mmol) KOAc were added. Final purification by column chromatography (CH/EtOAc 3:1, size: 24.5 x 3.0 cm, 80 g silica gel) yielded the pure product.

$C_{12}H_{10}O_5N_3Cl$ [311.7]

yield: 410.0 mg (41 %), yellow solid

R_f (CH/ EtOAc 3:1): 0.36

^{1}H-NMR (300 MHz, DMSO-d$_6$): δ (ppm) = 9.43 (s, 1H, OH), 8.10 (d, ^3J = 8.7 Hz, 1H, Ar-H), 8.01 (d, ^4J = 2.4 Hz, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 7.77 (dd, ^3J = 8.7 Hz, ^4J = 2.4 Hz, 1H, Ar-H), 4.26 (q, ^3J = 7.2 Hz, 2H, CH$_2$), 1.27 (t, ^3J = 7.2 Hz, 3H, CH$_3$).

^{13}C-NMR (75.5 MHz, DMSO-d$_6$): δ (ppm) = 161.0 (**C**=O), 144.6 (**C**$_q$-OH), 142.5 (**C**$_q$), 137.7 (**C**$_q$-Cl), 133.8 (**C**$_q$), 133.4 (**C**$_q$-NO$_2$), 129.1 (**C**H$_{Ar}$), 126.9 (**C**H$_{Ar}$), 126.3 (**C**H$_{Ar}$), 118.1 (**C**H$_{Ar}$), 60.1 (**C**H$_2$), 14.1 (**C**H$_3$).

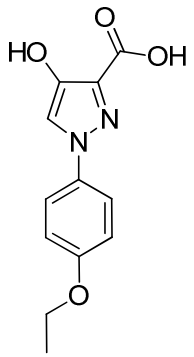
M.p.: 123-125 °C

GC-MS (NM_50_S2): t_R = 8.22 min (m/z = 311.0, 99.0 % M$^+$, BP).

HRMS (EI^+): *m/z*: calcd for $C_{12}H_{10}O_5N_3Cl$ $[M]^+$: 311.0309; found 311.0317.

6.3.2. Esterification of 4-hydroxy-1*H*-pyrazole-3-carboxylic acid 53

1-(4-Ethoxyphenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylic acid (53)



In a 100 mL one-neck round-bottom flask 2.00 g (7.25 mmol, 1.00 eq) ethyl 1-(4-ethoxy-phenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate **(52a)** were suspended in 24 mL EtOH and 8 mL 5 M NaOH were added. The brown mixture was stirred at 60 °C for 30 min, during which a red-brown solution was obtained. TLC analysis (THF) indicated full conversion of the starting material and 4 mL water and 1.11 mL of conc. H_2SO_4 were added. The solvent was removed on the rotary evaporator and the residue was dissolved in 30 mL DCM and 20 mL water. The layers were separated and the organic layer was washed with water (2 x 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to obtain 950 mg (53 %) crude product. Final purification by column chromatography (THF, size: 24.5 x 3.5 cm, 80 g silica gel) and basic/acidic work up (dissolving the product in DCM, alkalize with 10 % NaOH solution, extraction with water, acidify the aqueous layer with 5 % HCl solution, extract the product with DCM in the organic phase, drying, concentrating) yielded the pure product.

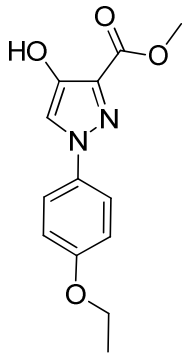
$C_{12}H_{12}O_4N_2$ [248.2]

yield: 0.73 g (41 %), brown solid

R_f (THF): 0.10

^{1}H-NMR (300 MHz, MeOD):	δ (ppm) = 8.00 (s, 1H, OH), 7.75 (s, 1H, Ar-H), 7.64 (d, ^{3}J = 8.4 Hz, 2H, Ar-H), 7.00 (d, ^{3}J = 8.4 Hz, 2H, Ar- H), 4.06 (q, ^{3}J = 6.9 Hz, 2H; CH_2), 1.40 (t, ^{3}J = 6.9 Hz, 3H; CH_3).
^{13}C-NMR (75.5 MHz, MeOD):	δ (ppm) = 166.4 (**C**=O), 159.9 ($\mathbf{C}_q$), 147.6 ($\mathbf{C}_q$-OH), 134.7 ($\mathbf{C}_q$), 132.4 ($\mathbf{C}_q$), 122.0 (2 $\mathbf{C}H_{Ar}$), 116.2 (2 $\mathbf{C}H_{Ar}$), 115.6 ($\mathbf{C}H_{Ar}$), 65.0 ($\mathbf{C}H_2$), 15.1 ($\mathbf{C}H_3$).
M.p.:	84-86 °C

Methyl 1-(4-ethoxyphenyl)-1*H*-pyrazole-3-carboxylate (54a)



A 20 mL Schlenk tube was charged with 80.0 mg (323 µmol, 1.00 eq) 1-(4-ethoxyphenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylic acid **(53)**. After adding 0.7 mL MeOH and 52.5 µL (970 µmol, 3.00 eq) conc. H_2SO_4 the mixture was refluxed for 6 h. TLC analysis (THF, CH/EtOAc 3:1) indicated full conversion of the starting material. After neutralization by adding 0.5 mL saturated aqueous $NaHCO_3$ solution, the mixture was extracted with EtOAc (3 x 10 mL), the layers were separated and the combined organic layers were washed with water (2 x 10 mL), dried over $MgSO_4$ and concentrated in vacuo to yield the pure product.

$C_{13}H_{14}O_4N_2$ [262.2]

yield:	11.8 mg (14 %), brown solid
R_f (CH/ EtOAc 3:1):	0.40
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 9.17 (s, 1H, OH), 7.97 (s, 1H, Ar-H), 7.70 (d, ^{3}J = 9.0 Hz, 2H, Ar-H), 7.04 (d, ^{3}J = 9.0 Hz, 2H,

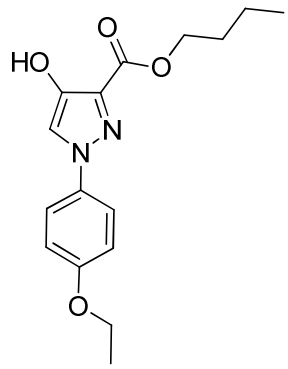
Ar-H), 4.06 (q, ^{3}J = 6.9 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 1.34 (t, ^{3}J = 6.9 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 161.9 (**C**=O), 157.4 ($\mathbf{C}_q$), 145.0 ($\mathbf{C}_q$-OH), 132.8 ($\mathbf{C}_q$), 120.2 ($\mathbf{C}_q$), 120.0 (2 $\mathbf{C}H_{Ar}$), 115.7 ($\mathbf{C}H_{Ar}$), 114.9 (2 $\mathbf{C}H_{Ar}$), 63.3 ($\mathbf{C}H_2$), 51.1 (O$\mathbf{C}H_3$), 14.5 ($\mathbf{C}H_3$).

M.p.: 125-128 °C

GC-MS: t_R = 7.89 min (m/z = 262.1, 99.0 % M^+, BP)

Butyl 1-(4-ethoxyphenyl)-1*H*-pyrazole-3-carboxylate (54b)



A 20 mL Schlenk tube was charged with 80.0 mg (323 µmol, 1.00 eq) 1-(4-ethoxyphenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylic acid **(53)**. After adding 0.7 mL *n*-BuOH and 52.5 µL (970 µmol, 3.00 eq) conc. H_2SO_4 the mixture was refluxed for 25 h. TLC analysis (THF, CH/EtOAc 3:1) indicated full conversion of the starting material. After neutralization by adding 0.5 mL saturated aqueous $NaHCO_3$ solution, the mixture was extracted with EtOAc (3 x 10 mL), the layers were separated and the combined organic layers were washed with water (2 x 10 mL), dried over $MgSO_4$ and concentrated in vacuo to yield the crude product. Final purification by column chromatography (CH/EtOAc 3:1, size: 9.5 x 2.0 cm, 10 g silica gel) yielded the pure product.

$C_{16}H_{20}O_4N_2$ [304.3]

yield: 55.5 mg (56 %), orange solid

R_f (CH/ EtOAc 3:1): 0.51

^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) = 7.96 (s, 1H, Ar-H), 7.70 (d, ^{3}J = 9.0 Hz, 2H, Ar-H), 7.03 (d, ^{3}J = 9.0 Hz, 2H, Ar-H), 4.24 (t, ^{3}J = 6.6 Hz,

2H, CH_2), 4.06 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.69-1.64 (m, 2H, CH_2), 1.43-1.38 (m, 2H, CH_2), 1.34 (t, ^3J = 6.9 Hz, 3H, CH_3), 0.92 (t, ^3J = 7.2 Hz, 3H, CH_3).

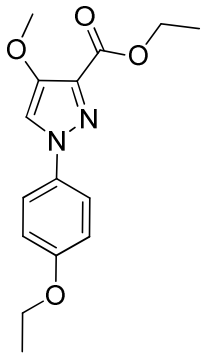
^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 161.6 (**C**=O), 157.3 ($\mathbf{C}_q$), 145.0 (**C**-OH), 132.8 ($\mathbf{C}_q$), 131.1 ($\mathbf{C}_q$), 120.0 (2 $\mathbf{C}H_{Ar}$), 114.9 (2 $\mathbf{C}H_{Ar}$), 114.8 ($\mathbf{C}H_{Ar}$), 63.4 ($\mathbf{C}H_2$), 63.3 ($\mathbf{C}H_2$), 30.3 ($\mathbf{C}H_2$), 18.6 ($\mathbf{C}H_2$), 14.5 ($\mathbf{C}H_3$), 13.5 ($\mathbf{C}H_3$).

M.p.: 60-61 °C

GC-MS: t_R = 8.64 min (m/z = 304.1, 99.0 % M^+, BP: 148.1).

6.3.3. Alkylation of 4-hydroxy-1*H*-pyrazole-3-carboxylate

Ethyl 1-(4-ethoxyphenyl)-4-methoxy-1*H*-pyrazole-3-carboxylate (55a)

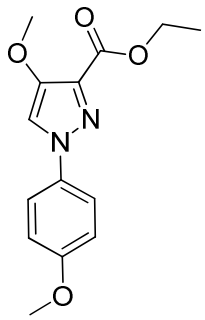


A 10 mL Schlenk tube was charged with 75.0 mg (270 µmol, 1.00 eq) ethyl 1-(4-ethoxy-phenyl)-4-hydroxy-1*H*-pyrazole-3-carboxylate **(52a)** which was dissolved in 0.6 mL DMF. 54.9 mg (400 µmol, 1.46 eq) K_2CO_3 and 18.0 µL (290 µmol, 1.06 eq) methyliodide were added and the brown suspension was stirred at rt over night. TLC analysis (CH/EtOAc 3:1) indicated 86 % conversion of the starting material. After adding once more 3.00 µL (40.0 µmol) methyliodide and stirring for a further hour at rt full conversion was detected. The DMF was removed at high vacuum and the residue was dissolved in EtOAc and water. The organic layer was washed with 15 mL saturated aqueous $NaHCO_3$ solution and 15 mL brine, dried over Na_2SO_4 and concentrated under reduced pressure. After drying under high vacuum the pure product was obtained.

$C_{15}H_{18}O_4N_2$ [290.0]

yield:	73.0 mg (93 %), dark brown solid
R_f (CH/ EtOAc 3:1):	0.16
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.35 (s, 1H, Ar-H), 7.74 (d, ^3J = 9.0 Hz, 2H, Ar-H), 7.05 (d, ^3J = 9.0 Hz, 2H, Ar-H), 4.27 (q, ^3J = 7.2 Hz, 2H, CH_2), 4.06 (q, ^3J = 6.9, Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3), 1.36-1.26 (m, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 161.8 (**C**=O), 158.9 ($\mathbf{C}_q$), 149.4 ($\mathbf{C}_q$-OH), 133.5 ($\mathbf{C}_q$), 131.7 ($\mathbf{C}_q$), 121.2 (2 $\mathbf{C}H_{Ar}$), 114.5 (2 $\mathbf{C}H_{Ar}$), 112.1 ($\mathbf{C}H_{Ar}$), 60.9 ($\mathbf{C}H_2$), 59.5 (O$\mathbf{C}H_3$), 55.6 (O$\mathbf{C}H_3$), 14.4 ($\mathbf{C}H_3$).
M.p.:	95-98 °C
GC-MS (NM_50_S2):	t_R = 8.44 min (m/z = 290.1, 99.0 % M^+, BP).
HRMS (EI^+):	*m/z*: calcd for $C_{15}H_{18}O_4N_2$ $[M]^+$: 290.1266; found 290.1267.

Ethyl 4-methoxy-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (55c)



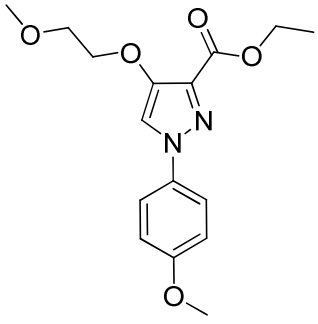
A 10 mL Schlenk tube was charged with 75.0 mg (286 µmol, 1.00 eq) ethyl 4-hydroxy-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate **(52c)** which was dissolved in 0.7 mL DMF. 57.8 mg (418 µmol, 1.46 eq) K_2CO_3 and 22.0 µL (344 µmol, 1.20 eq) methyliodide were added and the dark red suspension was stirred at rt over night. TLC analysis (CH/EtOAc 3:1) indicated full conversion of the starting material. The DMF was removed under high vacuum and the residue was dissolved in EtOAc and water. The organic layer was washed with 15 mL saturated aqueous $NaHCO_3$ solution and 15 mL brine, dried over Na_2SO_4 and concentrated

under reduced pressure. Drying at high vacuum yielded in the crude product (93 % purity, GC-MS) which was purified by column chromatography (CH/EtOAc 3:1, size: 20.0 x 15.0 cm, 10 g silica gel) to obtain the pure product.

$C_{14}H_{16}O_4N_2$ [276.2]

yield:	29.0 mg (37 %), orange-brown solid
R_f (CH/ EtOAc 3:1):	0.19
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 9.09 (s, 1H, OH), 7.97 (s, 1H, Ar-H), 7.73 (d, ^3J = 9.0 Hz, 2H, Ar-H), 7.05 (d, ^3J = 9.0 Hz, 2H, Ar-H), 4.28 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.80 (s, 3H, OCH_3), 1.30 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 161.6 (**C**=O), 158.1 (**C**$_q$), 145.0 (**C**$_q$-OH), 132.9 (**C**$_q$), 131.1 (**C**$_q$), 120.1 (2 **C**H$_{Ar}$), 114.9 (**C**H$_{Ar}$), 114.5 (2 **C**H$_{Ar}$), 59.7 (**C**H_2), 55.4 (O**C**H_3), 14.2 (**C**H_3).
M.p.:	68-70 °C
GC-MS (NM_50_S2):	t_R = 8.24 min (m/z = 276.1, 98.0 % M^+, BP).
HRMS (EI$^+$):	*m/z*: calcd for $C_{14}H_{16}O_4N_2$ $[M]^+$: 276.1110; found 276.1102.

Ethyl 4-(2-methoxyethoxy)-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (56)



A 10 mL Schlenk tube was charged with 250 mg (950 µmol, 1.00 eq) ethyl 4-hydroxy-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate **(52c)**, which was dissolved in 2.0 mL DMF. 200 mg (1.45 mmol, 1.50 eq) K_2CO_3 and 100 µL (1.15 mmol, 1.20 eq) 1-chloro-2-methoxyethane were added and the brown suspension was stirred at rt over night. TLC analysis (CH/EtOAc

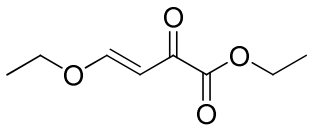
3:1) indicated no conversion of the starting material. Although further 200 mg (1.45 mmol, 1.50 eq) K_2CO_3 and 100 µL (1.15 mmol, 1.20 eq) 1-chloro-2-methoxyethane were added and the reaction mixture was stirred at rt over night no conversion was detected. But an increase of the temperature to 60 °C and further stirring over night at this temperature showed full conversion on TLC on the next day. The DMF was removed under high vacuum and the residue was dissolved in DCM and water. The organic layer was washed with 30 mL saturated aqueous $NaHCO_3$ solution and 30 mL brine, dried over Na_2SO_4 and concentrated under reduced pressure. Drying under high vacuum yielded in the pure product.

$C_{16}H_{20}O_5N_2$ [320.3]

yield:	214.8 mg (40 %), brown oil
R_f (CH/ EtOAc 1:1):	0.32
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.38 (s, 1H, Ar-H), 7.75 (d, ^3J = 9.0 Hz, 2H, Ar-H), 7.07 (d, ^3J = 9.0 Hz, 2H, Ar-H), 4.28 (q, ^3J = 6.9 Hz, 2H, CH_2), 4.13-4.10 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.68-3.65 (m, 2H, CH_2), 3.33 (s, 3H, OCH_3), 1.29 (t, ^3J = 6.9 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 160.8 (**C**=O), 158.1 ($\mathbf{C}_q$-OCH_3), 147.4 ($\mathbf{C}_q$), 132.8 ($\mathbf{C}_q$), 130.9 ($\mathbf{C}_q$), 119.9 (2 $\mathbf{C}H_{Ar}$), 114.5 (2 $\mathbf{C}H_{Ar}$), 114.3 ($\mathbf{C}H_{Ar}$), 71.4 ($\mathbf{C}H_2$), 70.1 ($\mathbf{C}H_2$), 59.8 ($\mathbf{C}H_2$), 58.3 ($O\mathbf{C}H_3$), 55.4 ($O\mathbf{C}H_3$), 14.1 ($\mathbf{C}H_3$).
GC-MS (NM_50_S2):	t_R = 9.08 min (m/z = 320.1, 99.0 % M^+, BP: 133.9).
HRMS (EI^+):	*m/z*: calcd for $C_{16}H_{20}O_5N_2$ $[M]^+$: 320.1372; found 320.1372.

6.3.4. Synthesis of aryl substituted ethyl 1*H*-pyrazolecarboxylates

(*E*)-Ethyl-4-ethoxy-2-oxobut-3-enoate (59)

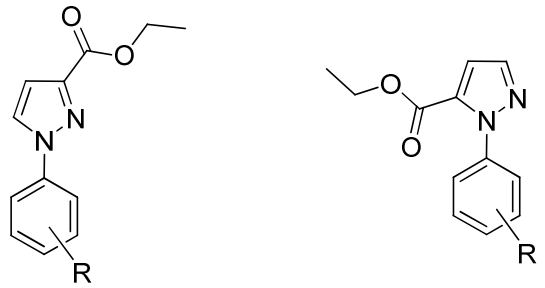


A 25 mL one-neck round-bottom flask was charged with 3.79 g (3.10 mL, 27.7 mmol, 1.00 eq) ethyl chlorooxoacetate **(57)** and 4.00 g (5.32 mL, 55.5 mmol, 2.00 eq) ethylvinylether **(58)**. After stirring of the colorless solution at rt over night, during which the color turned to yellow, GC-MS analysis showed complete conversion (95 % product). The mixture was concentrated to dryness under reduced pressure leading to the title compound.

$C_8H_{12}O_4$ [172.1]

yield:	4.74 g (>99 %), yellow-brown liquid
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.85 (d, ^3J = 12.6 Hz, 1H, CH), 6.16 (d, ^3J = 12.6 Hz, 1H, CH), 4.30 (q, ^3J = 14.1 Hz, 2 H, CH_2), 4.04 (d, ^3J = 14.1 Hz, 2H, CH_2), 1.39-1.33 (m, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 182.2 (**C**=O), 167.1 (**C**H), 162.4 (**C**=O), 101.8 (**C**H), 68.1 (**C**H_2), 62.2 (**C**H_2), 14.4 (**C**H_3), 14.0 (**C**H_3).
GC-MS (HS_50_S2):	t_R = 5.14 min (m/z = 171.9, 99 % M^+, BP: 70.9).

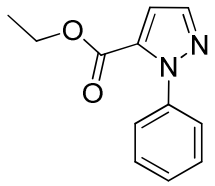
General procedure (GP-4):



A 100 mL Schlenk tube was charged with 1.00 eq (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** which was dissolved in glacial acetic acid. After adding 1.00 eq phenylhydrazine **(60a)** or phenylhydrazine hydrochloride **(60b-h)**, also dissolved in glacial acetic acid, the reaction mixture was heated to reflux (130 °C) and stirred at this temperature for 2 h. TLC analysis indicated full conversion of the starting material and GC-MS analysis confirmed this result. The mixture was cooled to rt, poured into 100 mL water and transferred to a separation funnel. The aqueous layer was extracted with EtOAc (5 x 30 mL) and the combined organic layers were washed with 50 mL water, saturated aqueous $NaHCO_3$ solution (2 x 50 mL) and once more with 50 mL water. After drying over $MgSO_4$ and concentration in vacuo a crude product mixture of ethyl 1-phenyl-1*H*-pyrazole-3-carboxylate and ethyl 1-phenyl-1*H*-

pyrazole-5-carboxylate was obtained. Separation of both products and final purification by column chromatography leaded to two pure compounds.

Ethyl 1-phenyl-1*H*-pyrazole-5-carboxylate ($61a_1$) [110]



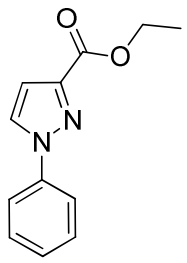
according to GP-4:

1.28 g (7.43 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 8 mL glacial acetic acid, 803 mg (730 µL, 7.43 mmol) phenylhydrazine **(60a)** in 11 mL glacial acetic acid, TLC (CH/EtOAc 3:1, R_f = 0.53), column chromatography (CH/THF 15:1, R_f = 0.29, size: 24.0 x 4.0 cm, 140 g silica gel).

$C_{12}H_{12}O_2N_2$ [216.0]

yield:	622.9 mg (39 %), yellow solid
R_f (CH/EtOAc 3:1):	0.53
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 7.81 (d, ^4J = 1.8 Hz, 1H, Ar-H), 4.47-7.43 (m, 5H, Ar-H), 7.09 (d, ^4J = 1.8 Hz, 1H, Ar-H), 4.17 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.15 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 158.4 (**C**=O), 139.9 (**C**$_q$), 139.7 (**C**H$_{Ar}$), 133.0 (**C**$_q$), 128.4 (2 **C**H$_{Ar}$), 128.3 (**C**H$_{Ar}$), 125.6 (2 **C**H$_{Ar}$), 112.4 (**C**H$_{Ar}$), 60.8 (**C**H$_2$), 13.7 (**C**H$_3$).
M.p.:	70-71 °C
GC-MS (NM_50_S2):	t_R = 6.27 min (m/z = 216.0, >99.0 % M^+, BP: 170.9).

Ethyl 1-phenyl-1*H*-pyrazole-3-carboxylate (61a$_2$) [110]



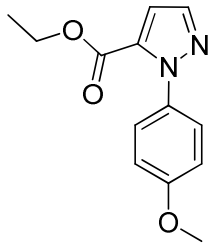
according to GP-4:

1.28 g (7.43 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 8 mL glacial acetic acid, 803 mg (730 µL, 7.43 mmol) phenylhydrazine **(60a)** in 11 mL glacial acetic acid, TLC (CH/EtOAc 3:1, R_f = 0.33), column chromatography (CH/THF 15:1, R_f = 0.14, size: 24.0 x 4.0 cm, 140 g silica gel).

$C_{12}H_{12}O_2N_2$ [216.0]

yield:	706.5 mg (44 %), yellow oil
R_f (CH/EtOAc 3:1):	0.33
^{1}H-NMR (300 MHz, DMSO-d$_6$):	δ (ppm) = 8.63 (d, ^4J = 2.4 Hz, 1H, Ar-H), 7.89 (d, ^3J = 7.8 Hz, 2H, Ar-H), 7.57-7.52 (m, 2H, Ar-H), 7.42-7.37 (m, 1H, Ar-H), 7.01 (d, ^4J = 2.4 Hz, 1H, Ar-H), 4.32 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.32 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d$_6$):	δ (ppm) = 161.4 (**C**=O), 144.2 (**C**$_q$), 139.1 (**C**$_q$), 129.7 (**C**H$_{Ar}$), 129.6 (2 **C**H$_{Ar}$), 127.4 (**C**H$_{Ar}$), 119.1 (2 **C**H$_{Ar}$), 110.1 (**C**H$_{Ar}$), 60.4 (**C**H$_2$), 14.1 (**C**H$_3$).
GC-MS (NM_50_S2):	t_R = 6.93 min (m/z = 216.0, >99.0 % M^+, BP: 170.9).

Ethyl 1-(4-methoxyphenyl)-1*H*-pyrazol-5-carboxylate (61b$_1$)



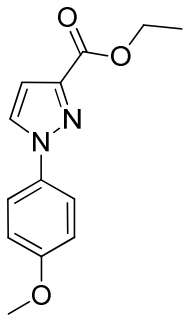
according to GP-4:

1.28 g (7.43 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 8 mL glacial acetic acid, 1.30 g (7.43 mmol) 4-methoxyphenylhydrazine hydrochloride **(60b)** in 18 mL glacial acetic acid, TLC (CH/ EtOAc 3:1, R_f = 0.40), column chromatography (CH/EtOAc 3:1, size: 33.0 x 3.0 cm, 150 g silica gel).

$C_{13}H_{14}O_3N_2$ [246.1]

yield:	358.2 mg (20 %), yellow solid
R_f (CH/ EtOAc 3:1):	0.40
^{1}H-NMR (300 MHz, DMSO-d$_6$):	δ (ppm) = 7.77-7.76 (m, 1H, Ar-H), 7.36 (d, ^3J = 9.0 Hz,, 2H, Ar-H), 7.05-7.00 (m, 3H, Ar-H), 4.17 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.17 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d$_6$):	δ (ppm) = 159.0 (**C**=O), 158.4 (**C**$_q$-OCH_3), 139.3 (**C**H$_{Ar}$), 133.1 (**C**$_q$), 132.9 (**C**$_q$), 127.0 (2 **C**H$_{Ar}$), 113.5 (2 **C**H$_{Ar}$), 112.1 (**C**H$_{Ar}$), 60.7 (**C**H_2), 55.4 (O**C**H_3), 13.8 (**C**H_3).
M.p.:	50-51 °C
GC-MS (NM_50_S2):	t_R = 7.00 min (m/z = 246.1, >99.0 % M^+, BP).
HRMS (EI$^+$):	*m/z*: calcd for $C_{13}H_{14}O_3N_2$ $[M]^+$: 246.1004; found 246.1005.

Ethyl 1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylate (61b$_2$)



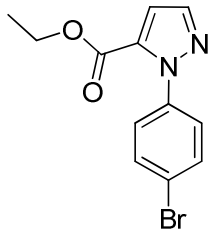
according to GP-4:

1.28 g (7.43 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 8 mL glacial acetic acid, 1.30 g (7.43 mmol) 4-methoxyphenylhydrazine hydrochloride **(69b)** in 18 mL glacial acetic acid, TLC (CH/ EtOAc 3:1, R_f = 0.33), column chromatography (CH/EtOAc 3:1, size: 33.0 x 3.0 cm, 150 g silica gel).

$C_{13}H_{14}O_3N_2$ [246.1]

yield:	955.9 mg (52 %), yellow-orange solid
R_f (CH/ EtOAc 3:1):	0.33
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.51 (d, ^4J = 2.4 Hz, 1H, Ar-H), 7.79 (d, ^3J = 9.0 Hz, 2H, Ar-H), 7.09 (d, ^3J = 9.0 Hz, 2H, Ar-H), 6.97 (d, ^4J = 2.4 Hz, 1H, Ar-H), 4.31 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3), 1.31 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 161.5 (**C**=O), 158.5 (**C**$_q$-OCH_3), 143.8 (**C**$_q$), 132.8 (**C**$_q$), 129.6 (**C**H_{Ar}), 120.8 (2 **C**H_{Ar}), 114.7 (2 **C**H_{Ar}), 110.0 (**C**H_{Ar}), 60.4 (**C**H_2), 55.5 (O**C**H_3), 14.2 (**C**H_3).
M.p.:	57 °C
GC-MS (NM_50_S2):	t_R = 7.63 min (m/z = 246.1, >99.0 % M^+, BP).

Ethyl 1-(4-bromophenyl)-1*H*-pyrazole-5-carboxylate (61c$_1$)



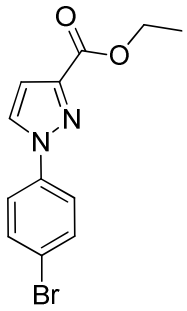
according to GP-4:

1.18 g (6.87 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 7.4 mL glacial acetic acid, 1.54 g (6.87 mmol) 4-bromophenylhydrazine hydrochloride **(60c)** in 21.3 mL glacial acetic acid, TLC (CH/ EtOAc 3:1, R_f = 0.55), column chromatography (CH/THF 15:1, R_f = 0.38 size: 23.0 x 3.5 cm, 85 g silica gel).

$C_{12}H_{11}O_2N_2Br$ [295.1]

yield:	278.4 mg (14 %), orange-yellow solid
R_f (CH/ EtOAc 3:1):	0.55
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 7.80 (d, ^4J = 1.8 Hz, 1H, Ar-H), 7.67 (d, ^3J = 8.4 Hz, 2H, Ar-H), 7.41 (d, ^3J = 8.4 Hz, 2H, Ar-H), 7.08 (d, ^4J = 1.8 Hz, 1H, Ar-H), 4.17 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.16 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 158.7 (**C**=O), 140.4 (**C**H$_{Ar}$), 139.4 (**C**$_q$), 133.4 (**C**$_q$), 131.7 (2 **C**H$_{Ar}$), 128.0 (2 **C**H$_{Ar}$), 121.6 (**C**$_q$-Br), 113.1 (**C**H$_{Ar}$), 61.3 (**C**H$_2$), 14.0 (**C**H$_3$).
M.p.:	72-73 °C
GC-MS (NM_50_S2):	t_R = 7.04 min (m/z = 294.9, > 99.0 % M^+, BP: 293.9).

Ethyl 1-(4-bromophenyl)-1*H*-pyrazole-3-carboxylate (61c$_2$)



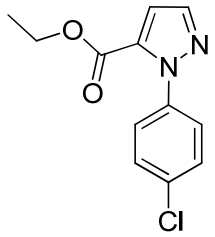
according to GP-4:

1.18 g (6.87 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 7.4 mL glacial acetic acid, 1.54 g (6.87 mmol) 4-bromophenylhydrazine hydrochloride **(60c)** in 21.3 mL glacial acetic acid, TLC (CH/ EtOAc 3:1, R_f = 0.43), column chromatography (CH/THF 15:1, R_f = 0.17 size: 23.0 x 3.5 cm, 85 g silica gel).

$C_{12}H_{11}O_2N_2Br$ [295.1]

yield:	685.0 mg (34 %), orange-yellow solid
R_f (CH/ EtOAc 3:1):	0.43
^{1}H-NMR (300 MHz, DMSO-d$_6$):	δ (ppm) = 8.55 (d, ^4J = 2.4 Hz, 1H, Ar-H), 7.81 (d, ^3J = 9.0 Hz, 2H, Ar-H), 7.70 (d, ^3J = 9.0 Hz, 2H, Ar-H), 6.98 (d, ^4J = 2.4 Hz, 1H, Ar-H), 4.30 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.29 (t, ^3J = 6.9 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d$_6$):	δ (ppm) = 161.6 (**C**=O), 144.8 (**C**$_q$), 138.5 (**C**$_q$), 132.7 (2 **C**H$_{Ar}$), 130.1 (**C**H$_{Ar}$), 121.3 (2 **C**H$_{Ar}$), 120.2 (**C**$_q$-Br), 110.7 (**C**H$_{Ar}$), 60.9 (**C**H$_2$), 14.3 (**C**H$_3$).
M.p.:	88-90 °C
GC-MS (NM_50_S2):	t_R = 7.72 min (m/z = 294.9, > 99.0 % M^+, BP: 248.9).

Ethyl 1-(4-chlorophenyl)-1*H*-pyrazole-5-carboxylate (61d$_1$)



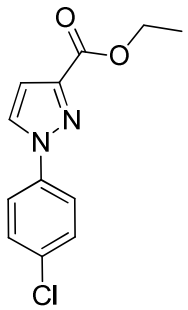
according to GP-4:

1.18 g (6.87 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 7.4 mL glacial acetic acid, 1.23 g (6.87 mmol) 4-chlorophenylhydrazine hydrochloride **(60d)** in 17.1 mL glacial acetic acid, TLC (CH/ EtOAc 3:1, R_f = 0.54), column chromatography (CH/THF 15:1, R_f = 0.38 size: 25.0 x 4.0 cm, 100 g silica gel).

$C_{12}H_{11}O_2N_2Cl$ [250.7]

yield:	369.8 mg (21 %), orange solid
R_f (CH/ EtOAc 3:1):	0.54
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.68 (d, ^4J = 1.8 Hz, 1H, Ar-H), 7.44-7.36 (m, 2H, Ar-H), 7.43 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.02 (d, ^4J = 1.8 Hz, 1H, Ar-H), 4.25 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.27 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 159.0 (**C**=O), 139.9 (**C**H$_{Ar}$), 138.7 (**C**$_q$), 134.5 (**C**$_q$), 133.4 (**C**$_q$-Cl), 128.7 (2 **C**H$_{Ar}$), 127.3 (2 **C**H$_{Ar}$), 112.8 (**C**H$_{Ar}$) 61.2 (**C**H$_2$), 14.0 (**C**H$_3$).
M.p.:	75-76 °C
GC-MS (NM_50_S2):	t_R = 6.76 min (m/z = 250.0, > 99.0 % M^+, BP).

Ethyl 1-(4-chlorophenyl)-1*H*-pyrazole-3-carboxylate (61d$_2$)



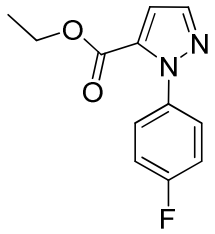
according to GP-4:

1.18 g (6.87 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 7.4 mL glacial acetic acid, 1.23 g (6.87 mmol) 4-chlorophenylhydrazine hydrochloride **(60d)** in 17.1 mL glacial acetic acid, TLC (CH/ EtOAc 3:1, R_f = 0.42), column chromatography (CH/THF 15:1, R_f = 0.17 size: 25.0 x 4.0 cm, 100 g silica gel).

$C_{12}H_{11}O_2N_2Cl$ [250.7]

yield:	568.8 mg (33 %), orange solid
R_f (CH/ EtOAc 3:1):	0.42
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.90 (d, ^4J = 2.4 Hz, 1H, Ar-H), 7.69 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.43 (d, ^3J = 8.7 Hz, 2H, Ar-H), 6.98 (d, ^4J = 2.4 Hz, 1H, Ar-H), 4.43 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.41 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 162.1 (**C**=O), 145.5 ($\mathbf{C}_q$), 138.1 ($\mathbf{C}_q$), 133.2 ($\mathbf{C}_q$-Cl), 129.6 (2 **C**H$_{Ar}$), 128.3 (**C**H$_{Ar}$), 121.2 (2 **C**H$_{Ar}$), 110.6 (**C**H$_{Ar}$) 61.2 (**C**H$_2$), 14.3 (**C**H$_3$).
M.p.:	79-82 °C
GC-MS (NM_50_S2):	t_R = 7.42 min (m/z = 250.0, > 99.0 % M^+, BP: 204.9).

Ethyl 1-(4-fluorophenyl)-1*H*-pyrazole-5-carboxylate (61e$_1$)



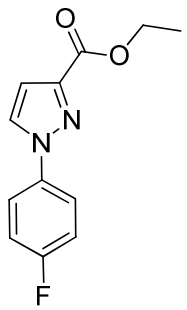
according to GP-4:

1.18 g (6.87 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 7.4 mL glacial acetic acid, 1.12 g (6.87 mmol) 4-fluorophenylhydrazine hydrochloride **(60e)** in 15.5 mL glacial acetic acid, TLC (CH/ EtOAc 3:1, R_f = 0.49), column chromatography (CH/THF 15:1, R_f = 0.35 size: 26.0 x 3.5 cm, 80 g silica gel).

$C_{12}H_{11}O_2N_2F$ [234.2]

yield:	248.2 mg (15 %), yellow solid
R_f (CH/ EtOAc 3:1):	0.49
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.68 (d, ^4J = 1.8 Hz, 1H, Ar-H), 7.43-7.38 (m, 2H, Ar-H), 7.17-7.11 (m, 2H, Ar-H), 7.02 (d, ^4J = 1.8 Hz , 1H, Ar-H), 4.24 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.26 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 164.1, 160.8 ($^1J_{C-F}$ = 248.3 Hz, **C**$_q$-F), 159.0 (**C**=O), 129.7 (**C**H$_{Ar}$), 136.4, 136.3 ($^4J_{C-F}$ = 3.2 Hz, **C**$_q$), 133.5 (**C**$_q$), 127.9, 127.8 ($^3J_{C-F}$ = 8.8 Hz, 2 **C**H$_{Ar}$), 115.6, 115.3 ($^2J_{C-F}$ = 23.1 Hz, 2 **C**H$_{Ar}$), 112.6 (**C**H$_{Ar}$), 61.2 (**C**H$_2$), 14.0 (**C**H$_3$).
M.p.:	84-85 °C
GC-MS (NM_50_S2):	t_R = 6.19 min (m/z = 234.0, > 99.0 % M^+, BP).

Ethyl 1-(4-fluorophenyl)-1*H*-pyrazole-3-carboxylate (61e$_2$)



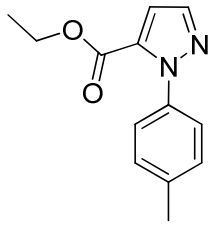
according to GP-4:

1.18 g (6.87 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 7.4 mL glacial acetic acid, 1.12 g (6.87 mmol) 4-fluorophenylhydrazine hydrochloride **(60e)** in 15.5 mL glacial acetic acid, TLC (CH/ EtOAc 3:1, R_f = 0.38), column chromatography (CH/THF 15:1, R_f = 0.18 size: 26.0 x 3.5 cm, 80 g silica gel).

$C_{12}H_{11}O_2N_2F$ [234.2]

yield:	552.8 mg (34 %), orange-yellow solid
R_f (CH/ EtOAc 3:1):	0.38
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.86 (d, ^4J = 2.4 Hz, 1H, Ar-H), 7.72-7.67 (m, 2H, Ar-H), 7.17-7.11 (m, 2H, Ar-H), 6.97 (d, ^4J = 2.4 Hz , 1H, Ar-H), 4.42 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.40 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 163.4, 160.1 ($^1J_{C-F}$ = 247.5 Hz, **C**$_q$-F),162.1 (**C**=O), 145.3 (**C**$_q$), 136.0, 135.9 ($^4J_{C-F}$ = 2.9 Hz, **C**$_q$), 128.5 (**C**H$_{Ar}$), 122.0, 121.9 ($^3J_{C-F}$ = 2.9 Hz, 2 **C**H$_{Ar}$), 116.4, 116.1 ($^2J_{C-F}$ = 23.1 Hz, 2 **C**H$_{Ar}$), 110.4 (**C**H$_{Ar}$), 61.1 (**C**H$_2$), 14.3 (**C**H$_3$).
M.p.:	51-52 °C
GC-MS (NM_50_S2):	t_R = 6.85 min (m/z = 234.0, > 99.0 % M^+, BP: 189.0).

Ethyl *p*-tolyl-1*H*-pyrazole-5-carboxylate ($61f_1$)



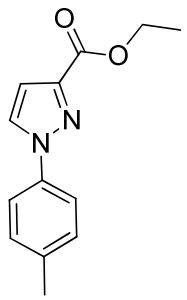
according to GP-4:

1.19 g (6.91 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 7.4 mL glacial acetic acid, 1.10 g (6.91 mmol) *p*-tolylhydrazine hydrochloride **(60f)** in 15.1 mL glacial acetic acid, TLC (CH/EtOAc 3:1, R_f = 0.58), column chromatography (CH/THF 15:1, R_f = 0.34, size: 22.0 x 2.5 cm, 30 g silica gel), purity of the product: 80 % (20 % Ethyl *p*-tolyl-1*H*-pyrazole-3-carboxylate **($61f_2$)**).

$C_{13}H_{14}O_2N_2$ [230.3]

yield:	465.8 mg (29 %), brown oil
R_f (CH/ EtOAc 3:1):	0.58
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.64 (d, ^4J = 1.8 Hz, 1H, Ar-H), 7.29-7.20 (m, 4H, Ar-H), 6.97 (d, ^4J = 1.8 Hz, 1H, Ar-H), 4.21 (q, ^3J = 7.2 Hz, 2H, CH_2), 2.38 (s, 3H, CH_3), 1.23 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 159.1 (**C**=O), 139.3 (**C**H_{Ar}), 138.6 (**C**$_q$), 129.9 (**C**$_q$), 129.1 (2 **C**H_{Ar}), 125.7 (2 **C**H_{Ar}), 120.0 (**C**$_q$-CH_3), 112.2 (**C**H_{Ar}), 61.0 (**C**H_2), 21.2 (**C**H_3), 14.0 (**C**H_3).
GC-MS (NM_50_S2):	t_R = 6.59 min (m/z = 230.0, 80.0 % M^+, BP).

Ethyl *p*-tolyl-1*H*-pyrazole-3-carboxylate ($61f_2$)



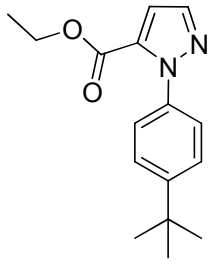
according to GP-4:

1.19 g (6.91 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 7.4 mL glacial acetic acid, 1.10 g (6.91 mmol) *p*-tolylhydrazine hydrochloride **(60f)** in 15.1 mL glacial acetic acid, TLC (CH/EtOAc 3:1, R_f = 0.44), column chromatography (CH/THF 15:1, R_f = 0.23, size: 22.0 x 2.5 cm, 30 g silica gel).

$C_{13}H_{14}O_2N_2$ [230.3]

yield:	79.7 mg (5 %), orange solid
R_f (CH/ EtOAc 3:1):	0.44
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.88 (d, ^4J = 2.4 Hz, 1H, Ar-H), 7.61 (d, ^3J = 8.1 Hz, 2H, Ar-H), 7.25 (d, ^3J = 8.1 Hz, 2H, Ar-H), 6.97 (d, ^4J = 2.4 Hz, 1H, Ar-H), 4.43 (q, ^3J = 7.2 Hz, 2H, CH_2), 2.38 (s, 3H, CH_3), 1.41 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 162.3 (**C**=O), 144.9 ($\mathbf{C}_q$), 137.5 ($\mathbf{C}_q$), 137.4 ($\mathbf{C}_q$-CH_3), 129.9 (2 **C**H_{Ar}), 128.3 (**C**H_{Ar}), 120.0 (2 **C**H_{Ar}), 110.1 (**C**H_{Ar}), 61.0 (**C**H_2), 20.9 (**C**H_3), 14.3 (**C**H_3).
M.p.:	43-45 °C
GC-MS (NM_50_S2):	t_R = 7.24 min (m/z = 230.0, > 99.0 % M^+, BP).

Ethyl 1-(4-*tert*-butylphenyl)-1*H*-pyrazole-5-carboxylate ($61g_1$)



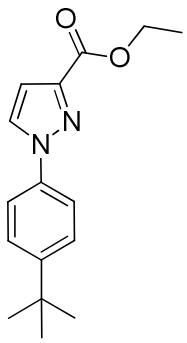
according to GP-4:

1.19 g (6.91 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 7.4 mL glacial acetic acid, 1.39 g (6.91 mmol) 4-*tert*-butylphenylhydrazine hydrochloride **(60g)** in 19.2 mL glacial acetic acid, TLC (CH/ EtOAc 3:1, R_f = 0.62), column chromatography (CH/THF 15:1, R_f = 0.43, size: 18.0 x 4.5 cm, 85 g silica gel).

$C_{16}H_{20}O_2N_2$ [272.3]

yield:	423.0 mg (22 %), orange liquid
R_f (CH/EtOAc 3:1):	0.62
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.67 (d, ^4J = 1.8 Hz, 1H, Ar-H), 7.46 (d, ^3J = 8.4 Hz, 2H, Ar-H), 7.34 (d, ^3J = 8.4 Hz, 2H, Ar-H), 7.01 (d, ^4J = 1.8 Hz, 1H, Ar-H), 4.24 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.35 (s, 9H, 3 CH_3), 1.24 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 159.2 (**C**=O), 151.6 ($\mathbf{C}_q$), 139.4 ($\mathbf{C}H_{Ar}$), 137.7 ($\mathbf{C}_q$), 133.3 ($\mathbf{C}_q$-*t*Bu), 125.4 (2 $\mathbf{C}H_{Ar}$), 125.4 (2 $\mathbf{C}H_{Ar}$), 112.3 ($\mathbf{C}H_{Ar}$), 61.0 ($\mathbf{C}H_2$), 34.7 ($\mathbf{C}_q$), 31.3 (3 $\mathbf{C}H_3$), 14.0 ($\mathbf{C}H_3$).
GC-MS (NM_50_S2):	t_R = 7.18 min (m/z = 272.1, > 99.0 % M^+, BP: 257.1)

Ethyl 1-(4-*tert*-butylphenyl)-1*H*-pyrazole-3-carboxylate ($61g_2$)



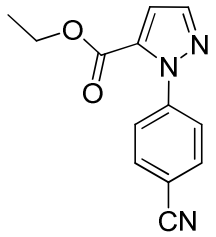
according to GP-4:

1.19 g (6.91 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 7.4 mL glacial acetic acid, 1.39 g (6.91 mmol) 4-*tert*-butylphenylhydrazine hydrochloride **(60g)** in 19.2 mL glacial acetic acid, TLC (CH/ EtOAc 3:1, R_f = 0.56), column chromatography (CH/THF 15:1, R_f = 0.25, size: 18.0 x 4.5 cm, 85 g silica gel).

$C_{16}H_{20}O_2N_2$ [272.3]

yield:	409.4 mg (22 %), brown oil
R_f (CH/EtOAc 3:1):	0.56
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.89 (d, ^4J = 2.4 Hz, 1H, Ar-H), 7.65 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.46 (d, ^3J = 8.7 Hz, 2H, Ar-H), 6.97 (d, ^4J = 2.4 Hz, 1H, Ar-H), 4.43 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.41 (t, ^3J = 7.2 Hz, 3H, CH_3), 1.34 (s, 9H, 3 CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 162.3 (**C**=O), 150.8 ($\mathbf{C}_q$), 144.9 ($\mathbf{C}_q$), 137.3 ($\mathbf{C}_q$-*t*Bu), 128.3 ($\mathbf{C}H_{Ar}$), 126.3 (2 $\mathbf{C}H_{Ar}$), 119.8 (2 $\mathbf{C}H_{Ar}$), 110.1 ($\mathbf{C}H_{Ar}$), 61.0 ($\mathbf{C}H_2$), 34.6 ($\mathbf{C}_q$), 31.3 (3 $\mathbf{C}H_3$), 14.3 ($\mathbf{C}H_3$).
GC-MS (NM_50_S2):	t_R = 7.88 min (m/z = 272.1, > 99.0 % M^+, BP: 257.1).
HRMS (EI^+):	*m/z*: calcd for $C_{16}H_{20}O_2N_2$ $[M]^+$: 272.1525; found 272.1531.

Ethyl 1-(4-cyanophenyl)-1*H*-pyrazole-5-carboxylate ($61h_1$)



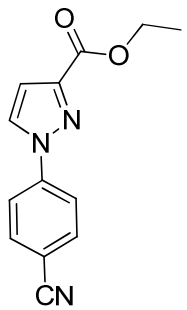
according to GP-4:

1.19 g (6.91 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 7.4 mL glacial acetic acid, 1.17 g (6.91 mmol) 4-cyanophenylhydrazine hydrochloride **(60h)** in 16.2 mL glacial acetic acid, TLC (CH/ EtOAc 3:1, R_f = 0.44), column chromatography (CH/EtOAc 3:1, size: 24.0 x 3.5 cm, 80 g silica gel).

$C_{13}H_{11}O_2N_3$ [241.2]

yield:	608.8 mg (37 %), yellow solid
R_f (CH/EtOAc 3:1):	0.44
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.77-7.73 (m, 3H, Ar-H), 7.59 (d, ^3J = 8.4 Hz, 2H, Ar-H), 7.76 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.06 (d, ^4J = 1.8 Hz, 1H, Ar-H), 4.27 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.29 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 158.9 (**C**=O), 143.4 ($\mathbf{C}_q$), 140.6 ($\mathbf{C}H_{Ar}$), 133.5 ($\mathbf{C}_q$), 132.4 (2 $\mathbf{C}H_{Ar}$), 126.5 (2 $\mathbf{C}H_{Ar}$), 118.0 (**C**N), 113.7 ($\mathbf{C}H_{Ar}$), 112.2 ($\mathbf{C}_q$-CN), 61.5 ($\mathbf{C}H_2$), 14.0 ($\mathbf{C}H_3$).
M.p.:	121-123 °C
GC-MS (NM_50_S2):	t_R = 7.11 min (m/z = 241.0, 99.0 % M^+, BP).

Ethyl 1-(4-cyanophenyl)-1*H*-pyrazole-3-carboxylate ($61h_2$)



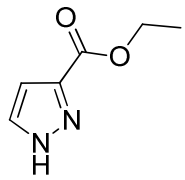
according to GP-4:

1.19 g (6.91 mmol) (*E*)-ethyl-4-ethoxy-2-oxobut-3-enoate **(59)** in 7.4 mL glacial acetic acid, 1.17 g (6.91 mmol) 4-cyanophenylhydrazine hydrochloride **(60h)** in 16.2 mL glacial acetic acid, TLC (CH/ EtOAc 3:1, R_f = 0.27), column chromatography (CH/EtOAc 3:1, size: 24.0 x 3.5 cm, 80 g silica gel).

$C_{13}H_{11}O_2N_3$ [241.2]

yield:	90.0 mg (5 %), yellow solid
R_f (CH/EtOAc 3:1):	0.27
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.02 (d, ^4J = 2.4 Hz, 1H, Ar-H), 7.90 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.76 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.02 (d, ^4J = 2.4 Hz, 1H, Ar-H), 4.43 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.41 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 161.7 (**C**=O), 146.4 ($\mathbf{C}_q$), 142.3 ($\mathbf{C}_q$), 133.6 (2 $\mathbf{C}H_{Ar}$), 128.3 ($\mathbf{C}H_{Ar}$), 119.9 (2 $\mathbf{C}H_{Ar}$), 117.9 (**C**N), 111.2 ($\mathbf{C}H_{Ar}$), 110.9 ($\mathbf{C}_q$-CN), 61.4 ($\mathbf{C}H_2$), 14.3 ($\mathbf{C}H_3$).
M.p.:	168-170 °C
GC-MS (NM_50_S2):	t_R = 7.80 min (m/z = 241.0, 99.0 % M^+, BP: 195.9).
HRMS (EI^+):	*m/z*: calcd for $C_{13}H_{11}O_2N_3$ $[M]^+$: 241.0851; found 241.0850.

Ethyl 1*H*-pyrazole-3-carboxylate (63) [109]

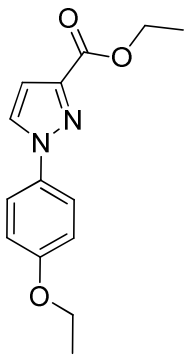


A 100 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged with 500 mg (4.46 mmol, 1.00 eq) 1*H*-pyrazol-3-carboxylic acid **(62)**, which was dissolved in 20 mL EtOH. After adding 1.31 g (720 µL, 13.4 mmol, 3.00 eq) conc. H_2SO_4 the colorless reaction mixture was heated to reflux (100 °C) and stirred at this temperature for 4 h. TLC analysis (DCM/MeOH 95:5) indicated full conversion of the starting material. After cooling to rt the mixture was transferred to a flask to remove the solvent at a rotary evaporator. The colorless residue was diluted in 20 mL water and neutralized with 17 mL saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (4 x 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to yield the pure title compound.

$C_6H_8O_2N_2$ [140.1]

yield:	582.5 mg (93 %), colorless solid
R_f (DCM/MeOH 95:5):	0.42
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 10.69 (bs, 1H, NH), 7.84 (d, ^4J = 2.1 Hz, 1H, Ar-H), 6.86 (d, ^4J = 2.1 Hz, 1H, Ar-H), 4.43 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.41 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 161.8 (**C**=O), 141.6 ($\mathbf{C}_q$), 132.3 ($\mathbf{C}H_{Ar}$), 107.8 ($\mathbf{C}H_{Ar}$), 61.1 ($\mathbf{C}H_2$), 14.3 ($\mathbf{C}H_3$).
M.p.:	158-161 °C
GC-MS (NM_50_S2):	t_R = 4.66 min (m/z = 140.1, 98.0 % M^+, BP: 95.0).

Ethyl 1-(4-ethoxyphenyl)-1*H*-pyrazole-3-carboxylate (61i$_2$)



A 10 mL Schlenk tube was dried under vacuum, filled with nitrogen and consecutively charged with 19.4 mg (102 µmol, 0.20 eq) CuI, 332 mg (1.02 mmol, 2.00 eq) Cs_2CO_3, 100 mg (714 µmol, 1.40 eq) ethyl 1*H*-pyrazole-3-carboxylate **(63)**, 102 mg (73.0 µL, 510 µmol, 1.00 eq) *p*-bromophenetol **(64)** and 1 mL anhydrous ACN. The light brown suspension was degassed by vaccum/N_2 cycles and stirred first at 82 °C for 7 h and than after adding 0.5 mL anhydrous DMF (solubility issue) at 120 °C for further 65 h. The GC-MS analysis showed full conversion. ACN and DMF were removed under high vacuum and the brown residue was suspended in 10 mL EtOAc. After filtration of the brown suspension through a pad of silica and flushing with 150 mL EtOAc the colorless filtrate was concentrated under reduced pressure furnishing 52.1 mg (39 %) crude product as a green-brown oil. Final purification by column chromatography (CH/EtOAc 3:1, size: 15.5 x 2.0 cm, 20 g silica gel) yielded the pure title compound.

$C_{14}H_{16}O_3N_2$ [260.0]

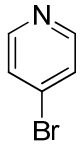
yield:	10.2 mg (8 %), orange solid
R_f (CH/ EtOAc 3:1):	0.40
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.51 (d, ^4J = 2.4 Hz, 1H, Ar-H), 7.78 (d, ^3J = 9.0 Hz, 2H, Ar-H), 7.07 (d, ^3J = 9.0 Hz, 2H, Ar-H), 6.97 (d, ^4J = 2.4 Hz, 1H, Ar-H), 4.31 (q, ^3J = 6.9 Hz, 2H, CH_2), 4.08 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.37-1.29 (m, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 161.4 (**C**=O), 157.6 (**C**$_q$), 143.6 (**C**$_q$), 132.5 (**C**$_q$), 129.5 (**C**H$_{Ar}$), 120.7 (2 **C**H$_{Ar}$), 115.0 (2 **C**H$_{Ar}$), 119.8 (**C**H$_{Ar}$), 63.4 (**C**H$_2$), 60.3 (**C**H$_2$), 14.5 (**C**H$_3$), 14.1 (**C**H$_3$).

M.p.: 88-90 °C

GC-MS (NM_50_S2): t_R = 7.72 min (m/z = 260.1, 98.0 % M^+, BP).

6.3.5. Synthesis of different biaryls replacing the pyrazole ring

4-Bromopyridine (66) [115]

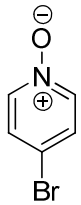


A 25 mL one-neck round-bottom flask was charged with 2.00 g (10.3 mmol, 1.00 eq) 4-bromopyridine hydrochloride **(65)** dissolved in 10 mL water. Slow addition of 2 mL 5 M NaOH solution resulted in a yellow mixture of two layers, which was stirred at rt for 10 min. The mixture was extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo.

C_5H_4NBr [157.9]

yield: 1.62 g (> 99 %), colorless liquid

4-Bromopyridine-*N*-oxid (67) [115]



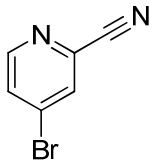
A 50 mL one-neck round-bottom flask was charged with 1.60 g (10.1 mmol, 1.00 eq) 4-bromopyridine **(66)** dissolved in 5 mL Et_2O. Addition of 2.80 g (16.2 mmol, 1.30 eq) *m*-chloroperoxybenzoic acid resulted in a colorless solution which was stirred at rt for 17 h, during which a colorless solid precipitated. The solid was filtrated through a fritted funnel,

washed with Et_2O and dried under high vacuum. The crude product was purified by column chromatography (DCM/MeOH 20:1, size: 15.0 x 6.0 cm, 200 g silica gel).

C_5H_4ONBr [173.9]

yield:	1.30 g (73 %), colorless solid
R_f (DCM/MeOH 20:1):	0.30
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.06 (d, ^3J = 7.2 Hz, 2H, Ar-H), 7.39 (d, ^3J = 7.2 Hz, 2H, Ar-H).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 140.1 (2 **C**H_{Ar}), 129.4 (2 **C**H_{Ar}), 119.4 (**C**$_q$-Br).
M.p.:	78-81 °C

4-Bromopicolinonitrile (68) [115]



A 25 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged with 1.00 g (5.75 mmol, 1.00 eq) 4-bromopyridine-*N*-oxide **(67)** suspended in 6.5 mL anhydrous ACN. Addition of 1.60 mL (11.5 mmol, 2.00 eq) absolute triethylamine resulted in a green-yellow suspension. After the addition of 2.10 mL (1.71 g, 17.3 mmol, 3.00 eq) trimethylsilylcyanide the yellow suspension was refluxed for 3.5 h, during which the suspension turned first into a yellow and later into a dark brown solution. TLC analysis (DCM/MeOH 9:1, R_f = 0.89) indicated full conversion of the starting material. The mixture was transfered in a 25 ml round-bottom flask and concentrated under reduced pressure (!!!HCN formation!!!). The residue was alkalized with 20 mL saturated aqueous K_2CO_3 solution and extracted with DCM (4 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Final silica gel filtration (CH/EtOAc 1:1) yielded the pure product.

$C_6H_3N_2Br$ [182.9]

yield:	997.0 mg (95 %), yellow solid

R_f (CH/ EtOAc 1:1): 0.80

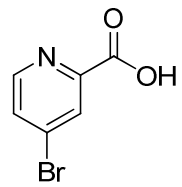
^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) = 8.62 (d, ^3J = 5.4 Hz, 1H, Ar-H), 8.45 (d, ^4J = 1.5 Hz, 1H, Ar-H), 8.06 (dd, ^3J = 5.4 Hz, ^4J = 1.8 Hz, 1H, Ar-H).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 151.9 (**C**H_{Ar}), 133.6 (**C**$_q$-CN), 133.2 (**C**$_q$-Br), 131.9 (**C**H_{Ar}), 131.0 (**C**H_{Ar}), 116.3 (**C**N).

M.p.: 87-89 °C

GC-MS (NM_50_S2): t_R = 4.90 min (m/z = 182.9, >99 % M^+, BP).

4-Bromopicolinic acid (69a)



A 25 mL two-neck round-bottom flask with reflux condenser was charged with 500 mg (2.73 mmol, 1.00 eq) 4-bromopicolinonitrile **(68)** in 2 mL water. After heating to 60 °C 0.4 mL 30 % aqueous NaOH solution was added and the mixture was refluxed over night. The mixture was cooled down to rt, acidified with 30 % aqueous HCl solution to pH 1-2 and stirred at 130 °C for 20 min before 2 mL absolute EtOH were added. The yellow suspension was stirred at 75 °C for 4.5 h before the hot reaction mixture was filtrated through a preheated fritted funnel. The orange filtrate was concentrated under reduced pressure and dried in high vacuum to obtain the crude product. The yellow solid was recrystallized from a solvent mixture of 25 mL dioxane/3 mL THF/7 mL MeOH and precipitated with Et_2O under ice cooling. The suspension was filtrated and the filtrate was concentrated under reduced pressure. After trituration in EtOH the pure product was obtained as a beige solid.

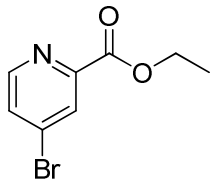
$C_6H_4O_2NBr$ [201.9]

yield: 107.6 mg (20 %), beige solid

^{1}H-NMR (300 MHz, D_2O): δ (ppm) = 8.66 (d, ^3J = 6.3 Hz, 1H, Ar-H), 8.39 (d, ^4J = 2.1 Hz, 1H, Ar-H), 8.11 (dd, ^3J = 6.3 Hz, ^4J = 2.1 Hz, 1H, Ar-H).

^{13}C-NMR (75.5 MHz, D_2O): δ (ppm) = 162.8 (**C**=O), 154.9 (**C**$_q$), 147.1 (**C**$_q$-Br), 142.6 (**C**H$_{Ar}$), 128.8 (**C**H$_{Ar}$), 127.2 (**C**H$_{Ar}$).

Ethyl 4-bromopicolinate (70a)



A 8 mL Schlenk tube was flushed with nitrogen and charged with 99.0 mg (490 µmol, 1.00 eq) 4-bromopicolinic acid **(69a)** suspended in 0.4 mL EtOH. After adding 79.0 µL (1.47 mmol, 3.00 eq) conc. H_2SO_4 the yellow suspension was refluxed for 3.5 h, during which the suspension turned into a yellow solution. TLC analysis (CH/EtOAC 3:1) indicated full conversion of the starting material. The mixture was hydrolyzed with 3 mL saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (2 x 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to yield a crude yellow oil. Final purification by column chromatography (CH/EtOAc 3:1, size: 12 x 2 cm, 20 g silica gel) resulted in the pure product.

$C_8H_8O_2NBr$ [229.9]

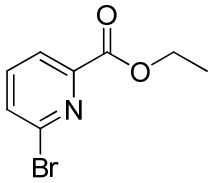
yield: 45.2 mg (40 %), colorless oil

R_f (CH/ EtOAc 3:1): 0.19

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.66 (d, ^3J = 5.1 Hz, 1H, Ar-H), 8.14 (d, ^4J = 2.1 Hz, 1H, Ar-H), 7.49 (dd, ^3J = 5.1 Hz, ^4J = 2.1 Hz, 1H, Ar-H), 4.49 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.45 (t, ^3J = 7.2 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 164.1 (**C**=O), 150.6 (**C**H$_{Ar}$), 149.5 (**C**$_q$), 145.4 (**C**$_q$-Br), 127.0 (**C**H$_{Ar}$), 125.6 (**C**H$_{Ar}$), 62.4 (**C**H$_2$), 14.3 (**C**H$_3$).

Ethyl 6-bromopicolinate (70b)

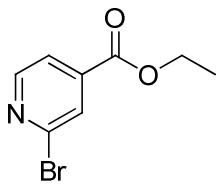


A 8 mL Schlenk tube was flushed with nitrogen and charged with 250 mg (1.24 mmol, 1.00 eq) 6-bromopicolinic acid **(69b)** suspended in 1.0 mL EtOH. After adding 200 µL (3.71 mmol, 3.00 eq) conc. H_2SO_4 the suspension was refluxed for 3 h. TLC analysis (CH/EtOAc 3:1) indicated full conversion of the starting material. The mixture was hydrolyzed with 5 mL saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Drying in high vacuum yielded the pure product.

$C_8H_8O_2NBr$ [229.9]

yield:	249.5 mg (88 %), beige solid
R_f (CH/ EtOAc 3:1):	0.44
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.07 (dd, ^3J = 6.6 Hz, ^4J = 1.8 Hz, 1H, Ar-H), 7.72-7.64 (m, 2H, Ar-H), 4.46 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.42 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 163.9 (**C**=O), 149.1 ($\mathbf{C}_q$), 142.1 ($\mathbf{C}_q$-Br), 139.1 ($\mathbf{C}H_{Ar}$), 131.6 ($\mathbf{C}H_{Ar}$), 123.9 ($\mathbf{C}H_{Ar}$), 62.3 ($\mathbf{C}H_2$), 14.2 ($\mathbf{C}H_3$).
M.p.:	32 °C
GC-MS (NM_50_S2):	t_R = 5.76 min (m/z = 230.0, 98 % M^+, BP: 157.0).

Ethyl 2-bromoisonicotinate (70c)

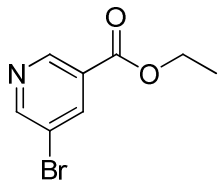


A 8 mL Schlenk tube was flushed with nitrogen and charged with 250 mg (1.24 mmol, 1.00 eq) 4-bromopyridine-4-carboxylic acid **(69c)** suspended in 1.0 mL EtOH. After adding 200 µL (3.71 mmol, 3.00 eq) conc. H_2SO_4 the suspension was refluxed for 3 h. TLC analysis (CH/EtOAc 3:1) indicated full conversion of the starting material. The mixture was hydrolyzed with 5 mL saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Drying in high vacuum and storage in the fridge over night yielded the pure product.

$C_8H_8O_2NBr$ [229.9]

yield:	225.1 mg (79 %), yellow solid
R_f (CH/ EtOAc 3:1):	0.58
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.51 (d, ^3J = 5.1 Hz, 1H, Ar-H), 8.03 (s, 1H, Ar-H), 7.80 (dd, ^3J = 5.1 Hz, ^4J = 1.2 Hz, 1H, Ar-H), 4.41 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.41 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 163.6 (**C**=O), 150.8 (**C**H_{Ar}), 142.7 (**C**$_q$), 140.2 (**C**$_q$-Br), 127.7 (**C**H_{Ar}), 121.9 (**C**H_{Ar}), 62.2 (**C**H_2), 14.1 (**C**H_3).
M.p.:	rt (22 °C)
GC-MS (NM_50_S2):	t_R = 5.61 min (m/z = 230.0, 95 % M^+, BP: 201.0).

Ethyl 5-bromonicotinate (70d)



A 8 mL Schlenk tube was flushed with nitrogen and charged with 250 mg (1.24 mmol, 1.00 eq) 5-bromonicotinic acid **(69d)** suspended in 1.0 mL EtOH. After adding 200 µL (3.71 mmol, 3.00 eq) conc. H_2SO_4 the suspension was refluxed for 3 h. TLC analysis (CH/EtOAc 3:1) indicated full conversion of the starting material. The mixture was hydrolyzed with 5 mL saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (2 x 10 mL). The combined

organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Drying in high vacuum yielded the pure product.

$C_8H_8O_2NBr$ [229.9]

yield:	228.2 mg (80 %), colorless solid
R_f (CH/ EtOAc 3:1):	0.58
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 9.12 (d, ^4J = 2.1 Hz, 1H, Ar-H), 8.83 (d, ^4J = 2.1 Hz, 1H, Ar-H), 8.44 (t, ^4J = 2.1 Hz, 1H, Ar-H), 4.42 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.41 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 163.9 (**C**=O), 154.1 (**C**H_{Ar}), 148.5 (**C**H_{Ar}), 139.7 (**C**H_{Ar}), 127.8 (**C**$_q$), 120.6 (**C**$_q$-Br), 62.0 (**C**H_2), 14.2 (**C**H_3).
M.p.:	38 °C
GC-MS (NM_50_S2):	t_R = 5.50 min (m/z = 230.0, 99 % M^+, BP: 184.0).

SUZUKI-COUPLING

Suzuki-coupling with $PdCl_2$(dppf) * DCM:

General procedure (GP-5):

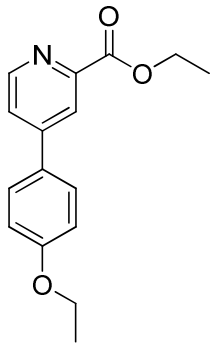
A Schlenk tube was dried under vacuum, filled with nitrogen and charged consecutively with 1.00 eq bromine substrate, 1.00 eq boronic acid, 2.10 eq CsF, 0.05 eq $PdCl_2$(dppf)*DCM and anhydrous DME (2 mL/0.15 mmol bromoarene). The suspension was degassed by vacuum/N_2 cycles and stirred at 80 °C. As TLC analysis or GC-MS analysis indicated full conversion of the starting material, the reaction mixture was cooled to rt and filtered through a pad of celite, which was rinsed with EtOAc and/or DCM. The solvent from the filtrate was removed under reduced pressure and final purification by column chromatography or silica gel filtration yielded the pure product.

Suzuki with S-Phos-ligand/Pd(OAc)$_2$:

General procedure (GP-6):

A Schlenk tube was dried under vacuum, filled with nitrogen and charged consecutively with 1.00 eq bromoarene, 1.50 eq boronic acid, 2.00 eq mortar powdered, anhydrous K_3PO_4, 0.01 eq $Pd(OAc)_2$, 0.02 eq **S-Phos,** and absolute toluene (2 mL/0.5 mmol bromoarene). The mixture was degassed by vacuum/N_2 cycles and stirred at 100 °C. As TLC analysis or GC-MS analysis showed full conversion of the starting material, the mixture was cooled to rt and filtered through a pad of celite, which was rinsed with EtOAc and/or DCM. The solvent from the filtrate was removed under reduced pressure and final purification by column chromatography or silica gel filtration yielded the pure product.

Ethyl 4-(4-ethoxyphenyl)picolinate (72a)



according to GP-5:

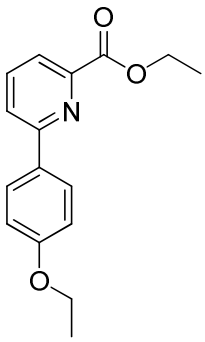
38.7 mg (168 µmol, 1.00 eq) ethyl-4-bromopicolinate **(70a)**, 27.9 mg (168 µmol, 1.00 eq) 4-ethoxyphenylboronic acid **(71)**, 24 h reaction time, column chromatography (CH/EtOAc 2:1, size: 16.0 x 2.0 cm, 10 g silica gel).

$C_{16}H_{17}O_3N$ [271.3]

yield:	21.3 mg (47 %), light yellow solid
R_f (CH/ EtOAc 2:1):	0.14
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.74 (d, ^3J = 5.1 Hz, 1H, Ar-H), 8.34 (d, ^4J = 1.2 Hz, 1H, Ar-H), 7.67-7.64 (m, 3H, Ar-H), 7.02 (d, ^3J =

	8.7 Hz, 2H, Ar-H), 4.52 (q, ^3J = 7.2 Hz, 2H, CH_2), 4.10 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.49-1.43 (m, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 165.3 (**C**=O), 160.4 ($\mathbf{C}_q$), 150.0 ($\mathbf{C}H_{Ar}$), 149.4 ($\mathbf{C}_q$), 148.4 ($\mathbf{C}_q$), 129.0 ($\mathbf{C}_q$), 128.3 (2 $\mathbf{C}H_{Ar}$), 123.8 ($\mathbf{C}H_{Ar}$), 122.4 ($\mathbf{C}H_{Ar}$), 115.2 (2 $\mathbf{C}H_{Ar}$), 63.7 ($\mathbf{C}H_2$), 62.1 ($\mathbf{C}H_2$), 14.7 ($\mathbf{C}H_3$), 14.4 ($\mathbf{C}H_3$).
M.p.:	47-48 °C
GC-MS (NM_50_S2):	t_R = 8.10 min (m/z = 271.1, 99 % M^+, BP: 199.1).
HRMS (EI^+):	*m/z*: calcd for $C_{16}H_{17}O_3N$ $[M]^+$: 271.1208; found 271.1220.

Ethyl 6-(4-ethoxyphenyl)picolinate (72b)



according to GP-5:

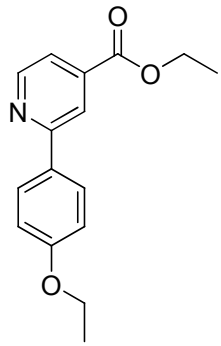
100 mg (435 µmol, 1.00 eq) ethyl-6-bromopicolinate **(70b)**, 72.2 mg (435 µmol, 1.00 eq) 4-ethoxyphenylboronic acid **(71)**, 4.5 h reaction time, column chromatography (CH/EtOAc 3:1, size: 17.0 x 2.0 cm, 25 g silica gel).

$C_{16}H_{17}O_3N$ [271.3]

yield:	96.0 mg (81 %), beige solid
R_f (CH/ EtOAc 3:1):	0.47
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.03 (d, ^3J = 9.0 Hz, 2H, Ar-H), 7.99-7.96 (m, 1H, Ar-H), 7.84-7.82 (m, 2H, Ar-H), 6.99 (d, ^3J = 9.0 Hz, 2H, Ar-H), 4.48 (q, ^3J = 7.2 Hz, 2H, CH_2), 4.09 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.48-1.42 (m, 6H, 2 CH_3).

^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 165.5 (**C**=O), 160.2 ($\mathbf{C}_q$), 157.2 ($\mathbf{C}_q$), 148.1 ($\mathbf{C}_q$), 137.5 ($\mathbf{C}H_{Ar}$), 130.8 ($\mathbf{C}_q$), 128.5 (2 $\mathbf{C}H_{Ar}$), 122.7 ($\mathbf{C}H_{Ar}$), 122.5 ($\mathbf{C}H_{Ar}$), 114.7 (2 $\mathbf{C}H_{Ar}$), 63.5 ($\mathbf{C}H_2$), 61.8 ($\mathbf{C}H_2$), 14.8 ($\mathbf{C}H_3$), 14.3 ($\mathbf{C}H_3$).
M.p.:	103-106 °C
GC-MS (NM_50_S2):	t_R = 7.95 min (m/z = 271.1, 98 % M^+, BP: 199.1).
HRMS (EI^+):	*m/z*: calcd for $C_{16}H_{17}O_3N$ $[M]^+$: 271.1208; found 271.1198.

Ethyl 2-(4-ethoxyphenyl)isonicotinate (72c)



according to GP-5:

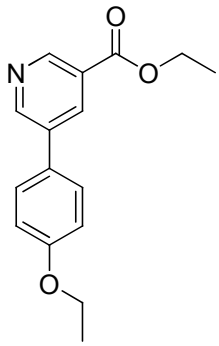
100 mg (435 µmol, 1.00 eq) ethyl-2-bromoisonicotinate **(70c)**, 72.2 mg (435 µmol, 1.00 eq) 4-ethoxyphenylboronic acid **(71)**, 4.5 h reaction time, column chromatography (CH/EtOAc 3:1, size: 17.0 x 2.0 cm, 25 g silica gel).

$C_{16}H_{17}O_3N$ [271.3]

yield:	107.3 mg (91 %), colorless solid
R_f (CH/ EtOAc 3:1):	0.47
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.78 (d, ^3J = 5.1 Hz, 1H, Ar-H), 8.24 (s, 1H, Ar-H), 8.01 (d, ^3J = 9.0 Hz, 2H, Ar-H), 7.72 (dd, ^3J = 5.1 Hz, ^4J = 1.8 Hz, 1H, Ar-H), 7.00 (d, ^3J = 9.0 Hz, 2H, Ar-H), 4.44 (q, ^3J = 7.2 Hz, 2H, CH_2), 4.10 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.46-1.40 (m, 6H, 2 CH_3).

^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 165.3 (**C**=O), 160.3 ($\mathbf{C}_q$), 157.9 ($\mathbf{C}_q$), 149.9 ($\mathbf{C}H_{Ar}$), 138.6 ($\mathbf{C}_q$), 130.6 ($\mathbf{C}_q$), 128.3 (2 $\mathbf{C}H_{Ar}$), 120.3 ($\mathbf{C}H_{Ar}$), 119.0 ($\mathbf{C}H_{Ar}$), 114.7 (2 $\mathbf{C}H_{Ar}$), 63.5 ($\mathbf{C}H_2$), 61.8 ($\mathbf{C}H_2$), 14.8 ($\mathbf{C}H_3$), 14.2 ($\mathbf{C}H_3$).
M.p.:	58-59 °C
GC-MS (NM_50_S2):	t_R = 7.89 min (m/z = 271.1, 99 % M^+, BP).

Ethyl 5-(4-ethoxyphenyl)nicotinate (72d)



according to GP-5

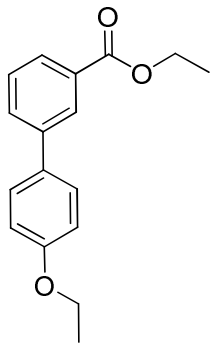
100 mg (435 µmol, 1.00 eq) ethyl-5-bromonicotinate **(70d)**, 72.2 mg (435 µmol, 1.00 eq) 4-ethoxyphenylboronic acid **(71)**, 4.5 h reaction time, column chromatography (CH/EtOAc 3:1, size: 16.0 x 2.0 cm, 20 g silica gel).

$C_{16}H_{17}O_3N$ [271.3]

yield:	108.4 mg (92 %), light yellow solid
R_f (CH/ EtOAc 3:1):	0.32
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 9.13 (s, 1H, Ar-H), 9.00 (s, 1H, Ar-H), 8.46 (s, 1H, Ar-H), 7.55 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.01 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.44 (q, ^3J = 7.2 Hz, 2H, CH_2), 4.09 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.47-1.40 (m, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 165.2 (**C**=O), 159.5 ($\mathbf{C}_q$-OCH_2CH_3), 150.7 ($\mathbf{C}H_{Ar}$), 148.1 ($\mathbf{C}H_{Ar}$), 136.3 ($\mathbf{C}_q$), 134.9 ($\mathbf{C}H_{Ar}$), 128.6 ($\mathbf{C}_q$), 128.3 (2 $\mathbf{C}H_{Ar}$), 126.4 ($\mathbf{C}_q$), 115.2 (2 $\mathbf{C}H_{Ar}$), 63.6 ($\mathbf{C}H_2$), 61.6 ($\mathbf{C}H_2$), 14.8 ($\mathbf{C}H_3$), 14.3 ($\mathbf{C}H_3$).

M.p.:	78-81 °C
GC-MS (NM_50_S2):	t_R = 7.95 min (m/z = 271.1, 99 % M^+, BP).
HRMS (EI^+):	*m/z*: calcd for $C_{16}H_{17}O_3N$ $[M]^+$: 271.1208; found 271.1208.

Ethyl 4`-ethoxybiphenyl-3-carboxylate (72e)



100 mg (70.0 µL, 437 µmol, 1.00 eq) ethyl-3-bromobenzoate **(70e)**, 72.5 mg (437 µmol, 1.00 eq) 4-ethoxyphenylboronic acid **(71)**, 7 h reaction time, column chromatography (CH/EtOAc 15:1, size: 12.5 x 2.0 cm, 15 g silica gel).

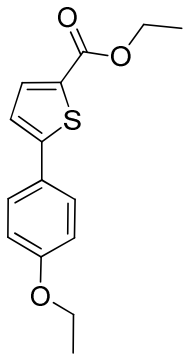
$C_{17}H_{18}O_3$ [270.3]

yield:	109.5 mg (93 %), colorless solid
R_f (CH/ EtOAc 15:1):	0.40
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.25 (t, ^4J = 1.5 Hz, 1H, Ar-H), 7.98 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.74 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.56 (d, ^3J = 9.0 Hz, 2H, Ar-H), 7.48 (t, ^3J = 7.8 Hz, 1H, Ar-H), 6.98 (d, ^3J = 9.0 Hz, 2H, Ar-H), 4.41 (q, ^3J = 7.2 Hz, 2H, CH_2), 4.09 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.47-1.39 (m, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.6 (**C**=O), 158.8 (**C**$_q$), 141.0 (**C**$_q$), 132.5 (**C**$_q$), 131.0 (**C**$_q$), 130.9 (**C**H$_{Ar}$), 128.7 (**C**H$_{Ar}$), 128.2 (2 **C**H$_{Ar}$), 127.7 (**C**H$_{Ar}$), 127.6 (**C**H$_{Ar}$), 114.8 (2 **C**H$_{Ar}$), 63.8 (**C**H_2), 61.0 (**C**H_2), 14.8 (**C**H_3), 14.3 (**C**H_3).
M.p.:	46-47 °C

GC-MS (NM_50_S2): t_R = 7.80 min (m/z = 270.1, 99 % M^+, BP).

HRMS (EI^+): *m/z*: calcd for $C_{17}H_{18}O_3$ $[M]^+$: 270.1256; found 270.1260.

Ethyl 5-(4-ethoxyphenyl)thiophene-2-carboxylate (72f)



according to GP-5:

185 mg (54.0 µL, 362 µmol, 1.00 eq) ethyl-5-bromothiophene-2-carboxylate **(70f)**, 60.1 mg (362 µmol, 1.00 eq) 4-ethoxyphenylboronic acid **(71)**, 14 h reaction time, column chromatography (CH/EtOAc 15:1, size: 14.0 x 2.5 cm, 24 g silica gel).

$C_{15}H_{16}O_3S$ [276.3]

yield: 40.4 mg (40 %), colorless solid

R_f (CH/ EtOAc 15:1): 0.48

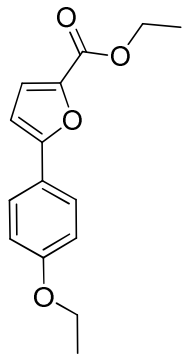
^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.73 (d, ^3J = 3.9 Hz, 1H, Ar-H), 7.56 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.17 (d, ^3J = 3.9 Hz, 1H, Ar-H), 6.92 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.36 (q, ^3J = 7.2 Hz, 2H, CH_2), 4.07 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.46-1.36 (m, 6H, 2 CH_3).

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 162.4 (**C**=O), 159.5 ($\mathbf{C}_q$), 151.3 ($\mathbf{C}_q$), 134.3 ($\mathbf{C}H_{Ar}$), 131.3 ($\mathbf{C}_q$), 127.5 (2 $\mathbf{C}H_{Ar}$), 126.1 ($\mathbf{C}_q$), 122.4 ($\mathbf{C}H_{Ar}$), 115.0 (2 $\mathbf{C}H_{Ar}$), 63.6 ($\mathbf{C}H_2$), 61.0 ($\mathbf{C}H_2$), 14.8 ($\mathbf{C}H_3$), 14.4 ($\mathbf{C}H_3$).

M.p.: 59-61 °C

GC-MS (NM_50_S2): t_R = 8.05 min (m/z = 276.1, 99 % M^+, BP).

Ethyl 5-(4-ethoxyphenyl)-furane-2-carboxylate (72g)



according to GP-5:

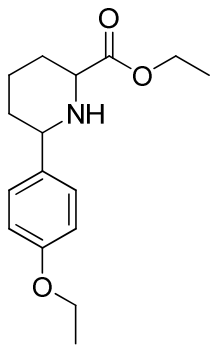
150 mg (685 µmol, 1.00 eq) ethyl-5-bromo-2-furoate **(70g)**, 114 mg (685 µmol, 1.00 eq) 4-ethoxyphenylboronic acid **(71)**, 24 h reaction time, column chromatography (CH/EtOAc 10:1, R_f = 0.36, size: 14.5 x 2.5 cm, 20 g silica gel).

$C_{15}H_{16}O_4$ [260.3]

yield:	32.4 mg (18 %), light yellow solid
R_f (CH/ EtOAc 15:1):	0.27
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 7.70 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.33 (d, ^3J = 3.9 Hz, 1H, Ar-H), 6.00 (d, ^3J = 8.7 Hz, 2H, Ar-H), 6.95 (d, ^3J = 3.9 Hz, 1H, Ar-H), 4.28 (q, ^3J = 7.2 Hz, 2H, CH_2), 4.05 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.34-1.26 (m, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 159.5 (**C**=O), 158.3 (**C**$_q$), 157.2 (**C**$_q$), 142.6 (**C**$_q$), 126.4 (2 **C**H$_{Ar}$), 121.7 (**C**$_q$), 120.8 (**C**H$_{Ar}$), 115.2 (2 **C**H$_{Ar}$), 106.5 (**C**H$_{Ar}$), 63.5 (**C**H$_2$), 60.8 (**C**H$_2$), 14.7 (**C**H$_3$), 14.4 (**C**H$_3$).
M.p.:	69-71 °C
GC-MS (NM_50_S2):	t_R = 7.50 min (m/z = 260.1, 98 % M^+, BP).

HRMS (EI^+): *m/z*: calcd for $C_{15}H_{16}O_4$ $[M]^+$: 260.1049; found 260.1034.

Ethyl 6-(4-ethoxyphenyl)piperidin-2-carboxylate (73)



A 10 mL two-neck round-bottom flask was dried under vaccum, filled with nitrogen and charged with 50.0 mg (185 µmol, 1.00 eq) ethyl 6-(4-ethoxyphenyl)picolinate **(72b)** dissolved in 1.5 mL absolute EtOH and 0.5 mL absolute DCM. 67.0 mg (295 µmol, 1.60 eq) platinum oxide were added and the solution was degassed by vacuum/H_2 cycles. The mixture was stirred at rt for 27 h under H_2 stream. GC-MS analysis showed full conversion (99 % product) of the starting material. After filtration through a pad of celite under argon atmosphere, elution with DCM and removal of the solvent under reduced pressure the crude product was obtained. Final purification by column chromatography (CH/EtOAc 8:1, R_f = 0.10, size 12.0 x 2.0 cm, 15 g silica gel) yielded the pure product.

$C_{16}H_{23}O_3N$ [277.3]

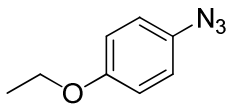
yield: 30.1 mg (59 %), colorless solid

R_f (CH/ EtOAc 3:1): 0.42

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.30 (d, ^3J = 8.4 Hz, 2H, Ar-H), 6.85 (d, ^3J = 8.4 Hz, 2H, Ar-H), 4.22-4.13 (m, 2H, CH_2), 4.02 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.62-3.59 (m, 1H, CH), 3.49-3.45 (m, 1H, CH), 2.10-1.96 (m, 2H, CH_2), 1.77-1.73 (m, 1H, CH), 1.55-1.49 (m, 3H, CH_2, CH), 1.40 (t, ^3J = 6.9 Hz, CH_3), 1.26 (t, ^3J = 7.2 Hz, CH_3).

^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 173.0 (**C**=O), 158.1 (**C**$_q$), 136.7 (**C**$_q$), 127.8 (2 **C**H$_{Ar}$), 114.3 (2 **C**H$_{Ar}$), 63.4 (**C**H$_2$), 61.2 (**C**H), 60.8 (**C**H$_2$), 59.9 (**C**H), 34.1 (**C**H$_2$), 28.4 (**C**H$_2$), 25.0 (**C**H$_2$), 14.9 (**C**H$_3$), 14.2 (**C**H$_3$).
M.p.:	32-34 °C
GC-MS (NM_50_S2):	t_R = 7.552 min (m/z = 277.1, 99 % M^+, BP: 161.1).
HRMS (EI^+):	*m/z*: calcd for $C_{16}H_{23}O_3N$ $[M]^+$: 277.1678; found 277.1690.

1-Azido-4-ethoxybenzene (74) [118]



A 25 mL one-neck round-bottom flask was charged with 250 mg (240 µL, 1.82 mmol, 1.00 eq) *p*-phenetidine **(49a)** and a mixture of 0.5 mL water and 0.91 mL conc. HCl. To this rose-grey suspension an aqueous solution of 189 mg (2.74 mmol, 1.50 eq) $NaNO_2$ in 0.5 mL water was added and the brown solution was stirred in an ice bath for 1 h. Addition of an aqueous solution of 237 mg (3.65 mmol, 2.00 eq) sodium azide in 1.4 mL water at 0 °C resulted in a light brown solution, which was stirred first at 0 °C for 30 min and then at rt for 1h. TLC analysis (CH/EtOAc 3:1) indicated full conversion of the starting material. The mixture was neutralized with solid $KHCO_3$ and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Final purification by column chromatography (CH, R_f = 0.19, size: 9.0 x 2.0 cm, 10 g silica gel) yielded the pure product.

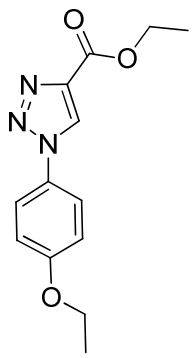
$C_8H_9ON_3$ [163.2]

yield:	250.0 mg (84 %), orange-brown liquid
R_f (CH/ EtOAc 3:1):	0.60
IR:	ν = 2102 cm^{-1} (s, N_3)
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 6.96-6.86 (m, 4H, Ar-H), 4.00 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.41 (t, ^3J = 6.9 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 156.3 (**C**$_q$-OCH_2CH_3), 132.1 (**C**$_q$-N_3), 119.9 (2 **C**H_{Ar}), 115.7 (2 **C**H_{Ar}), 63.8 (**C**H_2), 14.8 (**C**H_3).

GC-MS (NM_50_S2): t_R = 5.07 min (m/z = 163.1, 98 % M^+, BP: 107.1).

Ethyl 1-(4-ethoxyphenyl)-1*H*-1,2,3-triazol-4-carboxylate (76)



A 10 mL one-neck round-bottom flask was charged with 100 mg (613 µmol, 1.00 eq) 1-azido-4-ethoxybenzene **(74)** and 2.5 ml ACN. To this orange solution 60.2 mg (62.0 µL, 613 µmol, 1.00 eq) ethylpropiolate **(75)** were added. Afterwards an aqueous solution of 24.3 mg (123 µmol, 0.20 eq) sodium ascorbate in 0.1 mL water was added at first and than an aqueous solution of 10.7 mg (43 µmol, 0.07 eq) $CuSO_4$*5 H_2O in 0.1 mL water. The yellow solution was stirred at rt for 15.5 h, during which the solution turned orange. GC-MS analysis showed full conversion (92 % product) of the starting material. The mixture was concentrated under reduced pressure, the residue was dissolved in 10 mL DCM and extracted with water (2 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated at the rotary evaporator. Final purification by column chromatography (CH/EtOAc, size: 16.0 x 2.0 cm, 25 g silica gel) yielded the pure title compound.

$C_{13}H_{15}O_3N_3$ [261.3]

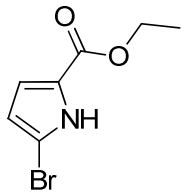
yield: 127.0 mg (79%), light yellow solid

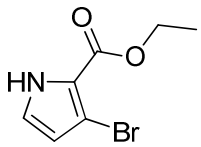
R_f (CH/ EtOAc 3:1): 0.25

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.41 (s, 1H, Ar-H), 7.63 (d, ^3J = 9.0 Hz, 2H, Ar-H), 7.01 (d, ^3J = 9.0 Hz, 2H, Ar-H), 4.45 (q, ^3J = 7.2 Hz, 2H, CH_2), 4.08 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.47-1.40 (m, 6H, 2 CH_3).

^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 160.7 (**C**=O), 159.7 ($\mathbf{C}_q$), 140.6 ($\mathbf{C}_q$), 129.5 ($\mathbf{C}_q$), 125.5 ($\mathbf{C}H_{Ar}$), 122.4 (2 $\mathbf{C}H_{Ar}$), 115.4 (2 $\mathbf{C}H_{Ar}$), 64.0 ($\mathbf{C}H_2$), 61.4 ($\mathbf{C}H_2$), 14.7 ($\mathbf{C}H_3$), 14.3 ($\mathbf{C}H_3$).
M.p.:	118-119 °C
GC-MS (NM_50_S2):	t_R = 8.10 min (m/z = 261.1, 99 % M^+, BP: 132).

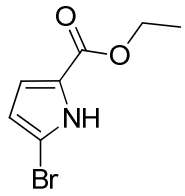
Ethyl 5/3-bromo-1*H*-pyrrole-2-carboxylate (78) [120]





A 250 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged with 1.00 g (7.19 mmol, 1.00 eq) ethyl pyrrole-2-carboxylate **(77)**, 24 mL absolute THF and 12 mL absolute MeOH. The mixture was cooled to 0 °C and 1.28 g (7.19 mmol, 1.00 eq) *N*-bromo-succinimide were added. The yellow solution was stirred at rt for 8 h, during which the color turned to colorless. GC-MS analysis indicated 95 % conversion of the starting material. The reaction mixture was hydrolyzed by 50 mL water, diluted with 40 mL EtOAc and transferred to a seperation funnel. The layers were separated and the aqueous layer was concentrated. The residue was dissolved in water and EtOAc, the layers were separated and the organic layer was combined with the first one. The combined organic layers were washed with 40 mL brine, dried over $MgSO_4$ and concentrated under reduced pressure. Final purification by column chromatography (CH/EtOAc 8:1, size: 4.5 x 21.0 cm, 150 g silica gel) led to the isolation of two compounds.

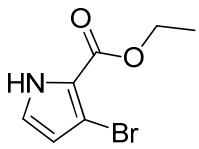
Ethyl 5-bromo-1*H*-pyrrole-2-carboxylate (78a)



$C_7H_8O_2NBr$ [218.0]

yield:	733.8 mg (47 %), colorless solid
R_f (CH/ EtOAc 8:1):	0.39
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 9.87 (bs, 1H, NH), 6.84-6.82 (m, 1H, Ar-H), 6.22-6.20 (m, 1H, Ar-H), 4.35 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.36 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 160.6 (**C**=O), 124.1 ($\mathbf{C}_q$-Br), 116.6 ($\mathbf{C}H_{Ar}$), 112.6 ($\mathbf{C}H_{Ar}$), 105.0 ($\mathbf{C}_q$), 60.7 ($\mathbf{C}H_2$), 14.4 ($\mathbf{C}H_3$).
M.p.:	85-87 °C
GC-MS (NM_50_S2):	t_R = 5.32 min (m/z = 218.0, 93 % M^+, BP: 173.0).

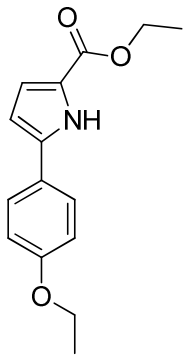
Ethyl 3-bromo-1*H*-pyrrole-2-carboxylate (78b)



$C_7H_8O_2NBr$ [218.0]

yield:	693.3 mg (44 %), colorless solid
R_f (CH/ EtOAc 8:1):	0.24
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 9.58 (bs, 1H, NH), 6.97-6.89 (m, 2H, Ar-H), 4.32 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.35 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 160.5 (**C**=O), 123.3 ($\mathbf{C}_q$-Br), 122.6 ($\mathbf{C}H_{Ar}$), 116.7 ($\mathbf{C}H_{Ar}$), 97.7 ($\mathbf{C}_q$), 60.8 ($\mathbf{C}H_2$), 14.3 ($\mathbf{C}H_3$).
GC-MS (NM_50_S2):	t_R = 5.68 min (m/z = 218.0, 83 % M^+, BP: 173.0).

Ethyl 5-(4-ethoxyphenyl)-1*H*-pyrrole-2-carboxylate (79a)



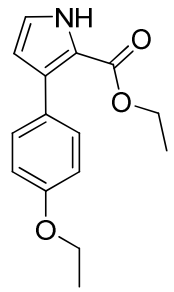
according to GP-5:

150 mg (688 µmol, 1.00 eq) ethyl 5-bromo-1*H*-pyrrole-2-carboxylate **(78a)**, 171 mg (1.03 mmol, 1.50 eq) 4-ethoxycarbonylphenylboronic acid **(71)**, reaction over night, column chromatography (CH/EtOAc 8:1, size: 16.0 x 2.0 cm, 25 g silica gel).

$C_{15}H_{17}O_3N$ [259.0]

yield:	112.5 mg (63 %), light brown solid
R_f (CH/ EtOAc 8:1):	0.26
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 11.93 (s, 1H, NH), 7.77 (d, ^3J = 8.7 Hz, 2H, Ar-H), 6.93 (d, ^3J = 8.7 Hz, 2H, Ar-H), 6.83-6.81 (m, 1H, Ar-H), 6.52-6.50 (m, 1H, Ar-H), 4.24 (q, ^3J = 6.9 Hz, 2H, CH_2), 4.04 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.35-1.27 (m, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 160.3 (**C**=O), 157.8 ($\mathbf{C}_q$-O), 137.2 ($\mathbf{C}_q$), 126.5 (2 $\mathbf{C}H_{Ar}$), 123.9 ($\mathbf{C}_q$), 122.4 ($\mathbf{C}_q$), 116.6 ($\mathbf{C}H_{Ar}$), 114.4 (2 $\mathbf{C}H_{Ar}$), 106.6 ($\mathbf{C}H_{Ar}$), 63.0 ($\mathbf{C}H_2$), 59.3 ($\mathbf{C}H_2$), 14.6 ($\mathbf{C}H_3$), 14.4 ($\mathbf{C}H_3$).
M.p.:	148-150 °C
GC-MS (NM_50_S2):	t_R = 7.79 min (m/z = 259.1, 98 % M^+, BP: 213.1).
HRMS (EI^+):	*m/z*: calcd for $C_{15}H_{17}O_3N$ $[M]^+$: 259.1208; found 259.1232.

Ethyl 3-(4-ethoxyphenyl)-1*H*-pyrrole-2-carboxylate (79b)



according to GP-5:

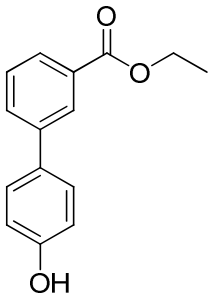
150 mg (688 µmol, 1.00 eq) ethyl 3-bromo-1*H*-pyrrole-2-carboxylate **(78b)**, 171 mg (1.03 mmol, 1.50 eq) 4-ethoxycarbonylphenylboronic acid **(71)**, reaction over night, column chromato-graphy (CH/EtOAc 8:1, size: 16.0 x 2.0 cm, 25 g silica gel).

$C_{15}H_{17}O_3N$ [259.0]

yield:	81.2 mg (46 %), light yellow solid
R_f (CH/ EtOAc 8:1):	0.16
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 11.94 (s, 1H, NH), 7.52 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.39 (bs, 1H, Ar-H), 7.08 (bs, 1H, Ar-H), 6.87 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.25 (q, ^3J = 6.9 Hz, 2H, CH_2), 4.00 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.34-1.27 (m, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 160.3 (**C**=O), 156.7 ($\mathbf{C}_q$-O), 127.0 ($\mathbf{C}_q$), 125.8 (2 **C**H_{Ar}), 124.8 ($\mathbf{C}_q$), 122.6 ($\mathbf{C}_q$), 120.2 (**C**H_{Ar}), 114.5 (2 **C**H_{Ar}), 111.4 (**C**H_{Ar}), 62.8 (**C**H_2), 59.5 (**C**H_2), 14.6 (**C**H_3), 14.3 (**C**H_3).
M.p.:	152-154 °C
GC-MS (NM_50_S2):	t_R = 7.99 min (m/z = 259.1, 99 % M^+, BP: 213.1).

6.3.6. Synthesis of different biaryls keeping the ethylester substituted phenyl ring

Ethyl 4`-hydroxybiphenyl-3-carboxylate (82a)



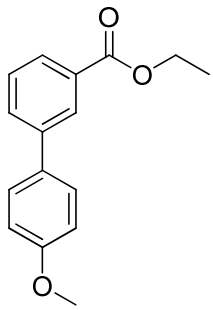
according to GP-5:

250 mg (170 µL, 1.09 mmol, 1.00 eq) ethyl-3-bromobenzoate **(80)**, 151 mg (1.09 mmol, 1.00 eq) 4-hydroxyphenylboronic acid **(81a)**, 5 h reaction time, column chromatography (1. CH/EtOAc 30:1, 2. CH/EtOAc 9:1, size: 23.0 x 1.0 cm, 10 g silica gel).

$C_{15}H_{14}O_3$ [242.3]

yield:	57.9 mg (22 %), beige solid
R_f (CH/ EtOAc 3:1):	0.40
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.24 (t, ^4J = 1.5 Hz, 1H, Ar-H), 8.00-7.97 (m, 1H, Ar-H), 7.75-7.71 (m, 1H, Ar-H), 7.53-7.46 (m, 3H, Ar-H), 6.95 (d, ^3J = 8.7 Hz, 2H, Ar-H), 5.34 (bs, 1H, OH), 4.42 (q, ^3J = 7.2 Hz, 2H, CH2), 1.42 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.9 (**C**=O), 155.6 ($\mathbf{C}_q$-OH), 141.0 ($\mathbf{C}_q$), 132.8 ($\mathbf{C}_q$), 131.0 ($\mathbf{C}H_{Ar}$), 130.9 ($\mathbf{C}_q$), 128.8 ($\mathbf{C}H_{Ar}$), 128.4 (2 $\mathbf{C}H_{Ar}$), 127.8 ($\mathbf{C}H_{Ar}$), 127.7 ($\mathbf{C}H_{Ar}$), 115.7 (2 $\mathbf{C}H_{Ar}$), 61.2 ($\mathbf{C}H_2$), 14.3 ($\mathbf{C}H_3$).
M.p.:	116-118 °C

Ethyl 4`-methoxybiphenyl-3-carboxylate (82b)



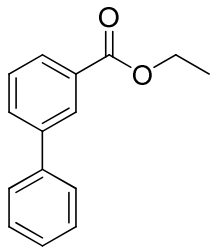
according to GP-5:

150 mg (100 µL, 655 µmol, 1.00 eq) ethyl-3-bromobenzoate **(80)**, 99.5 mg (655 µmol, 1.00 eq) 4-methoxyphenylboronic acid **(81b)**, 5.5 h reaction time, column chromatography (CH/EtOAc 9:1, size: 14.0 x 2.0 cm, 20 g silica gel).

$C_{16}H_{16}O_3$ [256.3]

yield:	110.4 mg (66 %), light yellow oil
R_f (CH/ EtOAc 9:1):	0.42
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.24 (t, ^4J = 1.5 Hz, 1H, Ar-H), 8.00-7.97 (m, 1H, Ar-H), 7.76-7.72 (m, 1H, Ar-H), 7.57 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.48 (t, ^3J = 7.8 Hz, 1H, Ar-H), 7.00 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.41 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 1.42 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.6 (**C**=O), 159.4 ($\mathbf{C}_q$-OCH_3), 141.0 ($\mathbf{C}_q$), 132.7 ($\mathbf{C}_q$), 130.9 (**C**H_{Ar}), 128.7 (**C**H_{Ar}), 128.2 (2 **C**H_{Ar}), 127.7 (**C**H_{Ar}), 127.6 (**C**H_{Ar}), 114.3 (2 **C**H_{Ar}), 61.0 (**C**H_2), 55.3 (O**C**H_3), 14.3 (**C**H_3).
GC-MS (NM_50_S2):	t_R = 7.63 min (m/z = 256.1, 99 % M^+, BP).

Ethyl-biphenyl-3-carboxylate (82c)

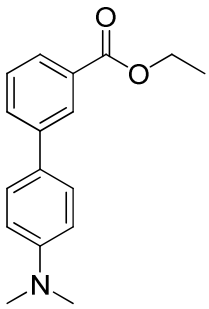


150 mg (100 µL, 655 µmol, 1.00 eq) ethyl-3-bromobenzoate **(80)**, 79.8 mg (655 µmol, 1.00 eq) phenylboronic acid **(81c)**, 4.5 h reaction time, column chromatography (CH/EtOAc 50:1, size: 13.0 x 2.0 cm, 20 g silica gel).

$C_{15}H_{14}O_2$ [226.3]

yield:	73.8 mg (50 %), colorless oil
R_f (CH/ EtOAc 50:1):	0.31
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.29-8.28 (m, 1H, Ar-H), 8.04 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.78 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.65-7.62 (m, 2H, Ar-H), 7.54-7.45 (m, 3H, Ar-H), 7.41-7.36 (m, 1H, Ar-H), 4.42 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.42 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.5 (**C**=O), 141.4 ($\mathbf{C}_q$), 140.2 ($\mathbf{C}_q$), 131.4 ($\mathbf{C}H_{Ar}$), 131.0 ($\mathbf{C}_q$), 128.8 (2 $\mathbf{C}H_{Ar}$), 128.7 ($\mathbf{C}H_{Ar}$), 128.3 ($\mathbf{C}H_{Ar}$), 128.2 ($\mathbf{C}H_{Ar}$), 127.7 ($\mathbf{C}H_{Ar}$), 127.2 (2 $\mathbf{C}H_{Ar}$), 61.1 ($\mathbf{C}H_2$), 14.3 ($\mathbf{C}H_3$).
GC-MS (NM_50_S2):	t_R = 6.90 min (m/z = 226.1, 99 % M^+, BP: 181.1).

Ethyl 4`-(dimethylamino)biphenyl-3-carboxylate (82d)



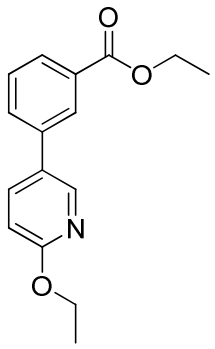
according to GP-5:

150 mg (100 µL, 655 µmol, 1.00 eq) ethyl-3-bromobenzoate **(80)**, 108 mg (655 µmol, 1.00 eq) 4-(dimethylamino)phenylboronic acid **(81d)**, 26 h reaction time, column chromatography (CH/EtOAc 19:1, size: 14.0 x 2.0 cm, 25 g silica gel).

$C_{17}H_{19}O_2N$ [269.3]

yield:	135.9 mg (77 %), colorless solid
R_f (CH/ EtOAc 19:1):	0.24
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.26 (s, 1H, Ar-H), 7.94 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.74 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.55 (d, ^3J = 9.0 Hz, 2H, Ar-H), 7.46 (t, ^3J = 7.8 Hz, 1H, Ar-H), 6.82 (d, ^3J = 9.0 Hz, 2H, Ar-H), 4.41 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.01 (s, 6H, 2 CH_3), 1.42 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.8 (**C**=O), 150.2 ($\mathbf{C}_q$-N(CH_3)$_2$), 141.4 ($\mathbf{C}_q$), 130.8 ($\mathbf{C}_q$), 130.4 (**C**H_{Ar}), 128.6 (**C**H_{Ar}), 128.0 ($\mathbf{C}_q$), 127.7 (2 **C**H_{Ar}), 127.2 (**C**H_{Ar}), 127.0 (**C**H_{Ar}), 112.7 (2 **C**H_{Ar}), 60.9 (**C**H_2), 40.5 (N(**C**H_3)$_2$), 14.4 (**C**H_3).
M.p.:	79-81 °C
GC-MS (NM_50_S2):	t_R = 8.29 min (m/z = 269.1, 99 % M^+, BP).
HRMS (EI$^+$):	*m/z*: calcd for $C_{17}H_{19}O_2N$ $[M]^+$: 269.1416; found 269.1421.

Ethyl 3-(6-ethoxypyridine-3-yl)-benzoate (82e)



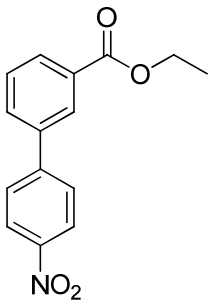
according to GP-5:

150 mg (100 µL, 655 µmol, 1.00 eq) ethyl-3-bromobenzoate **(80)**, 109 mg (655 µmol, 1.00 eq) 4-ethoxypyridine-3-boronic acid **(81e)**, 5 h reaction time, column chromatography (CH/EtOAc 9:1, R_f = 0.35, size: 17.0 x 2.0 cm, 25 g silica gel).

$C_{16}H_{17}O_3N$ [271.3]

yield:	90.5 mg (51 %), colorless solid
R_f (CH/ EtOAc 3:1):	0.65
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.40 (d, ^4J = 1.5 Hz, 1H, Ar-H), 8.20 (s, 1H, Ar-H), 8.02 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.85 (dd, ^3J = 8.4 Hz, ^4J = 2.4 Hz, 1H, Ar-H), 7.70 (m, 1H, Ar-H), 7.51 (t, ^3J = 7.8 Hz, 1H, Ar-H), 6.84 (d, ^3J = 8.7 Hz, 1H, Ar-H), 4.46 (m, 4H, 2 CH_2), 1.46-1.39 (m, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.4 (**C**=O), 163.4 (**C**$_q$-OCH_2CH_3), 144.7 (**C**$_q$), 138.0 (**C**$_q$), 137.7 (**C**$_q$), 131.2 (**C**H_{Ar}), 130.8 (**C**H_{Ar}), 129.0 (**C**H_{Ar}), 128.4 (**C**H_{Ar}), 127.7 (**C**H_{Ar}), 111.2 (**C**H_{Ar}), 62.3 (**C**H_2), 61.1 (**C**H_2), 14.6 (**C**H_3), 14.3 (**C**H_3).
M.p.:	68-70 °C
GC-MS (NM_50_S2):	t_R = 7.64 min (m/z = 271.1, 99 % M^+, BP: 256.1).
HRMS (EI^+):	*m/z*: calcd for $C_{16}H_{17}O_3N$ $[M]^+$: 271.1208; found 271.1220.

Ethyl 4`-nitrobiphenyl-3-carboxylate (82f)



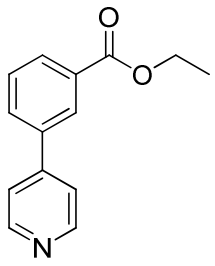
according to GP-5:

150 mg (100 µL, 655 µmol, 1.00 eq) ethyl-3-bromobenzoate **(80)**, 115 mg (655 µmol, 1.00 eq, 95 % purity) 3-thienylboronic acid **(81f)**, 4 h reaction time, column chromatography (CH/EtOAc 19:1, size: 15.0 x 2.0 cm, 20 g silica gel).

$C_{15}H_{13}O_4N$ [271.2]

yield:	129.4 mg (73 %), light yellow solid
R_f (CH/ EtOAc 19:1):	0.25
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.33-8.30 (m, 3H, Ar-H), 8.12 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.82-7.76 (m, 3H, Ar-H), 7.58 (t, ^3J = 7.8 Hz, 1H, Ar-H), 4.42 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.43 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.1 (**C**=O), 147.3 ($\mathbf{C}_q$-NO_2), 146.5 ($\mathbf{C}_q$), 139.0 ($\mathbf{C}_q$), 131.5 ($\mathbf{C}H_{Ar}$), 131.5 ($\mathbf{C}_q$), 129.8 ($\mathbf{C}H_{Ar}$), 129.2 ($\mathbf{C}H_{Ar}$), 128.4 ($\mathbf{C}H_{Ar}$), 127.9 (2 $\mathbf{C}H_{Ar}$), 124.2 (2 $\mathbf{C}H_{Ar}$ **C**H), 61.3 ($\mathbf{C}H_2$), 14.3 ($\mathbf{C}H_3$).
M.p.:	84-86 °C
GC-MS (NM_50_S2):	t_R = 8.16 min (m/z = 271.1, 99 % M^+, BP: 226.1).
HRMS (EI^+):	*m/z*: calcd for $C_{16}H_{23}O_3N$ $[M]^+$: 271.0845; found 271.0847.

Ethyl 3-(pyridine-4-yl)-benzoate (82g)



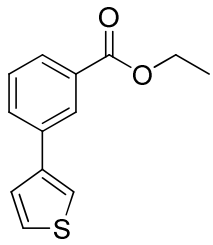
according to GP-5:

150 mg (100 µL, 655 µmol, 1.00 eq) ethyl-3-bromobenzoate **(80)**, 80.5 mg (655 µmol, 1.00 eq) 4-pyridineboronic acid **(81g)**, 24 h reaction time. silica gel filtration (CH/EtOAc 1:1, size: 7.0 x 3.0 cm).

$C_{14}H_{13}O_2N$ [227.3]

yield:	128.9 mg (87 %), brown soild
R_f (CH/ EtOAc 1:1):	0.26
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.72-8.71 (m, 2H, Ar-H), 8.31 (s, 1H, Ar-H), 8.11 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.83 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.59-7.54 (m, 3H, Ar-H), 4.41 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.42 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.0 (**C**=O), 150.0 (2 **C**H_{Ar}), 147.6 (**C**$_q$), 138.3 (**C**$_q$), 131.5 (**C**$_q$), 131.2 (**C**H_{Ar}), 130.1 (**C**H_{Ar}), 129.2 (**C**H_{Ar}), 128.1 (**C**H_{Ar}), 121.8 (2 **C**H_{Ar}), 61.3 (**C**H_2), 14.3 (**C**H_3).
M.p.:	52-53 °C
GC-MS (NM_50_S2):	t_R = 7.11 min (m/z = 227.1, 99 % M^+, BP: 182.1).

Ethyl 3-(thiophene-3-yl)benzoate (82h)



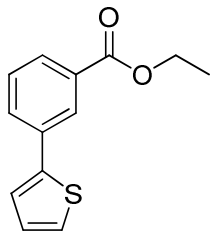
according to GP-5:

150 mg (100 µL, 655 µmol, 1.00 eq) ethyl-3-bromobenzoate **(80)**, 83.8 mg (655 µmol, 1.00 eq) 3-thienylboronic acid **(81h)**, 5 h reaction time, column chromatography (CH/EtOAc 50:1, size: 16.0 x 2.0 cm, 25 g silica gel).

$C_{13}H_{12}O_2S$ [232.3]

yield:	137.1 mg (90 %), light yellow solid
R_f (CH/ EtOAc 50:1):	0.26
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.28 (s, 1H, Ar-H), 7.97 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.78 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.54-7.53 (m, 1H, Ar-H), 7.49-7.42 (m, 3H, Ar-H), 4.41 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.42 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.5 (**C**=O), 141.3 ($\mathbf{C}_q$), 136.0 ($\mathbf{C}_q$), 131.0 ($\mathbf{C}_q$), 130.6 ($\mathbf{C}H_{Ar}$), 128.8 ($\mathbf{C}H_{Ar}$), 128.1 ($\mathbf{C}H_{Ar}$), 127.4 ($\mathbf{C}H_{Ar}$), 126.5 ($\mathbf{C}H_{Ar}$), 126.2 ($\mathbf{C}H_{Ar}$), 121.0 ($\mathbf{C}H_{Ar}$), 61.1 ($\mathbf{C}H_2$), 14.3 ($\mathbf{C}H_3$).
M.p.:	44 °C
GC-MS (NM_50_S2):	t_R = 7.02 min (m/z = 232.1, 99 % M^+, BP).

Ethyl 3-(thiophene-2-yl)benzoate (82i)



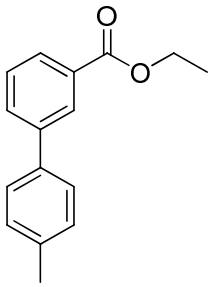
according to GP-5:

150 mg (100 µL, 655 µmol, 1.00 eq) ethyl-3-bromobenzoate **(80)**, 83.8 mg (655 µmol, 1.00 eq) 2-thienylboronic acid **(81i)**, 8.5 h reaction time, column chromatography (CH/EtOAc 50:1, size: 15.0 x 2.0 cm, 20 g silica gel).

$C_{13}H_{12}O_2S$ [232.3]

yield:	128.7 mg (85 %), yellow liquid
R_f (CH/ EtOAc 50:1):	0.29
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.29 (s, 1H, Ar-H), 7.96 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.79 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.48-7.38 (m, 2H, Ar-H), 7.33-7.31 (m, 1H, Ar-H), 7.12-7.09 (m, 1H, Ar-H), 4.42 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.42 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.3 (**C**=O), 143.2 ($\mathbf{C}_q$), 134.7 ($\mathbf{C}_q$), 131.2 ($\mathbf{C}_q$), 130.1 ($\mathbf{C}H_{Ar}$), 128.9 ($\mathbf{C}H_{Ar}$), 128.3 ($\mathbf{C}H_{Ar}$), 128.1 ($\mathbf{C}H_{Ar}$), 126.8 ($\mathbf{C}H_{Ar}$), 125.4 ($\mathbf{C}H_{Ar}$), 123.7 ($\mathbf{C}H_{Ar}$), 61.1 ($\mathbf{C}H_2$), 14.3 ($\mathbf{C}H_3$).
GC-MS (NM_50_S2):	t_R = 6.98 min (m/z = 232.1, 95 % M^+, BP).

BP-13: Ethyl 4`-methylbiphenyl-3-carboxylate (82j)



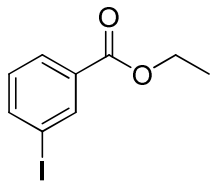
according to GP-5:

1.13 g (790 µL, 4.93 mmol, 1.00 eq) ethyl-3-bromobenzoate **(80)**, 737 mg (5.42 mmol, 1.10 eq) *p*-tolylboronic acid **(81j)**, 4 h reaction time, column chromatography (CH/EtOAc 50:1, size: 25.0 x 3.0 cm, 110 g silica gel).

$C_{16}H_{15}O_2$ [240.3]

yield:	991.1 mg (84 %), light yellow liquid
R_f (CH/ EtOAc 50:1):	0.27
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.07-8.06 (m, 1H, Ar-H), 7.80 (dd, ^4J = 1.2 Hz, ^3J = 7.8 Hz, 1H, Ar-H), 7.56 (dd, ^4J = 1.2 Hz, ^3J = 7.8 Hz, 1H, Ar-H), 7.34-7.29 (m, 3H, Ar-H), 7.07 (d, ^3J = 7.8 Hz, 2H, Ar-H), 4.20 (q, ^3J = 7.2 Hz, 2H, CH_2), 2.20 (s, 3H, CH_3), 1.21 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.6 (**C**=O), 141.3 ($\mathbf{C}_q$), 137.5 ($\mathbf{C}_q$), 137.3 ($\mathbf{C}_q$), 131.2 ($\mathbf{C}H_{Ar}$), 131.0 ($\mathbf{C}_q$), 129.6 (2 $\mathbf{C}H_{Ar}$), 128.7 ($\mathbf{C}H_{Ar}$), 128.0 (2 $\mathbf{C}H_{Ar}$), 127.0 (2 $\mathbf{C}H_{Ar}$), 61.0 ($\mathbf{C}H_2$), 21.1 ($\mathbf{C}H_3$), 14.3 ($\mathbf{C}H_3$).
GC-MS (NM_50_S2):	t_R = 7.21 min (m/z = 240.2, 99 % M^+, BP).

Ethyl 3-iodobenzoate (84)

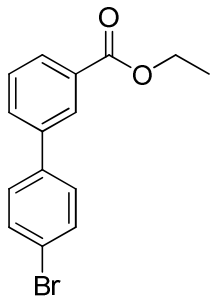


A 100 mL Schlenk tube was charged with 1.88 g (7.58 mmol, 1.00 eq) 3-iodobenzoic acid **(83)**, 6.2 ml EtOH and 1.2 mL (22.7 mmol, 3.00 eq) conc. H_2SO_4. The solution was refluxed for 2.5 h. GC-MS analysis and TLC analysis indicated full conversion of the starting material. The mixture was concentrated under reduced pressure and the residue was dissolved in 25 mL EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated under reduced pressure. Final Purification by column chromatography (CH → CH/EtOAc 10:1 → 8:1, size: 12.0 x 2.5 cm, 10 g silica gel) yielded the pure product.

$C_9H_9O_2I$ [276.1]

yield:	1.8 g (86 %), yellow oil
R_f (CH):	0.47
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.38 (t, ^4J = 1.5 Hz, 1H, Ar-H), 8.02-7.99 (m, 1H, Ar-H), 7.89-7.86 (m, 1H, Ar-H), 7.18 (t, ^3J = 8.1 Hz, 1H, Ar-H), 4.38 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.39 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 165.1 (**C**=O), 141.6 (**C**H_{Ar}), 138.4 (**C**H_{Ar}), 132.4 (**C**$_q$), 130.0 (**C**H_{Ar}), 128.7 (**C**H_{Ar}), 93.7 (**C**$_q$-I), 61.4 (**C**H_2), 14.3 (**C**H_3).
GC-MS (NM_50_S2):	t_R = 5.89 min (m/z = 276.0, 99 % M^+, BP: 231.0).

Ethyl 4`-bromo-(1,1`-biphenyl)-3-carboxylate (82k)

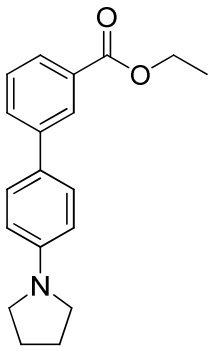


A 100 mL Schlenk tube was charged with 1.79 g (6.48 mmol, 1.00 eq) ethyl 3-iodobenzoate **(84)**, 1.30 g (6.48 mmol, 1.00 eq) 4-bromophenylboronic acid **(81k)**, 375 mg (324 µmol, 0.05 eq) $Pd[PPh_3]_4$, 32.6 mL absolute toluene and 18 mL EtOH. The suspension was degassed by vacuum/N_2 cycles and 5.4 mL of a 4 M aqueous Na_2CO_3 solution was added. The solution was stirred at 80 °C for 22 h. GC-MS analysis indicated full conversion of the starting material. The mixture was diluted with 50 mL EtOAc and 50 mL water. The layers were separated. The organic layer was washed with brine (2 x 50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Final Purification by column chromatography (CH/EtOAc 50:1, size: 23.0 x 5.5 cm, 80 g silica gel) yielded the pure product.

$C_{15}H_{13}O_2Br$ [270.3]

yield:	0.4 g (72 %), colorless solid
R_f (CH/ EtOAc 50:1):	0.17
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.24 (s, 1H, Ar-H), 8.05 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.75-7.73 (m, 1H, Ar-H), 7.61-7.58 (m, 2H, Ar-H), 7.54-7.48 (m, 2H, Ar-H), 7.34 (m, 1H, Ar-H), 4.42 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.42 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.4 (**C**=O), 140.2 ($\mathbf{C}_q$), 139.1 ($\mathbf{C}_q$), 132.0 (2 $\mathbf{C}H_{Ar}$), 131.2 ($\mathbf{C}_q$), 131.2 ($\mathbf{C}H_{Ar}$), 128.9 ($\mathbf{C}H_{Ar}$), 128.7 (2 $\mathbf{C}H_{Ar}$), 128.7 ($\mathbf{C}H_{Ar}$), 128.0 ($\mathbf{C}H_{Ar}$), 122.1 ($\mathbf{C}_q$-Br), 61.2 ($\mathbf{C}H_2$), 14.4 ($\mathbf{C}H_3$).
M.p.:	56 °C
GC-MS (NM_50_S2):	t_R = 7.71 min (m/z = 305.0, 99 % M^+, BP: 152.1).

Ethyl 4`-(pyrrolidin-1-yl)-(1,1`-biphenyl)-3-carboxylate (85a)



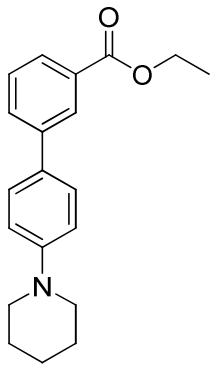
A 15 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged with 1.10 mg (1.23 µmol, 0.5 mol %) $Pd_2(dba)_3$, 1.10 mg (1.85 µmol, 0.75 mol %) (±)-BINAP, 33.1 mg (305 µmol, 1.40 eq) sodium *tert*-butoxide and 0.5 mL anhydrous toluene. Afterwards 75.0 mg (246 µmol, 1.00 eq) ethyl 4`-bromo-(1,1`-biphenyl)-3-carboxylate **(82k)**, 21.0 mg (24.2 µL, 295 µmol, 1.20 eq) pyrrolidine and 1.0 ml anhydrous toluene were added. The solution was degassed by vacuum/N_2 cycles and stirred at 80 °C for 22 h. TLC analysis indicated full conversion of the starting material. The yellow solution was hydrolyzed by 5 mL water and diluted with 2 mL brine and 5 mL Et_2O. The layers were separated and the organic layer was washed with water (2 x 5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Final purification by column chromatography (CH/EtOAc 50:1, size: 16.0 x 2.5 cm, 15 g silica gel) yielded the pure product.

$C_{19}H_{21}O_2N$ [295.4]

yield:	9.2 mg (13 %), beige solid
R_f (CH/ EtOAc 50:1):	0.38
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.10 (s, 1H, Ar-H), 7.87-7.79 (m, 2H, Ar-H), 7.56-7.53 (m, 3H, Ar-H), 6.64 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.34 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.28 (t, ^3J = 6.3 Hz, 4H, 2 CH_2), 1.97 (t, 4H, 2 CH_2), 1.34 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 165.8 (**C**=O), 147.4 ($\mathbf{C}_q$), 140.9 ($\mathbf{C}_q$), 130.4 ($\mathbf{C}_q$), 129.9 ($\mathbf{C}H_{Ar}$), 129.1 ($\mathbf{C}H_{Ar}$), 127.2 (2 $\mathbf{C}H_{Ar}$), 126.2 ($\mathbf{C}H_{Ar}$), 125.5 ($\mathbf{C}H_{Ar}$), 125.3 ($\mathbf{C}_q$), 112.0 (2 $\mathbf{C}H_{Ar}$), 60.7 ($\mathbf{C}H_2$), 47.2 (2 $\mathbf{C}H_2$), 24.9 (2 CH_2), 14.1 ($\mathbf{C}H_3$).

GC-MS (NM_50_S2): t_R = 9.81 min (m/z = 295.1, 99 % M^+, BP: 207.0).

Ethyl 4`-(piperidin-1-yl)-(1,1`-biphenyl)-3-carboxylate (85b)



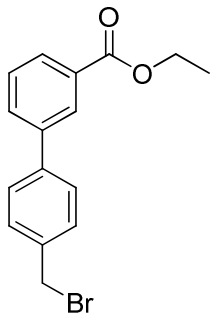
A 15 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged with 1.50 mg (1.64 µmol, 0.5 mol %) $Pd_2(dba)_3$, 3.10 mg (4.92 µmol, 1.5 mol %) (±)-BINAP, 44.1 mg (460 µmol, 1.40 eq) sodium *tert*-butoxide and 2.0 mL absolute toluene. Afterwards 100 mg (328 µmol, 1.00 eq) ethyl 4`-bromo-(1,1`-biphenyl)-3-carboxylate **(82k)**, 33.5 mg (38.9 µL, 394 µmol, 1.20 eq) piperidine and 3.0 ml absolute toluene were added. The solution was degassed by vacuum/N_2 cycles and stirred at 80 °C for 23 h. TLC analysis indicated no full conversion of the starting material. The temperature was increased to 125 °C and after further 17.5 h stirring the orange solution was filtrated through a pad of celite and eluted with 5 mL EtOAc and 10 mL DCM. The solvent was removed under reduced pressure and final purification by column chromatography (CH/EtOAc 50:1 → 19:1, size: 18.5 x 2.0 cm, 18 g silica gel) yielded the pure product.

$C_{20}H_{23}O_2N$ [309.4]

yield:	5.7 mg (6 %), yellow solid
R_f (CH/ EtOAc 19:1):	0.15
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.11 (d, ^4J = 1.5 Hz, 1H, Ar-H), 7.89-7.83 (m, 2H, Ar-H), 7.58-7.53 (m, 3H, Ar-H), 7.03 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.34 (q, ^3J = 6.9 Hz, 2H, CH_2), 3.23-3.20 (m, 4H, 2 CH_2), 1.62-1.57 (m, 6H, 3 CH_2), 1.34 (t, ^3J = 6.9 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 165.7 (**C**=O), 151.1 (**C**$_q$), 140.5 (**C**$_q$), 130.4 (**C**$_q$), 130.3 (**C**H$_{Ar}$), 129.2 (**C**H$_{Ar}$), 127.1 (2 **C**H$_{Ar}$), 126.7 (**C**H$_{Ar}$), 125.9 (**C**H$_{Ar}$), 115.7 (2 **C**H$_{Ar}$), 60.7 (**C**H$_2$), 48.9 (2 **C**H$_2$), 25.0 (2 CH$_2$), 23.8(**C**H$_2$), 14.1 (**C**H$_3$).
M.p.:	97-99 °C
GC-MS (NM_50_S2):	t_R = 9.84 min (m/z = 309.1, 99 % M^+, BP: 207.0).

Ethyl 4`-(bromomethyl)biphenyl-3-carboxylate (86)



A 100 mL two-neck round-bottom flask with reflux condenser and pressure compensation was flushed with argon and charged with 953 mg (3.96 mmol, 1.00 eq) ethyl 4`-methyl-biphenyl-3-carboxylate **(82j)** and 16 mL CCl_4. After addition of 776 mg (4.36 mmol, 1.10 eq) *N*-bromosuccinimide and 57.6 mg (238 µmol, 0.06 eq) dibenzoylperoxide the yellow suspension was refluxed for 4 h. GC-MS analysis showed 95 % conversion of the starting material. The mixture was filtered through a fritted funnel and the filtrate was concentrated under reduced pressure. Final purification by column chromatography (CH/EtOAc 60:1, size: 18.0 x 2.5 cm, 30 g silica gel) yielded the pure product.

$C_{16}H_{15}O_2Br$ [319.2]

yield:	1.02 g (80 %), colorless solid
R_f (CH/ EtOAc 60:1):	0.31
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.27 (s, 1H, Ar-H), 8.07-8.03 (m, 1H, Ar-H), 7.77 (dd, ^4J = 1.2 Hz, ^3J = 7.8 Hz, 1H, Ar-H), 7.66-7.48 (m, 5H, Ar-H), 4.56 (s, 2H, CH_2), 4.42 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.42 (t, ^3J = 7.2 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 166.4 (**C**=O), 140.6 ($\mathbf{C}_q$), 140.3 ($\mathbf{C}_q$), 137.3 ($\mathbf{C}_q$), 131.3 ($\mathbf{C}H_{Ar}$), 131.1 ($\mathbf{C}_q$), 129.6 (2 $\mathbf{C}H_{Ar}$), 128.9 ($\mathbf{C}H_{Ar}$), 128.6 ($\mathbf{C}H_{Ar}$), 128.2 ($\mathbf{C}H_{Ar}$), 127.6 (2 $\mathbf{C}H_{Ar}$), 61.1 ($\mathbf{C}H_2$), 33.1 ($\mathbf{C}H_2$), 14.3 ($\mathbf{C}H_3$).

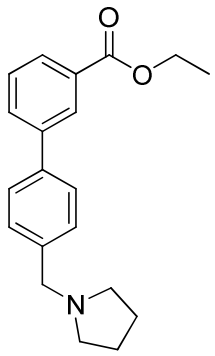
M.p.: 54-57 °C

GC-MS (NM_50_S2): t_R = 8.23 min (m/z = 319.1, 97 % M^+, BP: 239.1).

General Procedure (GP-8):

Two Schlenk tubes were dried in vacuum and flushed with nitrogen. The first tube was charged with 75.0 mg (235 µmol, 1.00 eq) ethyl 4`-(bromomethyl)biphenyl-3-carboxylate and 0.45 mL absolute THF. The solution was cooled to 0 °C. The second Schlenk tube was charged with 470 µmol (2.00 eq) amine and 0.25 mL absolute THF, which was then added to the cooled substrate solution. The suspension was stirred at rt for 2 h. GC-MS analysis indicated full conversion of the starting material. The mixture was transfered in a one-neck round-bottom flask and concentrated under reduced pressure. Final purification by column chromatography yielded the pure product.

Ethyl 4`-(pyrrolidin-1-ylmethyl)biphenyl-3-carboxylate (87a)



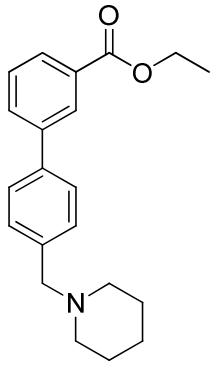
according to GP-8:

33.4 mg (38.6 µL, 470 µmol) pyrrolidine, column chromatography (1. CH/EtOAc 19:1, 2. EtOH, size: 6.0 x 3.5 cm).

$C_{20}H_{23}O_2N$ [309.4]

yield:	20.0 mg (28 %), yellow solid
R_f (EtOH):	0.39
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.44 (bs, 1H, Ar-H), 8.20-8.17 (m, 1H, Ar-H), 8.00-7.93 (m, 2H, Ar-H), 7.70-7.64 (m, 3H, Ar-H), 7.44-7.41 (m, 1H, Ar-H), 4.36-4.34 (m, 2H, CH_2), 3.61 (s, 2H, CH_2), 2.46-2.45 (m, 4H, 2 CH_2), 1.70 (bs, 4H, 2 CH_2), 1.37-1.32 (m, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 165.6 (**C**=O), 140.4 ($\mathbf{C}_q$), 139.4 ($\mathbf{C}_q$), 137.4 ($\mathbf{C}_q$), 131.2 ($\mathbf{C}H_{Ar}$), 130.5 ($\mathbf{C}_q$), 129.4 ($\mathbf{C}H_{Ar}$), 129.1 (2 $\mathbf{C}H_{Ar}$), 127.8 ($\mathbf{C}H_{Ar}$), 126.8 ($\mathbf{C}H_{Ar}$), 126.5 (2 $\mathbf{C}H_{Ar}$), 60.8 ($\mathbf{C}H_2$), 59.1 ($\mathbf{C}H_2$), 53.4 ($\mathbf{C}H_2$), 23.0 ($\mathbf{C}H_2$), 14.1 ($\mathbf{C}H_3$).
M.p.:	165-170 °C
GC-MS (NM_50_S2):	t_R = 8.94 min (m/z = 309.2, 97 % M^+, BP: 239.1).

Ethyl 4`-(piperidin-1-ylmethyl)biphenyl-3-carboxylate (87b)



according to GP-8:

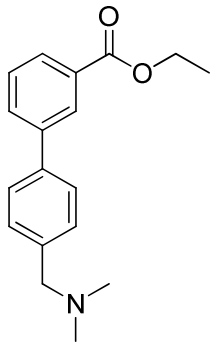
40.0 mg (46.4 µL, 470 µmol) piperidine, column chromatography (1. CH/EtOAc 19:1, 2. EtOH, size: 5.0 x 3.0 cm).

$C_{21}H_{25}O_2N$ [323.4]

yield:	40.1 mg (53 %), yellow solid
R_f (EtOH):	0.55

^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.16 (bs, 1H, Ar-H), 7.94 (d, ^{3}J = 7.5 Hz, 2H, Ar-H), 7.66-7.61 (m, 3H, Ar-H), 7.42-7.40 (m, 2H, Ar-H), 4.34 (q, ^{3}J = 6.9 Hz, 2H, CH_2), 3.49 (s, 2H, CH_2), 2.36 (bs, 4H, 2 CH_2), 1.50-1.49 (m, 4H, 2 CH_2), 1.39-1.31 (m, 5H, CH_2, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 165.5 (**C**=O), 140.4 ($\mathbf{C}_q$), 138.1 ($\mathbf{C}_q$), 137.6 ($\mathbf{C}_q$), 131.3 ($\mathbf{C}H_{Ar}$), 130.5 ($\mathbf{C}_q$), 129.5 (2 $\mathbf{C}H_{Ar}$), 129.4 ($\mathbf{C}H_{Ar}$), 127.8 ($\mathbf{C}H_{Ar}$), 126.8 ($\mathbf{C}H_{Ar}$), 126.5 (2 $\mathbf{C}H_{Ar}$), 62.2 ($\mathbf{C}H_2$), 60.8 ($\mathbf{C}H_2$), 53.7 ($\mathbf{C}H_2$), 25.3 ($\mathbf{C}H_2$), 23.8 ($\mathbf{C}H_2$), 14.1 ($\mathbf{C}H_3$).
M.p.:	168-173 °C
GC-MS (NM_50_S2):	t_R = 9.33 min (m/z = 323.2, 99 % M^+, BP: 239.1).

Ethyl 4`-((dimethylamino)methyl)biphenyl-3-carboxylate (87c)



according to GP-8:

240 µL (2.0 M in THF, 470 µmol) dimethylamine, column chromatography (EtOH, size: 19.0 x 1.5 cm, 20 g silica gel).

$C_{18}H_{21}O_2N$ [283.3]

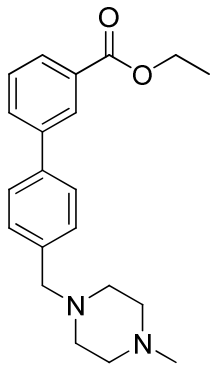
yield:	17.6 mg (26 %), yellow oil
R_f (EtOH):	0.23
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.18 (bs, 1H, Ar-H), 7.95 (dd, ^{4}J = 1.2 Hz, ^{3}J = 6.9 Hz, 2H, Ar-H), 7.67-7.59 (m, 3H, Ar-H), 7.41 (d, ^{3}J = 8.1 Hz, 2H, Ar-H), 4.35 (q, ^{3}J = 6.9 Hz, 2H, CH_2),

3.43 (s, 2H, CH_2), 2.17 (s, 6H, 2 CH_3), 1.35 (t, ^3J = 7.2 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 165.5 (**C**=O), 140.4 ($\mathbf{C}_q$), 138.8 ($\mathbf{C}_q$), 137.5 ($\mathbf{C}_q$), 131.2 ($\mathbf{C}H_{Ar}$), 130.5 ($\mathbf{C}_q$), 129.4 ($\mathbf{C}H_{Ar}$), 129.3 (2 $\mathbf{C}H_{Ar}$), 127.8 ($\mathbf{C}H_{Ar}$), 126.8 ($\mathbf{C}H_{Ar}$), 126.5 (2 $\mathbf{C}H_{Ar}$), 62.9 ($\mathbf{C}H_2$), 60.8 ($\mathbf{C}H_2$), 44.9 (N($\mathbf{C}H_3$)$_2$), 14.1 ($\mathbf{C}H_3$).

GC-MS (NM_50_S2): t_R = 7.91 min (m/z = 283.1, 99 % M^+, BP: 239.1).

Ethyl 4`-((4-methylpiperazin-1-yl)methyl)biphenyl-3-carboxylate (87d)



according to GP-8:

47.1 mg (52.2 µL, 470 µmol) 1-methylpiperazine, column chromatography (1. CH/EtOAc 19:1, 2. EtOH, size: 5.0 x 3.0 cm).

$C_{21}H_{26}O_2N_2$ [338.4]

yield: 48.7 mg (61 %), brown oil

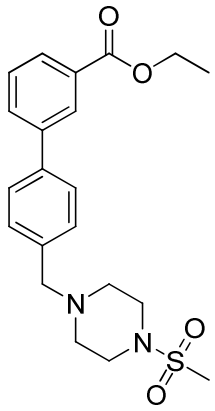
R_f (EtOH): 0.14

^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) = 8.16 (bs, 1H, Ar-H), 7.94 (d, ^3J = 7.8 Hz, 2H, Ar-H), 7.66-7.59 (m, 3H, Ar-H), 7.45-7.39 (m, 2H, Ar-H), 4.34 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.51 (s, 2H, CH_2), 3.06-3.02 (m, 2H, CH_2), 2.47-2.43 (m, 5H, CH_2, CH_3), 2.23-2.21 (m, 4H, 2 CH_2), 1.34 (t, ^3J = 7.2 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 165.5 (**C**=O), 140.4 ($\mathbf{C}_q$), 137.9 ($\mathbf{C}_q$), 137.7 ($\mathbf{C}_q$), 131.2 ($\mathbf{C}H_{Ar}$), 130.5 ($\mathbf{C}_q$), 129.5 (2 $\mathbf{C}H_{Ar}$), 129.4

	(**C**H_{Ar}), 127.8 (**C**H_{Ar}), 126.8 (**C**H_{Ar}), 126.5 (2 **C**H_{Ar}), 61.4 (**C**H_2), 60.8 (**C**H_2), 54.3 (**C**H_2), 52.0 (**C**H_2), 51.3 (**C**H_2), 45.3 (N-**C**H_3), 45.1 (N-**C**H_3), 42.8 (**C**H_2), 14.1 (**C**H_3) (Rotamere).
GC-MS (NM_50_S2):	t_R = 9.81 min (m/z = 338.3, 99 % M^+, BP: 267.1).
HRMS (EI^+):	*m/z*: calcd for $C_{21}H_{26}O_2N_2$ $[M]^+$: 338.1994; found 338.2012.

Ethyl 4`-((4-(methylsulfonyl)piperazin-1-yl)methyl)biphenyl-3-carboxylate (87e)



according to GP-8:

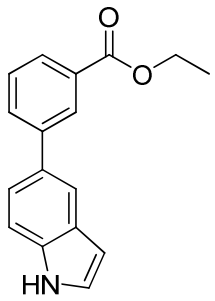
77.2 mg (470 µmol) 1-(methylsulfonyl)-piperazine, column chromatography (1. CH/EtOAc 19:1, 2. EE, size: 8.0 x 3.5 cm).

$C_{21}H_{26}O_4N_2S$ [402.5]

yield:	45.8 mg (48 %), colorless solid
R_f (CH/EtOAc 1:1):	0.33
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.27 (bs, 1H, Ar-H), 8.03 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.78-7.76 (m, 1H, Ar-H), 7.59 (d, ^3J = 8.1 Hz, 2H, Ar-H), 7.51 (t, ^3J = 7.8 Hz, 1H, Ar-H), 7.41 (d, ^3J = 8.1 Hz, 2H, Ar-H), 4.41 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.61 (s, 2H, CH_2), 3.27 (bs, 4H, 2 CH_2), 2.79 (s, 3H, N-CH_3), 2.60 (bs, 4H, 2 CH_2), 1.41 (t, ^3J = 7.2 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.5 (**C**=O), 144.9 ($\mathbf{C}_q$), 141.0 ($\mathbf{C}_q$), 139.4 ($\mathbf{C}_q$), 131.3 (2 $\mathbf{C}H_{Ar}$), 131.1 ($\mathbf{C}_q$), 129.6 ($\mathbf{C}H_{Ar}$), 128.8 ($\mathbf{C}H_{Ar}$), 128.3 ($\mathbf{C}H_{Ar}$), 128.1 ($\mathbf{C}H_{Ar}$), 127.2 (2 $\mathbf{C}H_{Ar}$), 62.2 ($\mathbf{C}H_2$), 61.1 ($\mathbf{C}H_2$), 52.3 ($\mathbf{C}H_2$), 45.9 ($\mathbf{C}H_2$), 34.2 (S-$\mathbf{C}H_3$), 14.3 ($\mathbf{C}H_3$).
M.p.:	97-98 °C
GC-MS (NM_100_L):	t_R = 16.26 min (m/z = 404.2, 99 % M^+, BP: 239.1).

Ethyl 3-(1*H*-indol-5-yl)-benzoate (90)



according to GP-6:

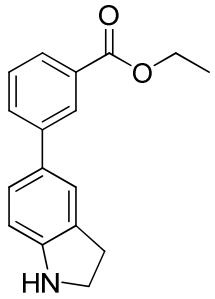
150 mg (765 µmol, 1.00 eq) 5-bromoindole **(88)**, 223 mg (1.145 mmol, 1.50 eq) 4-ethoxycarbonylphenylboronic acid **(89)**, 17.5 h reaction time, column chromatography (CH/EtOAc 8:1, size: 15.5 x 2.0 cm, 25 g silica gel).

$C_{17}H_{15}O_2N$ [265.3]

yield:	182.6 mg (90 %), colorless solid
R_f (CH/ EtOAc 8:1):	0.22
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.35 (t, ^4J = 1.5 Hz, 1H, Ar-H), 8.34 (bs, 1H, NH), 8.05 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.95 (s, 1H, Ar-H), 7.90-7.87 (m, 1H, Ar-H), 7.57-7.51 (m, 3H, Ar-H), 6.67 (t, ^4J = 2.4 Hz, 1H, Ar-H), 4.47 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.47 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.9 (**C**=O), 142.7 ($\mathbf{C}_q$), 135.5 ($\mathbf{C}_q$), 132.2 ($\mathbf{C}_q$), 131.7 ($\mathbf{C}H_{Ar}$), 130.8 ($\mathbf{C}_q$), 128.6 ($\mathbf{C}H_{Ar}$), 128.4

	(**C**H_{Ar}), 128.4 (**C**$_q$), 127.3 (**C**H_{Ar}), 125.0 (**C**H_{Ar}), 121.7 (**C**H_{Ar}), 119.3 (**C**H_{Ar}), 111.4 (**C**H_{Ar}), 103.0 (**C**H_{Ar}), 61.0 (**C**H_2), 14.4 (**C**H_3).
M.p.:	64-66 °C
GC-MS (NM_50_S2):	t_R = 9.12 min (m/z = 265.1, 99 % M^+, BP).
HRMS (EI^+):	*m/z*: calcd for $C_{17}H_{15}O_2N$ $[M]^+$: 265.1103; found 265.1089.

Ethyl 3-(indolin-5-yl)benzoate (91)



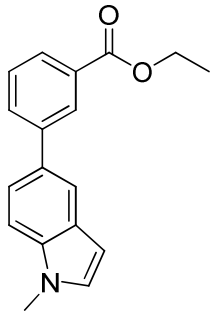
A 8 mL Schlenk tube was dried under vaccum, filled with nitrogen and charged with 60.0 mg (226 µmol, 1.00 eq) ethyl 3-(1*H*-indol-5-yl)-benzoate **(90)** and 0.5 mL glacial acetic acid, which was cooled to 0 °C (ice bath) and 21.4 mg (340 µmol, 1.50 eq) sodium cyanoborohydride were added at this temperature. The solution was stirred at rt over night. GC-MS analysis showed full conversion (99 % product) of the starting material. The mixture was hydrolyzed with 5 mL water, alkalized with 5 mL 3 M NaOH solution to pH 12 and extracted with DCM (3 x 10 mL). The combined organic layers were washed with 5 mL brine, dried over $MgSO_4$ and concentrated under reduced pressure. Final purification by column chromatography (CH/EtOAc 8:1, size: 13.0 x 2.0 cm, 8 g silica gel) yielded the pure product.

$C_{17}H_{17}O_2N$ [267.3]

yield:	27.5 mg (46 %), yellow solid
R_f (CH/ EtOAc 8:1):	0.13
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.21 (t, ^4J = 1.5 Hz, 1H, Ar-H), 7.93 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.72 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.47-

	7.41 (m, 2H, Ar-H), 7.32-7.29 (m, 1H, Ar-H), 6.72 (t, ^3J = 8.1 Hz, 1H, Ar-H), 4.41 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.63 (t, ^3J = 8.4 Hz, 2H, CH_2), 3.11 (t, ^3J = 8.4 Hz, 2H, CH_2), 1.41 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.8 (**C**=O), 151.3 ($\mathbf{C}_q$-N), 141.9 ($\mathbf{C}_q$), 130.9 ($\mathbf{C}_q$), 130.8 ($\mathbf{C}_q$), 130.7 ($\mathbf{C}H_{Ar}$), 130.2 ($\mathbf{C}_q$), 128.6 ($\mathbf{C}H_{Ar}$), 127.5 ($\mathbf{C}H_{Ar}$), 127.1 ($\mathbf{C}H_{Ar}$), 126.4 ($\mathbf{C}H_{Ar}$), 123.5 ($\mathbf{C}H_{Ar}$), 109.5 ($\mathbf{C}H_{Ar}$), 60.9 ($\mathbf{C}H_2$), 47.5 ($\mathbf{C}H_2$), 29.7 ($\mathbf{C}H_2$), 14.4 ($\mathbf{C}H_3$).
M.p.:	43 °C
GC-MS (NM_50_S2):	t_R = 8.82 min (m/z = 267.1, 95 % M^+, BP, 5 % starting material).

Ethyl 3-(1-methyl-1*H*-indol-5-yl)benzoate (92)

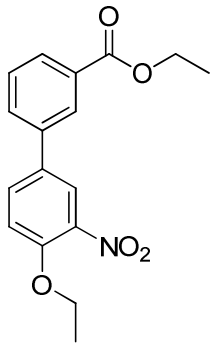


A 15 mL Schlenk tube was dried under vaccum, filled with nitrogen and charged with 82.0 mg (309 µmol, 1.00 eq) ethyl 3-(1*H*-indol-5-yl)-benzoate **(90)** and 1.0 mL absolute THF. The colorless solution was degassed by vacuum/N_2 cycles, 29.7 mg (1.24 mmol, 4.00 eq, hexane-washed) sodium hydride were added and the yellow solution was stirred first at rt for 3 d and then at 45 °C for 24 h. After addition of 38.5 µL (618 µmol, 2.00 eq) methyliodide the orange solution was stirred at 45 °C for 7 h. GC-MS analysis indicated full conversion of the starting material The mixture was concentrated under reduced pressure and the residue was dissolved in 10 mL water and 10 mL EtOAc. The layers were separated, the aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were concentrated. Purification by colum chromatography (CH/EtOAc 3:1, size: 7.0 x 3.0 cm, 15 g silica gel) yielded the product.

$C_{18}H_{17}O_2N$ [279.1]

yield:	9.0 mg (20 %), orange solid
R_f (CH/EtOAc 3:1):	0.51
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.34 (d, ^4J = 1.5 Hz, 1H, Ar-H), 7.97 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.88-7.83 (m, 2H, Ar-H), 7.50 (t, ^3J = 7.8 Hz, 2H, Ar-H), 7.40 (d, ^3J = 8.4 Hz, 1H, Ar-H), 7.10 (d, ^3J = 3.0 Hz, 1H, Ar-H), 6.55 (d, ^3J = 3.0 Hz, 1H, Ar-H), 4.41 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.84 (s, 3H, CH_3), 1.42 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.9 (**C**=O), 142.8 ($\mathbf{C}_q$), 136.5 ($\mathbf{C}_q$), 131.8 ($\mathbf{C}_q$), 131.7 ($\mathbf{C}H_{Ar}$), 130.9 ($\mathbf{C}_q$), 129.7 ($\mathbf{C}H_{Ar}$), 129.0 ($\mathbf{C}_q$), 128.7 ($\mathbf{C}H_{Ar}$), 128.4 ($\mathbf{C}H_{Ar}$), 127.4 ($\mathbf{C}H_{Ar}$), 121.3 ($\mathbf{C}H_{Ar}$), 119.6 ($\mathbf{C}H_{Ar}$), 109.6 ($\mathbf{C}H_{Ar}$), 101.4 ($\mathbf{C}H_{Ar}$), 61.0 ($\mathbf{C}H_2$), 33.0 (N-$\mathbf{C}H_3$), 14.4 ($\mathbf{C}H_3$).
GC-MS (NM_50_S2):	t_R = 9.02 min (m/z = 279.1, 97 % M^+, BP).

Ethyl 4-ethoxy-3`-nitrobiphenyl-3-carboxylate (93)



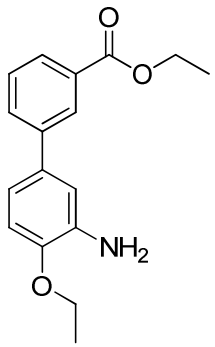
A 10 ml two-neck round-bottom flask with pressure compensation was charged with 500 mg (1.85 mmol, 1.00 eq) ethyl 4`-ethoxybiphenyl-3-carboxylate **(72e)** and 3.5 mL EtOH. The solution was cooled to 0 °C before 1.8 mL nitric acid were added dropwise at 0 °C. The orange suspension was stirred at 35 °C for 16 h. TLC analysis indicated no full conversion of the starting material. Additional 0.9 mL nitric acid were added at 0 °C and the suspension was stirred for further 3 d at 35 °C. The mixture was hydrolyzed by addition of 50 mL ice water and concentrated under reduced pressure. The orange residue was dissolved in 40 mL EtOAc

and washed with water (1 x 20 mL) and saturated aqueous $NaHCO_3$ solution (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Final purification by column chromatography (CH/EtOAc 15:1, size: 23.0 x 3.0 cm, 75 g silica gel) yielded the pure product.

$C_{17}H_{17}NO_5$ [315.1]

yield:	389.1 mg (67 %), yellow solid
R_f (CH/EtOAc 15:1):	0.11
^{1}H-NMR (300 MHz, MeOD):	δ (ppm) = 8.24 (t, ^4J = 1.5 Hz, 1H, Ar-H), 8.07 (d, ^4J = 2.4 Hz, 1H, Ar-H), 8.03-8.00 (m, 1H, Ar-H), 7.91-7.85 (m, 2H, Ar-H), 7.58 (t, ^3J = 7.2 Hz, 1H, Ar-H), 7.37 (d, ^3J = 8.7 Hz, 1H, Ar-H), 4.40 (q, ^3J = 7.2 Hz, 2H, CH_2), 4.27 (q, ^3J = 7.2 Hz, 2H, CH_2), 1.48-1.39 (m, 6H, CH_3).
^{13}C-NMR (75.5 MHz, MeOD):	δ (ppm) = 167.8 (**C**=O), 152.9 ($\mathbf{C}_q$), 140.3 ($\mathbf{C}_q$), 133.7 ($\mathbf{C}_q$), 133.3 ($\mathbf{C}H_{Ar}$), 132.6 ($\mathbf{C}_q$), 132.3 ($\mathbf{C}H_{Ar}$), 130.5 ($\mathbf{C}H_{Ar}$), 129.7 ($\mathbf{C}H_{Ar}$), 128.5 ($\mathbf{C}H_{Ar}$), 124.3 ($\mathbf{C}H_{Ar}$), 116.6 ($\mathbf{C}H_{Ar}$), 66.7 ($\mathbf{C}H_2$), 62.4 ($\mathbf{C}H_2$), 14.9 ($\mathbf{C}H_3$), 14.6 ($\mathbf{C}H_3$).
M.p.:	104 °C
GC-MS (NM_50_S2):	t_R = 7.76 min (m/z = 315.1, 99 % M^+, BP: 207.1).

Ethyl 3`-amino-4`-ethoxybiphenyl-3-carboxylate (94)



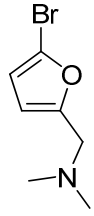
A 10 mL three-neck round-bottom flask was dried under vaccum, filled with nitrogen and charged with 25.0 mg (79.0 µmol, 1.00 eq) ethyl 4-ethoxy-3`-nitrobiphenyl-3-carboxylate **(93),** 2.4 mL absolute EtOH and 0.5 mL anhydrous EtOAc. To this yellow solution 5.4 mg

platinum on activated charcoal (5 % Pt) were added and the solution was degassed by vacuum/H_2 cycles. The mixture was stirred at rt over night under H_2 stream. TLC analysis showed no full conversion of the starting material. The temperature was increased to 40 °C and the solution was stirred for further 24 h. After filtration through a pad of celite under argon atmosphere, elution with DCM and removal of the solvent under reduced pressure the crude product was obtained. Final purification by column chromatography (CH/EtOAc 40:1 → 3:1, size: 14.0 x 2.0 cm, 25 g silica gel) yielded the pure product.

$C_{17}H_{19}NO_3$ [285.3]

yield:	11.7 mg (52 %), yellow solid
R_f (CH/EtOAc 3:1):	0.45
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.08 (s, 1H, Ar-H), 7.88-7.79 (m, 2H, Ar-H), 7.55 (t, ^3J = 7.8 Hz, 1H, Ar-H), 6.98 (d, ^4J = 2.1 Hz, 1H, Ar-H), 6.89-6.84 (m, 2H, Ar-H), 4.85 (s, 2H, NH_2), 4.34 (q, ^3J = 6.9 Hz, 2H, CH_2), 4.04 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.39-1.32 (m, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 168.3 (**C**=O), 148.5 (**C**$_q$), 143.2 (**C**$_q$), 138.4 (**C**$_q$), 134.1 (**C**$_q$), 132.2 (**C**H$_{Ar}$), 132.0 (**C**$_q$), 129.9 (**C**H$_{Ar}$), 128.4 (2 **C**H$_{Ar}$), 118.2 (**C**H$_{Ar}$), 115.1 (**C**H$_{Ar}$), 113.0 (**C**H$_{Ar}$), 65.1 (**C**H$_2$), 62.3 (**C**H$_2$), 15.3 (**C**H$_3$), 14.7 (**C**H$_3$).
M.p.:	44 °C
GC-MS (NM_100_L):	t_R = 7.39 min (m/z = 285.1, 99 % M^+, BP: 256.1).

1-(5-Bromofuran-2-yl)-*N*,*N*-dimethylmethanamine (96a) [135]



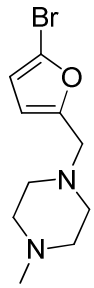
A 100 mL Schlenk tube was dried under vacuum and flushed with nitrogen and charged with 300 mg (1.71 mmol, 1.00 eq) 5-bromo-2-furancarboxaldehyde **(95)**, 860 µL (1.71 mmol, 1.00

eq, 2.0 M in THF) dimethylamine and 9.0 mL DCE. 726 mg (3.43 mmol, 2.00 eq) sodiumtriacetoxyboro-hydride and 170 µL acetic acid were added and the suspension was stirred at rt for 4 h. GC-MS analysis indicated full conversion of the starting material and the mixture was concentrated under reduced pressure. The residue was dissolved in 20 mL DCM and washed with 20 mL saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and the solvent was removed at the rotary evaporator to yield the product, which was used for the next reaction without further purification.

$C_7H_{10}ONBr$ [204.0]

yield:	261.8 mg (75 %), red liquid
R_f (EtOAc):	0.18
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 6.48 (d, ^3J = 3.3 Hz, 1H, Ar-H), 6.34 (d, ^3J = 3.0 Hz, 1H, Ar-H), 3.39 (s, 2H, CH_2), 2.13 (s, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 154.7 (**C**$_q$), 119.9 (**C**$_q$-Br), 112.0 (**C**H$_{Ar}$), 111.3 (**C**H$_{Ar}$), 54.7 (**C**H$_2$), 44.3 (2 **C**H$_3$).
GC-MS (NM_50_S2):	t_R = 4.37 min (m/z = 204.0, 99 % M^+, BP: 158.9).

1-(5-Bromofuran-2-yl)-4-methylpiperazine (96b)



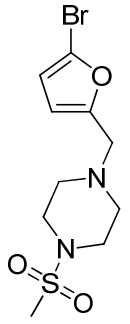
A 100 mL Schlenk tube was dried under vacuum flushed with nitrogen and charged with 300 mg (1.71 mmol, 1.00 eq) 5-bromo-2-furancarboxaldehyde **(95)**, 190 µL (1.71 mmol, 1.00 eq) 1-methylpiperazine and 9.0 mL DCE. 726 mg (3.43 mmol, 2.00 eq) sodiumtriacetoxyborohydride and 170 µL acetic acid were added and the suspension was stirred at rt for 4 h. GC-MS analysis indicated full conversion of the starting material and the mixture was concentrated under reduced pressure. The residue was dissolved in 20 mL DCM

and washed with 20 mL saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and the solvent was removed at the rotary evaporator to yield the product, which was used for the next reaction without further purification.

$C_{10}H_{15}ON_2Br$ [259.1]

yield:	410.2 mg (92 %), yellow solid
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 6.48 (d, ^3J = 3.3 Hz, 1H, Ar-H), 6.34 (d, ^3J = 3.3 Hz, 1H, Ar-H), 3.44 (s, 2H, CH_2), 2.36-2.29 (m, 8H, 4 CH_2), 2.13 (s, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 154.2 (**C**$_q$), 120.0 (**C**$_q$-Br), 112.0 (**C**H$_{Ar}$), 111.6 (**C**H$_{Ar}$), 54.4 (2 **C**H$_2$), 53.7 (**C**H$_2$), 51.9 (2 **C**H$_2$), 45.6 (**C**H$_3$).
M.p.:	68-71 °C
GC-MS (NM_100_L):	t_R = 4.71 min (m/z = 259.1, 99 % M^+, BP: 56.1).

1-((5-Bromofuran-2-yl)methyl)-4-(methylsulfonyl)piperazine (96c)



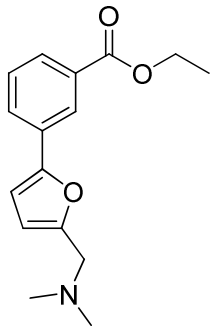
A 100 mL Schlenk tube was dried under vacuum flushed with nitrogen and charged with 300 mg (1.71 mmol, 1.00 eq) 5-bromo-2-furancarboxaldehyde **(95)**, 282 mg (1.71 mmol, 1.00 eq) 1-(methylsulfonyl)-piperazine and 9.0 mL DCE. 726 mg (3.43 mmol, 2.00 eq) sodiumtriacetoxyborohydride and 170 µL acetic acid were added and the suspension was stirred at rt for 4 h. GC-MS analysis indicated full conversion of the starting material and the mixture was concentrated under reduced pressure. The residue was dissolved in 20 mL DCM and washed with 20 mL saturated $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$

and the solvent was removed at the rotary evaporator to yield the product, which was used for the next reaction without further purification.

$C_{10}H_{15}O_3N_2BrS$ [323.2]

yield:	536.3 mg (97 %), light orange solid
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 6.50 (d, ^3J = 3.0 Hz, 1H, Ar-H), 6.39 (d, ^3J = 3.0 Hz, 1H, Ar-H), 3.54 (s, 2H, CH_2), 3.12-3.08 (m, 4H, 2 CH_2), 2.86 (s, 3H, CH_3), 2.51-2.45 (m, 4H, 2 CH_2).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 153.7 (**C**$_q$), 120.2 (**C**$_q$-Br), 112.1 (**C**H$_{Ar}$), 111.9 (**C**H$_{Ar}$), 53.2 (**C**H$_2$), 51.2 (2 **C**H$_2$), 45.2 (2 **C**H$_2$), 33.6 (**C**H$_3$).
M.p.:	125-128 °C
GC-MS (NM_100_L):	t_R = 6.47 min (m/z = 323.1, 99 % M^+, BP: 161.0).

Ethyl 3-(5-((dimethylamino)methyl)furan-2-yl)benzoate (97a)



according to GP-6:

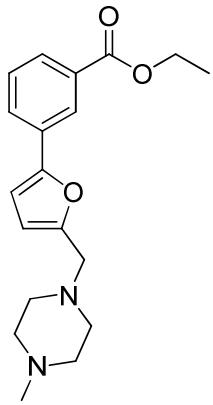
231 mg (1.13 mmol, 1.00 eq) 1-(5-bromofuran-2-yl)-*N*,*N*-dimethylmethanamine **(96a)**, 330 mg (1.70 mmol, 1.50 eq) 3-ethoxycarbonylphenylboronic acid **(89)**, reaction over night, column chromatography (1. CH/EtOAc 1:1, 2. EtOH, size: 2.0 x 17.0 cm, 20 g silica gel).

$C_{16}H_{19}O_3N$ [273.1]

yield:	209.9 mg (68 %), yellow oil

R_f (EtOH):	0.42
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.18 (s, 1H, Ar-H), 7.95-7.92 (m, 1H, Ar-H), 7.84 (dd, ^4J = 1.2 Hz, ^3J = 7.8 Hz, 1H, Ar-H), 7.56 (t, ^3J = 7.8 Hz, 1H, Ar-H), 7.01 (d, ^3J = 3.0 Hz, 1H, Ar-H), 6.42 (d, ^3J = 3.3 Hz, 1H, Ar-H), 4.35 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.49 (s, 2H, CH_2), 2.19 (s, 6H, 2 CH_3), 1.34 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 165.4 (**C**=O), 152.9 ($\mathbf{C}_q$), 151.1 ($\mathbf{C}_q$), 130.7 ($\mathbf{C}_q$), 130.5 ($\mathbf{C}_q$), 129.3 ($\mathbf{C}H_{Ar}$), 127.6 ($\mathbf{C}H_{Ar}$), 127.5 ($\mathbf{C}H_{Ar}$), 123.1 ($\mathbf{C}H_{Ar}$), 110.8 ($\mathbf{C}H_{Ar}$), 107.4 ($\mathbf{C}H_{Ar}$), 60.8 ($\mathbf{C}H_2$), 55.0 ($\mathbf{C}H_2$), 44.4 (2 $\mathbf{C}H_3$), 14.1 ($\mathbf{C}H_3$).
GC-MS (NM_50_S2):	t_R = 7.40 min (m/z = 273.1, 99 % M^+, BP: 229.1).
HRMS (EI^+):	*m/z*: calcd for $C_{16}H_{19}O_3N$ $[M]^+$: 273.1365; found 273.1367.

Ethyl 3-(5-((4-methylpiperazin-1-yl)methyl)furan-2-yl)benzoate (97b)



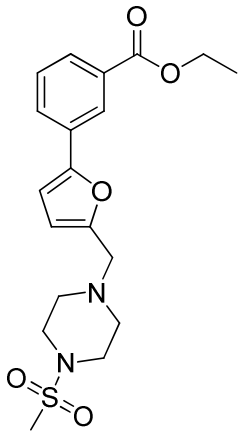
according to GP-6:

250 mg (966 µmol, 1.00 eq) 1-(5-bromofuran-2-yl)-4-methylpiperazine **(96b)**, 281 mg (1.45 mmol, 1.50 eq) 3-ethoxycarbonylphenylboronic acid **(89)**, reaction over night, column chromatography (EtOH, size: 1.5 x 14.5 cm, 15 g silica gel).

$C_{19}H_{24}O_3N_2$ [328.4]

yield:	139.0 mg (44 %), yellow oil
R_f (EtOH):	0.16
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.18 (s, 1H, Ar-H), 7.93 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.84 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.56 (t, ^3J = 7.8 Hz, 1H, Ar-H), 7.00 (d, ^3J = 3.3 Hz, 1H, Ar-H), 6.42 (d, ^3J = 3.3 Hz, 1H, Ar-H), 4.35 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.55 (s, 2H, CH_2), 2.43-2.31 (m, 8 H, 4 CH_2), 2.13 (s, 3H, CH_3), 1.34 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 165.4 (**C**=O), 152.4 ($\mathbf{C}_q$), 151.1 ($\mathbf{C}_q$), 130.7 ($\mathbf{C}_q$), 130.5 ($\mathbf{C}_q$), 129.3 ($\mathbf{C}H_{Ar}$), 127.7 ($\mathbf{C}H_{Ar}$), 127.6 ($\mathbf{C}H_{Ar}$), 123.2 ($\mathbf{C}H_{Ar}$), 111.1 ($\mathbf{C}H_{Ar}$), 107.5 ($\mathbf{C}H_{Ar}$), 60.8 ($\mathbf{C}H_2$), 54.5 (2 $\mathbf{C}H_2$), 53.9 ($\mathbf{C}H_2$), 52.1 (2 $\mathbf{C}H_2$), 45.6 ($\mathbf{C}H_3$), 14.1 ($\mathbf{C}H_3$).
GC-MS (NM_50_S2):	t_R = 8.80 min (m/z = 328.2, 99 % M^+, BP: 257.1).
HRMS (EI^+):	*m/z*: calcd for $C_{19}H_{24}O_3N_2$ $[M]^+$: 328.1787; found 328.1808.

Ethyl 3-(5-((4-(methylsulfonyl)piperazin-1-yl)methyl)furan-2-yl)benzoate (97c)



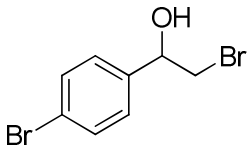
according to GP-6:

250 mg (774 µmol, 1.00 eq) 1-((5-bromofuran-2-yl)methyl)-4-(methylsulfonyl)piperazine **(96c)**, 225 mg (1.16 mmol, 1.50 eq) 3-ethoxycarbonylphenylboronic acid **(89)**, reaction over night, column chromatography (EtOAc, size: 1.5 x 17.0 cm, 17 g silica gel).

$C_{19}H_{24}O_5N_2S$ [392.4]

yield:	225.1 mg (74 %), orange solid
R_f (EtOAc):	0.22
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.19 (s, 1H, Ar-H), 7.95 (dd, ^4J = 1.5 Hz, ^3J = 7.8 Hz, 1H, Ar-H), 7.86-7.84 (m, 1H, Ar-H), 7.56 (t, ^3J = 7.8 Hz, 1H, Ar-H), 7.02 (d, ^3J = 3.3 Hz, 1H, Ar-H), 6.46 (d, ^3J = 3.3 Hz, 1H, Ar-H), 4.35 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.64 (s, 2H, CH_2), 3.14-3.11 (m, 4 H, 2 CH_2), 2.86 (s, 3H, CH_3), 2.55-2.49 (m, 4 H, 2 CH_2), 1.34 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 165.4 (**C**=O), 151.9 (**C**$_q$), 151.4 (**C**$_q$), 130.6 (**C**$_q$), 130.5 (**C**$_q$), 129.3 (**C**H$_{Ar}$), 127.7 (**C**H$_{Ar}$), 127.6 (**C**H$_{Ar}$), 123.2 (**C**H$_{Ar}$), 111.4 (**C**H$_{Ar}$), 107.5 (**C**H$_{Ar}$), 60.8 (**C**H$_2$), 53.5 (**C**H$_2$), 51.3 (2 **C**H$_2$), 45.2 (2 **C**H$_2$), 33.6 (**C**H$_3$), 14.1 (**C**H$_3$).
M.p.:	120-122 °C
GC-MS (NM_100_L):	t_R = 12.07 min (m/z = 392.1, 99 % M^+, BP: 229.1).

2-Bromo-1-(4-bromophenyl)ethanol (99) [136]



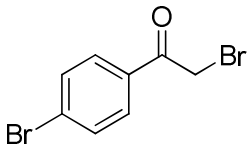
A 50 mL one-neck round-bottom flask was charged with 500 mg (360 µL, 2.73 mmol, 1.00 eq) 4-bromostyrene **(98)**, 11.0 mL acetone and 21.1 mg (274 µmol, 0.10 eq) ammonium acetate. A solution of 535 mg (3.01 mmol, 1.10 eq) *N*-bromosuccinimide in 2.7 mL water was added and the yellow solution was stirred at rt for 2 h. GC-MS analysis indicated 95 % conversion of the starting material. The mixture was concentrated under reduced pressure and the residue was dissolved in 20 mL EtOAc and 20 mL water. The layers were separated and the organic phase was washed with 20 mL water. The combined organic layers were dried

over Na_2SO_4 and the solvent was removed under reduced pressure. Final purification by silica gel filtration (1. CH, 2. CH/EtOAc 1:1) yielded the product with 94 % purity.

$C_8H_8OBr_2$ [280.0]

yield:	702.0 mg (92 %), yellow solid
R_f (CH/EtOAc 1:1):	0.78
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.51 (d, ^3J = 8.4 Hz, 2H, Ar-H), 7.26 (d, ^3J = 8.4 Hz, 2H, Ar-H), 4.91-4.87 (m, 1H, CH), 3.64-3.46 (m, 2H, CH_2).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 139.2 (**C**$_q$), 131.8 (**C**H$_{Ar}$), 127.7 (**C**H$_{Ar}$), 122.4 (**C**$_q$-Br), 73.1 (**C**H), 39.8 (**C**H$_2$).
M.p.:	63-65 °C
GC-MS (NM_50_S2):	t_R = 6.26 min (m/z = 279.9, 94 % M^+, BP: 185.0).

2-Bromo-1-(4-bromophenyl)ethanone (101)

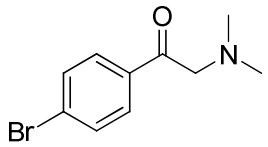


A 50 mL one-neck round-bottom flask was charged with 659 mg (2.35 mmol, 1.00 eq) 2-bromo-1-(4-bromophenyl)ethanol **(99)** and 9.5 mL DCE. The mixture was cooled to 0 °C and a solution of 355 mg (2.35 mmol, 1.00 eq) sodium bromate, 59.9 mg (588 µmol, 0.25 eq) sodium bromide in 4.8 mL water was added dropwise. 1.86 mL conc. H_2SO_4 were added and the two phase system was stirred at rt for 4.5 h ensuring that the phases were maintained separate (Schotten-Baumann conditions). TLC analysis indicated full conversion of the starting material. The mixture was washed with 20 mL water and the organic layer was washed with 20 mL $Na_2S_2O_3$ solution (50 % in water). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to yield the pure product.

$C_8H_6OBr_2$ [277.9]

yield:	640.1 mg (98 %), yellow solid
R_f (CH/EtOAc 19:1):	0.42
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 7.93 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.78 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.93 (s, 2H, CH_2).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 190.9 (**C**=O), 132.9 ($\mathbf{C}_q$), 131.8 (2 $\mathbf{C}H_{Ar}$), 130.6 (2 $\mathbf{C}H_{Ar}$), 127.9 ($\mathbf{C}_q$-Br), 33.9 ($\mathbf{C}H_2$).
M.p.:	107-110 °C
GC-MS (NM_50_S2):	t_R = 6.19 min (m/z = 277.9, 98 % M^+, BP: 183.0).

1-(4-Bromophenyl)-2-(dimethylamino)ethanone (102)



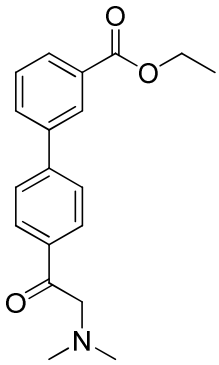
A 20 mL Schlenk tube was flushed with nitrogen and charged with 85.0 mg (306 µmol, 1.00 eq) 2-bromo-1-(4-bromophenyl)ethanone **(101)** and 1.0 mL absolute THF. The yellow solution was cooled to 0 °C and 310 µL (612 µmol, 2.00 eq, 2.0 M in THF) dimethylamine was added dropwise. The yellow suspension was stirred at rt for 2.5 h. GC-MS analysis indicated full conversion of the starting material and the reaction mixture was concentrated under reduced pressure. The yellow oily residue was dissolved in 10 mL water and 10 mL DCM, the layers were separated and the aqueous layer was extracted with 10 mL DCM a second time. The combined organic layers were dried over Na_2SO_4 and the solvent was removed at the rotary evaporator to yield the product, which was contaminated with BHT, the stabilizer of THF. The product was used with this impurity in the next step, where it could be removed by column chromatography.

$C_{10}H_{12}ONBr$ [242.1]

yield:	98.1 mg (> 99 %), yellow oil (BHT as impurity)
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 7.91 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.73 (d, ^3J = 8.7 Hz, 2H, Ar-H), 3.77 (s, 2H, CH_2), 2.26 (s, 6H, 2 CH_3).

GC-MS (NM_50_S2): t_R = 5.99 min (m/z = 242.1, 99 % M^+, BP: 58.1).

Ethyl 4`-(2-(dimethylamino)acetyl)biphenyl-3-carboxylate (103)



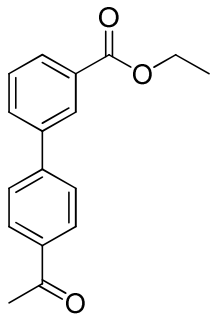
according to GP-6:

70.0 mg (289 µmol, 1.00 eq) 1-(4-bromophenyl)-2-(dimethylamino)ethanone **(102)**, 84.1 mg (434 µmol, 1.50 eq) 3-ethoxycarbonylphenylboronic acid **(89)**, reaction over night, column chromatography (1. CH/EtOAc 1:1, 2. EtOAc, 3. EtOH, size: 15.0 x 2.5 cm, 20 g silica gel).

$C_{19}H_{21}O_3N$ [311.3]

yield:	11.3 mg (13 %), yellow oil
R_f (EtOH):	0.29
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.30 (s, 1H, Ar-H), 8.09-8.06 (m, 3H, Ar-H), 7.81-7.78 (m, 1H, Ar-H), 7.70 (d, ^3J = 8.4 Hz, 2H, Ar-H), 7.57-7.52 (m, 1H, Ar-H), 4.42 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.92 (s, 2H, CH_2), 2.49 (s, 6H, 2 CH_3), 1.42 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 204.2 (C=O), 166.3 (**C**=O), 145.0 ($\mathbf{C}_q$), 140.1 ($\mathbf{C}_q$), 134.8 ($\mathbf{C}_q$), 131.5 ($\mathbf{C}H_{Ar}$), 131.5 ($\mathbf{C}_q$), 129.3 ($\mathbf{C}H_{Ar}$), 129.0 ($\mathbf{C}H_{Ar}$), 128.8 (2 $\mathbf{C}H_{Ar}$), 128.3 ($\mathbf{C}H_{Ar}$), 127.3 (2 $\mathbf{C}H_{Ar}$), 64.9 ($\mathbf{C}H_2$), 61.2 ($\mathbf{C}H_2$), 45.4 (N($\mathbf{C}H_3$)$_2$), 14.3 ($\mathbf{C}H_3$).

Ethyl 4`-acetylbiphenyl-3-carboxylate (105)



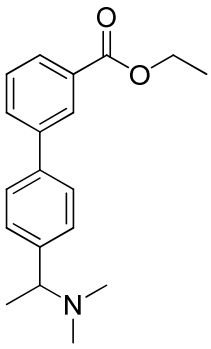
according to GP-6:

300 mg (1.51 mmol, 1.00 eq) 4-bromoacetophenone **(104)**, 438 mg (2.26 mmol, 1.50 eq) 3-ethoxycarbonylphenylboronic acid **(89)**, 3.5 h reaction time, column chromatography (CH/EtOAc 19:1, size: 2.5 x 13.0 cm, 25 g silica gel).

$C_{17}H_{16}O_3$ [268.3]

yield:	333.0 mg (82 %), yellow solid
R_f (CH/ EtOAc 19:1):	0.23
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.24 (s, 1H, Ar-H), 8.08-8.00 (m, 4H, Ar-H), 7.76-7.72 (m, 1H, Ar-H), 7.85 (d, ^3J = 8.4 Hz, 2H, Ar-H), 7.66 (t, ^3J = 7.8 Hz, 1H, Ar-H), 4.35 (q, ^3J = 7.2 Hz, 2H, CH_2), 2.62 (s, 3H, CH_3), 1.35 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 197.3 (**C**=O), 165.4 (**C**=O), 143.3 ($\mathbf{C}_q$), 139.3 ($\mathbf{C}_q$), 135.9 ($\mathbf{C}_q$), 131.6 ($\mathbf{C}H_{Ar}$), 130.6 ($\mathbf{C}_q$), 129.5 ($\mathbf{C}H_{Ar}$), 128.9 (2 $\mathbf{C}H_{Ar}$), 128.8 ($\mathbf{C}H_{Ar}$), 127.2 ($\mathbf{C}H_{Ar}$), 126.9 (2 $\mathbf{C}H_{Ar}$), 60.8 ($\mathbf{C}H_2$), 26.7 ($\mathbf{C}H_3$), 14.0 ($\mathbf{C}H_3$).
M.p.:	57–59 °C
GC-MS (NM_50_S2):	t_R = 8.02 min (m/z = 268.1, 99 % M^+, BP: 253.0).

Ethyl 4`-(1-dimethylamino)ethyl)biphenyl-3-carboxylate (106a)



A 10 mL Schlenk tube was dried under vacuum flushed with nitrogen and charged with 60.0 mg (224 µmol, 1.00 eq) ethyl 4`-acetylbiphenyl-3-carboxylate **(105)**, 0.3 mL absolute THF and 560 µL (1.12 mmol, 5.00 eq, 2.0 M in THF) dimethylamine. To the yellow solution 62.3 µL acetic acid and 14.1 mg (224 µmol, 1.00 eq) sodiumcyanoborohydride were added and the yellow suspension was stirred at 65 °C for 4 d. GC-MS analysis indicated full conversion of the starting material and the mixture was concentrated under reduced pressure. The residue was dissolved in 10 mL 4 M HCl solution and extracted with EtOAc (3 x 15 mL). The aqueous layer was alkalized with solid K_2CO_3 to ph 10 and once more extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed at the rotary evaporator. Purification by silica gel filtration (1. EtOAc, 2. EtOH) yielded the product.

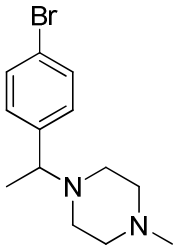
$C_{19}H_{23}O_2N$ [297.3]

yield:	15.5 mg (23 %), colorless oil
R_f (EtOH):	0.13
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.28 (d, ^4J = 1.8 Hz, 1H, Ar-H), 8.02-8.00 (m, 1H, Ar-H), 7.78 (dd, ^3J = 7.8 Hz, ^4J = 0.9 Hz, 1H, Ar-H), 7.58 (d, ^3J = 8.4 Hz, 2H, Ar-H), 7.50 (t, ^3J = 7.8 Hz, 1H, Ar-H), 7.39 (d, ^3J = 8.4 Hz, 2H, Ar-H), 4.40 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.30 (q, ^3J = 6.6 Hz, 1H, CH), 2.23 (s, 6H, 2 CH_3), 1.44-1.39 (m, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.6 (**C**=O), 143.8 ($\mathbf{C}_q$), 141.2 ($\mathbf{C}_q$), 138.8 ($\mathbf{C}_q$), 131.3 ($\mathbf{C}H_{Ar}$), 131.0 ($\mathbf{C}_q$), 128.7 ($\mathbf{C}H_{Ar}$), 128.2 ($\mathbf{C}H_{Ar}$), 128.1 ($\mathbf{C}H_{Ar}$), 128.0 (2 $\mathbf{C}H_{Ar}$), 127.0 (2 $\mathbf{C}H_{Ar}$),

65.6 (**C**H), 61.0 (**C**H_2), 43.2 (N(**C**H_3)$_2$), 20.2 (**C**H_3), 14.4 (**C**H_3).

GC-MS (NM_50_S2): t_R = 8.11 min (m/z = 297.1, 99 % M^+, BP: 282.1).

1-(1-(4-Bromophenyl)ethyl)-4-methylpiperazine (107)



A 20 mL Schlenk tube was flushed with nitrogen and charged with 200 mg (1.01 mmol, 1.00 eq) 4-bromoacetophenone **(104)**, 1.0 mL absolute THF and 2.50 mL (5.02 mmol, 5.00 eq, 2.0 M in THF) 1-methylpiperazine. To the colorless solution 0.28 mL acetic acid and 63.1 mg (1.01 mmol, 1.00 eq) sodiumcyanoborohydride were added and the yellow suspension was stirred at rt for 10 d before the suspension was heated up to 65 °C and further stirring at this temperature for 24 h. GC-MS analysis indicated full conversion of the starting material and the mixture was concentrated under reduced pressure. The residue was dissolved in 10 mL 4 M HCl solution and extracted with EtOAc (3 x 15 mL). The aqueous layer was alkalized with solid K_2CO_3 to ph 10 and once more extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed at the rotary evaporator to yield the product.

$C_{13}H_{19}N_2Br$ [283.2]

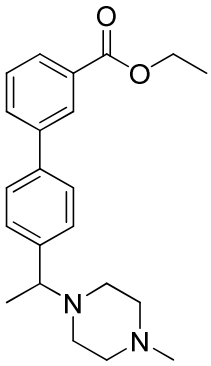
yield: 200.9 mg (71 %), light yellow solid

^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) = 7.48 (d, ^3J = 8.4 Hz, 2H, Ar-H), 7.24 (d, ^3J = 8.4 Hz, 2H, Ar-H), 3.33 (q, ^3J = 6.6 Hz, 1H, CH), 2.99-2.95 (m, 1H, CH), 2.75-2.71 (m, 1H, CH), 2.26 (bs, 4H, 2 CH_2), 2.16 (s, 2H, CH_2), 2.10 (s, 3H, N-CH_3), 1.2 (d, ^3J = 6.6 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 143.3 (**C**$_q$), 130.9 (2 **C**H$_{Ar}$), 129.4 (2 **C**H$_{Ar}$), 119.5 (**C**$_q$-Br), 62.9 (**C**H), 54.9 (**C**H$_2$), 52.4 (**C**H$_2$), 49.9 (**C**H$_2$), 49.6 (**C**H$_2$), 45.6, 45.3 (N-**C**H$_3$), 19.2 (**C**H$_3$). (Rotamere)

GC-MS (NM_50_S2): t_R = 6.78 min (m/z = 283.1, 99 % M^+, BP: 99.1).

Ethyl 4`-(1-(4-methylpiperazin-1-yl)ethyl)biphenyl-3-carboxylate (106b)



according to GP-6:

75.0 mg (265 µmol, 1.00 eq) 1-(1-(4-bromophenyl)ethyl)-4-methylpiperazine **(107)**, 77.1 mg (397 µmol, 1.50 eq) 3-ethoxycarbonylphenylboronic acid **(89)**, 4 h reaction time, column chromatography (1. EtOAc, 2. EtOH, size: 14.0 x 2.0 cm, 20 g silica gel).

$C_{22}H_{28}O_2N_2$ [352.4]

yield: 54.9 mg (59 %), colorless oil

R_f (EtOH): 0.11

^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) = 8.17 (s, 1H, Ar-H), 7.95-7.92 (m, 2H, Ar-H), 7.65-7.61 (m, 3H, Ar-H), 7.40 (d, ^3J = 8.1 Hz, 2H, Ar-H), 4.34 (q, ^3J = 7.2 Hz, 2H, CH$_2$), 3.40-3-34 (m, 1H, CH), 2.29 (bs, 8H, 4 CH$_2$), 2.11 (s, 3H, CH$_3$), 1.34 (t, ^3J = 7.2 Hz, 3H, CH$_3$), 1.29 (d, ^3J = 6.6 Hz, 3H, CH$_3$).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 165.5 (**C**=O), 143.7 (**C**$_q$), 140.4 (**C**$_q$), 137.4 (**C**$_q$), 131.2 (**C**H$_{Ar}$), 130.5 (**C**$_q$), 129.3 (**C**H$_{Ar}$), 128.0 (2 **C**H$_{Ar}$), 127.7 (**C**H$_{Ar}$), 126.9 (**C**H$_{Ar}$), 126.5 (2 **C**H$_{Ar}$), 63.4

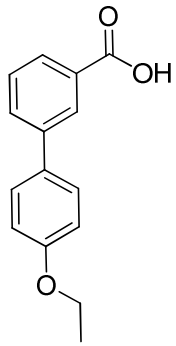
(**C**H), 60.7 (**C**H_2), 54.9 (2 **C**H_2), 49.7 (**C**H_2), 45.6 (**C**H_3), 19.4 (**C**H_3), 14.1 (**C**H_3).

GC-MS (NM_50_S2): t_R = 10.02 min (m/z = 352.2, 97 % M^+, BP: 99.1).

6.3.7. Diversification of the ethylester functionality

6.3.7.1. Esters

4`-Ethoxybiphenyl-3-carboxylic acid (109)



500 mg (2.49 mmol, 1.00 eq) 3-bromobenzoic acid **(108)**, 413 mg (2.49 mmol, 1.00 eq) 4-ethoxyphenylboronic acid **(71)**, 1.17 g (7.72 mmol, 3.10 eq) CsF, 102 mg (124 µmol, 0.05 eq) $PdCl_2$(dppf)*DCM and 20.0 mL anhydrous DME. The orange suspension was degassed by vacuum/N_2 cycles and stirred at 80 °C for 9 h. TLC analysis (DCM/MeOH 9:1) indicated full conversion of the starting material. The reaction mixture was hydrolyzed with 6 mL 5 % HCl solution, extracted with EtOAc (2 x 5 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure and final purification by column chromatography (DCM/MeOH 20:1, size: 17.0 x 2.0 cm, 25 g silica gel) yielded the pure product.

$C_{15}H_{14}O_3$ [242.3]

yield: 576.9 mg (96 %), brown solid

R_f (DCM/MeOH 20:1): 0.33

^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) = 13.05 (s, 1H, OH), 8.13 (s, 1H, Ar-H), 7.89-7.85 (m, 2H, Ar-H), 7.82 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.56

(t, ^3J = 7.8 Hz, 1H, Ar-H), 7.03 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.07 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.35 (t, ^3J = 6.9 Hz, 3H, CH_3).

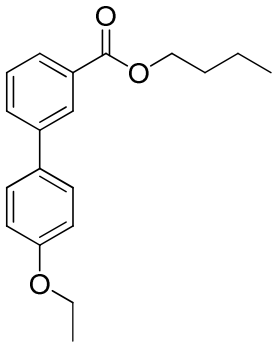
^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 167.1 (**C**=O), 158.3 (**C**H_{Ar}), 140.0 (**C**$_q$), 135.4 (**C**$_q$), 131.2 (**C**H_{Ar}), 130.4 (**C**H_{Ar}), 129.1 (**C**H_{Ar}), 127.7 (2 **C**H_{Ar}), 127.4 (**C**$_q$), 126.6 (**C**$_q$), 114.8 (2 **C**H_{Ar}), 63.0 (**C**H_2), 14.5 (**C**H_3).

M.p.: 144-146 °C

General procedure (GP-7):

A 8 mL Schlenk tube was dried under vacuum filled, with nitrogen and charged with 60.0 (250 µmol, 1.00 eq) 4`-ethoxybiphenyl-3-carboxylic acid **(109)** and 14.00 eq of the diverse alcohols (*n*-BuOH, hexanol, 2-methoxyethanol, trifluoroethanol). 40.0 µL (740 µmol, 3.00 eq) conc. H_2SO_4 were added and the brown suspension was refluxed for 3-5 h until TLC (DCM/MeOH 20:1, CH/EtOAc 3:1) indicated full conversion of the starting material. The mixture was hydrolyzed with 3 mL saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Final purification by silica gel filtration or column chromatography and drying under high vacuum yielded the pure product.

Butyl 4`-ethoxybiphenyl-3-carboxylate (110a)



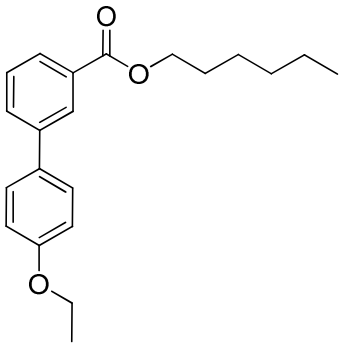
according to GP-7:

320 µL (3.47 mmol) *n*-BuOH, refluxing for 3 h, TLC analysis (DCM/MeOH 20:1, R_f = 0.96), silica gel filtration (CH/EtOAc 3:1).

$C_{19}H_{22}O_3$ [298.3]

yield:	63.3 mg (86 %), light yellow solid
R_f (CH/ EtOAc 3:1):	0.76
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.23 (d, ^4J = 1.5 Hz, 1H, Ar-H), 8.00-7.96 (m, 1H, Ar-H), 7.75-7.72 (m, 1H, Ar-H), 7.55 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.48 (t, ^3J = 7.8 Hz, 1H, Ar-H), 6.99 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.35 (t, ^3J = 6.6 Hz, 2H, CH_2), 4.09 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.80-1.73 (m, 2H, CH_2), 1.50-1.43 (m, 5H, CH_2, CH_3), 0.99 (t, ^3J = 6.9 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.7 (**C**=O), 158.8 ($\mathbf{C}_q$), 141.0 ($\mathbf{C}_q$), 132.5 ($\mathbf{C}_q$), 131.0 ($\mathbf{C}_q$), 130.9 ($\mathbf{C}H_{Ar}$), 128.7 ($\mathbf{C}H_{Ar}$), 128.2 (2 $\mathbf{C}H_{Ar}$), 127.7 ($\mathbf{C}H_{Ar}$), 127.6 ($\mathbf{C}H_{Ar}$), 114.8 (2 $\mathbf{C}H_{Ar}$), 64.9 ($\mathbf{C}H_2$), 63.5 ($\mathbf{C}H_2$), 30.8 ($\mathbf{C}H_2$), 19.3 ($\mathbf{C}H_2$), 14.8 ($\mathbf{C}H_3$), 13.8 ($\mathbf{C}H_3$).
M.p.:	44-45 °C
GC-MS (NM_50_S2):	t_R = 8.35 min (m/z = 298.1, 99 % M^+, BP).
HRMS (EI^+):	*m/z*: calcd for $C_{19}H_{22}O_3$ $[M]^+$: 298.1569; found 298.1570.

Hexyl 4`-ethoxybiphenyl-3-carboxylate (110b)



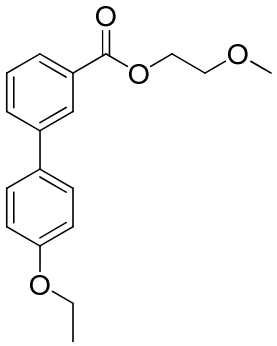
according to GP-7:

430 µL (3.47 mmol) 1-hexanol, refluxing for 4 h, TLC analysis (DCM/MeOH 20:1, R_f = 0.98), silica gel filtration (CH/EtOAc 20:1).

$C_{21}H_{26}O_3$ [326.3]

yield:	26.7 mg (33 %), light yellow oil
R_f (CH/ EtOAc 20:1):	0.60
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.23 (s, 1H, Ar-H), 7.97 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.74 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.55 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.48 (t, ^3J = 7.8 Hz, 1H, Ar-H), 6.99 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.34 (t, ^3J = 6.6 Hz, 2H, CH_2), 4.09 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.83-1.74 (m, 2H, CH_2), 1.50-1.41 (m, 5H, CH_2, CH_3), 1.38.1.33 (m, 4H, 2 CH_2), 0.91 (t, ^3J = 6.9 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.7 (**C**=O), 158.8 (**C**$_q$), 141.0 (**C**$_q$), 132.5 (**C**$_q$), 131.0 (**C**$_q$), 130.9 (**C**H$_{Ar}$), 128.7 (**C**H$_{Ar}$), 128.2 (2 **C**H$_{Ar}$), 127.7 (**C**H$_{Ar}$), 127.6 (**C**H$_{Ar}$), 114.9 (2 **C**H$_{Ar}$), 65.2 (**C**H_2), 63.5 (**C**H_2), 31.5 (**C**H_2), 28.7 (**C**H_2), 25.7 (**C**H_2), 22.6 (**C**H_2), 14.8 (**C**H_3), 14.0 (**C**H_3).
GC-MS (NM_50_S2):	t_R = 9.06 min (m/z = 326.2, 99 % M^+, BP).
HRMS (EI^+):	*m/z*: calcd for $C_{21}H_{26}O_3$ $[M]^+$: 326.1882; found 326.1858.

2-Methoxyethyl-4`-ethoxybiphenyl-3-carboxylate (110c)



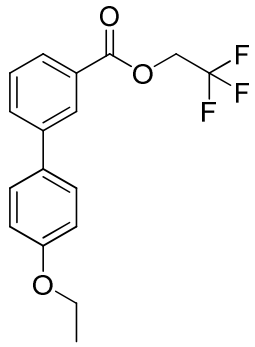
according to GP-7:

270 µL (3.47 mmol) 2-methoxyethanol, refluxing for 4 h, TLC analysis (DCM/MeOH 20:1, R_f = 0.82), column chromatography (CH/EtOAc 3:1, size: 11.0 x 3.0 cm, 20 g silica gel).

$C_{18}H_{20}O_4$ [300.3]

yield:	35.0 mg (50 %), light yellow solid
R_f (CH/ EtOAc 3:1):	0.47
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.25 (s, 1H, Ar-H), 7.99 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.74 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.55 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.48 (t, ^3J = 7.8 Hz, 1H, Ar-H), 6.98 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.52-4.49 (m, 2H, CH_2), 4.09 (q, ^3J = 6.9 Hz, 2H, CH_2), 3.76-3.73 (m, 2H, CH_2), 3.44 (s, 3H, OCH_3), 1.45 (t, ^3J = 6.9 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 166.7 (**C**=O), 158.9 ($\mathbf{C}_q$), 141.1 ($\mathbf{C}_q$), 132.5 ($\mathbf{C}_q$), 131.2 ($\mathbf{C}H_{Ar}$), 130.6 ($\mathbf{C}_q$), 128.8 ($\mathbf{C}H_{Ar}$), 128.2 (2 $\mathbf{C}H_{Ar}$), 127.9 ($\mathbf{C}H_{Ar}$), 127.8 ($\mathbf{C}H_{Ar}$), 114.9 (2 $\mathbf{C}H_{Ar}$), 70.6 ($\mathbf{C}H_2$), 64.2 ($\mathbf{C}H_2$), 63.6 ($\mathbf{C}H_2$), 59.1 (O$\mathbf{C}H_3$), 14.9 ($\mathbf{C}H_3$).
M.p.:	51-53 °C
GC-MS (NM_100_L):	t_R = 7.15 min (m/z = 300.1, 99 % M^+, BP).
HRMS (EI^+):	*m/z*: calcd for $C_{18}H_{20}O_4$ $[M]^+$: 300.1362; found 300.1368.

2,2,2-Trifluoroethyl-4`-ethoxybiphenyl-3-carboxylate (110d)



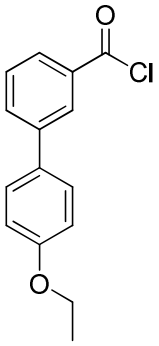
according to GP-7:

250 µL (3.467 mmol) trifluoroethanol, refluxing for 5 h, TLC analysis (DCM/MeOH 20:1, R_f = 0.94), column chromatography (CH/EtOAc 20:1, size: 12.0 x 2.0 cm, 15 g silica gel).

$C_{17}H_{15}O_3F_3$ [324.3]

yield:	40.5 mg (51 %), colorless solid
R_f (CH/ EtOAc 20:1):	0.35
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.26 (s, 1H, Ar-H), 7.99 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.79 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.57-7.49 (m, 3H, Ar-H), 6.99 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.74 (q, $^3J_{H-F}$ = 8.4 Hz, 2H, CH_2), 4.09 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.46 (t, ^3J = 6.9 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 165.0 (**C**=O), 159.0 ($\mathbf{C}_q$), 141.4 ($\mathbf{C}_q$), 132.1 ($\mathbf{C}_q$), 132.0 ($\mathbf{C}H_{Ar}$), 129.0 ($\mathbf{C}H_{Ar}$), 128.8 ($\mathbf{C}_q$), 128.2 (2 $\mathbf{C}H_{Ar}$), 128.1 ($\mathbf{C}H_{Ar}$), 128.0 ($\mathbf{C}H_{Ar}$), 124.9, 121.3 ($^1J_{C-F}$ = 277.2 Hz, **C**-F), 114.9 (2 $\mathbf{C}H_{Ar}$), 63.6 ($\mathbf{C}H_2$), 61.6, 61.1, 60.6, 60.1 ($^2J_{C-F}$ = 36.7 Hz, $\mathbf{C}H_2$-CF_3) 14.8 ($\mathbf{C}H_3$).
M.p.:	75-76 °C
GC-MS (NM_100_L):	t_R = 7.27 min (m/z = 324.1, 99 % M^+, BP: 296.1).
HRMS (EI^+):	*m/z*: calcd for $C_{17}H_{15}O_3F_3$ $[M]^+$: 324.0973; found 324.0968.

4`-Ethoxybiphenyl-3-carbonyl chloride (111)



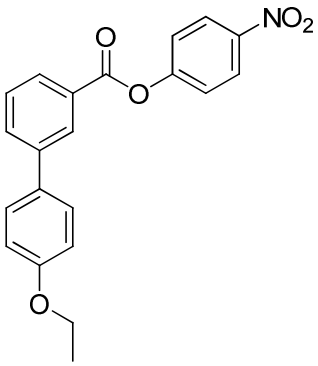
A 10 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged with 100 mg (413 µmol, 1.00 eq) 4`-ethoxybiphenyl-3-carboxylic acid **(109)**, 450 µL (6.20 mmol, 15.00 eq) thionylchloride and two drops anhydrous DMF. The dark brown suspension was stirred at 75 °C for 23 h. The excessive thionylchloride was removed under reduced pressure with a

cooling trap between flask and high vacuum connection. The crude brown oil was used in the next reaction without further purification.

$C_{15}H_{13}O_2Cl$ [260.8]

yield:	120.3 mg (> 99 %), brown oil
R_f (DCM/MeOH 20:1):	0.96

4-Nitrophenyl-4`-ethoxybiphenyl-3-carboxylate (110e)



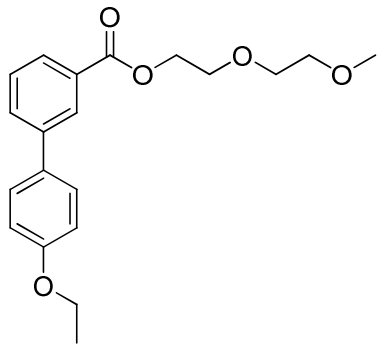
A 15 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged at 0 °C with 323 mg (1.24 mmol, 1.00 eq) 4`-ethoxybiphenyl-3-carbonyl chloride **(111)**, 4 mL absolute DCM, 200 µL (2.48 mmol, 2.00 eq) pyridine and 172 mg (1.24 mmol, 1.00 eq) *p*-nitrophenol. The brown solution was stirred at 45 °C for 16 h. TLC analysis indicated full conversion of the starting material. The mixture was hydrolyzed by addition of 8 mL water and 10 mL brine and extracted with DCM (3 x 8 mL). The combined organic layers were washed with 10 mL 5 % aqueous HCl solution and 10 mL 1M NaOH, dried over $MgSO_4$ and concentrated under reduced pressure. Final Purification by column chromatography (CH/EtOAc 50:1, size: 16.0 x 2.5 cm, 20 g silica gel) yielded the pure product.

$C_{21}H_{17}NO_5$ [363.4]

yield:	41.6 mg (9 %), beige solid
R_f (CH/EtOAc 50:1):	0.09
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.38-8.33 (m, 3H, Ar-H), 8.14-8.11 (m, 1H, Ar-H), 7.88-7.85 (m, 1H, Ar-H), 7.61-7.56 (m, 3H, Ar-H),

	7.46-7.43 (m, 2H, Ar-H), 7.02-6.99 (m, 2H, Ar-H), 4.09 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.46 (t, ^3J = 6.9 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 164.3 (**C**=O), 159.1 ($\mathbf{C}_q$), 155.7 ($\mathbf{C}_q$), 145.4 ($\mathbf{C}_q$), 141.6 ($\mathbf{C}_q$), 132.3 ($\mathbf{C}H_{Ar}$), 131.9 ($\mathbf{C}_q$), 129.2 ($\mathbf{C}H_{Ar}$), 129.0 ($\mathbf{C}_q$), 128.4 ($\mathbf{C}H_{Ar}$), 128.3 ($\mathbf{C}H_{Ar}$), 128.2 (2 $\mathbf{C}H_{Ar}$), 125.3 (2 $\mathbf{C}H_{Ar}$), 122.7 (2 $\mathbf{C}H_{Ar}$), 115.0 (2 $\mathbf{C}H_{Ar}$), 63.6 ($\mathbf{C}H_2$), 14.8 ($\mathbf{C}H_3$).
M.p.:	90 °C

2-(2-Methoxyethoxy)ethyl 4`-ethoxybiphenyl-3-carboxylate (110f)



A 10 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged at 0 °C with 107 mg (413 µmol, 1.00 eq) 4`-ethoxybiphenyl-3-carbonyl chloride **(111)**, 1.3 mL absolute DCM, 66.7 µL (826 µmol, 2.00 eq) pyridine and 49.6 mg (48.5 µL, 413 µmol, 1.00 eq) 2-(2-methoxyethoxy)ethanol. The orange solution was stirred at 45 °C for 24 h. TLC analysis indicated full conversion of the starting material. The mixture was hydrolyzed by addition of 10 mL water and extracted with DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Final purification by column chromatography (CH/EtOAc 3:1, size: 16.0 x 2.5 cm, 23 g silica gel) yielded the pure product.

$C_{20}H_{24}O_5$ [343.6]

yield:	31.0 mg (22 %), orange oil
R_f (CH/EtOAc 3:1):	0.35

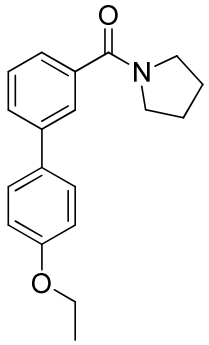
^{1}H-NMR (300 MHz, DMSO-d_6): δ (ppm) = 8.13 (d, ^{4}J = 1.5 Hz, 1H, Ar-H), 7.92-7.88 (m, 2H,Ar-H), 7.64-7.57 (m, 3H, Ar-H), 7.05 (d, ^{3}J = 8.7 Hz, 2H, Ar-H), 4.43-4.40 (m, 2H, CH_2), 4.07 (q, ^{3}J = 6.9 Hz, 2H, CH_2), 3.78-3.75 (m, 2H, CH_2), 3.61-3.58 (m, 2H, CH_2), 3.47-3.43 (m, 2H, CH_2), 3.23 (s, 3H, OCH_3), 1.35 (t, ^{3}J = 6.9 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 165.6 (**C**=O), 158.5 ($\mathbf{C}_q$), 140.3 ($\mathbf{C}_q$), 131.1 ($\mathbf{C}_q$), 130.9 ($\mathbf{C}H_{Ar}$), 130.2 ($\mathbf{C}_q$), 129.3 ($\mathbf{C}H_{Ar}$), 127.8 (2 $\mathbf{C}H_{Ar}$), 127.3 ($\mathbf{C}H_{Ar}$), 126.5 ($\mathbf{C}H_{Ar}$), 114.9 (2 $\mathbf{C}H_{Ar}$), 71.2 ($\mathbf{C}H_2$), 69.6 ($\mathbf{C}H_2$), 68.2 ($\mathbf{C}H_2$), 64.1 ($\mathbf{C}H_2$), 63.0 ($\mathbf{C}H_2$), 58.0 ($\mathbf{C}H_3$), 14.5 ($\mathbf{C}H_3$).

GC-MS (NM_100_L): t_R = 8.20 min (m/z = 344.1, 98 % M^+, BP: 225.0).

6.3.7.2. Amides

4`-Ethoxy-(pyrrolidin-1-yl)biphenyl-3-carboxamide (112a)



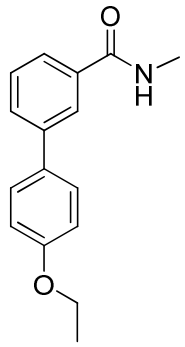
A 10 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged with 75.0 mg (310 µmol, 1.00 eq) 4`-ethoxybiphenyl-3-carboxylic acid **(109)**, 1.3 mL absolute THF and 33.1 mg (38.2 µL, 465 µmol, 1.50 eq) pyrrolidine. The light yellow suspension was cooled to 0 °C. At this temperature 71.3 mg (372 µmol, 1.20 eq) EDC were added and the suspension was stirred at rt for 24 h. TLC analysis indicated full conversion of the starting material. The mixture was concentrated under reduced pressure and the brown residue was dissolved in 10 mL water and 10 mL EtOAc. The layers were separated, the aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$ and

concentrated under reduced pressure. Final purification by column chromatography (CH/EtOAc 1:2, size: 15.0 x 2.0 cm, 18 g silica gel) yielded the pure product.

$C_{19}H_{21}O_2N$ [295.1]

yield:	57.6 mg (63 %), orange solid
R_f (CH/EtOAc 1:2):	0.47
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 7.70-7.68 (m, 2H, Ar-H), 7.62 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.48-7.40 (m, 2H, Ar-H), 7.01 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.06 (q, ^3J = 6.9 Hz, 2H, CH_2), 3.50-3.39 (m, 4H, 2 N-CH_2), 1.90-1.78 (m, 4H, 2 CH_2), 1.34 (t, ^3J = 6.9 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 168.0 (**C**=O), 158.3 (**C**$_q$), 139.6 (**C**$_q$), 137.8 (**C**$_q$), 131.5 (**C**$_q$), 128.7 (**C**H$_{Ar}$), 127.8 (2 **C**H$_{Ar}$), 127.2 (**C**H$_{Ar}$), 125.1 (**C**H$_{Ar}$), 124.5 (**C**H$_{Ar}$), 114.8 (2 **C**H$_{Ar}$), 63.0 (O**C**H$_2$), 48.8 (**C**H$_2$), 45.8 (**C**H$_2$), 25.9 (**C**H$_2$), 23.8 (**C**H$_2$), 14.6 (**C**H$_3$).
M.p.:	94 °C
GC-MS (NM_100_L):	t_R = 8.75 min (m/z = 295.1, 99 % M^+, BP: 255.0).

4`-Ethoxy-*N*-methylbiphenyl-3-carboxamide (112b)



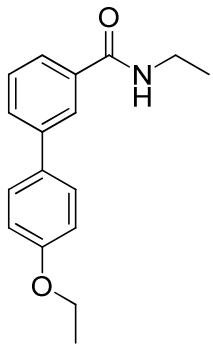
A 25 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged with 75.0 mg (310 µmol, 1.00 eq) 4`-ethoxybiphenyl-3-carboxylic acid **(109)**, 31.4 mg (465 µmol, 1.50 eq) methylamine hydrochloride, 1.3 mL absolute THF and 37.5 µL (465 µmol, 1.50 eq) pyridine. The orange suspension was cooled to 0 °C. At this temperature 71.3 mg (372 µmol,

1.20 eq) EDC were added and the suspension was stirred at rt for 20 h. TLC analysis indicated full conversion of the starting material. The mixture was concentrated under reduced pressure and the brown residue was dissolved in 10 mL water and 10 mL EtOAc. The layers were separated, the aqueous layer was extracted with EtOAc (3 x 7 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Final purification by column chromatography (CH/EtOAc 1:2, size: 12.0 x 2.0 cm, 12 g silica gel) yielded the pure product.

$C_{16}H_{17}O_2N$ [255.1]

yield:	9.6 mg (12 %), colorless solid
R_f (CH/EtOAc 1:2):	0.45
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 7.95 (s, 1H, Ar-H), 7.69-7.64 (m, 2H, Ar-H), 7.54 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.46 (t, ^3J = 7.8 Hz, 1H, Ar-H), 6.98 (d, ^3J = 9.0 Hz, 2H, Ar-H), 6.17 (bs, 1H, NH), 4.08 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.04 (d, ^3J = 4.8 Hz, 3H, N-CH_3), 1.45 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 168.3 (**C**=O), 158.9 ($\mathbf{C}_q$), 141.4 ($\mathbf{C}_q$), 135.2 ($\mathbf{C}_q$), 132.6 ($\mathbf{C}_q$), 129.6 ($\mathbf{C}H_{Ar}$), 129.0 ($\mathbf{C}H_{Ar}$), 128.2 (2 $\mathbf{C}H_{Ar}$), 125.3 ($\mathbf{C}H_{Ar}$), 124.8 ($\mathbf{C}H_{Ar}$), 114.9 (2 $\mathbf{C}H_{Ar}$), 63.6 ($\mathbf{C}H_2$), 26.9 (N-$\mathbf{C}H_3$), 14.9 ($\mathbf{C}H_3$).
M.p.:	140 °C

4`-Ethoxy-*N*-ethyl-(1,1`-biphenyl)-3-carboxamide (112c)



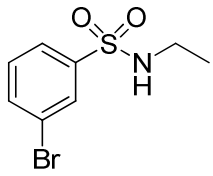
A 15 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged with 75.0 mg (310 µmol, 1.00 eq) 4`-ethoxybiphenyl-3-carboxylic acid **(109)**, 2 mL absolute THF and 200 µL (465 µmol, 1.50 eq) ethylamine. The suspension was cooled to 0 °C. At this temperature 71.3 mg (372 µmol, 1.20 eq) EDC were added and the suspension was stirred at rt for 24 h. TLC analysis indicated full conversion of the starting material. The mixture was concentrated under reduced pressure and the brown residue was dissolved in 10 mL water and 10 mL EtOAc. The layers were separated, the aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Final purification by column chromatography (CH/EtOAc 1:1, size: 18.0 x 2.5 cm, 18 g silica gel) yielded the pure product.

$C_{17}H_{19}O_2N$ [269.3]

yield:	4.8 mg (6 %), colorless solid
R_f (CH/EtOAc 1:1):	0.51
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.59-8.57 (m, 1H, NH), 8.06 (s, 1H, Ar-H), 7.78-7.74 (m, 2H, Ar-H), 7.66 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.50 (t, ^3J = 7.8 Hz, 1H, Ar-H), 7.04 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.08 (q, ^3J = 7.2 Hz, 2H, CH_2), 3.31-3.29 (m, 2H, N-CH_2), 1.41 (t, ^3J = 6.9 Hz, 3H, CH_3), 1.35 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 165.7 (**C**=O), 158.3 (**C**$_q$), 139.7 (**C**$_q$), 135.1 (**C**$_q$), 131.7 (**C**$_q$), 128.7 (**C**H$_{Ar}$), 128.5 (**C**H$_{Ar}$), 127.8 (2 **C**H$_{Ar}$), 125.5 (**C**H$_{Ar}$), 124.6 (**C**H$_{Ar}$), 114.7 (2 **C**H$_{Ar}$), 63.0 (**C**H_2), 34.0 (N-**C**H_2), 14.7 (**C**H_3), 14.6 (**C**H_3).
M.p.:	124 °C

6.3.7.3. Sulfonamides

3-Bromo-*N*-ethylbenzenesulfonamide (114a)

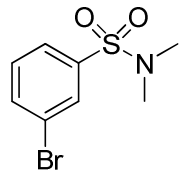


A 10 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged with 100 mg (56.4 µL, 391 µmol, 1.00 eq) 3-bromobenzene-1-sulfonylchloride **(113)** and 0.5 mL absolute THF. The solution was cooled to 0 °C and 2.0 mL (1.96 mmol, 5.00 eq, 2.0 M in THF) ethylamine were added. The light yellow suspension was stirred at rt for 20 h. TLC analysis showed full conversion of the starting material. The mixture was diluted with 10 mL EtOAc and washed with 15 mL 5 % aqueous HCL solution. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Final purification by column chromatography (CH(EtOAc 8:1, size: 16.0 x 2.5 cm, 24 g silica gel) yielded the pure product.

$C_8H_{10}NO_2SBr$ [264.1]

yield:	58.0 mg (56 %), colorless solid
R_f (CH:EtOAc 8:1):	0.15
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.02 (t, ^4J = 1.8 Hz, 1H, Ar-H), 7.82-7.78 (m, 1H, Ar-H), 7.73-7.69 (m, 1H, Ar-H), 7.40 (t, ^3J = 8.1 Hz, 1H, Ar-H), 4.40 (bs, 1H, NH), 3.10-3.00 (m, 2H, CH_2), 1.14 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 141.9 (**C**$_q$-SO_2), 135.7 (**C**H$_{Ar}$), 130.6 (**C**H$_{Ar}$), 130.0 (**C**H$_{Ar}$), 125.6 (**C**H$_{Ar}$), 123.1 (**C**$_q$-Br), 38.4 (**C**H_2), 15.2 (**C**H_3).
GC-MS (NM_50_S2):	t_R = 6.79 min (m/z = 264.0, 98 % M^+, BP: 155.0).

3-Bromo-*N*,*N*-dimethylbenzenesulfonamide (114b)

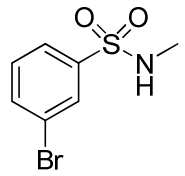


A 15 ml Schlenk tube was charged with 48.5 mg (587 µmol, 1.50 eq) dimethylamine hydrochloride, 200 µL (1.96 mmol, 5.00 eq) pyridine and 4.3 mL absolute DCM. The solution was cooled to 0 °C before 100 mg (60 µL, 391 µmol, 1.00 eq) 3-bromobenzene-sulfonylchloride **(113)** were added. After stirring at rt for 16.5 h TLC analysis indicated full conversion of the starting material. The mixture was diluted with 5 mL saturated $NaHCO_3$ solution and 5 mL Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with NaH_2PO_4 solution (4 x 10 mL) and brine (2 x 5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. As it was still pyridine in the crude product, it was washed once more with NaH_2PO_4 solution (4 x 10 mL), dried and concentrated under reduced pressure. Final purification by column chromatography (CH/EtOAc 3:1, size: 16.5 x 2.0 cm, 14 g silica gel) yielded the pure product.

$C_8H_{10}O_2NSBr$ [264.1]

yield:	44.0 mg (43 %), colorless solid
R_f (CH:EtOAc 3:1):	0.25
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.93 (s, 1H, Ar-H), 7.75-7.70 (m, 2H, Ar-H), 7.43 (t, ^3J = 8.1 Hz, 1H, Ar-H), 2.74 (s, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 137.6 (**C**$_q$-SO_2), 135.7 (**C**H_{Ar}), 130.5 (**C**H_{Ar}), 130.5 (**C**H_{Ar}), 126.2 (**C**H_{Ar}), 123.2 (**C**$_q$-Br), 37.9 (2 **C**H_3).
GC-MS (NM_50_S2):	t_R = 6.57 min (m/z = 264.0, 99 % M^+, BP: 207.0).

3-Bromo-*N*-methylbenzenesulfonamide (114c) [143]

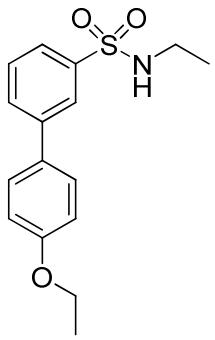


A 100 ml Schlenk tube was charged with 180 mg (2.66 mmol, 1.70 eq) methylamine hydrochloride, 600 µL (7.83 mmol, 5.00 eq) pyridine and 17.2 mL absolute DCM. The solution was cooled to 0 °C before 400 mg (226 µL, 1.57 mmol, 1.00 eq) 3-bromobenzene-sulfonylchloride **(113)** were added. After stirring at 80 °C for 24 h. TLC analysis indicated full conversion of the starting material. The mixture was diluted with 30 mL saturated $NaHCO_3$ solution and 30 mL Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with NaH_2PO_4 solution (4 x 10 mL) and brine (2 x 5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. As it was still pyridine in the crude product, it was washed once more with NaH_2PO_4 solution (3 x 10 mL), dried and concentrated under reduced pressure. Final purification by column chromatography (CH/EtOAc 3:1, size: 17.0 x 2.0 cm, 14 g silica gel) yielded the pure product.

$C_7H_8O_2NSBr$ [250.1]

yield:	58.9 mg (15 %), colorless solid
R_f (CH:EtOAc 3:1):	0.22
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.01 (t, ^4J = 1.8 Hz, 1H, Ar-H), 7.80 (d, ^3J = 7.8 Hz, 1H, Ar-H), 7.74-7.71 (m, 1H, Ar-H), 7.41 (t, ^3J = 7.8 Hz, 1H, Ar-H), 4.41 (bs, 1H, NH), 2.70 (d, ^3J = 5.1 Hz, 3H, CH_3-N).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 140.8 ($\mathbf{C}_q$-SO_2), 135.8 ($\mathbf{C}H_{Ar}$), 130.6 ($\mathbf{C}H_{Ar}$), 130.1 ($\mathbf{C}H_{Ar}$), 125.7 ($\mathbf{C}H_{Ar}$), 123.2 ($\mathbf{C}_q$-Br), 29.4 ($\mathbf{C}H_3$).
GC-MS (NM_50_S2):	t_R = 6.70 min (m/z = 249.9, 99 % M^+, BP: 154.9).

4`-Ethoxy-*N*-ethylbiphenyl-3-sulfonamide (115a)



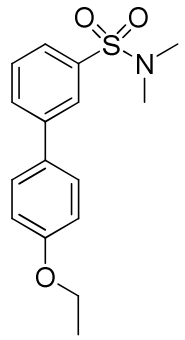
A 25 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged with 50.0 mg (189 µmol, 1.00 eq) 3-bromo-*N*-ethylbenzenesulfonamide **(114a)** and 3 mL anhydrous DME. 36.5 mg (220 µmol, 1.00 eq) 4-ethoxyboronic acid **(71)**, 104 mg (681 µmol, 3.10 eq) CsF and 9.0 mg (11.0 µmol, 0.05 eq) $PdCl_2$(dppf)*DCM were added consecutively. The dark brown suspension was degassed by vacuum/N_2 cycles and stirred at 80 °C for 17 h. TLC analysis indicated full conversion of the starting material. The reaction mixture was hydrolyzed by 10 mL 5 % aqueous HCL solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were concentrated under reduced pressure and final purification by column chromato-graphy (CH/EtOAc 3:1, size: 16.0 x 2.5 cm, 20 g silica gel) yielded the pure product.

$C_{16}H_{19}O_3SN$ [305.3]

yield:	46.4 mg (80 %), colorless solid
R_f (CH/EtOAc 3:1):	0.34
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.05 (t, ^4J = 1.5 Hz, 1H, Ar-H), 7.80-7.74 (m, 2H, Ar-H), 7.58-7.51 (m, 3H, Ar-H), 7.01-6.97 (m, 2H, Ar-H), 4.37 (t, ^3J = 6.0 Hz, 1H, NH), 4.10 (q, ^3J = 7.2 Hz, 2H, OCH_2), 3.10-3.01 (m, 2H, CH_2), 1.45 (t, ^3J = 6.9 Hz, 3H, CH_3), 1.13 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 159.2 (**C**$_q$), 142.0 (**C**$_q$), 140.4 (**C**$_q$), 131.5 (**C**$_q$), 130.6 (**C**H$_{Ar}$), 129.5 (**C**H$_{Ar}$), 128.2 (2 **C**H$_{Ar}$), 125.0 (**C**H$_{Ar}$), 124.9 (**C**H$_{Ar}$), 115.0 (2 **C**H$_{Ar}$), 63.6 (**C**H$_2$), 38.3 (**C**H$_2$-N), 15.2 (**C**H$_3$), 14.8 (**C**H$_3$).
M.p.:	81 °C

GC-MS (NM_50_S2): t_R = 9.24 min (m/z = 305.1, 99 % M^+, BP).

4`-Ethoxy-*N*,*N*-dimethyl-(1,1`-biphenyl)-3-sulfonamide (115b)



according to GP-5:

44.0 mg (167 µmol, 1.00 eq) 3-bromo-*N*,*N*-dimethylbenzenesulfonamide **(114b)**, 27.6 mg (167 µmol, 1.00 eq) 4-ethoxyphenylboronic acid **(71)**, 20 h reaction time, silica gel filtration (CH/EtOAc 3:1).

$C_{16}H_{19}O_3NS$ [305.3]

yield: 44.0 mg (86 %), yellow solid

R_f (CH/EtOAc 3:1): 0.36

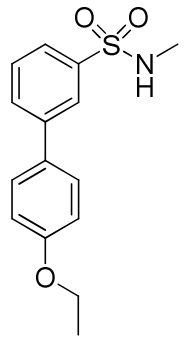
^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.94 (t, ^4J = 1.5 Hz, 1H, Ar-H), 7.79-7.76 (m, 1H, Ar-H), 7.71-7.68 (m, 1H, Ar-H), 7.60-7.52 (m, 3H, Ar-H), 6.99 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.09 (q, ^3J = 7.2 Hz, 2H, CH_2), 2.74 (s, 6H, 2 CH_3), 1.45 (t, ^3J = 7.2 Hz, 3H, CH_3).

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 159.3 (**C**$_q$), 142.0 (**C**$_q$), 136.0 (**C**$_q$), 131.6 (**C**$_q$), 130.8 (**C**H$_{Ar}$), 129.4 (**C**H$_{Ar}$), 128.3 (2 **C**H$_{Ar}$), 125.7 (2 **C**H$_{Ar}$), 115.1 (2 **C**H$_{Ar}$), 63.7 (**C**H$_2$), 38.1 (2 **C**H$_3$), 14.9 (**C**H$_3$).

M.p.: 114 °C

GC-MS (NM_50_S2): t_R = 8.94 min (m/z = 305.1, 99 % M^+, BP).

4`-Ethoxy-*N*-methyl-(1,1`-biphenyl)-3-sulfonamide (115c)



A 15 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged consecutively with 58.9 mg (235 µmol, 1.00 eq) 3-bromo-*N*-methylbenzenesulfonamide **(114c)**, 39.1 mg (235 µmol, 1.00 eq) 4-ethoxyphenylboronic acid **(71)**, 9.60 mg (12.0 µmol, 0.05 eq) $PdCl_2$(dppf)*DCM, 111 mg (729 µmol, 3.10 eq) CsF and 2.3 mL anhydrous DME. The suspension was stirred at 80 °C for 22 h. TLC analysis and GC-MS analysis indicated full conversion of the starting material. The reaction mixture was hydrolyzed by addition of 10 mL 5 % aqueous HCl solution and diluted with 10 mL EtOAc. The layers were separated and the organic layer was washed with 8 mL 5 % aqueous HCl solution, dried over $MgSO_4$ and concentrated under reduced pressure. Final purification by column chromatography (CH/EtOAc 3:1, size: 17.5 x 2.0 cm, 14 g silica gel) yielded the pure product.

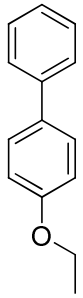
$C_{15}H_{17}O_3NS$ [291.4]

yield:	56.7 mg (86 %), beige solid
R_f (CH/EtOAc 3:1):	0.27
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.04 (s, 1H, Ar-H), 7.79-7.74 (m, 2H, Ar-H), 7.58-7.52 (m, 3H, Ar-H), 6.98 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.54 (d, ^3J = 5.1 Hz, 1H, NH), 4.08 (q, ^3J = 7.2 Hz, 2H, CH_2), 2.69 (d, ^3J = 5.1 Hz, 3H, CH_3-N), 1.45 (t, ^3J = 7.2 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 159.2 (**C**$_q$), 142.1 (**C**$_q$), 139.3 (**C**$_q$), 131.4 (**C**$_q$), 130.7 (**C**H$_{Ar}$), 129.5 (**C**H$_{Ar}$), 128.2 (2 **C**H$_{Ar}$), 125.1 (**C**H$_{Ar}$), 125.1 (**C**H$_{Ar}$), 115.0 (2 **C**H$_{Ar}$), 63.6 (**C**H$_2$), 29.4 (**C**H$_3$-N), 14.8 (**C**H$_3$).
M.p.:	132 °C

GC-MS (NM_50_S2): t_R = 9.22 min (m/z = 291.0, 99 % M^+, BP).

6.3.7.4. Non-esterified biphenyls

4-Ethoxybiphenyl (117a)



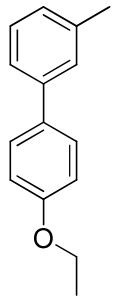
according to GP-5:

150 mg (102 µL, 956 µmol, 1.00 eq) bromobenzene **(116a)**, 159 mg (956 µmol, 1.00 eq) 4-ethoxyphenylboronic acid **(71)**, 6.5 h reaction time, column chromatography (CH, size: 6.0 x 4.0 cm, 12 g silica gel).

$C_{14}H_{14}O$ [198.0]

yield:	207.0 mg (93 %), beige solid
R_f (CH):	0.16
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.58-7.51 (m, 4H, Ar-H), 7.45-7.40 (m, 2H, Ar-H), 7.33-7.28 (m, 1H, Ar-H), 6.99-6.96 (m, 2H, Ar-H), 4.09 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.45 (t, ^3J = 6.9 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 158.5 (**C**$_q$), 140.9 (**C**$_q$), 133.6 (**C**$_q$), 128.7 (2 **C**H$_{Ar}$), 128.1 (2 **C**H$_{Ar}$), 126.7 (2 **C**H$_{Ar}$), 126.6 (**C**H$_{Ar}$), 114.7 (2 **C**H$_{Ar}$), 63.5 (**C**H$_2$), 14.9 (**C**H$_3$).
M.p.:	69 °C
GC-MS (NM_50_S2):	t_R = 6.45 min (m/z = 189.1, 98 % M^+, BP: 170.1).

4`-Ethoxy-3-methyl-1,1`-biphenyl (117b)



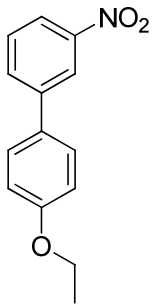
according to GP-5:

150 mg (100 µL, 877 µmol, 1.00 eq) 3-bromotoluene **(116b)**, 146 mg (877 µmol, 1.00 eq) 4-ethoxyphenylboronic acid **(71)**, reaction over night, column chromatography (CH, size: 15.5 x 2.5 cm, 10 g silica gel).

$C_{15}H_{16}O$ [212.3]

yield:	155.6 mg (84 %), yellow solid
R_f (CH):	0.05
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.53 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.39-7.30 (m, 3H, Ar-H), 7.14 (d, ^3J = 7.2 Hz, 1H, Ar-H), 6.99 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.09 (q, ^3J = 6.9 Hz, 2H, CH_2), 2.43 (s, 3H, CH_3), 1.46 (t, ^3J = 6.9 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 158.4 (**C**$_q$), 140.8 (**C**$_q$), 138.2 (**C**$_q$), 133.7 (**C**$_q$), 128.6 (**C**H$_{Ar}$), 128.1 (2 **C**H$_{Ar}$), 127.5 (**C**H$_{Ar}$), 127.3 (**C**H$_{Ar}$), 123.8 (**C**H$_{Ar}$), 114.7 (2 **C**H$_{Ar}$), 63.5 (**C**H$_2$), 21.5 (**C**H$_3$), 14.9 (**C**H$_3$).
M.p.:	48 °C
GC-MS (NM_50_S2):	t_R = 6.74 min (m/z = 212.1, 99 % M^+, BP: 184.1).

4`-Ethoxy-3-nitrobiphenyl (119)



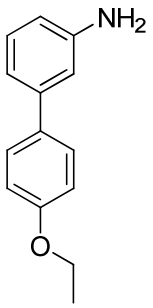
according to GP-6:

500 mg (2.49 mmol, 1.00 eq) *p*-bromophenetole **(64)**, 622 mg (3.73 mmol, 1.50 eq) 3-nitrophenylboronic acid **(118)**, reaction over night, silica gel filtration (CH/EtOAc 25:1).

$C_{14}H_{13}O_3N$ [243.2]

yield:	412.4 mg (68 %), light yellow solid
R_f (CH/EtOAc 25:1):	0.34
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.40 (d, ^4J = 1.8 Hz, 1H, Ar-H), 8.15-8.12 (m, 1H, Ar-H), 7.88-7.85 (m, 1H, Ar-H), 7.59-7.54 (m, 3H, Ar-H), 7.00 (d, ^3J = 8.7 Hz, 2H, Ar-H), 4.09 (q, ^3J = 6.9 Hz, 2H, CH_2), 1.46 (t, ^3J = 6.9 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 159.4 (**C**$_q$), 148.7 (**C**$_q$), 142.5 (**C**$_q$), 132.4 (**C**H$_{Ar}$), 130.8 (**C**$_q$), 129.6 (**C**H$_{Ar}$), 128.2 (2 **C**H$_{Ar}$), 121.3 (**C**H$_{Ar}$), 121.3 (**C**H$_{Ar}$), 115.1 (2 **C**H$_{Ar}$), 63.6 (**C**H$_2$), 14.8 (**C**H$_3$).
M.p.:	72-73 °C
GC-MS (NM_50_S2):	t_R = 7.65 min (m/z = 243.1, 92 % M^+, BP: 215.1).

4`-Ethoxybiphenyl-3-amine (120)



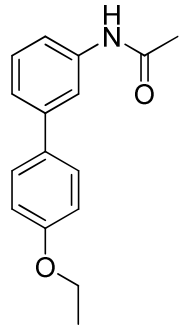
A 25 mL three-neck round-bottom flask was dried under vaccum, filled with nitrogen and charged with 374 mg (1.54 mmol, 1.00 eq) 4`-ethoxy-3-nitrobiphenyl **(119)** and 6.4 mL anhydrous EtOAc. To this yellow solution 129 mg palladium on activated charcoal (10 % Pd) were added and the solution was degassed by vacuum/H_2 cycles. The mixture was stirred at rt over night under H_2 atmosphere. GC-MS analysis showed full conversion of the starting material. After filtration through a pad of celite under argon atmosphere and elution with EtOAc and DCM the solvent was removed under reduced pressure. The obtained product was used for the next reactions without further purification.

$C_{14}H_{15}ON$ [213.1]

yield:	278.8 mg (85 %), light yellow solid
R_f (CH/EtOAc 8:1):	0.25
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.49 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.21 (t, ^3J = 7.8 Hz, 1H, Ar-H), 6.97-6.93 (m, 3H, Ar-H), 6.88-6.87 (m, 1H, Ar-H), 6.64 (dd, ^4J = 1.5 Hz, ^3J = 7.8 Hz, 1H, Ar-H), 4.07 (q, ^3J = 6.9 Hz, 2H, CH_2), 3.59 (bs, 2H, NH_2), 1.44 (t, ^3J = 6.9 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 158.4 (**C**$_q$), 146.6 (**C**$_q$), 142.0 (**C**$_q$), 133.7 (**C**$_q$), 129.6 (**C**H$_{Ar}$), 128.0 (2 **C**H$_{Ar}$), 117.3 (**C**H$_{Ar}$), 114.6 (2 **C**H$_{Ar}$), 113.5 (2 **C**H$_{Ar}$), 63.5 (**C**H$_2$), 14.9 (**C**H$_3$).
M.p.:	84-87 °C
GC-MS (NM_50_S2):	t_R = 7.39 min (m/z = 213.1, 96 % M^+, BP: 185.1).

6.3.7.5. Acetamide

***N*-(4`-ethoxybiphenyl-3-yl)acetamide (121)**



A 10 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged with 79.8 mg (374 µmol, 1.00 eq) 4`-ethoxybiphenyl-3-amine **(120)**, 42.3 µL (450 µmol, 1.20 eq) acetanhydride and 1.0 mL absolute DCM. The white suspension was stirred at rt for 2 h. GC-MS analysis indicated full conversion of the starting material. The reaction mixture was transferred to a separation funnel and washed with saturated $NaHCO_3$ solution (2 x 5 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to obtain the pure product without further purification.

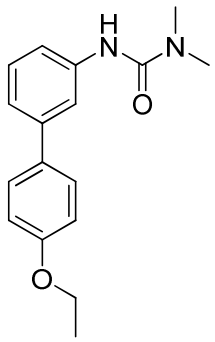
$C_{16}H_{17}O_2N$ [255.3]

yield:	70.7 mg (74 %), light yellow solid
R_f (CH/EtOAc 1:1):	0.61
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 7.69 (s, 1H, Ar-H), 7.53 (bs, 1H, NH), 7.50-7.44 (m, 3H, Ar-H), 7.36-7.27 (m, 2H, Ar-H), 6.94 (d, ^3J = 8.4 Hz, 2H, Ar-H), 4.06 (q, ^3J = 6.9 Hz, 2H, CH_2), 2.18 (s, 3H, CH_3), 1.43 (t, ^3J = 6.9 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 168.4 (**C**=O), 158.6 ($\mathbf{C}_q$), 141.7 ($\mathbf{C}_q$), 138.3 ($\mathbf{C}_q$), 133.0 ($\mathbf{C}_q$), 129.3 ($\mathbf{C}H_{Ar}$), 128.1 (3 $\mathbf{C}H_{Ar}$), 122.6 ($\mathbf{C}H_{Ar}$), 118.2 ($\mathbf{C}H_{Ar}$), 114.7 (2 $\mathbf{C}H_{Ar}$), 63.5 ($\mathbf{C}H_2$), 24.6 ($\mathbf{C}H_3$), 14.8 ($\mathbf{C}H_3$).
M.p.:	168-170 °C
GC-MS (NM_50_S2):	t_R = 8.46 min (m/z = 255.1, 99 % M^+, BP: 185.1).

HRMS (EI^+): *m/z*: calcd for $C_{16}H_{17}O_2N$ $[M]^+$: 255.1259; found 255.1270.

6.3.7.6. Urea

_N_-(4`-ethoxybiphenyl-3-yl)-_N_,_N_-dimethylurea (122)



A 10 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged with 80.4 mg (377 µmol, 1.00 eq) 4`-ethoxybiphenyl-3-amine **(120)** and 1.0 mL absolute EtOAc. The light yellow solution was cooled to 0 °C and 52.0 µL (375 µmol, 1.00 eq) triethylamine and 41.4 µL (450 µmol, 1.20 eq) dimethylcarbamoyl chloride were added dropwise. The solution was first stirred at rt for 5 h and then at 40 °C over night. TLC analysis indicated no full conversion of the starting material. The temperature was increased to 85 °C and the colorless suspension was refluxed at this temperature for another night. TLC analysis indicated full conversion of the starting material and the mixture was hydrolyzed by addition of 5 mL of water, transferred to a separation funnel and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure to obtain the crude product which was purified by column chromatography (CH/EtOAc 1:1, size: 1.5 x 15.5 cm, 10 g silica gel).

$C_{17}H_{20}O_2N_2$ [284.3]

yield: 28.6 mg (27 %), beige solid

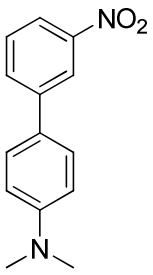
R_f (CH/EtOAc 1:1): 0.23

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.31 (bs, 1H, NH), 7.73 (s, 1H, Ar-H), 7.52 (d, ^3J = 8.7 Hz, 2H, Ar-H), 7.44 (d, ^3J = 7.8 Hz, 1H, Ar-H),

	7.29-7.24 (m, 1H, Ar-H), 7.17-7.15 (m, 1H, Ar-H), 7.00 (d, ^{3}J = 8.4 Hz, 2H, Ar-H), 4.05 (q, ^{3}J = 6.6 Hz, 2H, CH_2), 2.94 (s, 6H, 2 CH_3), 1.34 (t, ^{3}J = 6.9 Hz, 3H, CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 158.0 (**C**=O), 155.6 ($\mathbf{C}_q$), 141.1 ($\mathbf{C}_q$), 139.8 ($\mathbf{C}_q$), 132.5 ($\mathbf{C}_q$), 128.6 ($\mathbf{C}H_{Ar}$), 127.5 (2 $\mathbf{C}H_{Ar}$), 119.3 ($\mathbf{C}H_{Ar}$), 117.8 ($\mathbf{C}H_{Ar}$), 117.3 ($\mathbf{C}H_{Ar}$), 114.6 (2 $\mathbf{C}H_{Ar}$), 63.0 ($\mathbf{C}H_2$), 36.1 (2 $\mathbf{C}H_3$), 14.6 ($\mathbf{C}H_3$).
M.p.:	164-167 °C
GC-MS (NM_50_S2):	t_R = 7.38 min (99 % purity, BP: 239.1, no M^+ visible).
HRMS (EI^+):	*m/z*: calcd for $C_{15}H_{13}O_2N$, BP: 239.0946; found 239.0940.

6.3.8. Synthesis of the optimized inhibitor compound

***N*,*N*-Dimethyl-3`-nitrobiphenyl-4-amine (124)**



according to GP-5:

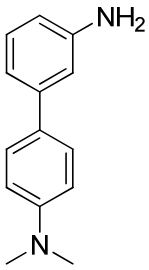
250 mg (1.25 mmol, 1.00 eq) 4-bromo-*N*,*N*-dimethylaniline **(123)**, 209 mg (1.25 mmol, 1.00 eq) 3-nitrophenylboronic acid **(118)**, reaction over night, silica gel filtration (CH/EtOAc 19:1).

$C_{14}H_{14}O_2N_2$ [242.2]

yield:	272.9 mg (90 %), orange solid
R_f (CH/ EtOAc 19:1):	0.35
^{1}H-NMR (300 MHz, $CDCl_3$):	δ (ppm) = 8.41 (d, ^{4}J = 2.1 Hz, 1H, Ar-H), 8.09-8.06 (m, 1H, Ar-H), 7.86 (dd, ^{3}J = 7.8 Hz, ^{4}J = 0.9 Hz, 1H, Ar-H),

	7.56-7.53 (m, 3H, Ar-H), 6.82 (d, ^{3}J = 8.7 Hz, 2H, Ar-H), 3.03 (s, 6H, 2 CH_3).
^{13}C-NMR (75.5 MHz, $CDCl_3$):	δ (ppm) = 150.6 (**C**$_q$-N(CH_3)$_2$), 148.8 (**C**$_q$), 142.8 (**C**$_q$), 131.8 (**C**H$_{Ar}$), 129.4 (**C**H$_{Ar}$), 127.7 (2 **C**H$_{Ar}$), 126.1 (**C**$_q$), 120.7 (**C**H$_{Ar}$), 120.5 (**C**H$_{Ar}$), 112.6 (2 **C**H$_{Ar}$), 40.4 (N(**C**H_3)$_2$).
M.p.:	153-155 °C
GC-MS (NM_50_S2):	t_R = 8.15 min (m/z = 242.0, 98 % M^+, BP).

$N^{4`}$,$N^{4`}$-dimethylbiphenyl-3,4`-diamine (125)



A 25 mL two-neck round-bottom flask was dried under vaccum, filled with nitrogen and charged with 250 mg (1.03 mmol, 1.00 eq) *N*,*N*-dimethyl-3`-nitrobiphenyl-4-amine **(124)**, 4.0 mL absolute EtOH and 3.0 mL anhydrous EtOAc. To the yellow solution 86.2 mg palladium on activated charcoal (10 % Pd) were added and the solution was degassed by vacuum/H_2 cycles. The mixture was stirred at rt over night under H_2 atmosphere. GC-MS analysis showed full conversion of the starting material. After filtration through a pad of celite under argon atmosphere and elution with EtOAc and MeOH the solvent was removed under reduced pressure. The obtained product was used for the next reactions without further purification.

$C_{14}H_{16}N_2$ [212.2]

yield:	207.4 mg (95 %), brown solid
R_f (CH/ EtOAc 19:1):	0.05
^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 7.40 (d, ^{3}J = 9.0 Hz, 2H, Ar-H), 7.03 (t, ^{3}J = 7.8 Hz, 1H, Ar-H), 6.78-6.75 (m, 3H, Ar-H), 6.70 (d, ^{3}J

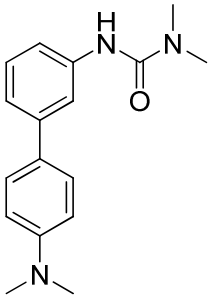
= 7.8 Hz, 1H, Ar-H), 6.47-6.44 (m, 1H, Ar-H), 5.04 (bs, 2H, NH_2), 2.91 (s, 6H, 2 CH_3).

^{13}C-NMR (75.5 MHz, DMSO-d_6): δ (ppm) = 149.5 (**C**$_q$-N(CH_3)$_2$), 148.8 (**C**$_q$), 140.8 (**C**$_q$), 129.1 (**C**H$_{Ar}$), 128.6 (**C**$_q$), 126.7 (2 **C**H$_{Ar}$), 113.4 (**C**H$_{Ar}$), 112.5 (2 **C**H$_{Ar}$), 111.8 (**C**H$_{Ar}$), 111.1 (**C**H$_{Ar}$), 40.0 (N(**C**H$_3$)$_2$).

M.p.: 65-68 °C

GC-MS (NM_50_S2): t_R = 7.78 min (m/z = 212.1, 98 % M^+, BP).

3-(4`-(dimethylamino)biphenyl-3-yl)-*N*,*N*-dimethylurea (126)



A 25 mL Schlenk tube was dried under vacuum, filled with nitrogen and charged with 439 mg (2.07 mmol, 1.00 eq) $N^{4`}$,$N^{4`}$-dimethylbiphenyl-3,4`-diamine **(125)** and 6.0 mL absolute DCM. The brown solution was cooled to 0 °C and 290 µL (2.07 mmol, 1.00 eq) triethylamine and 290 µL (3.11 mmol, 1.50 eq) dimethylcarbamoyl chloride were added dropwise. The solution was first stirred at 50 °C for 3 d. GC-MS analysis indicated full conversion of the starting material and the mixture was hydrolyzed by addition of 6 mL of water, transferred to a round-bottom flask and concentrated. The residue was dissolved in 30 mL DCM and dried over Na_2SO_4. The solvent was removed under reduced pressure to obtain the crude product, which was purified by column chromatography (CH/EtOAc 1:1, size: 2.0 x 17.0 cm, 25 g silica gel).

$C_{17}H_{21}ON_3$ [283.2]

yield: 315.2 mg (54 %), beige solid

R_f (CH/ EtOAc 1:1): 0.24

^{1}H-NMR (300 MHz, DMSO-d_6):	δ (ppm) = 8.28 (s, 1H, Ar-H), 7.70 (s, 1H, Ar-H), 7.45 (d, ^{3}J = 8.4 Hz, 2H, Ar-H), 7.40-7.38 (m, 1H, Ar-H), 7.23 (t, ^{3}J = 7.8 Hz, 1H, Ar-H), 7.15-7.13 (m, 1H, Ar-H), 6.79 (d, ^{3}J = 8.4 Hz, 2H, Ar-H), 2.94-2.93 (m, 12H, 4 CH_3).
^{13}C-NMR (75.5 MHz, DMSO-d_6):	δ (ppm) = 155.7 (C=O), 149.7 (**C**$_q$-N(CH_3)$_2$), 141.0 (**C**$_q$), 140.2 (**C**$_q$), 128.5 (**C**H$_{Ar}$), 127.8 (**C**$_q$), 128.8 (2 **C**H$_{Ar}$), 118.8 (**C**H$_{Ar}$), 117.2 (**C**H$_{Ar}$), 116.8 (**C**H$_{Ar}$), 112.5 (2 **C**H$_{Ar}$), 40.0 (N(**C**H_3)$_2$), 36.1 (N(**C**H_3)$_2$).
M.p.:	165-167 °C
GC-MS (NM_50_S2):	t_R = 7.65 min (98 % purity, BP: 238.0, no M^+ visible).
HRMS (EI$^+$):	*m/z*: calcd for $C_{17}H_{21}ON_3$ $[M]^+$: 283.1685; found 283.1707.

7. References

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8. Abbreviations

Analytical methods:

TLC	thin layer chromatography
GC	gaschromatography
GC-MS	gaschromatography mass spectrometry
ESI-MS	elektrospray ionization mass spectrometry
EI-MS	elektroionisation mass spectrometry
HRMS	high resolution mass spectrometry
NMR	nuclear magnetic resonance
^{1}H-NMR	proton NMR
^{13}C-NMR	carbon NMR
APT	attached proton test
NOE	Nuclear-Overhauser effect
NOESY	Nuclear Overhauser Effect spectroscopy
HSQC	heteronuclear single quantum coherence
HMBC	heteronuclear multiple-bond correlation
COSY	correlated spectroscopy
MS	mass spectrometry
IR	infrared
s	singlet
bs	broad singlet
d	doublet
dd	doublet of doublet
t	triplet
q	quadruplet
m	multiplet
Hz	Hertz
MHz	Mega-Hertz
Ppm	parts per million
J	coupling constant
Ar	aryl
min	minute

h	hour
d	day
t_R	retention time
δ	chemical shift
calcd.	calculated
M^+	molecule peak
BP	basis peak
m/z	mass rate
R_f	ratio of fronts
M.p.	melting point
eV	electron volt

Solvents:

ACN	acetonitrile
THF	tetrahydrofuran
1,2-DCE	1,2-dichloroethane
DCM	dichloromethane
DME	1,2-dimethoxyethane
DMSO	dimethylsulfoxide
DMSO-d_6	deuterated dimethylsulfoxide
Et_2O	diethylether
EtOH	ethanol
MeOH	methanol
MeOD	deuterated methanol
DMF	*N*,*N*-dimethylformamide
EtOAc	ethylacetate
CH	cyclohexane
BuOH	butanol
$CDCl_3$	deuterated chloroform
D_2O	deuterated water

Reagents:

NaO*t*Bu	sodium *tert*.butoxide
NEt_3	triethylamine
NBS	*N*-bromosuccinimide
DBPO	dibenzoylperoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide)
DCC	*N,N'*-dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
CDI	*N,N´*-carbonyldiimidazole
DIBAL-H	diisobutylaluminium hydride
BuLi	butyllithium
(±)-BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
$Pd_2(dba)_3$	tris(dibenzylideneacetone)-dipalladium(0)
$PdCl_2$(dppf) * DCM	[1,1`-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex with DCM
Ni-Al	nickel-aluminium
Boc	*tert*. Butyloxycarbonyl
MeI	methyliodide
*m*CPBA	*meta*-chloroperoxybenzoic acid
TMSCN	trimethylsilyl cyanide
BHT	*tert.*-butylhydroxytoluene
PEG	polyethylene glycol

Biologival abbreviations:

ATGL	Adipose Triglyceride lipase
HSL	Hormone-sensitive lipase
MGL	Monoglyceride lipase
DAGL	Diacylglycerol lipase
PLP	phospholipase
LPL	lipoprotein lipase
TG	triglyceride

DG	diglyceride
MG	monoglyceride
G	glycerol
TAG	triacylglycerol
NEFA	non-esterified fatty acids
LD	lipid droplet
WAT	white adipose tissue
BAT	brown adipose tissue
FA	fatty acid
FFA	free fatty acid
Ser	serine
Asp	asparagine
His	histidine
PKA	protein kinase A
Wt	wild-type
Ko	knock-out
Pat	patatin
COS-7	cell line derived from kidney cells of the African green monkey
ABHD5	Abhydrolase domain containing 5
CGI-58	comparative gene identification 58
CDS	Chanarin-Dorfman syndrome
NLSD	neutral lipid storage disease
NLSDI	neutral lipid storage disease with ichthyosis
NLSDM	neutral lipid storage disease with myopathy
LLC	Lewis lung carcinoma
B16	melanoma cells
HTS	High-throughput screening
TOS	target-oriented synthesis
DOS	diversity-oriented synthesis
SH	serine hydrolase
2-AG	2-arachidonoyl-glycerol
CB1/2	cannabinoid receptor 1/2
THL	tetrahydrolipstatin
IC_{50}	half maximal inhibitory concentration

I_{200}	inhibition using an inhibitor concentration of 200 µM
EDTA	ethylenediaminetetraacetic acid
BSA	bovine serum albumin
DMEM	Dulbecco's Modified Eagle's Medium
3T3-L1	cell line derived from 3T3 cells (standard fibroblast cell line)
SGBS	Simpson–Golabi–Behmel syndrome
SPF	specific pathogen free

Others:

m	meta
p	para
o	ortho
tert.	tertiary
rt	room temperature
eq	equivalent
Fig.	figure
Å	angstrom
kDa	kilodalton
cm	centimeter
nm	nanometer
g	gramm
mg	milligramm
µmol	micromol
mmol	millimol
mL	milliliter
µL	microliter
ppm	parts per million
conc.	concentrated
M	Molar
N	Normal
µM	micromolar
U	unit
et. al.	et alii

quant.	quantitative
Y	yield
%	percent
°C	degree celsius
GP	general procedure
3-D	three dimensional
No.	number
vs.	versus

9. Danksagung

An dieser Stelle möchte ich mich ganz herzlich bei Prof. Rolf Breinbauer dafür bedanken, dass er mir die Möglichkeit gegeben hat unter seiner Betreuung in Graz meine Doktorarbeit anzufertigen und mir das überaus interessante und interdisziplinäre Thema bereitstellte. Ich bin dankbar, dass er sich gemeinsam mit mir in die Tiefen der Molekularbiologie vorgekämpft und mich stets durch seinen enormen Enthusiasmus, seine Diskussionbereitschaft und Lösungsfindung unterstützt hat.

Bei Martina Schweiger, Matthias Romauch und Robert Zimmermann vom Institut für „Molekulare Biowissenschaften“ der Karl-Franzens-Universität in Graz möchte ich mich ganz herzlich für die erfolgreiche Zusammenarbeit in den letzten 3 Jahren bedanken. Es hätte mir kaum etwas besseres passieren können als mit dieser Gruppe gemeinsam an diesem Projekt zu arbeiten und die zwei großen Bereiche, Chemie und Biologie, so erfolgreich zu kombinieren. Vielen Dank für die Unterstützung beim Einarbeiten in die biologischen Grundlagen und Techniken und für die stetige Beantwortung meiner vielen Fragen, die nur Chemiker haben können.

Herrn Prof. Ernst Lankmayr gilt ein besonderer Dank für das Anfertigen des Zweitgutachtens.

Mein Dank gilt der gesamten Arbeitsgruppe, besonders Martin Peters, Hilmar Schröder, Joanna Krysiak und Jana Rentner für die stete Diskussionsbereitschaft und sehr gute Unterstützung bei der praktischen Arbeit. Uns ist es gelungen gemeinsam so manch große Herausforderung zu meistern.

Bedanken möchte ich mich auch bei den vielen Studenten, die im Laufe der Zeit ihre Praktika in unseren Laboren durchgeführt und so unseren Arbeitskreis verstärkt haben, sowohl mit Ihrer Mitarbeit als auch mit Ihrem studentischen frischen Wind, den sie so hinein gebracht haben. Ein besonderer Dank geht dabei an Michaela Melcher, die über ein gesamtes Jahr aufopferungsvoll und mit großer Freude und Motivation gemeinsam mit mir am Thema gearbeitet hat und wir so in enger Zusammenarbeit schnell Veränderungen und Verbesserungen erreichen konnten. Ausserdem danke ich Christina Wappl, Sandra Pötz, Matthias Eichinger, Eveline Brodl, Michael Tüchler, Birgit Pichler und Bettina Grumm.

Herrn Prof. Jörg Weber und Carina Illaszewicz-Trattner danke ich für die Anfertigung der NMR-Spektren und für die steten Bemühungen um Problemlösungen. Für die Aufnahme der HRMS-Spektren gilt mein Dank Prof. Robert Saf und seiner Arbeitsgruppe.

Der vermutlich größte Dank gilt meinen Eltern und Großeltern, die mich darin bestärkt haben nach Graz zu gehen und mir es trotz der Entfernung durch ihre moralische Unterstützung, Geduld und positiven Zuspruch ermöglicht haben meine Arbeit erfolgreich abzuschließen. Sie hatten immer ein offenes Ohr für Sorgen und Probleme und schenkten mir großes Vertrauen, so dass ich meinen Weg erfolgreich gehen konnte.