Julia Blesl, BSc MSc

Synthesis and Biological Characterization of Teraryl-based alpha-Helix Mimetics

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Abstract

Protein-protein interactions (PPIs) play a central role in all biological systems, but PPIs have long been considered as poorly druggable targets. Moreover, targeting PPIs is a very challenging task, because of a relativly large protein contact sureface area. Over the past decade, the number of successful examples has been growing due to better characterization of protein-protein interfaces. The dysfunction of PPIs is linked to many diseases and therefore the inhibition of such PPIs is considered as a promising strategy for next-generation therapeutics. In more than 60 % of the interaction sites α-helices play a prominent role and so the design of scaffolds that could mimic α-helical structures are of major interst.

This was the motivation for the development of teraryl mimetics containing polar heterocycles. A building block concept for the synthesis of teraryls was developed which contains two sets of building blocks mimicking the side chains of natural amino acids relevant for PPI. Central to our strategy for the assembly of teraryls are core building blocks featuring two leaving groups with different reactivity in Pd-catalyzed cross-coupling reactions. As leaving groups on the one hand iodine is introduced and on the other hand bromine is installed. The second set of building blocks are 3,5-substituted pyridineboronic acid esters to improve the solubility and bioavailability of the synthesized molecules. The assembly of the building blocks is performed by a two-step sequential SUZUKI-MIYAURA cross-coupling procedure. High regioselectivity is ensured by a switch of the corresponding base between the two steps.

Kurzfassung

Protein-Protein Interaktionen (PPI) spielen eine wichtige Rolle in allen biologischen Systemen, jedoch wurden PPI lange als durch Medikamente schwer adressierbares Ziel angesehen. Zudem ist die Inhibirung von PPI aufgrund der relativ großen Proteinkontaktoberfläche eine sehr anspruchsvolle Aufgabe. In den letzten Jahren ist aufgrund der besseren Charakterisierung von Protein-Protein-Grenzflächen die Anzahl von erfolgreichen Beispielen gestiegen. Die Fehlfunktion von PPI ist mit verschiedenen Krankheiten verbunden und daher ist die Inhibierung von PPI ein vielversprechender Anstatz für neue Medikamente. In über 60 % der PPIs ist nur eine Seite der α-Helix für die Wechselwirkung von Bedeutung und deshalb ist die Entwicklung von Verbindungen, welche α-helicale Strukturen nachahmen können, von hohem Interesse.

Für die Entwicklung von Teraryl-Mimetika, welche polare Heterozyklen enthalten, wurde eine modulare Synthese entwickelt. Die Teraryle bestehen aus zwei verschiedenen Bausteinen, welche die Seitenketten natürlicher Aminosäuren nachahmen. Wichtig für die Zusammenführung der Bausteine ist der Mittelbaustein, welcher zwei Abgangsgruppen unterschiedlicher Reaktivität für die Pd-katalysierte Kupplung besitzt. Als Abgangsgruppe wird einerseits Iod und andererseits Brom eingeführt. Der zweite Baustein sind 3,5-substituierte Pyridin-Boronsäureester, um die Löslichkeit zu verbessern und für eine bessere Bioverfügbarkeit der hergestellten Moleküle zu sorgen. Die Zusammenführung der Bausteine erfolgt durch eine Pd-katalysierte SUZUKI-MIYAURA Kreuzkupplung. Hohe Regioselektivität wird durch den Tausch der Basen zwischen den zwei Schritten ermöglicht.

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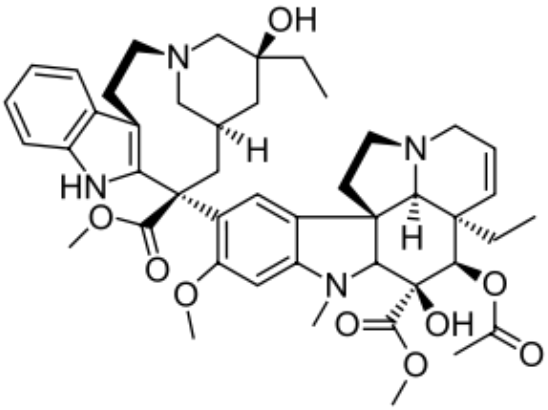
1. Introduction

Rational drug design is a method for the discovery of drugs alternative to the screening of thousands of samples extracted from natural products and has revolutionized the pharmaceutical industry. However, the understanding of protein structure and function is necessary for the design of new therapeutics. Despite all investments, like protein-crystallography, computational chemistry, high-throughput screenings as well as genetics, the number of new drugs approved by the FDA per year is reaching a plateau, which makes the development of new drugs rather complex.[1] Until recently, one major reason is that most of the available small molecule drugs target only enzymes, ion channels or receptors. For the expansion of the target space it was recognized, that proteins do not operate alone, but they interact with other proteins and biomolecules by complex interaction mechanisms. STELZL *et al.* were able to identify new protein-protein interactions by screening a protein matrix of 4456 baits and 5632 preys using an automated yeast two hybrid (Y2H) interaction assay. 195 proteins involved in diseases and 342 uncharacterized proteins were found. Indeed, the drug discovery field is beginning to focus on new concepts, for example the interest for protein-protein interactions in the cell has been growing over the last decades.[2–4]

During the last decades, blocking of PPI has been explored extensively, because the dysfunction of PPIs is linked to various diseases including for example cancer, HIV and diabetes and therefore PPIs are promising targets for new therapeutics.[5] The development of new small molecule inhibitors of such PPIs is very challenging because it is very difficult to come up with small molecules which are interacting sufficiently with the large surfaces of proteins. However, small molecules to target PPIs are found in natural products and some of them are already used for the treatment of cancer.[6] For example the vinca alkaloid vinblastine (**A**) is an anticancer drug that was first isolated in 1960 from the alkaloids of Madagascar periwinkle (*Catharanthus roseus*) plant. Due to the binding of vinblastine to the tubulin heterodimer the polymerization of the microtubules is inhibited and prevents the cell proliferation process.[7]



A

Figure 1. Vinblastine, a vinca alkaloid.[8]

Many promising applications were found in the recent years, but it will be necessary to find more efficient synthetic routes for synthesizing small molecules and test their ability to act as therapeutics. Due to the importance of PPIs as promoising drug targets the BREINBAUER group has developed a modular synthesis of teraryls, which can mimic α-helices.[9,10] So far, only few general approaches have been established for the synthesis of small molecule mimetics[11,12] and therefore the synthesis of teraryls via robust sequential SUZUKI-MIYAURA cross-coupling is an efficent strategy.

2. Theoretical Background

Many biological processes are regulated by protein-protein interactions (PPIs) and PPIs play an essential role in many cellular processes.[2,13] The number of different protein-protein interactions in human cells is estimated to be between 130.000 to 650.000.[14,15] Misregulation of PPIs can cause many diseases including cancer, HIV, diabetes and neurodegenerative diseases.[5,16] In recent years the inhibition of protein-protein interactions has attracted intense interest as a promising target for therapeutics.[17] For the initial investigation of PPIs short peptide chains were used. However, these showed several limitations in their application as drugs such as conformational instability, poor proteolytic stability and bioavailability.[18]

Since the early 1980s different strategies to overcome these drawbacks have been reported.[19] Most important approaches include side chain to side chain cross-linking, *N*-terminal caps and peptide foldamers.[18] Due to the peptidic character of all these strategies, a fourth general strategy featuring nonpeptide scaffolds that mimic larger areas of the protein surface such as an α-helix were invented by HAMILTION *et al*. (Figure 2).[20]

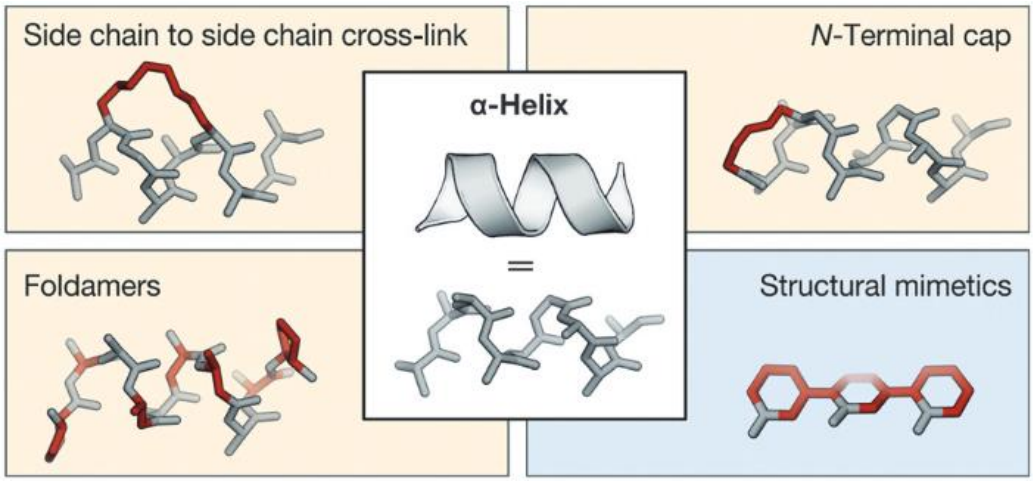


Figure 2. Schematic representation of an α-helix and general strategies for stabilization and mimicry of a helix. Picture taken from Ref.[18]

The nonpeptidic scaffold can be synthesized in a simple fashion by sequential NEGISHI-coupling reactions and the side chains in this structure have similar distances and angular relationships to those found in α-helices. HAMILTON showed by an X-ray crystal structure that a tris-ortho-substitued terphenyl can mimic the *i*, *i*+3 and *i*+7 residues of the α-helix by adopting a staggered conformation. As illustrated in Figure 3, all substituents are at the same side and the distances between these Me-groups are 5.10 Å (3,2'), 6.28 Å (2',2'') and 8.83 Å

(3,2''). These distances are in an appropriate correspondence to the *i*, *i*+3 and *i*+7 β-carbons in an α-helical peptide.[20]

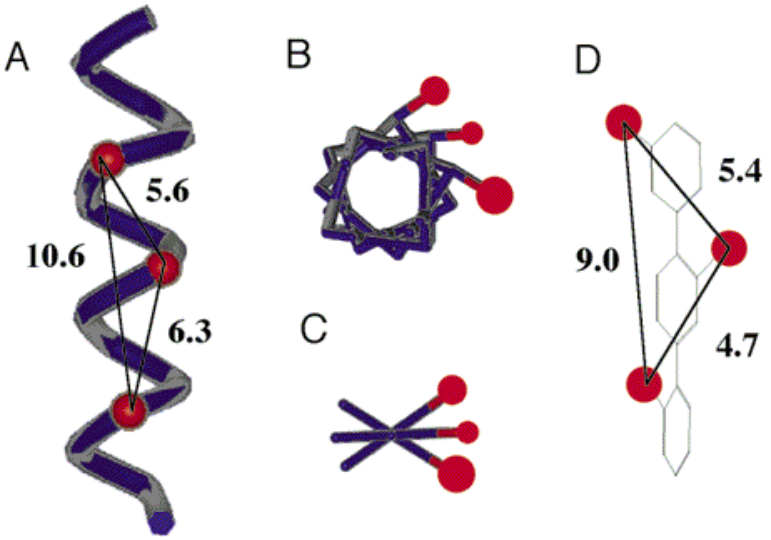


Figure 3. A) Schematic representation of an *R*-helical 12-mer peptide with substituents in *i*, *i* + 3, and *i* + 7 position, side view; B) top view; C) 3,2',2''-trisubstituted terphenyl, top view; D) side view. Picture taken from Ref.[20]

Side-chain to side-chain cross-links are short peptides which mainly mimic the parent peptide secondary structure. For the efficient stabilization of the helix intramolecular hydrogen bonds between the carbonyl oxygen and the amide proton have to be formed. Therefore, the careful selection of the length and the location of the bridges is necessary to avoid the interference with target binding. In contrast, structural mimetics are small molecules that do not have peptidic character and they are candidates for the inhibition of PPIs. Small molecules can project amino acid side-chains in orientation that mimic side-chains of protein secondary structures, such as α-helices and β-turns, which are very common in many protein-protein interfaces. Due to the strong potential for drug discovery the interest of researchers increased over the last decades to find small molecules, which mimic the α-helix, to inhibit PPIs.[15,18,21]

2.1. α-Helix peptidomimetics

α-Helices are the most common protein secondary structures which make approximately 40 % of structured protein domains and are often involed in protein-protein interactions.[22,23] They are typically 10 residues long (or 3 turns) and the projecting amino acid residues in *i*, *i*+3 or *i*+4 and *i*+7 positions are along one side of the α-helix.[22,24] The helix geometry is correlated to the amino acid sequence and α-helices are divided into three categories. About 15 % are linear, 20 % kinked and around 60 % have a curved geometry.[16,17,25,26]

HAMILTION *et al*. developed a very well fitting backbone structure to mimic α-helical peptide chains, but terphenyls have still several drawbacks. One limitation is the strong hydrophobic character of these structures, which has to be overcome. For increasing the water solubility, heterocycles were indroduced.[16,27] Therefore, many different non-peptidic small molecules α-helix mimetics have been presented in the literature, including for example indanes, terpyridines, trisubstituted imidazoles, polycyclic ethers, terephthalamides and enaminones (Figure 4), but most of the compounds have never been tested for their biological activity.[26–28]

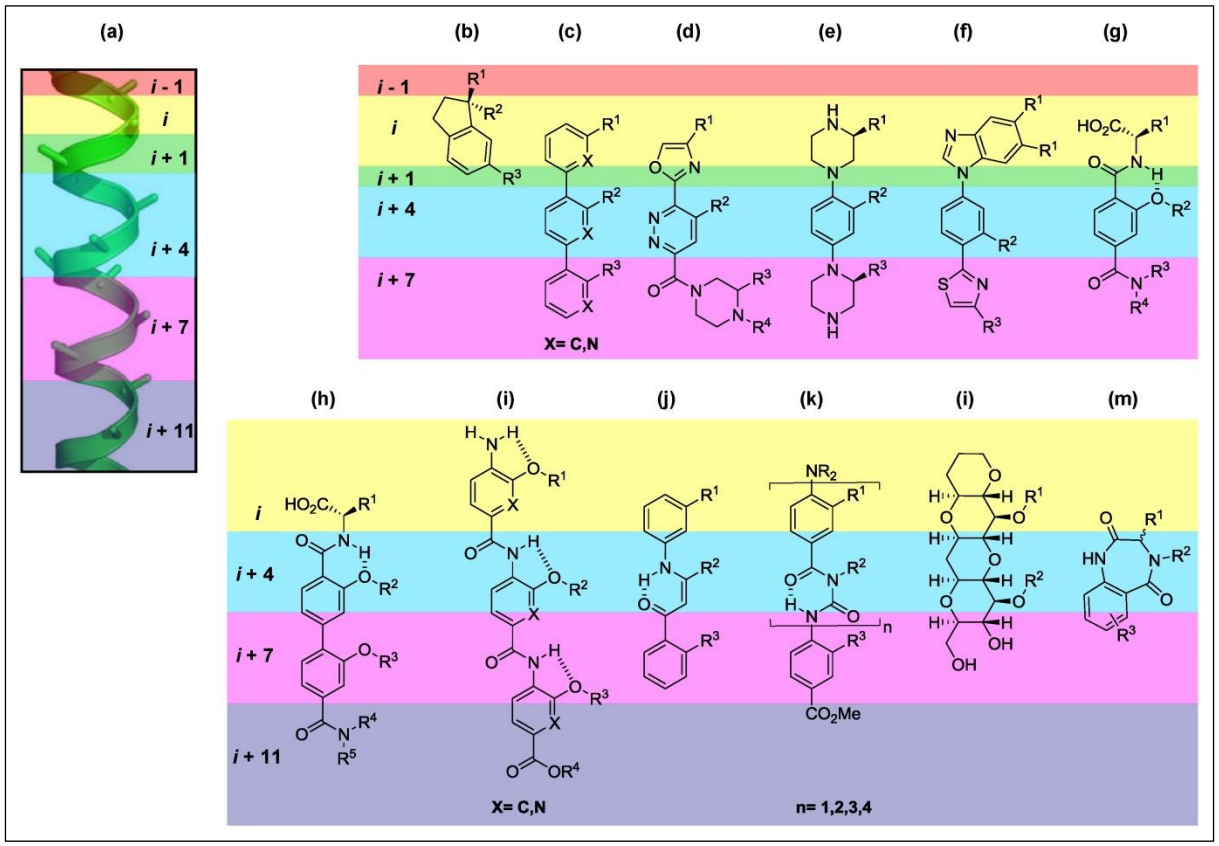
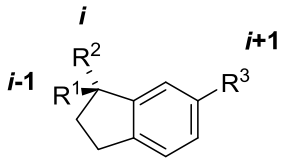


Figure 4. Schematic representations of (a) a natural α-helix with the *i*-1, *i*, *i*+1, *i*+4, *i*+7 and *i*+11 residues, (b) the 1,1,6-trisubstituted indane, (c) the terphenyl (X = C) and the terpyridine (X = N), (d) oxazole-pyridazine-piperazine, (e) 1,4-dipiperazino benzene, (f) 5-6-5 imidazole-phenylthiazole, (g) terephthalamide, (h) biphenyl 4,4'-dicarboxamide, (i) oligobenzamide (when X = C) and oligopyridine (when X = N), (j) enaminone, (k) benzoylurea, (l) 6/6/6/6 trans-fused polycyclic ether and (m) benzodiazepinedione based α-helix mimetics. Picture taken from Ref.[26]

2.1.1. Indanes template

In the beginning, 1,6-disubstituted and 1,1,6-trisubstituted indanes were designed to mimic two or three residues of an α-helix. Molecular modeling and X-ray crystallography showed that the substituent at position 1 will mimic the *i*-1 and *i* residue. Moreover, the amino acid

residue at the 6 position will mimic the *i*+1 residue (Figure 5). 1,1,6-Trisubstituted indanes are non-peptidic, low molecular weight α-helix mimetics which mimic two or three residues, but normally interacting residues are in positions *i*, *i*+3 or *i*+4 and *i*+7 and thus other small molecules have to be designed to mimic these positions.[16,26]

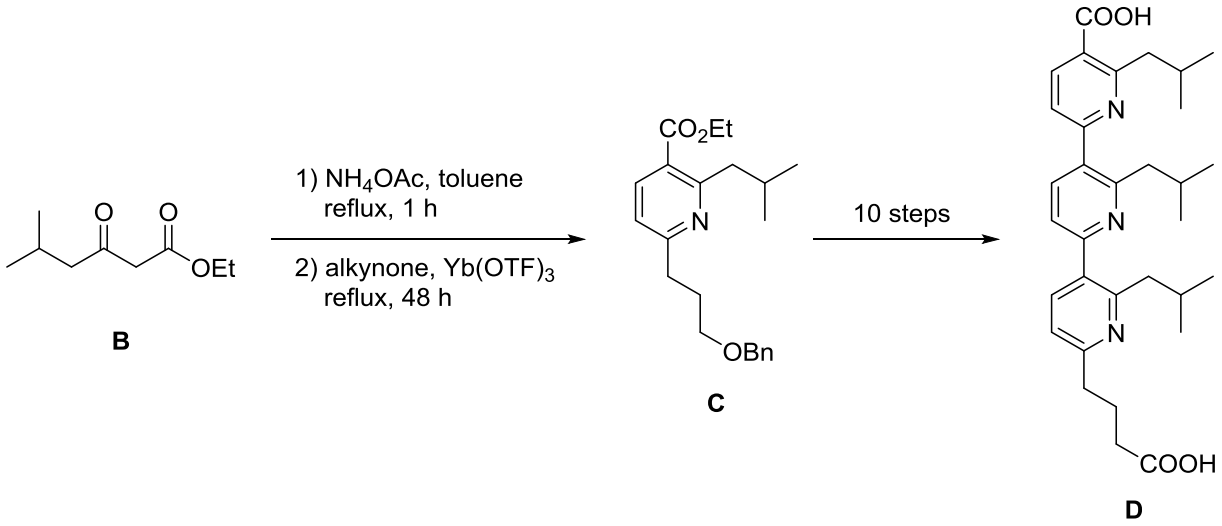


R^1, R^2, R^3 = amino acid side chains

Figure 5. Indane template mimicking an α-helix with *i*-1, *i*, *i*+1 residues.[16]

2.1.2. Terphenyl-inspired template

HAMILTON *et al*. identified a tris-ortho-substituted terphenyl which can mimic the *i*, *i*+4 and *i*+7 residues, but due to the poor water solubility and long synthesis sequences a heteroatom-based terpyridine scaffold was developed. Also this scaffold mimics the residues *i*, *i*+4 and *i*+7 of an α-helix and a significant improvement of aqueous solubility was suggested. This terpyridines were synthesized by heteroannulation methods first described by BOHLMANN and RAHTZ[29] and further developed by BAGLEY.[30] Therefore an one-pot condensation starting from a β-keto ester **B** and an alkynone with ammonium acetate and a Lewis acid catalyst was executed (Scheme 1).[31]



Scheme 1. Terpyridine synthesis.[31]

Finally, a 15 step synthesis starting from 1,4-butandiol was needed to yield terpyridine **D**. This terpyridine and other analogues should be tested for the inhibition of the interaction between Bcl-X_L/Bak, but results to these studies were never published.[31]

Other α-helix mimetics were developed by HAMILTON. In the case of diphenylindane-based mimetics the substituents can mimic the *i*, *i*+3, *i*+4 and *i*+7 of an α-helix. Moreover, to increase rigidity and water solubility and facilitate the synthesis of the mimetics terephthalamide-based derivatives were developed. In this case two functionalized carboxamide groups were installed instead of the outer phenyl rings in the terphenyl motif (Figure 6). Calculations indicated that a better water solubility and membrane permeability should be achieved with terephthalamide scaffolds.[16]

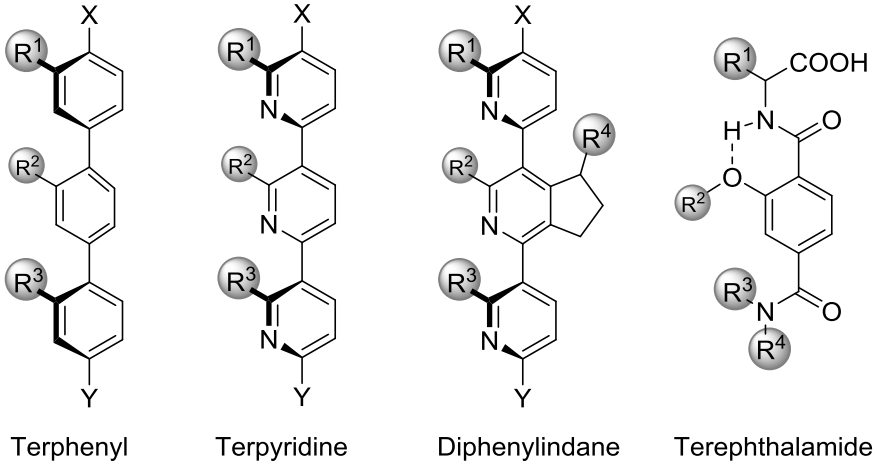
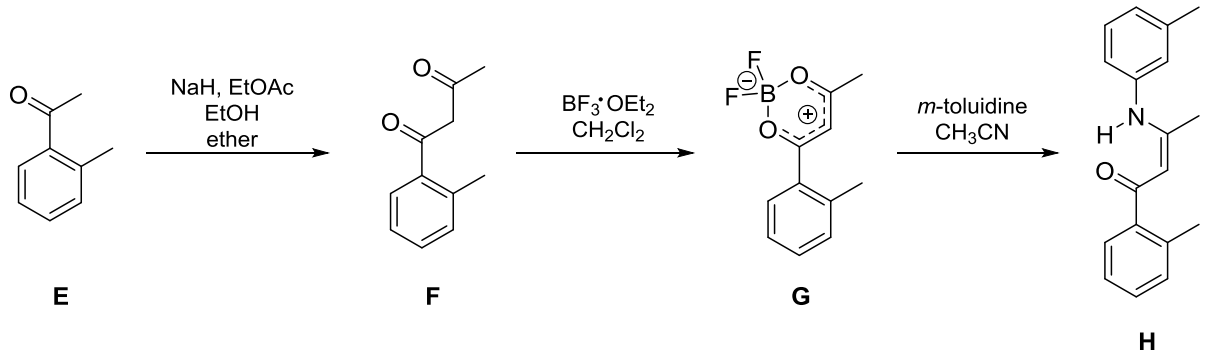


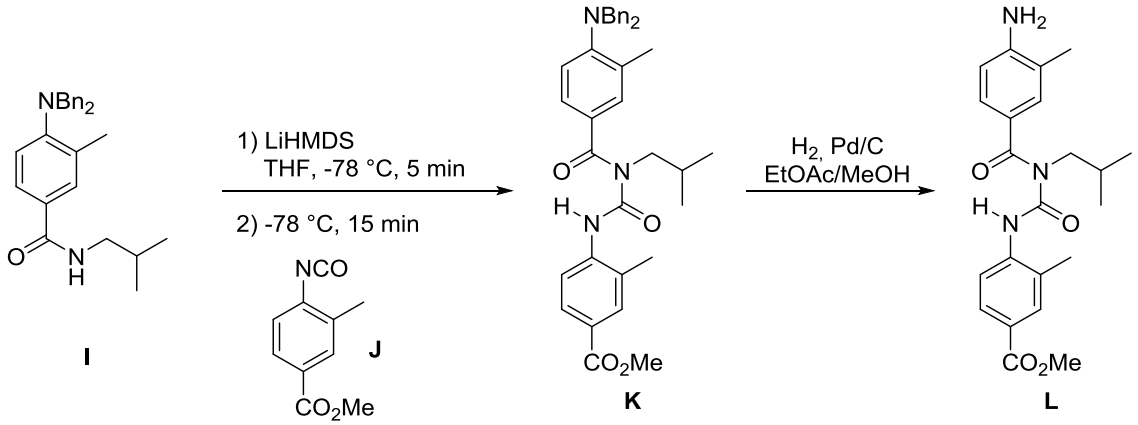
Figure 6. α-Helix mimetics developed by HAMILTON *et al*., showing the structural mimics of *i*, *i*+3, *i*+4 and *i*+7 residues of the helix.[16]

For the replacement of phenyl rings in the terphenyl scaffold with aromatic ring isosteres intramolecular hydrogen bonds were used. Therefore enaminones and benzoylurea functional groups were designed to mimic the *i*, *i*+4 and *i*+7 residue of an α-helix.[26] A straightforward synthesis of the enaminone derivatives is described by HAMILTON (Scheme 2). First a CLAISEN-condensation of 2'-methylacetophenone **E** and ethyl acetate was performed. In the second step the diketone **F** reacted with $BF_3{\cdot}Et_2O$ to yield 1,3-diketoatborondifluoride **G**. Finally, reaction of **G** with *m*-toluidine produced the enaminone **H** following a procedure by STEFANE and POLANC.[32,33]



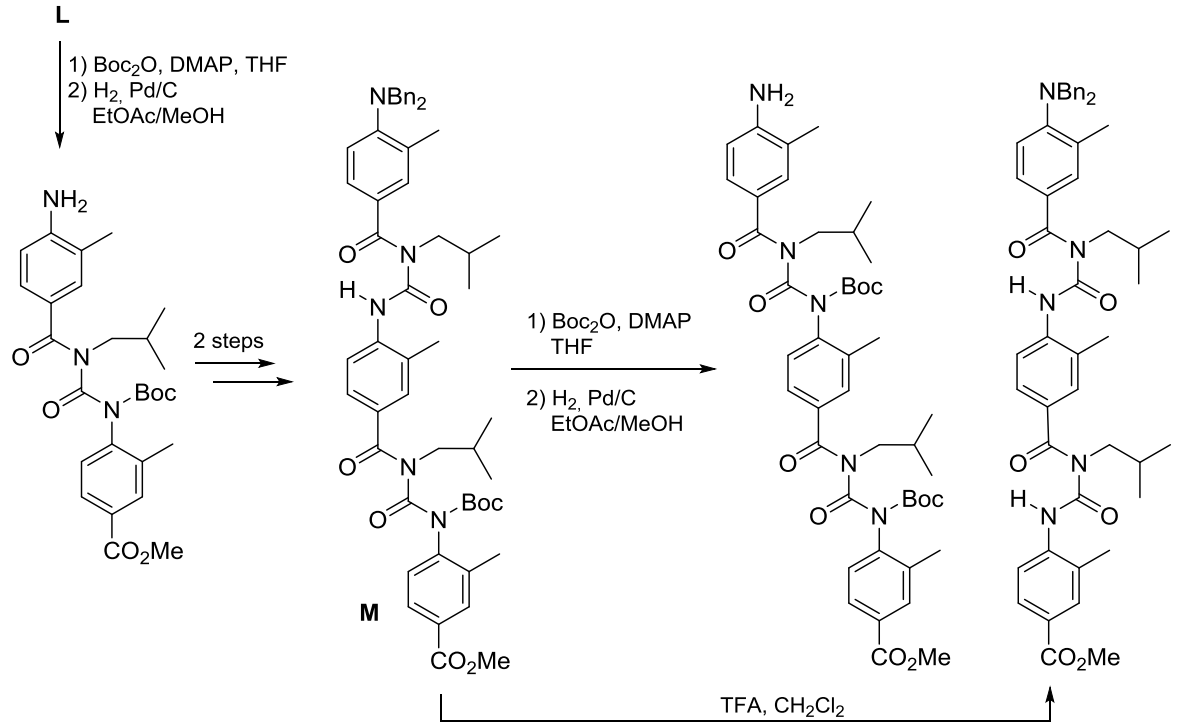
Scheme 2. Synthesis of enaminone **H**.[32]

Moreover, RODRIGUEZ and HAMILTON invented a new scaffold with increased synthetic accessibility and water solubility compared to the oligophenyl analogues. The benzoylurea oligomers alternate between aromatic rings and hydrogen-bonded acylurea structures. Therefore, an iterative synthesis of benzoylurea oligomers was developed by HAMILTON. In the first step deprotonation of amide **I** with LiHMDS followed by a nucleophilic attack on isocyanate **J** generates a bis(benzyl)-protected benzoylurea **K,** which after deprotection led to functionalized benzoylurea **L** (Scheme 3).[34]



Scheme 3. Synthesis of functionalized benzoylurea **L**.[34]

An important advantage of the benzoylurea system is the simple elongation of the scaffold by iteration of the synthetic route to mimic longer helices. Therefore RODRIGUEZ and HAMILTON described a straightforward and stepwise reaction sequence (see Scheme 4). First, **L** was protected with Boc, then debenzylation and formation of isocyanate followed by a reaction with a secondary amide and deprotection gave bis(benzoylurea) **M**. Repetition of this cycle produced hepta- and nonasubstituted mimetics. The nonasubstituted structure mimics 9 residues in a well defined manner from one face of a molecule and is able to span nearly 40 Å.[26,34]



Scheme 4. Synthesis of bis(benzoylurea) **M**.[34]

2.1.3. Polycyclic ether

OGURI *et al*. reported a strategy, inspired by marine toxins, to mimic an α-helix with polycyclic ethers. It was shown, that in a 6/6/6 tricyclic system the distance between skeletal oxygen atoms on the same side is with 4.8 Å almost identical to the interval between the *i* and *i*+4 residues in the α-helix, as illustrated in Figure 7.[35]

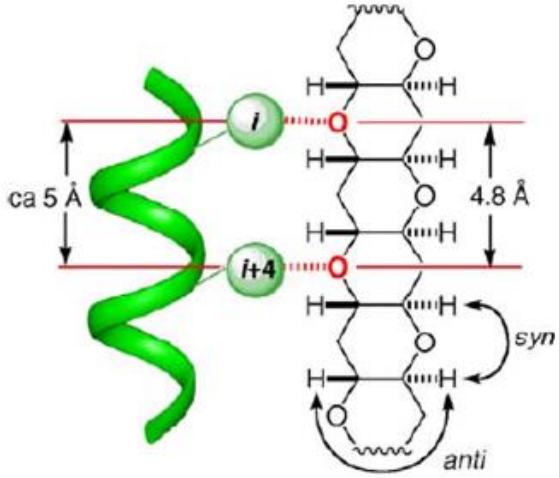
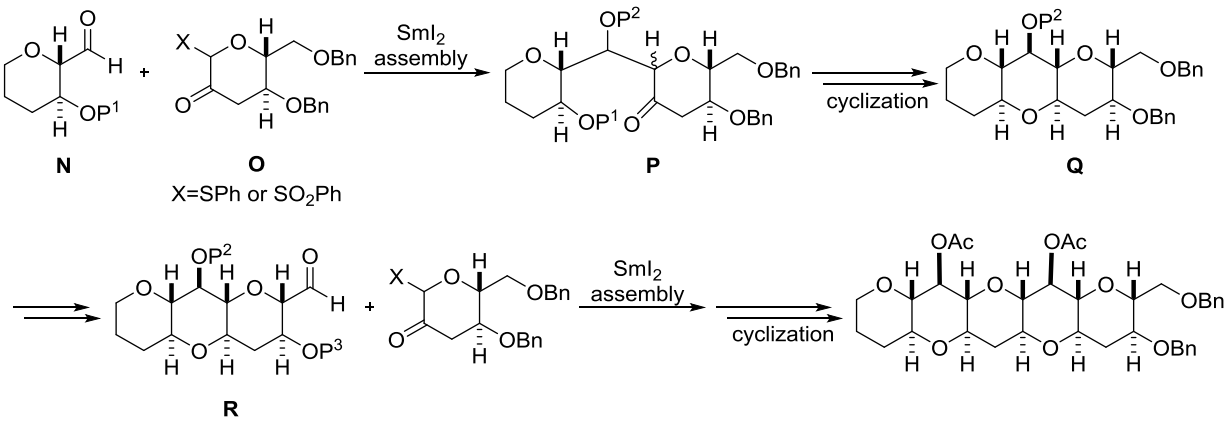


Figure 7. α-Helix and structure of a cyclic ether skeleton. Picture taken from Ref.[35]

For the synthesis of polycyclic ethers an efficient route was developed by OGURI. To form the cyclic ether scaffold a SmI_2-mediated Reformatsky-type reaction of aldehyde **N** and α-ketosulfide **O** was employed. Subsequent cyclization of compound **P** produced tricyclic ether **Q**, which is converted into aldehyde **R** and a second assembly followed by cyclization yielded the 6/6/6/6/6 cyclic ether scaffold (Scheme 5).[35]



Scheme 5. Synthesis of polycyclic ethers.[35]

2.1.4. Benzodiazepinedione

p53 protein is a tumor suppressor and plays a central role in regulating the cell cycle. The human double minute 2 (HDM2) oncoprotein is responsible for the activity and stability of the p53 protein via ubiquitination.[36] Therefore, the inhibition of HDM2 has attraced much interest for the development of anticancer drugs.[37] Several HDM2 antagonists have been described in the literature.[38,39] CUMMINGS *et al*. reported that substituents in tris-functionalized 1,4-benzodiazepine-2,5-diones (BDPs) have similar angular orientation as *i*, *i*+4 and *i*+7 positions on an α-helix (Figure 8).[26] Therefore 1,4-benzodiazepine-2,5-diones are a suitable template for inhibition of HDM2/p53 interaction.[40]

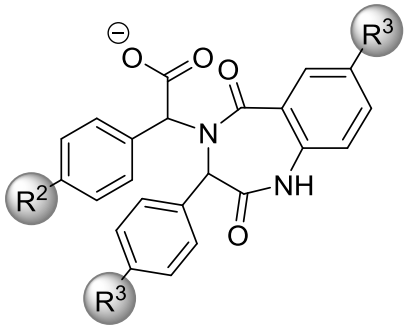


Figure 8. 1,4-Benzodiazepine-2,5-dione as synthetic small molecule.[16]

A library of derivatives of BDPs were synthesized and optimized by CUMMINGS and coworkers to mimic the *i*, *i*+4 and *i*+7 positions of the hydrophobic face of an α-helix.[41] Crystal structure and NMR studies confirmed that there is a similar binding mode between the substituted benzodiazepinedione inhibitor and the natural α-helix.[26,42]

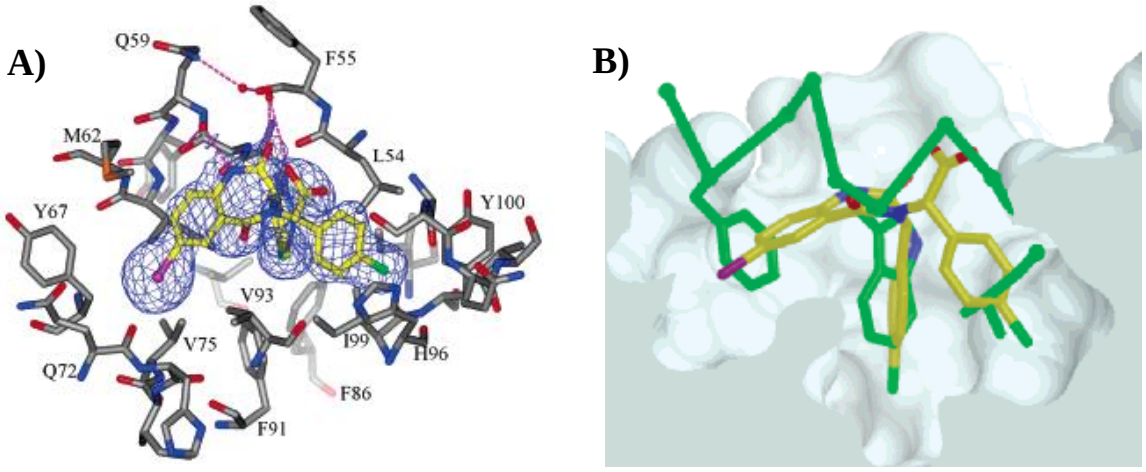


Figure 9. (A) Optimized BPD bound to the p53-binding site of HDM2. (B) Overlay of BPD (yellow) and the 9-mer peptide scaffold. Picture taken from Ref.[42]

2.2. Targets for α-helix mimetics that inhibit PPI

Many protein-protein interactions involving α-helices exist and numerous PPIs are linked to human diseases. Thus, the inhibition of a number of these interactions is important for therapeutic targets using the α-helix mimetic approach. Significant improvements were achieved in this field over the last decade.[12,16]

2.2.1. Human double minute 2 (HDM2) complexed with p53

As a tumor suppressor and transcription factor, p53 plays a central role in regulating the cell cycle.[43] In normal cells p53 is present in very low, often undetectable levels. The human double minute 2 protein, which is the human homolog of peptidic mouse double minute (MDM2), is responsible for the regulation of the p53 protein via the ubiquitin-dependent proteasome pathway.[44,45] p53 mutations are very widespread in human cancers and mutated or inactive p53 was found in over 50 % of cancerous tumors such as osteogenic sarcomas and soft-tissue sarcomas.[40,46] Also overexpression of HDM2 in cancer cells is known to inactivate p53 and can be linked to tumors.[16,47]

The crystal structure of the HDM2-p53 complex shows that HDM2 binds to p53 via a pocket-ligand type interaction and three key hydrophobic residues, Phe19, Trp23 and Leu26 in an α-helical conformation, are essential in this interaction.[16,47,48] According to literature, screening by GRASBERGER[42] and computational experiments by GALATIN[49] were reported, which were used to find inhibitors for the interaction between HDM2 and p53.

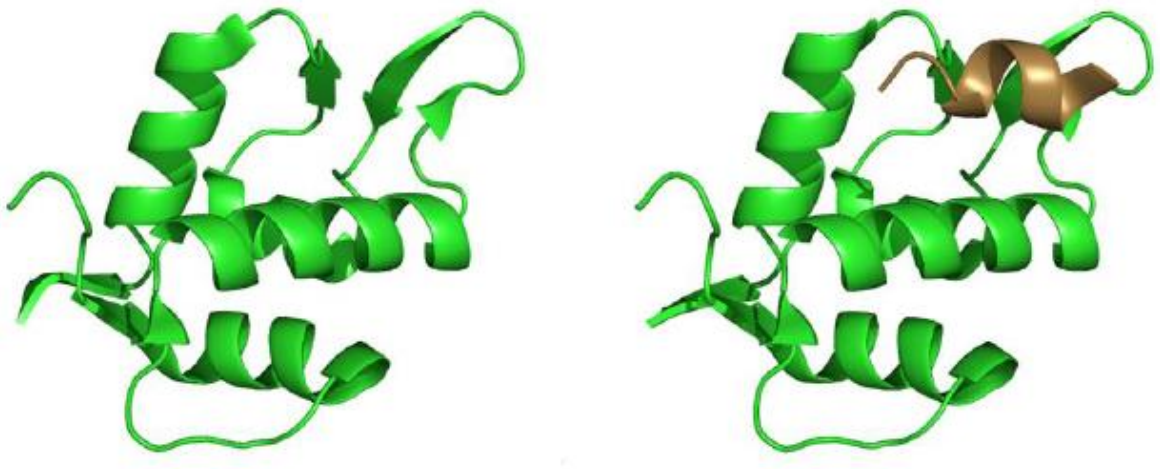


Figure 10. HDM2 and HDM2/p53-complex. Picture taken from Ref.[50]

HAMILTON *et al*. synthesized a set of terphenyls **S1-S3**, depicted in Figure 11. These compounds were tested in a fluorescence polarization (FP) competition assay with a fluorescein-labeled p53 peptide to estimate the affinities for the binding to HDM2. A decrease in the fluorescence polarization indicates the binding of the terphenyl into the hydrophobic cleft of HDM2.[47]

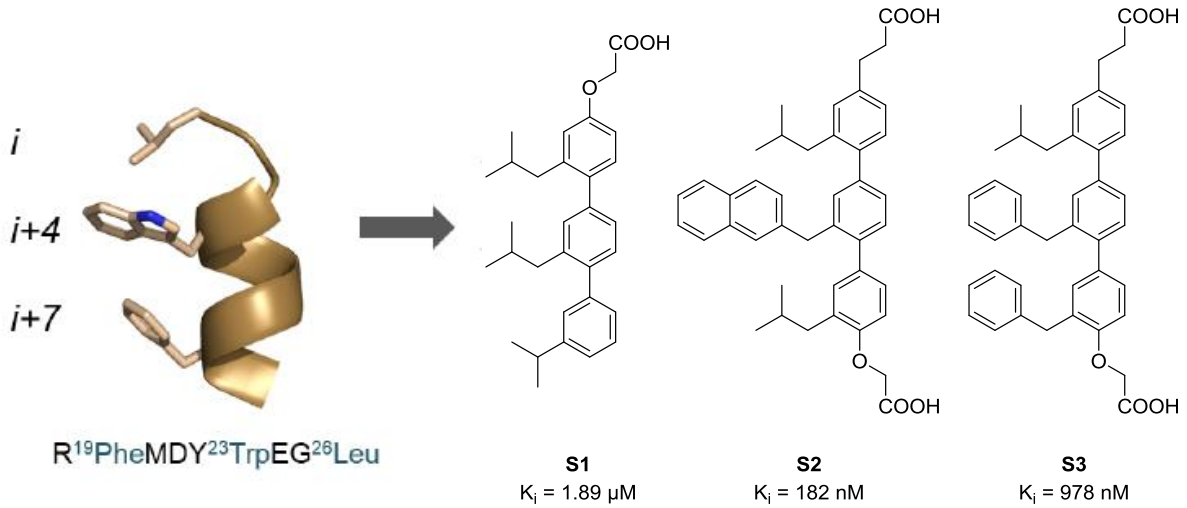


Figure 11. α-Helix of p53 and synthesized terphenyl mimetics. Picture taken from Ref.[50]

The terphenyl **S2** with isobutyl, 2-naphthylmethylene and a second isobutyl side-chain exhibited a K_i value of 182 nM. If only a few of the key side chains are present the affinity for HDM2 is significantly lower which indicates the importance of all three side chains. Due to their hydrophobic nature, several terphenyls showed in in vivo experiments membrane permeability. Moreover, they were able to initiate p53 accumulation and to activate p53 in tumor cells.[47,51]

In recent years several other groups have reported potent inhibitors of PPIs. For example SAR405838,[52] MK-8242,[53] DS-3032b,[54] NVP-CGM097,[55] RG7112,[56] HDM201,[54] RG7388,[57] ALRN-6924[58] and AMG232[59] have been discovered for the inhibition of MDM2 (Figure 12). Some of them reached clinical trials for anticancer treatment.[54]

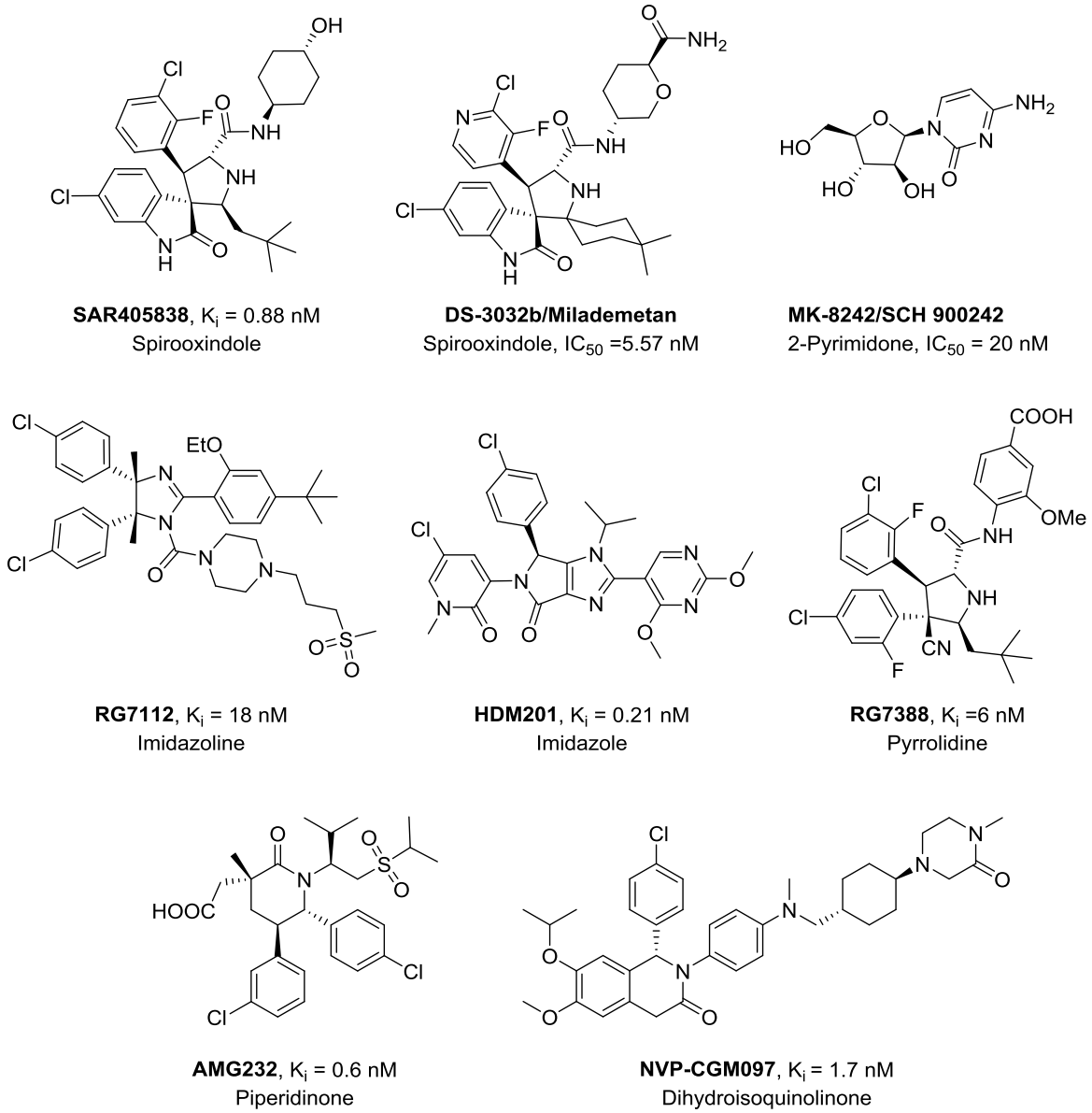


Figure 12. Representative MDM2 inhibitors in clinical trials.[45]

Researchers at JOHNSON & JOHNSON showed that benzodiazepinedione derivatives are able to interrupt the protein-protein interaction between p53 and MDM2.[42] Modification of 1,4-benzodiazepine-2,5-dione led to benzodiazepines **T1**-**T4** (Figure 13). Compounds **T3** and **T4** have a high binding affinity to MDM2 and showed better biological activity in wild-typ p53 osteosarcoma. Thus, these compounds are promising new MDM2 inhibitors.[45]

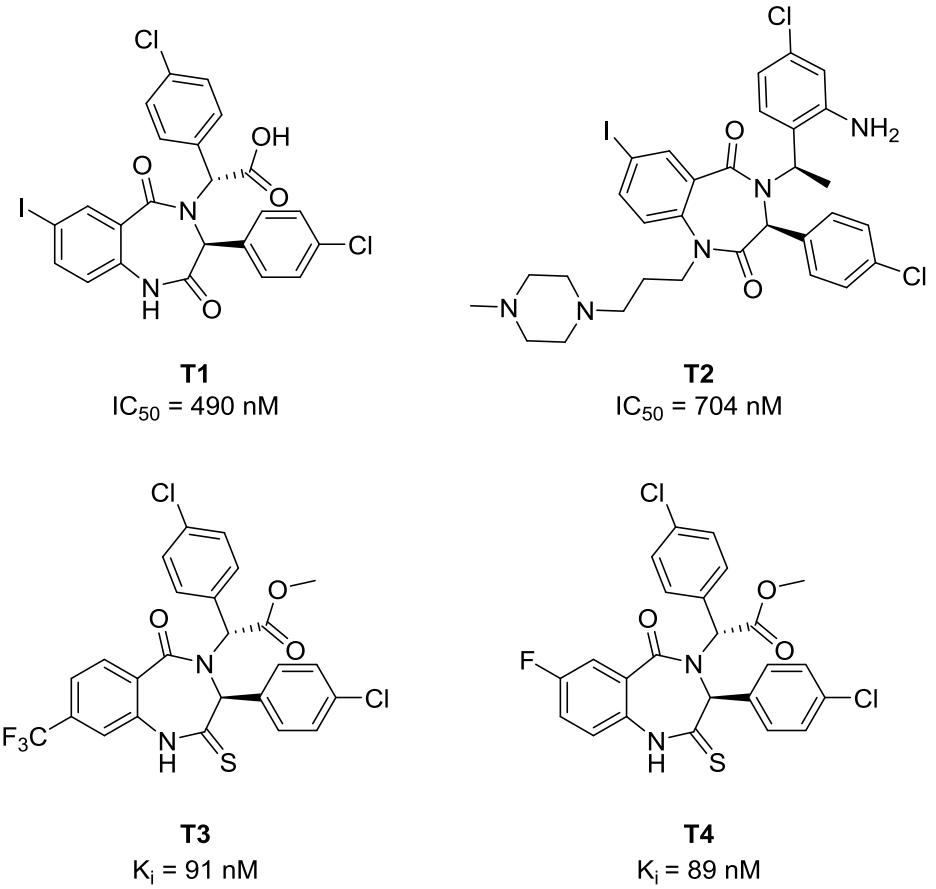


Figure 13. Benzodiazepines as inhibitors of the p53-MDM2 PPI.[45]

Researchers from HOFFMANN-LA ROCHE identified from a high-throughput screening a family of tetra-substituted imidazoles, named Nutlins, as inhibitors for p53-murine double minute 2 (MDM2) PPI. After optimization Nutlin-3 was found to be active against a wide range of cancer cells, but it was not used in an anticancer therapeutic.[39] Scientists from ROCHE discovered by further optimizing of Nutlin-3a the first MDM2 inhibitor, called RG7112, undergoing clinical trials (Figure 14).[45,60]

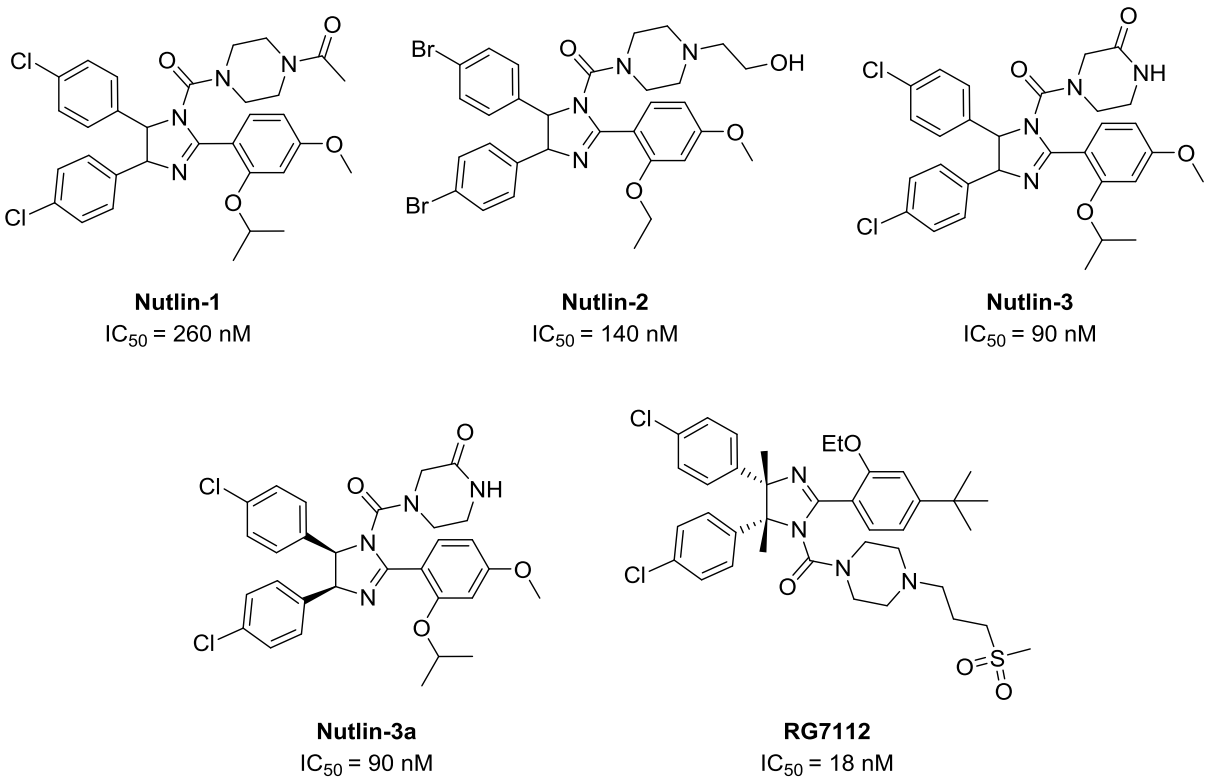


Figure 14. Nutlins constituents of murine double minute 2 (MDM2) inhibitors.[45]

DING *et al.* studied the structure of RG7112 and developed a second-generation MDM2 inhibitor, which is a pyrrolidine derivative called RG7388 (Isasanutlin). RG7388 has a better activity and selectivity and is currently in clinical studies on solid tumors and hematological tumors.[45,57]

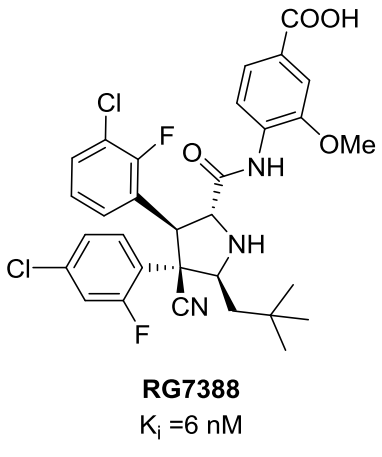


Figure 15. RG7388 as inhibitor of p53-MDM2.[45]

For targeting p53-MDM2/MDMX many small molecules are currently studied in clinical trials, depicted in Figure 16. COTI-2, RG7112, APG-115, SAR405838, NVP-CGM097, AMG-232 and HDM201 are now in phase I clinical trials for anticancer treatment. RG7388

has a low clearance, 1-day half-life and dose proportionality and has been recently tested in phase III. Unfortunately, no clinical drug, which targets p53-MDM2/MDMX, has reached the market so far.[45]

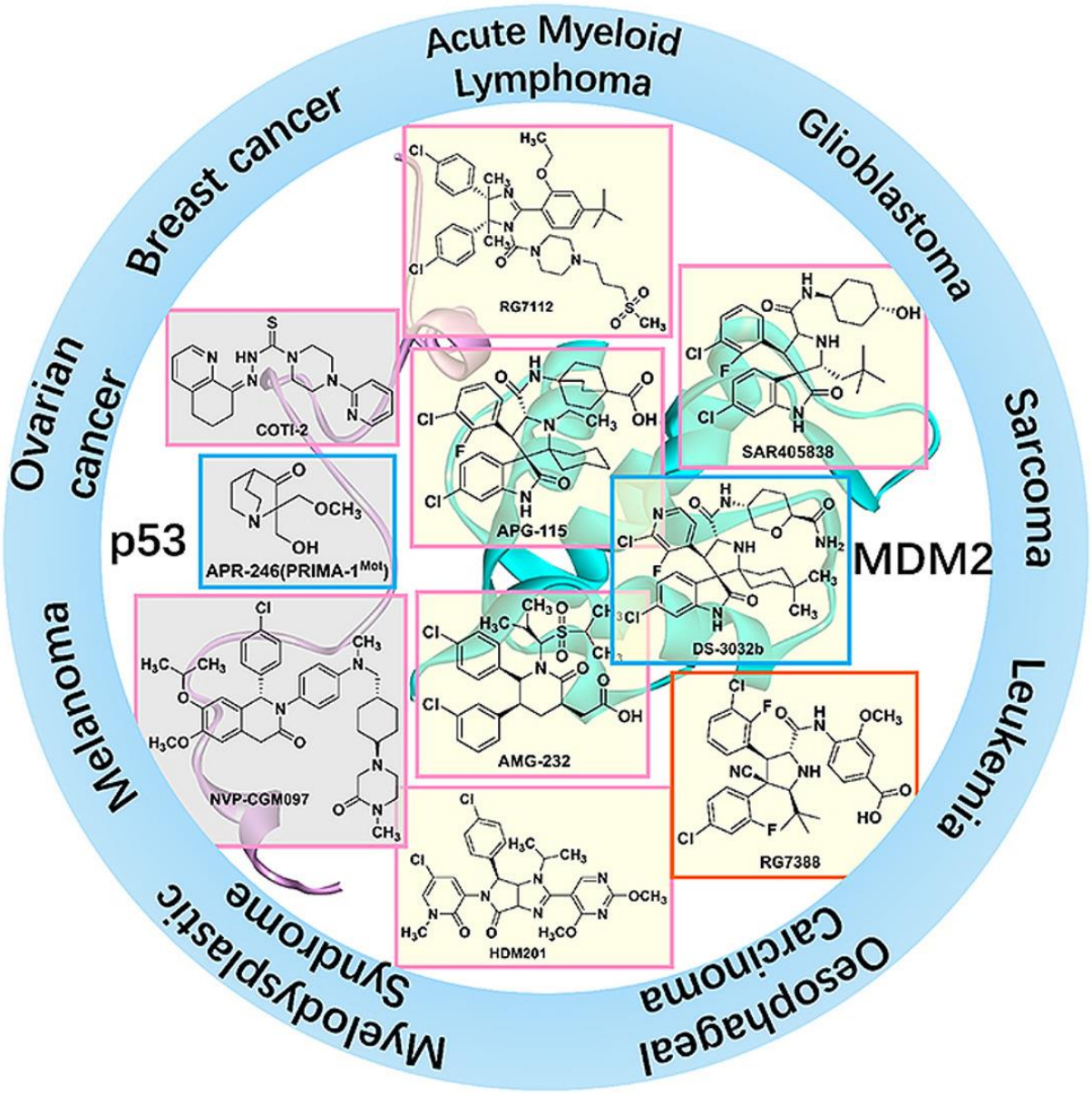


Figure 16. Small molecules in clinical trials for targeting p53 and/or MDM2. COTI-2, APR-246, and NVP-CGM097 are targeting p53 and RG7112, APG-115, AMG-232, HDM201, SAR405838, DS-3032b and RG7388 are targeting MDM2. Pink border: phase I, blue border: phase II, orange border: phase III.
Picture taken from Ref.[45]

2.2.2. Bcl-2 family

Proteins of the Bcl-2 family play a key role in the regulation of the cell death and are found in nearly all organisms like mammals, nematodes and fruitflies.[61] These proteins are divided into three groups, called anti-apoptotic, pro-apoptotic and death effector proteins. The first group inhibits apoptosis and includes for example Bcl-X_L, Bcl-2, Bcl-w, Mcl-1 and A1. Bax, Bak are death effector proteins and Bid, Bim, Bad and Puma belong to the second group.[62] Proteins from this group increase the cell death under stress conditions. Four different domains, namly BH1, BH2, BH3 and BH4, have been identified in proteins of the Bcl-2 family and in all members of the pro-apoptosis group the BH3 domain is essential for their function.[16,62,63]

The crystal strucure of Bak/Bcl-X_L complex and alanine scans identified four critical hydrophobic residues. Residues Val74, Leu78, Ile81 and Ile85 are on one face of the helix, corresponding to *i*, *i*+4, *i*+7 and *i*+11, and these amino acid chains are involed in the binding. Futhermore, an ion pair is formed between Asp83 and a lysine residue of Bcl-X_L, illustrated in Figure 17.[16,64]

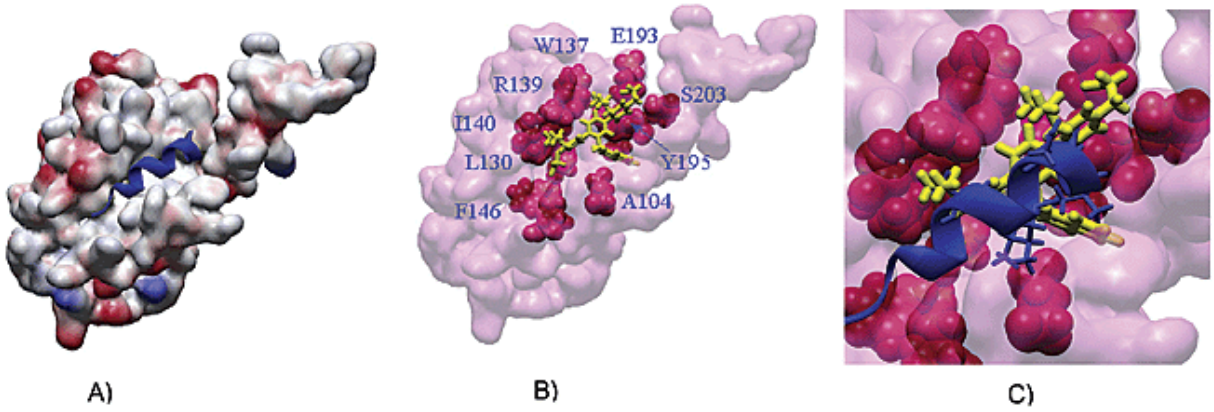
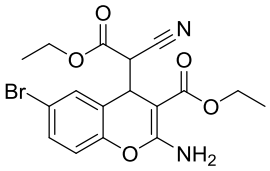
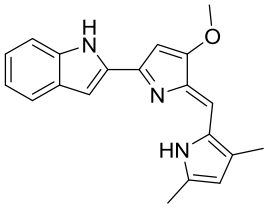
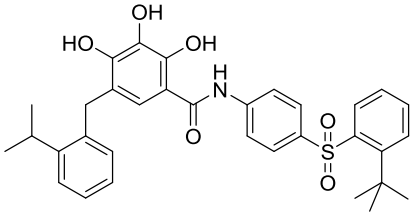
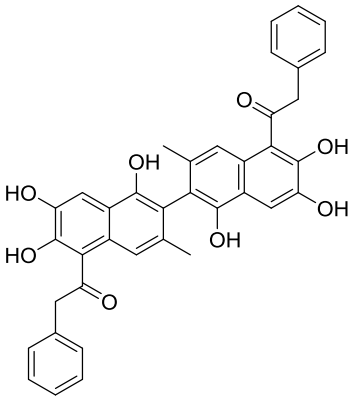


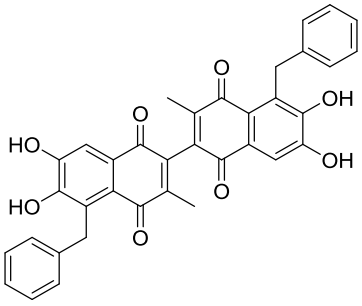
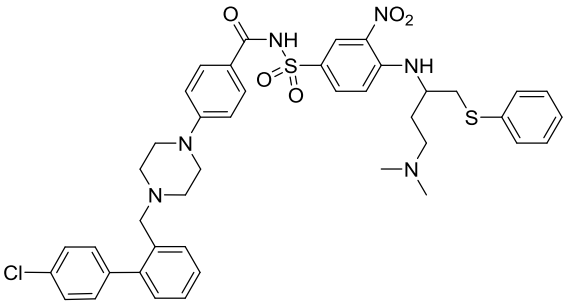
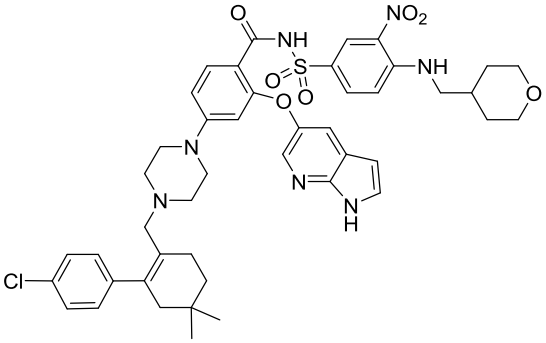
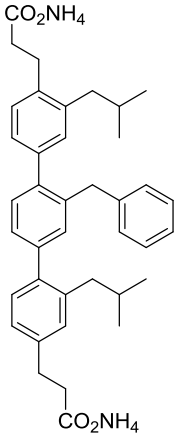
Figure 17. (A) Complex of Bak-BH3-peptide/Bcl-X_L. (B) Docking results of a terphenyl and Bcl-X_L. (C) Overlay of peptide. Picture taken from Ref.[64]

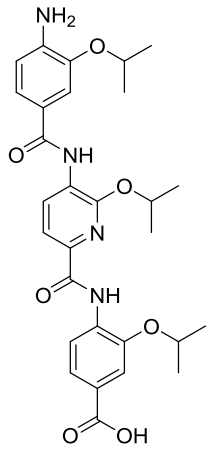
Over the last years, important progress has been made in finding small molecule Bcl-2 inhibitors.[64,65] The first reported small molecule inhibitor of Bcl-2 was HA14-1. Several other small-molecule inhibitors have been reported in the literature, for example GX15-070 (obatoclax), gyssypol derivatives,[66] ABT-737, ABT-263,[67] ABT-199,[68] S55746,[69] BH3-M6[70] and JY-1-106.[71] For the improvement of the pharmacological poperties a series of gossypol derivatives, like TW-37, BI79D10 and BI97D6 were reported. These derivaties are currently in preclinical stages. Through NMR-based fragment screening ABT-373 was

identified to bind to Bcl-2, Bcl-X_L and Bcl-w with high affinity. Due to low aqueous solubility ABT-263 and ABT-199 were invented. ABT-199 showed very good clinical results and is the first FDA approved drug for the treatment of CLL and AML. In Table 1 some small molecule inhibitors that target anti-apoptotic Bcl-2 proteins are listed and the status of the clinical studies is shown.[62]

Table 1. Small molecule inhibitors that target anti-apoptotic Bcl-2 proteins.[62]

Name	**Chemical structure**	**Targets (K_i (nM))**	**Status**
HA14-1		Bcl-2 (9000)	Preclinical
Obatoclax		Bcl-2 (1110), Bcl-X_L (4960), Bcl-w (7010), Mcl-1 (2000), A1 (5000)	Phase II
TW-37		Bcl-2 (290), Bcl-X_L (1110), Mcl-1 (260)	Preclinical
BI79D10		Bcl-2 (360), Bcl-X_L (190), Mcl-1 (520)	Preclinical

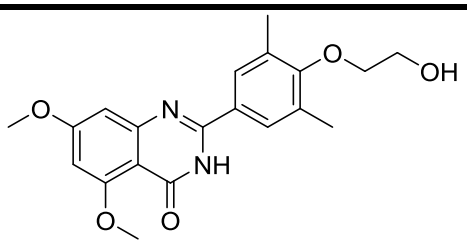
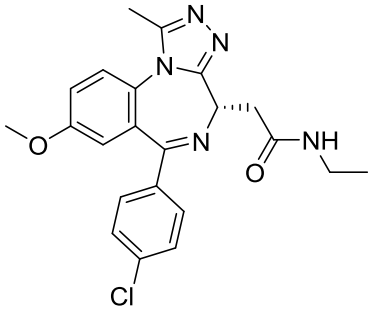
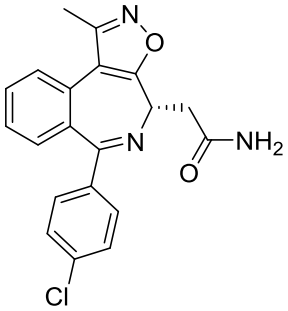
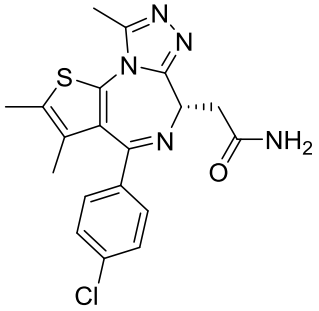
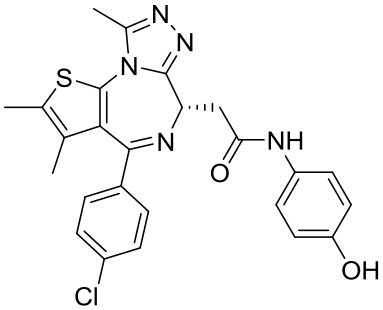
BI97D6		Bcl-2 (31), Bcl-X_L (76), Mcl-1 (25), A1 (122)	Preclinical
ABT-737		Bcl-2 (<1), Bcl-X_L (<0.5), Bcl-w (0.9)	Preclinical
ABT-199		Bcl-2 (<0.01)	Approved for patients with relapsed or refractory 17p-deleted CLL
BH3-M6		Bcl-X_L (1500), Mcl-1 (4900)	Preclinical

JY-1-106		Bcl-X_L (179), Mcl-1 (1790)	Preclinical

2.2.3. Bromodomain family

Bromodomains were first found by TAMKUN *et al*. in *Drosophila* gene bramah and later ZENG *et al*. identified the bromodomains as an acetyl-lysine binding protein. So far 56 modules of human bromodomains are known and these can be divided into eight groups. Central to all available bromodomains is the hydrophobic pocket formed by four α-helix bundles linked by diverse loop regions. Bromodomains are so called "readers" of lysine acetylation and they are responsible for transducing the signal and translating it into phenotype.[72] Disregulation of the acetylation levels is linked to cardiovascular disease. Therefore Apabetalone is now tested in clinical trials and reached phase III in 2017. Moreover inhibitors for the treatment of cancer are invented. For example GSK525762, CPI-0610, Ten-010 and OTX015 are currently in clinical trials for the treatment of cancer.[73] In Table 2 PPI inhibitors, which have reached clinical trials, are shown.

Table 2. Protein-protein interaction inhibitors that have reached clinical trials.[74]

Name	Chemical structure	Therapeutic area	Status
Apabetalone		Cardiovascular	Phase III
GSK525762		Cancer	Phase I/II
CPI-0610		Cancer	Phase I
Ten-010		Cancer	Phase I
OTX015		Cancer	Phase I

2.2.4. Smooth muscle myosin light chain kinase (smMLCK) with calmodulin (CaM)

Calmodulin (CaM) is a regulatory protein and interacts with a number of proteins. One interacting protein is the smooth muscle myosin light chain kinase (smMLCK), which is activated by $(Ca^{2+})_4$-CaM and initiates a signal cascade that leads to muscle contraction.[16,75] According to the crystal structure of CaM bound to the α-helix peptide of smMLCK the *i*, *i*+4 and *i*+7 (Trp800, Thr803, and Val807) residues of the α-helix are involved in the binding. For the development of inhibitors for CaM-smMLCK interaction HAMILTON and co-workers used the designed terphenyl scaffold. The synthesized tris-functionalized 3,2',2''-terphenyls **U1-U4** as a mimic of the calmodulin binding face of smMLCK are shown in Figure 18.[16,20]

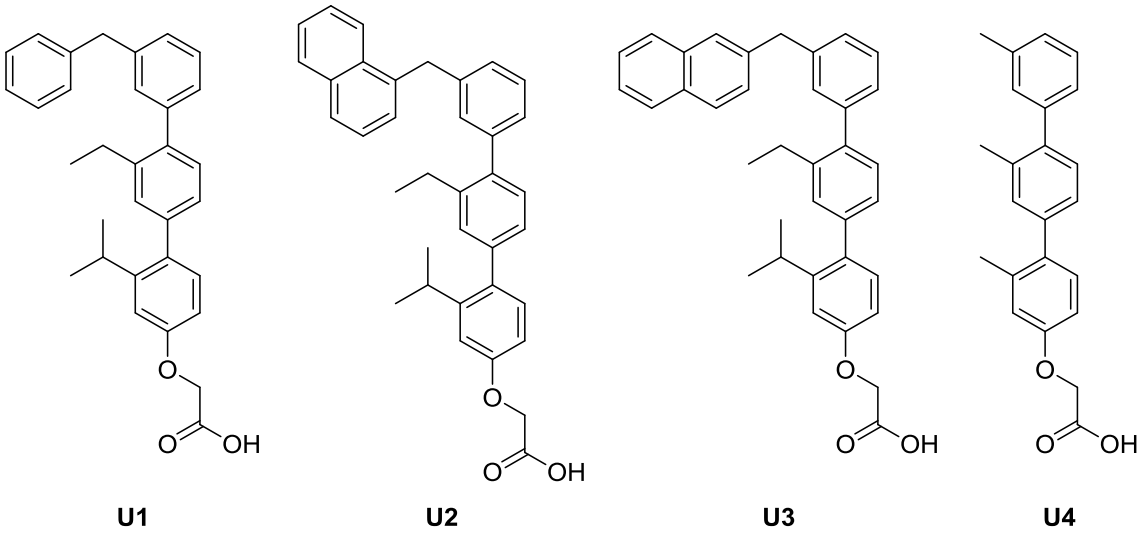


Figure 18. Terphenyls synthesized for the inhibition of smMLCK/CaM.[17]

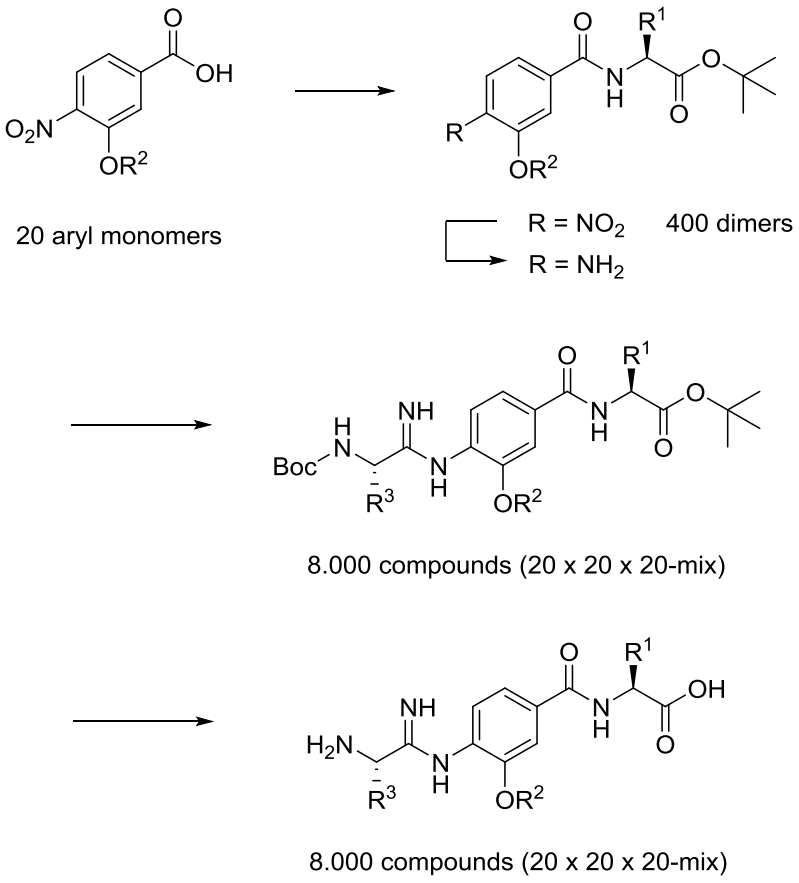
For better solubility in buffer with <1 % DMSO the free carboxylic acid was converted into the corresponding ammonium salt. The synthesized terphenyls were also tested by affinity chromatography and competition assay for the affinity to CaM. The terphenyls with the 1-naphthyl and the 2-naphthyl substituents are very potent inhibitors and show an IC_{50} of 9 nM and 20 nM. The potency of **T2** represents an 8-fold improvement over the peptide RS20.[16,20]

2.3. Modular synthesis of α-helix mimetics

For the synthesis of α-helix mimetics still long and time consuming linear syntheses are necessary. So far only few strategies have been reported in the literature for the synthesis of these molecules and for synthesizing libraries of α-helix mimetics by modular or combinatorial approaches.[11,12]

2.3.1. Triaryl amide scaffold

Inspired by the terphenyl scaffold of HAMILTON, BOGER *et al*. established a solution-phase synthesis of triaryl amide scaffolds. One advantage of this scaffold is the simple synthesis and due to the amide bonds greater flexibility, higher polarity and improved aqueous solubility were achieved.[76]



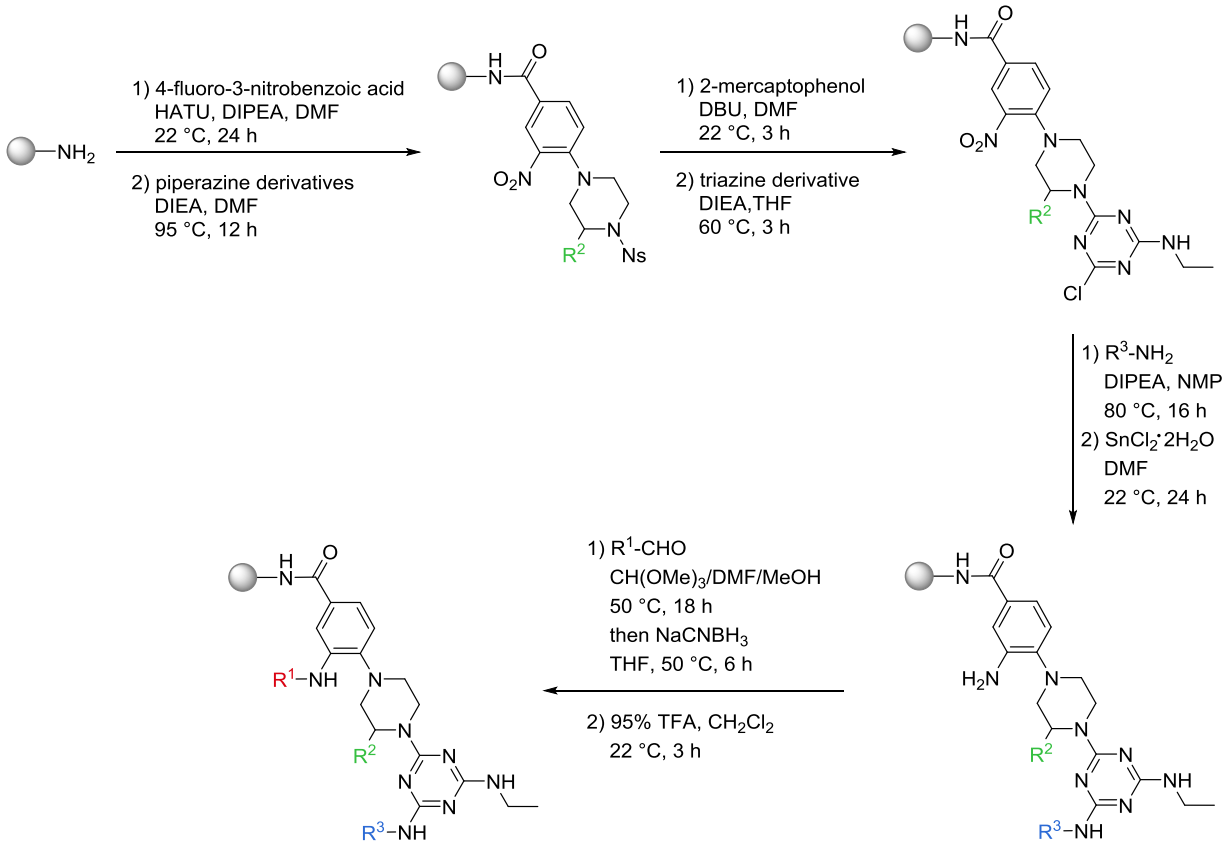
Scheme 6. Library synthesis of triaryl amide scaffolds.[76]

For the synthetic approach aryl nitro compounds were used as starting material. On the one hand the aryl nitro group acts as an amine protecting group and on the other hand it allows the introduction of different R^2 groups via nucleophilic aromatic substitution. The building blocks containing an amine and a carboxylic acid are connected by simple amide coupling (Scheme

6). 20 amino acid side chain variants were used and a 20 x 20 x 20 mix produces 8.000 compounds, representing all permutations of a naturally occurring α-helix. The isolation and purification of all intermediates was accomplished by an acid/base extraction protocol.[76,77] This α-helix mimetic library was screened against the NHR hydrophobic pocket of HIV-1 envelope glycoprotein gp41 and inhibition of the CHR α-helix led to small molecule inhibitors with a K_i value of 0.6 - 1.3 µM.[78]

2.3.2. Piperazine-triazine scaffold

LIM *et al*. developed a piperazine-triazine based scaffold as non-peptidic, α-helix mimetic small molecules, which were inspired by terphenyl scaffolds. For the synthesis solid-phase chemistry was used and rapid and easy access to different compounds is ensured (Scheme 7).[17,79]



Scheme 7. Solid-phase synthesis of a piperazine-triazine library.[79]

By screening the phenyl-piperazine-triazine library a selective inhibitor of the Mcl-1/BH3 PPI was identified and it was demonstrated that the scaffold is able to serve as an α-helix mimetic. The scaffold with three phenyl residues at R^1, R^2 and R^3 (PPT-31) was found to be the most potent inhibitor. Molecular modelling shows that PPT-31 overlays with the three key residues

Val220, Val216 and Leu213 of the α-helical BH3 peptide (Figure 19). The determination of the binding affinity of PPT-31 was done by a competitive fluorescent polarization assay with a K_i value of 7.3 µM.[79]

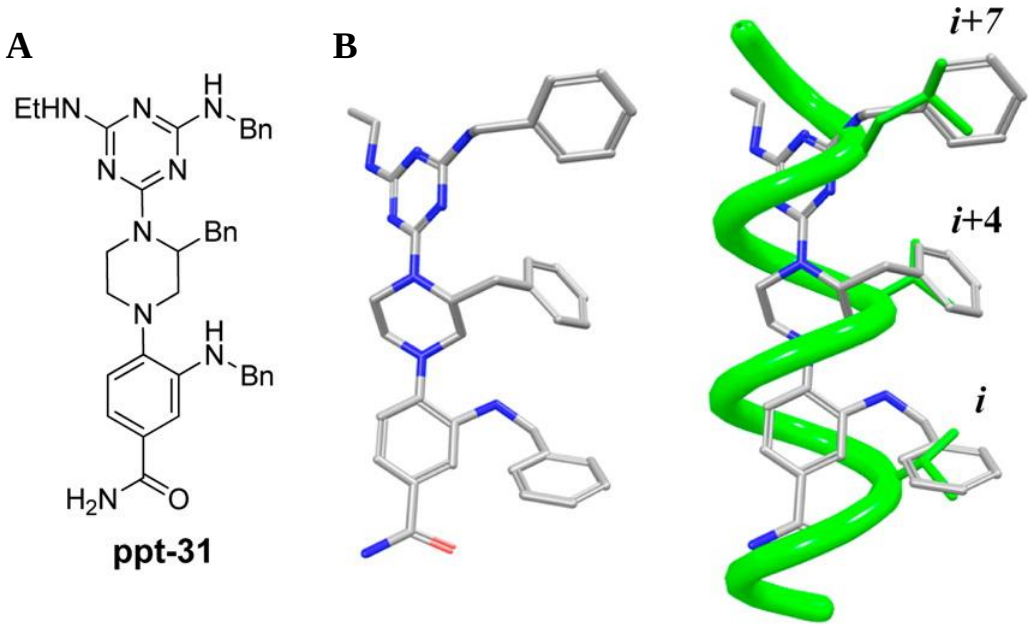


Figure 19. A) Chemical structure of PPT-31. B) Energy-minimized structure of PPT-31 and overlay of PPT-31with an α-helical peptide. Picture taken from Ref.[79]

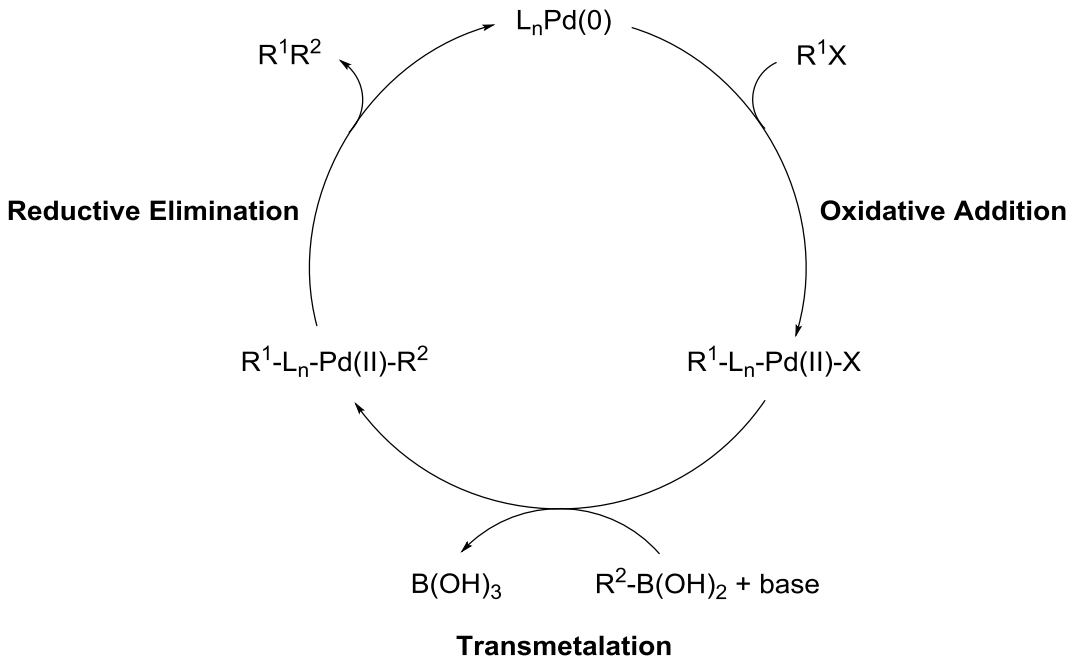
2.4. Palladium-catalyzed cross-coupling reactions

Nowadays cross-coupling reactions are one of the most general and straightforward method for the formation of carbon-carbon bonds. Nearly 60 years ago a C-C bond was typically formed by pericyclic reactions or by stoichiometric reactions of reactive nucleophiles with electrophiles.[80] In the 1960s cross-couplings were limited to Li- and Mg-organyls, but many side reactions and low chemoselectivity was observed.[81] In 1972 KUMADA *et al*. discovered a new cross-coupling of Grignard reagents catalyzed by a nickel-phosphine complex. The use of phosphine ligands made Ni-catalysis a widely applicable method and they also described a three step mechanism for the catalytic cycle.[82] In the same year HECK described the coupling of iodobenzene with styrene, today known as HECK-reaction. The coupling protocol was a milestone for the further development of organometallic catalysis in organic synthesis. NEGISHI first replaced Mg in the reaction developed by KUMADA *et al*. with Al. By screening Pd instead of Ni better selectivity was achieved and so a distinct advantage over Ni was demonstrated.[81,83] In 1977 the first use of Zn in the Pd- or Ni-catalyzed cross-coupling was reported by NEGISHI *et al*.[84] and FAUVARQUE and JUTAND.[85] In the same year KOSUGI *et al*.

published the first Pd-catalyzed cross-coupling with organotin reagents[86] and SUZUKI *et al*. described the first cross-coupling with Sn and B.[87] In 2010 the impact of Pd-catalyzed cross-coupling reactions in organic chemistry was recognized by the Nobel Prize for Chemistry for HECK, NEGISHI and SUZUKI.[80] The importance and broad application of the discovery of palladium-catalyzed cross-coupling reactions in industry as well as in academia is well documented in the literature.[88]

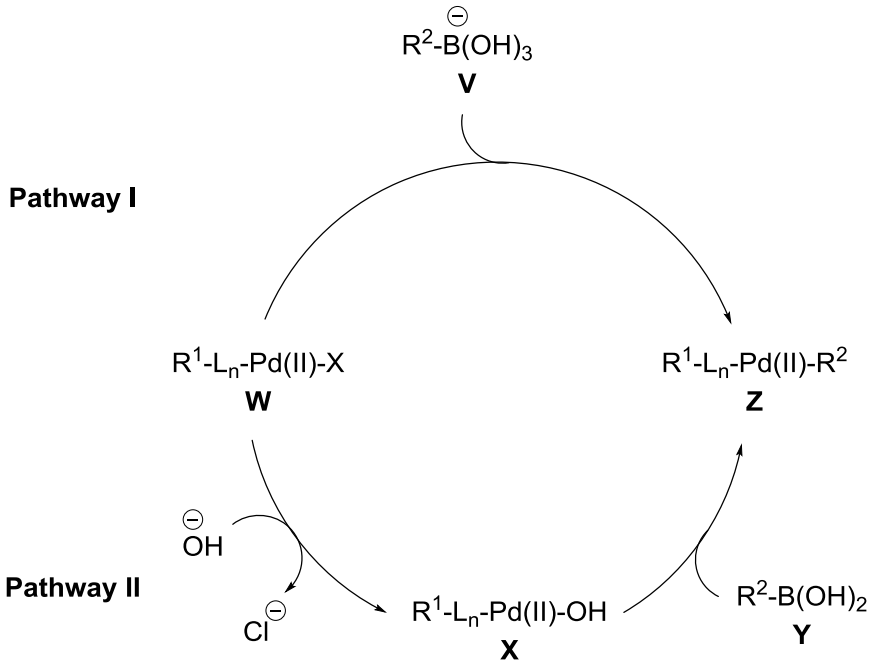
2.4.1. Mechanistic studies towards the Suzuki-Miyaura coupling

The general mechanism for the Pd-catalyzed cross coupling reaction is shown in Scheme 8. The catalytic cycle contains three key steps, namely oxidative addition, transmetalation and reductive elimination.[89]



Scheme 8. Mechanistic cycle for the SUZUKI cross-coupling reaction.[89]

The oxidative addition step and the reductive elimination are today well understood, but the the transmetalation step turned out to be more complex. In general two pathways are discussed for the transmetalation. The first pathway involves a nucleophilic attack of a borate **V,** which is formed before, to the palladium halide **W**. In the second pathway first the formation of a nucleophilic palladium hydroxocomplex **X** takes place and then complex **Z** is formed by transmetalation via a neutral boronic acid **Y** (Scheme 9).[50,90] DFT calculations by BRAGA *et al*. showed that pathway II is energetically more favored.[91]



Scheme 9. Two pathways for the key transmetalation step.[89]

Over the last years improvements of the cross-coupling reaction with different catalyst systems and ligands has been achieved and more and more complex compounds were synthesized via cross-coupling.[92] Moreover, general procedures for the coupling of heterocycles have been described in literature.[93]

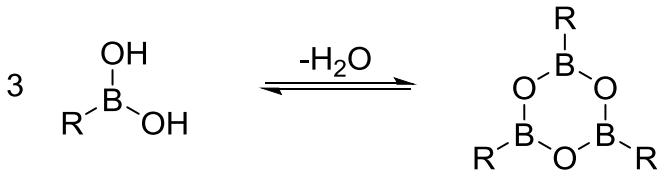
2.4.2. Boron reagents

The SUZUKI-MIYAURA coupling has broad application, because usually mild conditions can be used and a high tolerance for functional groups is given in this reaction. Organoboron reagents are relatively stable and in general environmentally unproblematic. Many different protocols have been established for the preparation of organoborons.[94]

2.4.2.1. Boronic acids

Boronic acids (Scheme 10) were the first used boron reagents for palladium-catalyzed cross-coupling reactions in 1981 and they are still often used due to their high atom-economy.[94] There are many methods for the preparation of boronic acids and the primary approach for the synthesis of these is via other organometallic reagents, such as organolithium- or organomagnesium-species. First the organometallic reagent is treated with boric esters ($B(O\textit{i}Pr)_3$ or $B(OMe)_3$) as an electrophile at low temperature to attenuate over-alkylation and then hydrolysis releases the free boronic acid. The low functional group tolerance is the major

disadvantage of this approach.[94-96] For the direct preparation of boronic acids palladium catalysis similar to the MIYAURA-borylation protocol is used. In this method bisboronic acids instead of B_2Pin_2 is used and the intermediate boronic acids can be further converted to other boron reagents.[94,97]



Scheme 10. General structure of boronic acids and entropically favored boroxines.[94]

2.4.2.2. Boronic esters

Numerous preparation methods for boronic esters are found in the literature and one approach is the synthesis via organometallic species such as GRIGNARD- or organolithium reagents.[10] A broad range of functional groups is tolerated by the use of KNOCHEL-type GRIGNARD-chemistry.[98] Moreover, boronic esters can be conveniently introduced via Pd-catalyzed MIYAURA borylation. This palladium-catalyzed conversion of an aryl- or alkenyl halide to the corresponding boronic esters is highly functional group tolerant.[94,99] The mechanism of this transformation is similar to the SUZUKI-MIYAURA cross-coupling involving oxidative addition, transmetalation and reductive elimination.[100] According to literature other methods are described, for example direct Ir-catalyzed CH-borylation,[101] electrophilic arene borylation[102] or introduction by a radical, metal-free pathway from aryl amines.[103]

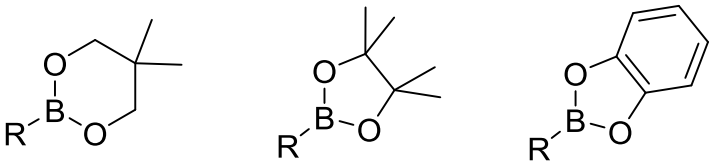
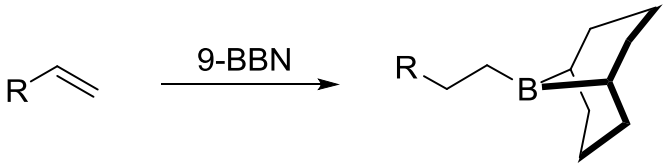


Figure 20. Examples for boronic esters used in SUZUKI-MIYAURA coupling.[104]

2.4.2.3. Organoboranes

Organoboranes are generally used in SUZUKI-MIYAURA coupling and the most common synthesis is hydroboration (Scheme 11). Thereby conversion of an alkene or alkyne by addition of a B-H bond gives the corresponding alkyl- or alkenylborane. It was soon discovered that trialkylboranes were formed when alkenes were treated with $NaBH_4$ and

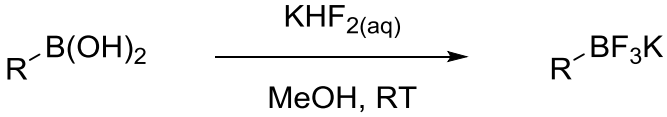
dialkyl boron and the addition of B-H occurred in a *syn*-selective anti-MARKOVNIKOV addition.[96,105]



Scheme 11. General example for preparation of organoborones via hydroboration.[96]

2.4.2.4. Organotrifluoroborate salts

In 1960 CHAMBERS first described potassium organotrifluoroborate salts,[106] but in the next thirty years only a handful publications on this topic were reported. For the preparation of BF_3K-salts in general boronic acids are treated with KHF_2 (Scheme 12). Isolation of the product is perforemd by precipitation or evaporation of the solvent. An alternative method for the synthesis of BF_3K-salts is the preparation via KF and tartaric acid. The isolation of the BF_3K-salts is fast and easy, because all co-products precipitate out of the solution and the salt is isolated by simple filtration and evaporation. Due to that the fluorinating agent can be used in stoichiometric amounts.[94],[107]



Scheme 12. General procedure for the synthesis of BF_3K-salts.[108]

2.4.2.5. *N*-Coordinated boronates

N-Coordinated boronates consist of a cyclic boronic ester scaffold with a central nitrogen atom and the most common *N*-coordinated boronates used in the SUZUKI-MIYAURA coupling are for example *N*-methyldiethanolamine, *N*-phenyldiethanolamine and *N*-methyl-iminodiacetic acid (MIDA) (Figure 21). In the early 1980s MIDA boronates were first prepared and characterized and later BURKE described the use in iterative SUZUKI-MIYAURA cross-coupling since the MIDA boronate itself does not undergo cross-couplings. Deprotection of the MIDA boronates takes only place after hydrolysis in NaOH(aq) and release of the reactive free boronic acid occurs.[109,110] Nowadays a plethora of MIDA boronates are commercially available, because of their growing popularity. One method for the preparation of MIDA boronates is the conversion of boronic acids to the corresponding

MIDA derivatives by heating with MIDA ligand under reflux and DEAN-STARK conditions.[94] A second approach for labile boronic acids was developed and therefore a one-pot lithiation/borylation protocol is used and in this method the isolation of instable boronic acids is not necessary.[111]

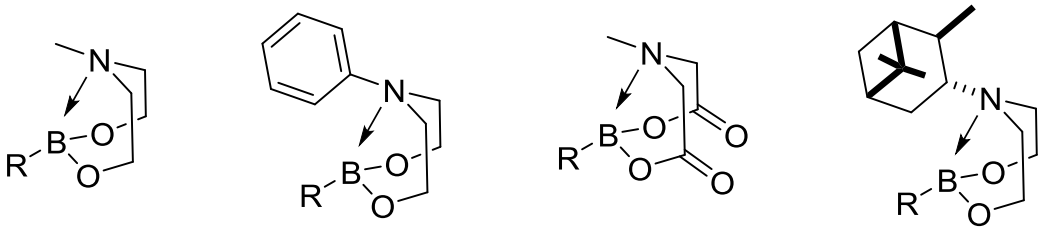
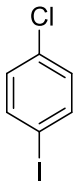
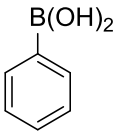
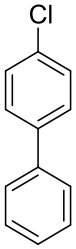
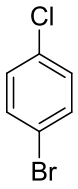
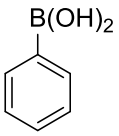
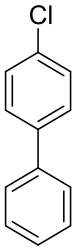
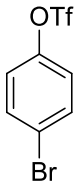
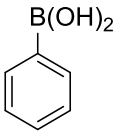
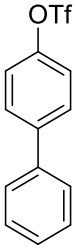
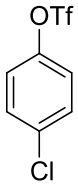
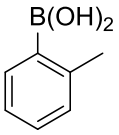
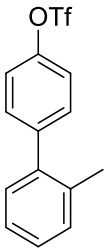
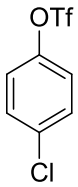
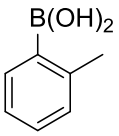
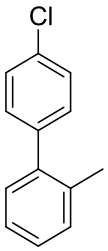


Figure 21. Examples for *N*-coordinated boronates.[109,110]

2.4.2.6. Chemoselective SUZUKI-MIYAURA cross-coupling

The SUZUKI–MIYAURA reaction is one of the most versatile methods for the formation of a carbon–carbon bond. The cross-coupling reactions often occur in very good chemo- and regioselectivity and have high tolerance for functional groups.[112] According to literature a broad range of new opportunities for the control of the chemoselectivity of cross-coupling reactions has been presented. High chemoselectivity could be obtained by tuning the catalytic system.[113] The rate of oxidative addition correlates in general with the reactivity order of halides and pseudo-halides, which is known to be in the order I > Br ~ OTf > Cl. In the literature various approaches for chemoselective SUZUKI-MIYAURA coupling reactions have been published.[9,114,115] FU *et al*. was able to show that chlorides could be coupled selectively in the presence of triflates, which should react faster under normal conditions.[115] Moreover, it was also shown that the control of the chemoselectivity is possible between the same halogens by substrate- or catalyst-control.[112] In substrate-controlled reactions the reaction site is controlled by steric and electronic properties of the substrate. By switching the catalyst the reaction site can be regulated in the case of catalyst-controlled reactions (Table 3).[116]

Table 3. Examples for chemoselective cross-coupling.[115]

Entry	Aryl Halide	Boronic acid	Product	Conditions[a]	Yield
1				0.5 % $Pd_2(dba)_3$ 1.2 % P(*t*-Bu)$_3$	98 %
2				0.5 % $Pd_2(dba)_3$ 1.2 % P(*t*-Bu)$_3$	97 %
3				0.5 % $Pd_2(dba)_3$ 1.2 % P(*t*-Bu)$_3$	98 %
4				1.5 % $Pd_2(dba)_3$ 3.0 % P(*t*-Bu)$_3$	95 %
5				3.0 % $Pd(OAc)_2$ 6.0 % PCy_3	87 %

[a] Standard conditions: 1.0 eq aryl halide, 1.0 eq boronic acid, 3.0 eq KF, THF, RT

For achieving chemoselectivity within the transmetalation step MIDA-protected boronic acids are used. These boronic acids undergo only cross-coupling reactions after deprotection with mild aqueous bases (Figure 22).[109]

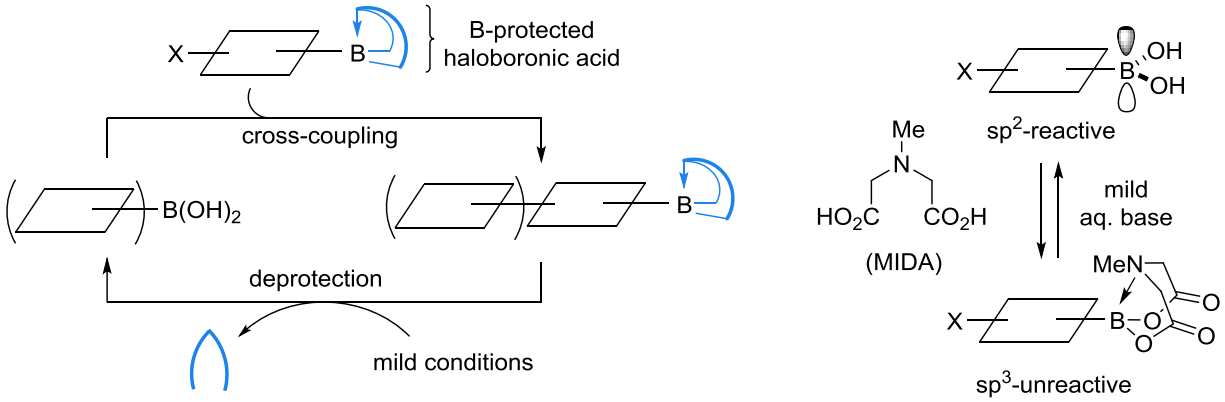


Figure 22. Iterative cross-coupling and MIDA protection/deprotection.[109]

With these strategies it has become to perform efficient iterative and sequential Pd-catalyzed cross-coupling reactions.[117]

3. Aim of the thesis

Protein-protein interactions play an important role in many cellular processes and have received increasing attention as promising drug targets in recent years.[17] A large number of protein-protein interactions is mediated by α-helices offering an opportunity for the inhibition of such interactions.[22,23,118]

HAMILTON *et al*. have presented a well-fitting backbone structure to mimic α-helices by suitably positioning amino acid side chains at the 2',3,3"-position of the terphenylic scaffold. If the side chains are placed in these positions, the amino acid residues in *i*, *i*+3 (or *i*+4) and *i*+7 of an α-helix can be mimicked (Figure 23).[20]

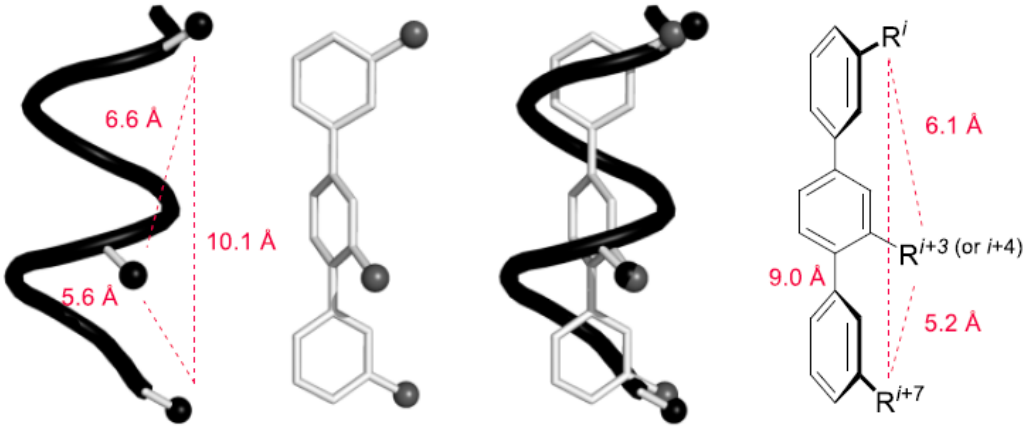
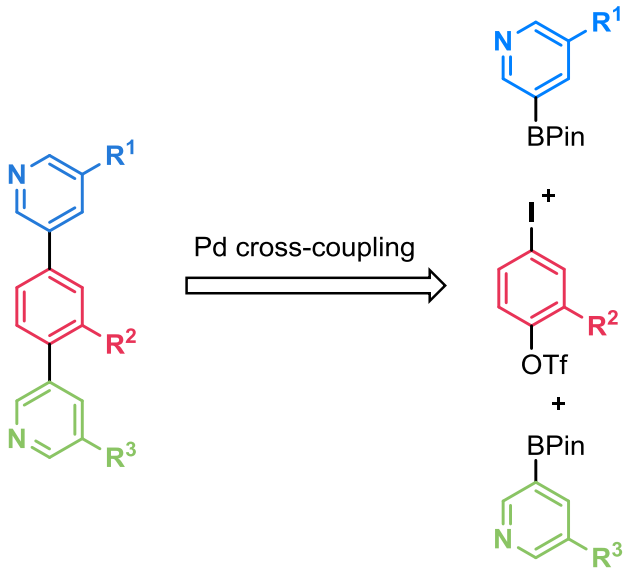


Figure 23. Overlay of an alpha-helix and a teraryl, picture taken from Ref.[50]

At the beginning short peptides were used as drug candiates, but due to several limitations small molecules were introduced, which are able to mimic an α-helix. For the efficient synthesis of small molecule inhibitors, the development of short and facile synthesis sequences was needed. HAMILTON's terphenylic scaffold is a promising approach, but a long reaction sequence made the synthesis difficult. A modular synthesis of terarylic scaffolds was developed in the BREINBAUER group.[9,10,119] Therefore teraryls can be divided into three single building blocks. It was shown, that the connection of the building blocks can be done by robust sequential SUZUKI-MIYAURA cross-coupling reactions. TROBE found optimized conditions for the Pd-catalyzed cross-coupling and one system for the coupling of different building blocks containing diverse functional groups was developed.

HAMILTON *et al*. used for the synthesis of the teraryl backbone three phenyl rings, but these apolar compounds had only poor solubility under physiological conditions. Therefore teraryls containing more polar heterocycles were introduced. In a retrosynthetic approach developed by the BREINBAUER group teraryls can be divided into a set of two different building blocks, which can be assembled in a two-step sequential SUZUKI-MIYAURA coupling, depicted in Scheme 13. Central to this strategy are the core building blocks featuring two different leaving groups and the second set of building blocks are 3,5-substituted pyridine boronic acid esters for the improvement of the solubility.



Scheme 13. Retrosynthetic approach for teraryl assembly.

In the approach of TROBE iodine and OTf-group were used as leaving groups in the core fragments. Due to the problem of hydrolysis of the triflate group in the SUZUKI-MIYAURA cross-coupling and the incompatibility of the triflate group with unprotected nucleophilic side chains, a core building block featuring two other leaving groups differentiated by their reactivity in cross-coupling reactions should be synthesized. Instead of the triflate group bromine should be introduced as the second leaving group (Figure 24). The different leaving groups of the core fragment should facilitate a chemoselective synthesis of teraryls without the use of protecting groups.[119] In some cases side chains have to be protected, because certain unprotected functional groups are not suitable for the SUZUKI-MIYAURA cross-coupling.

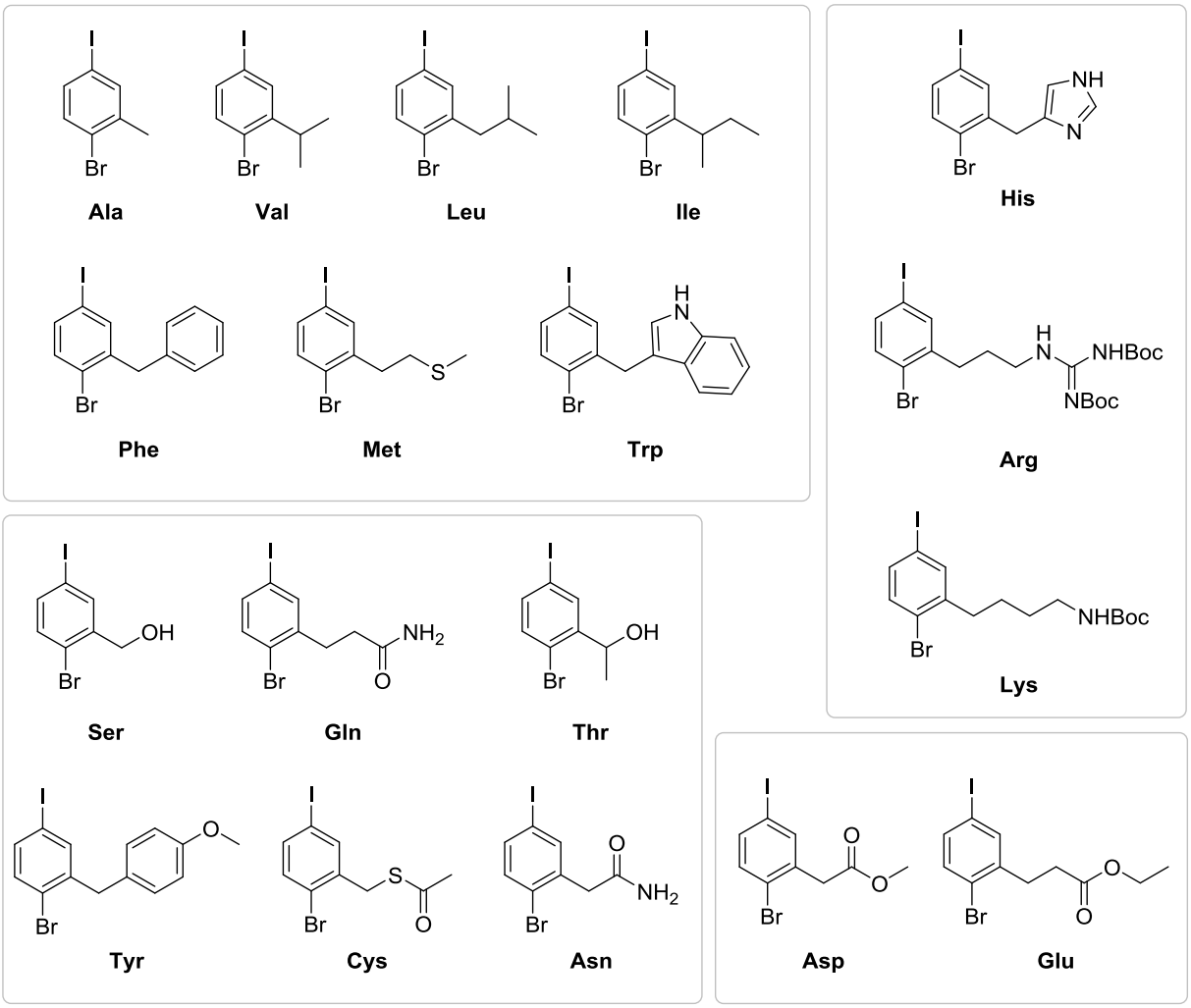


Figure 24. Target molecules for the core unit fragment library.

For the synthesis of teraryls different building blocks containing the same side chains like natural amino acids were chosen. In this work short and efficient synthetic routes for the core building blocks should be established with a main focus on the synthesis of the His core building block, which emerged as the only building block not accessible within the iodo/triflate series.

Due to the essential role of human Med15 in the regulation of cholesterol and fatty acid homeostasis teraryls may be useful small molecules inhibitors. Therefore, following a rational design approach teraryls should be synthesized and tested for their binding to Med15 KIX by fluorescence polarization.

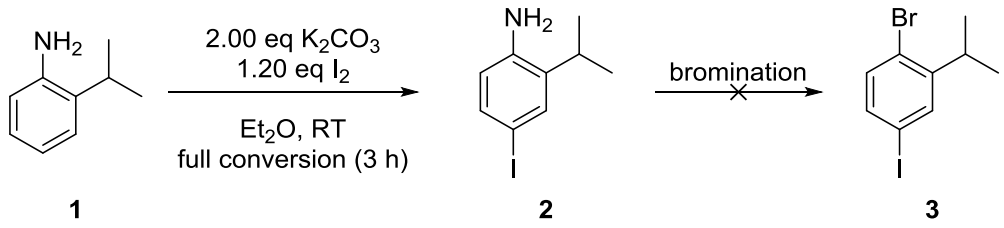
4. Results and Discussion

4.1. Synthesis of Core Building Blocks

The core building blocks feature two leaving groups with different reactivity in Pd-catalyzed cross coupling. As leaving groups on the one hand bromine is used and on the other hand iodine is introduced. In the cross-coupling reaction the iodine reacts first followed by bromine as the second leaving group. Moreover, the core fragments should contain the same side chains which are found in natural amino acids relevant for protein-protein interactions. For the synthesis of the core building blocks in most cases the side chain had to be introduced. Commercially available (2-bromo-5-iodophenyl)methanol (**9**) emerged as an attractive building block for the attachment of the different side chains. In some cases it was necessary to install first the side chain on a benzene scaffold followed by bromination and iodination to generate the desired core fragment.

4.1.1. Synthesis of the Valine building block

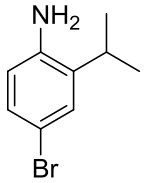
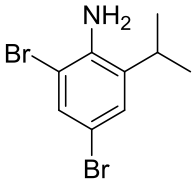
In the first attempt the valine building block should be synthesized in a two step route starting from 2-isopropylaniline (**1**). The attempted synthesis of 1-bromo-4-iodo-2-isopropylbenzene (**3**) is shown in Scheme 14.



Scheme 14. Synthesis of the valine building block

In the first step commercially available 2-isopropylaniline (**1**) was reacted with I_2 to achieve 4-iodo-2-isopropylaniline (**2**). First 0.92 eq I_2 were used but in this case incomplete conversion was achieved. Moreover, it was not possible to separate the product **2** from the starting material **1** via column flash chromatography. Therefore an excess of I_2 (1.20 eq) was used and after 3 h full conversion was monitored by GC-MS. In the next step bromination via a diazonium salt should be performed. Hence different bromination methods were screened (Table 4).

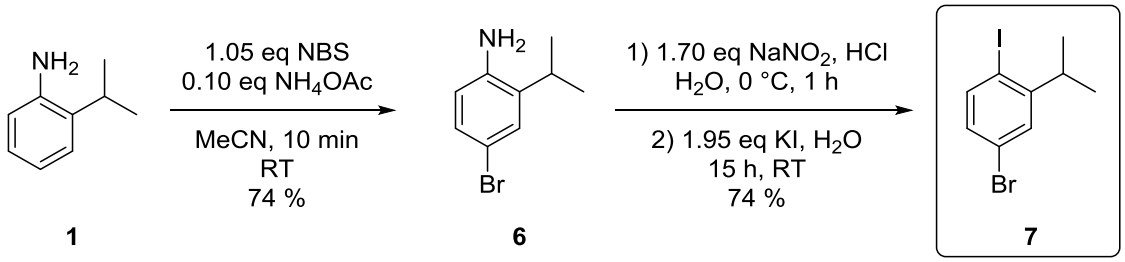
Table 4. Bromination methods for the synthesis of the valine building block.

Entry	Time	Conditions	Desired product	Side product
1	18 h	1) HBr, $NaNO_2$, 0 °C, 10 min 2) CuBr, HBr, 0 °C to 95 °C	-[a]	 **4**
2	18 h	1) isopentylnitrite, AcOH, H_2SO_4, 0 °C, 10 min 2) CuBr, HBr, 0 °C, 20 min	40 %[a]	 **5**
3	18 h	1) isopentylnitrite, AcOH, H_2SO_4, 0 °C, 25 min 2) CuBr, HBr, 0 °C, 30 min	< 10 %[a]	many side products, 10 % starting material
4	18 h	1) isopentylnitrite, AcOH, H_2SO_4, RT, 20 min 2) CuBr, HBr, RT, 30 min	< 10 %[a]	many side products, 80 % starting material

[a] According to GC-MS

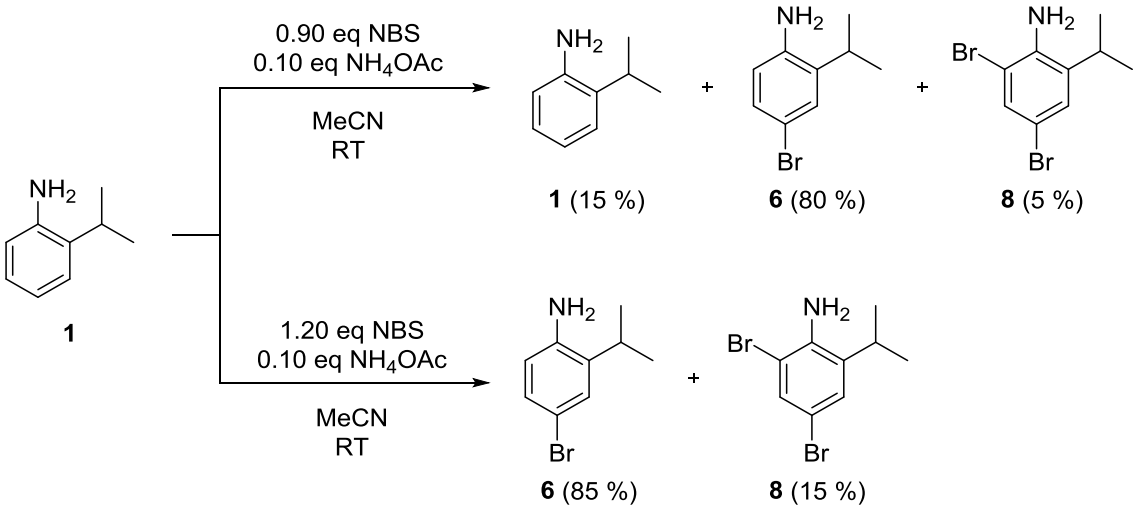
First HBr, $NaNO_2$ followed by the addition of CuBr and HBr were used but these reaction conditions showed no formation of the desired product (Table 4, Entry 1). The only formed product was 4-bromo-2-isopropylaniline (**4**) where exchange from iodine to bromine took place. The best result was achieved by using AcOH, H_2SO_4 and isopentylnitrite for the formation of the diazonium salt. The dropwise addition of isopentylnitrite was executed at 0 °C over 10 min but the conversion to the desired product was only 40 % (Table 4, Entry 2). The main product in this case was 2,4-dibromo-6-isopropylaniline (**5**). Slower addition of isopentylnitrite at 0 °C and RT (Table 4, Entries 3 and 4) also showed no noteworthy conversion (<10 %) to the desired product. In these cases many side products were formed and by addition of isopentylnitrite at RT 80 % starting material remained unconverted.

To overcome these problems the valine building block was synthesized in another two step synthesis following the procedure of MASSON *et al*. for this substance (Scheme 15).[120] 2-Isopropylaniline (**1**) was first brominated and in the second step the iodine was introduced.



Scheme 15. Synthesis of the valine building block.

The bromination was first attempted with 0.90 eq NBS to avoid overbromination but a mixture of starting material **1** (15 %), desired product **6** (80 %) and overbrominated product **8** (5 %) was achieved. However, this reaction mixture was not separable via flash column chromatography. When an excess of NBS (1.05 eq) was used full conversion of the starting material **1** was obtained after 10 min. Also here 15 % overbrominated product **8** was formed, but in this case the desired product **6** was easily separable from the overbrominated product **8** via flash column chromatography (see Scheme 16).

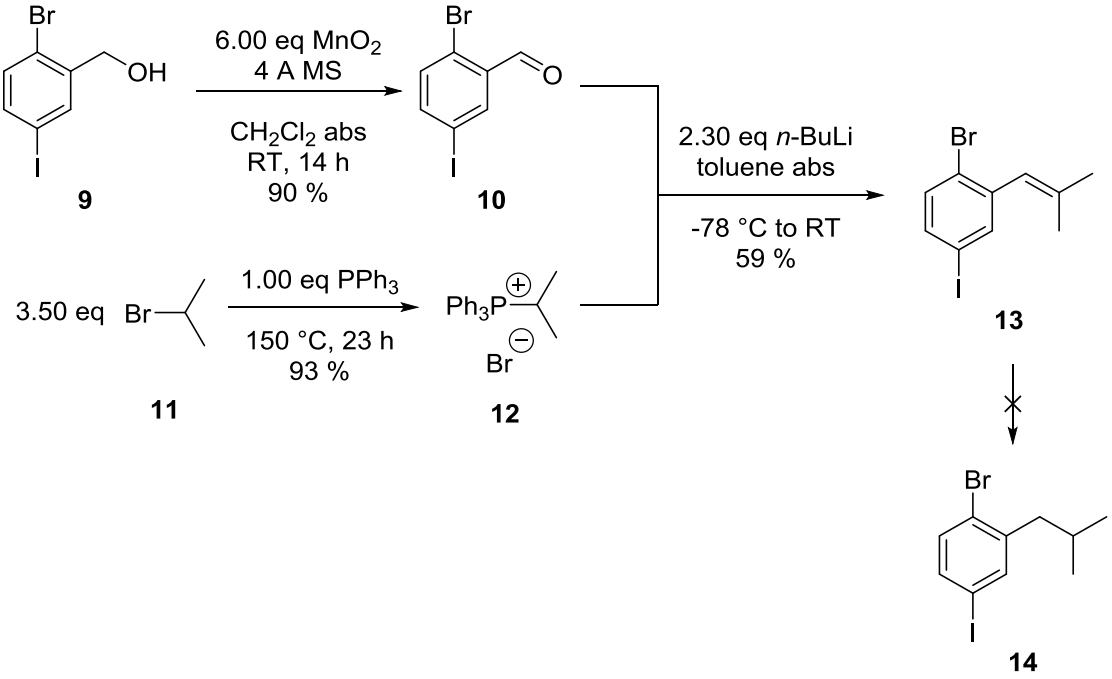


Scheme 16. Bromination of 2-isopropylaniline (**1**).

In the next step the iodination of 4-bromo-2-isopropylaniline (**6**) was performed. Therefore a diazonium salt was formed with $NaNO_2$ and HCl in H_2O at 0 °C. After stirring the reaction mixture at 0 °C for 1 h a solution of KI in H_2O was added and after stirring overnight full conversion to the desired product **7** was achieved, which was isolated by column chromatography in 74 % yield.

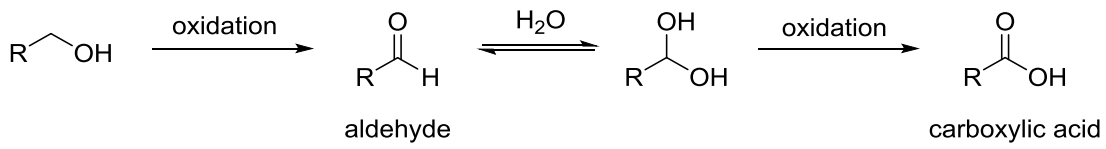
4.1.2. Synthesis of the Leucine building block

The Leu building block should be synthesized via a WITTIG-reaction starting from commercially available (2-bromo-5-iodophenyl)methanol (**9**) and the phosponium salt **12** shown in Scheme 17. Afterwards the double bond should be reduced to yield 1-bromo-4-iodo-2-isobutylbenzene (**14**).



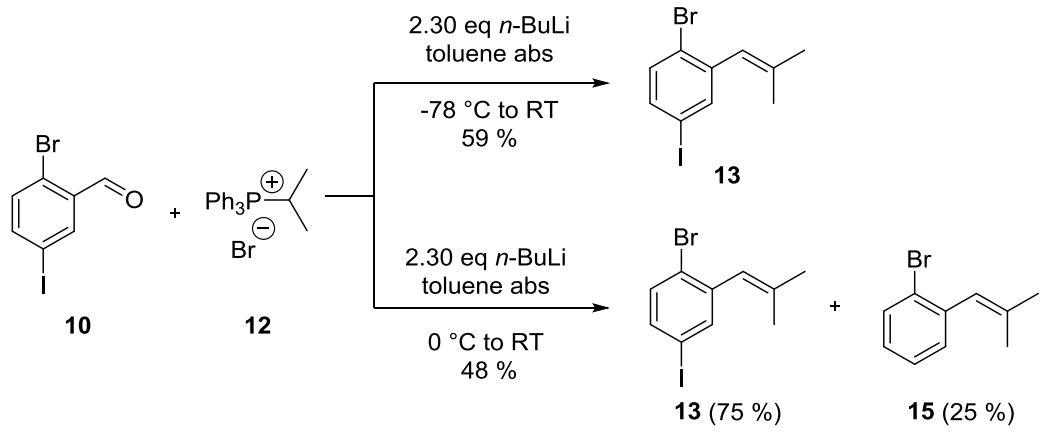
Scheme 17. First attempt for the synthesis of the leucine building block.

First alcohol **9** was oxidized using 6.00 eq activated MnO_2. Here 4 Å molecular sieves were added to the reaction solution to avoid overoxidation to the carboxylic acid by formation of the aldehyde hydrate (Scheme 18). After full conversion of starting material **9** was indicated by GC-MS, MnO_2 was removed by filtration through a pad of silica. Substrate **10** was obtained in high yield of 90 % and was used without further purification in the WITTIG-reaction.



Scheme 18. Overoxidation of aldehyde to the carboxylic acid.

In the next step a WITTIG-reaction was performed. The phosphonium salt **12** was synthesized from 2-bromopropane (**11**) and PPh_3. The reaction had to be performed in a glass pressure tube and was heated up to 150 °C for 23 h. Product **12** was collected by filtration in 93 % yield. Then salt **12** was first deprotonated with *n*-BuLi in abs. toluene. After 1 h of deprotonation of **12** a solution of aldehyde **10** in toluene was added at -78 °C. It turned out to be crucial for this reaction to add the aldehyde at -78 °C, otherwise the iodine was cleaved off (Scheme 19). Purification of the crude product via flash chromatography furnished product **13** in moderate yield of 59 %.



Scheme 19. WITTIG-reaction by different temperatures.

The last step was the reduction of the double bound. Therefore a reduction with diimide was considered as an alternative to hydrogenation reactions with Pd. The use of H_2 and Pd/C was not possible because these conditions also removed the iodine. The driving force of this reaction is the oxidation of the diimide to N_2 by the transfer of two hydrogens to the double bond. Diimide itself is a very unstable compound and therefore different precursors (Figure 25) can be used. By the use of these precursors diimide is released in situ by treatment with acid or base.

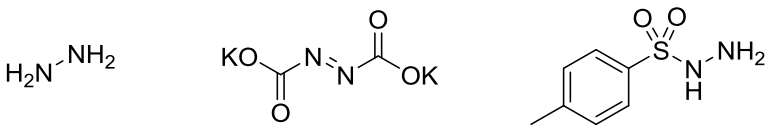


Figure 25. Diimide precursor: hydrazine, potassium azadicarboxylate (PADA), p-tosyl hydrazide (p-THA).

For the reduction of the double bond from compound **13** potassium azadicarboxylate (PADA) and p-tosyl hydrazide (p-THA) were used as diimide precursor (Table 5). The reaction with PADA in 1,2-DME gave no conversion to the desired product (Table 5, Entry 1). The

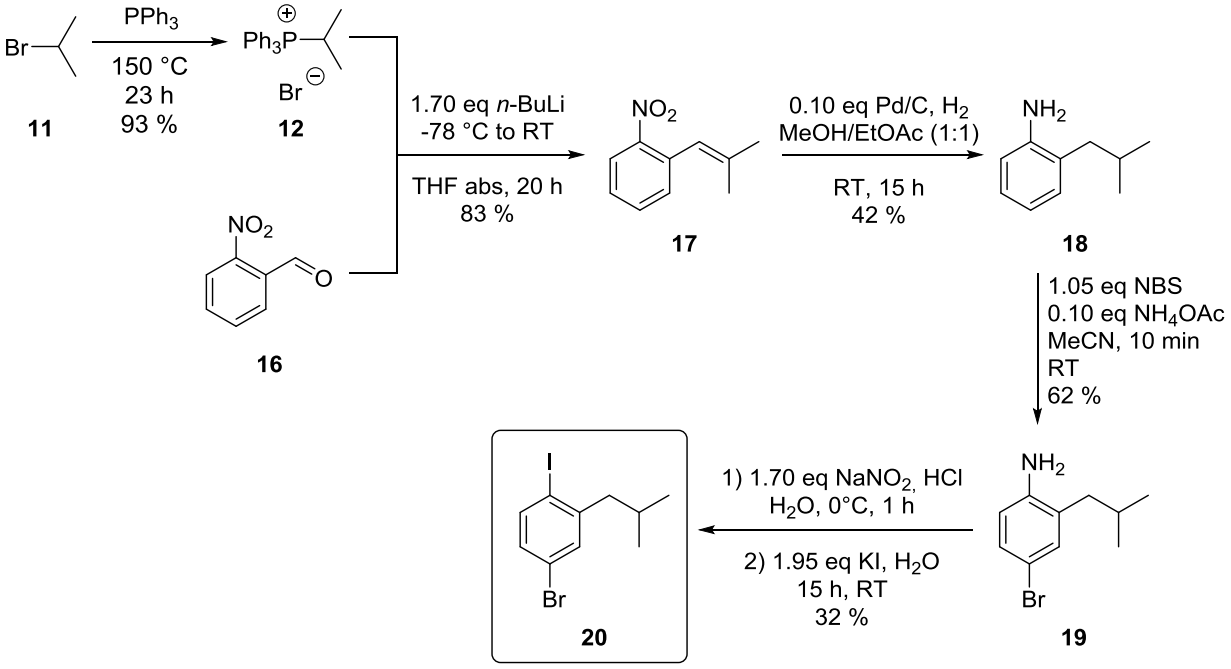
conversion of the reduction with p-tosyl hydrazide was with 10 % very low (Table 5, Entry 2). An excess of 64.0 eq of p-THA showed also only 11 % conversion to the desired product (Entry 3). After testing different diimide precursors the results were rather disappointing so this reaction route was not longer pursued.

Table 5. Screened methods for the reduction of the double bond.

Entry	Time	Conditions	Solvent	Temperature	Conversion to the desired product
1	72 h	3.0 eq PADA AcOH	1,2-DME	50 °C	-[a]
2	72 h	6.3 eq p-THA, 6.3 eq $NaOAc \cdot 3H_2O$	THF	70 °C	10 %[a]
3	72 h	64.0 eq p-THA, 64.2 eq $NaOAc \cdot 3H_2O$	THF	70 °C	11 %[a]

[a] According to GC-MS.

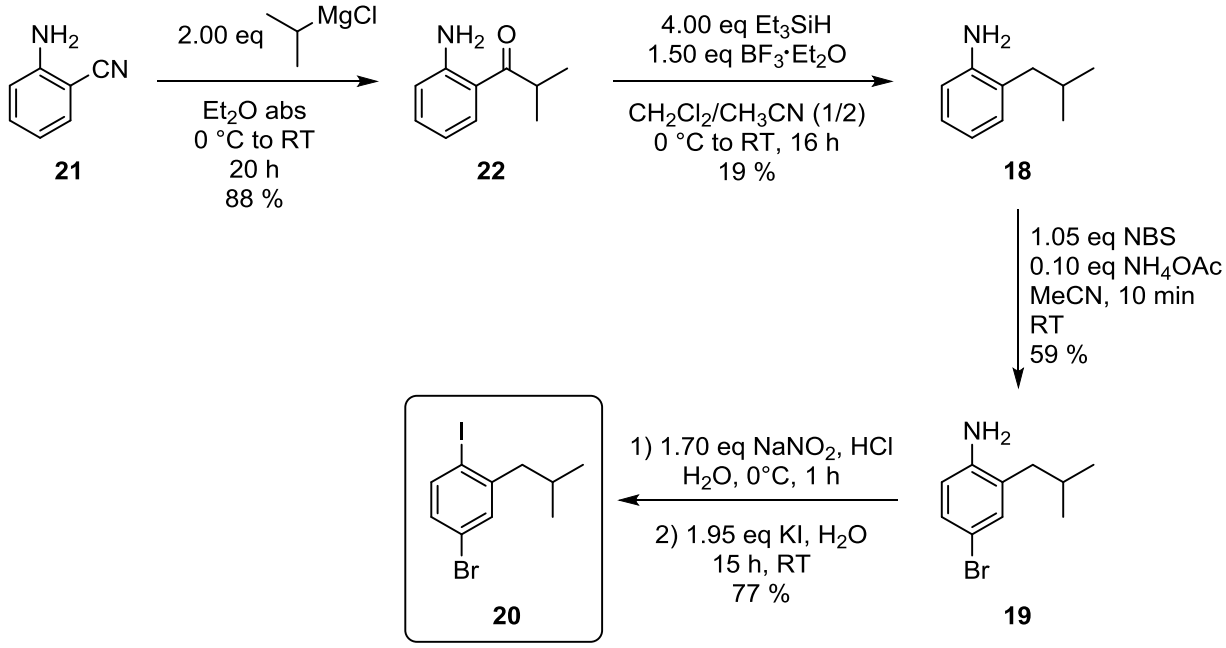
The second reaction route contains five steps and the final product **20** was isolated in 6 % overall yield. The reaction sequence was started with 2-nitrobenzaldehyde (**16**) to overcome the problem with the reduction of the double bound. Therefore the bromine and the iodine were introduced after the reduction step (Scheme 20).



Scheme 20. Reaction route for the synthesis of the leucine building block.

The first step was again a WITTIG-reaction. The deprotonation of the phosphonium salt **12** was performed similarly to the first reaction route (Scheme 17). Then double bond and also the nitro group were reduced with Pd/C and H_2 in this step. The last two steps were then the bromination and iodination of substrate **18** like in section 4.1.1.

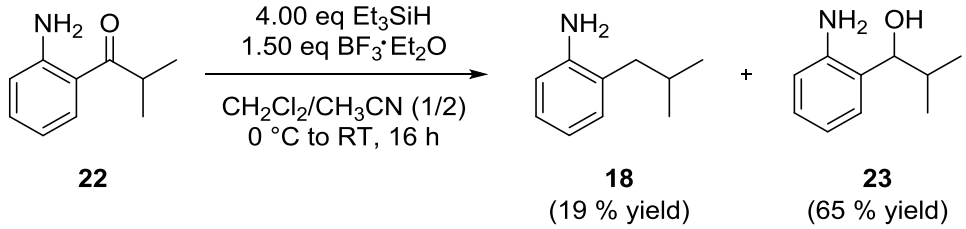
Another approach for the synthesis of the leucine building block was needed, because of the long reaction sequence over five steps in low overall yield. In the alternative synthesis depicted in Scheme 21 starting from 2-aminobenzonitrile (**21**) first the introduction of the Leu-side chain was accomplished by a GRIGNARD-reaction, followed by removal of the carbonyl group and bromination and iodination as final steps.



Scheme 21. Synthesis of the leucine building block.

For the first step a slightly modified literature procedure by CASPERS *et al.* was used.[121] 2-Aminobenzonitrile (**21**) was reacted with *i*-propylmagnesiumchloride to form in a GRIGNARD-reaction ketone **22**. Full conversion was achieved after 22 h and compound **22** was isolated after filtration through a pad of silica in 88 % yield.

In the next step the carbonyl group should be removed by the use of Et_3SiH and $BF_3{\cdot}Et_2O$. First 1-(2-aminophenyl)-2-methylpropan-1-one (**22**) was treated with 4.00 eq Et_3SiH and 1.50 eq $BF_3{\cdot}Et_2O$, but in this case only 19 % of the desired product **18** was isolated. The main formed product was 1-(2-aminophenyl)-2-methylpropan-1-ol (**23**), which was isolated in 65 % yield.



Scheme 22. Removal of the carbonyl group.

Furthermore it was tried to remove the carbonyl-group with Zn, Fe or Sn instead of Et_3SiH and $BF_3{\cdot}Et_2O$. The different screened reagents are listed in Table 6.

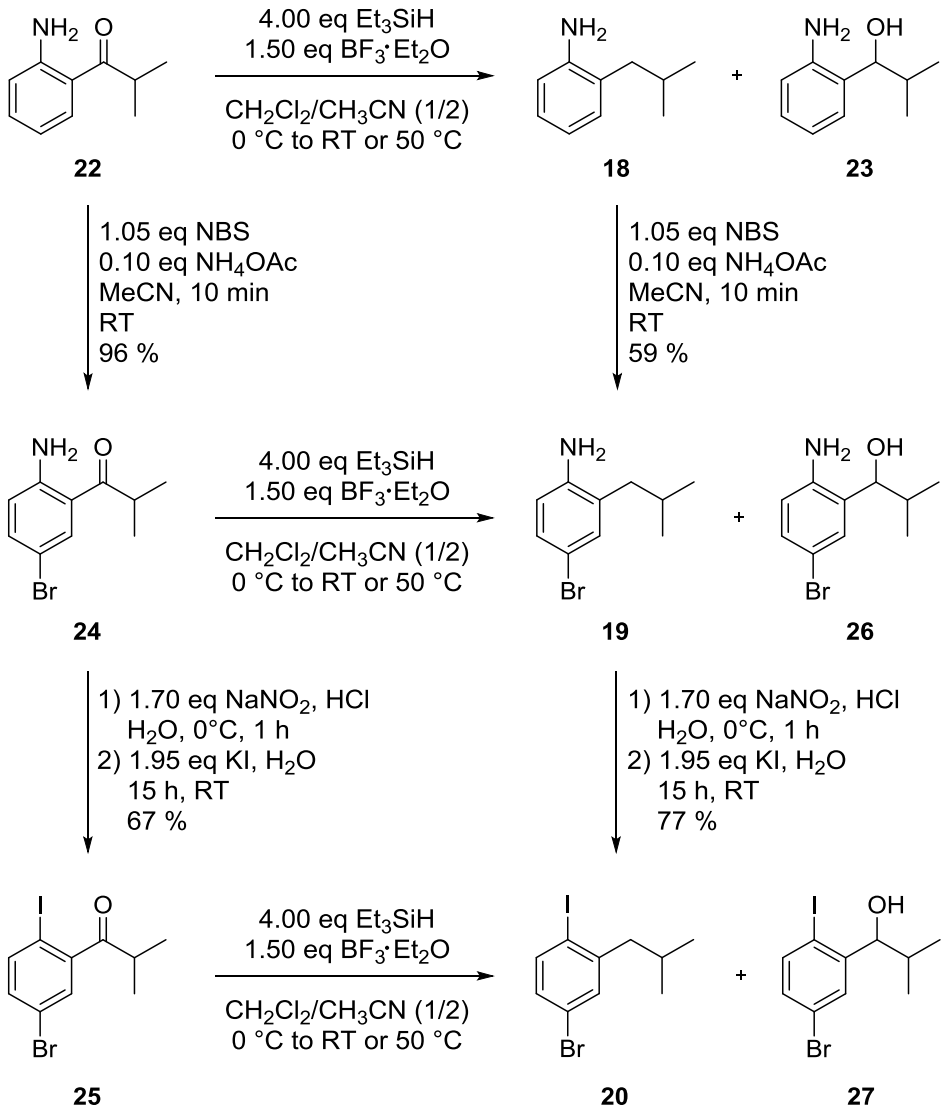
Table 6. Screened methods for the removal of the carbonyl-group.

Entry	Time	Conditions	Solvent	Temperature	Conversion
1	48 h	10.0 eq Zn 20.0 eq HCl	MeOH	RT	10 %[a]
2	48 h	10.0 eq Fe 20.0 eq HCl	MeOH	RT	-[a]
3	48 h	10.0 eq Sn 20.0 eq HCl	MeOH	RT	-[a]

[a]According to GC-MS.

In all cases only low or no conversion to the desired product **18** was achieved. According to GC-MS no conversion was obtained if Sn and Fe were used. By the addition of Zn and HCl full conversion was obtained after 48 h, but only 10 % of the desired product **18** were generated (Table 6, Entry 1). The main product was alcohol **23**. Due to these disappointing results, this route was not followed up.

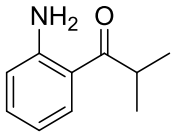
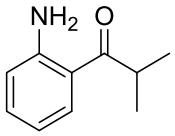
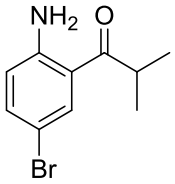
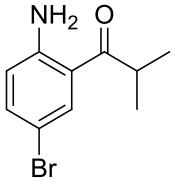
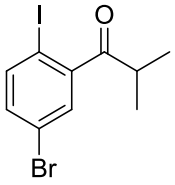
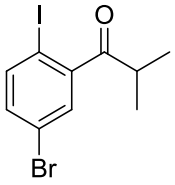
In the meanwhile substrate **22** was brominated and then iodination was done by the same procedure like for the Val core fragment (section 4.1.1). Next compounds **22**, **24** and **25** were reacted with Et_3SiH and $BF_3{\cdot}Et_2O$ for the removal of the carbonyl group (Scheme 23).



Scheme 23. Different methods to remove the carbonylgroup.

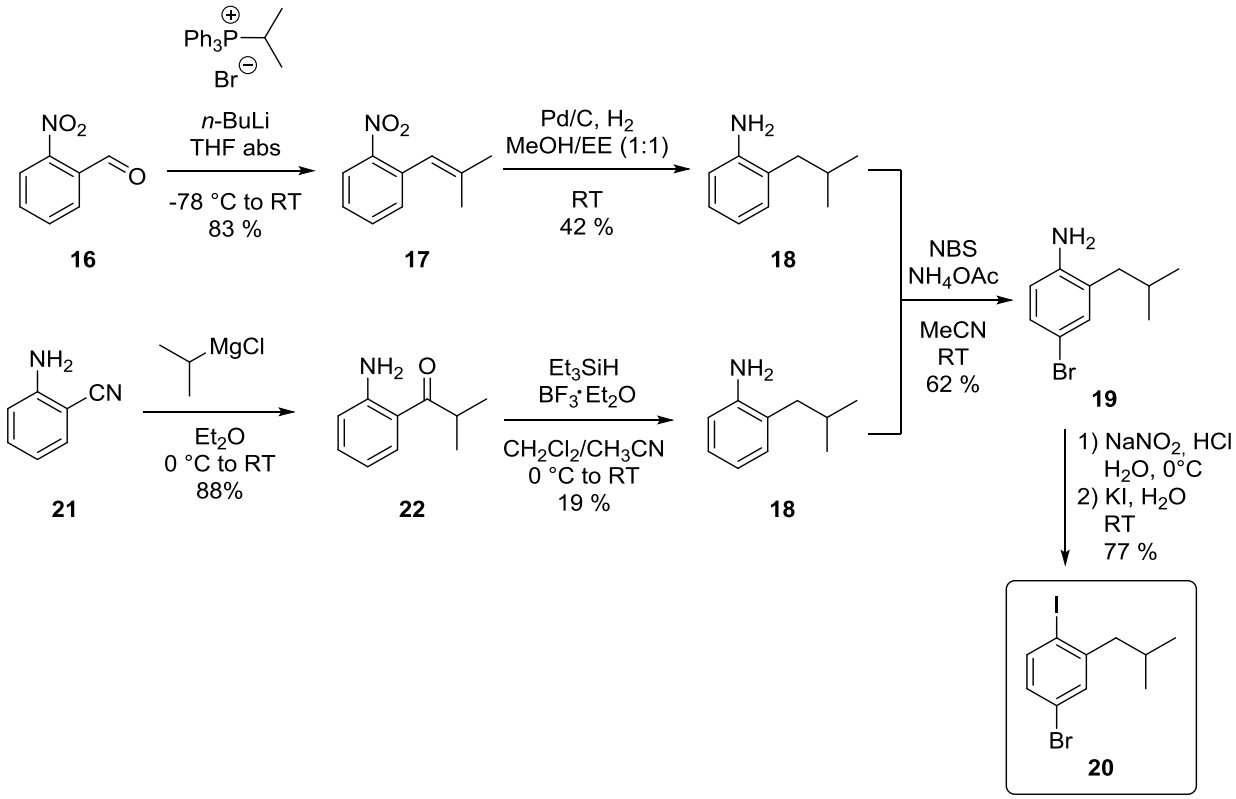
In all cases the same reaction conditions and solvents were used and the reactions were stirred at RT and also at 50 °C. Best results were achieved when compound **22** was used without any halogens (Table 7, Entries 1 and 2). By heating up the reaction mixture to 50 °C the formation of desired product **18** was faster and up to 49 % conversion to product **18** was obtained. The removal of the carbonyl-group was also done with compound **24** and **25** (Entry 4 – 6), but in these cases less formation of the desired product was achieved. Especially the reaction with compound **25** shows only 4 % conversion after 60 h at 50 °C. This indicates that the reaction is hindered due to the large size of the iodine.

Table 7. Screened methods for the removal of the carbonyl-group.

Entry	Starting material	Conditions	Temp.	Time	Conversion to the product	Conversion to the alcohol
1	 **22**	4.00 eq Et_3SiH 1.50 eq $BF_3{\cdot}Et_2O$ $MeCN/CH_2Cl_2$ (2/1)	RT	5 h	25 %	75 %
				20 h	27 %	73 %
				60 h	30 %	70 %
2	 **22**	4.00 eq Et_3SiH 1.50 eq $BF_3{\cdot}Et_2O$ $MeCN/CH_2Cl_2$ (2/1)	50 °C	5 h	31 %	69 %
				20 h	33 %	67 %
				60 h	49 %	51 %
3	 **24**	4.00 eq Et_3SiH 1.50 eq $BF_3{\cdot}Et_2O$ $MeCN/CH_2Cl_2$ (2/1)	RT	5 h	10 %	90 %
				20 h	12 %	88 %
				60 h	15 %	85 %
4	 **24**	4.00 eq Et_3SiH 1.50 eq $BF_3{\cdot}Et_2O$ $MeCN/CH_2Cl_2$ (2/1)	50 °C	5 h	16 %	84 %
				20 h	21 %	79 %
				60 h	31 %	69 %
5	 **25**	4.00 eq Et_3SiH 1.50 eq $BF_3{\cdot}Et_2O$ $MeCN/CH_2Cl_2$ (2/1)	RT	5 h	-	100 %
				20 h	1 %	99 %
				60 h	1 %	99 %
6	 **25**	4.00 eq Et_3SiH 1.50 eq $BF_3{\cdot}Et_2O$ $MeCN/CH_2Cl_2$ (2/1)	50 °C	5 h	1 %	99 %
				20 h	2 %	98 %
				60h	4 %	96 %

[a]According to GC-MS.

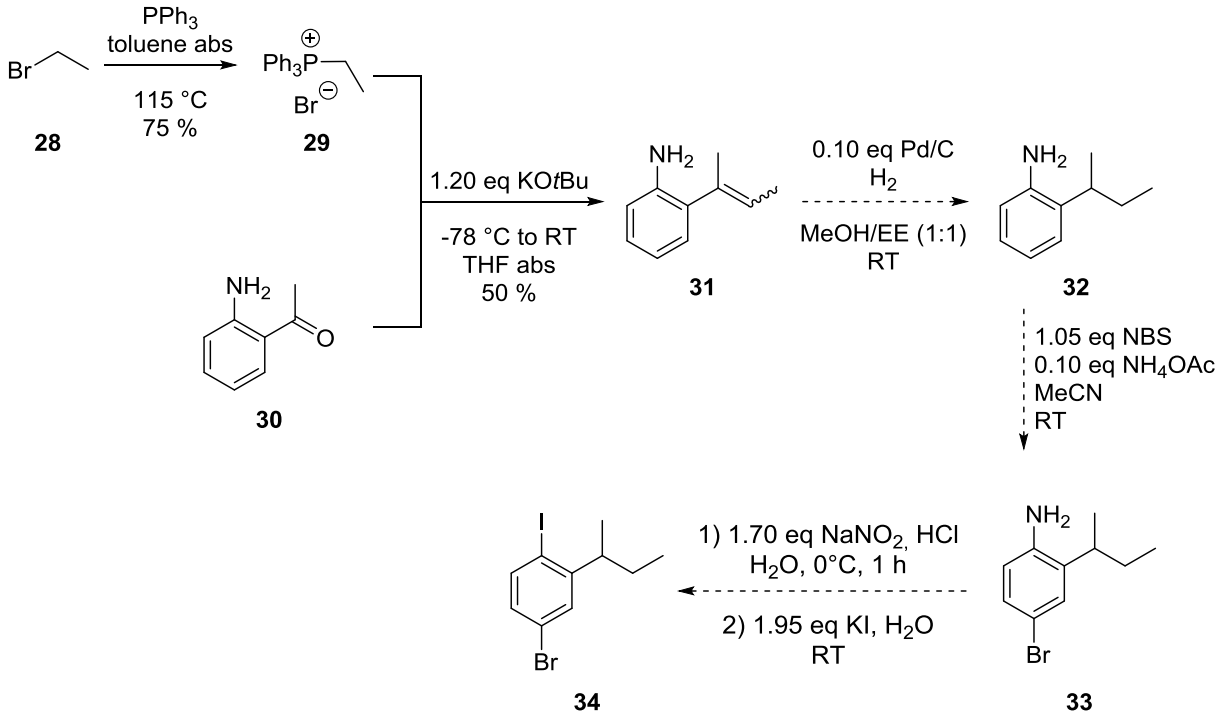
The leucine core fragment was synthesized via two different reaction routes (Scheme 24). In the first route five steps were needed and the overall yield was 6 %. Therefore a second synthesis was invented starting from 2-aminobenzonitrile (**21**). In this reaction sequence only four steps are necessary, but the overall yield was in the same order of magnitude with 7 %. Further optimization of the removal of the carbonyl-group has to be done for a better overall yield.



Scheme 24. Overview of the synthesis of the leucine building block.

4.1.3. Synthesis of the Isoleucine building block

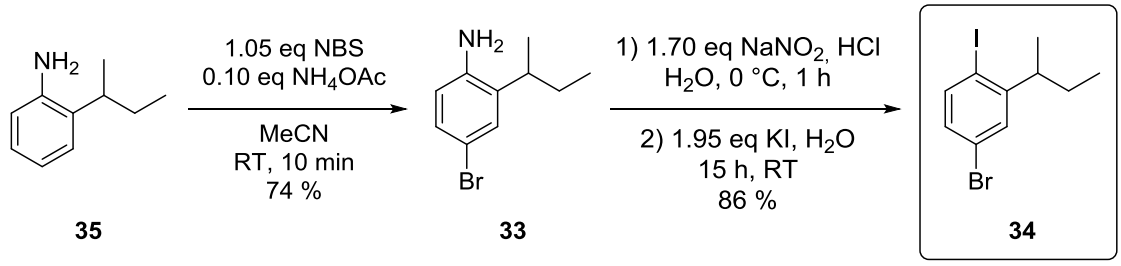
The first attempt for the synthesis of the isoleucine building block was similar to the second synthesis of the leucine buling block (see section 4.1.2). 4-Bromo-2-(sec-butyl)-1-iodobenzene (**34**) should be generated in a five step synthesis starting from 1-(2-aminophenyl)ethan-1-one (**30**) shown in Scheme 25.



Scheme 25. Attempted synthesis of the isoleucine buiding block **34**.

First, starting material **30** was converted in a WITTIG-reaction with phosphonium salt **29**. Following a literature procedure ethyltriphenylphosphonium bromide (**29**) was synthesized from bromoethane (**28**) and triphenylphosphine in abs. toluene.[122] Salt **29** was easily isolated by filtration and a colorless powder was isolated in 75 % yield. For the WITTIG-reaction a similar procedure described by BOELKE *et al.*[123] was used, in which phosphonium salt **29** was first deprotonated with KO*t*Bu and then the generated WITTIG-ylide was converted with ketone **30** to 2-(but-2-en-2-yl)aniline (**31**). The desired product was isolated by column chromatography in 50 % yield as *E*/*Z* mixture of 3/1.

In the meanwhile 2-(sec-butyl)aniline (**35**) became commercially available at a very attractive price. From then on, aniline **35** was purchased as starting material for the isoleucine building block synthesis in two steps as illustrated in Scheme 26.

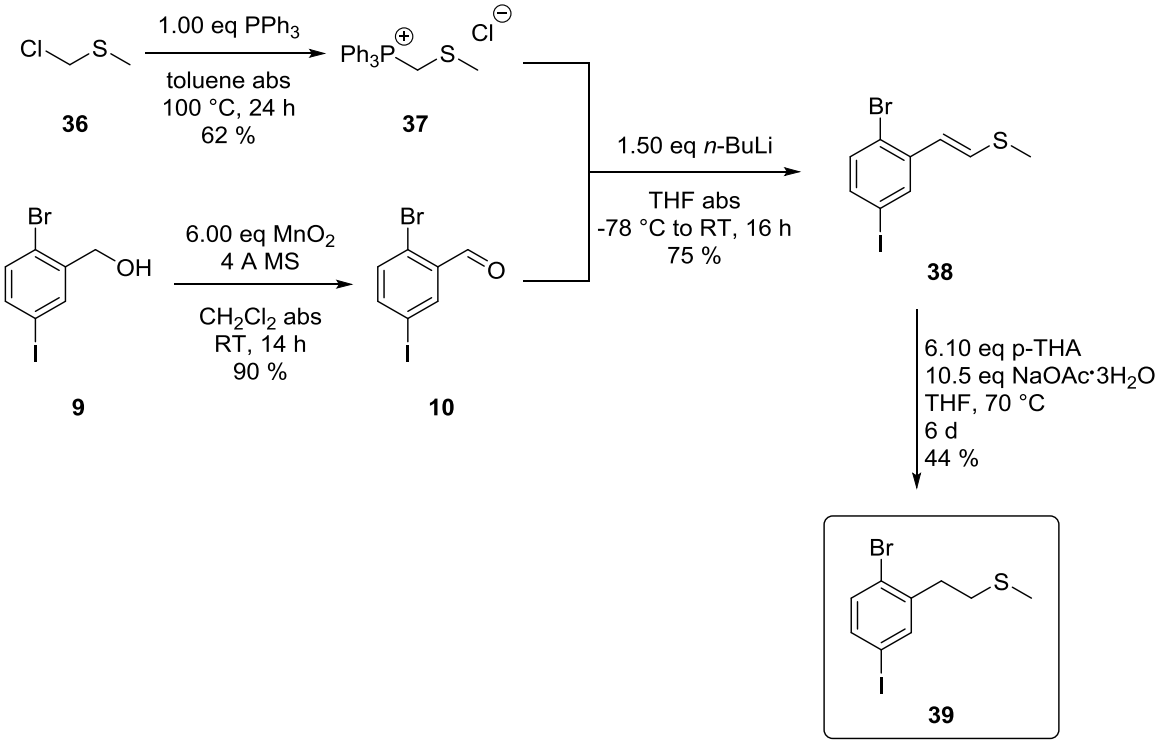


Scheme 26. Synthesis of isoleucine building block **34**.

Starting from compound **35** a simple bromination and iodination was performed to obtaine 4-bromo-2-(sec-butyl)-1-iodobenzene (**34**) in 71 % isolated yield over two steps. Like in the procedure for the bromination described for the Val core fragment (see section 4.1.1) 1.05 eq NBS had to be used otherwise too much overbrominated product was formed.

4.1.4. Synthesis of the Methionine building block

Scheme 27 displays the synthesis of the methionine building block. (2-Bromo-5-iodophenethyl)(methyl)sulfane (**39**) was generated in a convergent synthesis over 4 steps starting from commercially available (2-bromo-5-iodophenyl)methanol (**9**), which also represents the serine buling block, and chloro-methylmethylsulfide (**36**).



Scheme 27. Synthesis of the methionine building block **39**.

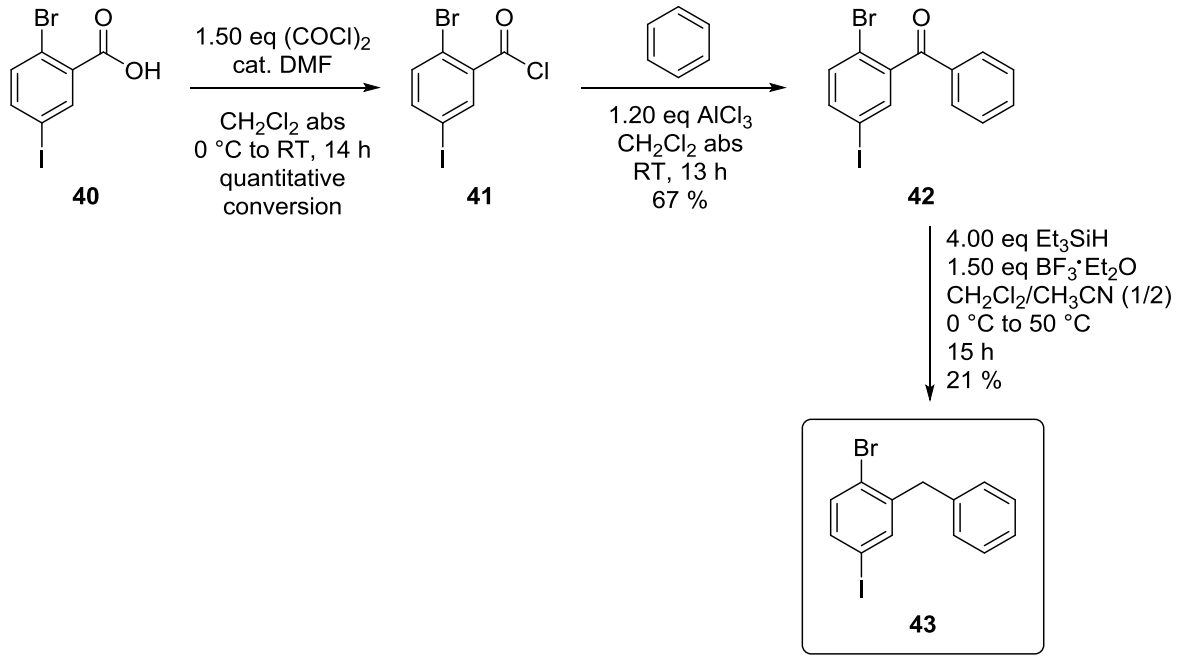
In the first step alcohol **9** was oxidized to 2-bromo-5-iodobenzaldehyde (**10**) using 6.00 eq MnO_2. To avoid overoxidation to the carboxylic acid 4Å molecular sieves were added to the reaction mixture, as outlined above (section 4.1.2). In parallel, phosphonium salt **37** was generated from chloromethylmethylsulfide (**36**) and triphenylphosphine. The colorless solution had to be heated up to 100 °C and after 24 h salt **37** was isolated by simple filtration to obtain the desired product **37** in 62 % yield.

For the formation of (*E*)/(*Z*)-(2-bromo-5-iodostyryl)(methyl)sulfane (**38**) a WITTIG-reaction was performed. First phosphonium salt **37** had to be deprotonated with *n*-BuLi at -78 °C. After 1 h of deprotonation of the WITTIG-ylide **37** at -78 °C a solution of aldehyde **10** in abs. THF was added. After 16 h full conversion was achieved and purification via flash chromatography furnished product **38** in 75 % yield as *E*/*Z* mixture of 1/1.4.

Finally, to obtain the methionine building block **39** the double bond had to be reduced. Therefore the diimide precursor p-tosyl hydrazide was used. As described in 4.1.2 it was not possible to reduce the double bond with Pd because of the bromine and the iodine on substrate **38**. The reduction had to be done at 70 °C. After a reaction time of 6 d only 83 % conversion was achieved but due to the very slow product formation the reaction was stopped at this time. Then product **39** was attempted to isolate via column flash chromatography but in the first try with 100 % cyclohexane as eluent (2-bromo-5-iodophenethyl)(methyl)sulfane (**39**) was not separable from remaining starting material **38** and p-tosyl hydrazide. Therefore a change of the eluent to CH/toluene (100:1) was executed and the methionine building block was isolated in 44 % yield.

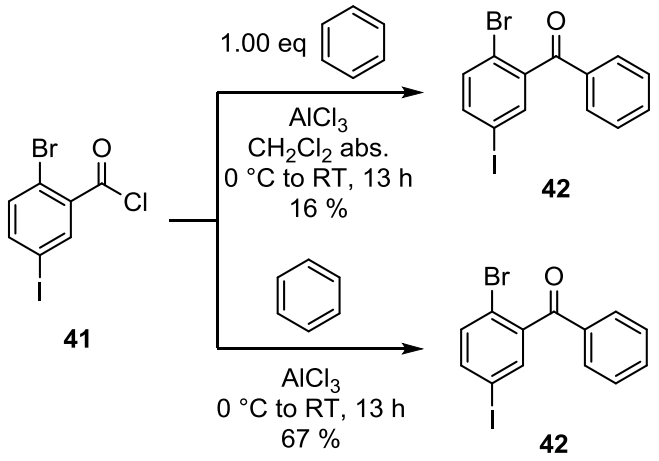
4.1.5. Synthesis of the Phenylalanine building block

2-Benzyl-1-bromo-4-iodobenzene (**43**) was synthesized similar to the tyrosine building block (see section 4.1.6). For the synthesis of the phenylalanine core fragment benzene was used in the FRIEDEL-CRAFTS-acylation instead of anisole (Scheme 28).



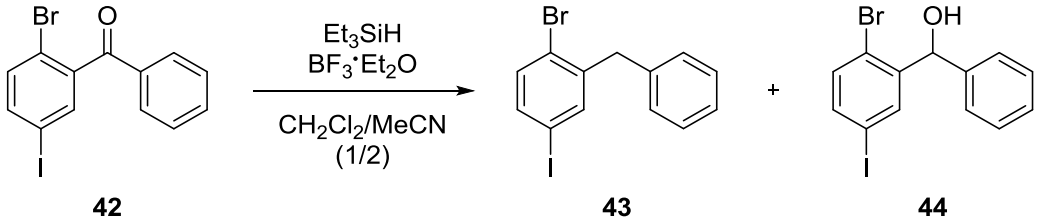
Scheme 28. Sythesis of the phenylalanine building block **43**.

The first reaction step was performed with the same conditions like in the synthesis of Tyr core fragment (see section 4.1.6). In the next step (2-bromo-5-iodophenyl)(phenyl)methanone (**44**) should be achieved also in a FRIEDEL-CRAFTS acylation. First the same conditions like in the synthesis for (2-bromo-5-iodophenyl)(4-methoxyphenyl)methanone (**45**) were used, but when compound **41** was converted with 1.00 eq benzene only 16 % product **42** could be isolated after flash chromatography. Therefore, the reaction was done with benzene as reagent as well as solvent. In this case (2-bromo-5-iodophenyl)(phenyl)methanone (**42**) was isolated after flash chromatography in 67 % yield (Scheme 29).



Scheme 29. FRIEDEL-CRAFTS-acylation of 2-bromo-5-iodobenzoyl chloride (**41**).

In the last step the carbonyl group should be removed with the same conditions like the removal of the carbonyl group in the tyrosine building block. Therefore, Et_3SiH and $BF_3{\cdot}Et_2O$ and as solvent a mixture of CH_2Cl_2 and CH_3CN (1/2) were used too. First the reaction was done at RT, but the desired product **43** was achieved in only 26 % conversion according to GC-MS. The major product was alcohol **44** (Scheme 30). This poor conversion reflects the less pronounced +M-effect of a phenyl vs. p-MeO-phenylgroup, which is key in the formation of the benzhydryl-carbocation intermediate.

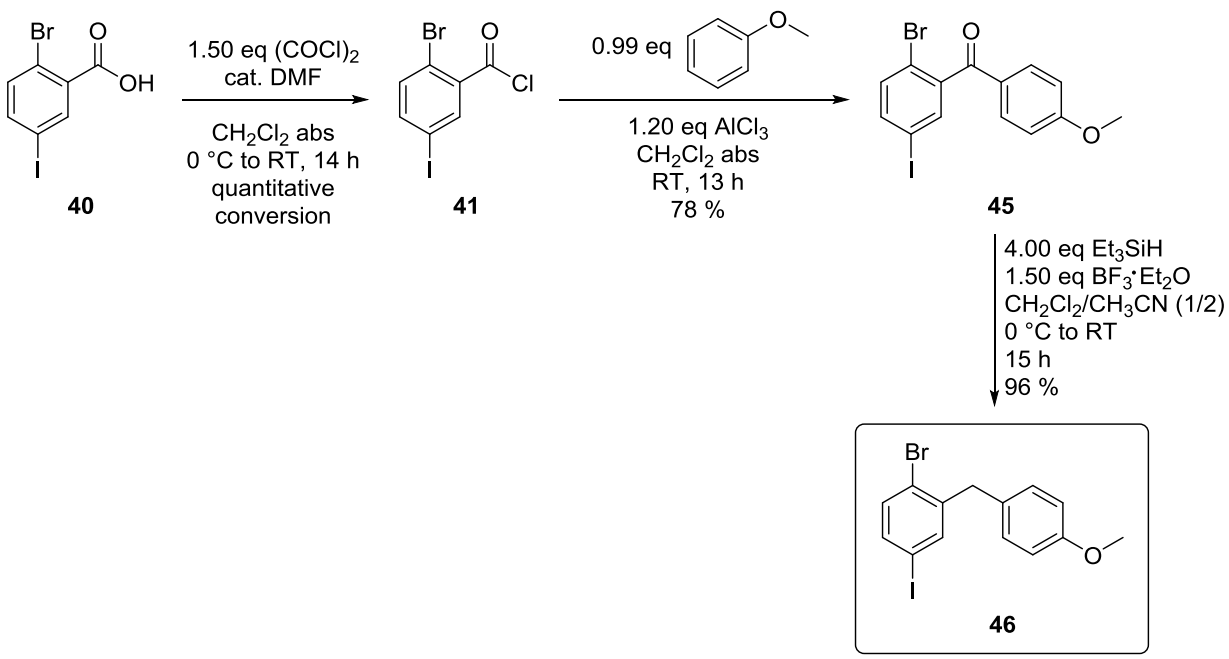


Scheme 30. Removal of the carbonyl group.

To obtain more of the desired product **43** the reaxtion mixture was heated to 50 °C. After 4 d complete conversion was obtained and the reaction mixture was quenched by the addition of KOH solution. Extraction and subsequent column chromatography furnished desired product **43** in 21 % yield.

4.1.6. Synthesis of the Tyrosine building block

As illustrated in Scheme 31 the tyrosine building block was synthesized following the procedure from KANG.[124] The linear three step synthesis started from 2-bromo-5-iodobenzoic acid (**40**).



Scheme 31. Synthesis of the tyrosine building block **46**.

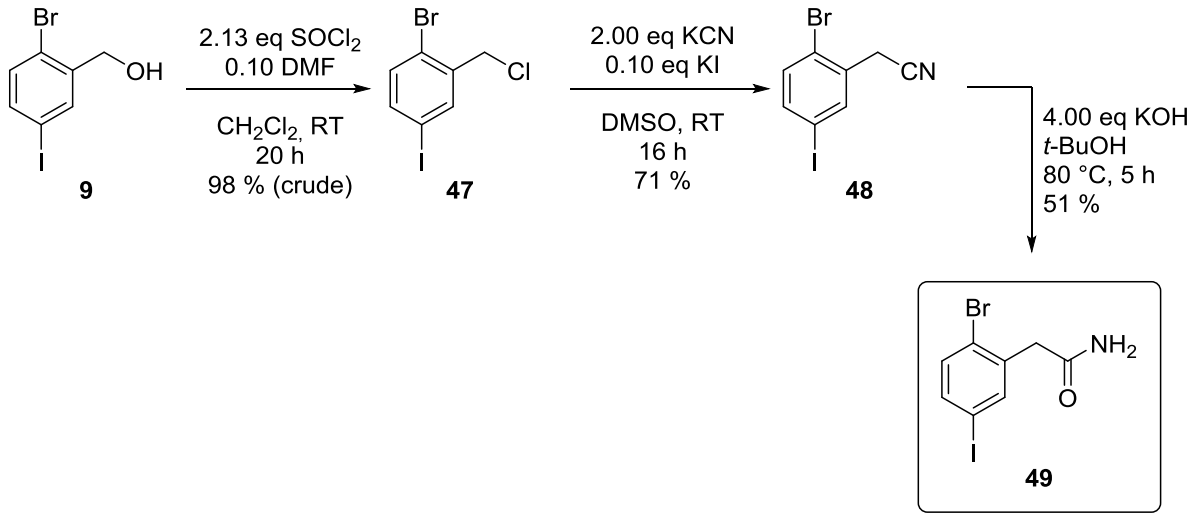
In the first step 2-bromo-5-iodobenzoic acid (**40**) was converted with oxalylchloride to 2-bromo-5-iodobenzoyl chloride (**41**). Before the addition of oxalylchloride the reaction mixture had to be cooled to 0 °C. After full conversion the solvent and the excess of oxalylchoride was removed in vacuum using a cooling trap and the crude product was used without further purification in the next step.

For the subsequent FRIEDEL-CRAFTS acylation with 2-bromo-5-iodobenzoyl chloride (**41**) and anisole it was nessesary to add $AlCl_3$ in portions over 10 min at 0 °C and the reaction mixture was stirred at this temperature for further 15 min. After full conversion the reaction mixture was poured onto ice. After extraction with CH_2Cl_2 and column chromatography (2-bromo-5-iodophenyl)(4-methoxyphenyl)methanone (**45**) could be isolated in 78 % yield. Furthermore 0.99 eq anisole had to be used, because when 1.00 eq anisole was used not the whole amount of it was consumed and in the column chromatography the desired product **45** could not be separated from remaining anisole.

In the last step the carbonyl group was reduced with Et_3SiH and $BF_3{\cdot}Et_2O$. As solvent a mixture of CH_2Cl_2 and CH_3CN (1/2) was used. First substrate **45** was dissolved in CH_2Cl_2 and Et_3SiH was added. Afterwards the solution was cooled to 0 °C and then $BF_3{\cdot}Et_2O$ was added. The reaction was stirred at RT and after 15 h complete conversion was obtained. Product **46** was isolated via column chromatography in 96 % yield.

4.1.7. Synthesis of the Asparagine building block

The asparagine core block was synthesized in three steps as shown in Scheme 32. First, (2-bromo-5-iodophenyl)methanol (**9**) was converted to 1-bromo-2-(chloromethyl)-4-iodobenzene (**47**) in the presence of $SOCl_2$. After complete conversion the excess of $SOCl_2$ was removed in vacuum using a cooling trap and the crude product was used without further purification in the next step.



Scheme 32. Synthesis of the asparagine building block **49**.

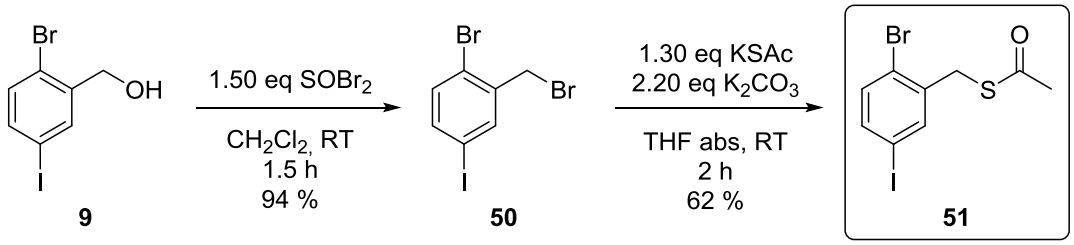
The next step was the synthesis of 2-(2-bromo-5-iodophenyl)acetonitrile (**48**). Therefore, the chlorinated compound **47** was reacted with KCN and catalytic amounts of KI in DMSO. The reaction was stirred overnight at RT and conversion was indicated by GC-MS. After full conversion the product was isolated after extraction with Et_2O and column chromatography in 71 % yield. Product **48** could not be isolated totally pure, because not all impurities could be removed by column chromatography.

In the last step the conversion of the nitrile to the amide in presence of KOH and *t*BuOH was performed. First, 2-(2-bromo-5-iodophenyl)acetonitrile (**48**) was dissolved in *t*BuOH and then

fine powderd KOH was added. After full addition the reaction mixture was heated to 80 °C until full conversion (5 h) was obtained. The reaction mixture was then quenched by the addition of H_2O and extracted with $CHCl_3$. After purification via column chromatography product **49** was isolated in 51 % yield.

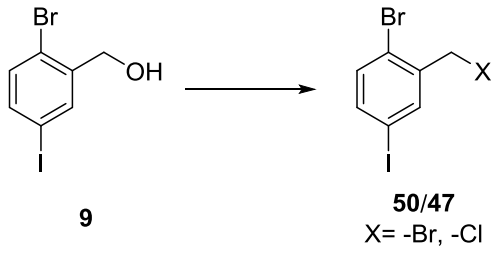
4.1.8. Synthesis of the Cysteine building block

The cysteine building block was synthesized in 2 steps starting from commercially available (2-bromo-5-iodophenyl)methanol (**9**) by conversion of the OH-group to a bromine followed by a nucleophilic substitution. The synthesis of (2-bromo-5-iodobenzyl) ethanethioate (**51**) is depicted in Scheme 33.



Scheme 33. Synthesis of the cysteine building block **51**.

For the synthesis of the cysteine building block also (2-bromo-5-iodophenyl)methanol (**9**) could be used as starting material. First the hydroxy function had to be transformed into a leaving group. Therefore different conditions for the formation of a leaving group were screened (Scheme 34, Table 8).



Scheme 34. Conversion of hydroxy function into different leaving groups.

Table 8. Screened conditions for the introduction of leaving groups.

Entry	Reagents	Solvent	Temperature	Yield	X
1	1.10 eq PBr_3	CH_2Cl_2	0 °C → RT	47 %[a]	-Br
2	1.10 eq PBr_3	Et_2O	0 °C → RT	51 %[b]	-Br
3	1.50 eq $SOBr_2$	CH_2Cl_2	RT	94 %[b]	-Br
4	2.00 eq $SOCl_2$	CH_2Cl_2	RT	98 %[a]	-Cl

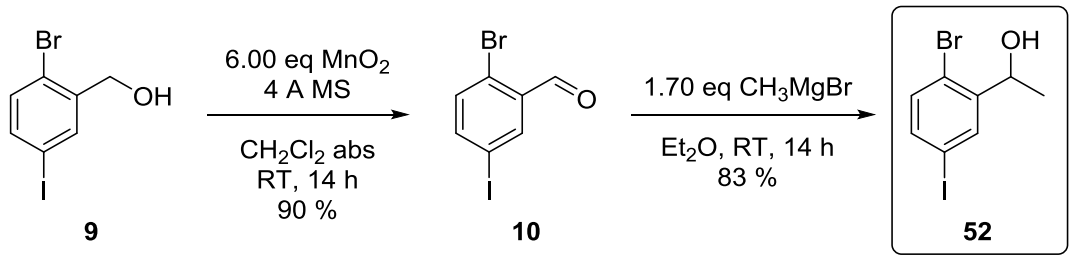
[a] crude product, [b] isolated yield

The best result was achieved with $SOBr_2$ in CH_2Cl_2 at RT (Table 8, Entry 3). In this case 94 % of the desired product **50** were isolated after column chromatography. When PBr_3 in CH_2Cl_2 was used only 47 % of crude product could be achieved (Table 8, Entry 1). Here no column chromatography was done, because of the low yield of the crude product. By changing the solvent from CH_2Cl_2 to Et_2O 51 % 1-bromo-2-(bromomethyl)-4-iodobenzene could be isolated after column chromatography. With $SOCl_2$ in CH_2Cl_2 (Table 8, Entry 4) 98 % crude product were obtained.

In the last step a nucleophilic substitution reaction was performed to achieve a thioester derivative.[125] Therefore the benzylic bromine was substituted with thioacetic acid to get the desired product **51** as protected thiol. The crude product was purified via column chromatography in 62 % yield (Scheme 33).

4.1.9. Synthesis of the Threonine building block

For the synthesis of the Thr core building block a two step route starting from (2-bromo-5-iodophenyl)methanol (**9**) was performed, shown in Scheme 35. In the first step alcohol **9** was oxidized to 2-bromo-5-iodobenzaldehyde (**10**) using 6.00 eq MnO_2. To avoid overoxidation to the carboxylic acid 4Å molecular sieves were added to the reaction mixture as discussed above (section 4.1.2).

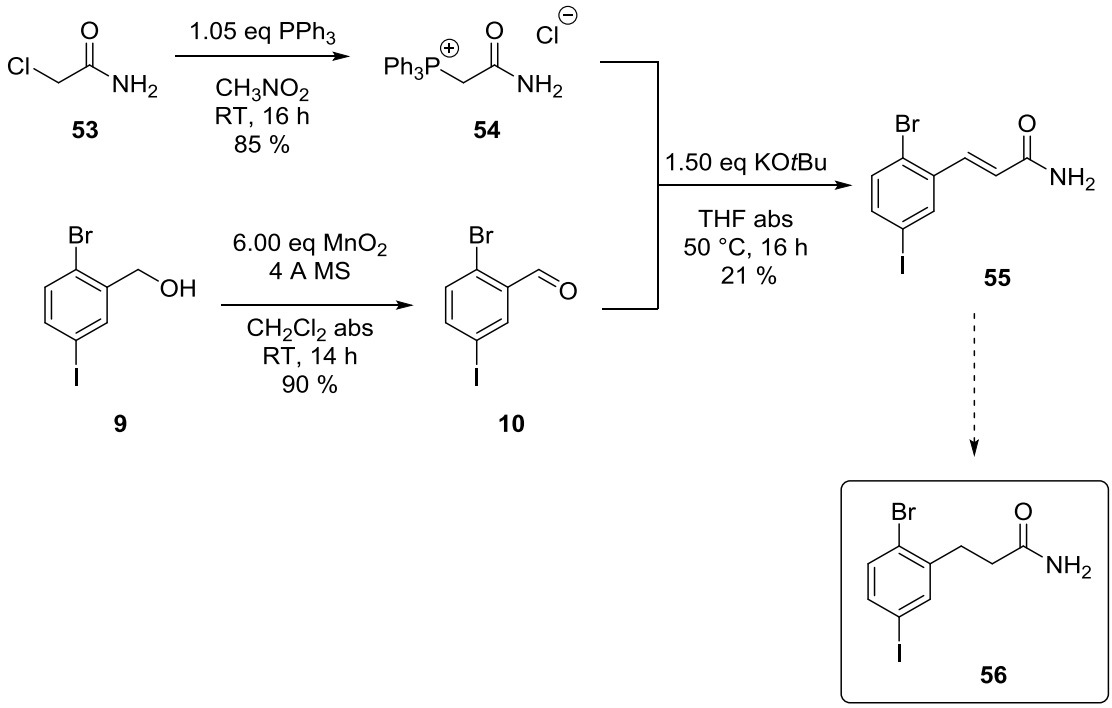


Scheme 35. Synthesis of the threonine building block **52**.

In the second step a GRIGNARD-reaction was done to achieve the Thr building block. 2-Bromo-5-iodobenzaldehyde (**9**) was dissolved in Et_2O. Afterwards 1.20 eq MeMgBr solution were added and the colorless suspension was stirred at RT for 5 h. According to TLC incomplete conversion was indicated and so additional 0.5 eq MeMgBr soltion were added. After stirring for further 11 h TLC and GC-MS indicated full conversion. The crude product was extracted and purification was done via flash column chromatography to isolate product **52** in 83 % yield.

4.1.10. Synthesis of the Glutamine building block

For the synthesis of the Gln core fragment in the first step a Wittig-reation was performed and in the second step the reduction of the double bond should yield 3-(2-bromo-5-iodophenyl)propanamide **56** (Scheme 36).

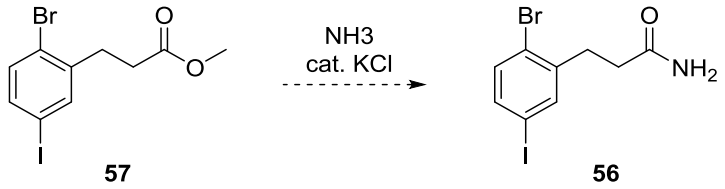


Scheme 36. Synthesis of the glutamine building block **56**.

The first step was the oxidation of alcohol **9** using 6.00 eq MnO_2 (see section 4.1.2). Then compound **55** was synthesized via WITTIG-reaction. After 1 h deprotonation of the phosponium salt **54** with KO*t*Bu in abs. THF at 50 °C aldehyde **10** was added. Afterwards it was necessary to heat the reaction to 80 °C to achieve full conversion after 16 h. Purification via flash chromatography furnished product **55** in 21 % yield.

In the last step the double bond should be reduced using PADA or p-tosyl hydrazide as diimide precursor. By using p-THA for the reduction after 14 h many side products were achieved but the right product mass was not found according to HPLC-MS. In parallel the reduction with PADA was performed. In this case only one product was formed, but very low conversion of the starting material was achieved after 96 h reaction time. Moreover, the further addition of PADA did not lead to a better conversion. Maybe another solvent and higher temperature would favour the formation of the desired product.

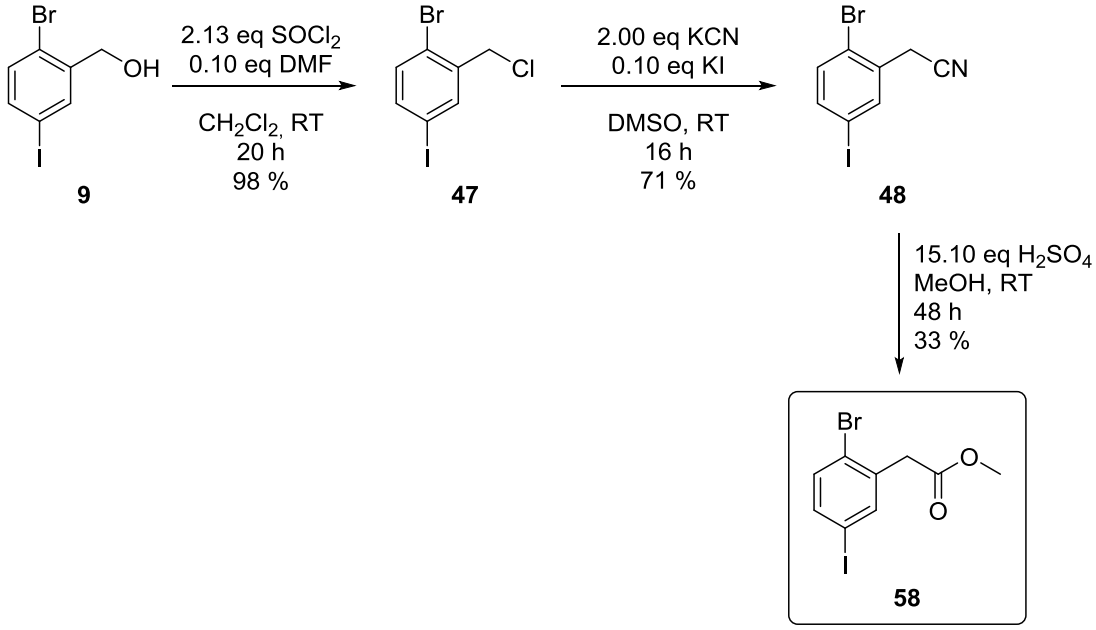
As alternative the glutamine building block could be synthesized by aminolysis with NH_3. Therefore, methyl 3-(2-bromo-5-iodophenyl)propanoate (**57**) will be used as starting material and after reaction with NH_3 and cat. KCl desired product **56** should be obtained.



Scheme 37. Aminolyse with NH_3 for the generation of the glutamine building block.

4.1.11. Synthesis of the Aspartic acid building block

In the first attempt the aspartic acid core block was synthesized from (2-bromo-5-iodophenyl)methanol (**9**) in three steps shown in Scheme 38. For the first and second step the same procedure as for the asparagine building block was used (see section 4.1.7). First alcohol **9** was converted to 1-bromo-2-(chloromethyl)-4-iodobenzene (**47**) in the presence of $SOCl_2$. After complete conversion $SOCl_2$ was removed in vacuum using a cooling trap and the crude product **47** was used without further purification in the next step.



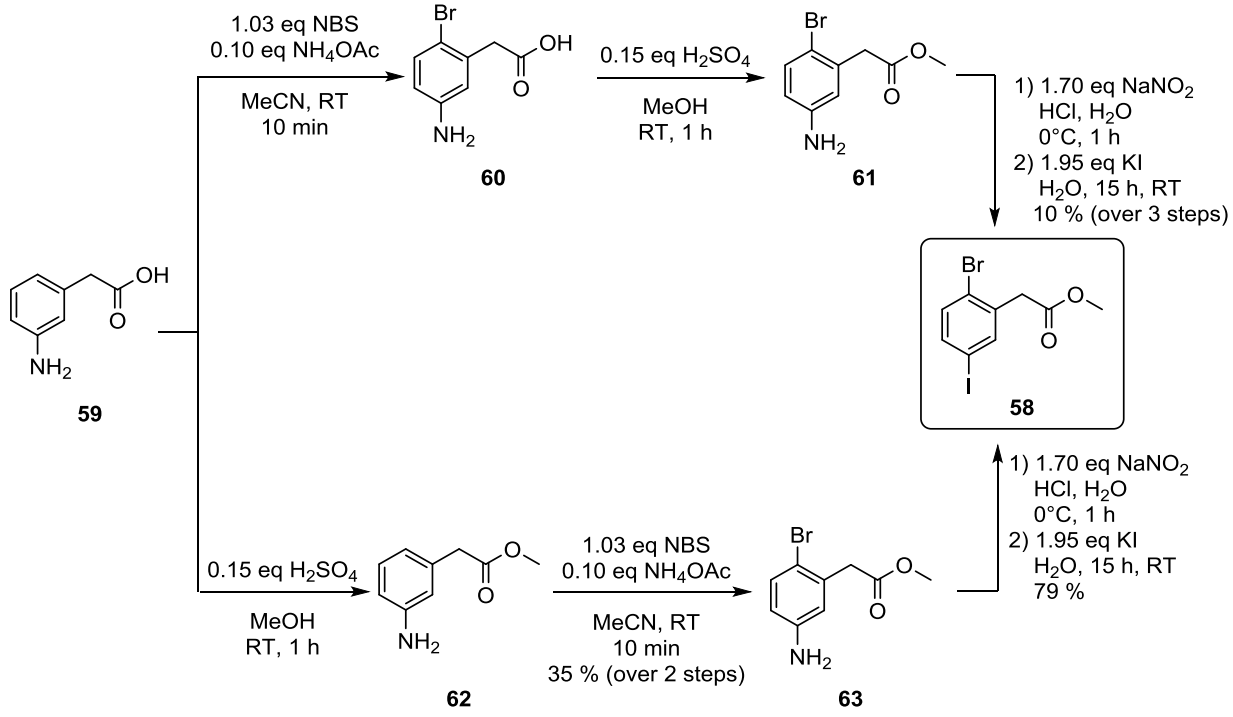
Scheme 38. First route for the synthesis of the aspartic acid building block **58**.

The next step was the synthesis of 2-(2-bromo-5-iodophenyl)acetonitrile (48). The chlorinated compound 47 was reacted with KCN and a catalytic amount of KI in DMSO. The reaction

was stirred overnight at RT and conversion was monitored by GC-MS. The product was isolated after extraction with Et_2O and column chromatography in 71 % yield. Product 48 could not be isolated totally pure, because not all impurities could be removed by column chromatography.

In the last step the conversion of the nitrile to the carboxylic acid in the presence of H_2SO_4 was executed. Due to the use of MeOH as solvent the carboxylic acid was directly converted to the methyl ester **58**. First 2-(2-bromo-5-iodophenyl)acetonitrile (**48**) was dissolved in MeOH and then the reaction mixture was cooled to 0 °C in an ice bath before carefully adding H_2SO_4. After completion of addition the reaction mixture was heated to 65 °C until full conversion (48 h) was obtained. The reaction mixture was then extracted with CH_2Cl_2 and the crude product was purified by column chromatography. Methyl 2-(2-bromo-5-iodophenyl)acetate (**58**) was isolated in moderate yield (33 %), because the product was not fully separable from by-products during column chromatography and only pure fractions were processed further.

An alternative route was invented to overcome the problems in the isolation und the use of KCN in the synthesis. Therefore methyl 2-(2-bromo-5-iodophenyl)acetate (**58**) was isolated in another three step synthesis starting from 2-(3-aminophenyl)acetic acid (**59**) (Scheme 39).

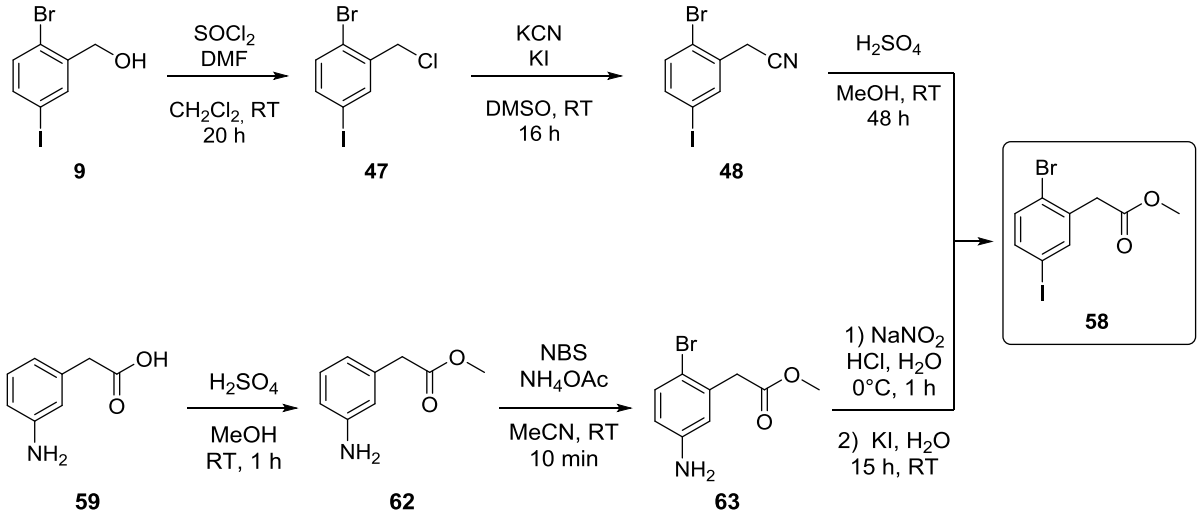


Scheme 39. Second route for the synthesis of the aspartic acid building block **58**.

On the one hand 2-(3-aminophenyl)acetic acid (**59**) was first brominated, then esterification took place and the final step was the iodination to produce the aspartic acid building block. During the bromination reaction incomplete conversion resulted from the addition of 1.05 eq NBS. Also too much overbrominated product was formed and so an inseparable mixture of starting material **59**, product **60** and overbrominated product was generated. After esterification and iodination only less than 10 % of the desired product **58** were obtained and thus this reaction route was not followed up.

When changing the sequence of events first starting material **59** was converted into the methyl ester. 2-(3-Aminophenyl)acetic acid (**59**) was suspended in MeOH and conc. H_2SO_4 was added dropwise. After full conversion the solvent was removed and the crude product was used in the bromination step without further purification. For the bromination the same procedure as for the valine building block was used (section 4.1.1), but instead of 1.05 eq NBS only 1.03 eq NBS were used to get less overbrominated product. According to GC-MS only 9 % of overbrominated product were formed, which was easily separable from methyl 2-(5-amino-2-bromophenyl)acetate (**63**) via column chromatography. The brominated product **63** was isolated in 35 % yield over 2 steps. In analogy to the Val core fragment in the final step iodination of compound **63** was done and product **58** was obtained in 79 % isolated yield.

The overall yields in the two reaction sequences were in the same order of magnitude with 23 % in the first sequence and 27 % in the second route. In the first synthesis a big problem was the isolation of product **58**.

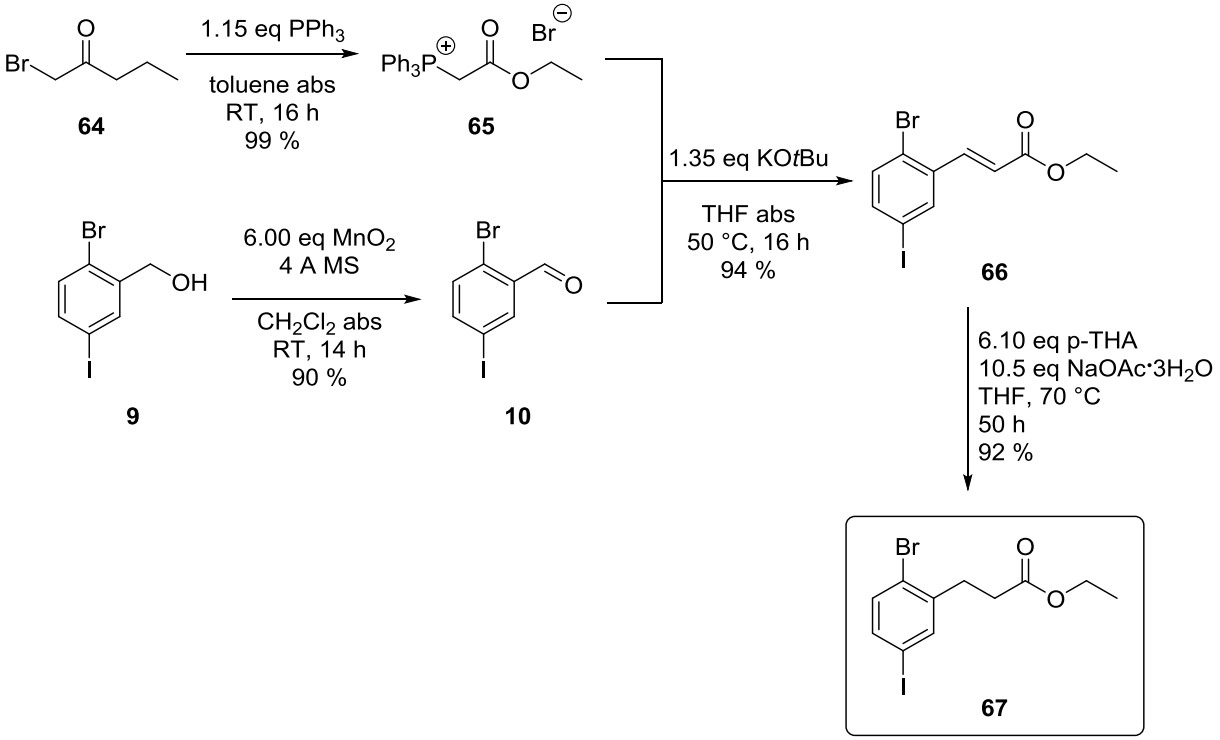


Scheme 40. Tested reaction sequences for the synthesis of aspartic acid building block **58**.

Therefore the second reaction route was selected for the synthesis of the methyl 2-(2-bromo-5-iodophenyl)acetate (**58**). Starting from compound **59** esterification furnished the methyl ester, followed by bromination and iodination producing aspartic acid core fragment **58**.

4.1.12. Synthesis of the Glutamic acid building block

The Glu building block was synthesized in four steps according to the synthesis route depicted in Scheme 41 starting from (2-bromo-5-iodophenyl)methanol (**9**) and 1-bromopentan-2-one (**64**).



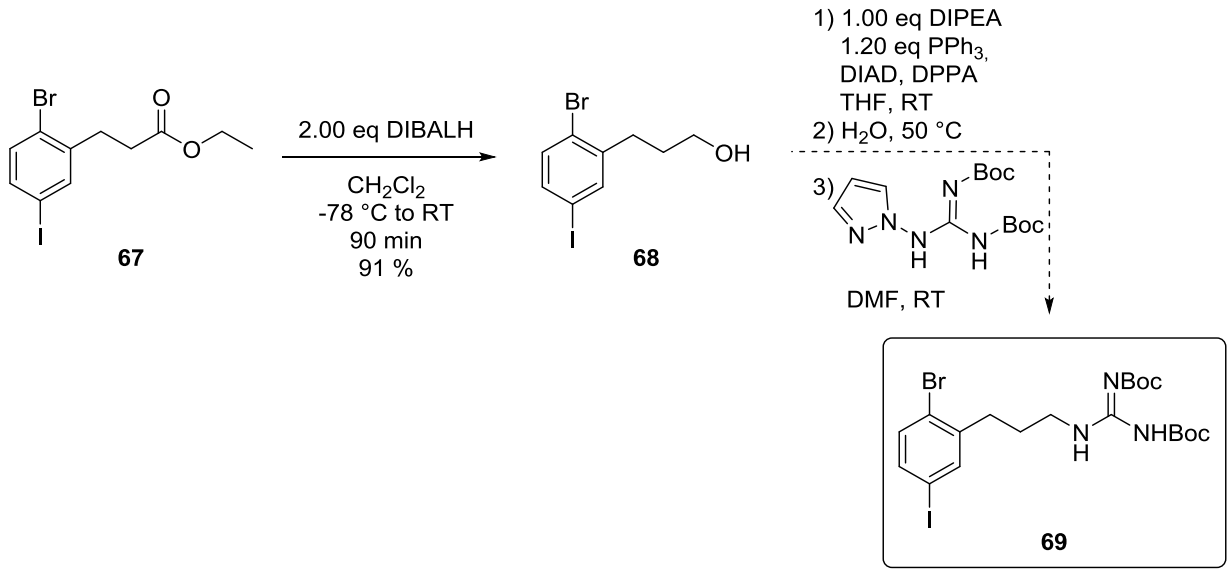
Scheme 41. Synthesis of the glutamic acid building block **67**.

The first step was again the oxidation of alcohol **9** using 6.00 eq MnO_2 (see section 4.1.2). Then compound **66** was synthesized via WITTIG-reaction. After 1 h deprotonation of the phosponium salt **65** with KO*t*Bu in abs. THF aldehyde **10** was added. Afterwards it was necessary to heat the reaction to 50 °C to achieve full conversion after 16 h. Purification via flash chromatography furnished product **66** in excellent yield of 94 %. An *E*/*Z* mixture of 4/1 was achieved but due to the planned reduction of the double bond in the next step the selectivity was not optimized.

In the last step the double bond was reduced using p-tosyl hydrazide as diimide precursor instead of Pd because the use of Pd is not possible with halogenated compounds like substrate **66**. The reduction had to be done at 70 °C and after 50 h quantitative conversion was achieved and the Glu building block **67** was isolated after column chromatography in 92 % yield.

4.1.13. Synthesis of the Arginine building block

The synthesis of the arginine building block should be performed in two steps. In the first step the already synthesizied Glu core fragment was reduced to the corresponding alcohol **68**. In the last step the hydroxyl group should be converted to the corresponding amine via MITSUNOBU-STAUDINGER sequence and the amine should be used without further purification in the guanylation reaction.



Scheme 42. Attempted synthesis of the arginine building block **69**.

First the generation of 3-(2-bromo-5-iodophenyl)propan-1-ol (**68**) was performed by the reduction of ester **67**. Ethyl 3-(2-bromo-5-iodophenyl)propanoate (**67**) was dissolved in abs. CH_2Cl_2 and the solution was cooled to -78 °C. 2.00 eq DIBALH were added dropwise to the solution and after complete addition of DIBALH the reaction mixture was allowed to warm up to RT. After 90 min full conversion of the starting material was indicated by GC-MS, the reaction was quenched by the addition of MeOH and afterwards Rochelle salt solution was added. Then the suspension had to be stirred overnight for phase separation. After simple

extraction with CH_2Cl_2 the crude product was purified via flash column chromatography. Product **68** was isolated in 91 % yield.

In the next step a MITSUNOBU-STAUDINGER sequence for the generation of the corresponding amine should be performed. The azide intermediate should not be isolated and the amine should be used without further purification in the guanylation reaction. For the guanylation reaction the commercially available guanylation reagent, shown in Figure 26, should be used.

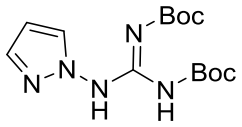
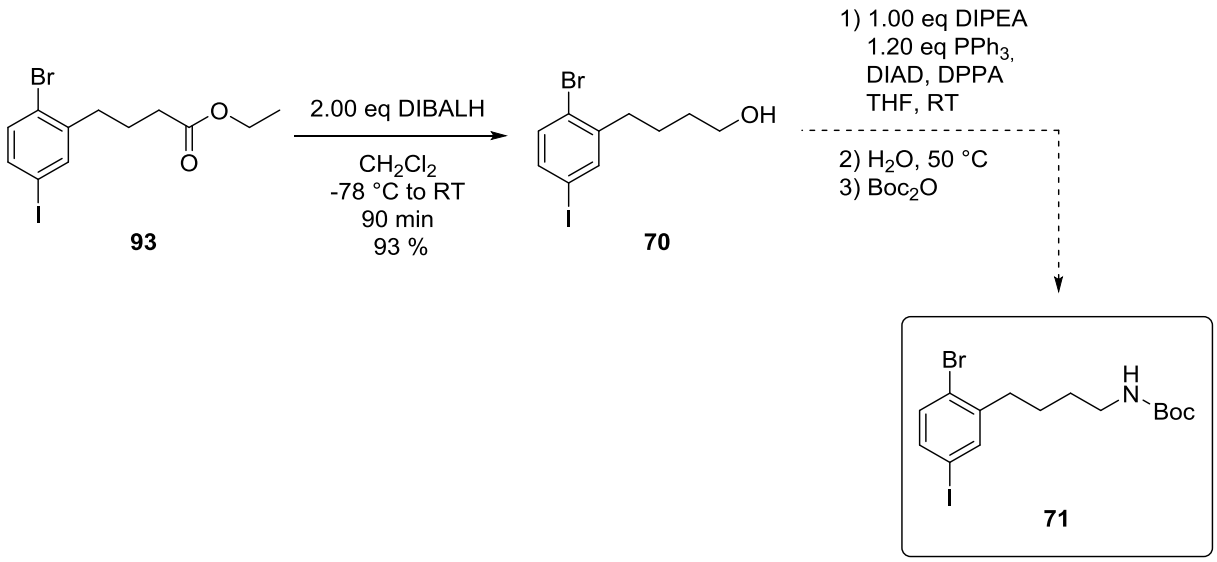


Figure 26. Guanylation reagent.

For the MITSUNOBU-STAUDINGER reaction alcohol 68 was dissolved in THF and the solution was cooled to 0 °C. Then 1.00 eq DIPEA, 1.20 eq PPh_3, 1.20 eq DIAD and 1.20 eq DPPA were added and the pale yellow suspension was stirred at RT for 3 h. After 3 h incomplete conversion of alcohol 68 was detected by TLC and GC-MS. Addition of additional 1.00 eq DIPEA, 1.20 eq PPh_3, 1.20 eq DIAD and 1.20 eq DPPA and heating up to 50 °C also did not achieve in complete conversion. So the reaction conditions have to be optimized to achieve the Arg building block.

4.1.14. Synthesis of the Lysine building block

The synthesis of the lysine building block should be performed similar to the synthesis of the Arg building block (see section 4.1.12). Therefore the C-elongated Glu core building block was reduced to the corresponding alcohol **70** and then a MITSUNOBU-STAUDINGER sequence should lead to an amine, which could be protected with tert-butyloxycarbonyl protecting group.



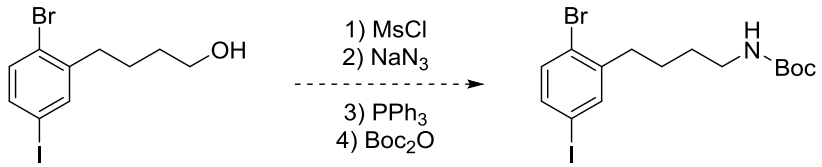
Scheme 43. Attempted synthesis of the lysine building block **71**.

First, the generation of 4-(2-bromo-5-iodophenyl)butan-1-ol (**70**) was performed by the reduction of the C-elongated Glu core building block **93**. Ester **93** was first dissolved in abs. CH_2Cl_2 and the solution was cooled to -78 °C. 2.00 eq DIBALH were added to the solution dropwise and after complete addition of DIBALH the reaction mixture was allowed to warm up to RT. After 2 h full conversion of the starting material was indicated by GC-MS and the reaction was quenched by the addition of MeOH and afterwards Rochelle salt solution was added. Then the suspension had to be stirred for 4 h for phase separation. After simple extraction with CH_2Cl_2 the crude product was purified by flash column chromatography. Product **70** was isolated in 93 % yield.

In the next step a MITSUNOBU-STAUDINGER sequence for the generation of the corresponding amine should be performed. The azide intermediate should be not isolated and the amine should be used without further purification for the protection with tert-butyloxycarbonyl group. For the MITSUNOBU-STAUDINGER reaction alcohol **70** was dissolved in THF and the

solution was cooled to 0 °C. Then 1.00 eq DIPEA, 1.20 eq PPh_3, 1.20 eq DIAD and 1.20 eq DPPA were added and the pale yellow suspension was stirred at RT for 3 h. After 3 h incomplete conversion of alcohol **70** was detected by TLC and GC-MS. Addition of further 1.00 eq DIPEA, 1.20 eq PPh_3, 1.20 eq DIAD and 1.20 eq DPPA and heating up to 50 °C also did not lead to complete conversion.

As an alternative method for the synthesis of the lysine building block the reaction sequence shown in Scheme 44 could be performed. The first step would be mesylation, followed by the transformation to an azide and in the last step the amine should be generated, which could be protected with Boc_2O for the later cross-coupling.

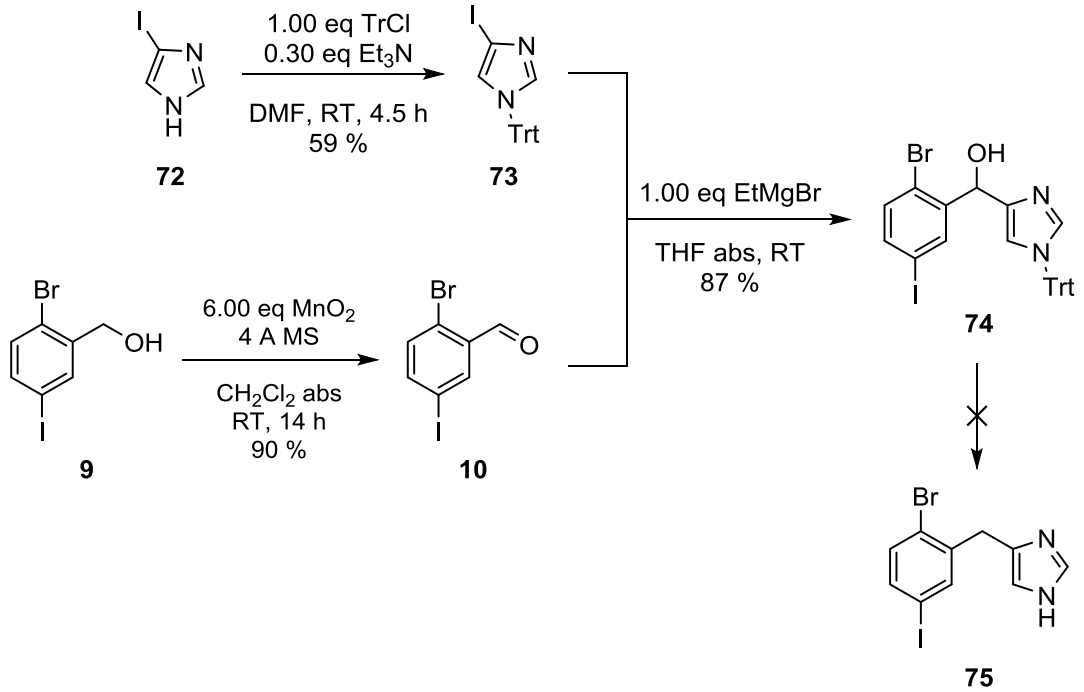


Scheme 44. Alternative synthesis of the lysine building block.

4.1.15. Synthesis of the Histidine building block

For the synthesis of the His-core building block a slightly modified procedure by WIJTMANS *et al.* was attempted.[126] WIJTMANS showed that a protected imidazole reacts with EtMgBr to an imidazolyl-GRIGNARD reagent. After metal halogen exchange an aldehyde is added to form benzyl-1*H*-imidazoles.

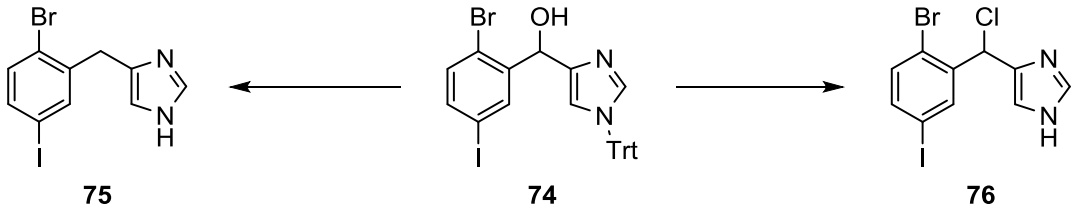
First, commercially available 4-iodo-1*H*-imidazole (**72**) was protected with a trityl group following the same procedure described by KIRK.[127] To a solution of **72** in DMF Et_3N and triphenylmethylchloride were added and the reaction mixture was stirred at RT for 3 h. After collection of the precipitate by filtration 4-iodo-1-trityl-1*H*-imidazole (**73**) was isolated in 59 % yield. Following a slightly modified procedure by WIJTMANS this protected imidazole **73** was dissolved in abs. THF and then reacted with a solution of EtMgBr in Et_2O. After complete metal halogen exchange, which was monitored by a H_2O quench via HPLC-MS, 2-bromo-5-iodobenzaldehyde (**10**) was added to obtain product **74** in 87 % isolated yield after purification via column chromatography (Scheme 45).



Scheme 45. First attempt for the synthesis of the histidine core building block.

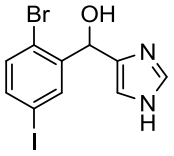
The last step was the removal of the OH-group. On the one hand the OH-group should be removed directly and on the other hand a conversion of the OH-group to a chlorine and later

removal of the Cl-group should be pursued (Scheme 46). Therefore different methods were tried for the synthesis of the His core building block, which are shown in Table 9.



Scheme 46. Removal or conversion of the OH-group.

Table 9. Tested methods for the removal or conversion of the OH-group.

Entry	Time	Conditions	Solvent	 77	side products
1	18 h	8.0 eq Et_3SiH 8.0 eq TFA	CH_2Cl_2	40 % [a]	60 % [a]
2	18 h	$SOCl_2$	-	35 % [a]	65 % [a]
3	18 h	$SOCl_2$ 35 °C	-	41 % [a]	59 % [a]
4	18 h	1.2 eq CBr_3Cl 3.0 eq PPh_3	CH_2Cl_2	39 % [a]	61 % [a]
5	18 h	1.2 eq BF_3*Et_2O 0.48 eq H_2O	Et_2O	30 % [a]	70 % [a]

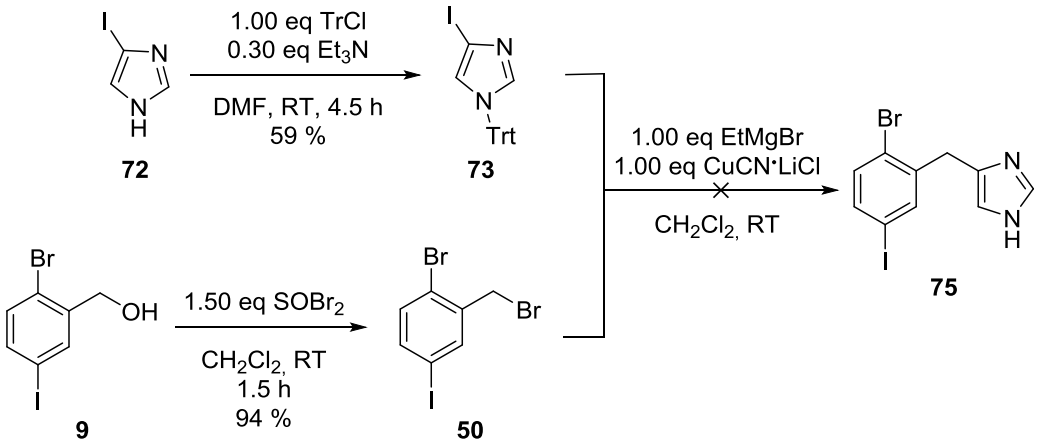
[a] According to HPLC-MS.

First the removal of the OH-function was treid with Et_3SiH and TFA (Table 9, Entry 1). Deprotection of the imidazole occurred due to the acidic conditions and only (2-bromo-5-iodophenyl)(1*H*-imidazol-4-yl)methanol (**77**) according to HPLC-MS was produced. Therefore, different chlorination reactions were tried. First thionylchloride was used in CH_2Cl_2 to form 4-((2-bromo-5-iodophenyl)chloromethyl)-1*H*-imidazole (**76**) but no conversion to the desired product was observed by HPLC-MS (Table 9, Entry 2). Therefore, $SOCl_2$ neat at 35 °C were tested, but also in this case no desired product formation was achieved (Table 9, Entry 3). In a third approach for chlorination an APPEL-reaction should be performed. Therefore, trichlorobromomethane and triphenylphosphine were used. However,

also this reaction resulted not in the desired outcome (Table 9, Entry 4). In all cases no desired product was formed and on these grounds this route was discarded.

Another approach for the synthesis of the His core fragment was needed. Therefore, also a GRIGNARD-reaction described by WIJTMANS *et al.* with protected 4-iodo-1*H*-imidazole was attempted. In this case first a magnesium-copper exchange should be performed, followed by reaction of an benzylbromide with the resulting cuprate to generate the essential benzylic C-C bond.[126]

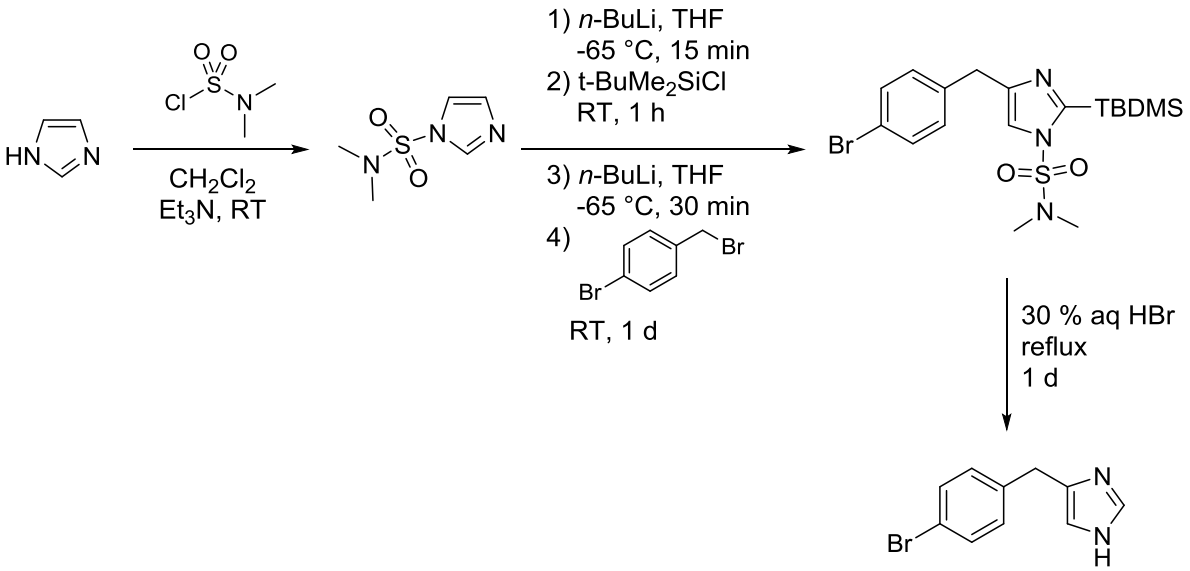
For this approach the already synthesized 4-iodo-1-trityl-1*H*-imidazole (**73**) and 1-bromo-2-(bromomethyl)-4-iodobenzene (**50**) were used for the GRIGNARD-reaction, depicted in Scheme 47. Compound **73** was first dissolved on the one hand in CH_2Cl_2 and on the other hand in THF. Then EtMgBr was added and after stirring for 1 h at RT CuCN·LiCl-solution was added to form the cuprate. Afterwards 1-bromo-2-(bromomethyl)-4-iodobenzene (**50**) was added and the reaction was monitored by HPLC-MS. After 19 h reaction time still starting material was left. The reaction mixture was stirred for another 20 h, but after longer reaction time no fundamental conversion to the desired product was obtained and due to significant byproduct formation in both cases these reaction routes were rejected.



Scheme 47. Attempted synthesis of the histidine building block.

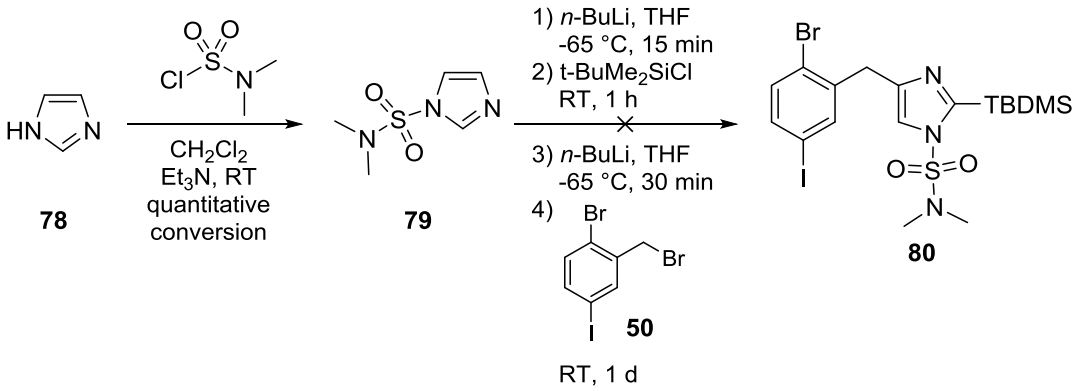
WIJTMANS *et al.* also described another method for the synthesis of benzyl-1*H*-imidazole. In the event WIJTMANS used a protected imidazole which was converted to 4-(4-bromobenzyl)-2-(tert-butyldimethylsilyl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide in a one-pot reaction. In this step a protection, metalation and subsequent functionalization of the imidazole takes place by the repeated addition of *n*-BuLi and electrophiles. In this case t-

butyldimethylsilylchloride and 1-bromo-4-(bromomethyl)benzene were used as electrophiles. In the last step acidic deprotection furnished the target compound in over 90 % yield (Scheme 48).[126]



Scheme 48. Synthetic pathway for 4-(4-bromo-benzyl)-1*H*-imidazole described by WIJTMANS *et al.*[126]

Due to the similarity to our His-core fragment this synthesis seemed to be a promising route for the synthesis of 4-(2-bromo-5-iodobenzyl)-1*H*-imidazole, shown in Scheme 49. For the first step Et_3N and *N*,*N*-dimethylsulfamoylchloride were added dropwise to a solution of imidazole (**78**) in CH_2Cl_2 and afterwards. After 22 h compound **79** was obtained in quantitative yield after simple extraction and was used in the next step without further purification.

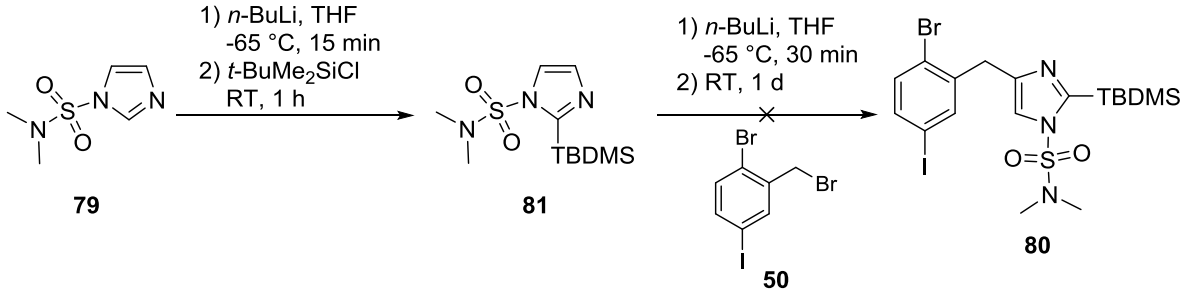


Scheme 49. Attempted synthesis for the His core fragment (**80**).

When the one-pot reaction was done following the procedure by WIJTMANS *et al.*,[126] the protected imidazole **79** was dissolved in abs. THF and cooled to -78 °C. Afterwards *n*-BuLi

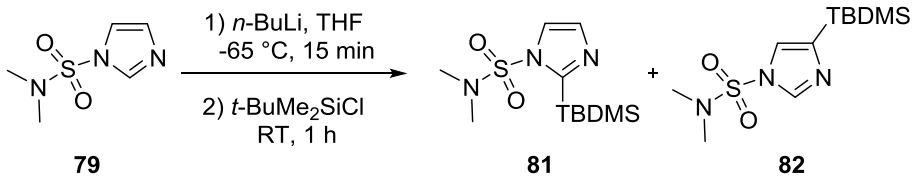
was added dropwise while maintaining a temperature of -65 °C. The reaction mixture was stirred for 15 min and then *t*-BuMe$_2$SiCl was added dropwise while maintaining a temperature of -60 °C to generate 2-(*tert*-butyldimethylsilyl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (**81**). Next the mixture was slowly warmed up to RT and was stirred for 1 h to achieve complete conversion to the protected imidazole **81**. Then the suspension was cooled to -78 °C again and *n*-BuLi was added dropwise. After further 30 min at this temperature a solution of 1-bromo-4-(bromomethyl)benzene (**50**) in abs. THF was added at -60 °C and the reaction mixture was stirred overnight at RT. According to HPLC-MS no product was formed and also after column chromatography no product could be isolated.

So it was necessary to isolate the protected imidazole, which is generated in situ in the one-pot reaction, to ensure complete conversion to the protected imidazole **81** (see Scheme 50).



Scheme 50. Attempted synthesis for the His core fragment (**80**).

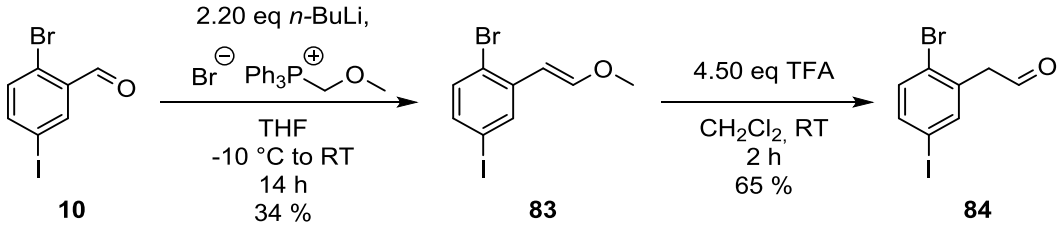
The protection of *N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (**79**) has been described by LEE *et al.*, so following this procedure product **81** was isolated in 73 % yield.[128] First *t*-BuMe$_2$SiCl was added in portions over 5 min. In this case desired product **81** was generated as well as compound **82** (Scheme 51) in 59 % resp. 41 %. Then a solution of *tert*-butyldimethylsilyl chloride in abs. THF was added over 35 min. Slower addition of dissolved *t*-BuMe$_2$SiCl resulted in a better ratio of desired product **81** and compound **82**. These compounds were separable via column chromatography and 86 % desired product **81** were obtained.



Scheme 51. Synthesis of protected imidazole **81**.

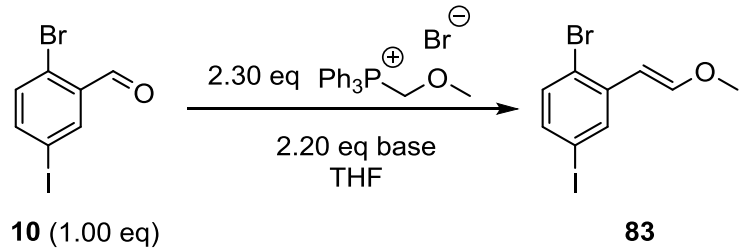
With the protected imidazole **81** in hands the second step was tried again. Substrate **81** was dissolved in abs. THF and cooled to -78 °C. Afterwards *n*-BuLi was added dropwise and the reaction mixture was stirred at -78 °C for 30 min. After 30 min 1-bromo-4-(bromomethyl)benzene (**50**) dissolved in abs. THF was added while maintaining a temperature of -78 °C. Then the reaction mixture was stirred overnight at RT. According to HPLC-MS full conversion of the starting material was achieved but after column chromatography no product could be isolated.

Another approach to synthesize the His building block was needed. Therefore the imidazole part should be formed by an addition of tosylmethyl isocyanide (TosMIC) to an aldehyde following by the treatment with 7M NH_3 solution. First, 2-(2-bromo-5-iodophenyl)acetaldehyde (**84**) had to be synthesiszed. The first attempted synthesis of aldehyde **84** is shown in Scheme 52.



Scheme 52. Synthesis of 2-(2-bromo-5-iodophenyl)acetaldehyde (**84**).

Starting from already generated 2-bromo-5-iodobenzaldehyde (**10**) (see section 4.1.2) a WITTIG-reaction with commercially available (methoxymethyl)triphenyl phosphonium bromide was performed. First phosphonium bromide was dissolved in abs. THF and cooled to the desired temperature. The deprotonation of the WITTIG-ylide was performed by the addition of *n*-BuLi or KOtBu. After 1 h a solution of 2-bromo-5-iodobenzaldehyde (**10**) in abs. THF was added dropwise and the reaction was stirred at RT for 5 to 18 h. Different conditions were tested, shown in Table 10.



Scheme 53. Wittig reaction for the synthesis of **83**.

Table 10. Screened conditions for the WITTIG-reaction.

Entry	Time	Base	Temperature	Product	Isolated yield
1	5 h	*n*-BuLi	-10 °C	full conversion[a]	34 %
2	18 h	*n*-BuLi	-30 °C	full conversion[a] (mixture of product with and without iodine)	-
3	18 h	*n*-BuLi	-35 °C	mixture of starting material and product with and without iodine[b]	-
4	6 h	*n*-BuLi	0 °C	mixture of starting material and product with and without iodine[b]	-
5	5 h	KO*t*Bu	0 °C	no conversion[b]	-

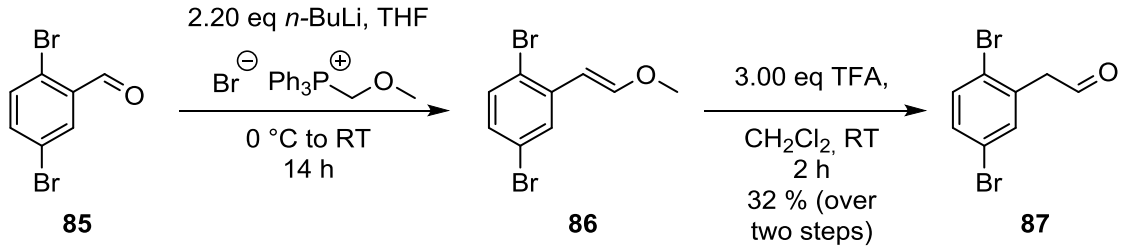
[a] According to TLC, [b] according to GC-MS.

For the deprotonation of the WITTIG-ylide on the one hand KOtBu and on the other hand *n*-BuLi were used. If KO*t*Bu was used as base no conversion was achieved (Table 10, Entry 5). Therefore *n*-BuLi was the base of choice. The deprotonation to the yilde and the reaction with aldehyde **10** was done at different temperatures. The best result was achieved at a temperature of -10 °C (Table 10, Entry 1). If higher or lower temperatures were used for the reaction in most cases incomplete conversion was obtained and also partly iodine was cleaved off (Table 10, Entry 2 – 4). So these reactions yielded an inseparable mixture of starting material **10** and product with and without iodine. On these grounds only the reaction with *n*-BuLi as base and at -10 °C was purified by column chromatography, but only 34 % yield of the desired product **79** was achieved.

In the next step the formation of aldehyde **84** was done by the addition of TFA. First 1.50 eq TFA were used, but incomplete conversion to the desired product **84** was achieved. Hence another 3.00 eq of TFA were added to obtain full conversion. After extraction and purification

by column chromatography product **84** was isolated in 65 % yield. The reaction sequence with the best result in the WITTIG-reaction (Table 10, Entry 1) was repeated two times but in all cases also at -10 °C the iodine was partly cleaved off and the outcome of this reaction was not reproducible.

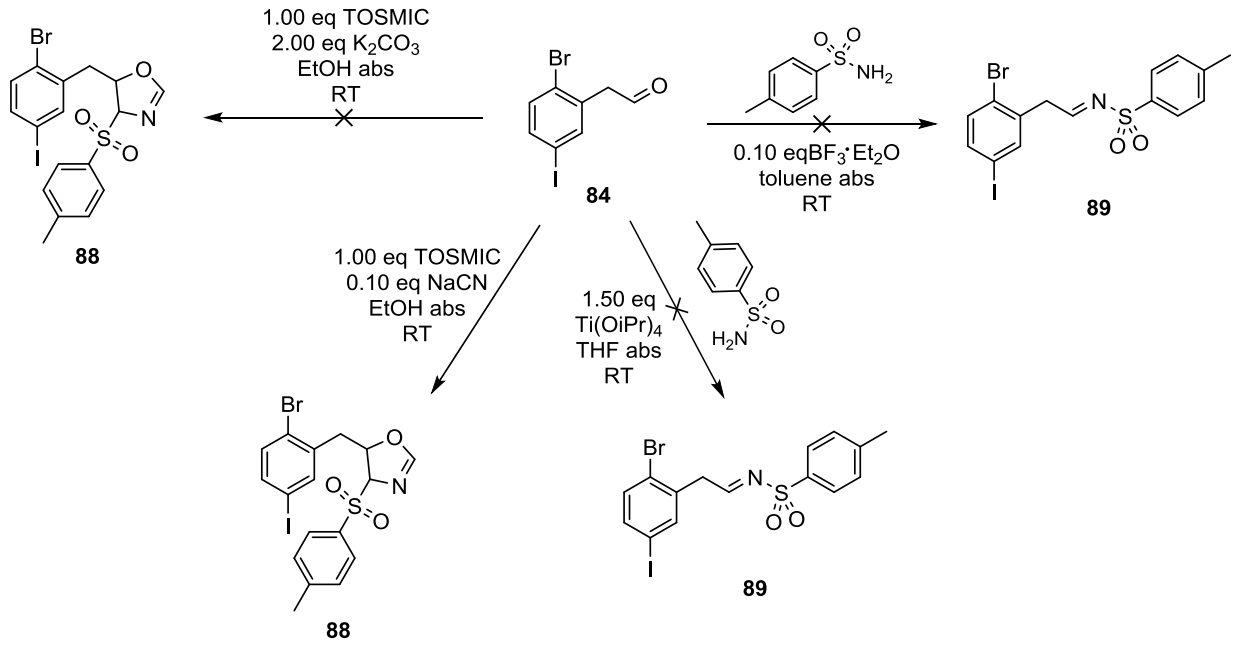
Due to the partial cleavage of the iodine in the synthesis of aldehyde **84** starting from 2-bromo-5-iodobenzaldehyde **10** an alternative route was necessary. Therefore 2,5-dibromobenzaldehyde (**85**) was used as starting material for the WITTIG-reaction with (methoxymethyl)triphenyl phosphonium bromide. In the last step aldehyde **87** was generated by the addition of TFA (see Scheme 54).



Scheme 54. Alternative synthesis of aldehyde **87**.

First, commercially available 2,5-dibromobenzaldehyde (**85**) was reacted with (methoxymethyl)triphenyl phosphonium bromide in a WITTIG-reaction. Deprotonation of the ylide was achieved by the addition of *n*-BuLi. Here it was only necessary to cool the reaction mixture to 0 °C because no iodine could be cleaved off during the WITTIG-reaction. Furthermore, the crude product **86** was not purified after extraction and it was used without further purification in the next step. Then the crude compound **86** was dissolved in CH_2Cl_2 and cooled to 0 °C. As addition of 1.50 eq TFA led to in incomplete conversion another 1.50 eq TFA were added and then full conversion was achieved. The crude product was purified via column chromatography and generated 2-(2,5-dibromophenyl)acetaldehyde (**87**) in 46 % yield over 2 steps. In comparison to the formation of 2-(2-bromo-5-iodophenyl)acetaldehyde (**84**) (22 % yield over two steps) a better yield was achieved for the synthesis of 2-(2,5-dibromophenyl)acetaldehyde (**87**).

2-(2-Bromo-5-iodophenyl)acetaldehyde (**84**) as well as 2-(2,5-dibromophenyl)acetaldehyde (**87**) were used for further reactions to synthesize the His building block. Compound **84** was reacted on the one hand with TosMIC to generate oxazoline **88** and on the other hand 4-methylbenzenesulfonamide was used to gain substrate **89** as depicted in Scheme 55.

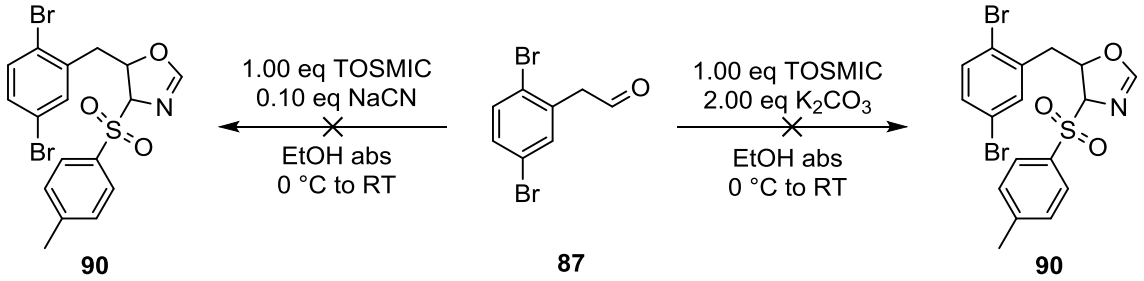


Scheme 55. Different routes for the formation of the His core fragment.

First, oxazoline **88** should be formed by a cycloaddition with TosMIC. Therefore, TosMIC was dried before use in vacuum and afterwards abs. EtOH was added. The suspension was cooled to 0 °C and then 2-(2-bromo-5-iodophenyl)acetaldehyde (**84**) was added. Two different bases (NaCN and K_2CO_3) were used for this reaction. When K_2CO_3 was used no desired product was formed according to GC-MS. By addition of NaCN as base full conversion was achieved as indicated by TLC and GC-MS and the right product mass was found. However, after flash chromatography no desired product **88** could be identified by NMR which indicated a possible instability of oxazoline **88**.

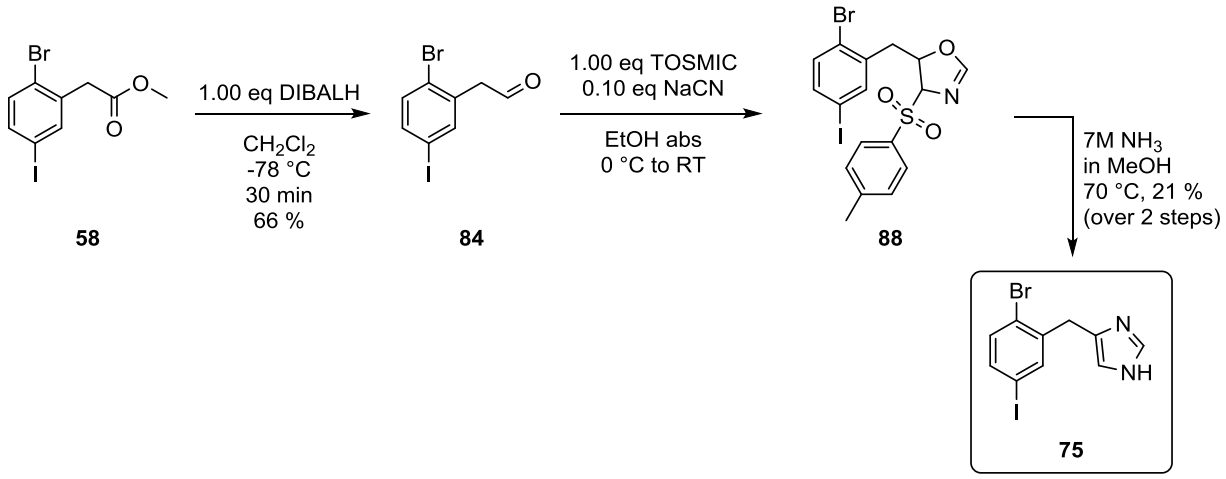
Reactions with 4-methylbenzenesulfonamide and benzaldehydes and subsequent addition of TosMIC are known in literature.[129] Following a similar procedure like CASTELLANO *et al*.[130] 2-(2-bromo-5-iodophenyl)acetaldehyde (**84**) was reacted with p-toluenesulfonamide in the presence of $BF_3{\cdot}Et_2O$ (Scheme 55). Also a similar prodecure with using Ti(O*i*Pr)$_4$ instead of $BF_3{\cdot}Et_2O$ was tried. In both cases no product was formed so these reactions were not followed up.

Formation of the oxazoline via addition of TosMIC was also done with 2-(2,5-dibromo-phenyl)acetaldehyde (**87**) shown in Scheme 56. The same conditions like before were used and generation of the oxazoline was indicated by GC-MS, but also in this case no desired product was formed (Scheme 56).



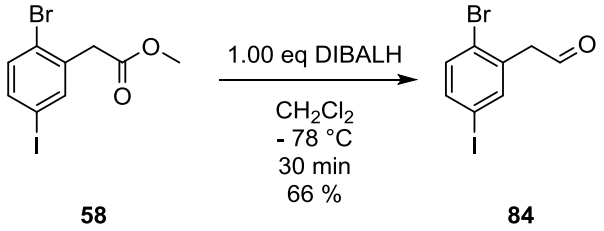
Scheme 56. Different routes for the formation of the histidine core fragment.

The reaction sequence to gain aldehyde **84** was changed because of low yield and the partial cleavage of the iodine during the WITTIG-reaction. Therefore, 2-(2-bromo-5-iodophenyl)acetaldehyde **84** was synthesized from Asp core fragment, followed by addition of TosMIC and reaction with NH_3 in the last step to form the desired His core fragment as illustrated in Scheme 57.



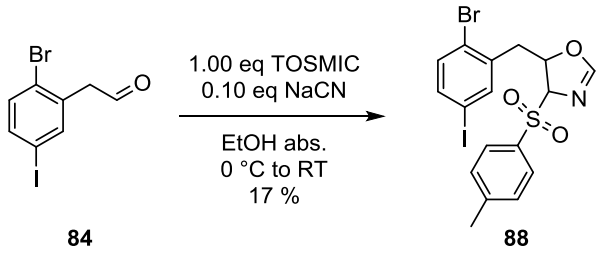
Scheme 57. Synthesis of the histidine core fragment.

First reduction of methylester **58** to aldehyde **84** was achieved by the addition of DIBAL-H (Scheme 58). The Asp building block was dissolved in CH_2Cl_2 and then cooled to -78 °C. Afterwards DIBAL-H was added carefully and the reaction was stirred for 30 min at -78 °C. It was absolutely necessary to do the reaction at -78 °C and with 1.00 eq DIBAL-H otherwise the reaction would produce the corresponding alcohol. After complete conversion the reaction mixture was quenched by the addition of 25 % tartraric acid solution and the reaction mixture was allowed to warm up to RT. The crude product was purified via column chromatography and compound **84** was isolated in 66 % yield.



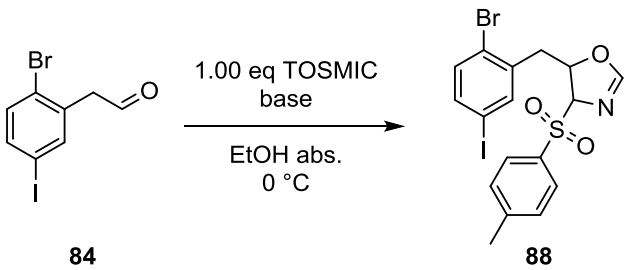
Scheme 58. Synthesis of 2-(2-bromo-5-iodophenyl)acetaldehyde (**84**).

In the next step the formation of the oxazoline **88** by addition of TosMIC was investigated. Therefore, similar conditions (1.00 eq aldehyde, 1.00 eq TosMIC, 0.11 eq NaCN) like before were used (Scheme 59). First, TosMIC was dried in vacuum for 20 min, followed by addition of abs. EtOH and cooling to 0 °C. Afterwards aldehyde **84** and the base (NaCN) were added. The conversion was monitored by GC-MS. According to GC-MS after 1 h 82 % conversion was achieved and after 3 h 92 % were converted to the desired product **88**. The reaction was stopped at this point and column chromatography was done, but the oxazoline **88** was isolated in only 17 % yield. The low yield and many spots on TLC indicated that product **88** is not very stable during column chromatography. Moreover, NMR showed more impurities after column chromatography than the crude product.



Scheme 59. Formation of the oxazoline **88**.

Due to the low yield for the formation of the oxazoline and the use of NaCN various other conditions were tested to find the optimal conditions for the conversion of aldehyde **84** to the desired oxazoline **88** (Scheme 60). Beside NaCN also K_2CO_3 and K_3PO_4 were used as base. In all cases EtOH was used as solvent. The screened conditions are shown in Table 11.



Scheme 60. Conversion of aldehyde **84** to oxazoline **88**.

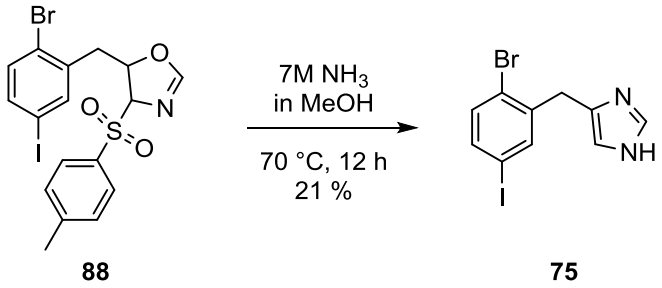
Table 11. Screened methods for the formation of oxazoline **88**.

Entry	Base	Temperature	Time	Conversion of starting material
1	NaCN (0.11 eq)	0 °C → RT	1 h	full conversion[a]
2	K_2CO_3 (2.00 eq)	RT	1 h	37 %[a]
			20 h	full conversion[a] (no desired product)
3	K_2CO_3 (0.11 eq)	0 °C → RT	30 min	no conversion[b]
			15 h	full conversion[b]
4	K_3PO_4 (2.00 eq)	0 °C	30 min	70 %[b]
			15 h	full conversion[b]
5	K_3PO_4 (1.00 eq + 1.00 eq after 30 min)	0 °C	30 min	no conversion[a]
			2 h	full conversion[a]
6	K_3PO_4 (fine powdered, 2.00 eq)	0 °C	30 min	full conversion[b]
7	K_3PO_4 (fine powdered, 1.50 eq)	0 °C	30 min	full conversion[b]
8	K_3PO_4 (fine powdered, 1.00 eq)	0 °C	30 min	full conversion[b]
9	K_3PO_4 (fine powdered, 0.50 eq)	0 °C	30 min	full conversion[b]
10	K_3PO_4 (fine powdered, 0.10 eq)	0 °C → RT	30 min	no conversion[b]
			20 h	full conversion[b]

[a] According to GC-MS, [b] according to HPLC-MS.

As alternative to NaCN, K_2CO_3 was used as base. On the one hand 2.00 eq were added to the reaction mixture and on the other hand only 0.11 eq K_2CO_3 were used for the formation of oxazoline **88** (Table 11, Entries 2 and 3). By addition of 2.00 eq K_2CO_3 reaction control after 1 h indicated incomplete conversion, therefore the reaction was stirred for further 19 h, which resulted in complete conversion, but due to GC-MS the desired oxazoline was convered to an unknown compound. 0.11 eq K_2CO_3 were used for the addition of TosMIC too. In this case after 1 h no conversion was achieved, but by stirring the reaction at RT for 15 h full conversion to the desired product **88** was obtained. Moreover a milder base was tried for the formation to oxazoline **88**. Hence, K_3PO_4 were added as base. First 2.00 eq and 1.00 eq K_3PO_4 were used (Table 11, Entries 4 and 5). By using 2.00 eq K_3PO_4 after 30 min at RT 70 % conversion were observed via HPLC-MS and after stirring overnight aldehyde **84** was fully converted to compound **88**. In the case of 1.00 eq base no conversion was achieved after 30 min at 0 °C. Therefore additonal 1.00 eq K_3PO_4 were added and after 2 h at RT HPLC-MS showed complete conversion to the oxazoline **88**. In the meanwhile the reaction was tried with fine powdered K_3PO_4. Different equivalents (2.00 eq, 1.50 eq, 1.00 eq, 0.50 eq and 0.10 eq) of base were used (Table 11, Entries 6 - 10). In all cases except the use of 0.10 eq K_3PO_4 full conversion to oxazoline **88** was achieved after 30 min. To overcome the problem of purification via column chromatography all products were extracted with H_2O and CH_2Cl_2 and were used without further purification in the next step. To have enough oxazoline **88** in hands a bigger scale (250 mg aldehyde **84**) was executed. First 0.50 eq K_3PO_4 were added to the reaction mixture, but after 30 min incomplete conversion was obtained. Addition of further 1.00 eq delivered full conversion after 30 min. This indicated that more base has to be added to have shorter reaction times. The crude product was used without further purification in the last step.

For the formation of the His core fragment oxazoline **88** was reacted with 7M NH_3 solution in MeOH, shown in Scheme 61. The crude oxazoline **88** was suspended in 7M NH_3 solution in MeOH and transferred to a pressure tube. The suspension was stirred at 70 °C overnight.



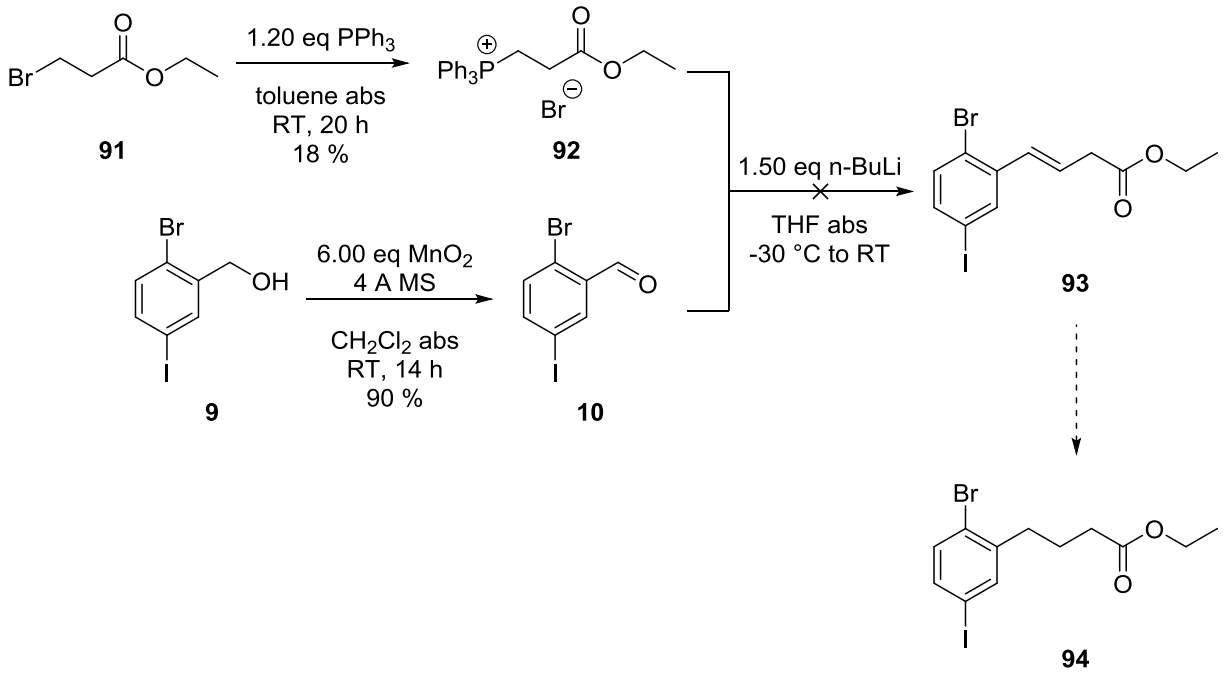
88 **75**

Scheme 61. Last step for the synthesis of the histidine core fragment.

The conversion to the desired product **75** was monitored via HPLC-MS and afterwards the solvent was removed under reduced pressure. The crude product was purified via column chromatography with CH_2Cl_2/MeOH and the fraction control had to be done via HPLC-MS for identification of the desired product **75**. The His core building block was isolated in 21 % yield.

4.1.16. Synthesis of the C-elongated Glutamic acid building block

The first attempt for the synthesis of the C-elongated Glu core building block should be done in a four step route starting from (2-bromo-5-iodophenyl)methanol (**9**) and 3-bromopropanoate (**91**) shown in Scheme 63.



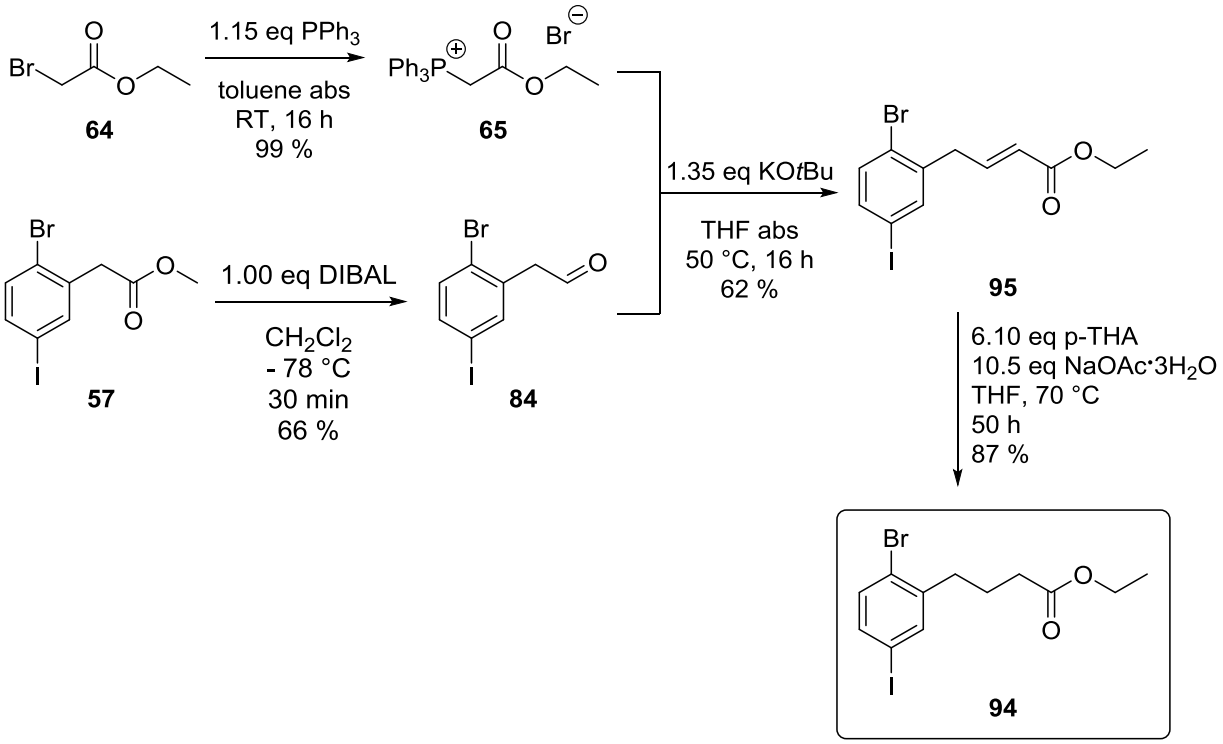
Scheme 62. Attempted synthesis of the C-Glu building block **94**.

In the first step phosphonium salt **92** was generated starting from ethyl 3-bromopropanoate (**91**) and PPh_3. Salt **92** was only isolated in 18 % yield, because conversion was not complete after stirring the reaction for 20 h at RT. To achieve better yield the reaction mixture has to be heated up. In parallel alcohol **9** was oxidized using activated MnO_2 as described in section 4.1.1. Then Wittig-reaction should gain ethyl (*E*)/(*Z*)-4-(2-bromo-5-iodophenyl)but-3-enoate (**93**), but no conversion to the desired product **93** could be achieved.

Therefore another reaction sequence was needed to introduce the ester side chain. Also in that case the double bond should be generated via WITTIG-reaction. The same phosphonium salt **65** as for the synthesis of the Glu core building block and as aldehyde 2-(2-bromo-5-iodophenyl)acetaldehyde (**84**) was used (Scheme 63).

First aldehyde **84** was synthesized starting from the Asp core building block as described for the His fragment in section 4.1.15. The already prepared phosphonium salt **65** was then deprotonated by the addition of KO*t*Bu. Afterwards aldehyde **84** was added to deprotonated **65** and the reaction was stirred at 50 °C for 16 h. Ethyl (*E*)/(*Z*)-4-(2-bromo-5-iodophenyl)but-

2-enoate (**95**) was isolated via column chromatography in moderate yield of 62 % and as *E*/*Z* a mixture of of 2:1.

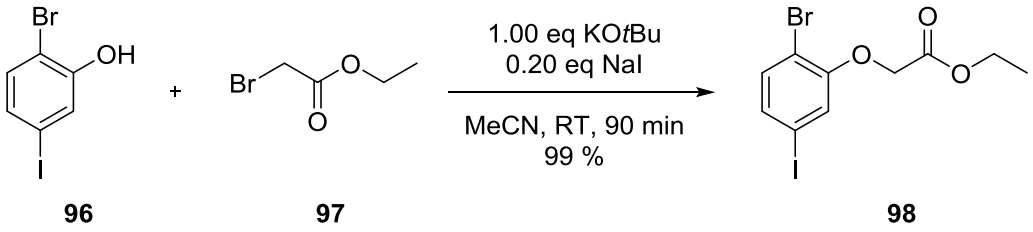


Scheme 63. Synthesis of the C-elongated Glu building block **94**.

An optimization of the *E*/*Z* selectivity was not nessesary, as in the following step the double bond of compound **95** was reduced anyway. Also in this case Pd/C could not be used for the reduction of the halogenated compound **95**. Therefore p-tosyl hydrazide had to be used. The reaction was stirred for 16 h at 50 °C, but incomplete conversion was detected. It was necessary to heat the reaction to 70 °C and after another 8 h full conversion was indicated by TLC. Then ethyl 4-(2-bromo-5-iodophenyl)butanoate (**94**) was isolated by column chromatography in 87 % yield.

4.1.17. Synthesis of the O-Glutamic acid building block

For the synthesis of the O-Glu core building block 5-bromo-2-iodophenol (**96**) was reacted with ethylbromoacetate (**97**) to yield ethyl 2-(2-bromo-5-iodophenoxy)acetate (**98**) in one step. The synthesis is depicted in Scheme 64.



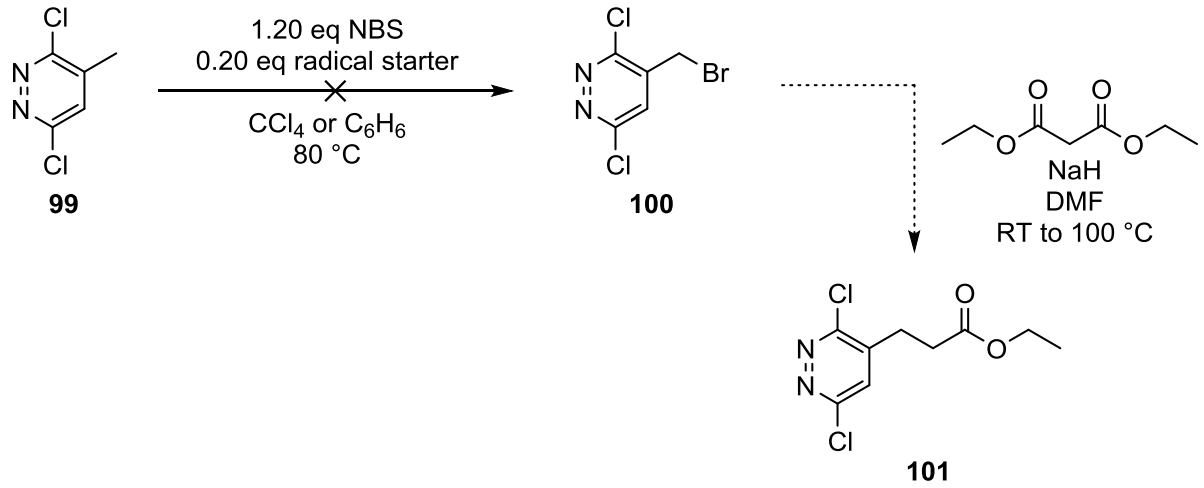
96 **97** **98**

Scheme 64. Synthesis of the O-Glu core building block.

First 5-bromo-2-iodophenol (**96**), KO*t*Bu and NaI were suspended in CH_3CN. Afterwards ethylbromoacetate (**97**) was added slowly and after complete addition the suspension was stirred at RT for 90 min. Complete conversion was indicated via TLC and then the reaction mixture was extracted with EtOAc and the crude product was purified via flash column chromatography delivering product **98** in 99 % yield.

4.1.18. Synthesis of the Pyridazine Glutamate building block

In the first attempted synthesis of the pyridazine Glu building block first a radical reaction to achieve 4-(bromomethyl)-3,6-dichloropyridazine (**100**) was performed. In the next step the Glu side chain should be introduced to yield the pyridazine Glu building block, shown in Scheme 65.



Scheme 65. Attempted synthesis of the pyridazine Glu building block.

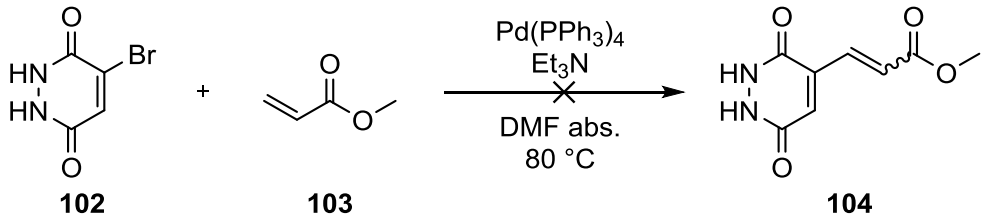
Different conditions were screened for the radical reaction, depicted in Table 12. Therefore 1.20 eq NBS and as radical starter benzoyl peroxide (DBPO) or azobisisobutyronitrile (AIBN) were used. As solvents on the one hand CCl_4 and on the other hand benzene was used. When only 100 mg of starting material were used no conversion was achieved in all cases after 20 h at 80 °C (Table 12, Entries 1 – 6). In entry 7 and 8 500 mg starting material were used and in both cases as radical starter DBPO was utilized. In entry 7 degassed CCl_4 and in entry 8 not degassed CCl_4 were used. In both cases similar conversions were achieved after 24 h but only 8 % (Entry 7) and 9 % (Entry 8) conversion to the desired product was obtained. In both cases an unknown by-product was formed in 35 % (Entry 7) and 32 % (Entry 8). Due to the main formation of the by-product this route was discarded.

Table 12. Screened conditions for the radical reaction.

Entry	Solvent	Conditions	Time	starting material[c]	Product[c]	by-products[c]
1	benzene degassed	NBS, DBPO 80 °C Argon[b]	1 h	100 %	-	-
			8 h	100 %	-	-
			20 h	100 %	-	-
2	benzene degassed	NBS, AIBN 80 °C argon[b]	1 h	100 %	-	-
			8 h	100 %	-	-
			20 h	100 %	-	-
3	CCl_4 degassed	NBS, DBPO 80 °C argon[b]	1 h	100 %	-	-
			8 h	100 %	-	-
			20 h	100 %	-	-
4	CCl_4 degassed	NBS, AIBN 80 °C argon[b]	1 h	100 %	-	-
			8 h	100 %	-	-
			20 h	100 %	-	-
5	CCl_4	NBS, DBPO 80 °C air[b]	1 h	100 %	-	-
6	CCl_4	NBS, AIBN 80 °C air[b]	1 h	100 %	-	-
7	CCl_4 degassed	NBS, DBPO 80 °C air[a]	30 min	100 %	-	-
			16 h	72 %	4 %	24 %
			24 h	57 %	8 %	35 %
8	CCl_4	NBS, DBPO 80 °C air[a]	30 min	100 %	-	-
			16 h	68 %	8 %	24 %
			24 h	59 %	9 %	32 %

[a] 500 mg starting material, [b] 100 mg starting material, [c] according to GC-MS.

Another approach for the synthesis of the pyridazine Glu building block was the formation of compound **104** via a HECK-reaction. 4-Bromo-1,2-dihydropyridazine-3,6-dione (**102**) should be converted with methyl acrylate (**103**) to methyl (*E*)/(*Z*)-3-(3,6-dioxo-1,2,3,6-tetrahydropyridazin-4-yl)acrylate (**104**), shown in Scheme 66.



Scheme 66. Attempted synthesis of the pyridazine Glu building block.

The HECK-reaction was performed with 4-bromo-1,2-dihydropyridazine-3,6-dione (**102**) and methyl acrylate (**103**) in the presence of $Pd(PPh_3)_4$ and Et_3N as base. Full conversion was achieved after 12 h indicated by TLC and the product was purified via flash column chromatography. According to NMR no desired product **104** was generated, but an internal disproportionation of the double bond took place and compound **105** was isolated in 63 % yield.

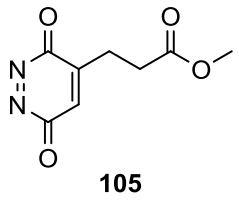
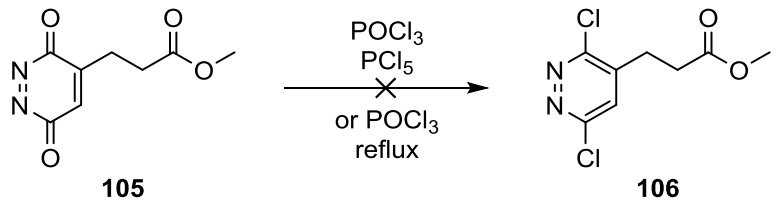


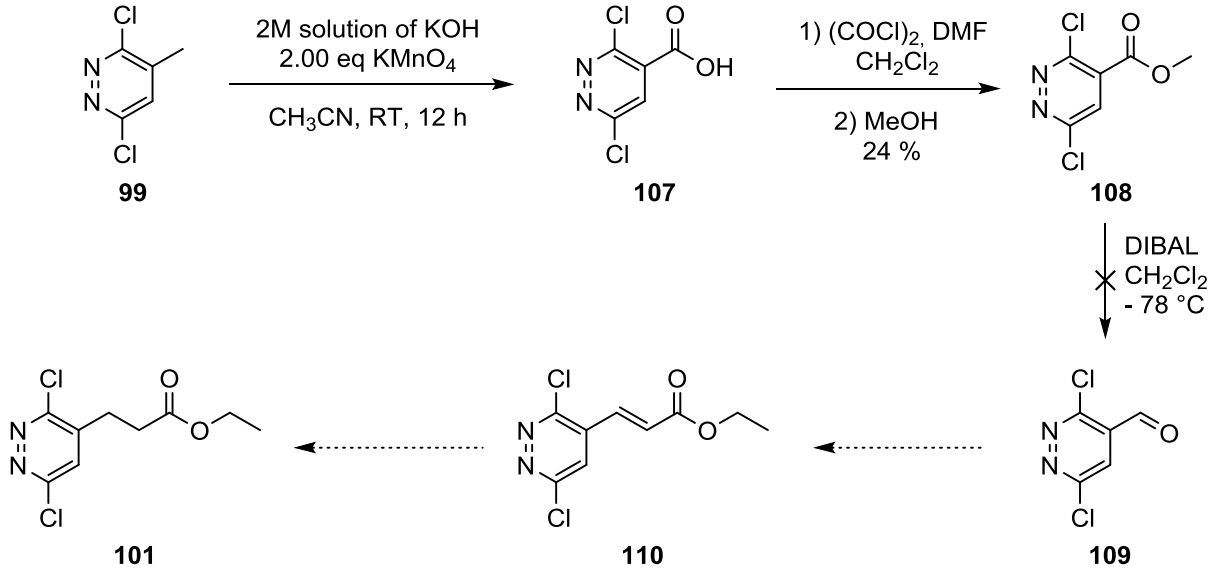
Figure 27. Formed product during the HECK-reaction.

With compound **105** in hands chlorination should be performed to achieve methyl 3-(3,6-dichloropyridazin-4-yl)propanoate (**106**). On the one hand $POCl_3$ and PCl_5 and on the other hand only $POCl_3$ was ussed but in both cases no desired product **106** was formed according to GC-MS. Moreover many side products were generated and therefore another approach was needed.



Scheme 67. Chlorination of methyl 3-(3,6-dioxo-3,6-dihydropyridazin-4-yl)propanoate (**105**).

For the synthesis of the pyridazine glutamate building block another approach was conceived. 3,6-Dichloro-4-methylpyridazine (**99**) was first converted to acid **107** and afterwards esterification, reduction to the aldehyde and subsequent WITTIG-reaction and reduction of the double bond should be performed. The attempted synthesis is shown in Scheme 68.

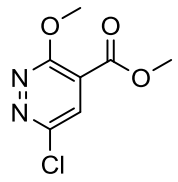


Scheme 68. Attempted synthesis of the pyridazine glutamate building block.

In the first step the formation of 3,6-dichloropyridazine-4-carboxylic acid (**107**) was performed according to the procedure from LISCIO *et al.*[131] Commercially available 3,6-dichloro-4-methylpyridazine (**99**) was dissolved in CH_3CN and after addition of a 2M solution of KOH 2.00 eq $KMnO_4$ were added in portions over 40 min. After stirring overnight TLC indicated incomplete conversion, but it was decided to work the reaction up. The reaction mixture was extracted with EtOAc to remove the starting material. Afterwards the aqueous phase was acidified to pH 1 with conc. HCl and the aqueous phase was extracted ten times with EtOAc. The crude product was used without further purification in the next step.

Next the esterification of 3,6-dichloropyridazine-4-carboxylic acid (**107**) should be performed. In the first approach a simple FISCHER-esterification was executed in MeOH but

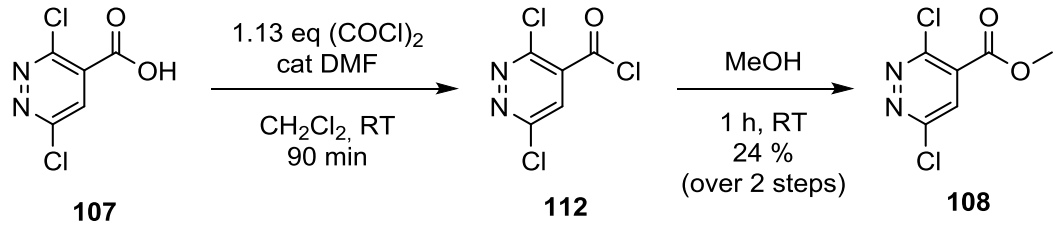
after isolation of the product via column chromatography not the desired product was formed. The isolated product was methyl 6-chloro-3-methoxypyridazine-4-carboxylate (**111**), shown in Figure 28.



111

Figure 28. Formed product during the FISCHER-esterification.

Another method for the synthesis of methyl 3,6-dichloropyridazine-4-carboxylate (**108**) was necessary. Therefore 3,6-dichloropyridazine-4-carboxylic acid (**107**) was first converted to 3,6-dichloropyridazine-4-carbonyl chloride (**112**) and in a second step the esterification of the chlorinated compound **112** was performed. The reaction sequence is depicted in Scheme 69.

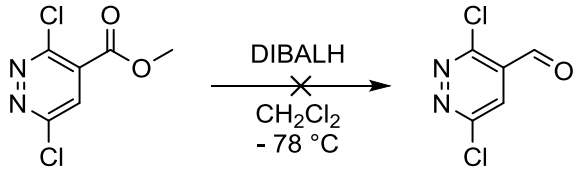


107 **112** **108**

Scheme 69. Esterification of 3,6-dichloropyridazine-4-carboxylic acid (**107**)

First, substrate **107** was converted to 3,6-dichloropyridazine-4-carbonyl chloride (**112**) by the addition of $(COCl)_2$. After 90 min complete conversion was achieved and the solvent and remaining oxalylchloride was removed under high vacuum using a cooling trap. Product **112** was used without further purification in the next step. Next compound **112** was converted to ester **108** by the addition of MeOH. After 1 h full conversion was detected by GC-MS and the product was purified via column chromatography in 24 % yield over two steps.

In the next step the reduction of ester **108** to 3,6-dichloropyridazine-4-carbaldehyde (**109**) should be performed (Scheme 70). Ester **108** was dissolved in CH_2Cl_2 and cooled to -78 °C. Afterwards DIBALH (1.00 eq, 1.50 eq and 2.00 eq) was added slowly and the reaction mixture was stirred for 15 min (see Table 12).



108 **109**

Scheme 70. Attempted reduction of ester **108**.

Table 13. Screened equivalents of DIBALH for the reduction to 3,6-dichloropyridazine-4-carbaldehyde (**109**).

Entry	Time	DIBALH	Starting material [a]	Product [a]	Side product 1 [a]	Side product 2 [a]
1	15 min	1.00 eq	34 %	30 %	16 %	20 %
2	15 min	1.50 eq	-	31 %	42 %	27 %
3	15 min	2.00 eq	-	10 %	90 %	-

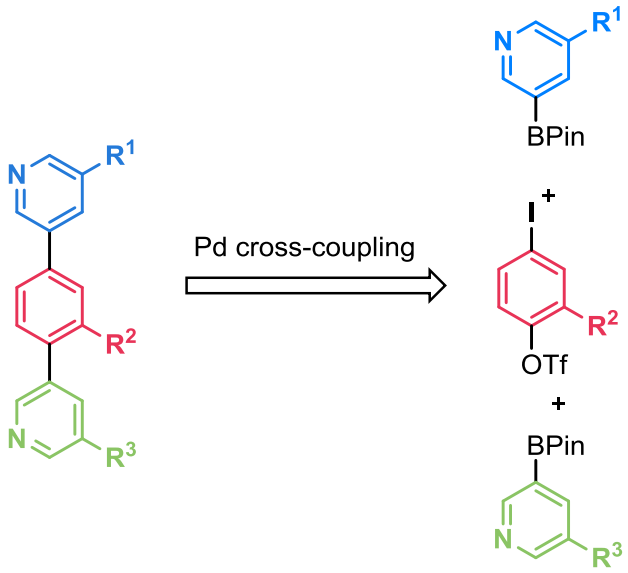
[a] According to GC-MS.

First only 1.00 eq DIBALH was used for the reduction to aldehyde **109** (Table 13, Entry 1). After 15 min incomplete conversion was indicated by GC-MS. In this case 34 % starting material was left and only 30 % conversion to the desired product was achieved. Moreover two unknown side products were obtained. By the use of 1.50 eq and 2.00 eq DIBALH (Table 13, Entries 2 and 3) full conversion was achieved after 15 min but in these cases the desired product was formed only in 31 % (Entry 2) and 10 % (Entry 3).

In the course of the PhD thesis the pyridazine Glu building block could not be produced yet.

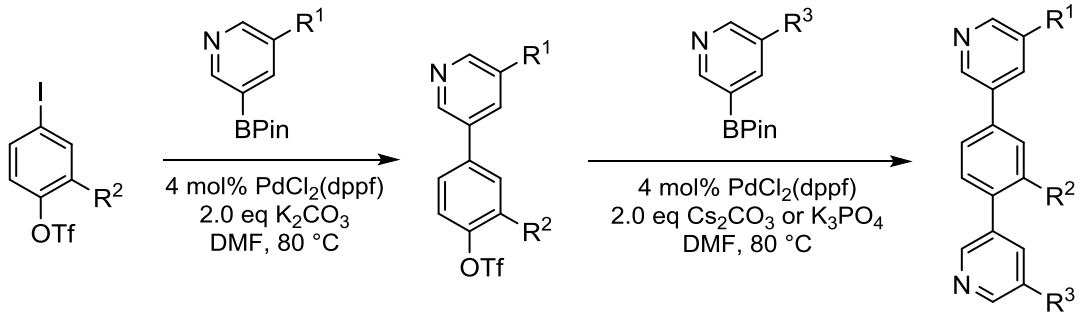
4.2. Assembly of teraryls

The teraryl assembly was performed via a two-step sequential SUZUKI-MIYAURA coupling procedure. Therefore two different building blocks were used. On the one hand core building blocks featuring two leaving groups with differentiated reactivity in the Pd-catalyzed cross-coupling were used and on the other hand 3,5-substituted pyridine boronic acid esters to improve the solubility, which should lead to a better bioavailability, were required. In the beginning as leaving groups in the core fragment iodine and OTf-group were used. The retrosynthesis is illustrated in Scheme 71.



Scheme 71. Retro-synthesis of teraryls.

Various conditions had been screened for the optimization of the Pd-catalyzed cross-coupling by TROBE.[50] Different bases, solvents, mol% of catalyst loading and temperatures were tested. In the first coupling step selectively the iodine underwent cross-coupling reaction. For this step the optimized conditions were 4 mol% $PdCl_2$(dppf) in DMF as solvent at 80 °C and K_2CO_3 as base were used. The best conditions for the coupling of triflate in the second step were found to be also 4 mol% $PdCl_2$(dppf) and DMF as solvent. As bases Cs_2CO_3 or K_3PO_4 can be used and the reaction temperature was in this case 80 °C too. Chemoselectivity was reached by a switch of the corresponding base from K_2CO_3 to Cs_2CO_3 or K_3PO_4 between the two steps (Scheme 72).



Scheme 72. General reaction scheme for sequential SUZUKI-MIYAURA cross-coupling.

One problem in the SUZUKI-MIYAURA cross-coupling by the use of the core building blocks with iodine and OTf-group as leaving groups is the hydrolysis of the triflate (see Figure 29). This resulted in lower yields and therefore another leaving group was needed.

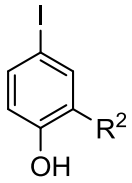
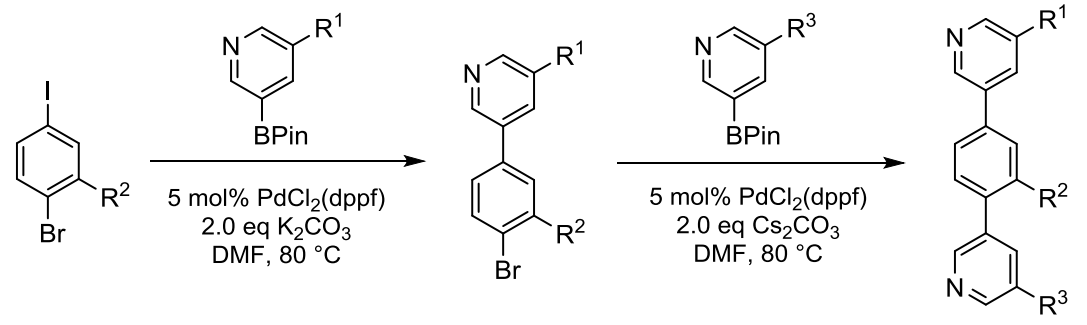


Figure 29. Byproduct from SUZUKI-MIYAURA cross-coupling.

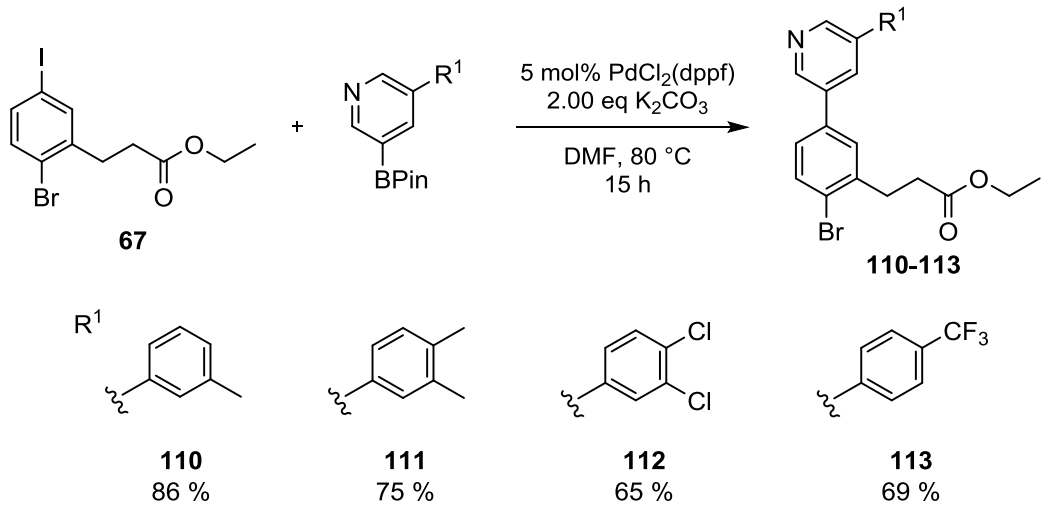
To overcome the byproduct formation of the hydrolyzed triflate bromine was installed instead of triflate. For the coupling with the 1-bromo-4-iodo-core fragments similar conditions like before were used. In the first coupling step 5 mol% $PdCl_2$(dppf), K_2CO_3 as base in DMF at 80 °C were used. For the second cross-coupling step the same conditions were used but K_2CO_3 was replaced with Cs_2CO_3 (Scheme 73).



Scheme 73. General reaction scheme for sequential SUZUKI-MIYAURA cross-coupling.

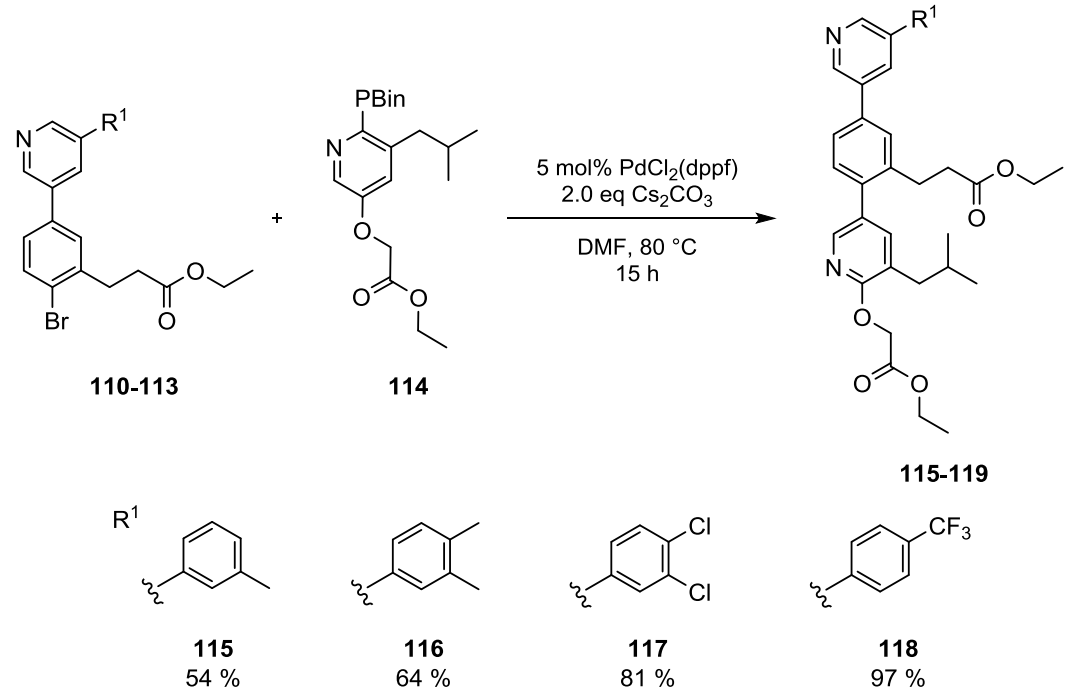
According to the procedure above different teraryls were synthesized for testing as SREBP/Med 15 inhibitors (see section 4.3). In the first step Glu core building block, with bromine and iodine as leaving groups, was reacted with different boronic acid esters to

generate diphenyls **110-113**. For optimization of the structure of the inhibitors, first different boronic acid esters for the top part were tested (Scheme 74). Purification of the products was performed via column chromatography and compounds **110-113** were isolated in 65 to 86 % yield.



Scheme 74. First coupling for the synthesis of **110-113**.

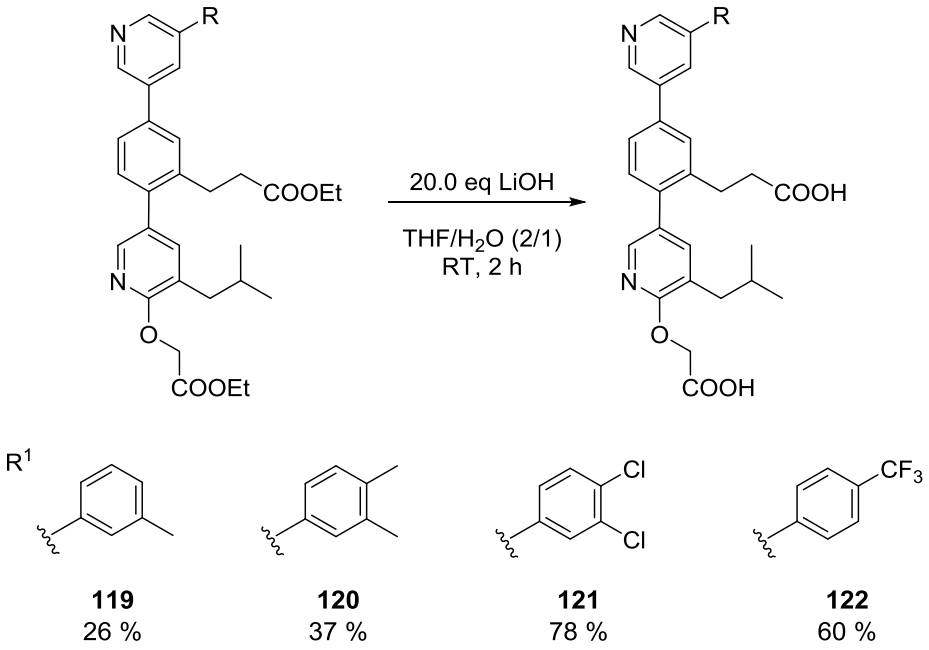
In the second cross-coupling step the same reaction conditions as before were used (Scheme 75). As base Cs_2CO_3 instead of K_2CO_3 was added and boronic acid ester **114** was used to achieve teraryls **115-118**.



Scheme 75. Second coupling for the synthesis of **115-118**.

Teraryls **115** and **116** were isolated in only 54 % and 64 % yield because of impurities in the EtOAc a second column chromatography had to be executed. Much better yields were achieved in the isolation of **117** (81 %) and **118** (97 %) after column chromatography (see Scheme 75).

In the last step the saponification of the ethyl esters was performed. 20.0 eq LiOH were added to a solution of teraryls **115-118** in THF/dist. H_2O (2/1) and the colorless suspension was stirred at RT until full conversion was detected by HPLC-MS. After adjusting the aqueous phase to pH of 1 the product was extracted with CH_2Cl_2 and later purified via preparative HPLC (Scheme 76).



Scheme 76. Saponification of teraryls **119-122**.

Compounds **119** and **120** were isolated in low yields (26 % and 37 %) after preparative HPLC because a byproduct with similar retention time was formed. This byproduct was not totally separable from product **119** and **120** and to achieve pure product only pure fractions according to HPLC-MS were pooled. Better yields were obtained in the saponification of **117** and **118**. In these cases 78 % and 60 % yield of the desired products were achieved. Compounds **119-122** were isolated over 3 steps, starting from Glu core fragment and two different boronic acid esters, in overall yields from 12 % to 41 %, shown in Figure 30.

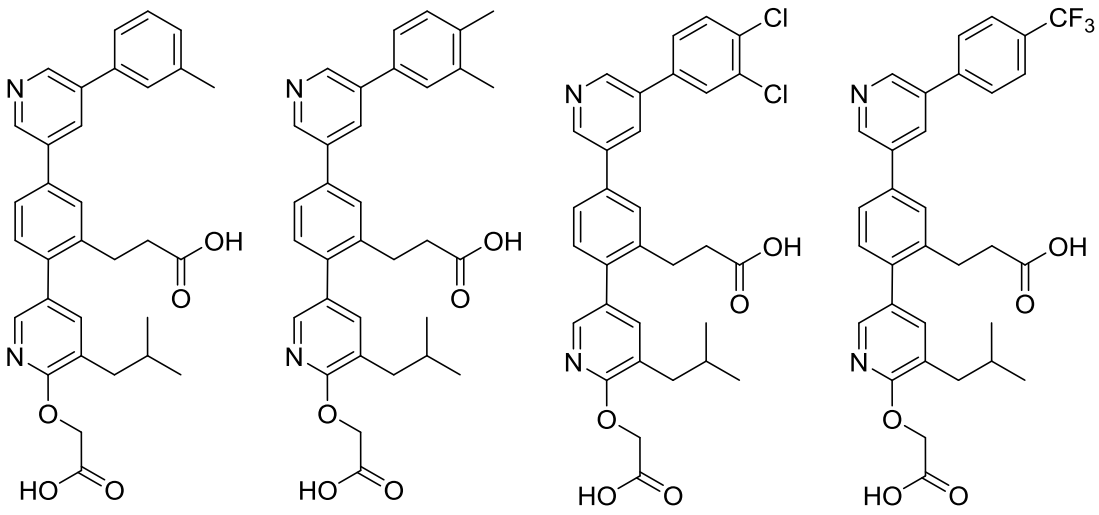
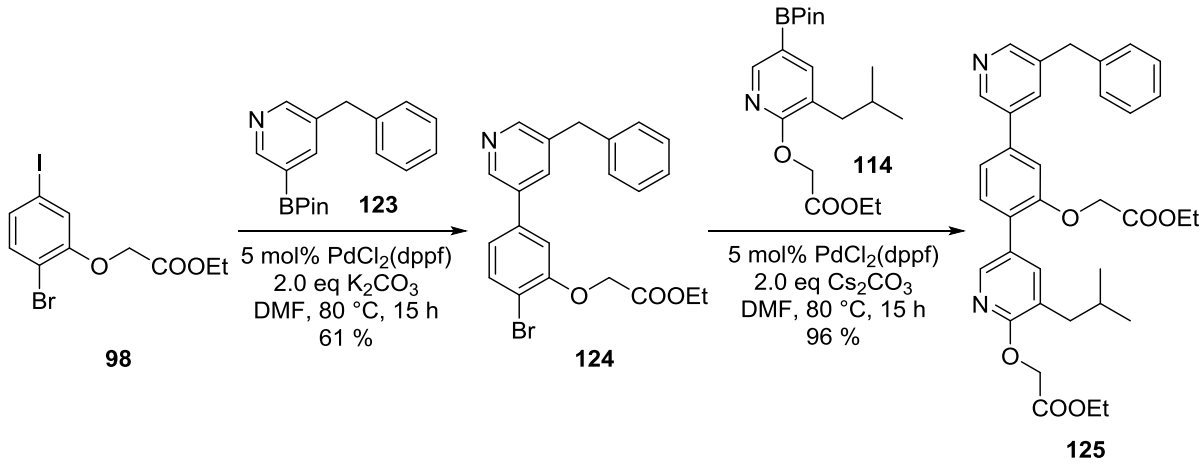


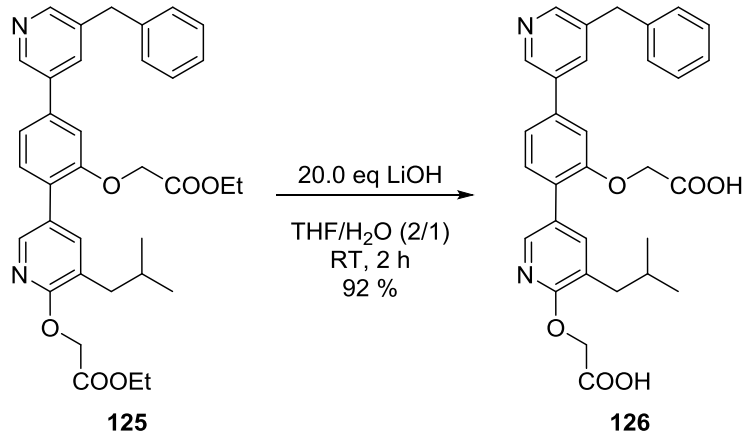
Figure 30. Overall yields of compounds **119**-**122**.

Moreover different middle building blocks were synthesized, for example ethyl 2-(2-bromo-5-iodophenoxy)acetate (**98**) was used as core fragment. Teraryl **125** was synthesized as described in the procedure before. The first cross-coupling reaction was performed with 2-(2-bromo-5-iodo-phenoxy)acetate (**98**) and 3-benzyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine and after colum chromatography compound **124** was isolated in 61 % yield. The second coupling was done with boronic acid ester **114** and the teraryl **125** was isolated in 96 % yield (Scheme 79).



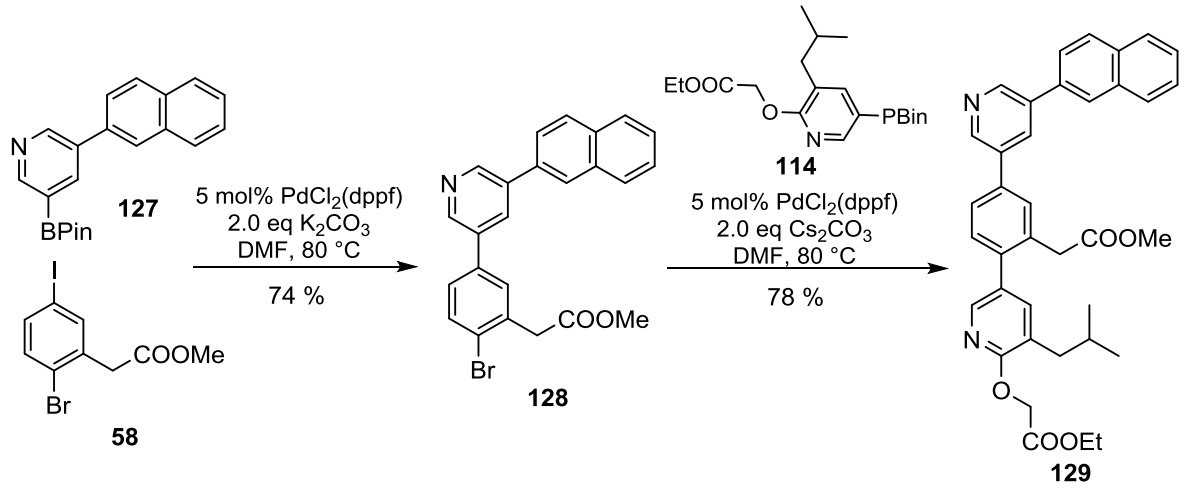
Scheme 77. Cross-coupling reaction for the synthesis of compound **125**.

In the last step both esters were saponified. Therefore, teraryl 1**25** was reacted with LiOH in THF/H_2O and after 2 h full conversion was achieved. According to HPLC-MS and NMR, teraryl **125** was pure and no purification via preparative HPLC was needed (Scheme 78).



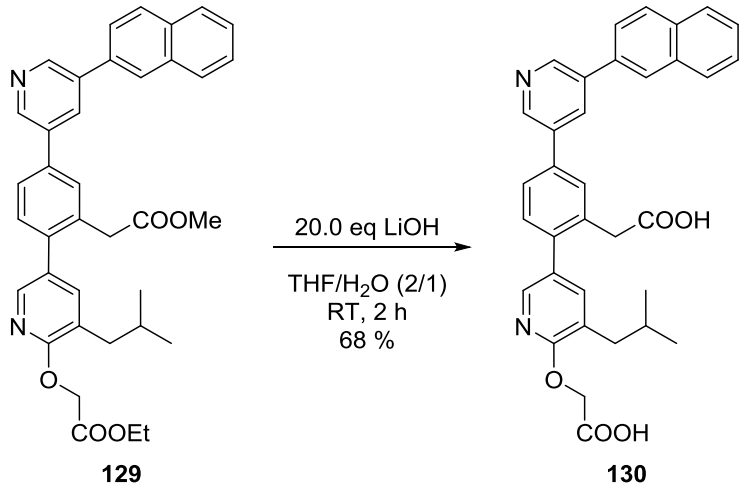
Scheme 78. Saponification of teraryl **125**.

Moreover, the Asp and the C-elongated Glu core fragment were used for the synthesis of terayls. Teraryls **130** and **132** were synthesizied as described in the procedure before (Scheme 79).



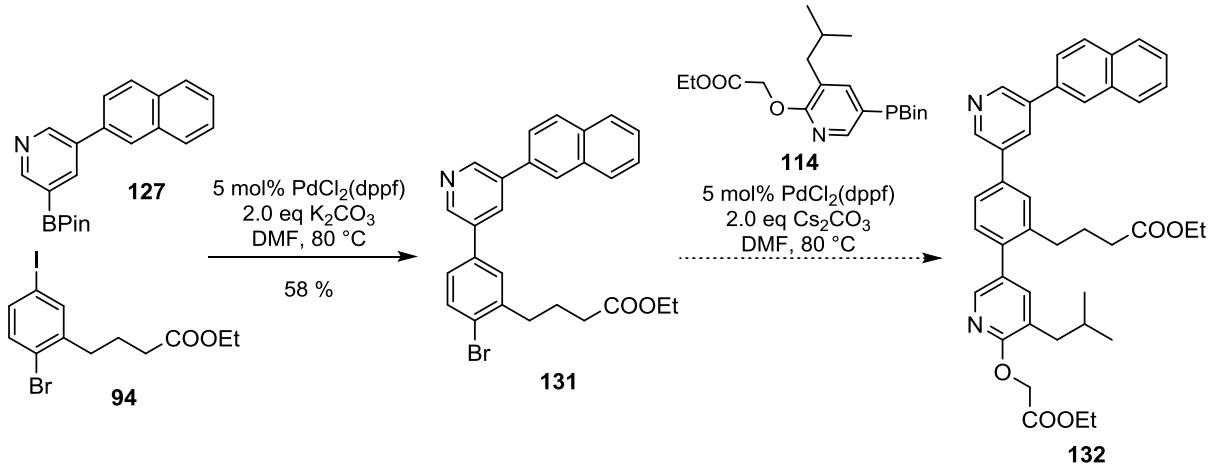
Scheme 79. Synthesis of teraryl **129**.

In the first coupling the Asp building block **58** was reacted with 3-(naphthalen-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**127**). After 14 h full conversion was achieved and the crude product was purified via column chromatography. The diaryl was isolated in 74 % yield. In the second coupling boronic acid ester **114** was reacted with diaryl **128** and the teraryl **129** was isolated in 78 % yield. In the last step the saponification of teraryl **129** delivered **130** in 68 % yield.



Scheme 80. Saponification of teraryl **129**.

For the synthesis of the teraryl with the C-elongated Glu builing block only the first step was performed so far. Therefore the middle building block **94** was reacted with 3-(naphthalen-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine **126**. After complete conversion was achieved, the crude product was purified via column chromatography. The diaryl **131** was isolated in 58 % yield. The last two steps are again the second coupling and final saponification to generate the teraryl.



Scheme 81. Synthesis of teraryl **132**.

4.3. Biological data

In eukaryotes, the mediator complex is a transcriptional cofactor and has up to 30 subunits. One of the subunits is Med15 located in the tail. Human Med15 (hMed15) consists of 788 amino acids and on the *N*-terminus a KIX domain is located. The KIX domain of hMed15 binds to the sterol regulatory element binding protein (SREBP) and hMed15 is essential for the regulation of cholesterol and fatty acid homeostasis. In the beginning the KIX domain was found in the CREB-binding protein (CBP), which is a histone transferase. The CBP protein is an established target in many typs of cancer.[132]

Different tearyls were synthesized in the BREINBAUER group to test the binding to Med15 KIX by fluorescence polarization by the ARTHANARI group. In the beginning teraryls with three substituents were tested. Due to the large area of interaction also teraryls with four substituents were synthesized (Figure 31).

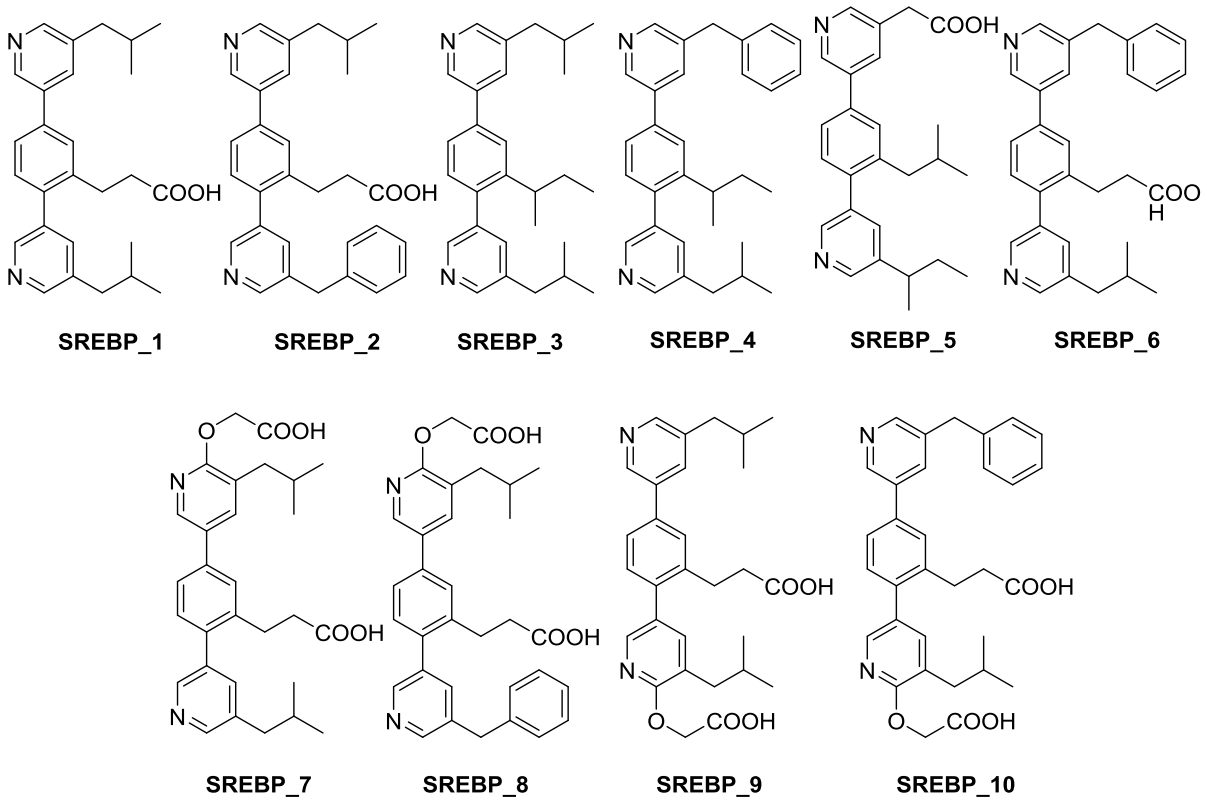


Figure 31. Tested teraryls for the binding to Med15.

The FP assay shows that a building block with an acid side chain is essential for the binding. Moreover, better IC_{50} values were achieved by using teraryls with four substituents (Figure 32).

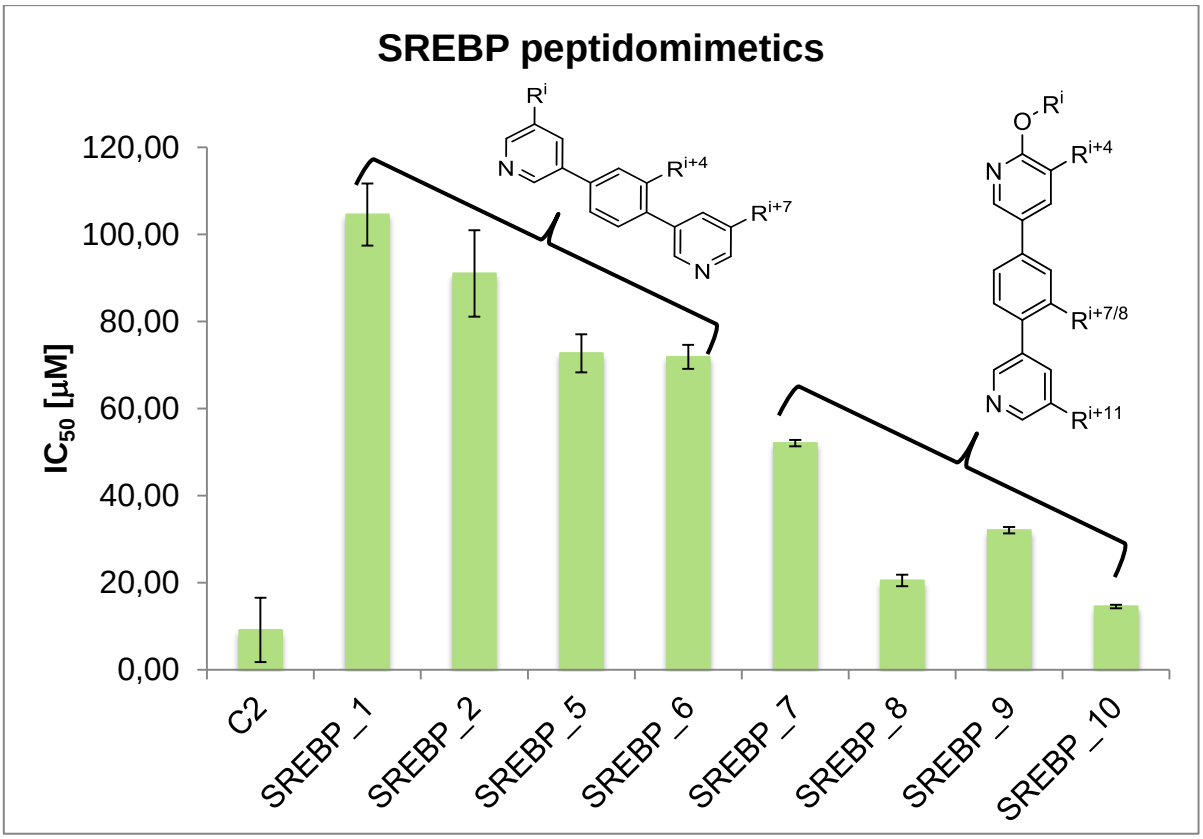


Figure 32. IC_{50} values of the tested teraryls.

Second a series of teraryls were synthesized in the BREINBAUER group (Figure 33 and Figure 35) in which on the one hand the top pyridine ring was modified and on the other hand different side chains were introduced at the bottom pyridine ring. Moreover, the core fragment was modified with an additional O, but unfortunately the oxygen did not result in a better IC_{50} value (Figure 34). Also introducing Asp core fragment instead of Glu building block did not lead to a better IC_{50} (Figure 36). So far the best IC_{50} value (1.85) was achieved by compound SREBP_33.

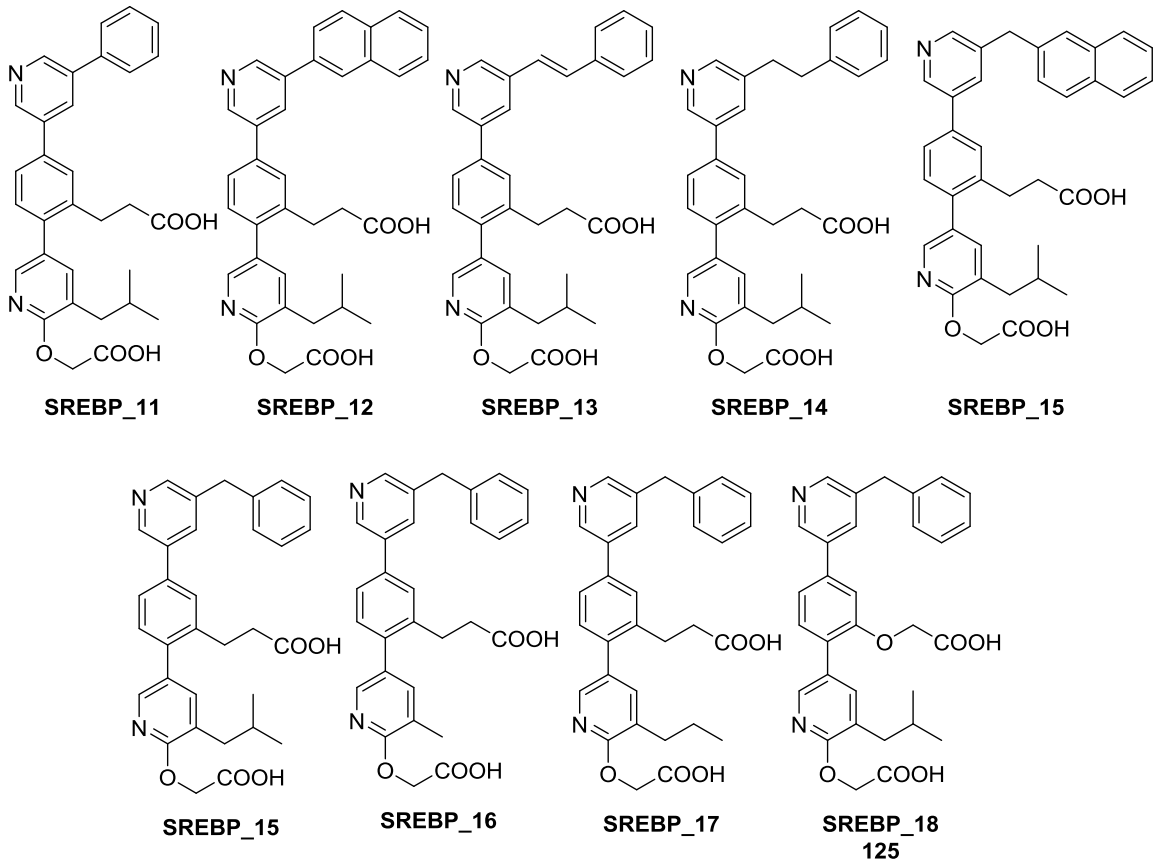


Figure 33. Tested teraryls for the binding to Med15.

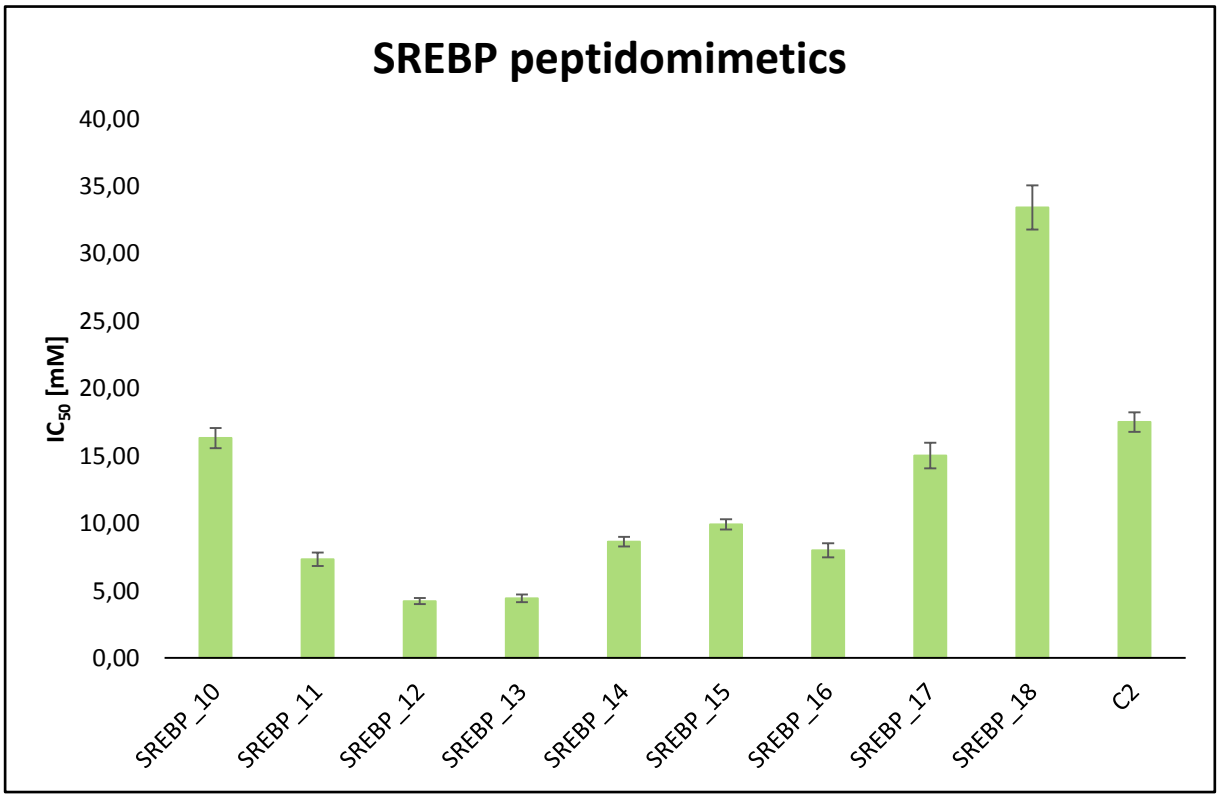


Figure 34. IC_{50} values of the tested teraryls.

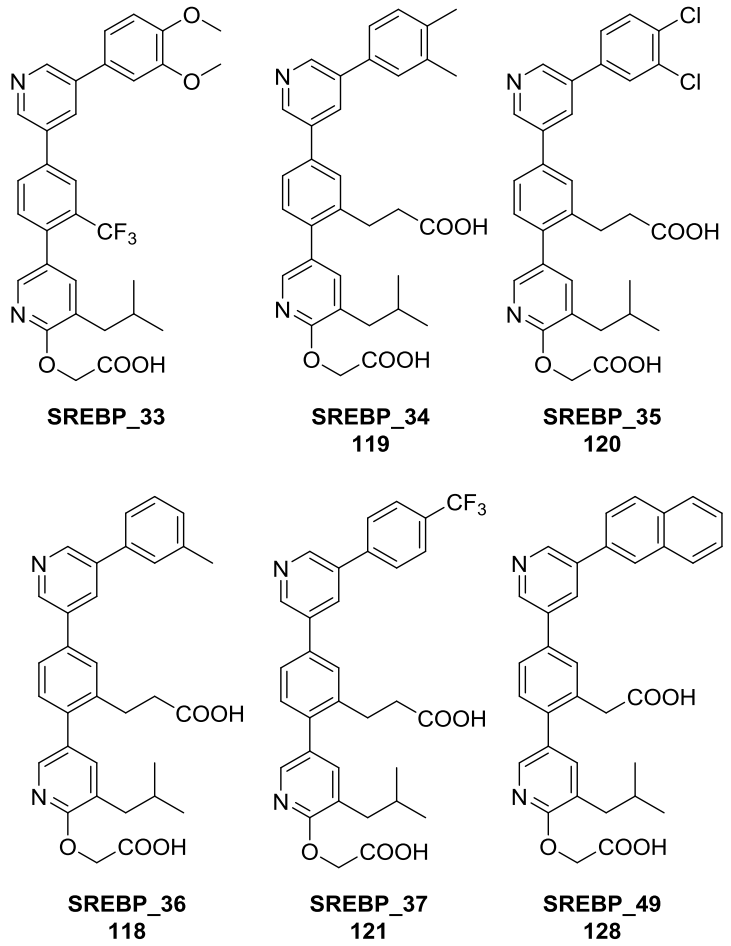


Figure 35. Tested teraryls for the binding to Med15.

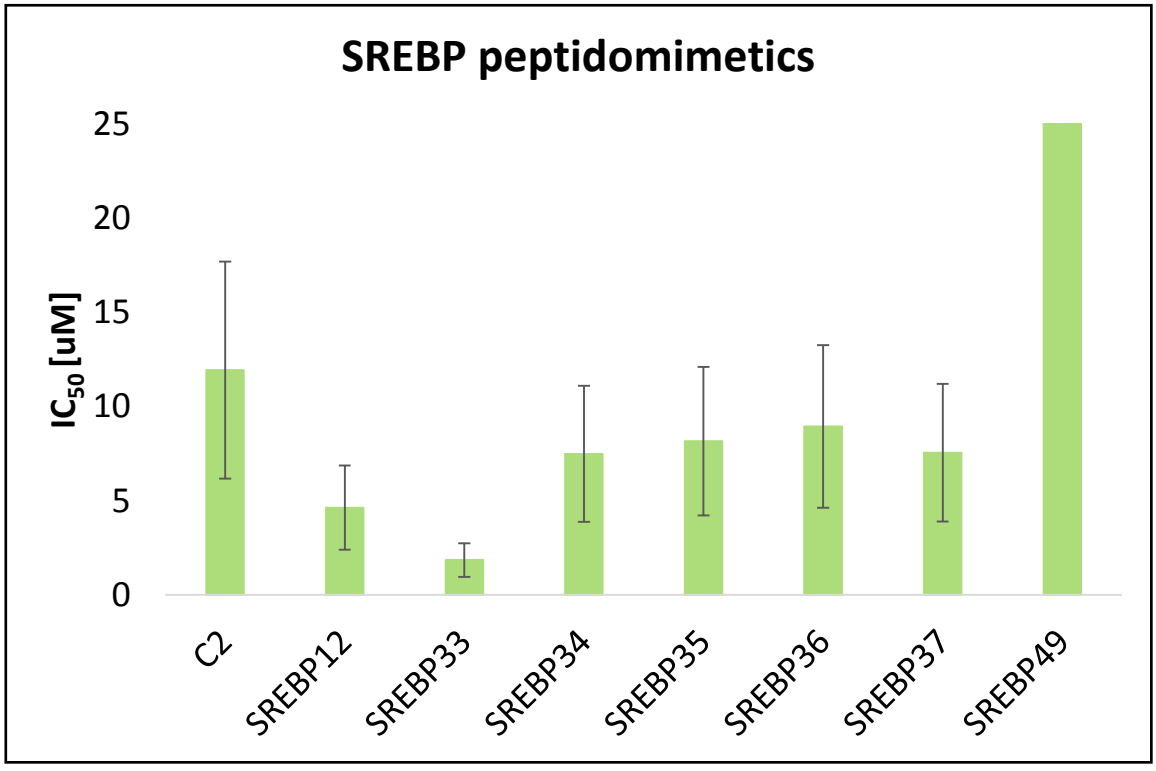


Figure 36. IC_{50} values of the tested teraryls.

5. Summary

α-Helices are the most common protein secondary structurs with more than 60 % involvement in protein-protein interactions. In the interaction of proteins α-helices are often involed and therefore PPIs have received increasing interest as potential drug targets.

The relevance for the use of small molecules as inhibitors of PPIS has been demonstrated with the identification of hotspot areas.[3] Over the last few years various backbone structures and synthetic approaches have been developed by chemists, based on these promising data (Figure 37).

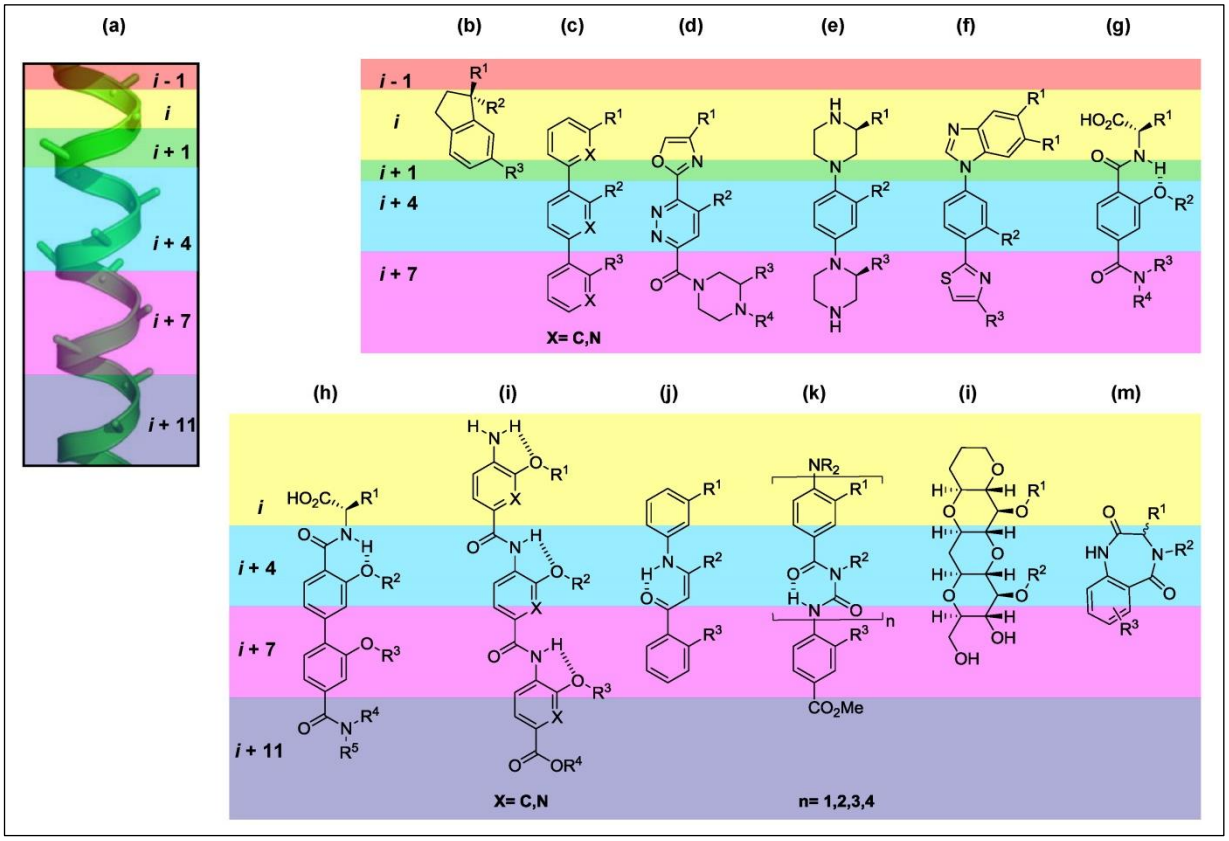


Figure 37. Overview of α-helix mimetics, picture taken from Ref.[26]

A rapid approach for the synthesis of small molecules, which can mimic an α-helix, would be desirable because of the common occurrence of this secondary structure motif and the growing importance of PPIs in medicinal chemistry. So far, only a few general approaches by LIM[17,79] and BOGER[76–78] have been established for the efficient synthesis of α-helix mimetics libraries.

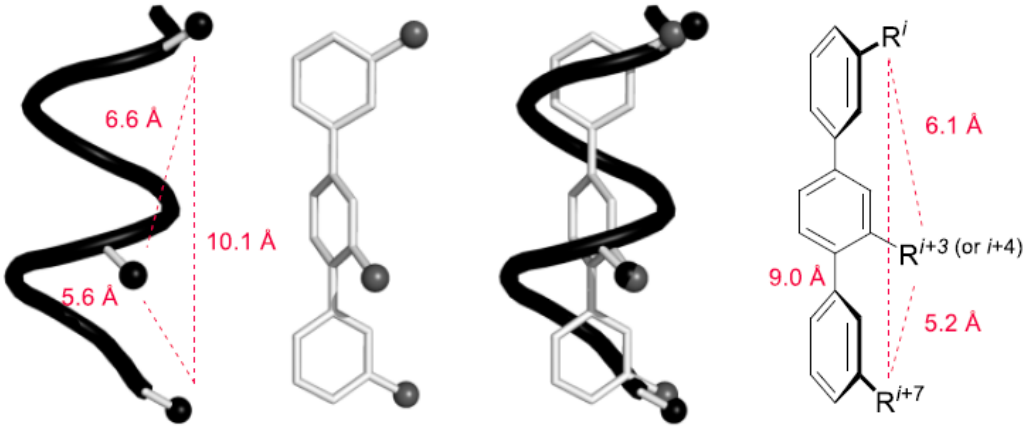
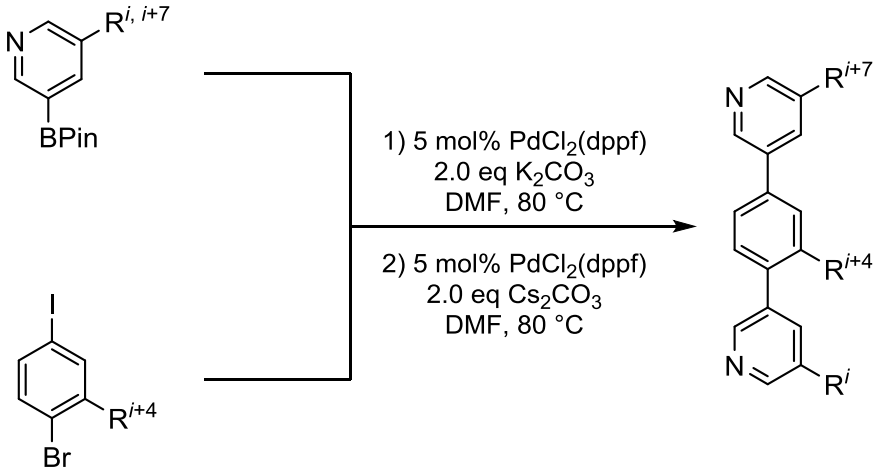


Figure 38. Overlay of an α-helix and a teraryl, picture taken from Ref.[50]

Based on the terphenylic concept of HAMILTON (Figure 38) the BREINBAUER group was able to develop a modular strategy using building blocks.[50] To overcome the poor solubility in aqueous solvents two of the three phenyl rings in HAMILTON's first suggested backbone were exchanged with more polar pyridine rings. The assembly of these building blocks was performed by a sequential two step SUZUKI-MIYAURA coupling procedure.



Scheme 82. Modular approach for teraryl synthesis.

For this approach it was necessary to have a core building block with two different leaving groups to achieve regioselectivity in Pd-catalyzed cross-coupling. Due to the problem of hydrolysis of triflates during the cross coupling reactions, bromine was installed as a second leaving group (Scheme 82). The side chains at the core fragment were chosen according to the side chains of natural amino acids involved in protein-protein interactions.

The core building blocks with side chains identical to natural amino acids were synthesized in 2 to 4 steps in 7 % and 80 % overall yields. The synthesis of the core fragments Gln, Trp, Arg and Lys could not be finished yet (Figure 39).

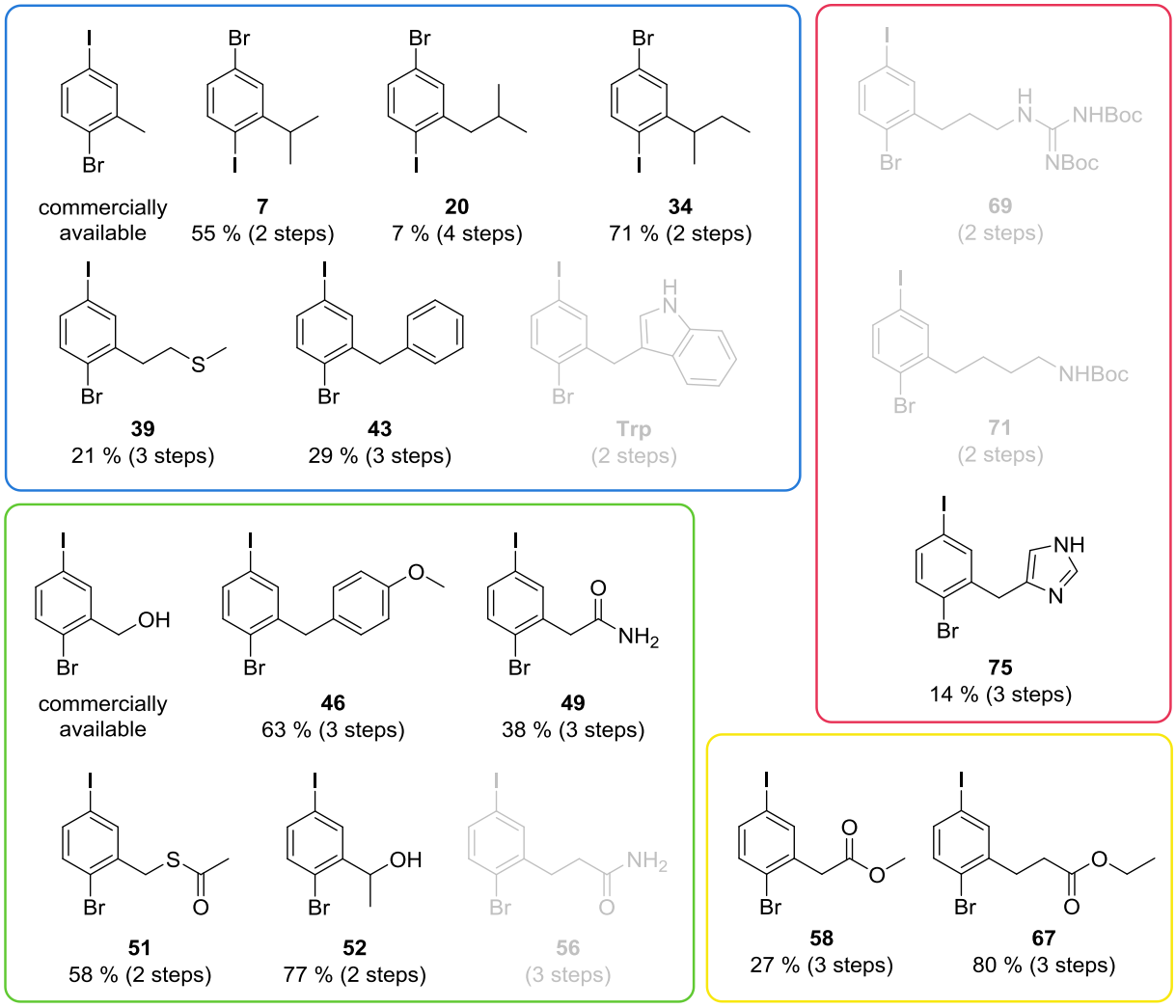
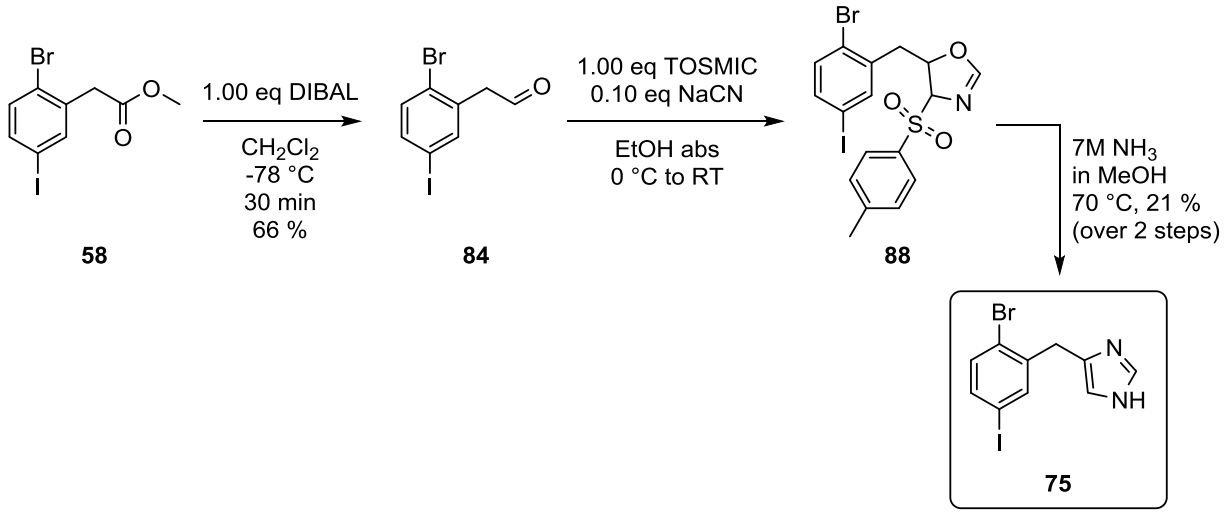


Figure 39. Overview of the synthesized core unit fragments.

The main focus was the synthesis of the His core fragment which has been the only building block that was not accessible in the iodo-triflate series. Different reaction routes had to be explored until finally a three step route starting from Asp core building block could be developed (Scheme 83). In this synthesis the His building block could be produced in 14 % overall yield.



Scheme 83. Synthesis of the histidine core fragment.

Moreover, two core building blocks with modified side chains were synthesized, shown in Figure 40. The C-elongated Glu building block **94** was synthesized in 4 steps and 36 % overall yield. For the generation of the O-Glu building block **98** only one step was necessary. In this case 99 % yield of the desired product was obtained.

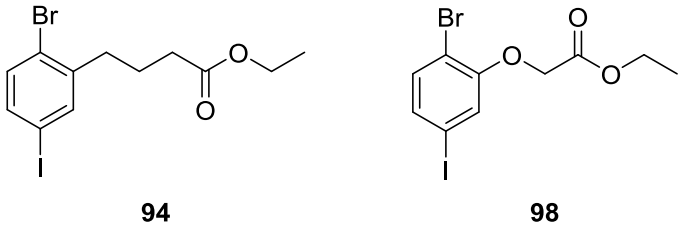
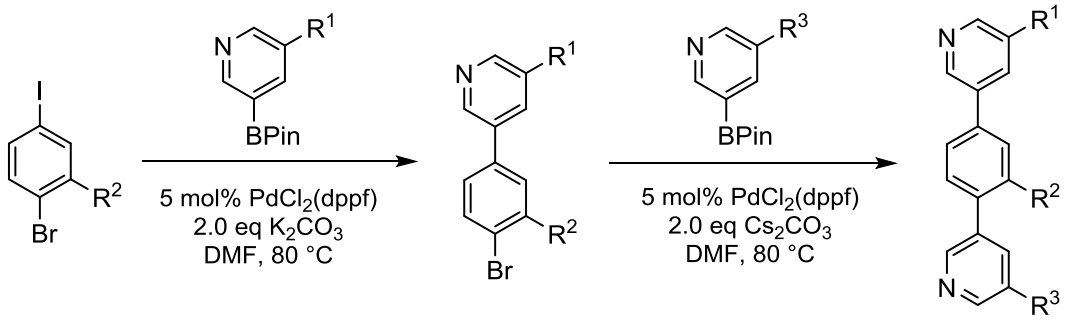


Figure 40. Synthesized core building blocks with modified side chains.

For the assembly of teraryls similar cross-coupling conditions, as identified by TROBE for the iodo-triflate compounds were used. $PdCl_2$(dppf) was found as suitable catalyst, faster reactions were achieved by using DMF as solvent and 80 °C reaction temperature. In the first coupling step selectively the iodine underwent cross-coupling reaction by the use of K_2CO_3 as base. In the second step a switch of the base to Cs_2CO_3 was executed to ensure high regioselectivity (Scheme 84).



Scheme 84. General SUZUKI-MIYAURA coupling conditions.

Several teraryls for testing as SREBP/Med 15 inhibitors were synthesized. On the one hand various top pyridine building blocks were used and on the other hand different core fragments were tested. The IC_{50} values of teraryls **118**-**121** were all in the same range (7.5 to 8.9 µM). In the case of the different core fragments **125** and **129** the IC_{50} values are moderate with around 50 µM (**125**) and 30 µM (**129**).

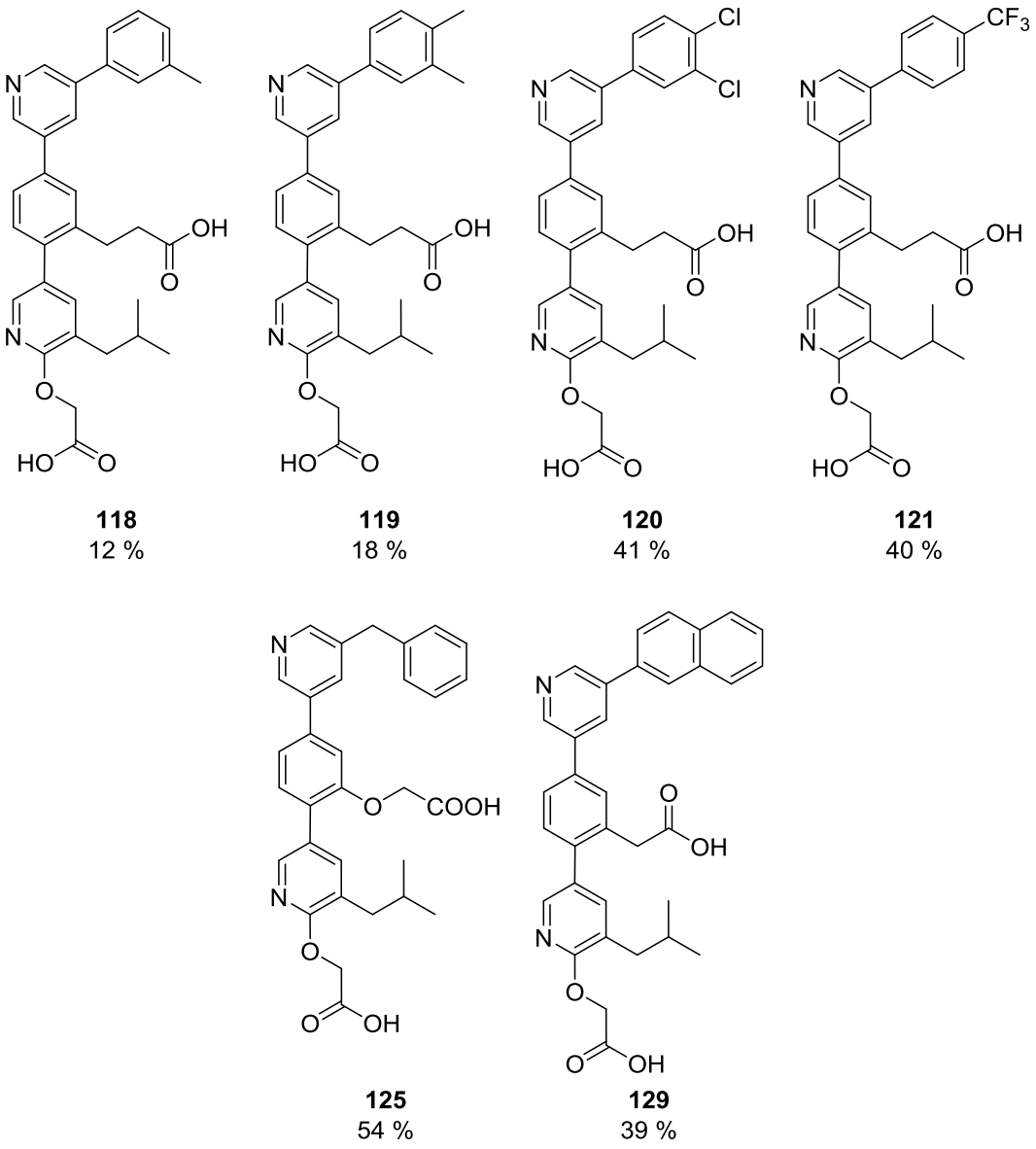
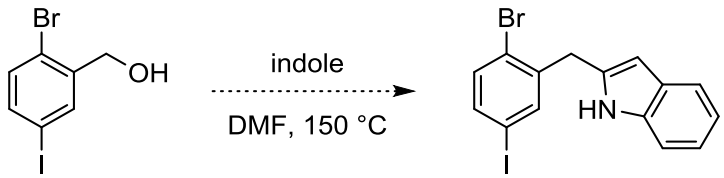


Figure 41. Synthesized teraryls for testing as Med15 inhibitors.

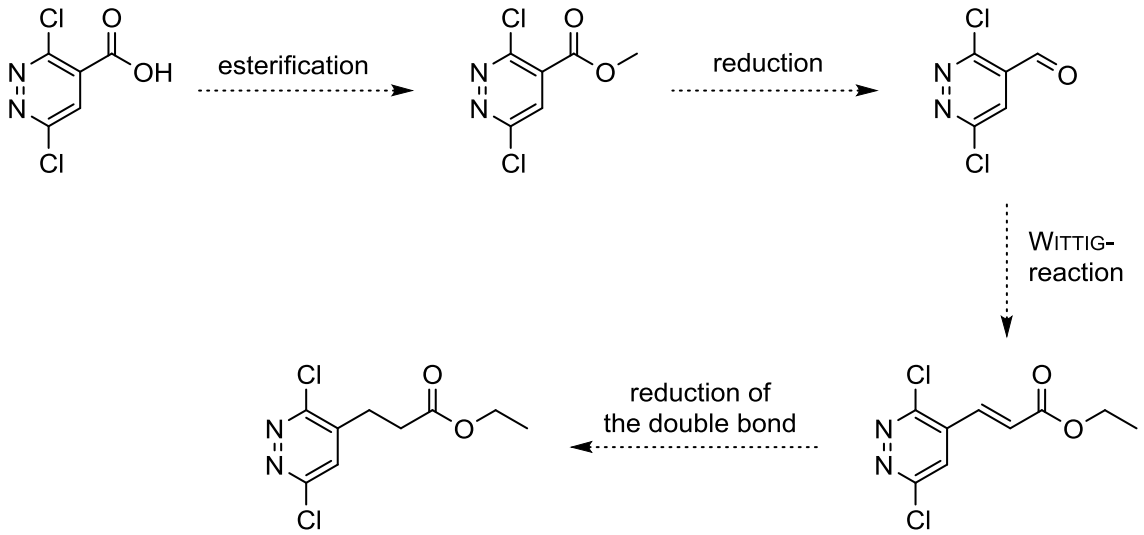
6. Outlook

Future work should aim for the synthesis of the not finished core fragments. The synthesis of Gln, Arg and Lys has to be finished. The synthesis of the tryptophan building block could be attempted via FRIEDEL-CRAFTS alkylation (Scheme 86). Moreover, the synthesis of some core building blocks needs to be further optimized. Due to low overall yields and long reaction sequences the production of larger amounts of the desired building blocks is prohibited. For rapid access to a library of teraryl, it would be necessary to have the core building blocks and the pyridine building blocks in gram quantities in stock.



Scheme 85. Planned synthesis of tryptophan building block.

Moreover, the synthesis of the pyridazine Glu building block has to be finished. Optimization of the esterification step will be necessary. So far esterification was performed over two steps, first reaction with oxalylchloride to form the acid chloride and then esterification with MeOH was performed. Use of DCC or EDC will furnish the esterified product in one step and might give better yield. In the next step a reduction of the ester to the aldehyde should be performed, followed by a WITTIG-reaction and the reduction of the double bond (Scheme 86).



Scheme 86. Planned synthesis of the pyridazine-Glu building block.

Several teraryls for testing as SREBP/Med 15 inhibitors were already synthesized, but there are still approaches for new teraryls, which are worth to try. For the synthesis of the teraryl with the C-elongated core fragment the second coupling and saponification has to be performed. Due to solubility problems, it will be very helpful to have a more polar compound. Therefore, the synthesis of a teraryl with the pyridazine Glu core fragment will be attractive to see the influense of the additional nitrogens on binding and solubility (Figure 42).

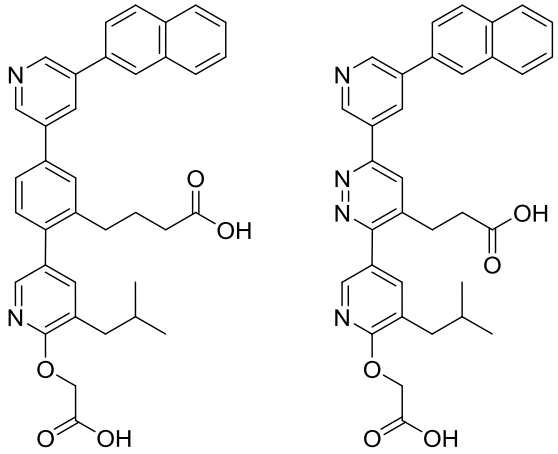


Figure 42. Teraryls for testing as Med15 inhibitor.

For the coupling of the pyridazine Glu core fragment featuring two chlorine leaving groups on the core fragment new conditions for the selective coupling of one chlorine with the pyridine building block will require further opitimization to achieve teraryl assembly.

7. Experimental Section

7.1. General Aspects

All commercially available reagents and solvents were purchased from Sigma-Aldrich, Alfa Aesar, ABCR, Fisher Scientific, Acros Organics, Roth or VWR, were of reagent grade or better and were used without further purification except otherwise stated. When it was required, e.g. with ethereal solvents, non-dry solvents were distilled before use.

Reactions carried out under inert conditions were performed with standard Schlenk techniques under exclusion of oxygen. The reaction vessel was evacuated, flame dried, and flushed with argon or nitrogen gas for three times. Herein solvents were dried and/or degassed with common methods and afterwards stored under inert gas atmosphere (argon or N_2) over molecular sieves. In some cases, when explicitly mentioned, dry solvents were received from the mentioned suppliers. The addition of chemicals was conducted under argon or nitrogen counter flow, which should exclude traces of moisture and oxygen. In general, when high vacuum was stated in experimental procedures, typically a vacuum of 10^{-2}-10^{-3} mbar was applied. All reactions were stirred with Teflon-coated magnetic stirring bars unless otherwise stated.

Oxidation sensitive reactions were accomplished under argon or nitrogen atmosphere and absolute and degassed solvents were used. Degassing of solvents was performed by bubbling argon from a balloon via cannula through the solvent during ultrasonification for about 20 min.

In general, temperatures were measured externally if not otherwise stated. When working at a temperature of 0 °C, an ice-water bath served as the cooling medium. Lower temperatures were achieved by either using an acetone/dry ice cooling bath or a cryostatic temperature regulator. Reactions, which were carried out at higher temperatures than RT, were heated in a silicon oil bath on a heating plate (RCT basic IKAMAG® safety control, 0-1500 rpm) equipped with an external temperature controller.

For hydrogenation reactions special safety conditions were necessary. During work up the catalyst filtration was carried out via an inverse filter funnel containing a pad of Celite under inert gas, the product has been isolated, the catalyst pad was rinsed with water and the used catalyst was then stored under wet conditions.

7.2. Solvents

Dry solvents were stored over molecular sieves. Molecular sieves (Sigma-Aldrich, beads with 8-12 mesh) were activated in a round-bottom flask with a gas inlet adapter by heating them carefully in a heating mantle at level 1 for approximately 24 h under high vacuum until complete dryness was obtained. These activated molecular sieves were stored at RT under argon atmosphere.

Acetonitrile (C_2H_3N; MeCN): MeCN was purchased without any stabilizer from Acros Organics in 99.9 % purity. It was stored over 3 Å molecular sieves under argon atmosphere in a brown 1 L Schlenk-bottle.

Dichloromethane (CH_2Cl_2; Methylenechloride) dry: EtOH stabilized dichloromethane was dried over phosphorus pentoxide, distilled, heated under reflux over CaH_2 for 24 h. Then it was distilled into a 1 L amber Schlenk-flask. Dried CH_2Cl_2 was stored over 4 Å molecular sieves under argon atmosphere.

1,2-Dimethoxyethane ($C_4H_{10}O_2$; DME): 1,2-Dimethoxyethane was purchased from Sigma Aldrich (38568, puriss., dried over molecular sieves, 99.5 %) and directly used in the experiments.

***N*,*N*-Dimethylformamide dry (C_3H_7NO; DMF):** *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.

Tetrahydrofuran dry (C_4H_8O; THF): Tetrahydrofuran was dried over an aluminium oxide column under inert conditions. Dried THF (after Fisher titration 15 ppm) was then distilled over $LiAlH_4$ to remove the BHT-stabilizer. The absolute THF was then stored over 4 Å molecular sieves under argon atmosphere in a brown 1 L Schlenk-bottle.

Toluene (C_7H_8): Toluene was purchased from Sigma Aldrich (99.7 %), dried over an aluminium oxide column under inert conditions and filled in a brown 1 L Schlenk bottle over 4 Å molecular sieves under argon atmosphere.

Ethanol (C_2H_6O; EtOH): Ethanol was dried over sodium, distilled under argon atmosphere and stored over 3 Å molecular sieves in a brown 1 L Schlenk bottle under argon atmosphere.

For reactions which could be performed without inert conditions, as well as for work up and further purification procedures the following solvents listed below were used. All solvents

were used without further purification except Et_2O and THF. These two were distilled before use and stored over solid KOH in amber light glass bottles.

1,4-Dioxane ($C_4H_8O_2$): 1,4-Dioxane was purchased from Acros Organics (117110025, with a minimum content of 99%) in a 2.5 L glass bottle and used without further purification.

Methanol (CH_4O; MeOH): Methanol with a minimum content of 99.99 % was purchased in 5 L plastic bottles and used without further purification (VWR Chemicals 20847.360).

Ethanol (C_2H_6O; EtOH): Ethanol was purchased from Merck (1 % ethylmethylketone as stabilizer) and directly used in the reactions.

Iso-propanol (C_3H_8O; i-PrOH): Iso-propanol was purchased from Merck-Schuchardt with a minimum content of 99.9% und used without further purification.

Diethylether ($C_4H_{10}O$; Et_2O): Commercially available diethylether was distilled to remove the stabilizer BHT (2,6-di-tert-butyl-4-methylphenole) and stored over KOH in a brown glass bottle.

Ethylacetate ($C_4H_8O_2$; EtOAc): Ethylacetate with a minimum content of 99.99 % was purchased in 5 L cans and used without further purification (VWR Chemicals 23882.321).

Cyclohexane (C_6H_{12}): Cyclohexane with a minimum content of 99.99 % was purchased in 5 L cans and used without further purification (VWR Chemicals 23224.362).

Triethylamine ($C_6H_{15}N$; Et_3N): Triethylamine was dried by heating at reflux temperature over CaH_2 and stored under argon atmosphere over 4 Å molecular sieves in a brown 1 L Schlenk-bottle.

Dichloromethane (CH_2Cl_2; Methylenechloride): Methylenechloride was purchased with a minimum content of 98% in 5 L cans and used without further purification.

Saturated NaCl solution (brine): Solid NaCl was dissolved in H_2O until remaining solid was left.

Saturated $NaHCO_3$ solution: Solid $NaHCO_3$ was dissolved in H_2O until remaining solid was left.

Saturated Na_2CO_3 solution: Solid Na_2CO_3 was dissolved in H_2O until remaining solid was left.

Rochelle salt: Rochelle salt ($KNaC_4H_4O \cdot 4\ H_2O$) was added to distilled water until saturation was obtained.

7.3. Analytical Methods

7.3.1. Thin Layer Chromatography (TLC)

Thin layer chromatography was most commonly used for control of reaction conversion. The analytical method was performed using TLC-plates from Merck (TLC aluminium foil, silica gel 60 F254, 20 x 20 cm). The compounds were generally visualized with UV-light (254 nm and/or 366 nm), and by the listed staining solutions followed by additional heat treatment with hot-air flow.

The R_f-values and applied solvent composition are detailed in the procedures.

Cerium ammonium molybdate (CAM): 2.0 g cer(IV)-sulfate, 50.0 g ammonium molybdate and 50 mL conc. H_2SO_4 were added to 400 mL distilled water.

Potassium permanganate ($KMnO_4$): 1.5 g $KMnO_4$, 10 g K_2CO_3, and 1.25 mL 10 % NaOH in 200 mL dist. H_2O.

7.3.2. Flash chromatography

For preparative column chromatography silicagel 60, purchased from ACROS Organics, was used (particle size between 35 µm and 70 µm) under applied pressure. Typically, the mass of used silica was 50 to 100 times (w/w) of the mass of the crude product. The crude procduct was either dissolved in the eluent or in the case of an insoluble sample, it was dissolved in an appropriate solvent (EtOAc or CH_2Cl_2) and subsequently adsorbed on the 1.5 fold excess of silica gel. Afterwards the solvent was removed on a rotary evaporator and the adsorbed crude material dried under high vaccum. The R_f-values of the desired compound in the elution solvent was set to be around 0.20. The appropriately sized columns and applied solvent compositions are given in the experimental procedures. For optimal separation of the compounds the overall length of the SiO_2 pad was between 15 and 30 cm. The volume of each collected fraction was adjusted between 20 % and 30 % of the silica gel volume.

7.3.3. Gas chromatography with Mass Selective Detection (GC-MS)

GC-MS analyses were performed on an Agilent Technologies 7890A GC system equipped with a 5975C mass selective detector (inert MSD with Triple Axis Detector system) by electron-impact ionization (EI) with a potential of E = 70 eV. Herein, the samples were separated depending on their boiling point and polarity. The desired crude materials or pure compounds were dissolved either in DCM or EtOAc and the solutions were injected by

employing the autosampler 7683B in a split mode 1/20 (inlet temperature: 280 °C; injection volume: 0.1 µL). Separations were carried out on an Agilent Technologies J&W GC HP-5MS capillary column ((5 %-phenyl)methylpolysiloxane, 30 m x 0.2 mm x 0.25 µm) with a constant helium flow rate (He 5.0 (Air Liquide), 1.085 mL/min, average velocity: 41.6 cm/s). A general gradient temperature method was used:

Method_1: initial temperature: 50 °C for 1 min, ramp 40 °C/min linear increase to 300 °C, 300 °C for 5 min, 1 min post-run at 300 °C, detecting range: 50.0 – 550.0 amu, solvent delay: 2.80 min.

The conversion of starting material and/or product formation was determined by integration of the peaks in the chromatogram. All stated values are only relative values due to the fact that no internal standards were used in all performed experiments. Therefore retention time of main products and intensities of the molecular fragments relative to the base peak are documented for each experiment.

7.3.4. High Pressure Liquid Chromatography (HPLC)

Analytical high-performance liquid chromatography was performed on an "Agilent Technologies 1200 Series" HPLC system with 1260 HiP Degasser G4225A, binary pump SL G1312, autosampler HiP-ALS SL G1367C, thermostated column compartment TCC SL G1316B, multiple wavelength detector G1365C MWD SL with deuterium lamp (λ = 190 – 400 nm) and subsequent connected mass detector (Agilent Technologies 6120 Quadrupole LC/MS) with an electrospray ionization (ESI) source. The separation was performed with a reversed phase column:

"Poroshell® 120 SB-C18EC, 3.0 x 100 mm, 2.7 µm" from Agilent Technologies with a Merck LiChroCART® 4-4 pre-column

Signals were detected at 210 nm or 254 nm. As mobile phase acetonitrile (VWR HiPerSolv, HPLC-MS grade) and water (deionized and filtered through a 0.2 µm cellulose nitrate membrane filter) with 0.01 % formic acid were used. The following methods were used:

Methode_2: 0.0 – 6.0 min 98 % water/ 0.1 % HCOOH and 2 % MeOH linear decrease to 100 % MeOH, 6.0 – 8.0 min 100 % MeOH; 0.7 mL/min, 30 °C.

Methode_3: 0.0 – 4.0 min 98 % water/ 0.1 % HCOOH and 2 % MeOH linear decrease to 100 % MeOH, 4.0 – 6.0 min 100 % MeOH; 0.7 mL/min, 30 °C.

Semi-preparative HPLC

For semi-preparative HPLC a Thermo Scientific Dionex Ulti Mate 3000 Instrument was used. Semi-preparative HPLC was carried out utilizing a Macherey-Nagel VP 125/21 Nucleodur 100-5 C18 ec column.

Method_4: 0.0 – 18.0 min 30 % water/ 0.1 % HCOOH and 70 % MeCN linear decrease to 100 % MeCN, 18.0 – 23.0 min 100% MeCN.

7.3.5. High Resolution Mass spectroscopy (HRMS)

The determination of high resolution mass was performed by Prof. Robert Saf and Ing. Karin Bartl (TU Graz) in a positive reflector on a MALDI-TOF/TOF (Bruker Ultraflex Extreme) with nanostructured laser disorption ionisation (naldi) plates [Bruker MSP 96 NALDI target plate, #252248].

Mass range:	200-600 Da
Laser frequency:	1000 Hz
Laser intensity:	20-80%
Sample rate:	4.0 GS/s
Reflector gain:	3.0 x

The mass spectra were analyzed with FlexAnalysis 3.0 software (Bruker Daltonics).

7.3.6. Nuclear Magnetic Resonance Spectrometry (NMR)

For recording nuclear magnetic resonance spectra a Bruker Avance III 300 MHz FT NMR spectrometer with autosampler (300.36 MHz-^{1}H-NMR and 75.5 MHz-^{13}C-NMR) or a Varian Unity Inova 500 spectrometer (499.87 MHz-^{1}H-NMR and 125.69 MHz-^{13}C-NMR) were used The residual protonated solvent signals serve as internal standard for interpretation of the chemical shifts δ (^{1}H-, ^{13}C- and APT-NMR). To facilitate the interpretation, the ^{13}C-spectra were proton decoupled to gain better identification of the peaks. APT spectra are recorded for differentiation of C-atoms if necessary.

The chemical shift δ is indicated in ppm (parts per million) and the coupling constant J in Hz (Hertz). For the signal multiplicities the following abbreviations were most commonly used: s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), t (triplet), q (quadruplet), sext (sextet), hept (heptett), m (multiplet), dd (doublet of doublet), dt (doublet of triplet) and dq (doublet of quadruplet). Quaternary carbons are indicated as C_q, arylic carbon atoms as C^{Ar} and aromatic protons as H^{Ar}.

7.3.7. Determination of the melting point

The melting points were determined using "Mel-Temp®" melting point apparatus with integrated microscope attachment. Melting points are uncorrected and related to further standards.

7.3.8. Titration of Stock Solutions

Diverse stock solutions had to be titrated before their use in order to determine their exact concentration. Due to their sensitivity to hydrolysis of several reagents, some of these titrations had to be carried out under inert conditions in oven-dried, evacuated and argon purged Schlenk flaks. Each titration was performed at least for three times, from which the mean value of the determined concentration was taken for further experiments. The prepared stock solutions were immediately used after their titration.

7.3.8.1. Titration of Alkyl-Li solution

A flame dried Schlenk-flask was charged with 2.0 mL abs. THF and 300 mg diphenylacetic acid. The alkyl-Li solution was added dropwise under inert conditions. The equivalence point was indicated by a color change from colorless to yellow. To ensure a precise titration a triple determination was performed. The titration was carried out before every use of the n-BuLi solution.[133]

7.3.8.2. General procedure for titration of GRIGNARD-reagent solutions

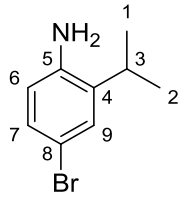
A flame dried Schlenk-flask was charged with 200.0 mL abs. degassed toluene and 20.0 mL abs. 2-butanol. This stock solution was stored under an atmosphere of argon over 3 Å molecular sieves (stable over months). The concentration of this stock solution (c = 0.86 M) was used as reference for the titration of GRIGNARD-reagent solutions and was determined by NMR.

In a flame dried and argon flushed 10 mL Schlenk-tube 1 mg o-phenanthroline was dissolved in 2 mL anhydrous toluene and 0.5 mL of the GRIGNARD-reagent to be titrated were added under inert conditions. The solution was titrated with a standard solution (0.86 M) of butan-2-ol in toluene under inert conditions. The equivalence point was indicated by a color change from purple to yellow. The added moles of butan-2-ol are equal to the moles GRIGNARD-reagent in the given aliquot. To ensure a precise titration a triple determination was performed. The titration was carried out before every use of the GRIGNARD solution.[134]

7.4. Experimental Procedures

7.4.1. Synthesis of the Valine building block

7.4.1.1. 4-Iodo-2-isopropylaniline (6)



6

This compound was prepared according to the literature.[120]

In a 100 mL one-neck round-bottom flask 29 mg (380 µmol, 0.10 eq) NH_4OAc were dissolved in 15 mL MeCN. 518 µL (3.70 mmol, 1.00 eq) 2-isopropylaniline (**1**) and 692 mg (3.89 mmol, 1.05 eq) NBS were added. The red suspension was stirred at RT for 10 min. After full conversion was detected by GC-MS the solvent was removed under reduced pressure. The residue was diluted with 20 mL EtOAc and washed with $NaHSO_3$ solution (3 x 20 mL). The combined aqueous layers were reextracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The red brown oil was purified via flash column chromatography (110 g SiO_2, 4.0 x 13.0 cm, eluent: cyclohexane/EtOAc = 12/1, fraction size: 50 mL).

Yield: 587 mg (2.76 mmol, 75 %), brown oil

$C_9H_{12}BrN$ [213.02 g/mol]

TLC: R_f = 0.15 (cyclohexane/EtOAc = 12/1, UV and $KMnO_4$)

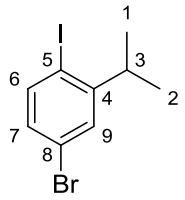
GC-MS (Method_1): t_R = 5.59 min, *m/z* = 213 (59 %), 198 (100 %), 171 (4 %), 119 (87 %), 91 (19 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.21 (d, $^3J_{HH}$ = 1.7 Hz, 1H, H-9), 7.10 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 2.0 Hz, 1H, H-7), 6.55 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-6), 3.65 (bs, 2H, NH_2), 2.84 (hept, $^3J_{HH}$ = 6.7 Hz, 1H, H-3), 1.24 (d, $^3J_{HH}$ = 6.8 Hz, 6H, H-1, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 142.5 (C_q, C-5), 134.9 (C_q, C-4), 129.3 (C-7), 128.5 (C-9), 117.4 (C-6), 111.1 (C_q, C-8), 28.0 (C-3), 22.2 (C-1, C-2) ppm.

Analytical data are in accordance with those reported.[120]

7.4.1.2. 1-Bromo-4-iodo-2-isopropylbenzene (7)



7

This compound was prepared according to the literature.[120]

In a 100 mL one-neck round-bottom flask 570 mg (2.68 mmol, 1.00 eq) 4-iodo-2-isopropylaniline (**6**) were suspended in 3 mL dist. H_2O and cooled to 0 °C. 1.6 mL conc. HCl were added dropwise. Then a cooled solution of 314 mg $NaNO_2$ in 2.4 mL H_2O was added at 0 °C and the suspension was stirred at 0 °C. After 1 h a solution of 866 mg KI in 3.5 mL H_2O was added dropwise at 0 °C. The brown suspension was stirred at RT for 16 h. After full conversion of the starting material was indicated by GC-MS, the reaction was diluted with 30 mL EtOAc and washed with $NaHSO_3$ solution (3 x 20 mL). The combined aqueous layers were reextracted with EtOAc (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The brown oil was purified via flash column chromatography (100 g SiO_2, 4.0 x 12.5 cm, eluent: cyclohexane, fraction size: 20 mL).

Yield: 637 mg (1.97 mmol, 73 %), brown oil

$C_9H_{10}BrI$ [323.90 g/mol]

TLC: R_f = 0.80 (cyclohexane, UV and $KMnO_4$)

GC-MS (Method_1): t_R = 5.66 min, *m/z* = 323 (100 %), 309 (100 %), 182 (57 %), 102 (49 %).

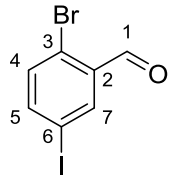
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.66 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-6), 7.34 (d, $^3J_{HH}$ = 2.1 Hz, 1H, H-9), 7.01 (dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2.3 Hz, 1H, H-7), 3.14 (hept, $^3J_{HH}$ = 6.8 Hz, 1H, H-3), 1.22 (d, $^3J_{HH}$ = 6.8 Hz, 6H, H-1, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 152.8 (C_q, C-4), 140.9 (C-6), 130.9 (C-7), 129.4 (C-9), 123.2 (C_q, C-8), 99.0 (C_q, C-5), 38.3 (C-3), 23.0 (C-1, C-2) ppm.

Analytical data are in accordance with those reported.[120]

7.4.2. Synthesis of the Leucine building block

7.4.2.1. 2-Bromo-5-iodobenzaldehyde (10)



10

In a 250 mL flame dried round-bottom flask equipped with a Schlenk adapter 2.40 g (7.67 mmol, 1.00 eq) (2-bromo-5-iodophenyl)-methanol (**9**) were dissolved in 75 mL abs. CH_2Cl_2. 1.5 g anhydrous 4 Å MS and 4.0 g (46.0 mmol, 5.99 eq) MnO_2 were added in a N_2-counterstream. The black reaction mixture was stirred overnight. After full conversion of the starting material was indicated by TLC and GC-MS (15 h) MnO_2 was removed via filtration through a pad of silica (20 g SiO_2, eluent: EtOAc, fraction size: 50 mL). The filtrate was collected and the solvent was removed under reduced pressure. The product was used without further purification.

Yield: 2.14 g (6.90 mmol, 90 %), colorless solid

C_7H_4BrIO [309.85 g/mol]

mp$^{exp.}$ = 103-107 °C

TLC: R_f = 0.67 (cyclohexane/EtOAc = 3/1, UV and CAM)

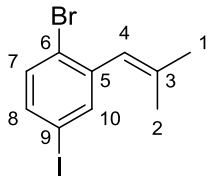
GC-MS (Method_1): t_R = 5.83 min, *m/z* = 310 (100 %), 283 (12 %), 202 (6 %), 157 (8 %), 127 (10 %), 75 (34 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 10.24 (s, 1H, H-1), 8.19 (d, $^4J_{HH}$ = 2.1 Hz, 1H, H-7), 7.74 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 2.1 Hz, 1H, H-5), 7.38 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-4) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 190.5 (C-1), 144.0 (C-5), 138.8 (C-7), 135.6 (C-4), 134.9 (C_q, C-2), 126.7 (C_q, C-3), 93.0 (C_q, C-6) ppm.

Analytical data are in accordance with those reported.[135]

7.4.2.2. 1-Bromo-4-iodo-2-(2-methylprop-1-en-1-yl)benzene (13)



13

In a flame dried 500 mL three-neck round-bottom flask equipped with reflux condenser and argon-inlet 285 mg (740 µmol, 2.30 eq) phosphonium-salt **12** were suspended in 3 mL absolute, degassed toluene. Then 300 µL (2.5M in hexane, 750 µmol, 2.33 eq) *n*-BuLi were added and the dark red suspension was stirred at RT for 1 h. In the meanwhile in another flame dried Schlenk-flask 100 mg (322 µmol, 1.00 eq) 2-bromo-5-iodobenzaldehyde were dissolved in 1 mL abs., degassed toluene. The dark red suspension of the phosphonium-ylide was cooled to -78 °C in a dry ice/acetone bath and the aldehyde (**10**) solution was added via syringe. This colorless solution was added at -78 °C to the phosphonium-salt suspension. After several min the suspension became brighter and a pale yellow precipitate was formed. The suspension was stirred overnight in the thawed dry ice/acetone bath. After full conversion of the starting material was indicated by TLC (16 h) the yellow suspension was quenched by the addition of 15 mL satd. NH_4Cl solution. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The crude product was dissolved in cyclohexane and filtered through a pad of silica (20 g SiO_2, eluent: cyclohexane, 50 mL fractions).

Yield: 63.4 mg (189 µmol, 59 %), colorless solid

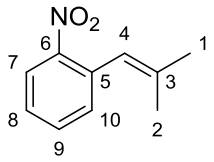
$C_{10}H_{10}BrI$ [335.90 g/mol]

TLC: R_f = 0.63 (cyclohexane, UV and $KMnO_4$)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.53 (d, $^3J_{HH}$ = 1.3 Hz, 1H, H-10), 7.35 (d, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.4 Hz 1H, H-8), 7.24 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H-7), 6.12 (s, 1H, H-4), 1.90 (s, 3H, H-1), 1.72 (s, 3H, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 141.0 (C_q, C-3), 139.7 (C-10), 138.2 (C_q, C-5), 136.6 (C-8), 134.14 (C-7), 124.2 (C_q, C-6), 124.0 (C-4), 91.9 (C_q, C-9), 26.3 (C-1), 19.5 (C-2) ppm.

7.4.2.3. 1-(2-Methylprop-1-en-1-yl)-2-nitrobenzene (17)



17

In a flame dried 100 mL three-neck round-bottom flask equipped with reflux condenser and argon-inlet 1.53 g (3.97 mmol, 1.20 eq) phosphonium-salt **12** were suspended in 10 mL abs., degassed THF. Then 2.3 mL (2.5M in hexane, 5.75 mmol, 1.74 eq) *n*-BuLi were added dropwise via a syringe. The dark red suspension was stirred at RT for 90 min. In the meanwhile in another flame dried Schlenk-flask 500 mg (3.31 mmol, 1.00 eq) 2-nitrobenzaldehyde (**16**) were suspended in 5 mL abs., degassed THF. The dark red suspension of phosphonium-ylide **12** was cooled to -78 °C in a dry ice/acetone bath and the 2-nitrobenzaldehyde (**16**) solution was added via syringe. After 20 min the reaction mixture turned into a light red suspension. The suspension was stirred overnight (16 h) at RT until complete conversion was indicated by TLC. The red suspension was quenched by the addition of 20 mL dist. H_2O. The phases were separated amd the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with satd. NaCl solution (1 x 50 mL), dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The brown crude product was purified via flash column chromatography (125 g SiO_2, 4.0 x 15.0 cm, eluent: cyclohexane/EtOAc = 50/1, R_f = 0.41, UV and $KMnO_4$, fraction size: 50 mL).

Yield: 485 mg (2.74 mmol, 83 %), yellow oil

$C_{10}H_{11}NO_2$ [177.08 g/mol]

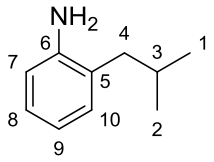
TLC: R_f = 0.63 (cyclohexane/EtOAc = 9/1, UV and $KMnO_4$)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.93 (d, $^3J_{HH}$ = 8.1 Hz, 1H, H-7), 7.54 (t, $^3J_{HH}$ = 7.5 Hz, 1H, H-9), 7.34 (m, 2H, H-8, H-10), 6.48 (s, 1H, H-4), 1.93 (s, 3H, H-1), 1.70 (s, 3H, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 148.8 (C_q, C-6), 138.1 (C_q, C-3), 133.8 (C_q, C-5), 132.5 (C-8), 132.4 (C-9), 127.2 (C-10), 124.4 (C-7), 121.0 (C-4), 26.3 (C-1), 19.6 (C-2) ppm.

Analytical data are in accordance with those reported.[136]

7.4.2.4. 2-Isobutylaniline (18)



18

This compound was prepared according to the literature.[137]

In a 50 mL two-neck round-bottom flask 458 mg (2.74 mmol, 1.00 eq) 1-(2-methylprop-1-en-1-yl)-2-nitrobenzene **17** were suspended in 14 mL MeOH/EtOAc (1:1). 292 mg (274 µmol, 0.10 eq) 10 % Pd/C were added in argon counterflow and the resulting black solution was degassed with vacuum/H_2-cycles. The black suspension was stirred at RT overnight under H_2-balloon atmosphere. After full conversion of the starting material was indicated by TLC and GC-MS, the reaction was filtered through a pad of celite under argon atmosphere and eluted with MeOH (3 x 20 mL). The solvent was removed under reduced pressure. The red oil was used without further purification in the next step.

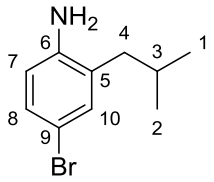
Yield: 172.8 mg (1.16 mmol, 42 %), colorless oil

$C_{10}H_{15}N$ [149.12 g/mol]

TLC: R_f = 0.33 (cyclohexane/EtOAc = 10/1, UV and $KMnO_4$)

GC-MS (Method_1): t_R = 4.75 min, *m/z* = 149 (22 %), 106 (100 %), 77 (10 %).

7.4.2.5. 4-Iodo-2-isobutylaniline (19)



19

In a 10 mL one-neck round-bottom flask 9.0 mg (117 µmol, 0.11 eq) NH_4OAc were dissolved in 5 mL MeCN. 166 mg (1.11 mmol, 1.00 eq) 2-isobutylaniline (**18**) and 208 mg (1.17 mmol, 1.05 eq) NBS were added. The red suspension was stirred at RT for 10 min. After full conversion was detected by GC-MS the solvent was removed under reduced pressure. The residue was diluted with 20 mL EtOAc and washed with $NaHSO_3$ solution (3 x 20 mL). The combined aqueous layers were reextracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The brown oil was purified via flash column chromatography (40 g SiO_2, 3.0 x 10.5 cm, eluent: cyclohexane/EtOAc = 20/1, R_f = 0.17, UV and CAM, fraction size: 20 mL).

Yield: 156 mg (688 µmol, 62 %), red-brown oil

$C_{10}H_{14}BrN$ [227.03 g/mol]

TLC: R_f = 0.17 (cyclohexane/EtOAc = 20/1, UV and CAM)

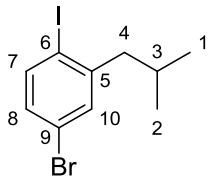
GC-MS (Method_1): t_R = 5.81 min, *m/z* = 227 (29 %), 184 (100 %), 104 (14 %), 78 (12 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.11 (m, 2H, H-8, H-10), 6.55 (d, $^3J_{HH}$ = 9.0 Hz, 1H, H-7), 3.60 (bs, 2H, NH_2), 2.33 (d, $^3J_{HH}$ = 7.2 Hz, 2H, H-4), 1.91 (hept, $^3J_{HH}$ = 6.7 Hz, 1H, H-3), 0.95 (d, $^3J_{HH}$ = 6.6 Hz, 6H, H-1, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 143.5 (C_q, C-6), 133.2 (C-10), 129.7 (C-8), 128.2 (C_q, C-5), 117.3 (C-7), 110.4 (C_q, C-9), 40.8 (C-4), 27.9 (C-3), 22.8 (C-1, C-2) ppm.

HRMS (DI-EI TOF): calcd. for $C_{10}H_{14}BrN^+$ $[M]^+$: 227.0310; found: 226.9697.

7.4.2.6. 1-Bromo-4-iodo-2-isobutylbenzene (20)



20

In a 50 mL one-neck round-bottom flask 122 mg (537 µmol, 1.00 eq) 4-iodo-2-isobutylaniline (**19**) were suspended in 2 mL dist. H_2O and cooled to 0 °C. 400 µL conc. HCl were added dropwise. Then a cooled solution of 73 mg $NaNO_2$ in 0.5 mL H_2O was added at 0 °C. The suspension was stirred at 0 °C. After 1 h a solution of 174 mg KI in 1.0 mL H_2O was added dropwise at 0 °C. The red-brown suspension was stirred at RT for 3.5 h. After full conversion of the starting material was indicated by GC-MS, the reaction was diluted with 20 mL EtOAc and washed with $NaHSO_3$ solution (3 x 20 mL). The combined aqueous layers were reextracted with EtOAc (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The brown oil was purified via flash column chromatography (10 g SiO_2, 2.0 x 6.5 cm, eluent: cyclohexane, R_f = 0.80, UV and $KMnO_4$, fraction size: 3 mL).

Yield: 57 mg (169 µmol, 32 %), orange oil

$C_{10}H_{12}BrI$ [337.92 g/mol]

TLC: R_f = 0.80 (cyclohexane, UV and $KMnO_4$)

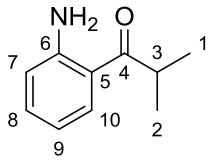
GC-MS (Method_1): t_R = 5.91 min, *m/z* = 338 (100%), 296 (93 %), 217 (19 %), 171 (32 %), 115 (23 %), 89 (51 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.65 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-7), 7.28 (d, $^3J_{HH}$ = 2.1 Hz, 1H, H-10), 7.01 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 2.2 Hz, 1H, H-8), 2.55 (d, $^3J_{HH}$ = 7.2 Hz, 2H, H-4), 1.96 (hept, $^3J_{HH}$ = 6.7, 1H, H-3), 0.95 (d, $^3J_{HH}$ = 6.6 Hz, 6H, H-, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 146.6 (C_q, C-5), 140.9 (C-7), 133.2 (C-10), 130.8 (C-8), 122.4 (C_q, C-9), 99.2 (C_q, C-6), 49.4 (C-4), 29.1 (C-3), 22.3 (C-1, C-2) ppm.

HRMS (DI-EI TOF): calcd. for $C_{10}H_{12}BrI^+$ $[M]^+$: 337.9167; found: 337.9179.

7.4.2.7. 1-(2-Aminophenyl)-2-methylpropan-1-one (22)



22

This compound was prepared similar to the literature.[121]

In a 250 mL Schlenk-flask 1.50 g (12.7 mmol, 1.00 eq) 2-aminobenzonitrile (**21**) were dissolved in 15 mL Et_2O and cooled to 0 °C. Then 12.7 mL (2M in THF, 25.4 mmol, 2.00 eq) iso-propylmagnesiumchloride were added dropwise. The mixture was allowed to warm up to RT overnight. After 16 h full conversion of the starting material was indicated by TLC and GC-MS, the reaction was cooled to -78 °C in a dry ice/acetone bath. 20% HCl were added carefully. After warming to ambient temperature the phases were separated. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with sat. NaCl solution and dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The brown oil was purified via filtration through a pad of silica (50 g SiO_2, eluent: cyclohexane/EtOAc = 3/1, R_f = 0.51, UV and $KMnO_4$, fraction size: 80 mL). The filtrate of fraction 1 and 2 was collected and the solvent was removed under reduced pressure.

Yield: 1.83 g (11.2 mmol, 88 %), yellow/brown oil

$C_{10}H_{13}NO$ [163.22 g/mol]

TLC: R_f = 0.51 (cyclohexane/EtOAc = 3/1, UV and $KMnO_4$)

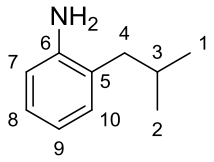
GC-MS (Method_1): t_R = 5.44 min, *m/z* = 162 (64 %), 144 (41 %), 130 (42 %), 119 (100 %), 106 (5 %), 92 (34 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.75 (d, $^3J_{HH}$ = 7.7 Hz, 1H, H-10), 7.24 (t, $^3J_{HH}$ = 7.6 Hz, 1H, H-8), 6.71 – 6.57 (m, 2H, H-7, H-9), 6.28 (bs, 2H, NH_2), 3.58 (hept, 1H, H-3), 1.19 (d, $^3J_{HH}$ = 6.8 Hz, 6H, H1, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 207.2 (C_q, C-4), 151.0 (C_q, C-6), 134.2 (C-8), 131.1 (C-10), 117.7 (C-7), 117.0 (C_q, C-5), 115.8 (C-9), 35.4 (C-3), 19.7 (C-1, C-2) ppm.

Analytical data are in accordance with those reported.[121]

7.4.2.8. 2-Isobutylaniline (18)



18

In a 25 mL Schlenk-flask 1.00 g (6.13 mmol, 1.00 eq) 1-(2-aminophenyl)-2-methylpropan-1-one (**22**) and 3.90 mL (24.4 mmol, 3.99 eq) Et_3SiH were dissolved in 9 mL $MeOH/CH_2Cl_2$ (2/1) and cooled to 0 °C. 1.10 mL (8.91 mmol, 1.45 eq) $BF_3{\cdot}Et_2O$ were added dropwise. The dark red solution was stirred for 20 min at 0 °C in an ice bath and then the solution was allowed to warm up to RT overnight. After 16 h full conversion of the starting material was indicated by TLC and GC-MS. Then the solution was quenched by the addition of 10 mL conc. KOH solution, the phases were separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The orange oil was purified via flash chromatography (125 g SiO_2, eluent: cyclohexane/EtOAc = 6/1, R_f = 0.48, UV and $KMnO_4$, fraction size: 75 mL).

Yield: 172 mg (1.15 mmol, 19 %), yellow oil

$C_{10}H_{15}N$ [149.24 g/mol]

TLC: R_f = 0.48 (cyclohexane/EtOAc = 6/1, UV and $KMnO_4$)

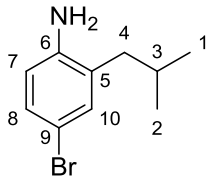
GC-MS (Method_1): t_R = 4.74 min, *m/z* = 149 (27 %), 132 (2 %), 106 (100 %), 91 (2 %), 77 (10 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.04 (m, 2H, H-8, H-10), 6.72 (m, 2H, H-7, H-9), 3.52 (s, 2H, NH_2), 2.39 (d, $^3J_{HH}$ = 7.2 Hz, 2H, H-4), 1.94 (hept, $^3J_{HH}$ = 6.7 Hz, 1H, H-3), 0.97 (d, $^3J_{HH}$ = 6.6 Hz, 6H, H-1, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 144.3 (C_q, C-6), 130.9 (C-8), 127.0 (C-10), 126.1 (C_q, C-5), 118.7 (C-7), 115.9 (C-9), 41.0 (C-4), 28.0 (C-3), 22.9 (C-1, C-2) ppm.

Analytical data are in accordance with those reported.[137]

7.4.2.9. 4-Iodo-2-isobutylaniline (19)



19

In a 50 mL one-neck round-bottom flask 7.3 mg (94.7 µmol, 0.10 eq) NH_4OAc were dissolved in 10 mL MeCN. 137 mg (916 µmol, 1.00 eq) 2-isobutylaniline (**18**) and 171 mg (962 µmol, 1.05 eq) NBS were added. The red suspension was stirred at RT for 10 min. After full conversion was detected by GC-MS the solvent was removed under reduced pressure. Then the residue was diluted with 15 mL CH_2Cl_2 and washed with $NaHSO_3$ solution (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The black oil was purified via flash column chromatography (25 g SiO_2, 2.5 x 9.0 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.26, UV and $KMnO_4$, fraction size: 8 mL). Fractions 8 to 16 were combined and concentrated under reduced pressure.

Yield: 123 mg (541 µmol, 59 %), red-brown oil

$C_{10}H_{14}BrN$ [228.13 g/mol]

TLC: R_f = 0.28 (cyclohexane/EtOAc = 9/1, UV and $KMnO_4$)

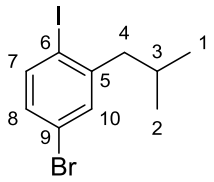
GC-MS (Method_1): t_{R1} = 5.79 min, *m/z* = 227 (30 %), 184 (100 %), 117 (5 %), 104 (14 %), 78 (9 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.11 (m, 2H, H-8, H-10), 6.55 (d, $^3J_{HH}$ = 9.0 Hz, 1H, H-7), 3.60 (s, 2H, NH_2), 2.33 (d, $^3J_{HH}$ = 7.2 Hz, 2H, H-4), 1.91 (hept, $^3J_{HH}$ = 6.7 Hz, 1H, H-3), 0.95 (d, $^3J_{HH}$ = 6.6 Hz, 6H, H-1; H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 143.6 (C_q, C-6), 133.2 (C-10), 129.7 (C-8), 128.2 (C_q, C-5), 117.3 (C-7), 110.4 (C_q, C-9), 40.8 (C4), 27.9 (C3), 22.8 (C-1, C-2) ppm.

HRMS (DI-EI TOF): calcd. for $C_{10}H_{14}BrN^+$ $[M]^+$: 227.0310; found: 226.9697.

7.4.2.10. 1-Bromo-4-iodo-2-isobutylbenzene (20)



20

In a 50 mL one-neck round-bottom flask 97 mg (425 µmol, 1.00 eq) 4-iodo-2-isopropylaniline (**19**) were suspended in 550 µL H_2O and cooled to 0 °C in an ice bath. 300 µL conc. HCl were added dropwise. Then a cooled solution of 50 mg $NaNO_2$ in 330 µL H_2O was added at 0 °C and the suspension was stirred at 0 °C. After 1 h a cooled solution of 138 mg KI in 550 µL H_2O was added dropwise at 0 °C. The red-brown suspension was stirred at RT for 16 h. After full conversion of the starting material was indicated by GC-MS, the reaction was diluted with 10 mL CH_2Cl_2 and washed with $NaHSO_3$ solution (3 x 10 mL). The combined aqueous layers were reextracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The red/brown oil was purified via flash column chromatography (10 g SiO_2, 2.0 x 6.5 cm, eluent: cyclohexane, R_f = 0.76, UV and $KMnO_4$, fraction size: 3 mL). Fractions 2 to 4 were combined and the solvent was removed under reduced pressure.

Yield: 111 mg (327 µmol, 77 %), yellow oil

$C_{10}H_{12}BrI$ [339.01 g/mol]

TLC: R_f = 0.76 (cyclohexane, UV and $KMnO_4$)

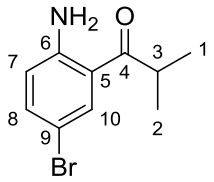
GC-MS (Method_1): t_{R1} = 5.91 min, *m/z* = 338 (100%), 296 (93 %), 217 (19 %), 171 (32 %), 115 (23 %), 89 (51 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.65 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-7), 7.28 (d, $^3J_{HH}$ = 2.1 Hz, 1H, H-10), 7.01 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 2.2 Hz, 1H, H-8), 2.55 (d, $^3J_{HH}$ = 7.2 Hz, 2H, H-4), 1.96 (hept, $^3J_{HH}$ = 6.7, 1H, H-3), 0.95 (d, $^3J_{HH}$ = 6.6 Hz, 6H, H-, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 146.6 (C_q, C-5), 140.9 (C-7), 133.2 (C-10), 130.8 (C-8), 122.4 (C_q, C-9), 99.2 (C_q, C-6), 49.4 (C-4), 29.1 (C-3), 22.3 (C-1, C-2) ppm.

HRMS (DI-EI TOF): calcd. for $C_{10}H_{12}BrI^+$ $[M]^+$: 337.9167; found: 337.9179.

7.4.2.11. 1-(2-Amino-5-bromophenyl)-2-methylpropan-1-one (24)



24

In a 50 mL one-neck round-bottom flask 14.3 mg (186 µmol, 0.10 eq) NH_4OAc were dissolved in 15 mL MeCN. 300 mg (1.84 mmol, 1.00 eq) 1-(2-aminophenyl)-2-methylpropan-1-one (**22**) and 344 mg (1.93 mmol, 1.05 eq) NBS were added. The red suspension was stirred at RT for 10 min. After full conversion was detected by GC-MS the solvent was removed under reduced pressure. Then the residue was diluted with 15 mL CH_2Cl_2 and washed with $NaHSO_3$ solution (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The black oil was purified via flash column chromatography (50 g SiO_2, 2.5 x 12.0 cm, eluent: cyclohexane/EtOAc = 20/1, fraction size: 20 mL).

Yield: 398 mg (1.64 mmol, 89 %), yellow solid

$C_{10}H_{12}BrNO$ [241.01 g/mol]

TLC: R_f = 0.33 (cyclohexane/EtOAc = 9/1, UV and $KMnO_4$)

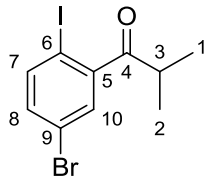
GC-MS (Method_1): t_R = 6.09 min, *m/z* =.241 (34 %), 198 (100 %), 170 (22 %), 145 (9 %), 91 (14 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.84 (d, $^3J_{HH}$ = 2.0 Hz, 1H, H-10), 7.31 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 2.2 Hz, 1H, H-8), 6.56 (d, $^3J_{HH}$ = 8.8 Hz, 1H, H-7), 6.31 (bs, 2H, NH_2), 3.50 (hept, $^3J_{HH}$ = 6.6 Hz, 1H, H-3), 1.20 (d, $^3J_{HH}$ = 6.8 Hz, 6H, H-1, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 206.2 (C_q, C-4), 149.8 (C_q, C-6), 136.8 (C-10), 133.3 (C-8), 119.4 (C-7), 118.2 (C_q, C-5), 106.9 (C_q, C-9), 35.5 (C-3), 19.7 (C-1, C-2) ppm.

HRMS (DI-EI TOF): calcd. for $C_{10}H_{12}BrNO^+$ $[M]^+$: 241.0102; found: 241.0102.

7.4.2.12. 1-(5-Bromo-2-iodophenyl)-2-methylpropan-1-one (25)



25

In a 50 mL one-neck round-bottom flask 372 mg (1.54 mmol, 1.00 eq) 1-(2-amino-5-bromophenyl)-2-methylpropan-1-one (**24**) were dissolved in 1.75 mL H_2O and cooled to 0 °C. 1.00 mL conc. HCl was added dropwise. Then a cooled solution of 181 mg (2.62 mmol, 1.71 eq) $NaNO_2$ in 1.20 mL H_2O was added at 0 °C and the suspension was stirred at 0 °C. After 1 h an ice cold solution of 498 mg (3.00 mmol, 1.95 eq) KI in 2.00 mL H_2O was added dropwise at 0 °C. The red-brown suspension was stirred at RT for 16 h. After full conversion of the starting material was indicated by GC-MS, the reaction was diluted with 20 mL CH_2Cl_2 and washed with $NaHSO_3$ solution (1 x 30 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The red/brown oil was purified via flash column chromatography (50 g SiO_2, 2.5 x 12.5 cm, eluent: cyclohexane/EtOAc = 75/1, fraction size: 20 mL).

Yield: 365 mg (1.03 mmol, 67 %), yellow/orange oil

$C_{10}H_{10}BrIO$ [351.90 g/mol]

TLC: R_f = 0.29 (cyclohexane/EtOAc = 75/1, UV and $KMnO_4$)

GC-MS (Method_1): t_R = 6.32 min, *m/z* = 352 (19 %), 309 (100 %), 283 (21 %), 185 (8 %), 154 (10 %), 75 (17 %).

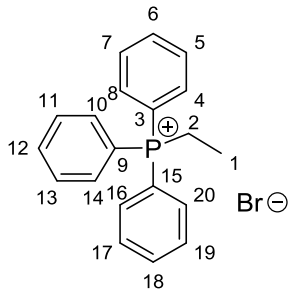
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.73 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-7), 7.36 (d, $^3J_{HH}$ = 2.2 Hz, 1H, H-10), 7.24 (dd, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 2.3 Hz, 1H, H-8), 3.27 (hept, $^3J_{HH}$ = 6.9 Hz, 1H, H-3), 1.21 (d, $^3J_{HH}$ = 6.9 Hz, 6H, H-1, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 207.7 (C_q, C-4), 147.2 (C_q, C-5), 141.6 (C-7), 134.3 (C-8), 130.6 (C-10), 122.6 (C_q, C-9), 89.4 (C_q, C-6), 39.8 (C-3), 18.2 (C-1, C-2) ppm.

HRMS (DI-EI TOF): calcd. for $C_{10}H_{10}BrIO^+$ $[M]^+$: 351.8960; found: 351.8948.

7.4.3. Synthesis of the Isoleucine building block

7.4.3.1. Ethyltriphenylphosphonium bromide (29)



29

In a flame dried 250 mL Schlenk-flask 10.0 g (38.1 mmol, 1.20 eq) triphenylphosphine were dissolved in 40 mL abs. toluene. Then 3.4 mL (45.7 mmol, 1.00 eq) bromoethane were added and the colorless solution was stirred at 115 °C. After 40 h the reaction mixture was allowed to cool to RT, and the resulting colorless solid collected by filtration and washed with toluene (3 x 20 mL). After drying in vacuum of the filter cake, compound **29** was isolated as a colorless powder.

Yield: 10.57 g (28.6 mmol, 75 %), colorless solid

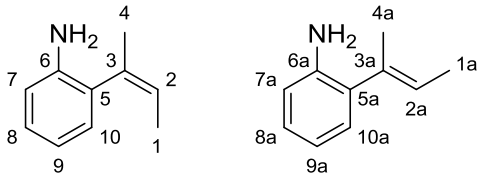
$C_{20}H_{20}BrP$ [370.05 g/mol]

mp$^{exp.}$ = 195-198 °C (**mp**^{lit} = 206 – 208 °C)[138]

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.93 – 7.42 (m, 15H, H-4, H-5, H-6, H-7, H-8, H-10, H-11, H-12, H-13, H-14, H-16, H-17, H-18, H-19, H-20), 3.79 (dq, $^{2}J_{HP}$ = 14.8 Hz, $^{3}J_{HH}$ = 7.4 Hz, 2H, H-2), 1.35 (dt, $^{3}J_{HP}$ = 20.0 Hz, $^{3}J_{HH}$ = 7.4 Hz, 3H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 135.1 (d, $^{4}J_{CP}$ = 2.9 Hz, C-6, C-12, C-18), 133.7 (d, $^{3}J_{CP}$ = 9.9 Hz, C-5, C-7, C-11, C-13, C-17, C-19), 130.6 (d, $^{2}J_{CP}$ = 12.5 Hz, C-4, C-8, C-10, C-14, C-16, C-20), 118.1 (d, $^{1}J_{CP}$ = 85.8 Hz, C-3, C-9, C-15), 17.2 (d, $^{1}J_{CP}$ = 51.7 Hz, C-2), 6.91 (d, $^{2}J_{CP}$ = 5.2 Hz, C-1) ppm.

7.4.3.2. 2-(But-2-en-2-yl)aniline (31)



31

In a flame dried 50 mL Schlenk-flask 1.64 mg (4.43 mmol, 1.20 eq) ethyltriphenyl-phosphonium bromide (**29**) were suspended in 9 mL THF. 498 mg (4.43 mmol, 1.20 eq) KO*t*Bu were added and the suspension became first yellow and then orange. The suspension was stirred for 1.5 h at RT. In the meanwhile another flame dried 8 mL Schlenk-flask was charged with 447 µL (3.70 mmol, 1.00 eq) 1-(2-aminophenyl)ethane-1-one (**30**) and diluted with 5 mL absolute THF. The 1-(2-aminophenyl)ethane-1-one solution was added via syringe and the suspension turned yellowish. The suspension was stirred at RT overnight. After full conversion of the starting material was indicated by TLC the solvent was removed under reduced pressure. The yellowish oil was purified via flash column chromatography (250 g SiO_2, 6.5 x 18.5 cm, eluent: cyclohexane/EtOAc = 30/1, fraction size: 150 mL).

Yield: 274 mg (1.86 mmol, 50 %), *E/Z* mixture = 3/1, yellow oil

$C_{10}H_{13}N$ [147.10 g/mol]

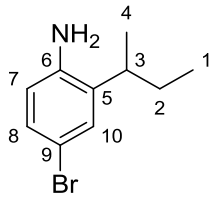
TLC: R_f = 0.31 and 0.33 (cyclohexane/EtOAc = 10/1, UV and $KMnO_4$)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.13 – 6.87 (m, 4H, H-9, H-9a, H-10, H-10a), 6.74 (m, 4H, H-7, H-7a, H-8, H-8a), 5.66 (m, 1H, H-2), 5.56 (m, 1H, H-2a), 3.64 (s, 4H, NH_2), 1.96 (m, 6H, H-4, H-4a), 1.78 (d, $^3J_{HH}$ = 6.7 Hz, 3H, H-1a), 1.47 (m, 3H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 143.2 (C_q, C-6a), 142.9 (C_q, C-6), 134.6 (C_q, C-5), 134.5 (C_q, C-5a), 131.9 (C_q, C-3), 128.9 (C-10a), 128.8 (C-10), 127.8 (C-9), 127.7 (C_q, C-3a), 127.6 (C-9a), 124.8 (C-2a), 123.6 (C-2), 118.5 (C-8), 118.4 (C-8a), 115.5 (C-7a), 115.1 (C-7), 24.7 (C-4), 17.2 (C-4a), 14.7 (C-1), 14.0 (C-1a) ppm.

HRMS (DI-EI TOF): calcd. for $C_{10}H_{13}N^+$ $[M]^+$: 147.1048; found: 147.1042.

7.4.3.3. 4-Bromo-2-(sec-butyl)aniline (33)



33

In a 50 mL one-neck round-bottom flask 26 mg (337 µmol, 0.10 eq) NH_4OAc were dissolved in 15 mL MeCN. 531 µL (3.35 mmol, 1.00 eq) 2-*sec*-butylaniline (**35**) and 626 mg (352 mmol, 1.05 eq) NBS were added. The red suspension was stirred at RT for 10 min. After full conversion was indicated by GC-MS the reaction was diluted with 20 mL EtOAc and washed with $NaHSO_3$ solution (3 x 20 mL). The combined aqueous layers were reextracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The red brown oil was purified via flash column chromatography (220 g SiO_2, 6.5 x 15.0 cm, eluent: cyclohexane/EtOAc = 10/1, R_f = 0.27, UV and $KMnO_4$, fraction size: 70 mL).

Yield: 627 mg (2.76 mmol, 82 %), darkred oil

$C_{10}H_{14}BrN$ [227.03 g/mol]

TLC: R_f = 0.27 (cyclohexane/EtOAc = 10/1, UV and $KMnO_4$)

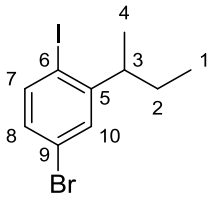
GC-MS (Method_1): t_R = 5.80 min, *m/z* = 227 (39 %), 198 (100 %), 184 (9 %), 119 (32 %), 91 (11 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.17 (d, $^3J_{HH}$ = 2.1 Hz, 1H, H-10), 7.09 (dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2.1 Hz, 1H, H-8), 6.56 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-7), 3.63 (s, 2H, NH_2), 2.59 (hex,$^3J_{HH}$ = 6.8 Hz, 1H, H-4), 1.61 (m, 2H, H-2), 1.23 (d, $^3J_{HH}$ = 6.8 Hz, 3H, H-3), 0.90 (t, $^3J_{HH}$ = 7.4 Hz, 3H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 142.9 (C_q, C-6), 134.1 (C_q, C-5), 129.3 (C-10), 129.2 (C-8), 117.6 (C-7), 111.1 (C_q, C-9), 34.9 (C-4), 29.5 (C-2), 20.1 (C-3), 12.3 (C-1) ppm.

HRMS (DI-EI TOF): calcd. for $C_{10}H_{14}BrN^+$ $[M]^+$: 227.0310; found: 227.0311.

7.4.3.4. 4-Bromo-2-(sec-butyl)-1-iodobenzene (34)



34

In a 100 mL one-neck round-bottom flask 750 mg (3.29 mmol, 1.00 eq) 4-iodo-2-isopropylaniline (**33**) were suspended in 3.5 mL H_2O and cooled to 0 °C. 2.0 mL conc. HCl were added dropwise. Then a cooled solution of 386 mg (5.59 mmol, 1.70 eq) $NaNO_2$ in 2.5 mL H_2O was added at 0 °C and the suspension was stirred at 0 °C. After 1 h a solution of 1.06 g KI in 4.3 mL H_2O was added dropwise at 0 °C. The brown suspension was stirred at RT for 16 h. After full conversion of the starting material was indicated by GC-MS, the reaction was diluted with 30 mL EtOAc and washed with $NaHSO_3$ solution (3 x 20 mL). The combined aqueous layers were reextracted with EtOAc (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The brown oil was purified via flash column chromatography (100 g SiO_2, 4.0 x 12.5 cm, eluent: cyclohexane, fraction size: 60 mL).

Yield: 637 mg (1.97 mmol, 73 %), brown oil

$C_{10}H_{12}BrI$ [339.01 g/mol]

TLC: R_f = 0.79 (cyclohexane, UV and $KMnO_4$)

GC-MS (Method_1): t_R = 5.88 min, *m/z* = 340 (60 %), 311 (100 %), 182 (40 %), 102 (26 %), 77 (22 %).

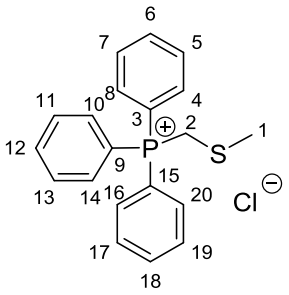
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.46 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-7), 7.06 (d, $^3J_{HH}$ = 2.2 Hz, 1H, H-9), 6.80 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 2.2 Hz, 1H, H-8), 2.73 (hex, $^3J_{HH}$ = 6.9 Hz, 1H, H-3), 1.37 (m, 2H, H-2), 0.98 (d, $^3J_{HH}$ = 6.8 Hz, 3H, H-4), 0.68 (t, $^3J_{HH}$ = 7.3 Hz, 3H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 152.0 (C_q, C-5), 140.8 (C-7), 130.9 (C-8), 129.8 (C-10), 123.1 (C_q, C-9), 99.9 (C_q, C-6), 45.1 (C-3), 30.5 (C-2), 20.9 (C-4), 12.1 (C-1) ppm.

HRMS (DI-EI TOF): calcd. for $C_{10}H_{12}BrI^+$ $[M]^+$: 337.9167; found: 337.9183.

7.4.4. Synthesis of the Methionine building block

7.4.4.1. 2-Bromo-5-iodobenzoyl chloride (37)



37

In a flame dried 250 mL Schlenk-flask 20.01 g (76.3 mmol, 1.00 eq) triphenylphosphine were dissolved in 40 mL toluene. Then 6.40 mL (77.5 mmol, 1.02 eq) chloromethyl-methylsulfide were added via a syringe. The colorless solution was stirred at 100 °C and after 2 h a colorless precipitate was formed. After 24 h the colorless suspension was cooled to 0 °C and the precipitate was collected by filtration and washed with cold toluene (3 x 15 mL). After drying of the filter cake in vacuum, compound **37** was isolated as a colorless powder.

Yield: 17.04 g (47.5 mmol, 92 %), colorless powder

$C_{20}H_{20}ClPS$ [358.86 g/mol]

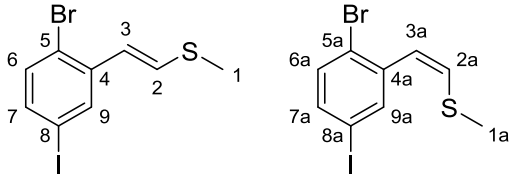
mp$^{exp.}$ = 209 - 217 °C (**mp**^{lit} = 220 – 222 °C)[139]

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.92 – 7.85 (m, 6H, H-5, H-7, H-11, H-13, H-17, H-19), 7.75 – 7.70 (m, 3H, H-6, H-12, H-18), 7.67 – 7.52 (m, 6H, H-4, H-8, H-10, H-14, H-16, H-20), 5.26 (d, $^{2}J_{HP}$ = 8.3 Hz, 2H, H-2), 2.11 (s, 3H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 135.0 (d, $^{4}J_{CP}$ = 2.9 Hz, C-6, C-12, C-18), 134.2 (d, $^{3}J_{CP}$ = 9.9 Hz, C-5, C-7, C-11, C-13, C-17, C-19), 130.21 (d, $^{2}J_{CP}$ = 12.6 Hz, C-4, C-8, C-10, C-14, C-16, C-20), 118.2 (d, $^{1}J_{CP}$ = 86.9 Hz, C-3, C-9, C-15), 25.8 (d, $^{1}J_{CP}$ = 51.8 Hz, C-2), 18.1 (d, $^{2}J_{CP}$ = 3.2 Hz, C-1) ppm.

Analytical data are in accordance with those reported.[140]

7.4.4.2. (2-Bromo-5-iodostyryl)(methyl)sulfane (38)



38

In a flame dried 100 mL Schlenk-tube 1.30 g (3.62 mmol, 1.50 eq) phosphonium-salt **37** were suspended in 15 mL abs. THF. Then the colorless suspension was cooled to -78 °C in a dry ice/acetone bath. Afterwards 1.5 mL (2.5M in hexane, 3.75 mmol, 1.50 eq) *n*-BuLi were added dropwise via a syringe. The dark red suspension was stirred at -78 °C for 1 h. In the meanwhile in another flame dried Schlenk-flask 751 mg (2.42 mmol, 1.00 eq) 2-bromo-5-iodobenzaldehyde (**10**) were dissolved in 5 mL abs. THF. Then the aldehyde solution was added via syringe to the ylide at -78 °C. After 20 min the reaction mixture became a light orange suspension and was stirred overnight (16 h) at RT until complete conversion was indicated by TLC. The orange suspension was quenched by the addition of 20 mL satd NH_4Cl-solution. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The yellow crude product was purified via column chromatography (125 g SiO_2, 4.5 x 8.5 cm, eluent: cyclohexane, fraction size: 50 mL).

Yield: 646 mg (1.82 mmol, 75 %), *E*/*Z* mixture = 1/1.4, colorless solid

C_9H_8BrIS [355.03 g/mol]

TLC: R_f = 0.58 and 0.62 (cyclohexane, UV and $KMnO_4$)

mp$^{exp.}$ = 35 - 40 °C

GC-MS (Method_1): t_{R1} = 6.89 min, t_{R2} = 7.04 min, *m/z* = 354 (15 %), 275 (100 %), 212 (8 %), 148 (65 %), 89 (19 %).

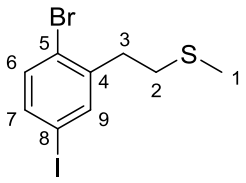
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.98 (d, $^3J_{HH}$ = 1.9 Hz, 1H, H-9), 7.73 (d, $^3J_{HH}$ = 1.9 Hz, 1H, H-9a), 7.42 – 7.17 (m, 4H, H-6, H-6a, H-7, H-7a), 6.82 (d, $^3J_{HH}$ = 15.3 Hz, 1H, H-3), 6.58 – 6.34 (m, 3H, H-2, H-2a, H-3a), 2.42 (s, 3H, H-1a), 2.40 (s, 3H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 139.1 (C_q, C-4), 138.4 (C_q, C-4a), 138.2 (C-9), 137.1 (C-7), 136.6 (C-7a), 135.0 (C-9a), 134.6 (C-6a), 134.4 (C-6), 133.1 (C-2), 131.0 (C-3), 123.7 (C_q,

C-5), 123.1 (C-2a), 122.3 (C_q, C-5a), 121.5 (C-3a), 92.8 (C_q, C-8), 92.1 (C_q, C-8a), 18.6 (C-1), 14.9 (C-1a) ppm.

HRMS (DI-EI TOF): calcd. for $C_9H_8BrIS^+$ $[M]^+$: 353.8575; found: 353.8580.

7.4.4.3. (2-Bromo-5-iodophenethyl)(methyl)sulfane (39)



39

In a 10 mL one-neck round-bottom flask 131 mg (368 µmol, 1.00 eq) (2-bromo-5-iodostyryl)(methyl)sulfane (**38**) were dissolved in 3 mL THF. Then 685 mg (3.68 mmol, 10.0 eq) p-tosylhydrazide, 181 mg (2.21 mmol, 6.00 eq) NaOAc and 40 µL (2.21 mmol, 6.00 eq) H_2O were added. The yellowish suspension was stirred at 70 °C until 83 % conversion was achieved (4 d). The orange suspension was distributed between satd. $NaHCO_3$-solution and CH_2Cl_2. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The yellow crude product was purified via flash column chromatography (25 g SiO_2, 2.5 x 8.5 cm, eluent: cyclohexane/EtOAc = 100:1, fraction size: 8 mL). Another flash column chromatography for purification had to be done (13 g SiO_2, 2.0 x 7.5 cm, eluent: cyclohexane/toluene = 100:1, fraction size: 5 mL) to produce pure product.

Yield: 57.2 mg (160 µmol, 44 %), colorless solid

$C_9H_{10}BrIS$ [357.05 g/mol]

TLC: R_f = 0.48 and 0.62 (cyclohexane/toluene = 100/1, UV and $KMnO_4$)

mp$^{exp.}$ = 43 - 45 °C

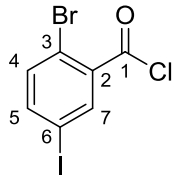
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.57 (d, $^4J_{HH}$ = 1.7 Hz, 1H, H-9), 7.39 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.7 Hz, 1H, H-7), 7.24 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-6), 3.00 – 2.91 (m, 2H, H-3), 2.73 (m, 2H, H-2), 2.16 (s, 3H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 142.2 (C_q, C-4), 139.5 (C-9), 137.2 (C-7), 134.6 (C-6), 124.3 (C_q, C-5), 92.7 (C_q, C-8), 36.1 (C-3), 33.8 (C-2), 15.8 (C-1) ppm.

HRMS (DI-EI TOF): calcd. for $C_9H_{10}BrIS^+$ $[M]^+$: 355.8731; found: 355.8674.

7.4.5. Synthesis of the Phenylalanine building block

7.4.5.1. 2-Bromo-5-iodobenzoyl chloride (41)



41

This compound was prepared according to the literature.[124]

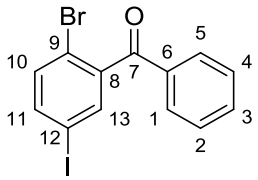
In a 100 mL one-neck round-bottom flask with Schlenk adapter 2.00 g (6.12 mmol, 1.00 eq) 2-bromo-5-iodobenzoic acid (**40**) were suspended in 25 mL CH_2Cl_2. The brown suspension was cooled to 0 °C. Then 790 µL (9.21 mmol, 1.51 eq) oxalylchloride were slowly added via a syringe. 0.2 mL DMF were added and the brown suspension was stirred at 0 °C for 20 min. Afterwards the suspension was allowed to warm up to RT. After full conversion of the starting material was indicated by GC-MS (16 h) the solvent was removed under high vacuum using a cooling trap. The crude product was used without further purification in the next step.

Yield: 2.33 g (6.75 mmol, 110 %), brown solid

C_7H_3BrClO [343.81 g/mol]

mp$^{exp.}$ = 57 - 59°C

7.4.5.2. (2-Bromo-5-iodophenyl)(phenyl)methanone (42)



42

This compound was prepared similar to the literature.[124]

In a flame dried 8 mL Schlenk-flask 300 mg (869 µmol, 1.00 eq) 2-bromo-5-iodobenzoyl chloride (**41**) were dissolved in 1 mL benzene. The orange/brown solution was cooled to 0 °C in an ice bath. Then 117 mg (878 µmol, 1.21 eq) $AlCl_3$ were added slowly over 5 min and the red/brown suspension was stirred at 0 °C for 20 min. Afterwards the suspension was allowed to warm up to RT. After full conversion of the starting material was indicated by TLC and GC-MS (16 h) the reaction mixture was poured onto ice. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The yellow oil was purified via flash column chromatography (25 g SiO_2, 2.5 x 9.0 cm, eluent: cyclohexane/EtOAc = 30/1, fraction size: 8 mL).

Yield: 225 mg (582 µmol, 67 %), brown solid

$C_{13}H_8BrIO$ [387.01 g/mol]

TLC: R_f = 0.59 (cyclohexane/EtoAc = 9/1), UV and $KMnO_4$)

mp$^{exp.}$ = 90 - 95°C

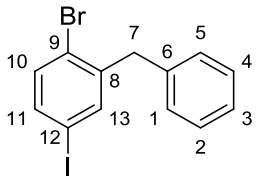
GC-MS (Method_1): t_R = 7.49 min, *m/z* = 386 (20 %), 309 (8 %), 281 (5 %), 154 (7 %), 105 (100 %), 77 (48 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.80 (d, $^3J_{HH}$ = 7.2 Hz, 2H, H-1, H-5), 7.65 (m, 3H, H-3, H-11, H-13), 7.49 (t, $^3J_{HH}$ = 7.6 Hz, 2H, H-2, H-4), 7.37 (d, $^3J_{HH}$ = 8.1 Hz, 1H, H-10) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 194.2 (C_q, C-7), 142.8 (C_q, C-8), 140.2 (C-11), 137.5 (C-13), 135.7 (C_q, C-6), 134.9 (C-10), 134.2 (C-3), 130.4 (C-1, C-5), 128.9 (C-2, C-4), 119.4 (C_q, C-9), 92.3 (C_q, C-12) ppm.

HRMS (DI-EI TOF): calcd. for $C_{13}H_8BrIO^+$ $[M]^+$: 385.8803; found: 385.8813.

7.4.5.3. 2-Benzyl-1-bromo-4-iodobenzene (43)



43

This compound was prepared similar to the literature.[124]

In a 8 mL Schlenk-flask 100 mg (258 µmol, 1.00 eq) ((2-bromo-5-iodophenyl)-(phenyl)methanone (**42**) and 170 µL (1.06 mmol, 4.12 eq) Et_3SiH were dissolved in 1.5 mL CH_3CN/CH_2Cl_2 (2/1). The colorless suspension was cooled to 0 °C. Then 390 µL (3.16 µmol, 12.23 eq) $BF_3{\cdot}Et_2O$ were slowly added via a syringe. The red suspension was stirred at 50 °C overnight. After full conversion (96 h) of the starting material was indicated by GC-MS the solution was quenched by the addition of 10 mL conc. KOH solution, the phases were separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The orange oil was purified via flash chromatography (10 g SiO_2, eluent: cyclohexane, R_f = 0.16, UV and $KMnO_4$, fraction size: 15 mL).

Yield: 20.6 mg (55.2 µmol, 21 %), colorless oil

$C_{13}H_{10}BrI$ [373.03g/mol]

TLC: R_f = 0.69 (cyclohexane, UV and $KMnO_4$)

GC-MS (Method_1): t_R = 7.14 min, *m/z* = 372 (37 %), 293 (9 %), 166 (100 %), 139 (9 %), 82 (9 %).

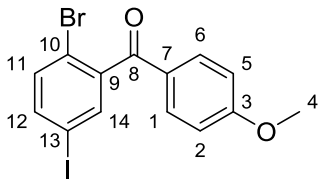
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.45 (d, $^4J_{HH}$ = 1.7 Hz, 1H, H-13), 7.39 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.9 Hz, 1H), 7.35 – 7.13 (m, 6H, H1, H-2, H-3, H-4, H-5, H-10), 4.05 (s, 3H, H-7) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 142.9 (C_q, C-8), 139.9 (C-13), 138.8 (C_q, C-6), 137.1 (C-11), 134.6 (C-10), 129.1 (C-1, C-5), 128.8 (C-2, C-4), 126.7 (C-3), 124.9 (C_q, C-9), 92.8 (C_q, C-12), 41.6 (C-7) ppm.

HRMS (DI-EI TOF): calcd. for $C_{13}H_{10}BrI^+$ $[M]^+$: 371.9011; found: 371.9024.

7.4.6. Synthesis of the Tyrosine building block

7.4.6.1. (2-Bromo-5-iodophenyl)(4-methoxyphenyl)methanone (45)



45

This compound was prepared according to the literature.[124]

In a flame dried 8 mL Schlenk-flask 100 mg (290 mmol, 1.00 eq) 2-bromo-5-iodobenzoyl chloride (**41**) were suspended in 1 mL CH_2Cl_2. The red-brown suspension was cooled to 0 °C. Then 31.3 µL (287 µmol, 0.99 eq) anisole were slowly added via a syringe. 47.0 mg (348 µmol, 1.20 eq) $AlCl_3$ were added slowly over 10 min and the brown suspension was stirred at 0 °C for 20 min. Afterwards the suspension was allowed to warm up to RT. After full conversion of the starting material was indicated by GC-MS (16 h) the reaction mixture was poured onto ice. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The red-brown oil was purified via flash column chromatography (13 g SiO_2, 2.0 x 7.0 cm, eluent: cyclohexane/EtOAc = 30/1, fraction size: 5 mL).

Yield: 94.2 mg (226 µmol, 78 %), colorless solid

$C_{14}H_{10}BrIO_2$ [417.04 g/mol]

mp$^{exp.}$ = 114 - 118 °C

TLC: R_f = 0.17 (cyclohexane/EtOAc = 30/1, UV and $KMnO_4$)

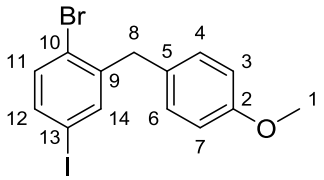
GC-MS (Method_1): t_R = 8.34 min, *m/z* = 416 (48 %), 311 (5 %), 281 (5 %), 135 (100 %), 77 (12 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.77 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H-1, H-6), 7.69 – 7.57 (m, 2H, H-12, H-14), 7.36 (d, $^3J_{HH}$ = 8.0 Hz, 1H, H-11), 6.95 (d, $^3J_{HH}$ = 8.8 Hz, 2H, H-2, H-5), 3.89 (s, 3H, H-4) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 192.8 (C_q, C-8), 164.5 (C_q, C-3), 143.2 (C_q, C-9), 139.9 (C-12), 137.3 (C-14), 134.8 (C-11), 132.8 (C-2, C-5), 128.7 (C_q, C-7), 119.4 (C_q, C-10), 114.2 (C-1, C-6), 92.3 (C_q, C-13), 55.7 (C-4) ppm.

HRMS (DI-EI TOF): calcd. for $C_{14}H_{10}BrIO_2^+$ $[M]^+$: 415.8909; found: 415.8912.

7.4.6.2. 1-Bromo-4-iodo-2-(4-methoxybenzyl)benzene (46)



46

This compound was prepared according to the literature.[124]

In a 8 mL Schlenk-flask 200 mg (480 µmol, 1.00 eq) (2-bromo-5-iodophenyl)(4-methoxyphenyl)methanone (**45**) and 310 µL (1.94 mmol, 4.05 eq) Et_3SiH were dissolved in 1.8 mL CH_3CN/CH_2Cl_2 (2/1). The colorless suspension was cooled to 0 °C. Then 90 µL (729 µmol, 1.52 eq) $BF_3{\cdot}Et_2O$ were slowly added via a syringe. The pink suspension was stirred at RT overnight. After full conversion (16 h) of the starting material was indicated by GC-MS the solution was quenched by the addition of 10 mL conc. KOH solution, the phases were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The orange oil was purified via flash chromatography (30 g SiO_2, eluent: cyclohexane (fraction 1 – fraction 42), cyclohexane/EtOAc = 100/1 (fraction 43 – fraction 55), R_f = 0.16, UV and $KMnO_4$, fraction size: 15 mL).

Yield: 185 mg (459 µmol, 96 %), colorless solid

$C_{14}H_{12}BrIO$ [403.06 g/mol]

TLC: R_f = 0.16 (cyclohexane, UV and $KMnO_4$)

mp$^{exp.}$ = 120 - 123 °C

GC-MS (Method_1): t_R = 7.79 min, *m/z* = 402 (100 %), 323 (20 %), 275 (8 %), 181 (24 %), 152 (46 %), 121 (46 %).

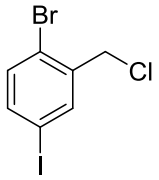
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.35 (d, $^{3}J_{HH}$ = 1.7 Hz, 1H, H-14), 7.31 (dd, $^{3}J_{HH}$ = 8.3 Hz, $^{4}J_{HH}$ = 1.9 Hz, 1H, H-12), 7.19 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H, H-11), 7.02 (d, $^{3}J_{HH}$ = 8.4 Hz, 2H, H-4, H-6), 6.78 (d, J = 8.5 Hz, 2H, H-3, H-7), 3.91 (s, 2H, H-8), 3.72 (s, 4H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 158.4 (C_q, C-2), 143.3 (C_q, C-9), 139.7 (C-14), 137.0 (C-12), 134.6 (C-11), 130.8 (C_q, C-5), 130.1 (C-4, C-6), 124.8 (C_q, C-10), 114.2 (C-3, C-7), 92.8 (C_q, C-13), 55.4 (C-1), 40.7 (C-8) ppm.

HRMS (DI-EI TOF): calcd. for $C_{14}H_{12}BrIO^{+}$ $[M]^{+}$: 401.9116; found: 401.9120.

7.4.7. Synthesis of the Asparagine building block

7.4.7.1. 1-Bromo-2-(chloromethyl)-4-iodobenzene (47)



47

In a 50 mL one-neck round-bottom flask 1.00 g (3.21 mmol, 1.00 eq) 2-bromo-5-iodobenzoylalcohol (**9**) were dissolved in 10 mL CH_2Cl_2. 25 µL (325 µmol, 0.10 eq) DMF were added. Then 500 µL thionylchloride were added slowly and the colorless suspension was stirred at RT. After full conversion was detected by TLC and GC-MS the solvent was removed under high vacuum using a cooling trap. The crude product was used without further purification in the next reaction.

Yield: 1.04 g (3.14 mmol, 98 %), brown solid

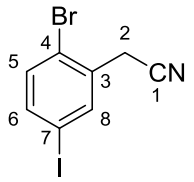
C_7H_5BrICl [329.83 g/mol]

TLC: R_f = 0.70 (cyclohexane/EtOAc = 10/1, UV and CAM)

mp$^{exp.}$ = 79 - 82 °C

GC-MS (Method_1): t_R = 6.03 min, *m/z* = 332 (100 %), 295 (100 %), 168 (16 %), 127 (29 %), 89 (58 %).

7.4.7.2. 2-(2-Bromo-5-iodophenyl)acetonitrile (48)



48

In a 25 mL one-neck round-bottom flask 500 mg (1.51 mmol, 1.00 eq) 1-bromo-2-(chloromethyl)-4-iodobenzene (**47**) were dissolved in 4 mL DMSO. Then 197 mg (3.03 mmol, 2.01 eq) KCN and 26 mg (157 µmol, 0.01 eq) KI were added. The reaction was stirred at RT overnight. After full conversion (16 h) was detected by GC-MS the reaction was diluted with 15 mL H_2O and extraced with EtOAc. The phases were separated and the organic phase was washed with H_2O (3 x 20 mL). The organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The light yellow solid was purified via flash column chromatography (40 g SiO_2, 4.0 x 9.5 cm, eluent: cyclohexane/EtOAc = 50/1, (fractions 1 – 30), cyclohexane/EtOAc = 30/1 (fractions 31 – 42), R_f = 0.11, UV and $KMnO_4$, fraction size: 25 mL).

Yield: 345 mg (1.49 mmol, 71 %), yellowish solid

C_8H_5BrIN [320.87 g/mol]

mp$^{exp.}$ = 87 – 91 °C

TLC: R_f = 0.32 (cyclohexane/EtOAc = 20/1, UV and $KMnO_4$)

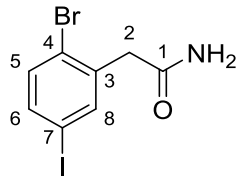
GC-MS (Method_1): t_R = 6.37 min, *m/z* = 321 (100 %), 242 (26 %), 194 (30 %), 167 (5 %), 115 (54 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.84 (s, 1H, H-8), 7.54 (d, ^{c}= 8.4 Hz, 1H, H-6), 7.32 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H-5), 3.79 (s, 2H, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 139.2 (C-6), 138.5 (C-8), 134.7 (C-5), 132.2 (C_q, C-3), 123.5 (C_q, C-4), 116.4 (C_q, C-1), 93.0 (C_q, C-7), 24.6 (C-2) ppm.

HRMS (DI-EI TOF): calcd. for $C_8H_5BrIN^+$ $[M]^+$: 320.8650; found: 320.8663.

7.4.7.3. 2-(2-Bromo-5-iodophenyl)acetamide (49)



49

In a 50 mL one-neck round-bottom flask 739 mg (2.30 mmol, 1.00 eq) 2-bromo-5-iodophenylacetonitrile (**48**) were suspended in 13 mL *tert*-butanol. Then 515 mg (9.18 mmol, 3.99 eq) fine powdered KOH were added. The yellow suspension was stirred at 80 °C. After full conversion of the starting material was indicated by TLC, the reaction was quenched by the addition of 50 mL dist H_2O. The aqueous phase was extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The brown solid was purified via flash column chromatography (60 g SiO_2, 3.0 x 23.0 cm, eluent: cyclohexane/EtOAc = 1/1, R_f = 0.20, UV and CAM, fraction size: 70 mL).

Yield: 395 mg (1.72 mmol, 51 %), colorless solid

C_8H_7BrINO [339.96 g/mol]

TLC: R_f = 0.20 (cyclohexane/EtOAc = 1/1, UV and CAM)

mp$^{exp.}$ = 176 - 182 °C

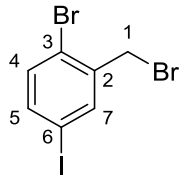
^{1}H-NMR (300.36 MHz, DMSO d_6): δ = 7.71 (d, $^3J_{HH}$ = 1.7 Hz, 1H, H-8), 7.51 (dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, H-6), 7.36 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H-5), 7.01 (s, 2H, NH_2), 3.54 (s, 2H, H-2) ppm.

^{13}C-NMR (75.53 MHz, DMSO d_6): δ = 170.4 (C_q, C-1), 140.3 (C-8), 138.7 (C_q, C-3), 137.1 (C-6), 134.1 (C-5), 124.5 (C_q, C-4), 93.2 (C_q, C-7), 41.5 (C-2) ppm.

HRMS (DI-EI TOF): calcd. for $C_8H_5BrIN^+$ $[M\text{-}H_2O]^+$: 320.8650; found: 320.8563.

7.4.8. Synthesis of the Cysteine building block

7.4.8.1. 1-Bromo-2-(bromomethyl)-4-iodobenzene (50)



50

In a flame dried 100 mL Schlenk-flask 1.00 g (3.20 mmol, 1.00 eq) 2-bromo-5-iodobenzylalcohol (**9**) was dissolved in 16 mL Et_2O. The colorless solution was cooled to 0 °C in an ice bath. Then 335 µL (3.52 µmol, 1.10 eq) PBr_3 were added via a syringe. The solution was stirred at RT. After full conversion (3 h) was indicated by GC-MS, the solution was cooled to 0 °C and 20 mL H_2O were slowly added. The phases were separated and the aqueous phase was extracted with Et_2O (2 x 50 mL). Then the combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The colorless crude product was purified via flash column chromatography (120 g SiO_2, 5.0 x 15.0 cm, eluent: cyclohexane, R_f = 0.48, UV and $KMnO_4$, fraction size: 75 mL).

Yield: 608 mg (1.62 mmol, 51 %), colorless solid

$C_7H_5Br_2I$ [375.83 g/mol]

mp$^{exp.}$ = 101 - 105 °C (**mp**$^{lit.}$ = 112 -114 °C)[141]

TLC: R_f = 0.48 (cyclohexane, UV and $KMnO_4$)

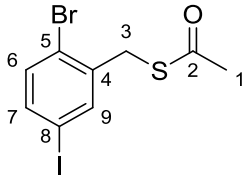
GC-MS (Method_1): t_R = 6.31 min, *m/z* = 376 (21 %), 297 (100 %), 168 (20 %), 127 (12 %), 89 (52 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.77 (d, $^3J_{HH}$ = 1.7 Hz, 1H, H-7), 7.47 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.7 Hz, 1H, H-5), 7.29 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H-4), 4.50 (s, 2H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 140.0 (C-7), 139.3 (C_q, C-2), 139.1 (C-5), 135.0 (C-4), 124.4 (C_q, C-3), 92.6 (C_q, C-6), 32.1 (C-1) ppm.

Analytical data are in accordance with those reported.[142]

7.4.8.2. (2-Bromo-5-iodobenzyl) ethanethioate (51)



51

In an 8 mL Schlenk-flask 200 mg (532 µmol, 1.00 eq) 1-bromo-2-(bromomethyl)-4-iodobenzene (**50**) were dissolved in 2 mL abs THF. Then 162 mg (1.17 mmol, 2.20 eq) K_2CO_3 were added. Afterwards 50 µL (700 µmol, 1.31 eq) thioacetic acid were added via a syringe over 1 min. The yellow suspension was stirred at RT. After full conversion of the starting material was indicated by GC-MS (90 min), the reaction was quenched by the addition of 1 mL HCl (1 M). Then 20 mL H_2O were added and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The yellow solid was purified via flash column chromatography (25 g SiO_2, 2.5 x 8.5 cm, eluent: cyclohexane/toluene = 4/1, fraction size: 8 mL).

Yield: 123 mg (332 µmol, 62 %), colorless solid

C_9H_8BrIOS [371.03 g/mol]

TLC: R_f = 0.72 (toluene, UV and $KMnO_4$)

mp$^{exp.}$ = 65 - 71 °C

GC-MS (Method_1): t_R = 6.89 min, *m/z* = 372 (2 %), 330 (3 %), 291 (100 %), 248 (5 %), 89 (7 %).

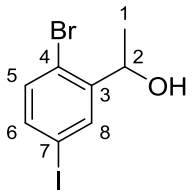
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.75 (d, $^3J_{HH}$ = 1.8 Hz, 1H, H-9), 7.41 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 1.9 Hz, 1H, H-7), 7.24 (d, $^3J_{HH}$ = 6.8 Hz, 1H, H-6), 4.14 (s, 2H, H-3), 2.35 (s, 3H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 194.6 (C_q, C-2), 139.9 (C-9), 139.6 (C_q, C-4), 138.1 (C-7), 134.5 (C-6), 124.5 (C_q, C-5), 92.6 (C_q, C-8), 33.5 (C-3), 30.5 (C-1) ppm.

HRMS (DI-EI TOF): calcd. for $C_9H_8BrIOS^+$ $[M]^+$: 369.8524; found: 369.8538.

7.4.9. Synthesis of the Threonine building block

7.4.9.1. 2-(2-Bromo-5-iodophenyl)acetamide (52)



52

In a 50 mL Schlenk-flask 1.00 g (3.22 mmol, 1.00 eq) 2-bromo-5-iodobenzaldehyde (**10**) was dissolved in 13 mL Et_2O. Then 1.90 mL (3.70 mmol, 1.70 eq) MeMgBr solution (3M in Et_2O) were slowly added. The colorless suspension was stirred at RT. After full conversion of the starting material was indicated by TLC (16 h), the reaction was extracted with 1M HCl (1 x 50 mL). Then the organic phase was extracted with satr $NaHCO_3$ solution (1 x 50 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The colorless solid was purified via flash column chromatography (100 g SiO_2, 5.0 x 14.0 cm, eluent: cyclohexane/EtOAc = 10/1, UV and CAM, fraction size: 50 mL).

Yield: 873 mg (2.67 mmol, 83 %), colorless solid

C_8H_8BrIO [326.96 g/mol]

TLC: R_f = 0.32 (cyclohexane/EtOAc = 10/1, UV and CAM)

mp$^{exp.}$ = 64 - 68 °C

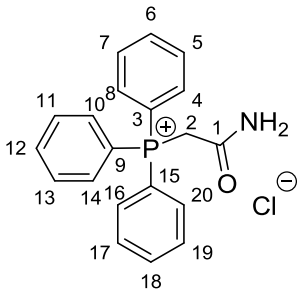
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.91 (d, $^3J_{HH}$ = 1.8 Hz, 1H, H-8), 7.43 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 1.9 Hz, 1H, H-6), 7.22 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H-5), 5.14 (q, $^3J_{HH}$ = 6.3 Hz, 1H, H-2), 2.04 (bs, 1H, OH), 1.46 (d, $^3J_{HH}$ = 6.3 Hz, 3H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 147.0 (C_q, C-3), 137.82 (C-6), 135.99 (C-8), 134.38 (C-5), 121.47 (C_q, C-4), 93.28 (C_q, C-7), 69.01 (C-2), 23.77 (C-1) ppm.

HRMS (DI-EI TOF): calcd. for $C_8H_8BrIO^+$ $[M]^+$: 325.8803; found: 325.8805.

7.4.10. Synthesis of the Glutamine building block

7.4.10.1. (2-Amino-2-oxoethyl)triphenylphosphonium chloride (54)



54

In a flame dried 250 mL Schlenk-flask 3.93 g (14.9 mmol, 1.05 eq) triphenylphosphine and 1.34 g (14.3 mmol, 1.00 eq) 2-chloroacetamide (**53**) were dissolved in 15 mL nitromethane. The brown solution was stirred at 105 °C. After 16 h the colorless suspension was cooled to RT and the precipitate was collected by filtration and washed with EtOAc (2 x 5 mL) and Et_2O (1 x 75 mL). The filter cake was dried in vacuum and compound **54** was isolated as a colorless powder.

Yield: 4.31 g (12.1 mmol, 85 %), colorless powder

$C_{20}H_{19}ClNOP$ [355.80 g/mol]

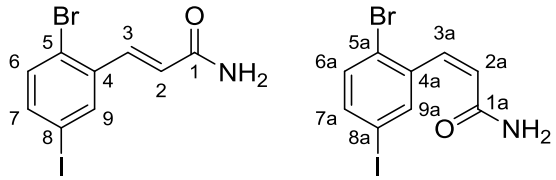
mp$^{exp.}$ = 215 - 219 °C (**mp**^{lit} = 222 – 226 °C)

^{1}H-NMR (300.36 MHz, DMSO-d_6): δ = 8.43 (bs, 1H, NH_2), 7.94 – 7.66 (m, 15H, H-4, H-5, H-6, H-7, H-8, H-10, H-11, H-12, H-13, H-14, H-16, H-17, H-18, H-19, H-20), 7.61 (bs, 1H, NH_2), 5.13 (d, $^2J_{HP}$ = 14.8 Hz, 2H, H-2). ppm.

^{13}C-NMR (75.53 MHz, DMSO-d_6): δ = 165.0 (d, $^2J_{CP}$ = 4.8 Hz, C-1), 134.7 (d, $^4J_{CP}$ = 2.8 Hz, C-6, C-12, C-18), 133.8 (d, $^3J_{CP}$ = 10.6 Hz, C-5, C-7, C-11, C-13, C-17, C-19), 129.9 (d, $^2J_{CP}$ = 12.8 Hz, C-4, C-8, C-10, C-14, C-16, C-20), 119.1 (d, $^1J_{CP}$ = 88.6 Hz, C-3, C-9, C-15), 31.2 (d, $^1J_{CP}$ = 57.9 Hz, C-2) ppm.

Analytical data are in accordance with those reported.[143]

7.4.10.2. (*E*)-3-(2-Bromo-5-iodophenyl)propanamide, (*Z*)-3-(2-Bromo-5-iodophenyl)-propanamide (55)



55

In a flame dried Schlenk-flask 541 mg (4.82 mmol, 1.50 eq) KO*t*Bu were dried in vacuum for 15 min. Then 1.72 g (4.88 mmol, 1.52 eq) phosphonium-salt **54** were added and it was again dried in vacuum for 15 min. Afterwards 15 mL abs. THF were added. The brownish suspension was stirred at 50 °C for 1 h. After 1 h 1.00 g (3.22 mmol, 1.00 eq) 2-bromo-5-iodobenzaldehyde (**10**) was added and the brown suspension was stirred overnight (16 h) at 80 °C until complete conversion was detected by TLC. The reaction was diluted with 50 mL CH_2Cl_2 and washed with brine (1 x 60 mL). The aqueous layer was reextracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The brown crude product was purified via flash column chromatography (450 g SiO_2, 7.5 x 21.0 cm, eluent: cyclohexane/EtOAc = 1/1, R_f = 0.31, UV and $KMnO_4$, fraction size: 50 mL).

Yield: 311 mg (884 µmol, 55 %), *E*/*Z* mixture = 2.8/1, orange solid

$C_{11}H_{10}BrIO_2$ [379.89 g/mol]

TLC: R_f = 0.53 (cyclohexane/EtOAc = 10/1, UV and $KMnO_4$)

^{1}H-NMR (300.36 MHz, DMSO d_6): <u>*E*-isomer:</u> δ = 7.99 (d, $^4J_{HH}$ = 1.6 Hz, 1H, H-9), 7.63 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, H-7), 7.50 (m, 3H, H-3, H-6), 7.30 (s, 2H, NH_2), 6.68 (d, $^3J_{HH}$ = 15.7 Hz, 1H, H-2) ppm.

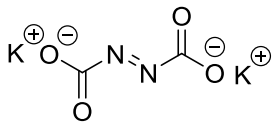
<u>*Z*-isomer:</u> δ = 7.83 (d, $^4J_{HH}$ = 1.4 Hz, 1H, H-9a), 7.61 (s, 1H, NH_2), 7.54 (dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, H-7a), 7.39 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-6a), 7.18 (s, 1H, NH_2), 6.66 (d, $^3J_{HH}$ = 12.2 Hz, 1H, H-3a), 6.17 (d, $^3J_{HH}$ = 12.2 Hz, 1H, H-2a) ppm.

^{13}C-NMR (75.53 MHz, DMSO d_6): <u>*E*-isomer:</u> δ = 165.7 (C_q, C-1), 139.3 (C-7), 136.7 (C_q, C-4), 135.8 (C-9), 135.6 (C-3), 134.9 (C-6), 126.8 (C-2), 123.8 (C_q, C-5), 94.0 (C_q, C-8) ppm.

APT (75.53 MHz, DMSO d_6): <u>*Z*-isomer:</u> δ = 166.4 (C_q, C-1a), 138.9 (C-3a), 138.3 (C_q, C-4a), 137.9 (C-7a), 134.5 (C-9a), 133.8 (C-6a), 127.0 (C-2a), 122.5 (C_q, C-5a), 92.5 (C_q, C-8a) ppm.

HRMS (DI-EI TOF): calcd. for $C_{11}H_{10}BrIO_2^+$ $[M]^+$: 352.8756; found: 352.8763.

7.4.10.3. Dipotassium Azodicarboxylate (PADA)



This compound was prepared according to the literature.[144]

In a 100 mL round-bottom flask 18.3 mL KOH solution (7M) were cooled to -10 °C by a cryostat. 5.84 g (50.3 mmol, 1.00 eq) azodicarbonamide were added in small portions. The yellow-orange suspension was stirred at -10 °C for 2 h. Then the yellow precipitate was collected by filtration and washed with cold MeOH (3 x 50 mL). The yellow powder was dried in vacuum.

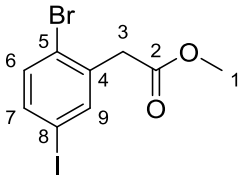
Yield: 9.44 g (48.6 mmol, 97 %), yellow solid

$C_2K_2N_2O_4$ [193.91 g/mol]

mp$^{exp.}$ = 294 - 310 °C

7.4.11. Synthesis of the Aspartate building block

7.4.11.1. Methyl 2-(2-bromo-5-iodophenyl)acetate (58)



58

In a 50 mL one-neck round-bottom flask 200 mg (621 µmol, 1.00 eq) 2-bromo-5-iodophenylacetonitrile (**48**) were suspended in 6 mL MeOH. The yellowish suspension was cooled to 0 °C and then 0.5 mL (9.38 mmol, 15.10 eq) conc. sulfuric acid were added. The reation was stirred at 65 °C. After full conversion (40 h) was detected by TLC the reaction was diluted with 20 mL dist. H_2O and extraced with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The light yellow solid was purified via flash column chromatography (25 g SiO_2, 2.5 x 9.0 cm, eluent: cyclohexane/EtOAc = 100/1, fraction size: 15 mL).

Yield: 73.0 mg (206 µmol, 33 %), colorless solid

$C_9H_8BrIO_2$ [354.97 g/mol]

mp$^{exp.}$ = 42 – 46 °C

TLC: R_f = 0.32 (cyclohexane/EtOAc = 20/1, UV and CAM)

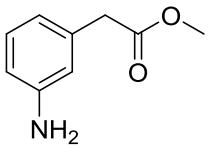
GC-MS (Method_1): t_R = 6.40 min, *m/z* = 356 (8 %), 323 (4 %), 297 (20 %), 275 (100 %), 207 (6 %), 89 (24 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.61 (d, $^3J_{HH}$ = 1.6 Hz, 1H, H-9), 7.45 (dd, $^3J_{HH}$ = 8.3, $^3J_{HH}$ = 1.7 Hz, 1H, H-7), 7.29 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-6), 3.73 (s, 5H, H-1, H-3) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 170.4 (C_q, C-2), 140.3 (C-9), 138.0 (C-7), 136.5 (C_q, C-4), 134.5 (C-6), 125.1 (C-5), 92.5 (C-8), 52.5 (C-3), 41.2 (C-1) ppm.

HRMS (DI-EI TOF): calcd. for $C_9H_8BrIO_2^+$ $[M]^+$: 353.8752; found: 353.8766.

7.4.11.2. Methyl 2-(3-aminophenyl)acetate (62)



62

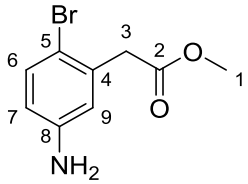
In a 100 mL one-neck round-bottom flask 4.59 g (30.4 mmol, 1.00 eq) 2-(3-aminophenyl) acetic acid (**59**) were suspended in 15 mL MeOH. Then 162 µL (3.04 mmol, 0.10 eq) conc. sulfuric acid were added. The reaction was stirred at RT. After full conversion (15 min) was detected by TLC the solvent was removed under reduced pressure. The crude product was used without further purification in the next reaction.

Yield: 5.64 g (34.1 mmol), brown oil

$C_9H_{11}NO_2$ [165.08 g/mol]

TLC: R_f = 0.68 (CH_2Cl_2/MeOH = 12/1 + acetic acid, UV and $KMnO_4$)

7.4.11.3. Methyl 2-(5-amino-2-bromophenyl)acetate (63)



63

In a 100 mL one-neck round-bottom flask 50.9 mg (660 µmol, 0.10 eq) NH_4OAc were dissolved in 15 mL MeCN. 1.09 g (6.60 mmol, 1.00 eq) methyl 2-(3-aminophenyl)acetate (**62**) and 1.21 g (6.80 mmol, 1.05 eq) NBS were added. The red-brown suspension was stirred at RT for 5 min. After full conversion was detected by GC-MS the reaction was diluted with 20 mL EtOAc and washed with $NaHSO_3$ solution (3 x 20 mL). The combined aqueous layers were reextracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The red brown oil was purified via flash column chromatography (125 g SiO_2, 5.0 x 15.0 cm, eluent: CH_2Cl_2 (fractions 1 – 21), CH_2Cl_2/MeOH = 100/1 (fractions 22 – 39), R_f = 0.16, UV and $KMnO_4$, fraction size: 80 mL).

Yield: 568 mg (2.34 mmol, 35 %), yellow/brown oil

$C_{10}H_{14}BrN$ [227.03 g/mol]

TLC: R_f = 0.16 (CH_2Cl_2, UV and $KMnO_4$)

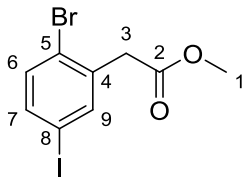
GC-MS (Method_1): t_R = 6.35 min, *m/z* = 243 (26 %), 186 (36 %), 164 (100 %), 149 (31 %), 105 (34 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.29 (d, $^3J_{HH}$ = 8.5 Hz, 4H, H-7), 6.62 (d, $^3J_{HH}$ = 2.4 Hz, 1H, H-9), 6.48 (dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2.5 Hz, 1H, H-6), 3.71 (s, 3H, H-1), 3.69 (s, 2H, H-3) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 171.3 (C_q, C-2), 146.1 (C_q, C-8), 134.7 (C_q, C-4), 133.4 (C-7), 118.0 (C-9), 115.9 (C-6), 112.9 (C_q, C-5), 52.3 (C-1), 41.6 (C-3) ppm.

HRMS (DI-EI TOF): calcd. for $C_{10}H_{14}BrN^+$ $[M]^+$: 242.9895; found: 242.9890.

7.4.11.4. Methyl 2-(2-bromo-5-iodophenyl)acetate (58)



58

In a 50 mL one-neck round-button flask 531 mg (2.18 mmol, 1.00 eq) methyl 2-(5-amino-2-bromophenyl)acetate (**63**) were suspended in 2.5 mL H_2O and cooled to 0 °C. 1.3 mL conc. HCl were added dropwise. Then a cooled solution of 255 mg (3.70 mmol, 1.70 eq) $NaNO_2$ in 1.7 mL H_2O was added at 0 °C. The suspension was stirred at 0 °C. After 1 h a solution of 704 mg KI in 2.8 mL H_2O was added dropwise at 0 °C. The brown suspension was stirred at RT for 18 h. After full conversion of the starting material was indicated by GC-MS, the reaction was diluted with 20 mL EtOAc and washed with $NaHSO_3$ solution (3 x 20 mL). The combined aqueous layers were reextracted with EtOAc (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The brown oil was purified via flash column chromatography (125 g SiO_2, 5.0 x 15.0 cm, eluent: cyclohexane/EtOAc = 75/1, fraction size: 70 mL).

Yield: 607 mg (1.72 mmol, 79 %), colorless solid

$C_9H_8BrIO_2$ [354.97 g/mol]

TLC: R_f = 0.49 (cyclohexane/EtOAc = 9:1, UV and $KMnO_4$)

mp$^{exp.}$ = 42 – 46 °C

GC-MS (Method_1): t_R = 5.88 min, *m*/*z* = 354 (7 %), 297 (25 %), 275 (100 %), 207 (16 %), 148 (12 %), 89 (14 %).

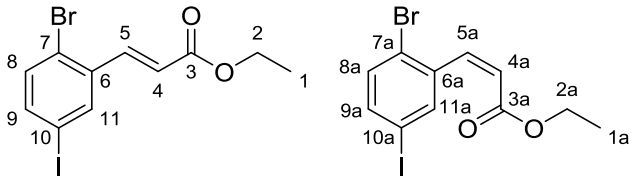
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.61 (d, $^3J_{HH}$ = 1.8 Hz, 1H, H-9), 7.45 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ 1.9 Hz, 1H, H-7), 7.29 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-6), 3.73 (s, 5H, H-1, H-3) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 170.4 (C_q, C-2), 140.3 (C-9), 138.0 (C-7), 136.5 (C_q, C-4), 134.5 (C-6), 125.1 (C_q, C-5), 92.5 (C_q, C-8), 52.5 (C-1), 41.2 (C-3) ppm.

HRMS (DI-EI TOF): calcd. for $C_9H_8BrIO_2^+$ $[M]^+$: 353.8752; found: 353.8766.

7.4.12. Synthesis of the Glutamic acid building block

7.4.12.1. Ethyl (*E*)-3-(2-bromo-5-iodophenyl)acrylate, Ethyl (*Z*)-3-(2-bromo-5-iodophenyl)acrylate (66)



66

In a flame dried Schlenk-flask 4.98 g (11.6 mmol, 1.23 eq) phosphonium-salt **65** and 1.42 g (12.8 mmol, 1.34 eq) KO*t*Bu were dried in vacuum for 1 h. Then 40 mL abs., degassed THF were added. The yellowish suspension was stirred at RT for 1 h. Then 2.94 g (9.49 mmol, 1.00 eq) 2-bromo-5-iodobenzaldehyde (**10**) were added to the ylide solution. The orange/yellow suspension was stirred overnight (16 h) at 50 °C until complete conversion was detected by TLC. The solvent was removed under reduced pressure. The yellow-brown crude product was purified via flash column chromatography (500 g SiO_2, 5.5 x 19.0 cm, eluent: cyclohexane/EtOAc = 75/1 (fraction 1-15), cyclohexane/EtOAc = 50/1 (fraction 16-23), R_f = 0.41, UV and $KMnO_4$, fraction size: 50 mL).

Yield: 3.38 g (8.90 mmol, 94 %), *E*/*Z* mixture = 4/1, colorless solid

$C_{11}H_{10}BrIO_2$ [379.89 g/mol]

TLC: R_f = 0.53 (cyclohexane/EtOAc = 10/1, UV and $KMnO_4$)

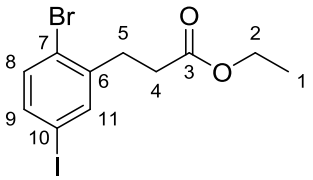
mp$^{exp.}$ = 65 - 72 °C

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.92 – 7.87 (m, 2H, H-5, H-11), 7.74 (d, $^3J_{HH}$ = 1.2 Hz, 1H, H-11a), 7.52 – 7.47 (m, 2H, H-9, H-9a), 7.33 – 7.27 (m, 2H, H-8, H-8a), 6.96 (d, $^3J_{HH}$ = 12.1 Hz, 1H, H-5a), 6.37 (d, $^3J_{HH}$ = 15.9 Hz, 1H, H-4), 6.07 (d, $^3J_{HH}$ = 12.1 Hz, 1H, H-4a), 4.28 (q, $^3J_{HH}$ = 7.1 Hz, 1H, H-2), 4.12 (q, $^3J_{HH}$ = 14.2, 7.1 Hz, 1H, H-2a), 1.34 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-1), 1.18 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-1a) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 166.1 (C_q, C-3), 141.5 (C-5), 140.7 (C-5a), 139.9 (C-9), 139.4 (C-11a), 138.6 (C-9a), 136.9 (C_q, C-6), 136.7 (C-11), 135.0 (C-8), 133.9 (C-8a), 125.0 (C_q, C-7), 123.0 (C-4a), 122.5 (C-4), 92.7 (C_q, C-10), 91.5 (C_q, C-10a), 61.0 (C-2), 60.7 (C-2a), 14.4 (C-1), 14.2 (C-1a) ppm. (C-3a, C-6a, C-7a not seen in the ^{13}C-NMR)

HRMS (DI-EI TOF): calcd. for $C_{11}H_{10}BrIO_2^+$ $[M]^+$: 379.8909; found: 379.8921.

7.4.12.2. Ethyl 3-(2-bromo-5-iodophenyl)propanoate (67)



67

A 250 mL one-neck round-bottom flask, equipped with reflux-condenser, was charged with 3.30 g (8.69 mmol, 1.00 eq) ethyl (*E*/*Z*)-3-(2-bromo-5-iodophenyl)acrylate (**66**) which was then dissolved in 70 mL THF. First 9.71 g (52.1 mmol, 6.00 eq) p-tosylhydrazide and afterwards 7.09 g (7.19 mmol, 6.0 eq) NaOAc were added and the pale yellow suspension was stirred at 70 °C until quantitative conversion (50 h) was detected by GC-MS. The reaction mixture was cooled to RT and 75 mL satd $NaHCO_3$-solution were added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (500 g SiO_2, 5.5 x 19.0 cm, eluent: cyclohexane/EtOAc = 75/1, R_f = 0.17, UV and $KMnO_4$).

Yield: 3.05 g (7.99 mmol, 92 %), colorless solid

$C_{11}H_{12}BrIO_2$ [381.91 g/mol]

TLC: R_f = 0.17 (cyclohexane/EtOAc = 75/1, UV and $KMnO_4$)

mp$^{exp.}$ = 42 - 46 °C

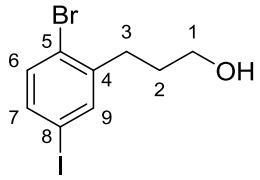
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.58 (d, $^3J_{HH}$ = 1.6 Hz, 1H, H-11), 7.38 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 1.8 Hz, 1H, H-9), 7.25 (d, $^3J_{HH}$ = 8.5 Hz, 1H, H-8), 4.15 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-2), 3.00 (t, $^3J_{HH}$ = 7.7 Hz, 2H, H-5), 2.62 (t, $^3J_{HH}$ = 7.7 Hz, 2H, H-4), 1.25 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 172.4 (C_q, C-3), 142.3 (C_q, C-6), 139.4 (C-11), 137.2 (C-9), 134.6 (C-8), 124.4 (C_q C-7), 92.6 (C_q, C-10), 60.8 (C-2), 34.0 (C-4), 31.2 (C-5), 14.4 (C-1) ppm.

HRMS (DI-EI TOF): calcd. for $C_{11}H_{12}BrIO_2^+$ $[M]^+$: 381.9065; found: 381.8986.

7.4.13. Synthesis of the Arginine building block

7.4.13.1. 3-(2-Bromo-5-iodophenyl)propan-1-ol (68)



68

In a flame dried 8 mL Schlenk flask 500 mg (1.31 mmol, 1.00 eq) ethyl 3-(2-bromo-5-iodophenyl)propanoate (**67**) were dissolved in 2 mL abs CH_2Cl_2. The solution was cooled to -78 °C in a dry ice/acetone bath. Then 2.60 mL (1M in CH_2Cl_2, 2.61 mmol, 2.00 eq) DIBALH were added via a syringe. The colorless solution was stirred at RT. After full conversion of the starting material was indicated by GC-MS (90 min) the reaction mixture was quenched carefully by the addition of 5.0 mL MeOH. Then 15 mL satd. Rochelle salt solution were added and the reaction was stirred for another 12 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (50 g SiO_2, 2.5 x 12.0 cm, eluent: cyclohexane/EtOAc = 8/1, R_f = 0.14, UV and $KMnO_4$, fraction size: 20 mL).

Yield: 407 mg (1.19 mmol, 91 %), colorless solid.

$C_9H_{10}BrIO$ [340.99 g/mol]

mp$^{exp.}$ = 49 – 53 °C

TLC: R_f = 0.14 (cyclohexane/EtOAc = 8/1, UV and $KMnO_4$)

GC-MS (Method_1): t_R = 6.64 min, *m/z* = 342 (42 %), 295 (21 %), 260 (28 %), 171 (25 %), 116 (100 %).

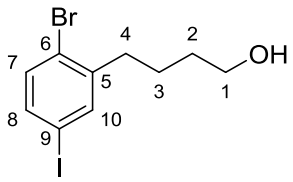
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.57 (d, $^3J_{HH}$ = 1.8 Hz, 1H, H-9), 7.37 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, H-7), 7.25 (d, $^3J_{HH}$ = 8.9 Hz, 1H, H-6), 3.70 (t, $^3J_{HH}$ = 6.2 Hz, 2H, H-1), 2.78 (t, $^3J_{HH}$ = 7.6 Hz, 2H, H-3), 1.95 – 1.74 (m, 2H, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 143.7 (C_q, C-4), 139.2 (C-9), 136.8 (C-7), 134.6 (C-6), 124.5 (C_q, C-5), 92.7 (C_q, C-8), 62.1 (C-1), 32.6 (C-2), 32.3 (C-3) ppm.

HRMS (DI-EI TOF): calcd. for $C_9H_{10}BrIO^+$ $[M]^+$: 339.8960; found: 339.8970.

7.4.14. Synthesis of the Lysine building block

7.4.14.1. 4-(2-bromo-5-iodophenyl)butan-1-ol (70)



70

In a flame dried 8 mL Schlenk flask 46 mg (116 µmol, 1.00 eq) ethyl 4-(2-bromo-5-iodophenyl)butanoate (**93**) were dissolved in 1 mL abs CH_2Cl_2. The solution was cooled to -78 °C in a dry ice/acetone bath. Then 235 µL (1M in CH_2Cl_2, 235 µmol, 2.01 eq) DIBALH were added via a syringe. The colorless solution was stirred at RT. After full conversion of the starting material was indicated by GC-MS (90 min) the reaction mixture was quenched carefully by the addition of 3.0 mL MeOH. Then 10 mL satd. Rochelle salt solution were added and the reaction was stirred for another 12 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (10 g SiO_2, 1.0 x 10.0 cm, eluent: cyclohexane/EtOAc = 6/1, R_f = 0.17, UV and $KMnO_4$, fraction size: 3 mL).

Yield: 38.4 mg (108 µmol, 93 %), colorless oil

$C_{10}H_{12}BrIO$ [355.01 g/mol]

TLC: R_f = 0.17 (cyclohexane/EtOAc = 6/1, UV and $KMnO_4$)

GC-MS (Method_1): t_R = 6.90 min, *m/z* = 354 (35 %), 310 (100 %), 257 (19 %), 130 (48 %), 89 (25 %).

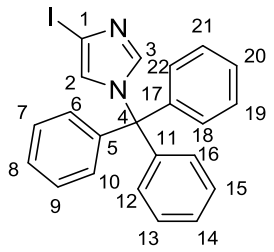
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.54 (d, $^4J_{HH}$ = 1.8 Hz, 1H, H-10), 7.35 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, H-8), 7.23 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H-7), 3.69 (m, 2H, H-1), 2.69 (t, $^3J_{HH}$ = 7.0 Hz, 2H, H-4), 1.73 – 1.58 (m, 4H, H-2, H-3) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 144.1 (C_q, C-5), 139.1 (C-10), 136.6 (C-8), 134.5 (C-7), 124.4 (C_q, C-6), 92.6 (C_q, C-9), 62.8 (C-1), 35.7 (C-4), 32.4 (C-2), 26.1 (C-3) ppm.

HRMS (DI-EI TOF): calcd. for $C_{10}H_{12}BrIO^+$ $[M]^+$: 353.9116; found: 353.9125.

7.4.15. Synthesis of the Histidine building block

7.4.15.1. 4-Iodo-1-trityl-1*H*-imidazole (73)



73

This compound was prepared according to the literature.[127]

A 50 mL round-bottom flask was charged with 951 mg (4.90 mmol, 1.0 eq) 4-iodo-1*H*-imidazole (**72**) dissolved in 10 mL DMF. 713 µL (520 mg, 5.14 mmol, 1.05 eq) Et_3N and 1.37 g (4.90 mmol, 1.0 eq) triphenylmethylchloride were added to this pale brown solution, which turned into a colourless suspension within 60 min. After quantitative conversion had been detected by TLC (24 h), the reaction mixture was poured into 50 mL ice water. The beige precipitate was collected by filtration. The crude product was triturated in 8 mL Et_2O and stirred for 10 min. The colorless solid was collected by filtration and dried in oil pump vacuo.

Yield: 1.26 g (2.89 mmol, 59 %), beige solid

$C_{22}H_{17}IN_2$ [436.30 g/mol]

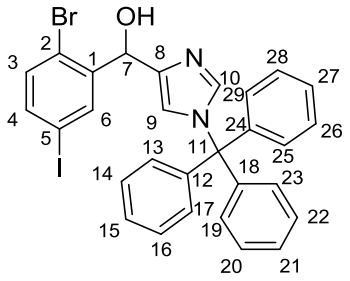
mp$^{exp.}$ = 235 – 237 °C (**mp**^{lit} = 224 – 225 °C)[127]

TLC: R_f = 0.55 (cyclohexane/EtOAc = 3/1, UV and CAM)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.34 – 7.28 (m, 10H, H-3, H-7, H-8, H-9, H-13, H-14, H-15, H-19, H-20, H-21), 7.12 – 7.06 (m, 6H, H-6, H-10, H-12, H-16, H-18, H-22), 6.88 (s, 1H, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 142.0 (C_q, C-5, C-11, C-17), 140.7 (C-3), 129.9 (C-6, C-10, C-12, C-16, C-18, C-22), 128.4 (C-8, C-10, C-20), 128.3 (C-7, C-9, C-13, C-15, C-19, C-21), 127.0 (C-2), 81.5 (C_q, C-1), 76.0 (C_q, C-4) ppm.

7.4.15.2. (2-Bromo-5-iodophenyl)(1-trityl-1*H*-imidazol-4-yl)methanol (74)



74

In a flame dried and argon flushed Schlenk-flask 140 mg (321 µmol, 1.00 eq) iodo-1-trityl-1*H*-imidazole (**73**) were dissolved in 2 mL abs. THF. 115 µL (322 µmol, 1.00 eq) EtMgBr solution (2.80 M in Et_2O) were added and the yellowish solution was stirred at RT for 90 min and after 10 min a colorless precipitate was formed. After quantitative iodine-magnesium exchange had been detected by HPLC-MS, 100 mg (322 µmol, 1.00 eq) 2-bromo-5-iodobenzaldehyde (**10**) were added. The color turned into yellow. After full conversion was detected by HPLC-MS (14 h), the reaction was quenched by the addition of 20 mL satd. NH_4Cl solution. The phases were separated and the aqueous phase was extracted with DCM (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The colorless crude product was purified via flash column chromatography (20 g SiO_2, 1.5 x 9.0 cm, eluent: cyclohexane/EtOAc = 2/1, R_f = 0.11, UV and CAM, fraction size: 10 mL).

Yield: 174 mg (281 µmol, 87 %), colorless solid

$C_{29}H_{22}BrIN_2O$ [621.32 g/mol]

mp$^{exp.}$ = 199 – 201 °C

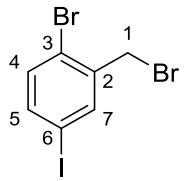
TLC: R_f = 0.11 (cyclohexane/EtOAc = 2/1, UV and CAM)

^{1}H-NMR (300.36 MHz, DMSO d_6): δ = 7.80 (d, $^3J_{HH}$ = 1.6 Hz, 1H, H-6), 7.49 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, H-4), 7.40 (m, 9H, H-14, H-15, H-16, H-20, H-21, H-22, H-26, H-27, H-28), 7.30 (m, 2H, H-3, H-10), 7.07 (m, 6H, H-13, H-17, H-19, H-23, H-25, H-29), 6.68 (s, 1H, H-9), 5.92 (d, $^3J_{HH}$ = 5.1 Hz, 1H, OH), 5.73 (d, $^3J_{HH}$ = 5.0 Hz, 1H, H-7) ppm.

^{13}C-NMR (75.53 MHz, DMSO d_6): δ = 145.5 (C_q, C-1), 142.5 (C_q, C-2), 142.1 (C-12, C-18, C-24), 138.0 (C-10), 137.6 (C-6), 137.3 (C-4), 134.1 (C-3), 129.2 (C-14, C-16, C-20, C-22, C-26, C-28), 128.2 (C-13, C-17, C-19, C-23, C-25, C-29), 128.1 (C-15, C-21, C-27), 122.0 (C_q, C-8), 119.0 (C-9), 93.3 (C-5), 74.6 (C_q, C-11), 68.4 (C-7) ppm.

HRMS (DI-EI TOF): calcd. for $C_{29}H_{22}BrIN_2O^+$ $[M]^+$: 619.9960; found: 619.9950.

7.4.15.3. 1-Bromo-2-(bromomethyl)-4-iodobenzene (50)



50

In a flame dried 10 mL Schlenk-flask 200 mg (639 µmol, 1.00 eq) 2-bromo-5-iodobenzylalcohol (**9**) were suspended in 5 mL CH_2Cl_2. Then 10 µL DMF and 70 µL (906 µmol, 1.42 eq) thionylbromide were added and the yellow/orange solution was stirred at RT. After full conversion (16 h) was indicated by TLC and GC-MS, 20 mL CH_2Cl_2 were added and the organic phase was washed with satd. $NaHCO_3$ solution (2 x 30 mL). Then the organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The colorless crude product was purified via flash column chromatography (30 g SiO_2, 2.5 x 9.5 cm, eluent: cyclohexane, R_f = 0.56, UV and $KMnO_4$, fraction size: 20 mL). Fractions 2 to 10 were combined and the solvent was removed under reduced pressure.

Yield: 227 mg (604 µmol, 94 %), colorless solid

$C_7H_5Br_2I$ [375.83 g/mol]

mp$^{exp.}$ = 105 – 108 °C (**mp**$^{lit.}$ = 112 – 114 °C)[141]

TLC: R_f = 0.56 (cyclohexane, UV and $KMnO_4$)

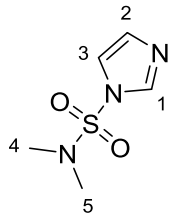
GC-MS (Method_1): t_R = 6.31 min, *m/z* = 376 (21 %), 297 (100 %), 168 (20 %), 127 (12 %), 89 (52 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.77 (d, $^3J_{HH}$ = 1.8 Hz, 1H, H-7), 7.47 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.8 Hz, 1H, H-5), 7.29 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-4), 4.50 (s, 2H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 140.0 (C-7), 139.3 (C_q, C-2), 139.1 (C-5), 135.0 (C-4), 124.4 (C_q, C-3), 92.6 (C_q, C-6), 32.1 (C-1) ppm.

Analytical data are in accordance with those reported.[142]

7.4.15.4. *N*,*N*-Dimethyl-1*H*-imidazole-1-sulfonamide (79)



79

This compound was prepared according to the literature.[126]

In a 50 mL one neck round-bottom flask 500 mg (7.35 mmol, 1.00 eq) imidazole (**78**) were dissolved in 5 mL CH_2Cl_2. Then 1.20 mL triethylamine were added. 790 µL (7.36 mmol, 1.00 eq) *N*,*N*-dimethylsulfamylchloride were added via a syringe over 5 min. The colorless suspension was stirred at RT. After full conversion (14 h) was indicated by HPLC-MS, 20 mL 10 % K_2CO_3 solution were added and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). Then the organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was used without further purification in the next step.

Yield: 1.30 g (7.45 mmol, 102 %), yellow/orange solid

$C_5H_9N_3O_2S$ [175.21 g/mol]

mp$^{exp.}$ = 48 - 50 °C (**mp**$^{lit.}$ = 45 – 48 °C)[145]

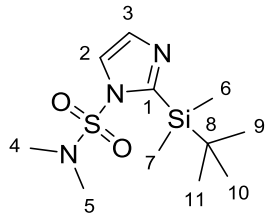
HPLC-MS (Method_2): t_R = 3.62 min, *m*/*z* + H = 176.

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.92 (s, 1H, H-1), 7.26 (s, 1H, H-3), 7.15 (s, 1H, H-2), 2.86 (s, 6H, H-4, H-5) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 136.8 (C-1), 130.6 (C-2), 117.9 (C-3), 38.3 (C-4, C-5) ppm.

Analytical data are in accordance with those reported.[126]

7.4.15.5. 2-(tert-Butyldimethylsilyl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (81)



81

This compound was prepared according to the literature.[128]

In a flame dried 20 mL Schlenk-flask 500 mg (11.4 mmol, 1.00 eq) *N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (**79**) were dissolved in 50 mL abs. THF. Then the yellow/orange solution was cooled to –78 °C in a dry ice/acetone bath. Afterwards 5.20 mL (2.2M in hexane, 11.4 mmol, 1.00 eq) *n*-BuLi were slowly added over 20 min. The solution turned dark red and was stirred at -78 °C for 75 min. Then 1.72 g (11.4 mmol, 1.00 eq) *t*-butyldimethyl-silylchloride were dissolved in 8 mL abs THF. The solution was added drop-wise over 35 min while maintaining a temperature of –60 °C. Then the red solution was slowly warmed to RT. After 82 % conversion (15 h) was indicated by HPLC-MS, 20 mL dist. H_2O were added and THF was removed under reduced pressure. The residue was extracted with EtOAc (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The colorless crude product was purified via flash column chromatography (300 g SiO_2, 6.5 x 20.0 cm, eluent: cyclohexane/EtOAc = 5/1, fraction size: 200 mL).

Yield: 2.42 g (8.34 mmol, 73 %), orange solid

$C_{11}H_{23}N_3O_2SSi$ [289.47 g/mol]

mp$^{exp.}$ = 49 – 61 °C (**mp**$^{lit.}$ = 63 – 66 °C)[146]

TLC: R_f = 0.24 (cyclohexane/EtOAc = 2/1, UV and $KMnO_4$)

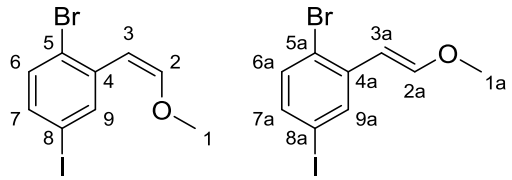
HPLC-MS (Method_2): t_R = 5.37 min, *m/z* + H = 291.

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.32 (s, 1H, H-3), 7.24 (s, 1H, H-2), 2.86 (s, 6H, H-4, H-5), 0.97 (s, 9H, H-9, H-10, H-11), 0.41 (s, 6H, H-6, H-7) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 153.1 (C_q, C-1), 130.8 (C-2), 120.3 (C-3), 38.4 (C-4, C-5), 27.2 (C-9, C-10, C-11), 18.2 (C-8), -3.8 (C-6, C-7) ppm.

Analytical data are in accordance with those reported.[128]

7.4.15.6. 1-Bromo-4-iodo-2-(2-methoxyvinyl)benzene (83)



83

In a flame dried 15 mL Schlenk-flask 1.00 g (2.92 mmol, 2.50 eq) (methoxymethyl)triphenylphosponiumchloride was suspended in 6.50 mL abs. THF. Then the colorless suspension was cooled to -10 °C. Afterwards 1.30 mL (2.2M in hexane, 2.86 mmol, 2.45 eq) *n*-BuLi were slowly added over 2 min. The suspension turned red and was stirred at 0 °C for 60 min. Then a solution of 363 mg (1.17 mmol, 1.00 eq) 2-bromo-5-iodobenzaldehyde (**10**) in 2 mL abs. THF was added. The solution was added dropwise over 2 min to the ylide solution. The yellow suspension was slowly warmed to RT. After full conversion (6 h) was indicated by TLC, THF was removed under reduced pressure. The yellow/brown crude product was purified via flash column chromatography (135 g SiO_2, 4.5 x 13.5 cm, eluent: cyclohexane, R_f = 0.32, UV and $KMnO_4$, fraction size: 75 mL). Fractions 6 to 12 were combined and the solvent was removed under reduced pressure.

Yield: 134 mg (395 µmol, 34 %), colorless oil

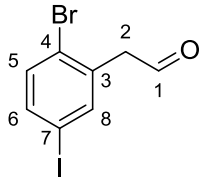
C_9H_8BrIO [338.97 g/mol]

TLC: R_f = 0.32 (cyclohexane, UV and $KMnO_4$)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 8.36 (d, $^3J_{HH}$ = 1.7 Hz, 1H, H-9), 7.65 (d, $^3J_{HH}$ = 1.7 Hz, 1H, H-9a), 7.33 – 7.17 (m, 4H, H-6, H-6a, H-7, H-7a), 6.97 (d, $^3J_{HH}$ = 12.9 Hz, 1H, H-2a), 6.27 (d, $^3J_{HH}$ = 7.2 Hz, 1H, H-2), 5.96 (d, $^3J_{HH}$ = 12.8 Hz, 1H, H-3a), 5.49 (d, $^3J_{HH}$ = 7.2 Hz, 1H, H-3), 3.81 (s, 3H, H-1), 3.73 (s, 3H, H-1a) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 151.5 (C-2a), 150.3 (C-2), 138.8 (C-9), 137.3 (C_q, C-4), 136.0 (C-7a), 135.9 (C-7), 134.5 (C-6a), 134.4 (C-9a), 134.1 (C-6), 122.5 (C_q, C-5), 103.5 (C-3a), 102.8 (C-3), 92.5 (C_q, C-8), 61.3 (C-1), 56.9 (C-1a) ppm. (C-4a, C-5a, C-8a not seen in the ^{13}C-NMR)

7.4.15.7. 2-(2-Bromo-5-iodophenyl)acetaldehyde (84)



84

In a 100 mL one-neck round-bottom flask 113 mg (333 µmol, 1.00 eq) 1-bromo-4-iodo-2-(2-methoxyvinyl)benzene (**83**) were dissolved in 3 mL CH_2Cl_2. The colorless solution was cooled to 0 °C. Then 60 µL (750 µmol, 2.00 eq) trifluoroacetic acid were added dropwise. The solution was stirred for 15 min at 0 °C and was then allowed to warm up to RT. After full conversion (7 h) was indicated by GC-MS 30 µL H_2O were added and the orange solution was stirred at RT for 2 h. Afterwards the reaction was quenched by the addition of satd $NaHCO_3$ solution. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4 x 10 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The orange crude product was purified via flash column chromatography (10 g SiO_2, 2.0 x 7.0 cm, eluent: cyclohexane/EtOAc = 20/1, R_f = 0.24, UV and $KMnO_4$, fraction size: 5 mL). Fractions 5 to 8 were combined and the solvent was removed under reduced pressure.

Yield: 70.3 mg (225 µmol, 65 %), colorless solid

C_8H_6BrIO [324.94 g/mol]

mp$^{exp.}$ = 58 – 66 °C

TLC: R_f = 0.24 (cyclohexane/EtOAc = 20/1, UV and CAM)

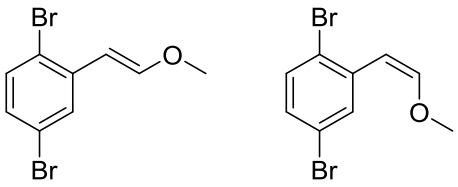
GC-MS (Method_1): t_R = 6.14 min, *m*/*z* = 324 (50 %), 295 (60 %), 245 (100 %), 217 (30 %), 171 (28 %), 89 (80 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 9.74 (s, 1H, H-1), 7.56 (d, $^3J_{HH}$ = 1.7 Hz, 1H, H-8), 7.49 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, H-6), 7.33 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H-5), 3.82 (s, 2H, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 197.33 (C-1), 140.50 (C-8), 138.39 (C-6), 135.11 (C_q, C-3), 134.66 (C-5), 124.97 (C_q, C-4), 92.81 (C_q, C-7), 50.15 (C-2) ppm.

HRMS (DI-EI TOF): calcd. for $C_8H_6BrIO^+$ $[M]^+$: 323.8647; found: 323.8658.

7.4.15.8. (*E*)-1,4-Dibromo-2-(2-methoxyvinyl)benzene, (*Z*)-1,4-Dibromo-2-(2-methoxyvinyl)benzene (86)



86

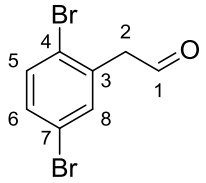
In a flame dried 50 mL three-neck round-bottom flask 1.50 g (4.38 mmol, 2.50 eq) (methoxymethyl)triphenylphosponiumchloride were suspended in 10 mL abs. THF. Then the colorless suspension was cooled to 0 °C. Afterwards 1.80 mL (2.36 M in hexane, 4.25 mmol, 2.43 eq) *n*-BuLi were slowly added over 5 min. The suspension turned red and was stirred at 0 °C for 60 min. Then a solution of 462 mg (1.75 mmol, 1.00 eq) 2-bromo-5-iodobenzaldehyde (**10**) in 4 mL abs. THF was added dropwise over 5 min. The yellow suspension was slowly warmed to RT. After full conversion (2 h) was indicated by GC-MS, 30 mL dist. H_2O were added and extracted with Et_2O (3 x 30 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The yellow/brown crude product was used without further purification.

Yield: 1.49 g (5.10 mmol, 292 %), yellow oil

$C_9H_8Br_2O$ [291.97 g/mol]

GC-MS (Method_1): t_R = 6.09 min, *m*/*z* = 292 (100 %), 249 (35 %), 198 (72 %), 170 (18 %), 132 (60 %), 89 (47 %).

7.4.15.9. 2-(2,5-Dibromophenyl)acetaldehyde (87)



87

In a 100 mL one-neck round-bottom flask 1.49 g (5.10 µmol, 1.00 eq) 1,4-dibromo-2-(2-methoxyvinyl)benzene (**86**, crude product) were dissolved in 60 mL CH_2Cl_2. The yellowish solution was cooled to 0 °C. Then 1.20 mL (7.79 µmol, 1.50 eq) trifluoroacetic acid were added drop-wise. The solution was stirred for 15 min at 0 °C and was then allowed to warm up to RT. After full conversion (2.5 h) was indicated by GC-MS the reaction was quenched by the addition of satd. $NaHCO_3$ solution. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The orange crude product was purified via flash column chromatography (125 g SiO_2, 5.0 x 12.0 cm, eluent: cyclohexane/EtOAc = 30/1, R_f = 0.34 (cyclohexane/EtOAc = 9/1), UV and $KMnO_4$, fraction size: 75 mL). Fractions 11 to 14 were combined and the solvent was removed under reduced pressure.

Yield: 224 mg (807 µmol, 46 %), colorless solid

$C_8H_6Br_2O$ [277.94 g/mol]

mp$^{exp.}$ = 62 -65 °C

TLC: R_f = 0.34 (cyclohexane/EtOAc = 9/1, UV and $KMnO_4$)

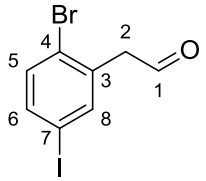
GC-MS (Method_1): t_R = 5.76 min, *m/z* = 288 (36 %), 249 (93 %), 197 (66 %), 170 (81 %), 89 (100 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 9.68 (s, 1H, H-1), 7.47 (d, $^3J_{HH}$ = 8.5 Hz, 1H, H-5), 7.38 (d, $^3J_{HH}$ = 2.1 Hz, 1H, H-8), 7.31 (dd, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 2.2 Hz, 1H, H-6), 3.84 (s, 2H, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 197.3 (C-1), 134.9 (C_q, C-3), 134.7 (C-8), 134.4 (C-5), 132.5 (C-6), 123.7 (C_q, C-4), 121.7 (C_q, C-7), 50.3 (C-2) ppm,

HRMS (DI-EI TOF): calcd. for $C_8H_6Br_2O^+$ $[M]^+$: 275.8785; found: 275.8787.

7.4.15.10. 2-(2-Bromo-5-iodophenyl)acetaldehyde (84)



84

In a flame dried 10 mL Schlenk-flask 200 mg (563 µmol, 2.50 eq) methyl 2-(2-bromo-5-iodophenyl)acetate **58** were dissolved in 2 mL abs CH_2Cl_2. Then the colorless solution was cooled to –78 °C. Afterwards 565 µL (565 µmol, 1.00 eq) DIBALH (1.0M in CH_2Cl_2) were slowly added over 5 min. The yellowish solution was stirred at -78 °C for 30 min. After full conversion was indicated by GC-MS, 5 mL 25 % tartaric acid solution were added and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (30 g SiO_2, 2.5 x 9.5 cm, eluent: cyclohexane/EtOAc = 30/1, R_f = 0.34 (cyclohexane/EtOAc = 9/1), UV and $KMnO_4$, fraction size: 10 mL).

Yield: 121 mg (372 µmol, 66 %), colorless solid

C_8H_6BrIO [324.94 g/mol]

mp$^{exp.}$ = 58 – 66 °C

TLC: R_f = 0.40 (cyclohexane/EtOAc = 9/1, UV and $KMnO_4$)

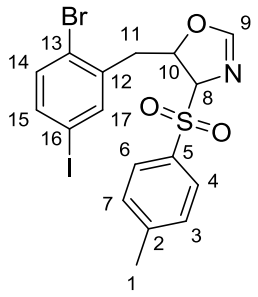
GC-MS (Method_1): t_R = 6.13 min, *m/z* = 324 (50 %), 295 (60 %), 245 (100 %), 217 (30 %), 171 (28 %), 89 (80 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 9.75 (s, 1H, H-1), 7.57 (d, $^3J_{HH}$ = 1.6 Hz, 1H, H-8), 7.49 (dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 1.9 Hz, 1H, H-6), 7.33 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-5), 3.82 (s, 2H, H-2) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 197.3 (C-1), 140.5 (C-8), 138.4 (C-6), 135.1 (C_q, C-3), 134.7 (C-5), 125.0 (C_q, C-4), 92.8 (C_q, C-7), 50.2 (C-2) ppm.

HRMS (DI-EI TOF): calcd. for $C_8H_6BrIO^+$ $[M]^+$: 323.8647; found: 323.8658.

7.4.15.11. 5-(2-Bromo-5-iodobenzyl)-4-tosyl-4,5-dihydrooxazole (88)



88

In a flame dried 8 mL Schlenk-flask 18.1 mg (92.3 µmol, 1.00 eq) p-tosylmethylisocyanide were dried in vacuum for 30 min. Then 500 µL abs. EtOH were added and the colorless suspension was cooled to 0 °C. Afterwards 30 mg (92.3 µmol, 1.00 eq) 2-(2-bromo-5-iodo-phenyl)acetaldehyde (**84**) were added at 0 °C. 0.8 mg (16.3 µmol, 0.18 eq) NaCN were added to the yellow suspension and the suspension was stirred at 0 °C for 30 min, followed by 60 min at RT. After 92 % conversion was indicated via HPLC-MS the reaction mixture was transferred to a separation funnel and extracted with H_2O and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (30 g SiO_2, Pasteur pipette, eluent: cyclohexane/EtOAc = 3/1, R_f = 0.22, UV and $KMnO_4$, fraction size: 0.5 mL).

Yield: 8.0 mg (15.4 µmol, 17 %), yellowish solid

$C_{17}H_{15}BrINO_3S$ [520.18 g/mol]

TLC: R_f = 0.22 (cyclohexane/EtOAc = 3/1, UV and $KMnO_4$)

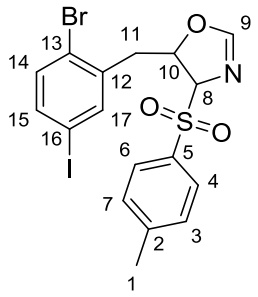
HPLC-MS (Method_2): t_R = 4.58 min, *m*/*z* + H = 521.

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.78 (d, $^3J_{HH}$ = 8.1 Hz, 2H, H-4, H-6), 7.56 (d, $^4J_{HH}$ = 1.6 Hz, 1H), 7.45 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.6 Hz, 1H, H-15), 7.36 (d, $^3J_{HH}$ = 7.9 Hz, 2H, H-3, H-7), 7.28 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-14), 7.02 (s, 1H, H-9), 5.33 (m, 1H, H-10), 4.93 (dd, $^3J_{HH}$ = 5.4 Hz, $^4J_{HH}$ = 1.1 Hz, 1H, H-8), 3.09 (m, 1H, H-11), 2.45 (s, 3H, H-1) ppm.

APT (75.53 MHz, $CDCl_3$): δ = 145.8 (C_q, C-5), 140.3 (C-17), 138.2 (C-15), 136.8 (C_q, C-12), 134.8 (C-14), 130.1 (C-3, C-7), 129.6 (C-4, C-6), 109.7 (C_q, C-2), 100.8 (C_q, C-13), 92.7 (C_q, C-16), 89.2 (C-9), 77.8 (C-10), 40.3 (C-11), 21.9 (C-1) ppm.

HRMS (DI-EI TOF): calcd. for $C_{10}H_7BrINO^+$ $[M]^+$: 362.8756; found: 362.8764.

7.4.15.12. 5-(2-Bromo-5-iodobenzyl)-4-tosyl-4,5-dihydrooxazole (88)



88

In a flame dried 8 mL Schlenk-flask 150 mg (769 µmol, 1.00 eq) p-tosylmethylisocyanide were dried in vacuum for 30 min. Then 2.0 mL abs. EtOH were added and the colorless suspension was cooled to 0 °C. Afterwards 250 mg (769 µmol, 1.00 eq) 2-(2-bromo-5-iodo-phenyl)acetaldehyde (**84**) were added at 0 °C. 245 mg (1.15 mmol, 1.50 eq) K_3PO_4 were added to the yellow suspension, which was stirred at 0 °C for 30 min, followed by 60 min at RT. After full conversion was indicated via GC-MS the reaction mixture was transferred to a separation funnel and extracted with H_2O and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was used without further purification in the next step.

Yield: 438 mg (842 µmol, 109 %), yellowish solid

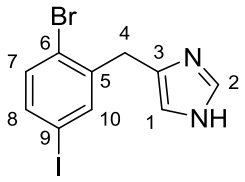
$C_{17}H_{15}BrINO_3S$ [520.18 g/mol]

TLC: R_f = 0.22 (cyclohexane/EtOAc = 3/1, UV and $KMnO_4$)

HPLC-MS (Method_2): t_R = 4.58 min, *m*/*z* + H = 521.

HRMS (DI-EI TOF): calcd. for $C_{10}H_7BrINO^+$ $[M]^+$: 362.8756; found: 362.8764.

7.4.15.13. 4-(2-Bromo-5-iodobenzyl)-1*H*-imidazole (75)



75

In a 8 mL pressure tube 100 mg (769 µmol, 1.00 eq) 5-(2-bromo-5-iodobenzyl)-4-tosyl-4,5-dihydrooxazole (**88**) were suspended in 2.0 mL 7M NH_3 solution in MeOH. The suspension was stirred overnight at 70 °C. After full conversion was indicated via HPLC-MS the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (20 g SiO_2, eluent: CH_2Cl_2/MeOH = 10/1, fraction size: 5.0 mL).

Yield: 59 mg (162 µmol, 21 %), yellowish solid

$C_{10}H_8BrIN_2$ [363.00 g/mol]

HPLC-MS (Method_2): t_R = 3.88 min, *m*/*z* + H = 364.

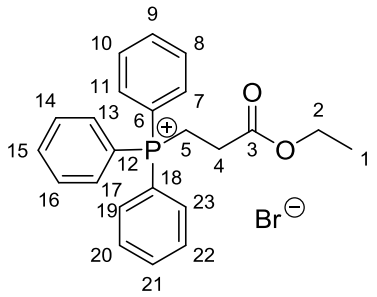
^{1}H-NMR (300.36 MHz, DMSO d_6): δ = 7.62 (s, 1H, H-2), 7.58 (d, $^4J_{HH}$ = 1.4 Hz, 1H, H-10), 7.49 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.4 Hz, 1H, H-8), 7.37 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H-7), 6.82 (s, 1H, H-1), 3.89 (s, 2H, H-4) ppm.

^{13}C-NMR (75.53 MHz, DMSO d_6): δ = 142.1 (C_q, C-5), 139.2 (C-10), 136.8 (C-8), 135.2 (C_q, C-3), 134.6 (C-2), 134.3 (C-7), 123.7 (C_q, C-7), 116.6 (C-1), 93.5 (C_q, C-9), 33.0 (C-4) ppm.

HRMS (DI-EI TOF): calcd. for $C_{10}H_8BrIN_2^+$ $[M]^+$: 361.8916; found: 361.8915.

7.4.16. Synthesis of the C-elongated Glu building block

7.4.16.1. (3-Ethoxy-3-oxopropyl)triphenylphosphonium bromide (92)



92

In a flame dried 100 mL Schlenk-flask 3.00 g (11.4 mmol, 1.20 eq) triphenylphosphine were dissolved in 15 mL abs. toluene. Then 1.20 mL (9.53 mmol, 1.00 eq) ethyl-3-bromopropanoate were added and the colorless solution was stirred at RT overnight. After 20 h the solvent was removed under reduced pressure. The colorless solid was washed with EtOAc (1 x 50 mL) and CH_2Cl_2 (1 x 50 mL) and then collected by filtration. The filter cake was dried in vacuum and compound **92** was isolated as a colorless powder.

Yield: 754 mg (1.70 mmol, 18 %), colorless solid

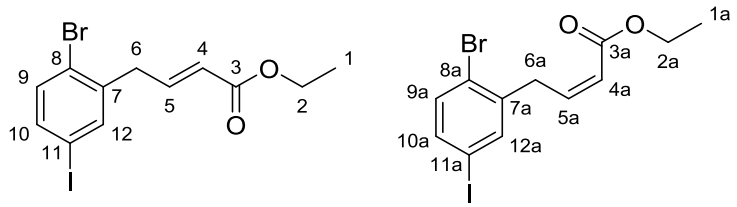
$C_{23}H_{24}BrO_2P$ [443.32 g/mol]

mp$^{exp.}$ = 111-113 °C

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.84 – 7.67 (m, 15H, H-7, H-8, H-9, H-10, H-11, H-13, H-14, H-15, H-16, H-17, H-19, H-20, H-21, H-22, H-23), 4.19 – 4.11 (m, 2H, H-5), 3.84 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-2), 2.93 (dt, $^3J_{HP}$ = 19.0, $^3J_{HH}$ = 6.6 Hz, 2H, H-4), 1.05 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 170.4 (d, $^3J_{CP}$ = 8.0 Hz, C-3), 135.3 (d, $^4J_{CP}$ = 3.0 Hz, C-9, C-15, C-21), 133.8 (d, $^3J_{CP}$ = 10.1 Hz, C-8, C-10, C-14, C-16, C-20, C-22), 130.6 (d, $^2J_{CP}$ = 12.6 Hz, C-7, C-11, C-13, C-17, C-19, C-23), 117.9 (d, $^1J_{CP}$ = 86.4 Hz, C-6, C-12, C-18), 61.6 (C-2), 27.4 (d, $^2J_{CP}$ = 3.4 Hz, C-4), 18.5 (d, $^1J_{CP}$ = 54.0 Hz, C-5), 14.0 (C-1) ppm.

7.4.16.2. (*E*)-Ethyl 4-(2-bromo-5-iodophenyl)butanoate, (*Z*)-Ethyl 4-(2-bromo-5-iodophenyl)butanoate (95)



95

In a flame dried Schlenk-flask 397 mg (924 µmol, 1.50 eq) phosphonium-salt **65** and 104 mg (926 µmol, 1.50 eq) KO*t*Bu were dried in vacuum for 1 h. Then 2 mL abs THF were added. The colorless suspension was stirred at RT for 1 h. After 1 h 200 mg (616 µmol, 1.00 eq) 2-(2-bromo-5-iodophenyl)acetaldehyde (**84**) were added. The yellow suspension was stirred at 50 °C until complete conversion was detected by TLC (14 h). The solvent was removed under reduced pressure. The yellow-brown crude product was purified via flash column chromatography (55 g SiO_2, 2.5 x 13.5 cm, eluent: cyclohexane/EtOAc = 20/1, fraction size: 20 mL).

Yield: 226 mg (572 µmol, 62 %), *E*/*Z* mixture = 2.3/1, colorless oil

$C_{12}H_{12}BrIO_2$ [395.03 g/mol]

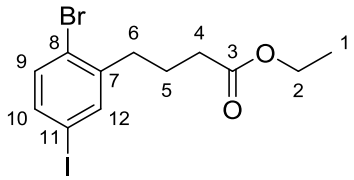
TLC: R_f = 0.63 (cyclohexane/EtOAc = 9/1, UV and $KMnO_4$)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.83 (d, $^4J_{HH}$ = 1.8 Hz, 1H, H-12), 7.51 (d, $^4J_{HH}$ = 1.8 Hz, 1H, H-12a), 7.46 – 7.33 (m, 2H, H-10, H-10a), 7.30 – 7.21 (m, 2H, H-9, H-9a), 7.08 – 6.94 (m, 1H, H-5a), 6.71 (d, $^3J_{HH}$ = 15.8 Hz, 1H, H-4), 6.36 – 6.20 (m, 1H, H-5), 5.78 (d, $^3J_{HH}$ = 15.6 Hz, 1H, H-4a), 4.19 (q, $^3J_{HH}$ = 7.1 Hz, 4H, H-2, H-2a), 3.58 (dd, $^3J_{HH}$ = 5.3 Hz, $^4J_{HH}$ = 1.0 Hz, 1H, H-6a), 3.29 (dd, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 1.0 Hz, 2H, H-6), 1.34 - 1.24 (m, 6H, H-1, H-1a) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 171.2 (C_q, C-3), 166.3 (C_q, C-3a), 144.5 (C-5a), 139.9 (C_q, C-7a), 139.5 (C-12a), 139.0 (C_q, C-7), 137.7 (C-10), 137.6 (C-10a), 136.0 (C-12), 134.7 (C-9a), 134.5 (C-9), 131.0 (C-4), 126.4 (C-5), 124.6 (C_q, C-8a), 123.6 (C-4a), 123.2 (C_q, C-8), 92.8 (C_q, C-11a), 92.7 (C_q, C-11), 61.1 (C-2), 60.6 (C-2a), 38.5 (C-6), 38.3 (C-6a), 14.4 (C-1, C-1a) ppm.

HRMS (DI-EI TOF): calcd. for $C_{12}H_{12}BrIO_2^+$ $[M]^+$: 393.9066; found: 393.9077.

7.4.16.3. Ethyl 4-(2-bromo-5-iodophenyl)butanoate (94)



94

A 50 mL one-neck round-bottom flask, equipped with reflux-condenser, was charged with a solution of 202 mg (512 µmol, 1.00 eq) ethyl 4-(2-bromo-5-iodophenyl)butanoate (**95**) in 5 mL THF. Then 573 mg (3.08 mmol, 6.01 eq) p-tosylhydrazide, 421 mg (5.13 mmol, 10.0 eq) NaOAc and 100 µL H_2O were added and the orange suspension was stirred at 70 °C until quantitative conversion (18 h) was indicated by GC-MS. The reaction mixture was cooled to RT and 10 mL satd. $NaHCO_3$-solution were added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (40 g SiO_2, 2.5 x 11.0 cm, eluent: cyclohexane/EtOAc = 20/1, fraction size: 20 mL).

Yield: 180 mg (454 µmol, 89 %), colorless oil

$C_{12}H_{14}BrIO_2$ [397.05 g/mol]

TLC: R_f = 0.59 (cyclohexane/EtOAc = 9/1, UV and $KMnO_4$)

GC-MS (Method_1): t_R = 7.12 min, *m/z* = 396 (10 %), 351 (17 %), 317 (100 %), 168 (9 %), 88 (34 %).

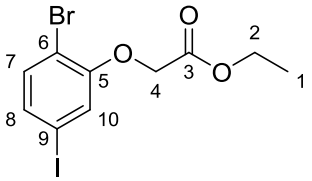
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.54 (d, $^4J_{HH}$ = 1.7 Hz, 1H, H-12), 7.36 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, H-10), 7.24 (d, $^3J_{HH}$ = 8.4 Hz, 1H, H-9), 4.14 (q, $^3J_{HH}$ = 7.2 Hz, 2H, H-2), 2.71 (t, $^3J_{HH}$ = 7.8 Hz, 2H, H-6), 2.36 (t, $^3J_{HH}$ = 7.4 Hz, 2H, H-4), 1.93 (pent, 2H, H-5), 1.27 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 173.2 (C_q, C-3), 143.4 (C_q, C-7), 139.3 (C-12), 136.9 (C-10), 134.6 (C-9), 124.5 (C_q, C-8), 92.6 (C_q, C-11), 60.6 (C-2), 35.2 (C-6), 33.7 (C-4), 25.0 (C-5), 14.4 (C-1) ppm.

HRMS (EI): calcd. for $C_{12}H_{14}BrIO_2^+$ $[M]^+$: 395.9222; found: 395.9215.

7.4.17. Synthesis of the O-Glutamate building block

7.4.17.1. Ethyl 2-(2-bromo-5-iodophenoxy)acetate (98)



98

In a flame dried 20 mL Schlenk-flask 200 mg (669 µmol, 1.00 eq) 5-bromo-2-iodophenol (**96**), 75.0 mg (669 mmol, 1.00 eq) KO*t*Bu and 20 mg (113 µmol, 0.20 eq) NaI were suspended in 5 mL CH_3CN. Then 75 µL (669 mmol, 1.00 eq) ethylbromoacetate (**97**) were added slowly via a syringe. The yellow/orange suspension was stirred at RT. After complete conversion was detected by TLC (14 h) 20 mL EtOAc and 40 mL satd. $NaHCO_3$-solution were added. The phases were separated and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The yellow/orange crude product was purified via flash column chromatography (30 g SiO_2, 2.5 x 10.0 cm, eluent: cyclohexane/EtOAc = 12/1, R_f = 0.32, UV and $KMnO_4$, fraction size: 20 mL).

Yield: 256 mg (665 µmol, 99 %), colorless solid

$C_{10}H_{10}BrIO_3$ [385.00 g/mol]

mp$^{exp.}$ = 65 - 66 °C

TLC: R_f = 0.28 (cyclohexane/EtOAc = 12/1, UV and $KMnO_4$)

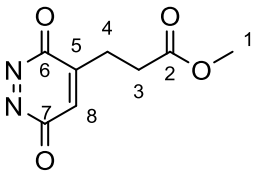
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.63 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H-7), 6.90 (dd, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 1.9 Hz, 1H, H-8), 6.84 (d, $^3J_{HH}$ = 1.7 Hz, 1H, H-10), 4.67 (s, 2H, H-4), 4.28 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-2), 1.31 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 168.9 (C_q, C-3), 157.6 (C_q, C-5), 140.7 (C-7), 126.8 (C-8), 122.8 (C_q, C-6), 116.1 (C-10), 84.9 (C_q, C-9), 66.6 (C-4), 61.8 (C-2), 14.3 (C-1) ppm.

HRMS (DI-EI TOF): calcd. for $C_{10}H_{10}BrIO_3^+$ $[M]^+$: 383.8858; found: 383.8871.

7.4.18. Pyridazine Glutamate building block

7.4.18.1. Methyl 3-(3,6-dioxo-3,6-dihydropyridazin-4-yl)propanoate (105)



105

In a flame dried 10 mL Schlenk-flask 200 mg (1.05 mmol, 1.00 eq) 4-bromo-1,2-dihydropyridazine-3,6-dione (**102**) were dissolved in 2 mL abs. DMF. Then 150 µL (1.66 mmol, 1.58 eq) methylacrylate (**103**), 60 mg (52.4 µmol, 0.05 eq) $Pd(PPh_3)_4$ and 290 µL (2.09 mmol, 2.00 eq) Et_3N were added and the orange solution was stirred for 16 h at RT. After complete conversion was detected by TLC the solvent was removed under reduced pressure. The orange crude product was purified via flash column chromatography (40 g SiO_2, 2.5 x 13.0 cm, eluent: CH_2Cl_2/MeOH + 0.5 % NH_3 = 10/1 (fractions 1–15), CH_2Cl_2/MeOH + 0.5 % NH_3 = 9/1 (fractions 16–42), CH_2Cl_2/MeOH + 0.5 % NH_3 = 8/1 (fractions 43–69), R_f = 0.21 (CH_2Cl_2/MeOH + 0.5 % NH_3 = 12/1), UV and $KMnO_4$, fraction size: 20 mL).

Yield: 130 mg (662 µmol, 63 %), yellowish solid

$C_8H_8N_2O_4$ [196.16 g/mol]

mp$^{exp.}$ = 135 - 142 °C

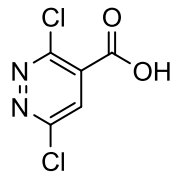
TLC: R_f = 0.21 (cyclohexane/EtOAc = 12/1, UV and $KMnO_4$)

^{1}H-NMR (300.36 MHz, CD_3OD): δ = 7.54 (s, 1H, H-8), 4.30 (t, $^3J_{HH}$ = 7.0 Hz, 2H, H-3), 3.67 (s, 3H, H-1), 2.81 (t, $^3J_{HH}$ = 7.0 Hz, 2H, H-4) ppm.

^{13}C-NMR (75.53 MHz, CD_3OD): δ = 173.1 (C_q, C-2), 157.7 (C_q, C-6), 154.3 (C_q, C-7), 131.1 (C_q, C-5), 130.3 (C-8), 52.3 (C-1), 49.0 (C-4), 33.2 (C-3) ppm.

HRMS (DI-EI TOF): calcd. for $C_8H_8N_2O_4^+$ $[M]^+$: 196.0484; found: 196.0444.

7.4.18.2. 3,6-Dichloropyridazine-4-carboxylic acid (107)



107

In a 250 mL one-neck round-bottom flask 4.50 g (27.6 mmol, 1.00 eq) 3,6-dichloro-4-methylpyridazine (**99**) were dissolved in 90 mL CH_3CN. Then a solution of 4.65 g (82.8 mmol, 3.00 eq) KOH in 41.5 mL H_2O was added. Afterwards 8.73 g (55.2 mmol, 2.00 eq) $KMnO_4$ were added in portions over 40 min. The red/brown suspension was stirred for 15 h at RT. After 15 h incomplete conversion was detected by TLC. Nevertheless the reaction mixture was extracted with EtOAc (2 x 50 mL) to remove remaining starting material. Afterwards the aqueous phase was acidified to pH 1 with conc. HCl and extracted with EtOAc (10 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was used without further purification in the next step.

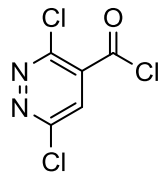
Yield: 2.53 g (13.1 mmol, 48 %), brown solid

$C_5H_2Cl_2N_2O_2$ [192.98 g/mol]

mp$^{exp.}$ = 132-135 °C

TLC: R_f = 0.05 (cyclohexane/EtOAc = 4/1, UV and $KMnO_4$)

7.4.18.3. 3,6-Dichloropyridazine-4-carbonyl chloride (112)



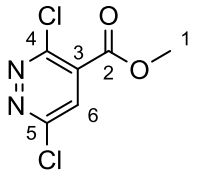
112

In a flame dried 25 mL Schlenk-flask 500 mg (2.59 mmol, 1.00 eq) 3,6-dichloropyridazine-4-carboxylic acid (**107**) were suspended in 10 mL abs. CH_2Cl_2. Then the yellow/orange suspension was cooled to 0 °C with an ice bath. Afterwards 250 µL (2.92 mmol, 1.13 eq) oxalylchloride and 50 µL (650 µmol, 0.25 eq) DMF were added and the suspension was stirred for 30 min at 0 °C. Then the ice bath was removed and the suspension was stirred at RT for 1 h. After complete conversion was indicated by GC-MS (quenching of the sample for the GC-MS analysis with MeOH) the solvent and exess oxalylchloride were removed under high vacuum using a cooling trap. The crude product was used without further purification in the next step.

Yield: 629 mg (3.27 mmol), red/brown oil

$C_5HCl_3N_2O$ [211.43 g/mol]

7.4.18.4. Methyl 3,6-dichloropyridazine-4-carboxylate (108)



108

In a 50 mL one-neck round-bottom flask 629 mg (2.99 mmol, 1.00 eq) 3,6-dichloropyridazine-4-carbonyl chloride (**112**) were dissolved in 10 mL MeOH. The red/brown solution was stirred for 15 min at RT. After complete conversion was indicated by GC-MS the solvent and excess oxalylchloride were removed under reduced pressure. The red/brown crude product was purified via flash column chromatography (60 g SiO_2, 5.0 x 10.0 cm, eluent: cyclohexane/EtOAc = 3/1, R_f = 0.73 (cyclohexane/EtOAc = 1/1), UV and $KMnO_4$, fraction size: 20 mL).

Yield: 148 mg (718 µmol, 24 %), brownish solid

$C_6H_4Cl_2N_2O_2$ [207.01 g/mol]

mp$^{exp.}$ = 34 - 36 °C

TLC: R_f = 0.73 (cyclohexane/EtOAc = 1/1, UV and $KMnO_4$)

GC-MS (Method_1): t_R = 7.12 min, *m*/*z* = 207 (100 %), 175 (35 %), 119 (52 %), 84 (66 %).

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 7.87 (s, 1H, H-5), 4.02 (s, 3H, H-1).ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 162.2 (C_q, C-2), 156.5 (C_q, C-5), 153.0 (C_q, C-4), 131.6 (C_q, C-3), 130.0 (C-6), 54.0 (C-1) ppm.

HRMS (DI-EI TOF): calcd. for $C_6H_4Cl_2N_2O_2^+$ $[M]^+$: 205.9650; found: 205.9640.

7.4.19. Synthesis of Teraryls

7.4.19.1. General procedure for the synthesis of teraryls by consecutive double Suzuki-coupling (1st step)

A flame dried Schlenk-flask was charged with 1.00 eq of the corresponding core building block, 1.00 eq to 1.10 eq of the boronic acid derivative, 2.0 eq K_2CO_3 and 5 mol% Pd(dppf)Cl_2. Then abs., degassed DMF (~0.2M) was added. The reaction mixture was stirred at 80 °C until full conversion was detected by TLC or HPLC-MS. The typically brown/black suspension was concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography.

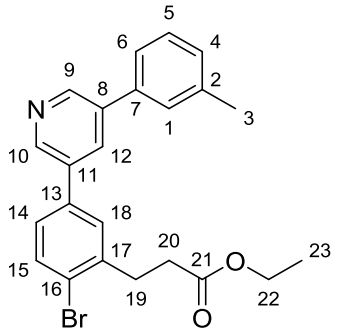
7.4.19.2. General procedure for the synthesis of teraryls by consecutive double Suzuki-coupling (2nd step)

Another flame dried Schlenk-flask was charged with 1.00 eq of the previously prepared diaryl, 1.05 to 1.10 eq of the second boronic acid pinacol ester, 2.00 eq Cs_2CO_3 and 5 mol% Pd(dppf)Cl_2. Then abs., degassed DMF (~0.2M) was added and the reaction mixture was stirred at 80 °C overnight. The typically brown/black suspension was concentrated to dryness and the crude product was purified via flash column chromatography.

7.4.19.3. General procedure for the deprotection of esters

In a one-neck round-bottom flask 1.00 eq of the previously prepared teraryl were dissolved in THF/H_2O (2/1). Then 20.0 eq LiOH were added and the colorless suspension was stirred at RT until full conversion was detected by HPLC-MS. Afterwards 1M HCl was added to the suspension to adjust pH = 1 and the suspension was extracted with CH_2Cl_2. The solvent of the combined organic phases was removed under reduced pressure. In some cases the product was purified via preparative HPLC.

7.4.19.4. Ethyl 3-(2-bromo-5-(5-(*m*-tolyl)pyridin-3-yl)phenyl)propanoate (110)



110

A flame dried 8 mL Schlenk-flask was charged with 134 mg (350 µmol, 1.00 eq) ethyl 2-(2-bromo-5-iodophenoxy)acetate (**67**), 103 mg (350 µmol, 1.00 eq) 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(*m*-tolyl)pyridine, 13 mg (17.8 µmol, 0.05 eq) Pd(dppf)Cl_2 and 97 mg (702 µmol, 2.01 eq) K_2CO_3. 2 mL abs., degassed DMF were added and the reaction mixture was stirred at 80 °C until full conversion (20 h) was detected by GC-MS. The red/brown suspension was then concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography (40 g SiO_2, 2.5 x 11.0 cm, eluent: cyclohexane/EtOAc = 7/1, R_f = 0.22, UV and $KMnO_4$, fraction size: 25 mL).

Yield: 127 mg (299 µmol, 86 %), pale yellow solid.

$C_{23}H_{22}BrNO_2$ [424.34 g/mol]

mp$^{exp.}$ = 46 – 47 °C

TLC: R_f = 0.22 (cyclohexane/EtOAc = 7/1, UV and $KMnO_4$)

GC-MS (Method_1): t_R = 12.09 min, *m/z* = 423 (3 %), 344 (55 %), 316 (100 %), 274 (21 %), 158 (14 %).

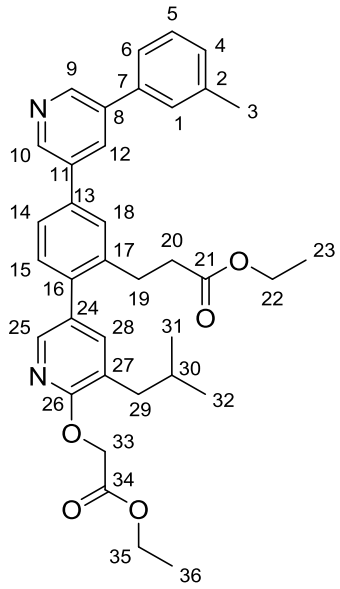
^{1}H-NMR (300.36 MHz, $CDCl_3$): 8.82 (d, $^4J_{HH}$ = 1.9 Hz, 1H, H-9), 8.76 (d, J = 2.0 Hz, 1H, H-10), 8.03 – 7.95 (m, 1H, H-12), 7.66 (d, $^3J_{HH}$ = 8.2 Hz, 1H, H-15), 7.53 (d, $^4J_{HH}$ = 2.0 Hz, 1H, H-18), 7.48 – 7.31 (m, 4H, H-1, H-5, H-6, H-14), 7.25 (d, $^3J_{HH}$ = 5.1 Hz, 1H, H-4), 4.15 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-22), 3.16 (t, $^3J_{HH}$ = 7.7 Hz, 2H, H-19), 2.71 (t, $^3J_{HH}$ = 7.7 Hz, 2H, H-20), 2.46 (s, 1H, H-3), 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-23) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 172.6 (C_q, C-21), 147.5 (C-9), 146.8 (C-10), 140.9 (C_q, C-17), 139.0 (C_q, C-2), 137.7 (C_q), 137.5 (C_q), 137.0 (C_q), 135.6 (C_q), 133.8 (C-15), 132.8 (C-

12), 129.4 (C-18), 129.3 (C^{Ph}), 129.2 (C^{Ph}), 128.1 (C^{Ph}), 126.9 (C-14), 124.6 (C_q, C-16) 124.5 (C-Ph), 60.8 (C-22), 34.3 (C-20), 31.7 (C-19), 21.7 (C-1), 14.4 (C-23) ppm.

HRMS (EI): calcd. for $C_{23}H_{22}BrNO_2^+$ $[M]^+$: 423.0834; found: 423.0830.

7.4.19.5. Ethyl 3-(2-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-5-(5-(m-tolyl)-pyridin-3-yl)phenyl)propanoate (115)



115

A flame dried 8 mL Schlenk-flask was charged with 56 mg (132 µmol, 1.00 eq) ethyl 3-(2-bromo-5-(5-(m-tolyl)pyridin-3-yl)phenyl)propanoate (**110**), 50 mg (138 µmol, 1.04 eq) ethyl 2-((3-isobutyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)oxy)acetate (**114**), 5.4 mg (7.38 µmol, 0.06 eq) $Pd(dppf)Cl_2$ and 86 mg (264 µmol, 2.00 eq) Cs_2CO_3. 1.5 mL abs DMF were added and the reaction mixture was stirred at 80 °C until full conversion was detected by TLC (20 h). The typically brown/black suspension was then concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography (25 g SiO_2, 2.5 x 9.0 cm, eluent: cyclohexane/EtOAc = 3/1, R_f = 0.33, UV and $KMnO_4$, fraction size: 8 mL). Fractions 5 to 19 were combined and the solvent was removed under reduced pressure.

Yield: 41.5 mg (71.5 µmol, 54 %), sticky colorless solid

$C_{36}H_{40}N_2O_5$ [580.73 g/mol]

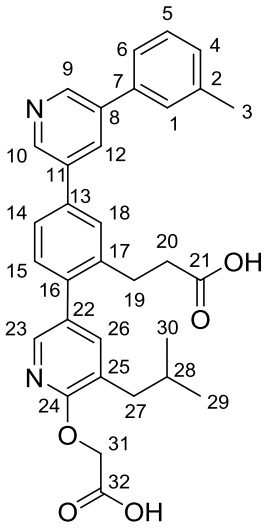
TLC: R_f = 0.33 (cyclohexane/EtOAc = 2/1, UV and $KMnO_4$)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 8.83 (s, 2H, H-9, H-10), 8.05 (s, 1H, H-12), 7.94 (d, $^{3}J_{HH}$ = 2.1 Hz, 1H, H-18), 7.57 – 7.30 (m, 8H, H-1, H-4, H-5, H-6, H-14, H-15, H-25, H-28), 4.96 (s, 2H, H-33), 4.25 (q, $^{3}J_{HH}$ = 7.1 Hz, 2H, H-35), 4.07 (q, $^{3}J_{HH}$ = 7.1 Hz, 2H, H-22), 3.02 (t, $^{3}J_{HH}$ = 7.9 Hz, 2H, H-19), 2.62 – 2.38 (m, 7H, H-3, H-20, H-29), 2.14 – 2.00 (m, 1H, H-30), 1.28 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H, H-36), 1.18 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H, H-23), 0.95 (d, $^{3}J_{HH}$ = 6.6 Hz, 6H, H-31, H-32) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 172.6 (C_q, C-21), 169.7 (C_q, C-34), 160.3 (C_q, C-36), 147.3 (C-9), 146.9 (C-10), 143.5 (C-18), 140.1 (C^{Ar}), 139.6 (C_q), 139.0 (C_q), 138.5 (C_q), 137.8 (C_q), 137.6 (C_q), 137.0 (C_q), 136.3 (C_q), 133.0 (C-12), 131.5 (C^{Ar}), 130.3 (C_q), 129.2 (C^{Ar}),128.3 (C^{Ar}), 128.2 (C^{Ar}), 125.4 (C^{Ar}), 124.5 (C^{Ar}), 123.8 (C_q), 62.7 (C-33), 61.1 (C-35), 60.6 (C-22), 39.3 (C-29), 35.5 (C-20), 28.62 (C-19), 28.1 (C-30), 22.7 (C-31, C-32), 21.7 (C-3), 14.3 (C-23, C-36) ppm.

HRMS (DI-EI TOF): calcd. for $C_{36}H_{40}N_2O_5^{+}$ $[M]^{+}$: 580.2937; found: 580.2939.

7.4.19.6. Ethyl 3-(2-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-5-(5-(m-tolyl) pyridin-3-yl)phenyl)propanoate (118)



118

In a 50 mL one-neck round-bottom flask 29.6 mg (51.0 µmol, 1.00 eq) ethyl 3-(2-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-5-(5-(*m*-tolyl)pyridin-3-yl)phenyl)propanoate (**115**) were dissolved in 1.5 mL THF/H_2O (2/1). Then 43.0 mg (1.02 mmol, 20.1 eq) LiOH were added and the colorless suspension was stirred at RT until full conversion was detected

by HPLC-MS (30 min). Afterwards 3 mL 1M HCl were added to the suspension to adjust to pH = 1 and the product was extracted with CH_2Cl_2 (5 x 10 mL). The solvent of the combined organic phases was removed under reduced pressure. The crude prodct was purified via preparative HPLC (Method_4)).

Yield: 7.0 mg (13.3 µmol, 26 %), colorless solid

$C_{32}H_{32}N_2O_5$ [524.62 g/mol]

mp$^{exp.}$ = 83 – 112 °C

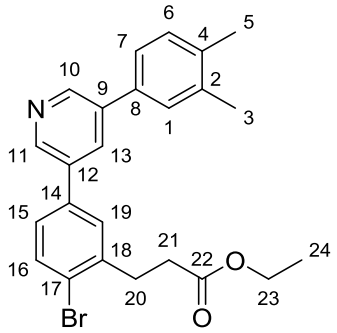
HPLC-MS (Method_2): t_R = 7.33 min, *m/z* + H = 525.

^{1}H-NMR (499.87 MHz, DMSO d_6): δ = 9.07 (s, 1H, H-9), 9.01 (s, 1H, H-10), 8.67 (s, 1H, H-12), 7.98 (s, 1H, H-26), 7.93 (s, 1H, H-18), 7.83 (d, $^3J_{HH}$ = 7.7 Hz, 1H, H-15), 7.75 (s, 1H, H-1), 7.71 (d, $^3J_{HH}$ = 7.4 Hz, 1H, H-6), 7.58 (s, 1H, H-23), 7.46 (t, $^3J_{HH}$ = 7.5 Hz, 1H, H-5), 7.37 (d, $^3J_{HH}$ = 7.8 Hz, 1H, H-14), 7.33 (d, $^3J_{HH}$ = 7.3 Hz, 1H, H-4), 4.90 (s, 2H, H-31), 2.89 (t, $^3J_{HH}$ = 8.0 Hz, 2H, H-19), 2.60 – 2.50 (m, 4H, H-20, H-27), 2.43 (s, 3H, H-3), 2.03 (m, 1H, H-28), 0.91 (d, $^3J_{HH}$ = 6.5 Hz, 6H, H-29, H-30) ppm.

^{13}C-NMR (125.69 MHz, DMSO d_6): δ = 173.5 (C_q, C-21), 170.3 (C_q, C-32), 159.7 (C_q, C-24), 143.2 (C-9, C-10, C-26), 139.9 (C-23), 139.6 (C_q), 138.5 (C_q), 138.3 (C_q), 137.2 (C_q), 136.7 (C_q), 135.6 (C-12), 135.1 (C_q), 131.0 (C-14), 129.7 (C-4), 129.5 (C_q), 129.1 (C-5), 128.1 (C-18), 128.0 (C-1), 125.2 (C-15), 124.5 (C-6), 122.6 (C_q), 62.1 (C-31), 38.3 (C-27), 34.6 (C-20), 27.8 (C-19), 27.3 (C-28), 22.3 (C-29, C-30), 21.0 (C-3) ppm.

HRMS (MALDI-TOF): calcd. for $C_{32}H_{32}N_2O_5H^+$ $[M+H]^+$: 525.2389; found: 525.2382.

7.4.19.7. Ethyl 3-(2-bromo-5-(5-(3,4-dimethylphenyl)pyridin-3-yl)phenyl)propanoate (111)



111

A flame dried 8 mL Schlenk-flask was charged with 134 mg (350 µmol, 1.00 eq) ethyl 3-(2-bromo-5-iodophenyl)propanoate (**67**), 108 mg (350 µmol, 1.00 eq) 3-(3,4-dimethylphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, 13 mg (17.8 µmol, 0.05 eq) Pd(dppf)Cl_2 and 97 mg (702 µmol, 2.00 eq) K_2CO_3. 2 mL abs, degassed DMF were added and the reaction mixture was stirred at 80 °C until full conversion was detected by GC-MS. The red/brown suspension was then concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography (40 g SiO_2, 2.5 x 10.5 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.23, UV and $KMnO_4$, fraction size: 25 mL).

Yield: 114 mg (260 µmol, 75 %), pale yellow solid

$C_{24}H_{24}BrNO_2$ [438.37 g/mol]

mp$^{exp.}$ = 68 – 70 °C

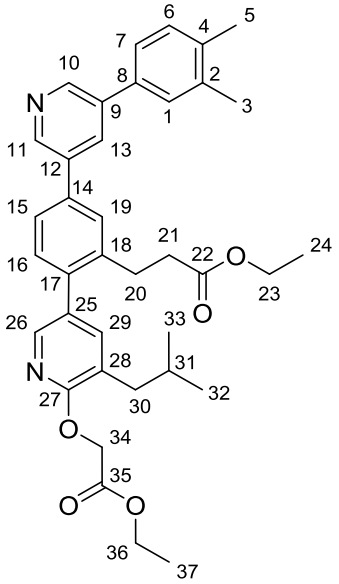
TLC: R_f = 0.23 (cyclohexane/EtOAc = 5/1, UV and $KMnO_4$)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 8.81 (d, $^4J_{HH}$ = 1.8 Hz, 1H, H-10), 8.74 (d, $^4J_{HH}$ = 1.9 Hz, 1H, H-11), 7.97 (s, 1H, H-13), 7.66 (d, $^3J_{HH}$ = 8.2 Hz, 1H, H-16), 7.53 (d, $^4J_{HH}$ = 1.9 Hz, 1H, H-19), 7.44 – 7.31 (m, 3H, H-1, H-6, H-15), 7.27 (d, $^3J_{HH}$ = 5.2 Hz, 1H, H-7), 4.15 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-23), 3.16 (t, $^3J_{HH}$ = 7.7 Hz, 2H, H-20), 2.71 (t, $^3J_{HH}$ = 7.7 Hz, 2H, H-21), 2.36 (s, 3H, H-3), 2.34 (s, 3H, H-5), 1.24 (t, $^4J_{HH}$ = 7.1 Hz, 3H, H-24) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 172.5 (C_q, C-22), 147.3 (C-10), 146.4 (C-11), 140.7 (C-18), 137.5 (C_q), 137.5 (C_q), 137.0 (C_q), 136.8 (C_q), 135.4 (C_q), 135.1 (C_q), 133.6 (C-16), 132.5 (C-13), 130.5 (C-7), 129.3 (C-19), 128.4 (C-1), 126.8 (C-15), 124.6 (C-6), 124.5 (C_q, C-17), 60.6 (C-23), 34.1 (C-21), 31.6 (C-20), 19.9 (C-3), 19.5 (C-5), 14.3 (C-24) ppm.

HRMS (DI-EI TOF): calcd. for $C_{24}H_{24}BrNO_2^+$ $[M]^+$: 437.0990; found: 437.0994.

7.4.19.8. Ethyl 3-(4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-3'',4''-dimethyl-[1,1':3',1''-terphenyl]-3-yl)propanoate (116)



116

A flame dried 8 mL Schlenk-flask was charged with 58 mg (132 µmol, 1.00 eq) ethyl 3-(2-bromo-5-(5-(3,4-dimethylphenyl)pyridin-3-yl)phenyl)propanoate (**111**), 53 mg (146 µmol, 1.10 eq) ethyl 2-((3-isobutyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-oxy)acetate (**114**), 5.5 mg (6.73 µmol, 0.05 eq) Pd(dppf)Cl_2 and 86.2 mg (265 µmol, 2.00 eq) Cs_2CO_3. 1.5 mL abs. DMF were added and the reaction mixture was stirred at 80 °C until full conversion was detected by TLC (20 h). The brown/black suspension was then concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography (25 g SiO_2, 2.5 x 9.0 cm, eluent: cyclohexane/EtOAc = 3/1, R_f = 0.35, UV and $KMnO_4$, fraction size: 8 mL).

Yield: 50.0 mg (84.1 µmol, 64 %), sticky brownish solid

$C_{37}H_{42}N_2O_5$ [594.75 g/mol]

TLC: R_f = 0.35 (cyclohexane/EtOAc = 3/1, UV and $KMnO_4$)

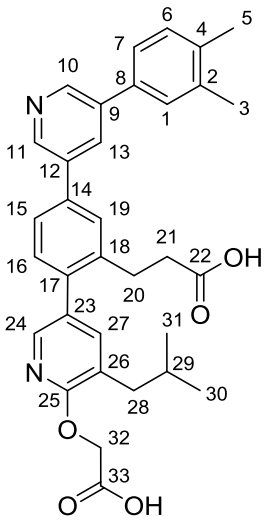
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 8.82 – 8.80 (m, 2H, H-10, H-11), 8.04 (s, 1H, H-13), 7.94 (d, $^3J_{HH}$ = 1.9 Hz, 1H, H-19), 7.56 - 7.29 (m, 7H, H-1, H-6, H-7, H-15, H-16, H-26, H-29), 4.96 (s, 2H, H-34), 4.25 (q, $^3J_{HH}$ = 7.1 Hz, 2H; H-36), 4.07 (q, $^3J_{HH}$ = 7.2 Hz, 2H, H-23), 3.02 (t, $^3J_{HH}$ = 7.8 Hz, 2H, H-20), 2.58 – 2.47 (m, 4H, H-21, H-30), 2.37 (s, 3H, H-3), 2.34 (s,

3H, H-5), 2.11 – 2.05 (m, 1H, H-31), 1.28 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-37), 1.18 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-24), 0.95 (d, $^3J_{HH}$ = 6.6 Hz, 6H, H-32, H-33) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 172.6 (C_q, C-22), 169.7 (C_q, C-35), 160.1 (C_q, C-27), 147.1 (C-10), 146.6 (C-11), 143.5 (C^{Ar}), 140.1 (C^{Ar}), 139.5 (C_q), 138.4 (C_q), 137.6 (C_q), 137.1 (C_q), 136.9 (C_q), 136.2 (C_q), 132.8 (C^{Ar}), 131.5 (C^{Ar}), 130.6 (C^{Ar}), 130.3 (C_q), 128.7 (C_q), 128.6 (C^{Ar}), 128.2 (C^{Ar}), 125.4 (C^{Ar}), 124.7 (C^{Ar}), 123.7 (C_q), 62.7 (C-34), 61.1 (C-36), 60.6 (C-23), 39.3 (C-21), 35.5 (C-30), 28.6 (C-20), 28.1 (C-31), 22.7 (C-32, C-33), 20.1 (C-1), 19.7 (C-4), 14.3 (C-24, C-37) ppm.

HRMS (DI-EI TOF): calcd. for $C_{37}H_{42}N_2O_5^+$ $[M]^+$: 594.3094; found: 594.3098.

7.4.19.9. Ethyl 3-(4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-3'',4''-dimethyl-[1,1':3',1''-terphenyl]-3-yl)propanoate (120)



120

In a 50 mL one-neck round-bottom flask 31.5 mg (53.0 µmol, 1.00 eq) ethyl 3-(4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-3",4"-dimethyl-[1,1':3',1"-terphenyl]-3-yl) propanoate (**116**) were dissolved in 1.5 mL THF/H_2O (2/1). Then 45.0 mg (1.07 mmol, 20.3 eq) LiOH were added and the colorless suspension was stirred at RT until full conversion was detected by HPLC-MS (30 min). Afterwards 3 mL 1M HCl were added to the suspension to adjust to pH = 1 and the product was extracted with CH_2Cl_2 (5 x 10 mL). The solvent of the combined organic phases was removed under reduced pressure. The crude prodct was purified via preparative HPLC (Method_4).

Yield: 10.4 mg (19.3 µmol, 37 %), colorless solid

$C_{33}H_{34}N_2O_5$ [538.64 g/mol]

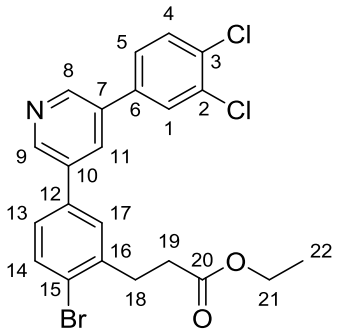
mp$^{exp.}$ = 67 – 80 °C

^{1}H-NMR (499.87 MHz, DMSO d_6): δ = 8.97 (s, 1H, H-10), 8.94 (s, 1H, H-11), 8.49 (s, 1H, H-13), 7.97 (d, $^3J_{HH}$ = 1.8 Hz, 1H, H-27), 7.89 (s, 1H, H-19), 7.79 (d, $^3J_{HH}$ = 7.8 Hz, 1H, H-16), 7.69 (s, 1H, H-1), 7.65 – 75.56 (m, 2H, H-6, H-24), 7.39 (m, 2H, H-7, H-17), 4.90 (s, 2H, H-32), 2.88 (t, $^3J_{HH}$ = 7.8 Hz, 2H, H-20), 2.53 -2.48 (m, 4H, H-21, H-28), 2.34(s, 3H, H-3), 2.30 (s, 3H, H-5), 2.11 – 1.95 (m, 1H, H-29), 0.90 (d, $^3J_{HH}$ = 6.5 Hz, 6H, H-30, H-31) ppm.

^{13}C-NMR (125.69 MHz, DMSO d_6): δ = 173.6 (C_q, C-22), 170.3 (C_q, C-33), 159.6 (C_q, C-25), 144.6 (C-10), 144.4 (C-11), 143.2 (C-24), 140.0 (C-27), 139.46 (C_q), 138.0 (C_q), 137.1 (C_q), 136.9 (C_q), 136.5 (C_q), 136.0 (C_q), 135.8 (C_q), 133.7 (C_q), 133.5 (CAr), 130.9 (C^{Ar}), 130.2 (C^{Ar}), 129.8 (C^{Ar}), 128.2 (C^{Ar}), 128.0 (C^{Ar}), 125.1 (C^{Ar}), 124.5 (C^{Ar}), 122.6 (C_q), 62.0 (C-32), 38.3 (C-28), 34.6 (C-21), 27.8 (C-20), 27.3 (C-29), 22.3 (C-30, C-31), 19.4 (C-3), 19.1 (C-5) ppm.

HRMS (MALDI-TOF): calcd. for $C_{33}H_{34}N_2O_5H^+$ $[M+H]^+$: 539.2546; found: 539.2595.

7.4.19.10. Ethyl 3-(2-bromo-5-(5-(3,4-dichlorophenyl)pyridin-3-yl)phenyl)propanoate (112)



112

A flame dried 8 mL Schlenk-flask was charged with 153 mg (340 µmol, 1.00 eq) ethyl 3-(2-bromo-5-iodophenyl)propanoate (**67**), 140 mg (340 µmol, 1.00 eq) 3-(3,4-dichlorophenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, 14.6 mg (20.0 µmol, 0.05 eq)

$Pd(dppf)Cl_2$ and 110 mg (797 µmol, 2.00 eq) K_2CO_3. 2 mL abs., degassed DMF were added and the reaction mixture was stirred at 80 °C until full conversion was detected by HPLC-MS. The brown suspension was then concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography (11 g SiO_2, 2.0 x 6.5 cm, eluent: cyclohexane/EtOAc = 4/1, R_f = 0.30, UV and $KMnO_4$, fraction size: 8 mL).

Yield: 124 mg (259 µmol, 65 %), yellow solid

$C_{22}H_{18}BrCl2NO_2$ [479.20 g/mol]

mp$^{exp.}$ = 78 -82 °C

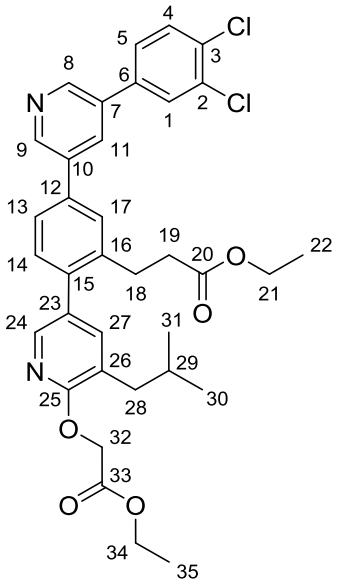
TLC: R_f = 0.30 (cyclohexane/EtOAc = 4/1, UV and $KMnO_4$)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 8.81 (s, 1H, H-8), 8.79 (s, 1H, H-9), 7.94 (s, 1H, H-11), 7.72 (d, $^4J_{HH}$ = 1.9 Hz, 1H, H-1), 7.67 (d, $^3J_{HH}$ = 8.2 Hz, 1H, H-14), 7.58 (d, $^3J_{HH}$ = 8.3 Hz, 1H, H-4), 7.52 (d, $^4J_{HH}$ = 1.9 Hz, 1H, H-17), 7.47 (dd, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, H-5), 7.34 (dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.0 Hz, 1H, H-13), 4.15 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-21), 3.16 (t, $^3J_{HH}$ = 7.7 Hz, 2H, H-18), 2.71 (t, $^3J_{HH}$ = 7.7 Hz, 2H, H-19), 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-22) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 172.6 (C_q, C-20), 147.7 (C-8), 147.1 (C-9), 141.1 (C_q, C-16), 137.7 (C_q, C-6), 137.0 (C_q, C-12), 135. 9 (C_q, C-3), 134.7 (C_q, C-2), 133.9 (C-14), 133.6 (C_q), 133.0 (C_q), 132.6 (C-4), 131.3 (C-4), 129.4 (C-17), 129.2 (C-1), 126.9 (C-13), 126.6 (C-5), 125.0 (C_q, C-15), 60.8 (C-21), 34.2 (C-19), 31.7 (C-18), 14.4 (C-22) ppm.

HRMS (DI-EI TOF): calcd. for $C_{22}H_{18}BrCl2NO_2^+$ $[M]^+$: 476.9898; found: 476.9896.

7.4.19.11. Ethyl 3-(3'',4''-dichloro-4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-[1,1':3',1''-terphenyl]-3-yl)propanoate (117)



117

A flame dried 8 mL Schlenk-flask was charged with 68.9 mg (144 µmol, 1.00 eq) ethyl 3-(2-bromo-5-(5-(3,4-dichlorophenyl)pyridin-3-yl)phenyl)propanoate (**112**), 61.9 mg (170 µmol, 1.19 eq) ethyl 2-((3-isobutyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)oxy)acetate (**114**), 5.3 mg (7.24 µmol, 0.05 eq) Pd(dppf)Cl_2 and 94 mg (289 µmol, 2.00 eq) Cs_2CO_3. 1.5 mL abs, degassed DMF were added and the reaction mixture was stirred at 80 °C until full conversion was detected by TLC. The brown suspension was then concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography (25 g SiO_2, 2.5 x 9.0 cm, eluent: cyclohexane/EtOAc = 4/1, fraction size: 7 mL).

Yield: 74.28 mg (117 µmol, 81 %), sticky colorless solid

$C_{35}H_{36}Cl_2N_2O_5$ [35.58 g/mol]

TLC: R_f = 0.33 (cyclohexane/EtOAc = 2/1, UV and $KMnO_4$)

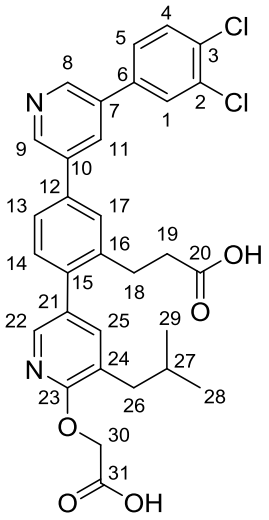
^{1}H-NMR (300.36 MHz, $CDCl_3$): 8.88 (s, 1H, H-8), 8.79 (s, 1H, H-9), 8.01 (s, 1H, H-11), 7.94 (d, $^4J_{HH}$ = 2.1 Hz, 1H, H-27), 7.74 (d, $^4J_{HH}$ = 1.9 Hz, 1H, H-17), 7.63 – 7.45 (m, 4H, H-1, H-4, H-5, H-13), 7.39 (d, $^4J_{HH}$ = 1.9 Hz, 1H, H-24), 7.32 (d, $^3J_{HH}$ = 7.8 Hz, 1H, H-14), 4.96 (s, 2H, H-32), 4.25 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-34), 4.07 (q, $^3J_{HH}$ = 7.6 Hz, 2H, H-21), 3.02 (t, $^4J_{HH}$ =

7.7 Hz, 2H, H-18), 2.63 – 2.42 (m, 4H, H-19, H-28), 2.15 – 1.98 (m, 1H, H-29), 1.30 - 1.16 (m, 6H, H-22, H-35), 0.95 (d, $^{3}J_{HH}$ = 6.6 Hz, 6H, H-30, H-31) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 172.5 (C_q, C-20), 169.7 (C_q, C-33), 160.2 (C_q, C-25), 147.8 (C-8), 146.9 (C-9), 143.5 (C-27), 140.0 (C-24), 139.7 (C_q), 138.8 (C_q), 137.9 (C_q), 137.0 (C_q), 136.6 (C_q), 134.6 (C_q), 133.6 (C_q), 132.9 (C_q), 132.8 (C-11), 131.6 (C-14), 131.3 (C^{Ar}), 130.2 (C_q), 129.3 (C^{Ar}), 128.3 (C^{Ar}), 126.6 (C^{Ar}), 125.4 (C^{Ar}), 123.8 (C_q), 62.7 (C-32), 61.1 (C-34), 60.6 (C-21), 39.3 (C-28), 35.4 (C-19), 28.6 (C-18), 28.1 (C-29), 22.7 (C-30, C-31), 14.3 (C-22, C-35) ppm.

HRMS (DI-EI TOF): calcd. for $C_{35}H_{36}Cl_2N_2O_5^+$ $[M]^+$: 634.2001; found: 634.2010.

7.4.19.12. Ethyl 3-(3'',4''-dichloro-4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-[1,1':3',1''-terphenyl]-3-yl)propanoate (121)



121

In a 50 mL one-neck round-bottom flask 51.8 mg (81.5 µmol, 1.00 eq) ethyl 3-(3",4"-dichloro-4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-[1,1':3',1"-terphenyl]-3-yl)-propanoate (**117**) were dissolved in 1.5 mL THF/ H_2O (2/1). Then 68.7 mg (1.64 mmol, 20.1 eq) LiOH were added and the colorless suspension was stirred at RT until full conversion was detected by HPLC-MS (30 min). Afterwards 4 mL 1 M HCl were added to the suspension to adjust to pH = 1 and the product was extracted with CH_2Cl_2 (5 x 15 mL). The solvent of the combined organic phases was removed under reduced pressure. The crude prodct was purified via preparative HPLC (Method_4).

Yield: 37 mg (63.9 µmol, 78 %), sticky colorless solid

$C_{31}H_{28}Cl_2N_2O_5$ [579.47 g/mol]

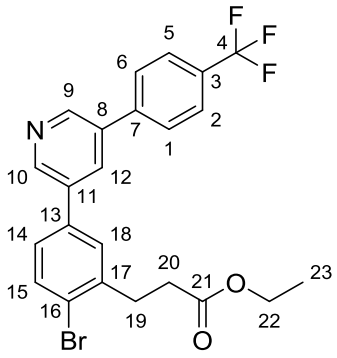
HPLC-MS (Method_2): t_R = 8.06 min, *m*/*z* + H= 579.

^{1}H-NMR (300.36 MHz, DMSO d_6): δ = 9.06 (s, 1H, H-8), 9.02 (s, 1H, H-9), 8.61 (s, 1H, H-11), 8.25 (d, $^4J_{HH}$ = 1.4 Hz, 1H, H-1), 8.02 – 7.87 (m, 3H, H-4, H-17, H-25), 7.86 – 7.74 (m, 2H, H-5, H-15), 7.58 (d, $^4J_{HH}$ = 1.3 Hz, 1H, H-22), 7.36 (d, $^3J_{HH}$ = 7.9 Hz, 1H, H-14), 4.90 (s, 2H, H-30), 2.94 – 2.83 (m, 2H, H-18), 2.59 – 2.41 (m, 4H, H19, H-26), 2.16 – 1.87 (m, 1H, H-27), 0.90 (d, $^3J_{HH}$ = 6.4 Hz, 6H, H-28, H-29) ppm.

^{13}C-NMR (75.53 MHz, DMSO d_6): δ = 173.6 (C_q, C-20), 170.3 (C_q, C-31), 159.7 (C_q, C-23), 145.5 (C-8), 144.9 (C-9), 143.2 (C^{Ar}), 140.0 (C-22), 139.5 (C_q), 138.1 (C_q), 137.0 (C_q), 136.1 (C_q), 135.5 (C_q), 134.3 (C-11), 134.1 (C_q), 132.03 (C_q), 131.5 (C_q), 131.2 (C^{Ar}), 130.9 (C-14), 129.8 (C_q), 129.3 (C-1), 128.1 (C^{Ar}), 127.6 (C^{Ar}), 125.2 (C^{Ar}), 122.7 (C_q), 62.1 (C-30), 38.3 (C-26), 34.6 (C-19), 27.8 (C-18), 27.4 (C-27), 22.3 (C-28, C-29) ppm.

HRMS (MALDI-TOF): calcd. for $C_{31}H_{28}Cl_2N_2O_5H^+$ $[M+H]^+$: 579.1453; found: 579.1487.

7.4.19.13. Ethyl 3-(2-bromo-5-(5-(4-(trifluoromethyl)phenyl)pyridin-3-yl)phenyl) propanoate (113)



113

A flame dried 8 mL Schlenk-flask was charged with 134 mg (350 µmol, 1.00 eq) ethyl 3-(2-bromo-5-iodophenyl)propanoate (**67**), 122 mg (350 µmol, 1.00 eq) 3-(4,4,5,5-tetramethyl-1,3,2-dioxa-borolan-2-yl)-5-(4-(trifluoromethyl)phenyl)pyridine, 13 mg (17.8 µmol, 0.05 eq) Pd(dppf)Cl_2 and 97 mg (702 µmol, 2.01 eq) K_2CO_3. 2 mL abs., degassed DMF were added and the reaction mixture was stirred at 80 °C until full conversion was detected by GC-MS (20 h). The red/brown suspension was then concentrated to dryness using a rotary evaporator.

The crude product was purified via flash column chromatography (40 g SiO_2, 2.5 x 11.5 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.23, UV and $KMnO_4$, fraction size: 25 mL).

Yield: 115 mg (240 µmol, 69 %), beige solid

$C_{23}H_{19}BrF_3NO_2$ [478.31 g/mol]

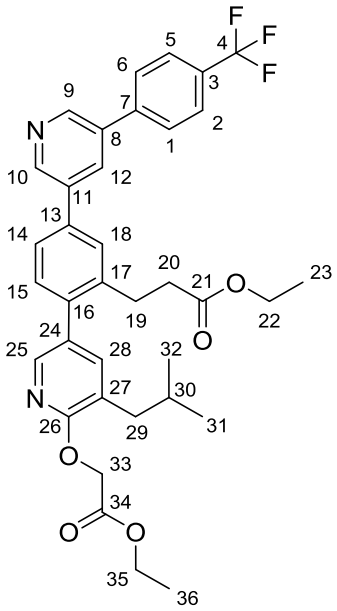
TLC: R_f = 0.23 (cyclohexane/EtOAc = 5/1, UV and $KMnO_4$)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 8.83 (s, 2H, H-9, H-10), 8.01 (s, 1H, H-12), 7.76 (s, 4H, H-1, H-2, H-5, H-6), 7.67 (d, $^3J_{HH}$ = 8.2 Hz, 1H, H-15), 7.54 (d, $^4J_{HH}$ = 1.7 Hz, 1H, H-18), 7.35 (dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, H-14), 4.14 (q, $^3J_{HH}$ = 7.1 Hz, 3H, H-22), 3.16 (t, $^3J_{HH}$ = 7.6 Hz, 2H, H-19), 2.71 (t, $^3J_{HH}$ = 7.7 Hz, 2H, H-20), 1.24 (t, $^3J_{HH}$ = 7.0 Hz, 3H, H-23) ppm.

^{3}C-NMR (75.53 MHz, $CDCl_3$): δ = 172.6 (C_q, C-21), 147.7 (C-9), 147.4 (C-10), 141.3 (C_q), 141.0 (C_q), 137.0 (C_q), 135.9 (C_q), 135.6 (C_q), 133.9 (C-15), 133.0 (C-12), 130.6 (C_q, $^2J_{CF}$ = 32.9 Hz, C-3), 129.4 (C-18), 127.8 (C-1, C-5), 126.9 (C-14), 126.3 ($^3J_{CF}$ = 3.7 Hz, C-2, C-4), 125.0 (C_q, C-16), 124.2 (C_q, $^1J_{CF}$ = 272.2 Hz, C-4), 60.8 (C-22), 34.2 (C-20), 31.7 (C-19), 14.4 (C-23) ppm.

HRMS (DI-EI TOF): calcd. for $C_{23}H_{19}BrF_3NO_2^+$ $[M]^+$: 477.0551; found: 477.0554.

7.4.19.14. Ethyl 3-(4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-4''-(trifluoro methyl)-[1,1':3',1''-terphenyl]-3-yl)propanoate (118)



118

A flame dried 8 mL Schlenk-flask was charged with 57.3 mg (120 µmol, 1.00 eq) ethyl 3-(2-bromo-5-(5-(4-(trifluoromethyl)phenyl)pyridin-3-yl)phenyl) propanoate (**113**), 54.2 mg (149 µmol, 1.10 eq) ethyl 2-((3-isobutyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-oxy)acetate (**114**), 4.4 mg (6.01 µmol, 0.05 eq) Pd(dppf)Cl_2 and 78.0 mg (239 µmol, 2.00 eq) Cs_2CO_3. 1.5 mL abs., DMF were added and the reaction mixture was stirred at 80 °C until full conversion (16 h) was detected by TLC. The brown suspension was then concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography (25 g SiO_2, 2.5 x 9.0 cm, eluent: cyclohexane/EtOAc = 4/1, R_f = 0.37 (cyclohexane/EtOAc = 2/1), UV and $KMnO_4$, fraction size: 7 mL).

Yield: 74.1 mg (117 µmol, 97 %), colorless solid.

$C_{36}H_{37}F_3N_2O_5$ [634.70 g/mol]

mp$^{exp.}$ = 98 – 102 °C

TLC: R_f = 0.37 (cyclohexane/EtOAc = 2/1, UV and $KMnO_4$)

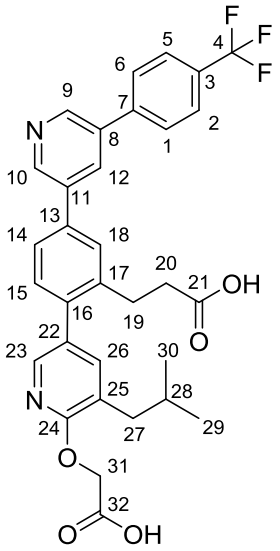
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 8.90 (d, $^4J_{HH}$ = 1.7 Hz, 1H, H-9), 8.85 (d, $^4J_{HH}$ = 1.8 Hz, 1H, H-10), 8.08 (s, 1H, H-12), 7.94 (d, $^4J_{HH}$ = 2.0 Hz, 1H, H-28), 7.78 (s, 4H, H-1, H-2, H-5, H-6), 7.64 – 7.50 (m, 2H, H-14, H-18), 7.42 – 7.30 (m, 2H, H-15, H-25), 4.96 (s, 2H, H-33), 4.25 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-35), 4.06 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-22), 3.01 (t, $^3J_{HH}$ = 5.7 Hz,

2H, H-19), 2.62 – 2.41 (m, 4H, H-20, H-29), 2.11 – 2.04 (m, 1H, H-30), 1.38 – 1.11 (m, 6H, H-23, H-36), 0.95 (d, $^{3}J_{HH}$ = 6.6 Hz, 6H, H-31, H-32) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 172.6 (C_q, C-21), 169.7 (C_q, C-34), 160.2 (C_q, C-26), 147.8 (C-9), 147.1 (C-10), 143.5 (C-28), 141.4 (C_q), 140.0 (C-25), 139.7 (C_q), 138.8 (C_q), 137.1 (C_q), 136.6 (C_q), 135.6 (C_q), 133.2 (C-12), 131.6 (C-15), 130.6 (C_q, $^{2}J_{CF}$ = 32.5 Hz, C-3), 130.2 (C_q), 128.3 (C-18), 127.8 (C-1, C-6), 126.3 ($^{3}J_{CF}$ = 3.8 Hz, C-2, C-5), 125.4 (C-14), 124.2 (C_q, $^{1}J_{CF}$ = 272.0 Hz, C-4), 123.8 (C_q), 62.7 (C-33), 61.1 (C-35), 60.6 (C-22), 39.3 (C-29), 35.4 (C-20), 28.6 (C-19), 28.1 (C-30), 22.7 (C-31, C-32), 14.3 (C-23, C-36) ppm.

HRMS (DI-EI TOF): calcd. for $C_{36}H_{37}F_3N_2O_5^+$ $[M]^+$: 634.2655; found: 634.2654.

7.4.19.15. Ethyl 3-(4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-4''-(trifluoro methyl)-[1,1':3',1''-terphenyl]-3-yl)propanoate (122)



122

In a 50 mL one-neck round-bottom flask 50.0 mg (78.8 µmol, 1.00 eq) ethyl 3-(4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-4''-(trifluoromethyl)-[1,1':3',1''-terphenyl]-3-yl)-propanoate (**118**) were dissolved in 1.5 mL THF/H_2O (2/1). Then 66.2 mg (1.58 mmol, 20.0 eq) LiOH were added and the colorless suspension was stirred at RT until full conversion was detected by HPLC-MS (30 min). Afterwards 4 mL 1M HCl were added to the suspension to adjust to pH = 1 and the product was extracted with CH_2Cl_2 (5 x 15 mL). The solvent of the

combined organic phases was removed under reduced pressure. The crude prodct was purified via preparative HPLC (Method_4).

Yield: 27.1 mg (46.8 µmol, 60 %), colorless solid

$C_{32}H_{29}F_3N_2O_5$ [578.59 g/mol]

mp$^{exp.}$ = 85 – 92 °C

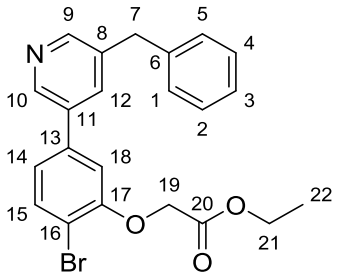
HPLC-MS (Method_2): t_R = 7.72 min, *m/z* + H = 580.

^{1}H-NMR (300.36 MHz, DMSO d_6): δ = 9.04 (s, 1H, H-9), 9.00 (d, $^4J_{HH}$ = 1.2 Hz, 1H, H-10), 8.54 (s, 1H, H-12), 8.13 (d, $^3J_{HH}$ = 8.0 Hz, 2H, H-1, H-6), 7.98 (d, $^4J_{HH}$ = 1.8 Hz, 1H, H-26), 7.92 – 7.89 (m, 3H, H-2, H-5, H-18), 7.80 (d, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 0.8 Hz, 1H, H-14), 7.58 (d, $^4J_{HH}$ = 1.6 Hz, 1H, H-23), 7.35 (d, $^3J_{HH}$ = 7.9 Hz, 1H, H-15), 4.90 (s, 2H, H-31), 2.97 – 2.79 (m, 2H, H-19), 2.57 – 2.53 (m, 2H, H-20, H-27), 2.03 (m, 1H, H-28), 0.90 (d, $^3J_{HH}$ = 6.5 Hz, 6H, H-29, H-30) ppm.

^{13}C-NMR (75.53 MHz, DMSO d_6): δ = 173.6 (C_q, C-21), 170.3 (C_q, C-32), 159.6 (24), 146.6 (C-9), 146.0 (C-10), 143.2 (C-26), 140.8 (C_q), 140.0 (C-23), 139.5 (C_q), 138.0 (C_q), 135.8 (C_q), 135.8 (C_q), 134.7 (C_q), 133.5 (C-12), 131.0 (C-15), 129.8 (C_q), 128.8 ($^2J_{CF}$ = 31.9 Hz, C-3), 128.2 (C-1, C-6), 128.1 (C-18), 125.9 ($^3J_{CF}$ = 3.5 Hz, C-2, C-5), 125.1 (C-14), 124.3 ($^1J_{CF}$ = 272.2 Hz, C-4), 122.6 (C_q), 62.1 (C-31), 38.3 (C-27), 34.6 (C-20), 27.8 (C-19), 27.4 (C-28), 22.3 (C-29, C-30) ppm.

HRMS (MALDI-TOF): calcd. for $C_{32}H_{29}F_3N_2O_5H^+$ $[M+H]^+$: 579.2107; found: 579.2198.

7.4.19.16. Ethyl 2-(5-(5-benzylpyridin-3-yl)-2-bromophenoxy)acetate (124)



124

A flame dried 25 mL Schlenk-flask was charged with 500 mg (1.30 mmol, 1.00 eq) ethyl 2-(2-bromo-5-iodophenoxy)acetate (**98**), 422 mg (1.43 mmol, 1.10 eq) 3-benzyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**123**), 48 mg (64.9 µmol, 0.05 eq) $Pd(dppf)Cl_2$ and 359 mg (2.60 mmol, 2.00 eq) K_2CO_3. 7 mL abs., degassed DMF were added and the

reaction mixture was stirred at 80 °C until full conversion was detected by HPLC-MS. The brown suspension was then concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography (150 g SiO_2, 4.5 x 16.5 cm, eluent: cyclohexane/EtOAc = 5/1, fraction size: 75 mL).

Yield: 338 mg (795 µmol, 61 %), colorless solid

$C_{22}H_{20}BrNO_3$ [425.06 g/mol]

mp$^{exp.}$ = 69 – 71 °C

TLC: R_f = 0.05 (cyclohexane/EtOAc = 5/1, UV and CAM)

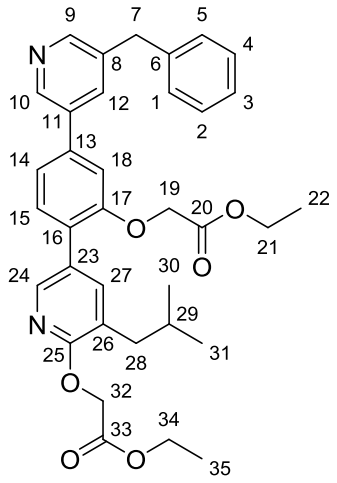
HPLC-MS (Method_2): t_R = 7.33 min, *m/z* + H = 426.

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 8.63 (s, 1H, H-10), 8.45 (s, 1H, H-9), 7.74 (s, 1H, H-12), 7.35 – 7.12 (m, 7H, H-1, H-2, H-3, H-4, H-5, H-14, H-15), 6.99 (s, 1H, H-18), 4.58 (s, 2H, H-19), 4.24 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-21), 4.04 (s, 2H, H-7), 1.28 (t, $^3J_{HH}$ = 7.0 Hz, 3H, H-22) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 168.1 (C_q, C-20), 155.5 (C_q, C-17), 148.7 (C-9), 147.8 (C-10), 139.9 (C_q, C-6), 137.6 (C-12), 136.0 (C_q, C-13), 132.9 (C_q, C-8), 132.1 (C-14), 129.1 (C-1, C-5), 128.8 (C-2, C-4), 126.7 (C_q, C-11), 126.6 (C-15), 125.4 (C-3), 122.7 (C_q, C-16), 116.0 (C-18), 65.8 (C-19), 61.7 (C-21), 39.2 (C-7), 14.3 (C-22) ppm.

HRMS (DI-EI TOF): calcd. for $C_{22}H_{20}BrNO_3^+$ $[M]^+$: 425.0627; found: 425.0627.

7.4.19.17. Ethyl-2-((5-(4-(5-benzylpyridin-3-yl)-2-(2-ethoxy-2-oxoethoxy)phenyl)-3-isobutylpyridin-2-yl)oxy)acetate (125)



125

A flame dried 15 mL Schlenk-flask was charged with 200 mg (469 µmol, 1.00 eq) ethyl 2-(5-(5-benzylpyridin-3-yl)-2-bromophenoxy)acetate (**124**), 180 mg (496 µmol, 1.06 eq) ethyl 2-((3-isobutyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)oxy)acetate (**114**), 17.5 mg (23.9 µmol, 0.05 eq) $Pd(dppf)Cl_2$ and 306 mg (939 µmol, 2.00 eq) Cs_2CO_3. 3 mL abs., degassed DMF were added and the reaction mixture was stirred at 80 °C until full conversion (20 h) was detected by HPLC-MS. The typically brown suspension was then concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography (75 g SiO_2, 5.0 x 10.0 cm, eluent: cyclohexane/EtOAc = 3/1, R_f = 0.12, UV and $KMnO_4$, fraction size: 50 mL).

Yield: 261 mg (448 µmol, 96 %), colorless solid

$C_{35}H_{38}N_2O_6$ [582.70 g/mol]

TLC: R_f = 0.12 (cyclohexane/EtOAc = 3/1, UV and $KMnO_4$)

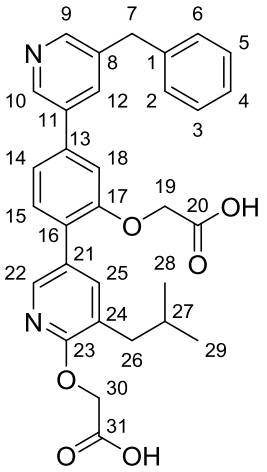
HPLC-MS (Method_2): t_R = 8.57 min, *m/z* + H = 583.

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 8.71 (s, 1H, H-10), 8.45 (s, 1H, H-9), 8.15 (d, $^3J_{HH}$ = 2.0 Hz, 1H, H-24), 7.83 (s, 1H, H-12), 7.55 (d, $^3J_{HH}$ = 1.9 Hz, 1H, H-27), 7.41 – 7.14 (m, 7H, H-1, H-2, H-3, H-4, H-5, H-14, H-15), 6.97 (s, 1H, H-18), 4.94 (s, 2H, H-19), 4.64 (s, 2H, H-32), 4.24 (m, 4H, H-21, H-32), 4.05 (s, 2H, H-7), 2.57 (d, $^3J_{HH}$ = 7.0 Hz, 2H, H-7), 2.09 – 2.06 (m, 1H, H-29), 1.32 – 1.19 (m, 6H, H-22, H-35), 0.95 (d, $^3J_{HH}$ = 6.5 Hz, 6H, H-30, H-31) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 169.6 (C_q, C-20), 168.6 (C_q, C-33), 160.6 (C_q, C-17), 155.4 (C_q, C-25), 148.2 (C-9), 147.7 (C-10), 142.1 (C-24), 139.9 (C_q), 139.8 (C_q), 138.1 (C-27), 137.9 (C-12), 136.1 (C_q), 133.5 (C_q), 131.5 (C^{Ar}), 130.1 (C_q), 129.1 (C-1, C-5), 128.8 (C-2, C-4), 126.6 (C^{Ar}), 126.5 (C_q), 124.3 (C_q), 120.8 (C^{Ar}), 111.0 (C-18), 65.9 (C-32), 62.7 (C-19), 61.6 (C-34), 61.1 (C-21), 39.3 (C-28), 39.2 (C-7), 28.3 (C-29), 25.0 (C-35), 22.6 (C-30, C-31), 14.3 (C-22) ppm.

HRMS (DI-EI TOF): calcd. for $C_{35}H_{38}N_2O_6^+$ $[M]^+$: 582.2730; found: 582.2739.

7.4.19.18. 2-(5-(5-Benzylpyridin-3-yl)-2-(6-(carboxymethoxy)-5-isobutylpyridin-3-yl)phenoxy) acetic acid (126)



126

In a 50 mL one-neck round-bottom flask 130 mg (223 µmol, 1.00 eq) ethyl-2-((5-(4-(5-benzyl pyridin-3-yl)-2-(2-ethoxy-2-oxoethoxy)phenyl)-3-isobutylpyridin-2-yl)oxy)acetate (**125**) were dissolved in 6 mL THF/H_2O (2/1). Then 188 mg (4.46 mmol, 20.0 eq) LiOH were added and the colorless suspension was stirred at RT until full conversion was detected by HPLC-MS (30 min). Afterwards 6 mL 1M HCl were added to the suspension to adjust to pH = 1 and the product was extracted with CH_2Cl_2 (5 x 15 mL). The solvent of the combined organic phases was removed under reduced pressure.

Yield: 108 mg (205 µmol, 92 %), colorless solid

$C_{31}H_{30}N_2O_6$ [526.59 g/mol]

mp$^{exp.}$ = 229 – 231 °C

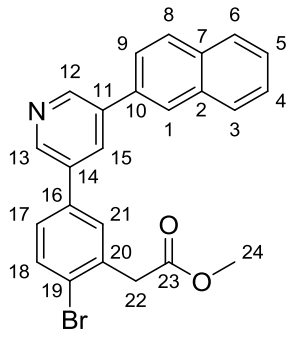
HPLC-MS (Method_2): t_R = 5.87 min, *m/z* + H = 527.

^{1}H-NMR (300.36 MHz, DMSO d_6): δ = 8.68 (s, 1H, H-10), 8.46 (s, 1H, H-9), 8.36 (s, 1H, H-24), 7.94 (s, 1H, H-12), 7.90 (s, 1H, H-27), 7.48 – 7.13 (m, 8H, H-1, H-2, H-3, H-4, H-5, H-14, H-15, H-18), 4.89 (s, 4H, H-19, H-30), 4.02 (s, 2H, H-7), 2.55 – 2.50 (m, 2H, H-26), 2.02 (m, 1H, H-27), 0.91 (d, $^3J_{HH}$ = 6.4 Hz, 6H, H-28, H-29) ppm.

^{13}C-NMR (75.53 MHz, DMSO d_6): δ = 170.3 (C_q, C-20), 170.2 (C_q, C-31), 160.2 (C_q), 155.1 (C_q), 147.7 (C-9), 147.2 (C-10), 141.9 (C-24), 140.5 (C_q), 138.5 (C_q), 137.8 (C-27), 137.0 (C-12), 131.1 (C-15), 129.1 (C_q), 128.7 (C-1, C-5), 128.6 (C-2, C-4), 126.3 (C-3), 125.2 (C_q), 123.3 (C_q,), 119.5 (C-19), 110.5 (C-30), 64.8 (C-19),62.2 (C-30), 38.4 (C-7), 38.1 (C-26), 27.65 (C-27), 22.4 (C-28, C-29) ppm.

HRMS (MALDI-TOF): calcd. for $C_{31}H_{30}N_2O_6H^+$ $[M+H]^+$: 526.2104; found: 527.2178.

7.4.19.19. Methyl 2-(2-bromo-5-(5-(naphthalen-2-yl)pyridin-3-yl)phenyl)acetate (128)



128

A flame dried 8 mL Schlenk-flask was charged with 133 mg (373 µmol, 1.00 eq) methyl 2-(2-bromo-5-iodophenyl)acetate (**58**), 130 mg (392 µmol, 1.05 eq) 3-(naphthalen-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**127**), 13.7 mg (18.7 µmol, 0.05 eq) Pd(dppf)Cl_2 and 103 mg (747 µmol, 2.00 eq) K_2CO_3. 2 mL abs. DMF were added and the reaction mixture was stirred at 80 °C until full conversion was detected by TLC (14 h). The brown/black suspension was then concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography (50 g SiO_2, 2.5 x 12.0 cm, eluent: cyclohexane/EtOAc = 3/1, R_f = 0.39, UV and $KMnO_4$, fraction size: 20 mL).

Yield: 119 mg (275 µmol, 74 %), colorless solid

$C_{24}H_{18}BrNO_2$ [432.32 g/mol]

mp$^{exp.}$ = 135 – 138 °C

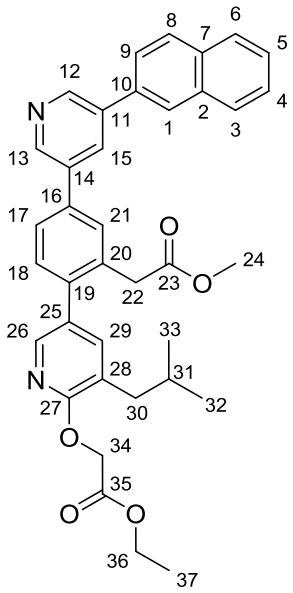
TLC: R_f = 0.39 (cyclohexane/EtOAc = 3/1, UV and $KMnO_4$)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 8.96 (s, 1H, H-12), 8.81 (s, 1H, H-13), 8.12 (s, 1H, H-15), 8.08 (s, 1H, H^{Naph}), 8.02 – 7.83 (m, 3H, H^{Naph}), 7.80 – 7.66 (m, 2H, H-18, H^{Naph}), 7.62 - 7.49 (m, 3H, H-21, H^{Naph}), 7.44 (dd, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.1 Hz, 1H, H-17), 3.90 (s, 2H, H-22), 3.76 (s, 3H, H-24) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 170.8 (C_q, C-23), 147.7 (C-12), 146.9 (C-13), 137.4 (C_q), 136.8 (C_q), 135.5 (C_q), 135.2 (C_q), 134.9 (C_q), 133.7 (C^{Ar}), 133.1 (C-7), 133.0 (C^{Ar}), 130.4 (C^{Ar}), 129.1 (C^{Ar}), 128.4 (C^{Ar}), 127.9 (C^{Ar}), 127.8 (C^{Ar}), 126.8 (C^{Ar}), 126.7 (C_q), 126.5 (C^{Ar}), 125.4 (C_q), 125.1 (C^{Ar}), 52.4 (C-24), 41.7 (C-22) ppm.

HRMS (DI-EI TOF): calcd. for $C_{24}H_{18}BrNO_2^+$ $[M]^+$: 431.0521; found: 431.0519.

7.4.19.20. Ethyl 2-((3-isobutyl-5-(2-(2-methoxy-2-oxoethyl)-4-(5-(naphthalen-2-yl)pyridin-3-yl)phenyl)pyridin-2-yl)oxy)acetate (129)



129

A flame dried 8 mL Schlenk-flask was charged with 77.3 mg (179 µmol, 1.00 eq) methyl 2-(2-bromo-5-(5-(naphthalen-2-yl)pyridin-3-yl)phenyl)acetate (**128**), 68.2 mg (188 µmol, 1.05 eq) ethyl 2-((3-isobutyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-oxy)acetate (**114**), 6.5 mg (8.94 µmol, 0.05 eq) Pd(dppf)Cl_2 and 359 mg (358 µmol, 2.00 eq)

Cs_2CO_3. 2 mL abs., degassed DMF were added and the reaction mixture was stirred at 80 °C until full conversion was detected by HPLC-MS. The brown suspension was then concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography (25 g SiO_2, 2.5 x 9.0 cm, eluent: cyclohexane/EtOAc = 4/1, fraction size: 8 mL).

Yield: 81.9 mg (139 µmol, 78 %), colorless solid

$C_{37}H_{36}N_2O_5$ [425.06 g/mol]

mp$^{exp.}$ = 115 – 122 °C

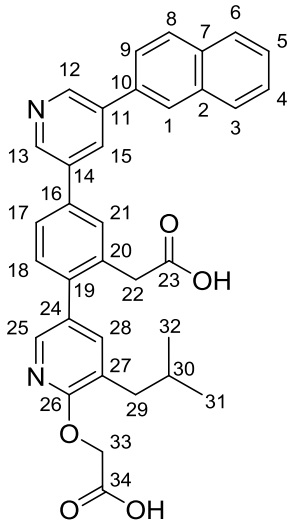
TLC: R_f = 0.30 (cyclohexane/EtOAc = 2/1, UV and $KMnO_4$)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 8.97 (s, 1H, H-12), 8.89 (s, 1H, H-13), 8.20 (s, 1H, H-15), 8.12 (s, 1H, H-21), 8.06 – 7.84 (m, 4H, H-18, H^{Naph}), 7.79 (dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.4 Hz 1H, H-17), 7.65 (m, 2H, H^{Ar}), 7.62 – 7.47 (m, 2H, H^{Ar}), 7.42 (m, 2H, H^{Ar}), 4.97 (s, 2H, H-34), 4.25 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H), 3.70 (s, 2H, H-22), 3.66 (s, 2H, H-24), 2.56 (d, $^3J_{HH}$ = 7.0 Hz, 2H, H-30), 2.18 – 1.91 (m, 1H, H-31), 1.35 – 1.19 (m, 3H, H-37), 0.91 (d, $^3J_{HH}$ = 6.9 Hz, 6H, H-32, H-33) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 172.1 (C_q, C-23), 169.6 (C_q, C-35), 160.3 (C_q, C-27), 147.6 (C-12), 147.1 (C-13), 143.7 (C^{Ar}), 140.2 (C^{Ar}), 139.1 (C_q), 137.6 (C_q), 135.1 (C_q), 133.8 (C_q), 133.4 (C_q), 133.2 (C_q), 133.1 (C^{Ar}), 131.5 (C^{Ar}), 130.0 (C_q), 129.6 (C^{Ar}), 129.1 (C^{Ar}), 128.4 (C^{Ar}), 127.9 (C^{Ar}), 126.8 (C^{Ar}), 126.7 (C_q), 126.5 (C^{Ar}), 126.4 (C_q), 125.2 (C^{Ar}), 123.8 (C_q), 62.7 (C-34), 61.1 (C-36), 52.3 (C-24), 39.3 (C-30), 38.9 (C-22), 28.1 (C-31), 22.7 (C-32, C-33), 14.3 (C-37) ppm.

HRMS (DI-EI TOF): calcd. for $C_{37}H_{36}N_2O_5^+$ $[M]^+$: 588.2624; found: 588.2624.

7.4.19.21. 2-(2-(6-(Carboxymethoxy)-5-isobutylpyridin-3-yl)-5-(5-(naphthalen-2-yl)-pyridin-3-yl)phenyl)acetic acid (130)



130

In a flame dried 25 mL one-neck round-bottom flask 63.4 mg (108 µmol, 1.00 eq) ethyl 2-((3-isobutyl-5-(2-(2-methoxy-2-oxoethyl)-4-(5-(naphthalen-2-yl)pyridin-3-yl)phenyl)pyridin-2-yl)oxy)acetate (**129**) were dissolved in 1.5 mL THF/H_2O (2/1). Then 90.5 mg (2.15 mmol, 20.0 eq) LiOH were added and the colorless suspension was stirred at RT until full conversion was detected by HPLC-MS (30 min). Afterwards 4 mL 1M HCl was added to the suspension to adjust to pH = 1 and the product was extracted with CH_2Cl_2 (5 x 15 mL). The solvent of the combined organic phases was removed under reduced pressure. The crude prodct was purified via preparative HPLC (Method_4).

Yield: 40.2 mg (73.5 µmol, 68 %), yellowish solid

$C_{34}H_{30}N_2O_5$ [546.62 g/mol]

mp$^{exp.}$ = 75 – 106 °C

HPLC-MS (Method_2): t_R = 7.69 min, *m*/*z* + H = 548.

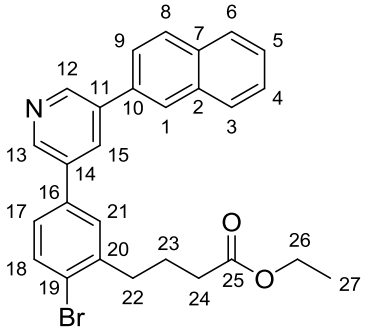
^{1}H-NMR (300.36 MHz, DMSO d_6): δ = 9.20 (s, 1H, H-12), 9.10 (s, 1H, H-13), 8.83 (s, 1H, H-15), 8.55 (s, 1H, H-21), 8.14 – 7.88 (m, 7H, H^{Ar}), 7.65 – 7.39 (m, 6H, H^{Ar}), 4.96 (d, $^4J_{HH}$ = 31.2 Hz, 2H, H-33), 3.74 (d, $^4J_{HH}$ = 36.1 Hz, 2H, H-22), 2.50 (s, 2H, H-29), 2.04 (m, 1H, H-30), 0.91 (d, $^3J_{HH}$ = 6.5 Hz, 6H, H-31, H-32) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 172.6 (C_q), 171.4 (C_q), 170.3 (C_q), 169.4 (C_q), 159.8 (C_q), 159.6 (C_q), 143.3 (C-12), 143.1 (C-13), 139.9 (C_q), 138.9 (C_q), 137.0 (C_q), 135.5 (C_q), 135.0 (C_q), 133.6 (C^{Ar}), 133.2 (C^{Ar}), 132.9 (C^{Ar}), 132.8 (C^{Ar}), 131.0 (C^{Ar}), 130.1 (C^{Ar}), 128.8

(C^{Ar}), 128.4 (C^{Ar}), 127.6 (C^{Ar}), 126.9 (C^{Ar}), 126.8 (C^{Ar}), 126.3 (C^{Ar}), 125.0 (C^{Ar}), 122.7 (C_q), 122.6 (C_q), 62.0 (C-33), 51.7 (C-22), 38.4 (C-29), 27.4 (C-30), 22.3 (C-31, C-32) ppm.

HRMS (MALDI-TOF): calcd. for $C_{34}H_{30}N_2O_5H^+$ $[M+H]^+$: 547.2233; found: 547.2273.

7.4.19.22. Ethyl 4-(2-bromo-5-(5-(naphthalen-2-yl)pyridin-3-yl)phenyl)butanoate (131)



131

A flame dried 8 mL Schlenk-flask was charged with 121 mg (305 µmol, 1.00 eq) ethyl 4-(2-bromo-5-iodophenyl)butanoate, 110 mg (332 µmol, 1.09 eq) 3-benzyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, 11.0 mg (15.2 µmol, 0.05 eq) Pd(dppf)Cl_2 and 84.0 mg (609 µmol, 2.00 eq) K_2CO_3. 2 mL abs DMF were added and the reaction mixture was stirred at 80 °C until full conversion was detected by TLC (14 h). The brown/black suspension was then concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography (25 g SiO_2, 2.5 x 10.0 cm, eluent: cyclohexane/EtOAc = 3/1, R_f = 0.38, UV and $KMnO_4$, fraction size: 10 mL).

Yield: 77.9 mg (177 µmol, 58 %), colorless oil

$C_{27}H_{24}BrNO_2$ [474.40 g/mol]

TLC: R_f = 0.38 (cyclohexane/EtOAc = 3/1, UV and $KMnO_4$)

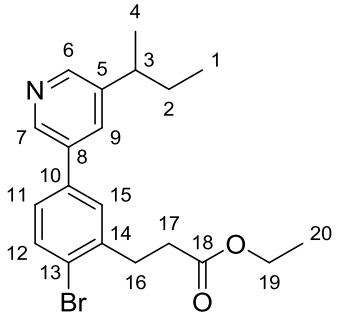
^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 8.96 (d, $^4J_{HH}$ = 1.6 Hz, 1H, H-12), 8.81 (d, $^4J_{HH}$ = 1.7 Hz, 1H, H-13), 8.12 (d, $^4J_{HH}$ = 7.7 Hz, 1H, H^{Ar}), 8.03 – 7.30 (m, 10H, H^{Ar}), 4.14 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-26), 2.87 (t, $^3J_{HH}$ = 7.3 Hz, H-22), 2.42 (t, $^3J_{HH}$ = 7.3 Hz, 2H, H-24), 2.05 (t, $^3J_{HH}$ = 7.5 Hz, 2H, H-23), 1.26 (t, $^3J_{HH}$ = 7.1 Hz, 3H, H-27) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 175.4 (C_q, C-25), 147.7 (C-12), 146.9 (C-13), 141.9 (C_q), 137.3 (C_q), 136.8 (C_q), 135.8 (C_q), 135.0 (C_q), 133.8 (C^{Ar}), 133.1 (C_q), 133.0 (C^{Ar}), 129.4

(C^{Ar}), 129.1 (C^{Ar}), 128.4 (C^{Ar}), 127.9 (C^{Ar}), 126.8 (C^{Ar}), 126.7 (C^{Ar}), 126.6 (C_q), 126.5 (C^{Ar}), 125.4 (C^{Ar}), 124.8 (C_q), 60.5 (C-26), 35.6 (C-22), 33.8 (C-24), 25.2 (C-23), 14.4 (C-27) ppm.

HRMS (DI-EI TOF): calcd. for $C_{27}H_{24}BrNO_2^+$ $[M]^+$: 473.0983; found: 473.0983.

7.4.19.23. Ethyl 3-(2-bromo-5-(5-(sec-butyl)pyridin-3-yl)phenyl)propanoate (133)



133

A flame dried 8 mL Schlenk-flask was charged with 500 mg (1.31 mmol, 1.00 eq) ethyl 3-(2-bromo-5-iodophenyl)propanoate (**68**), 359 mg (1.37 mmol, 1.05 eq) 3-(sec-butyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, 48 mg (65.6 µmol, 0.05 eq) $Pd(dppf)Cl_2$ and 362 mg (2.62 mmol, 2.00 eq) K_2CO_3. 7 mL abs., degassed DMF were added and the reaction mixture was stirred at 80 °C until full conversion was detected by TLC and HPLC-MS. The brown suspension was then concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography (130 g SiO_2, 5.0 x 16.5 cm, eluent: cyclohexane/EtOAc = 5/1, R_f = 0.20, UV and $KMnO_4$, fraction size: 75 mL).

Yield: 316 mg (810 µmol, 62 %), orange oil

$C_{20}H_{24}BrNO_2$ [390.32 g/mol]

TLC: R_f = 0.20 (cyclohexane/EtOAc = 5/1, UV and $KMnO_4$)

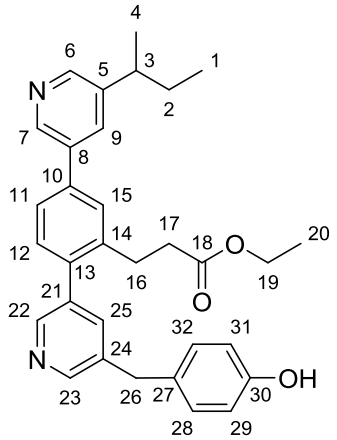
HPLC-MS (Method_2): t_R = 7.39 min, *m/z* + H = 390.

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 8.53 (d, $^4J_{HH}$ = 5.2 Hz, 1H, H-7), 8.35 (s, 1H, H-6), 7.60 (d, $^3J_{HH}$ = 8.1 Hz, 1H, H-12), 7.22 (d, $^4J_{HH}$ = 5.2 Hz, 1H, H-9), 7.16 (d, $^4J_{HH}$ = 1.7 Hz, 1H, H-15), 6.98 (dd, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.9 Hz, 1H, H-11), 4.12 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-19), 3.11 (t, $^3J_{HH}$ = 7.7 Hz, 2H, H-16), 2.78 – 2.62 (m, 3H, H-3, H-17), 1.62 – 1.44 (m, 2H, H-2), 1.23 (t, $^3J_{HH}$ = 7.7 Hz, 3H, H-20), 1.15 (d, J = 6.8 Hz, 3H, H-4), 0.69 (t, $^3J_{HH}$ = 7.3 Hz, 3H, H-1) ppm.

^{13}C-NMR (75.53 MHz, D_2O): δ = 172.5 (C_q, C-18), 154.3 (C_q, C-5), 150.0 (C-6), 149.1 (C-7), 140.1 (C_q, C-14), 137.7 (C_q, C-10), 136.6 (C_q, C-8), 133.0 (C-12), 131.7 (C-15), 129.3 (C-11), 123.9 (C_q, C-13), 120.9 (C-9), 60.7 (C-19), 36.3 (C-3), 34.2 (C-17), 31.5 (C16), 30.6 (C-2), 21.8 (C-4), 14.3 (C-20), 12.2 (C-1) ppm.

HRMS (DI-EI TOF): calcd. for $C_{20}H_{24}BrNO_2^+$ $[M]^+$: 389.0990; found: 389.0985.

7.4.19.24. Ethyl 3-(2-bromo-5-(5-(sec-butyl)pyridin-3-yl)phenyl)propanoate (134)



134

A flame dried 8 mL Schlenk-flask was charged with 180 mg (460 µmol, 1.00 eq) ethyl 3-(2-bromo-5-(5-(sec-butyl)pyridin-3-yl)phenyl)propanoate (**133**), 206 mg (484 µmol, 1.05 eq) 3-(4-((tert-butyl-dimethylsilyl)oxy)benzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, 17 mg (23.2 µmol, 0.05 eq) Pd(dppf)Cl_2 and 300 mg (921 µmol, 2.00 eq) Cs_2CO_3. 2 mL abs., degassed DMF were added and the reaction mixture was stirred at 80 °C until full conversion was detected by HPLC-MS. The brown suspension was then concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography (75 g SiO_2, 4.0 x 10.0 cm, eluent: cyclohexane/EtOAc = 1/1, fraction size: 40 mL).

Yield: 145 mg (294 µmol, 64 %), brown oil

$C_{32}H_{34}N_2O_3$ [494.64 g/mol]

TLC: R_f = 0.08 (cyclohexane/EtOAc = 5/1, UV and $KMnO_4$)

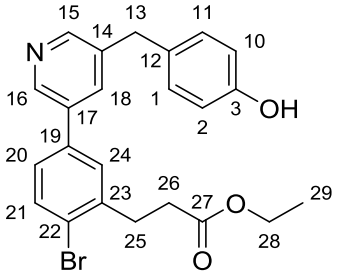
HPLC-MS (Method_2): t_R = 4.04 min, *m/z* + H = 495.

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 8.54 – 8.46 (m, 3H, H-6, H-7, H-22), 8.40 (s, 1H, H-23), 7.49 (s, 1H, H-9), 7.51 - 7.12 (m, 4H, H-11, H-12, H-15, H-25), 7.05 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H, H-28, H-32), 6.83 (d, $^{3}J_{HH}$ = 7.9 Hz, 1H, H-29, H-31), 4.08 – 3.98 (m, 4H, H-19, H-26), 2.94 – 2.80 (m, 3H, H-3, H-16), 2.41 (t, $^{3}J_{HH}$ = 7.7 Hz, 1H, H-17), 1.62 – 1.55 (m, 2H, H-2), 1.28 – 1.12 (m, 6H, H-4, H-20), 0.73 (t, $^{3}J_{HH}$ = 7.3 Hz, 3H, H-1) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 172.4 (C_q, C-18), 156.0 (C_q), 155.1 (C_q), 149.6 (C-23), 148.5 (C-22), 148.4 (C-6), 147.0 (C-7), 138.5 (C_q), 138.1 (C_q), 137.6 (C_q), 137.5 (C_q), 137.4 (C-9), 137.3 (C_q), 136.7 (C_q), 130.5 (2C, C^{Ar}), 130.2 (C-28, C-32), 127.8 (C^{Ar}), 122.0 (C_q), 121.3 (C^{Ar}), 116.0 (c-29, C-31), 60.6 (C-19), 38.2 (C-26), 36.4 (C-3), 35.3 (C-17), 30.6 (C-2), 28.2 (C-16), 21.9 (C-4), 14.3 (C-20), 12.2 (C-1) ppm.

HRMS (DI-EI TOF): calcd. for $C_{32}H_{34}N_2O_3^+$ $[M]^+$: 494.2569; found: 494.2560.

7.4.19.25. Ethyl 3-(2-bromo-5-(5-(4-((tert-butyldimethylsilyl)oxy)benzyl)pyridin-3 yl)phenyl)propanoate (135)



135

A flame dried 8 mL Schlenk-flask was charged with 400 mg (1.04 mmol, 1.00 eq) ethyl 3-(2-bromo-5-iodophenyl)propanoate (**68**), 447 mg (1.10 mmol, 1.05 eq) 3-(4-((tert-butyldimethylsilyl)oxy)benzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, 38.3 mg (52.3 µmol, 0.05 eq) $Pd(dppf)Cl_2$ and 298 mg (2.09 mmol, 2.00 eq) K_2CO_3. 3 mL abs, degassed DMF were added and the reaction mixture was stirred at 80 °C until full conversion was detected by TLC. The red/brown suspension was then concentrated to dryness using a rotary evaporator. The crude product was purified via flash column chromatography (120 5 g SiO_2, 5.0 x 15.5 cm, eluent: cyclohexane/EtOAc = 2/1, fraction size: 60 mL).

Yield: 304 mg (689 µmol, 66 %), brown oil

$C_{23}H_{22}BrNO_3$ [440.34 g/mol]

TLC: R_f = 0.10 (cyclohexane/EtOAc = 3/1, UV and $KMnO_4$)

^{1}H-NMR (300.36 MHz, $CDCl_3$): δ = 8.62 (s, 1H, H-9), 8.42 (s, 1H, H-10), 7.66 (s, 1H, H-12), 7.61 (d, $^3J_{HH}$ = , 1H, H-15), 7.42 (d, $^4J_{HH}$ = 1.9 Hz, 1H, H-18), 7.24 (dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 2.1 Hz, 1H, H-14), 7.03 (d, $^3J_{HH}$ = 8.3 Hz, 2H, H-1, H-5), 6.80 (d, $^3J_{HH}$ = 8.4 Hz, 2H, H-2, H-4), 4.13 (q, $^3J_{HH}$ = 7.1 Hz, 2H, H-22), 3.97 (s, 2H, H-7), 3.12 (t, $^3J_{HH}$ = 7.7 Hz, 2H, H-19), 2.68 (t, $^3J_{HH}$ = 7.7 Hz, 2H, H-20), 1.31 – 1.16 (m, 3H, H-29) ppm.

^{13}C-NMR (75.53 MHz, $CDCl_3$): δ = 172.7 (C_q, C-21), 155.6 (C_q, C-3), 148.6 (C-10), 145.2 (C-9), 140.8 (C-17), 137.8 (C_q, C-13), 137.13 (C_q, C-14), 135.9 (C_q, C-17), 135.3 (C-12), 133.7 (C-15), 130.7 (C_q, C-6), 130.1 (C-1, C-5), 129.3 (C-18), 126.9 (C-14), 124.7 (C_q, C-16), 116.0 (C-2, C-4), 60.8 (C-22), 38.3 (C-7), 34.2 (C-20), 31.7 (C-19), 14.3 (C-23) ppm.

HRMS (DI-EI TOF): calcd. for $C_{23}H_{22}BrNO_3^+$ $[M]^+$: 439.0783; found: 439.0783.

8. References

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9. Abbreviations

9.1. Amino Acid Abbreviation

Ala	Alanine
Arg	Arginine
Asn	Asparagine
Asp	Aspartic acid
Cys	Cysteine
Gln	Glutamine
Glu	Glutamic acid
Gly	Glycine
His	Histidine
Ile	Isoleucine
Leu	Leucine
Lys	Lysine
Phe	Phenylalanine
Met	Methionine
Pro	Proline
Ser	Serine
Thr	Threonine
Trp	Tryptophan
Tyr	Tyrosine
Val	Valine

9.2. Analytical Methods

APT	attached proton test
COSY	correlation spectroscopy
EI	electron impact ionisation
ESI	electronspray ionisation
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry

HSQC	heteronuclear single quantum coherence
NMR	nuclear magnetic resonance
TLC	thin layer chromatography
bs	broad singlet
d	doublet
dd	doublet of doublet
m	multiplet
pent	pentet
q	quadroplet
sept	septet
s	singlet
t	triplet
δ	chemical shift in ppm (parts per million)
Hz	Hertz
J	coupling constant
λ	wavelength
MALDI	matrix-assisted laser desorption/ionization
MHz	Megahertz
min	minute
m/z	mass to charge ratio
nm	nanometer
R_f	retardation factor
RT	room temperature
t_R	retention time
UV	ultraviolett
v/v	volume to volume ratio
w/w	mass to mass ratio

9.3. Chemical Formula

Ac	acetyl
AcCl	acetyl chloride
AcOH	acetic acid
B_2Pin_2	bis(pinacolato)diboron
Boc	*tertiary*-butyloxycarbonyl

Boc_2O	di-*tert*-butyldicarbonate
CAM	cerammoniummolybdate
CH	cyclohexane
dba	dibenzylideneacetone
1,2-DCE	1,2-dichloroethane
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	(4-dimethylamino)pyridine
1,2-DME	1,2-dimethoxyethane
DMEDA	*N*,*N*'-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMAc	*N*,*N*-dimethylacetamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
Et	ethyl
Et_2O	diethylether
Et_3N	triethylamine
EtOAc	ethylacetate
EtOH	ethanol
KO*t*Bu	potassium *tert*-butoxide
KSAc	potassium thioacetate
Me	methyl
MeCN	acetonitrile
$MeNO_2$	nitromethane
MeOH	methanol
MIDA	*N*-methyliminodiacetic acid
*n*BuLi	*n*-butyllithium
NBS	*N*-bromosuccinimide
OAc	acetate
PADA	potassium azodicarboxylate
RNA	ribonucleic acid
Tf	triflate
TFA	trifluoroacetic acid

Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
TBDMS	tert-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TIPS	triisopropylsilyl
TMS	tetramethylsilyl

9.4. Miscellaneous

Å	Ångström
AML	acute myeloid leukemia
APC	adenomatous polyposis coli
Bad	Bcl2-associated death promoter
Bak	Bcl2-antagonist/killer 1
Bcl-X_L	B-cell lymphoma-extra large
b_p	boiling point
calc.	calculated
CaM	calmoduline
CLL	chronic lymphocytic leukemia
c	concentration
d	day
°C	degree Celsius
dist.	distilled
eq	equivalents
et al.	et alii
eV	electronvolt
exp.	experimental
g	gram
GTP	guanosine-5'-triphosphate
h	hours
HDM2	human double minute 2
HIV	human immunodeficiency virus
IC_{50}	half minimal inhibitory concentration
K_i	inhibition constant
M	molar ($mol \cdot L^{-1}$)

µL	microliter
µm	micrometer
mbar	millibar
mg	milligram
mL	milliliter
mmol	millimol
µmol	micromol
m_p	melting point
NHR	nuclear receptor
nm	nanometer
%	percent
PDB	protein data bank
pH	pH-value
PPI	protein-protein interaction
ppm	parts per million
RDB	Rho-binding domain
ROCK	Rho-associated kinase
RT	room temperature
smMLCK	smooth muscle myosin light chain kinase
TCF	T-cell factor
tert	*tertiary*

10. Appendix

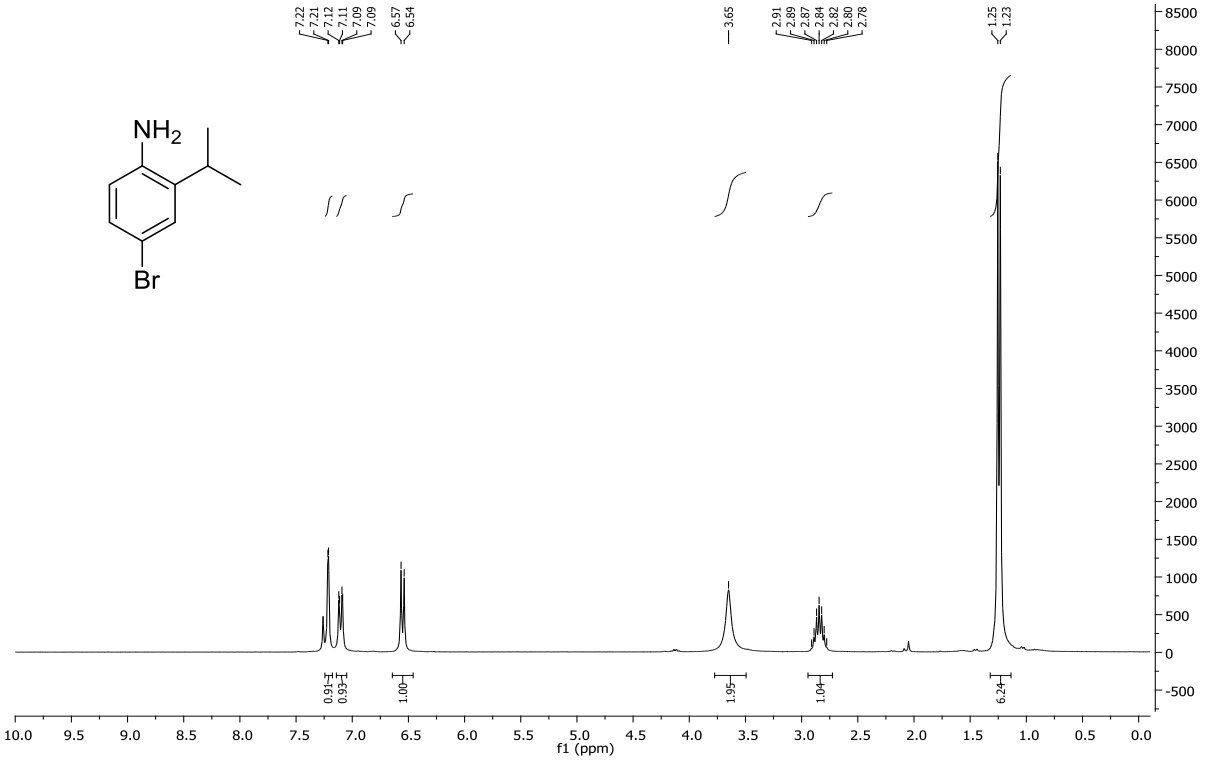

Figure 43. ^{1}H-NMR of 4-iodo-2-isopropylaniline (**6**).

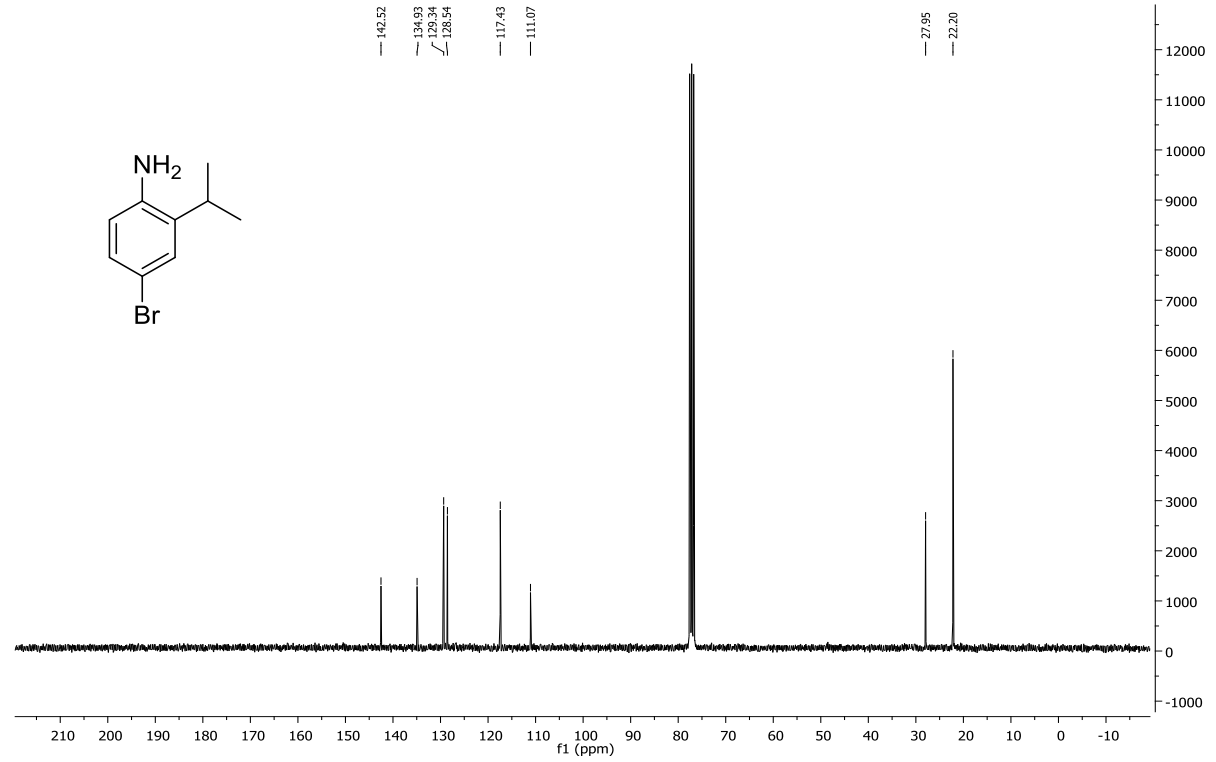

Figure 44. ^{13}C-NMR of 4-iodo-2-isopropylaniline (**6**).

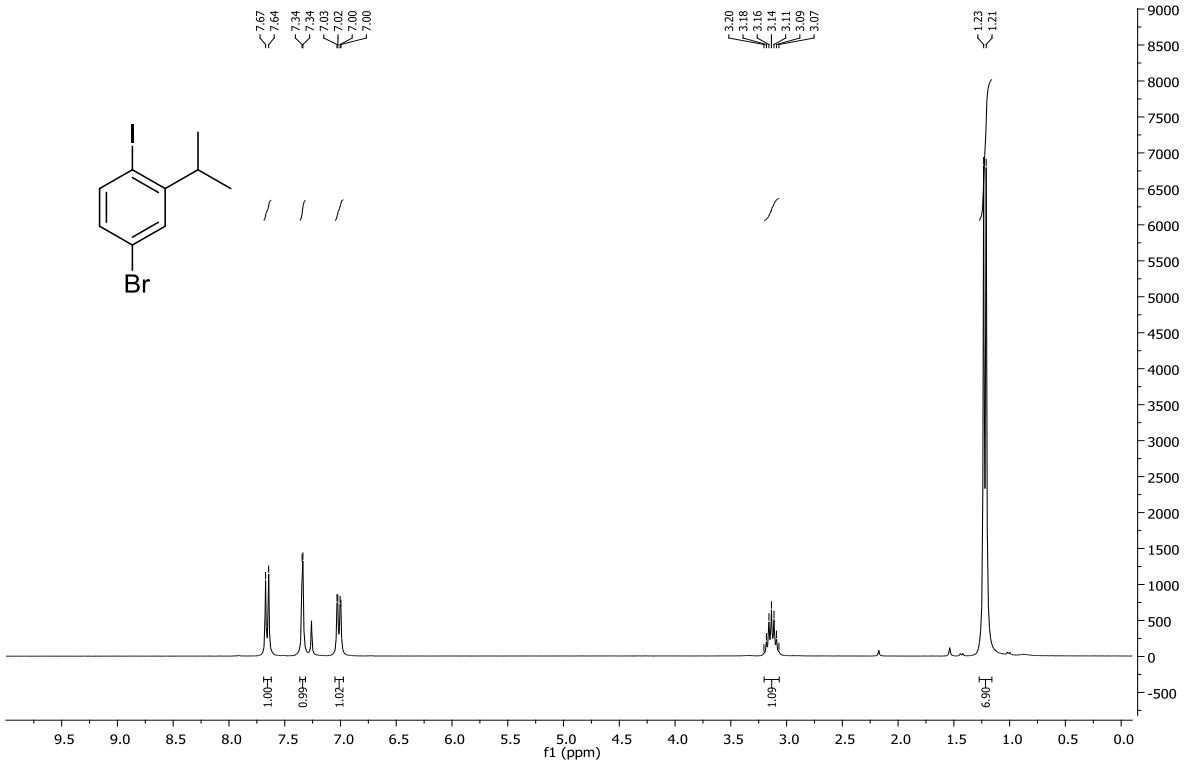

Figure 45. ^{1}H-NMR of 1-bromo-4-iodo-2-isopropylbenzene (**7**).

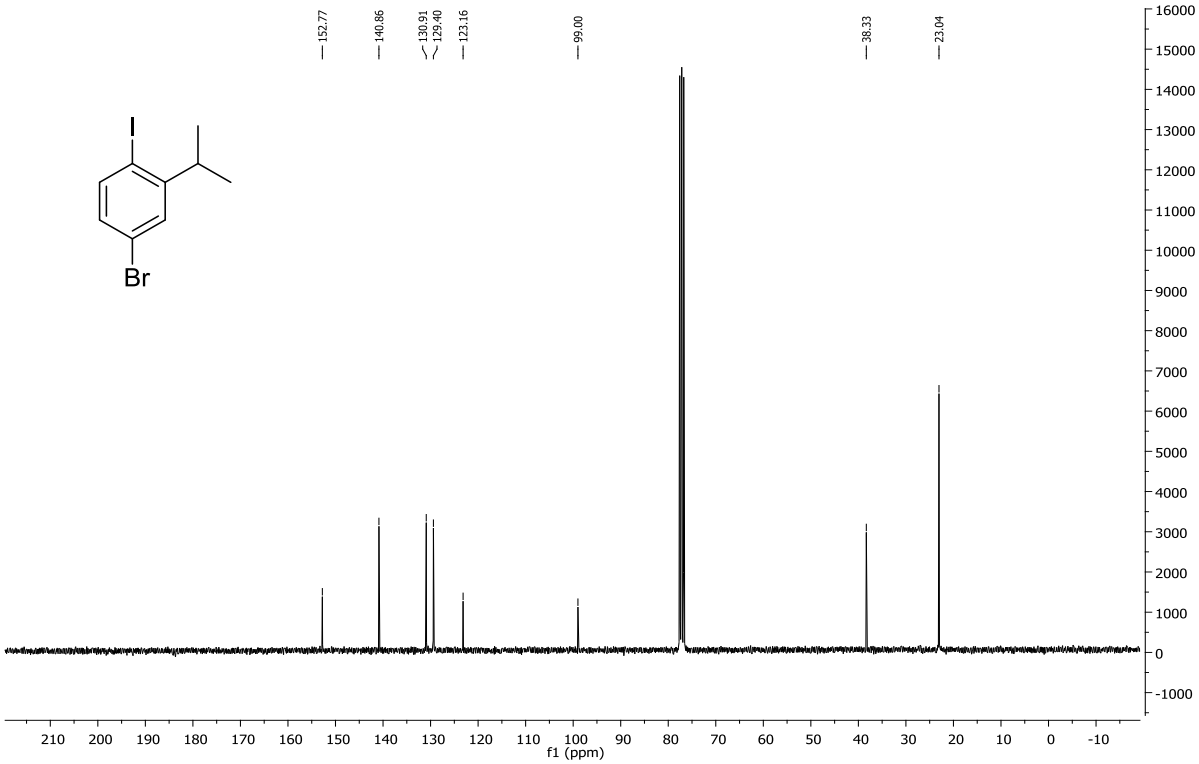

Figure 46. ^{13}C-NMR of 1-bromo-4-iodo-2-isopropylbenzene (**7**).

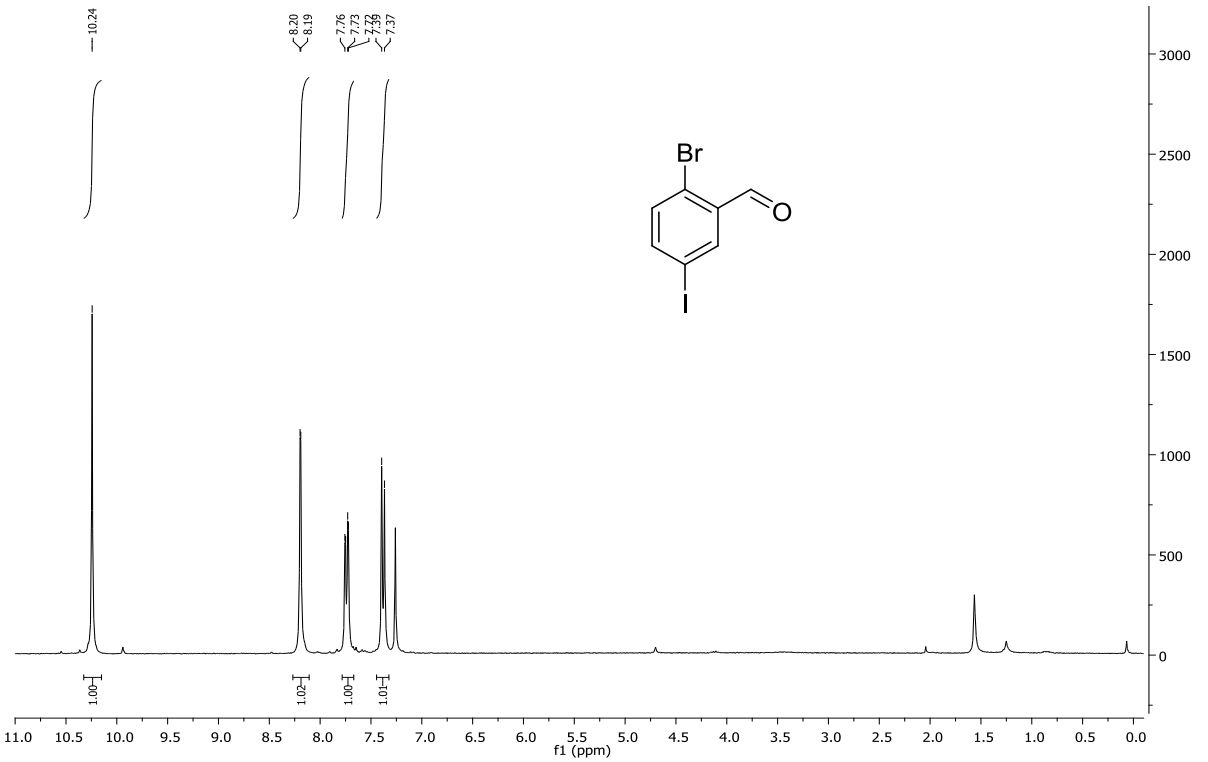

Figure 47. ^{1}H-NMR of 2-bromo-5-iodobenzaldehyde (**10**).

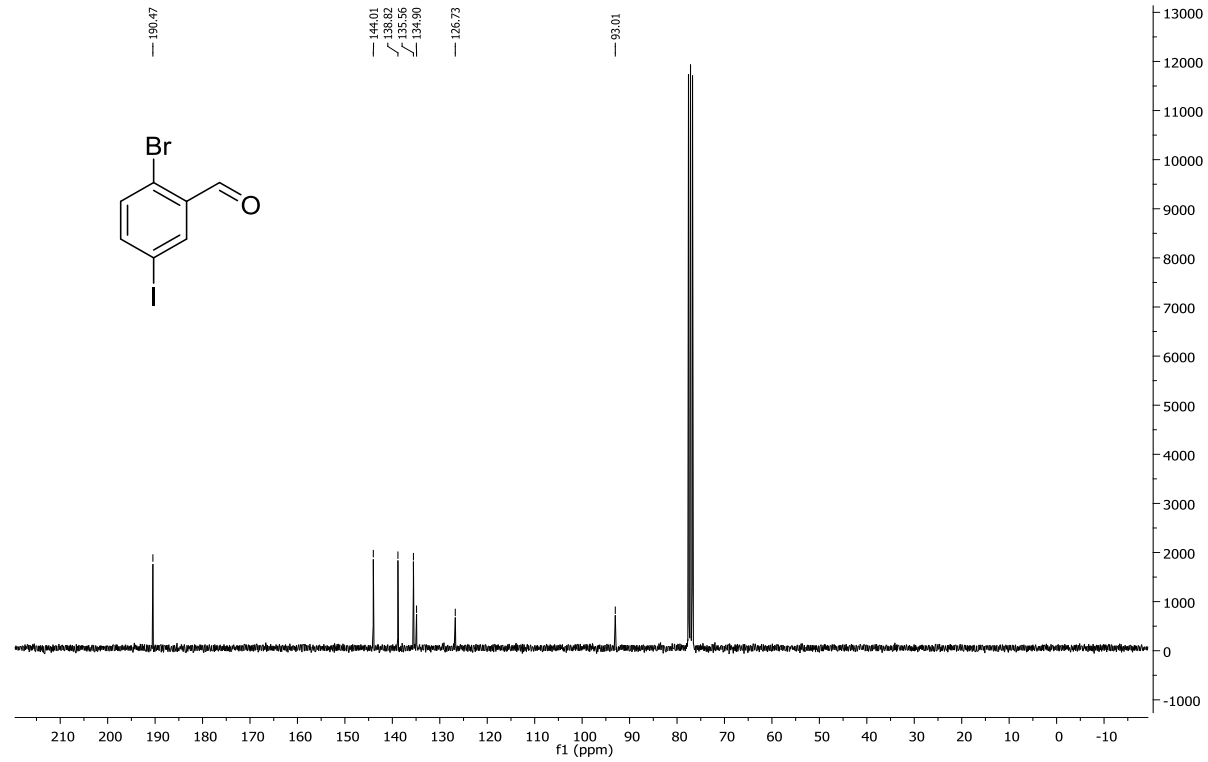

Figure 48. ^{13}C-NMR of 2-bromo-5-iodobenzaldehyde (**10**).

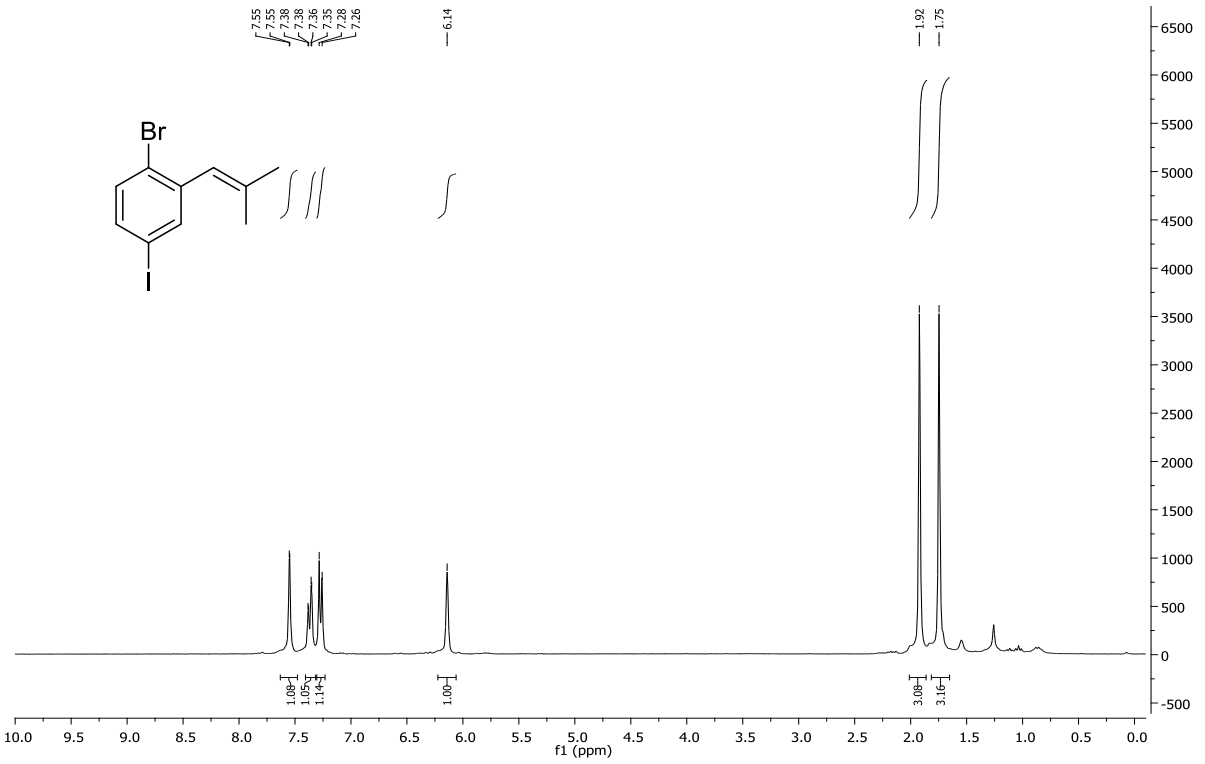

Figure 49. ^{1}H-NMR of 1-bromo-4-iodo-2-(2-methylprop-1-en-1-yl)benzene (**13**).

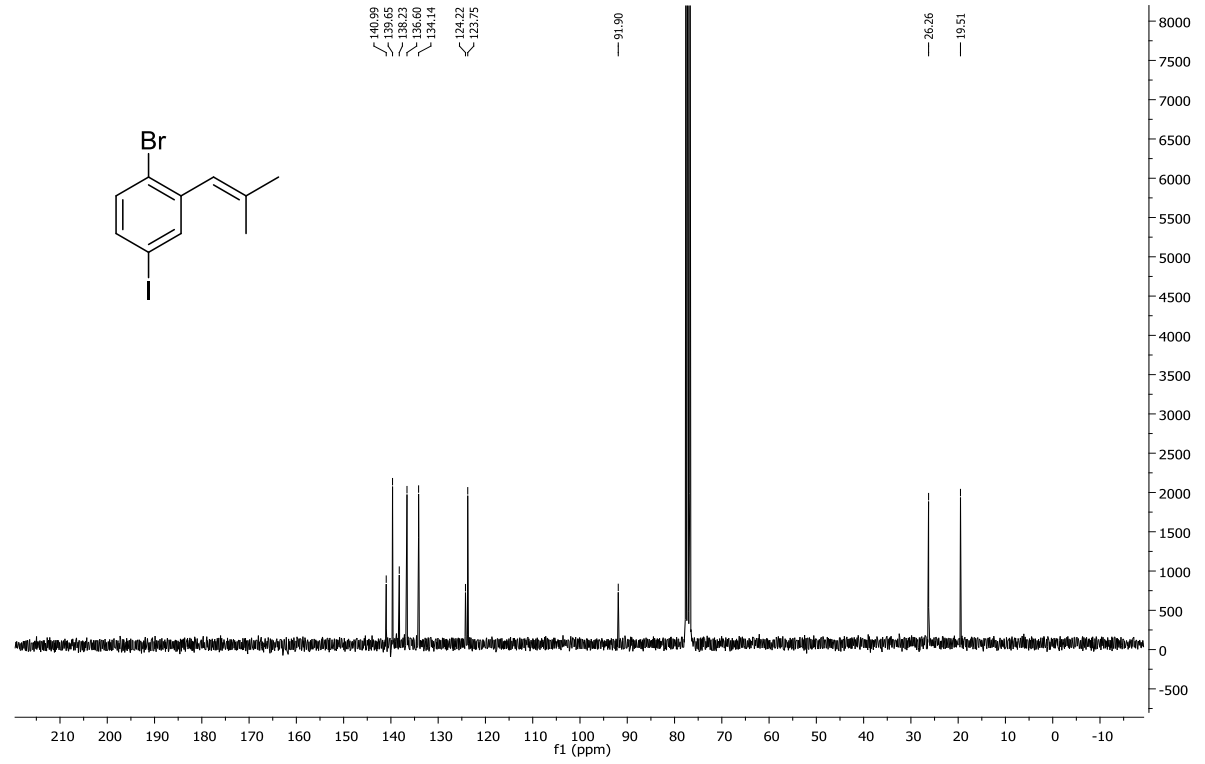

Figure 50. ^{13}C-NMR of 1-bromo-4-iodo-2-(2-methylprop-1-en-1-yl)benzene (**13**).

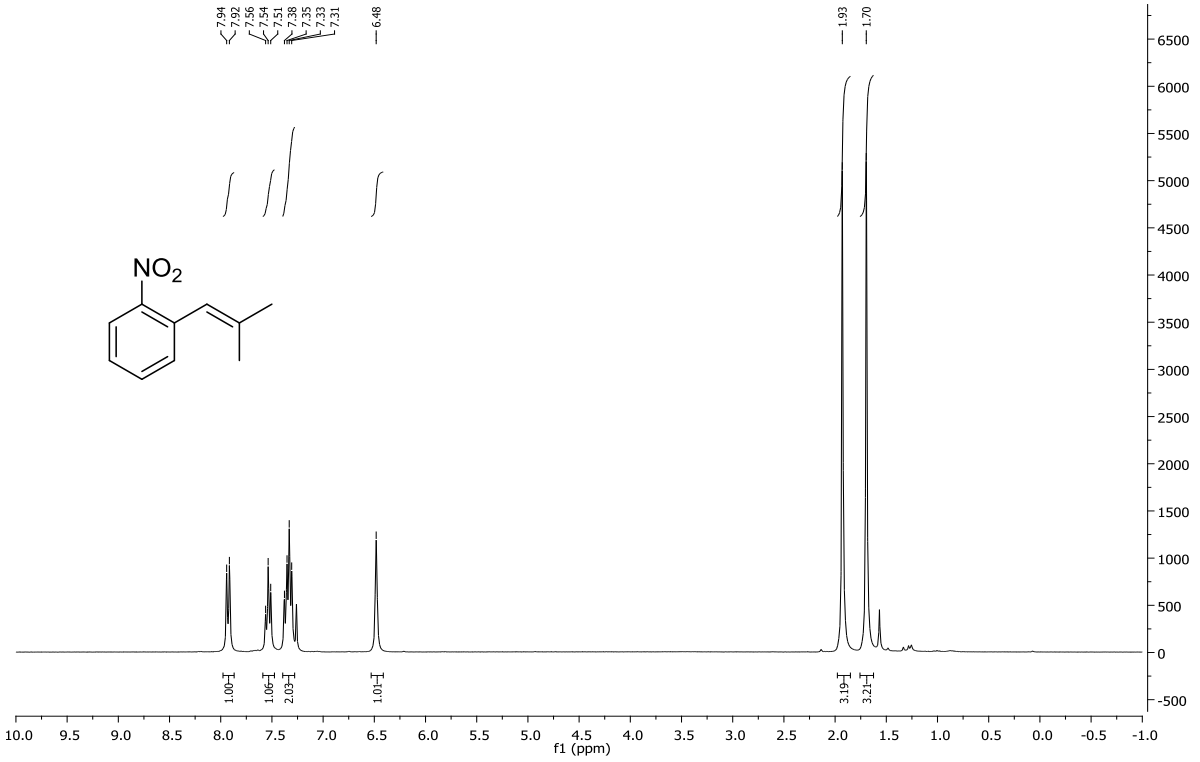

Figure 51. [1]H-NMR of 1-(2-methylprop-1-en-1-yl)-2-nitrobenzene (**17**).

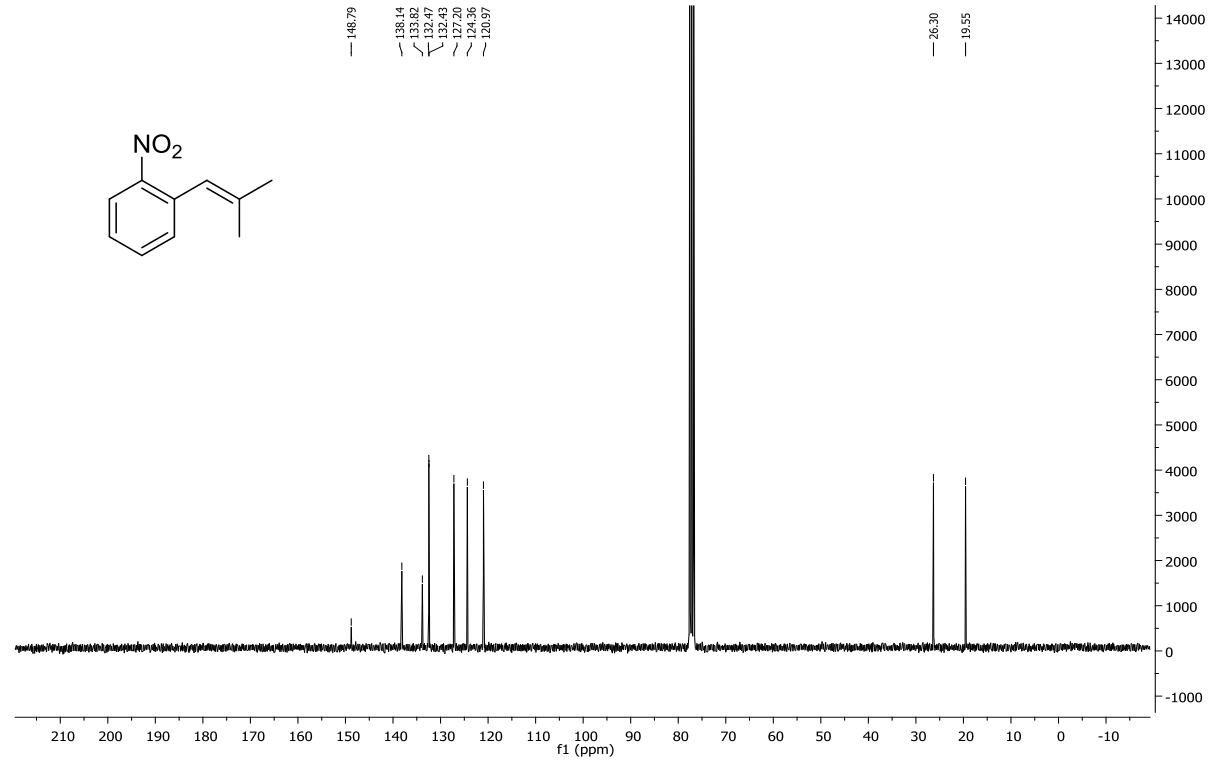

Figure 52. [13]C-NMR of 1-(2-methylprop-1-en-1-yl)-2-nitrobenzene (**17**).

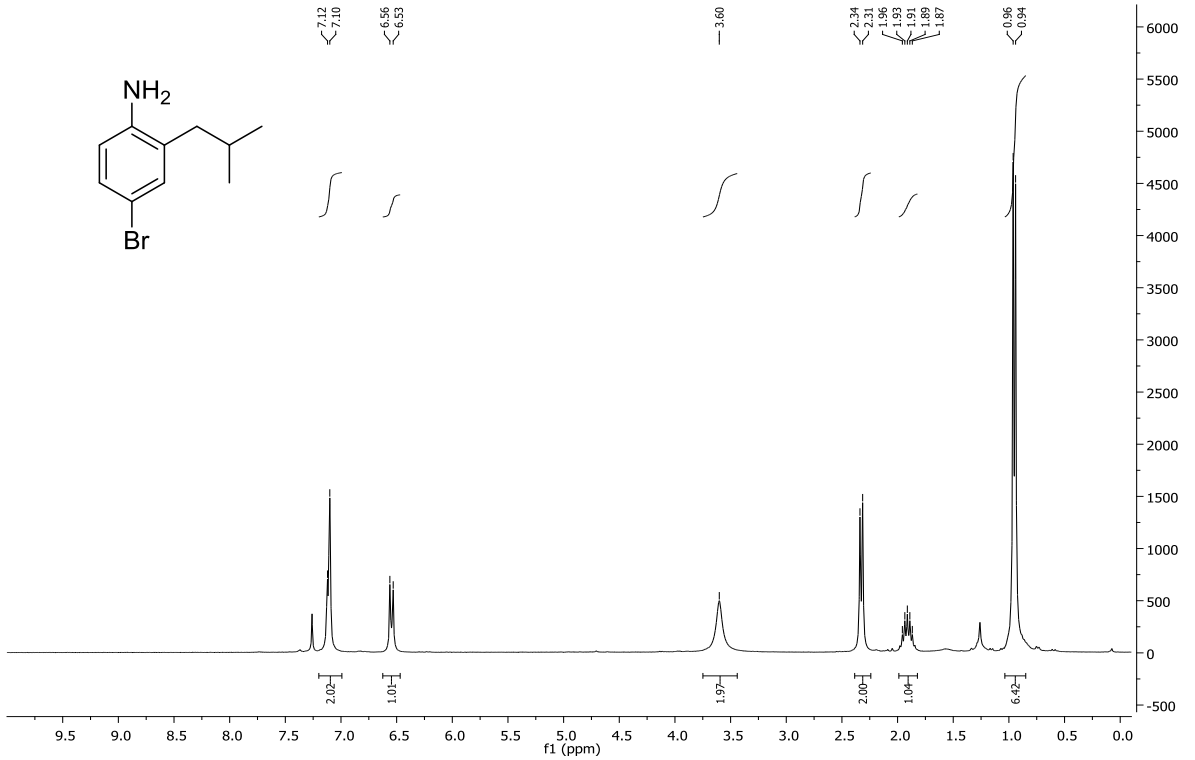

Figure 53. ^{1}H-NMR of 4-iodo-2-isobutylaniline (**19**).

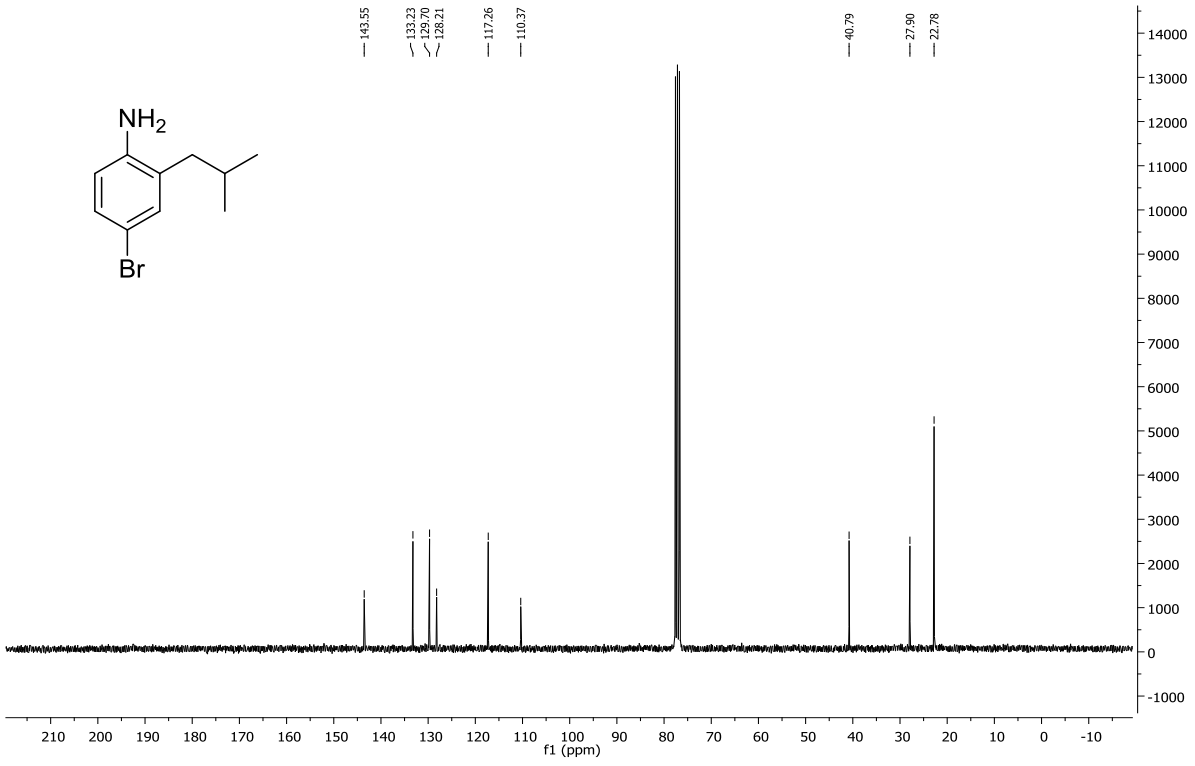

Figure 54. ^{13}C-NMR of 4-iodo-2-isobutylaniline (**19**).

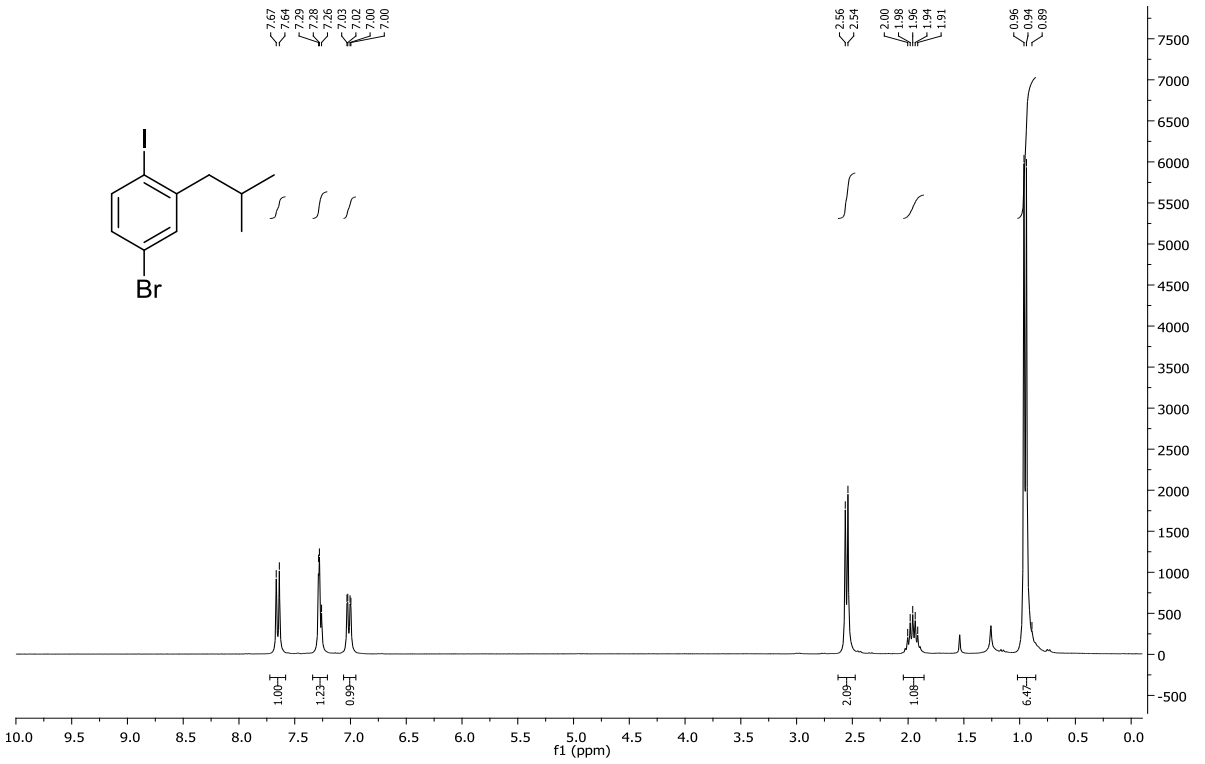

Figure 55. [1]H-NMR of 1-bromo-4-iodo-2-isobutylbenzene (**20**).

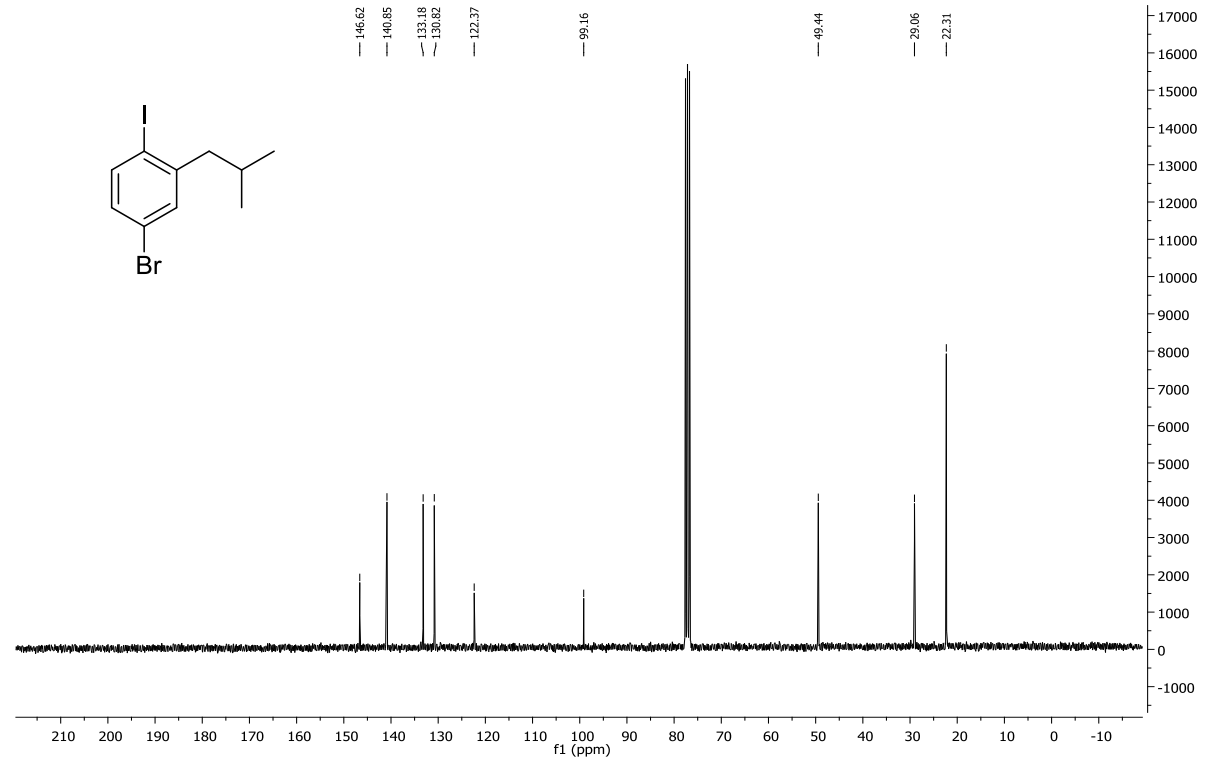

Figure 56. [13]C-NMR of 1-bromo-4-iodo-2-isobutylbenzene (**20**).

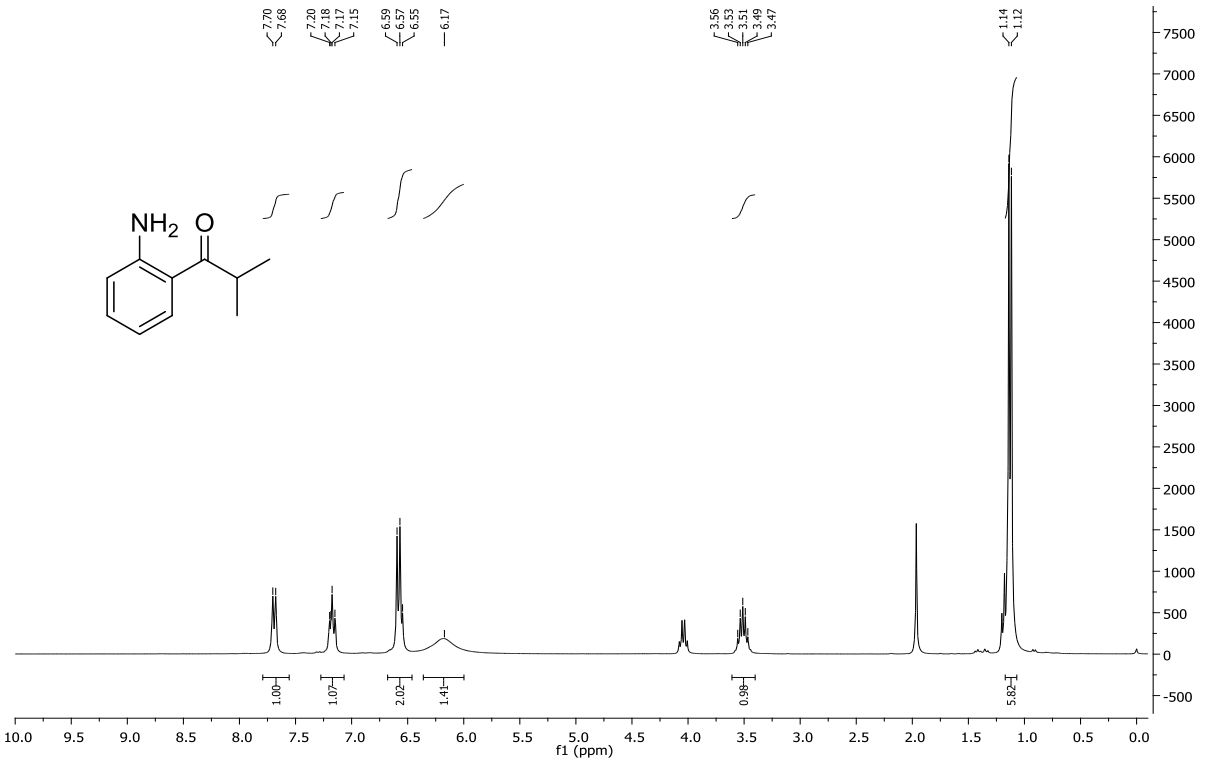

Figure 57. ^{1}H-NMR of 1-(2-aminophenyl)-2-methylpropan-1-one (**22**).

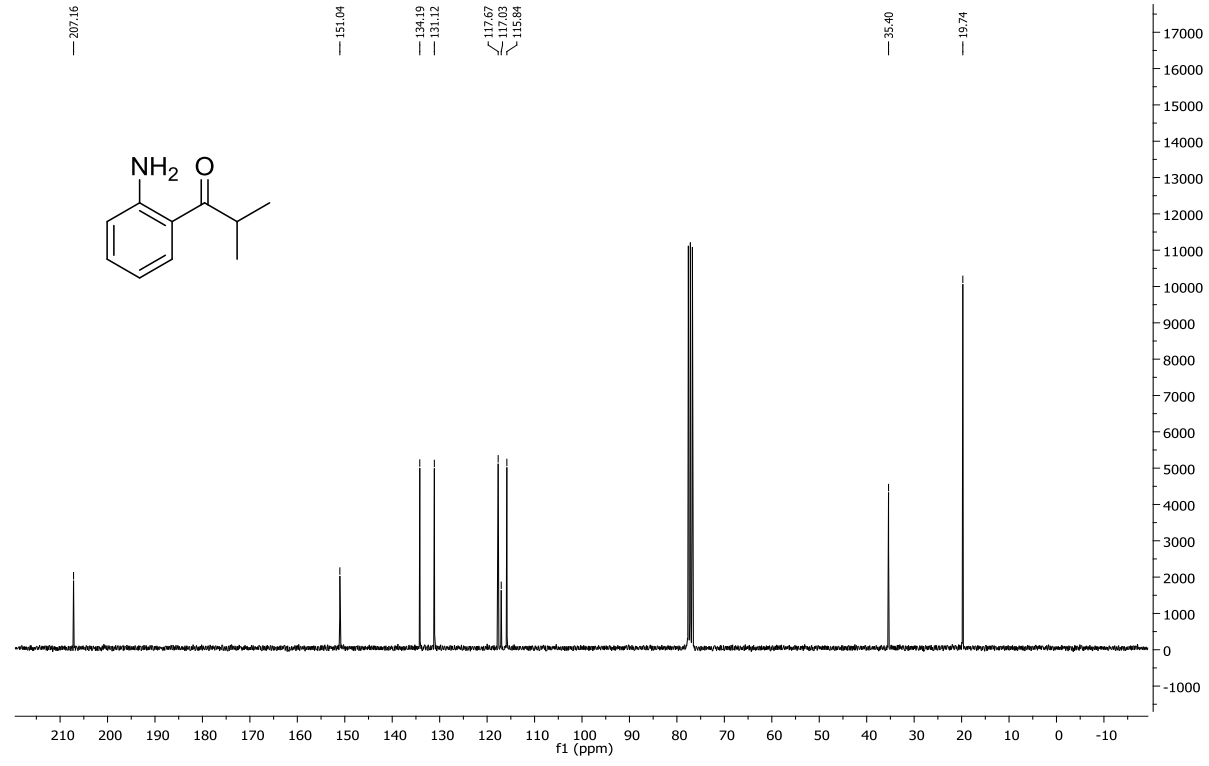

Figure 58. ^{13}C-NMR of 1-(2-aminophenyl)-2-methylpropan-1-one (**22**).

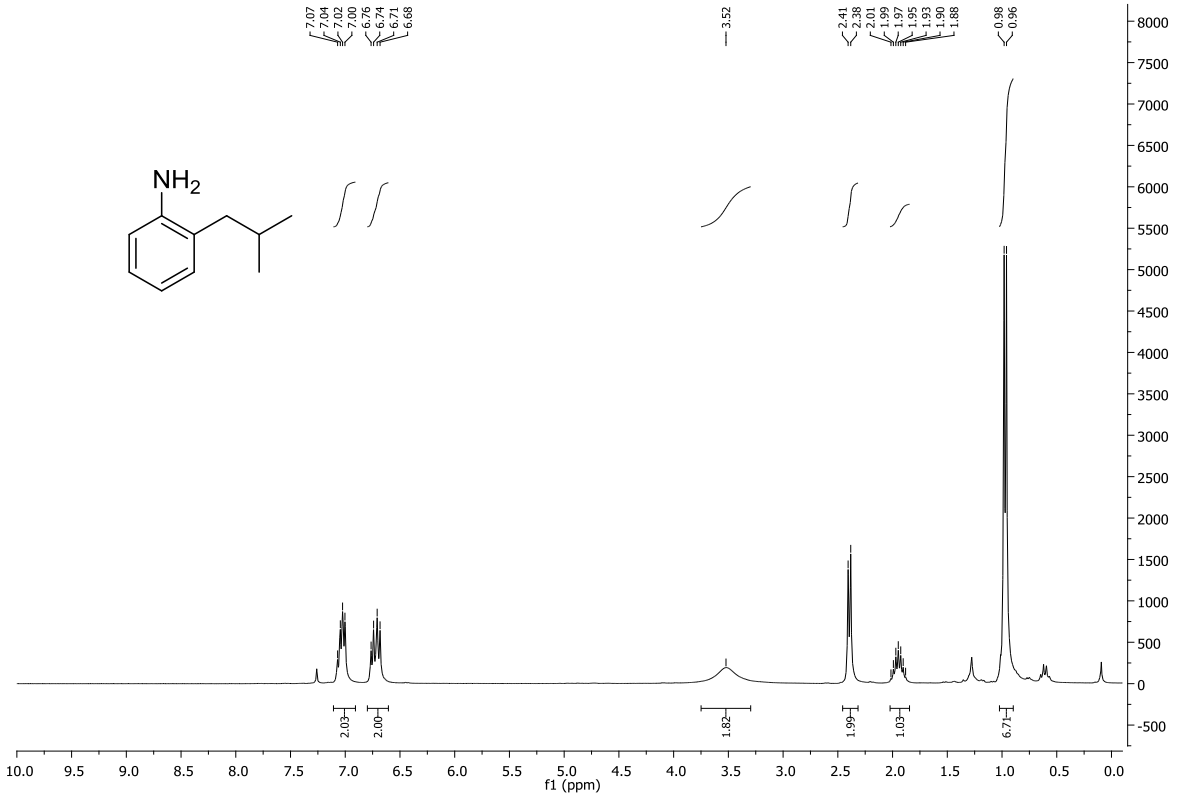

Figure 59. ^{1}H-NMR of 2-isobutylanilin (**18**).

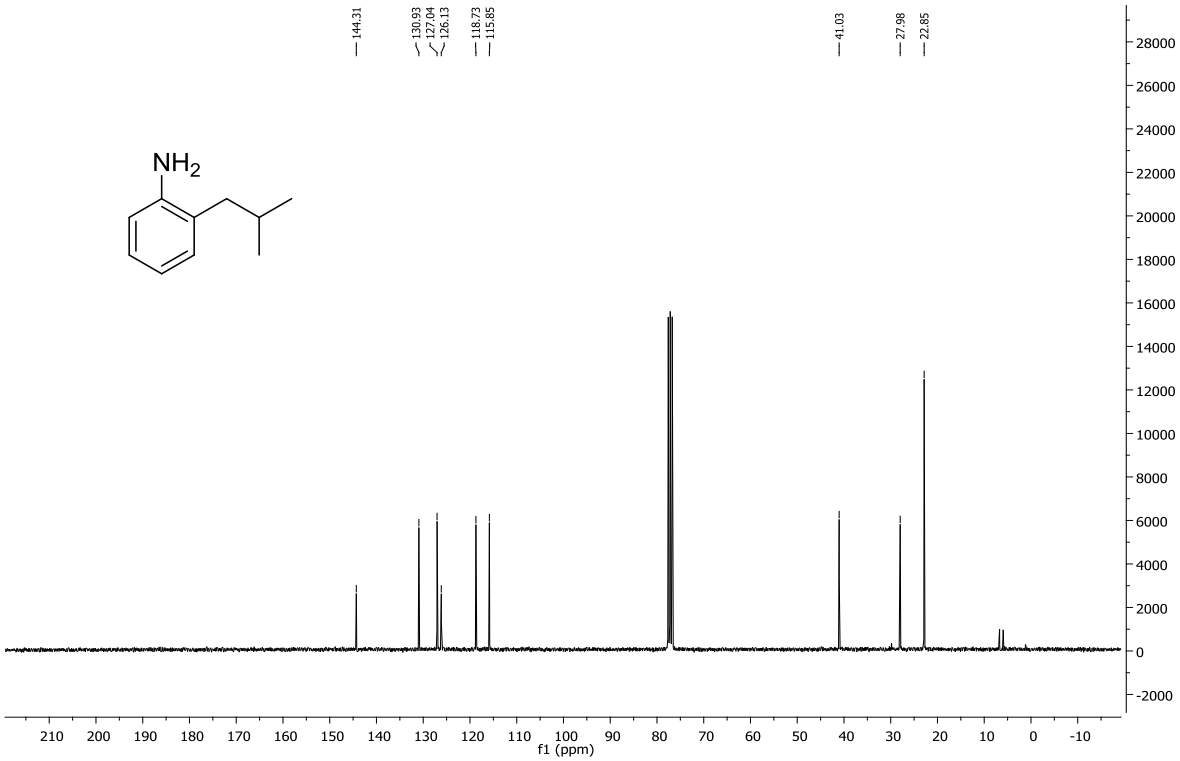

Figure 60. ^{13}C-NMR of 2-isobutylanilin (**18**).

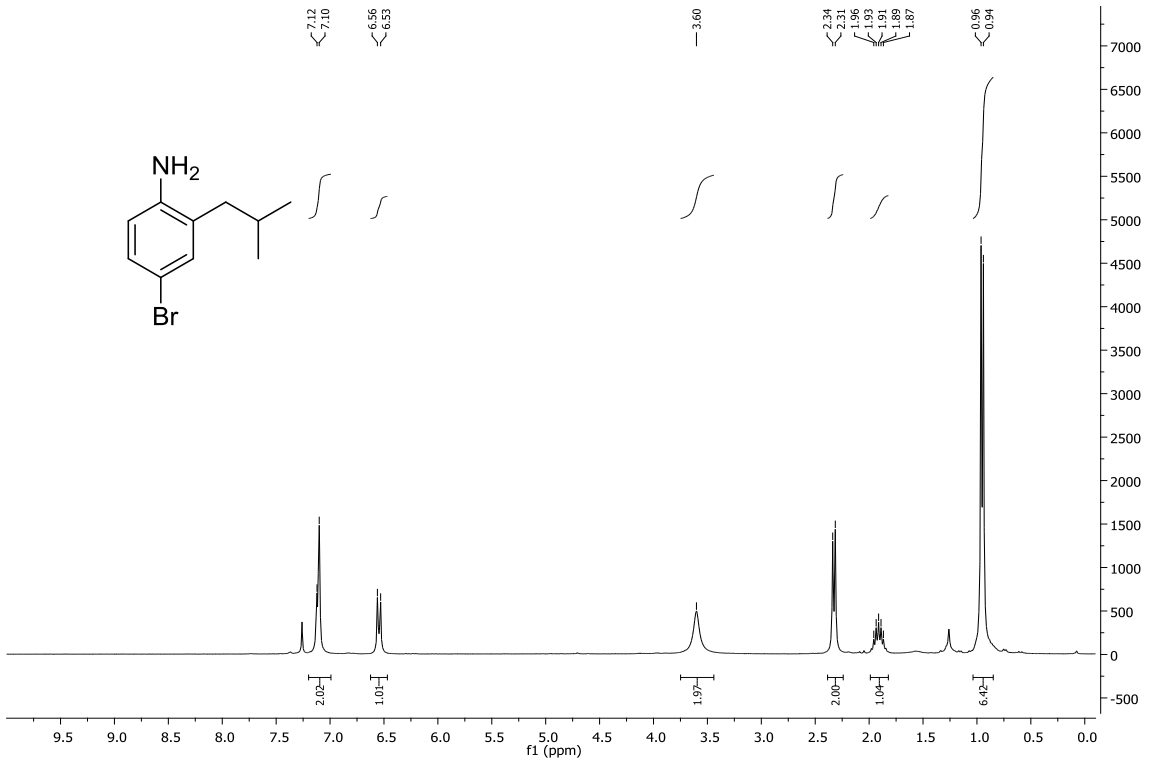

Figure 61. ^{1}H-NMR of 4-iodo-2-isobutylaniline (**19**).

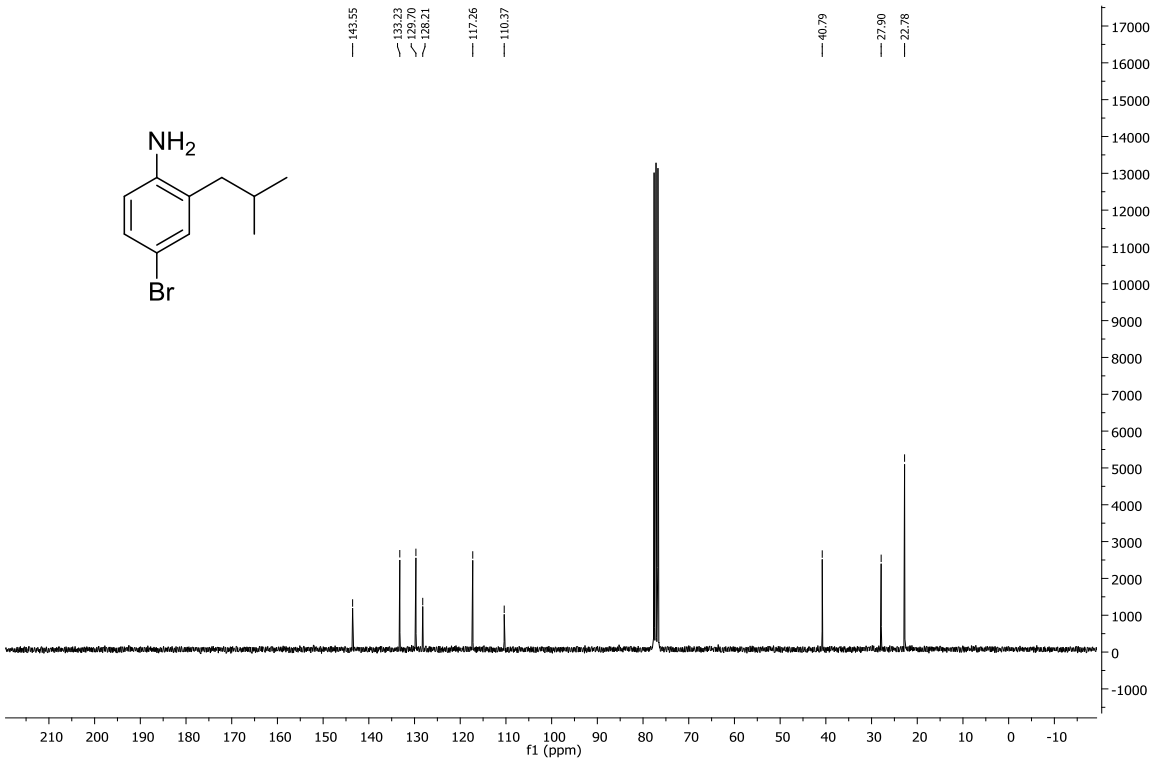

Figure 62. ^{13}C-NMR of 4-iodo-2-isobutylaniline (**19**).

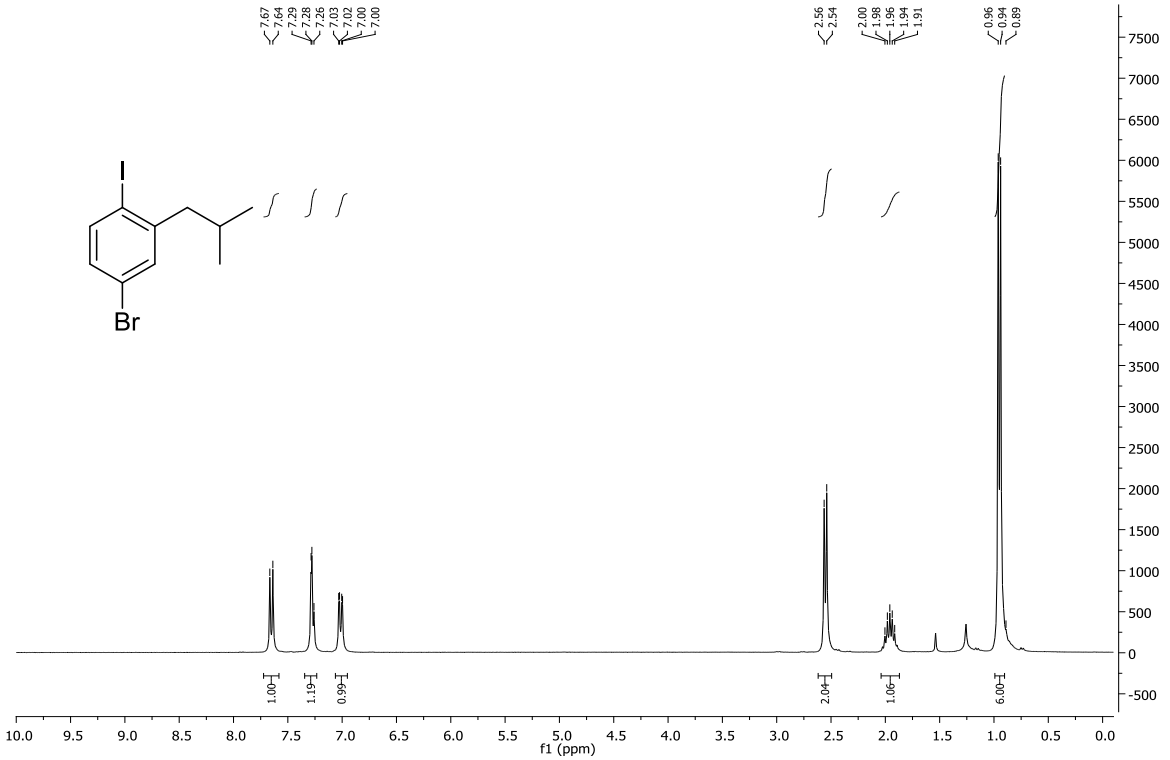

Figure 63. [1]H-NMR of 1-bromo-4-iodo-2-isobutylbenzene (**20**).

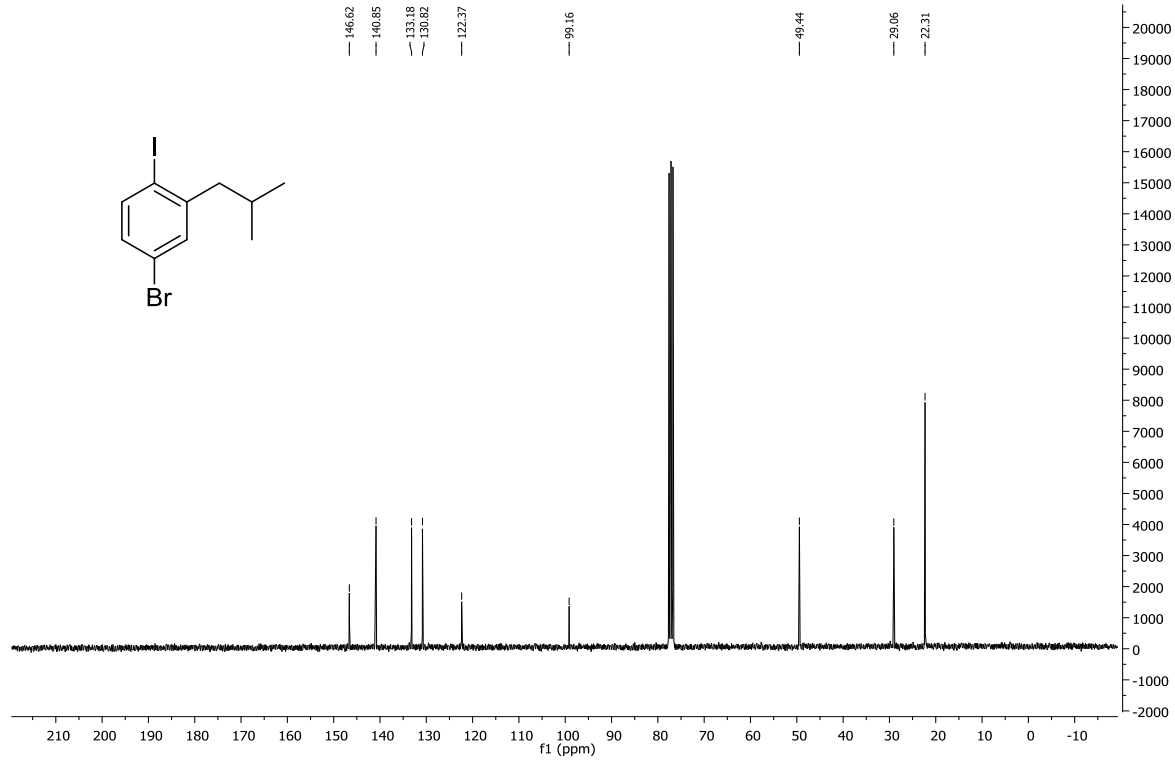

Figure 64. [13]C-NMR of 1-bromo-4-iodo-2-isobutylbenzene (**20**).

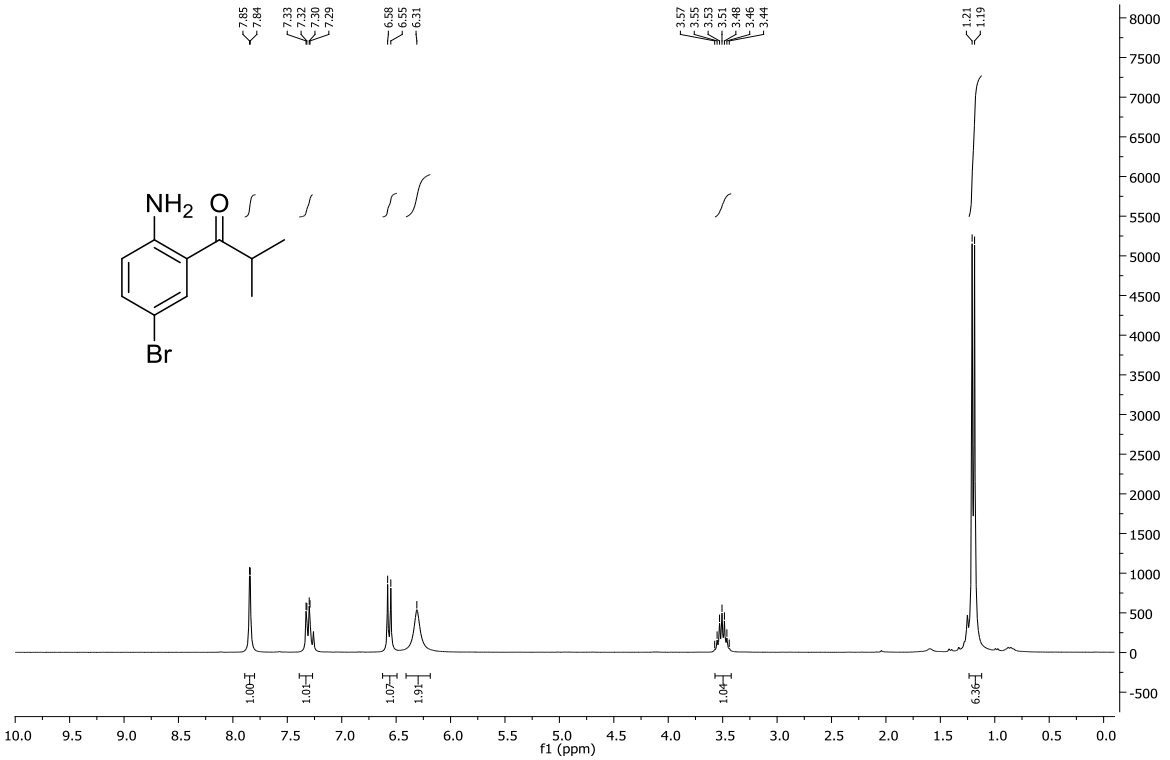

Figure 65. ^{1}H-NMR of 1-(2-amino-5-bromophenyl)-2-methylpropan-1-one (**24**).

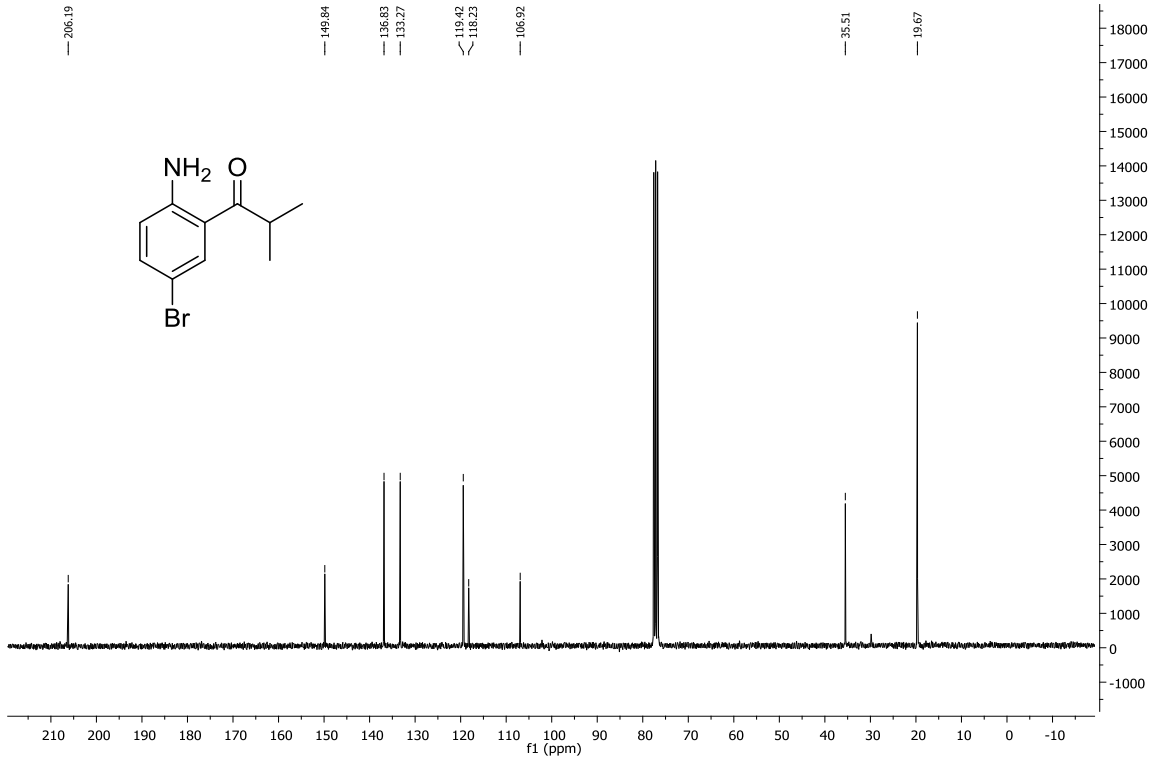

Figure 66. ^{13}C-NMR of 1-(2-amino-5-bromophenyl)-2-methylpropan-1-one (**24**).

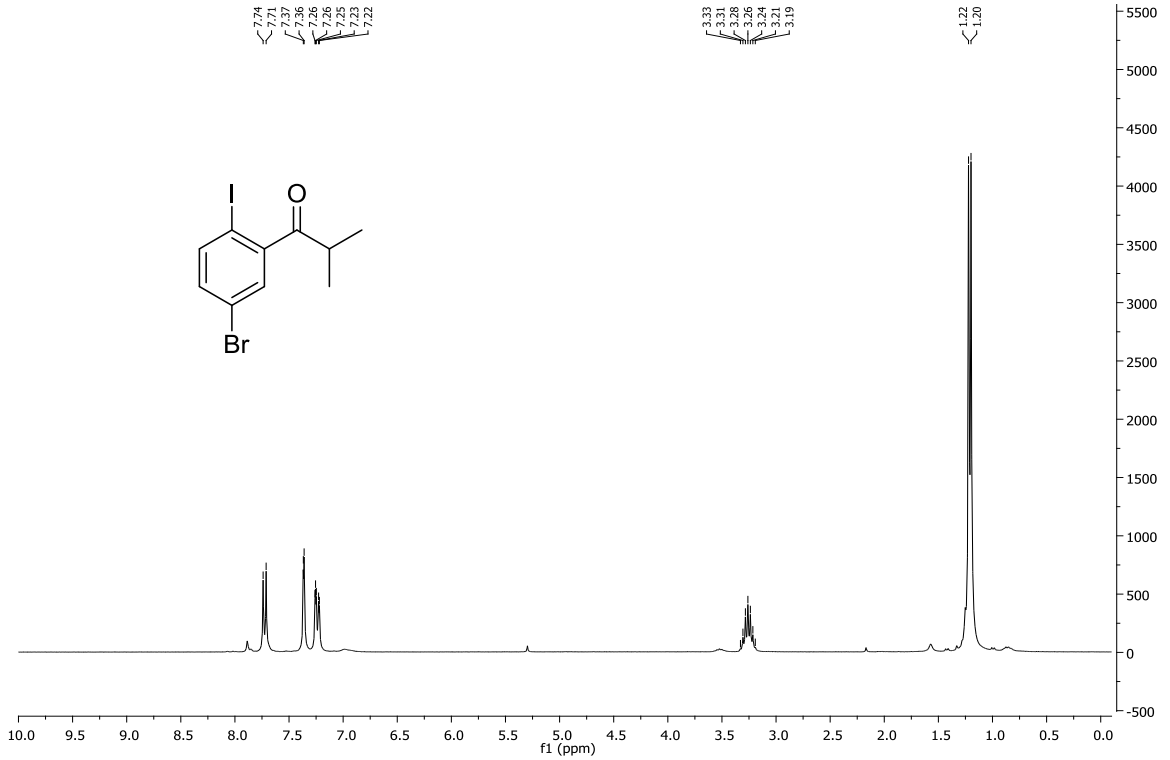

Figure 67. ^{1}H-NMR of 1-(5-**b**romo-2-iodophenyl)-2-methylpropan-1-one (**25**).

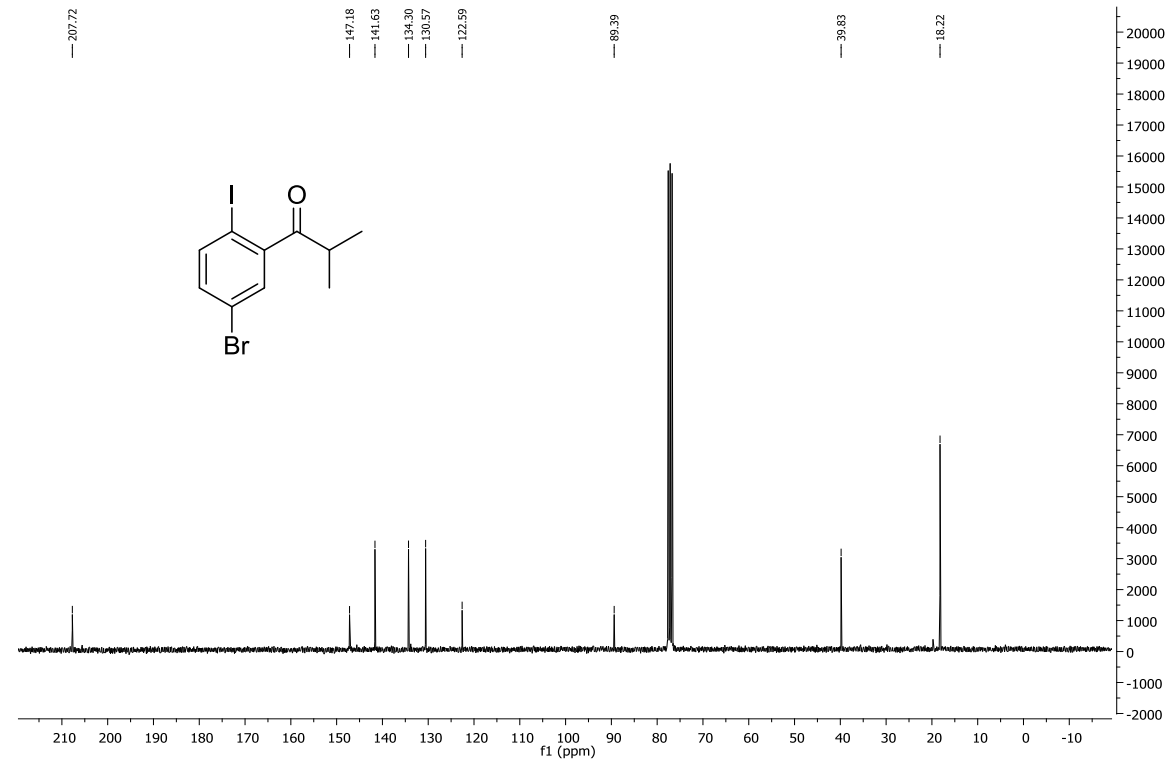

Figure 68. ^{13}C-NMR of 1-(5-**b**romo-2-iodophenyl)-2-methylpropan-1-one (**25**).

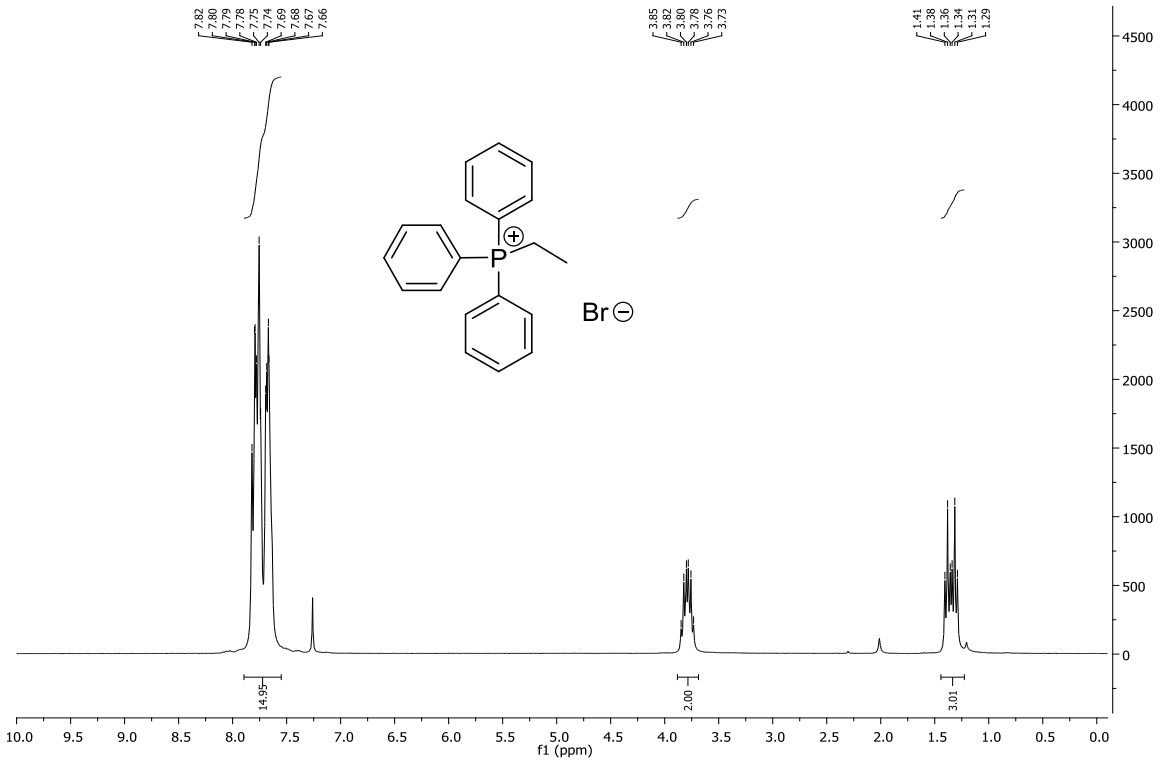

Figure 69. ^{1}H-NMR of ethyltriphenylphosphonium bromide (**29**).

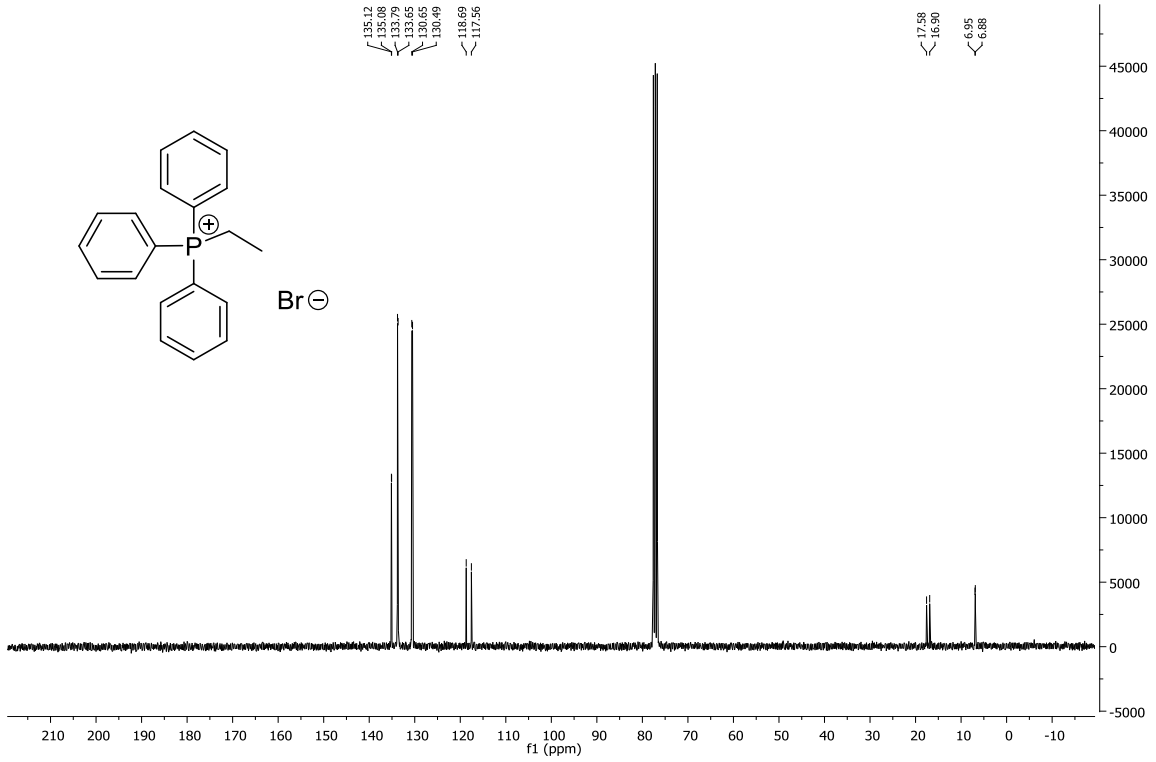

Figure 70. ^{13}C-NMR of ethyltriphenylphosphonium bromide (**29**).

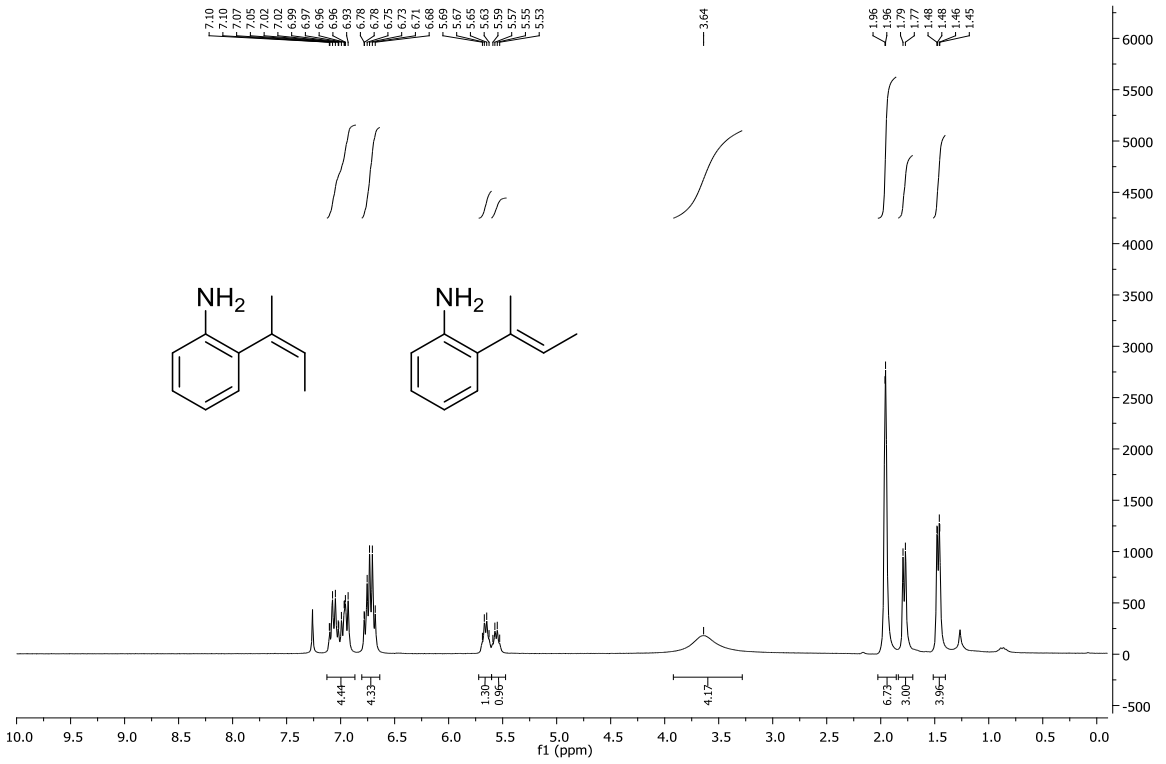

Figure 71. ^{1}H-NMR of (*E*/*Z*)-2-(but-2-en-2-yl)aniline (**31**).

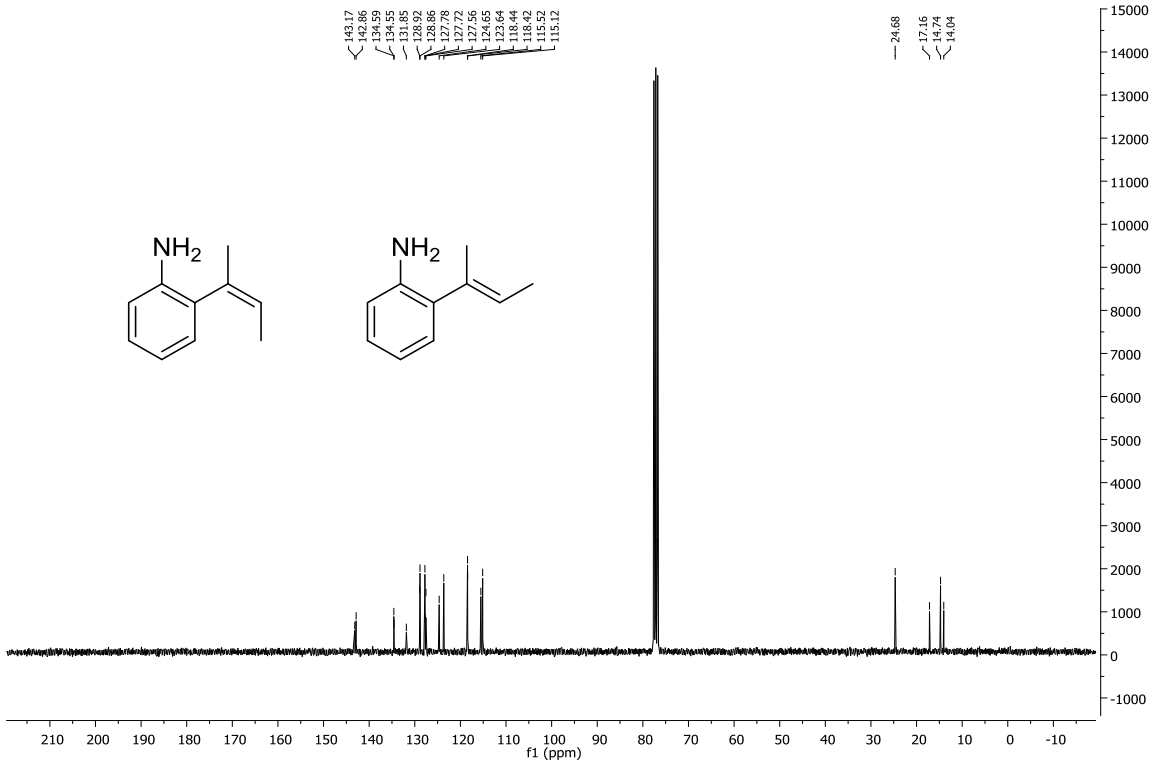

Figure 72. ^{13}C-NMR of (*E*/*Z*)-2-(but-2-en-2-yl)aniline (**31**).

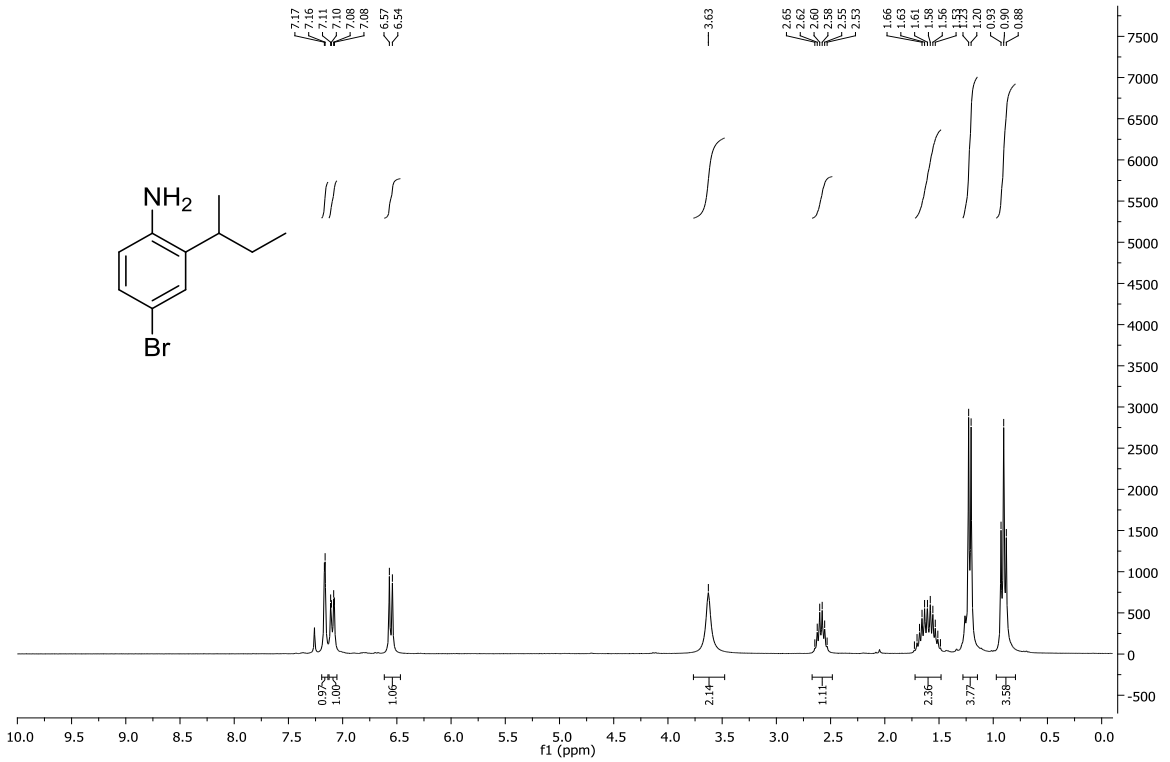

Figure 73. ^{1}H-NMR of 4-bromo-2-(sec-butyl)aniline (**33**).

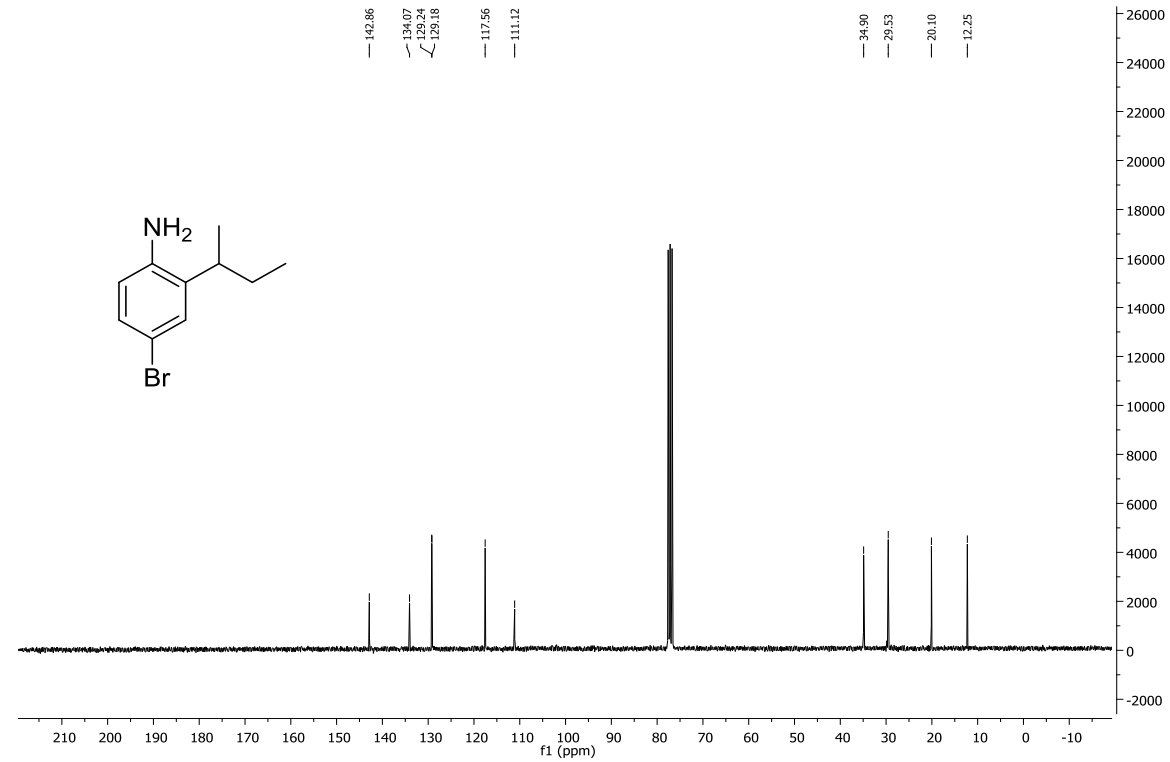

Figure 74. ^{13}C-NMR of 4-bromo-2-(sec-butyl)aniline (**33**).

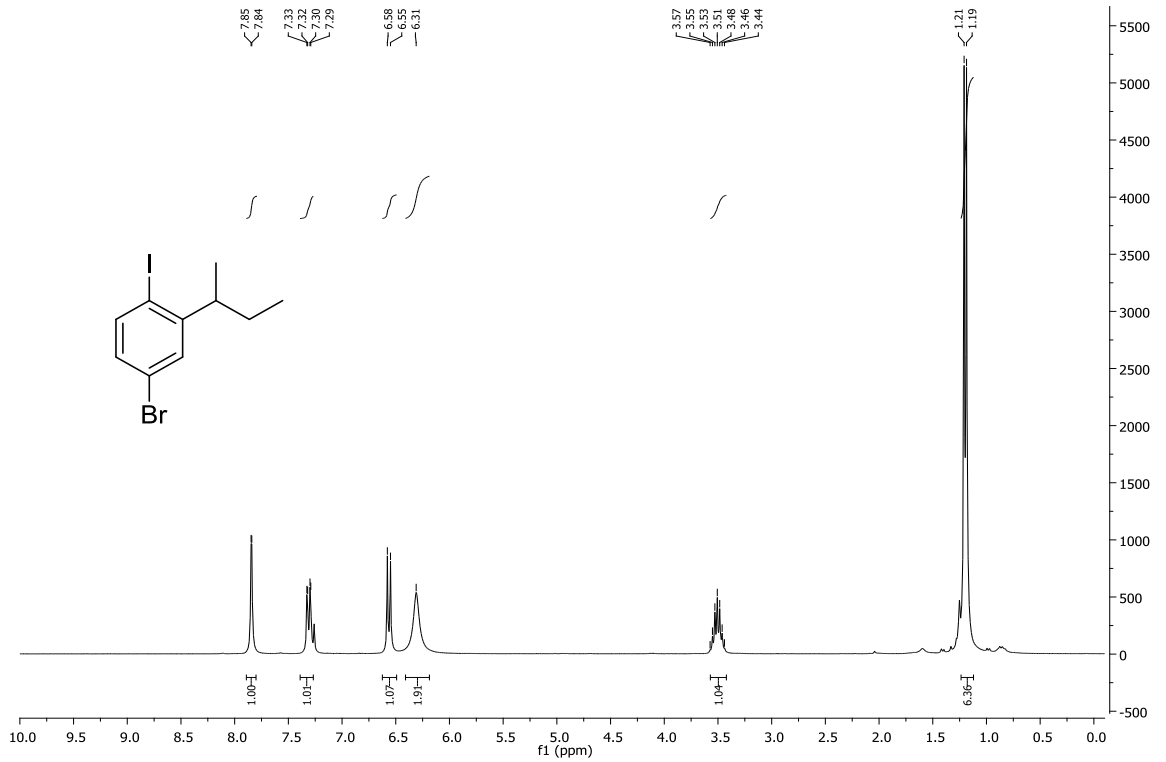

Figure 75. ^{1}H-NMR of 4-bromo-2-(sec-butyl)-1-iodobenzene (**34**).

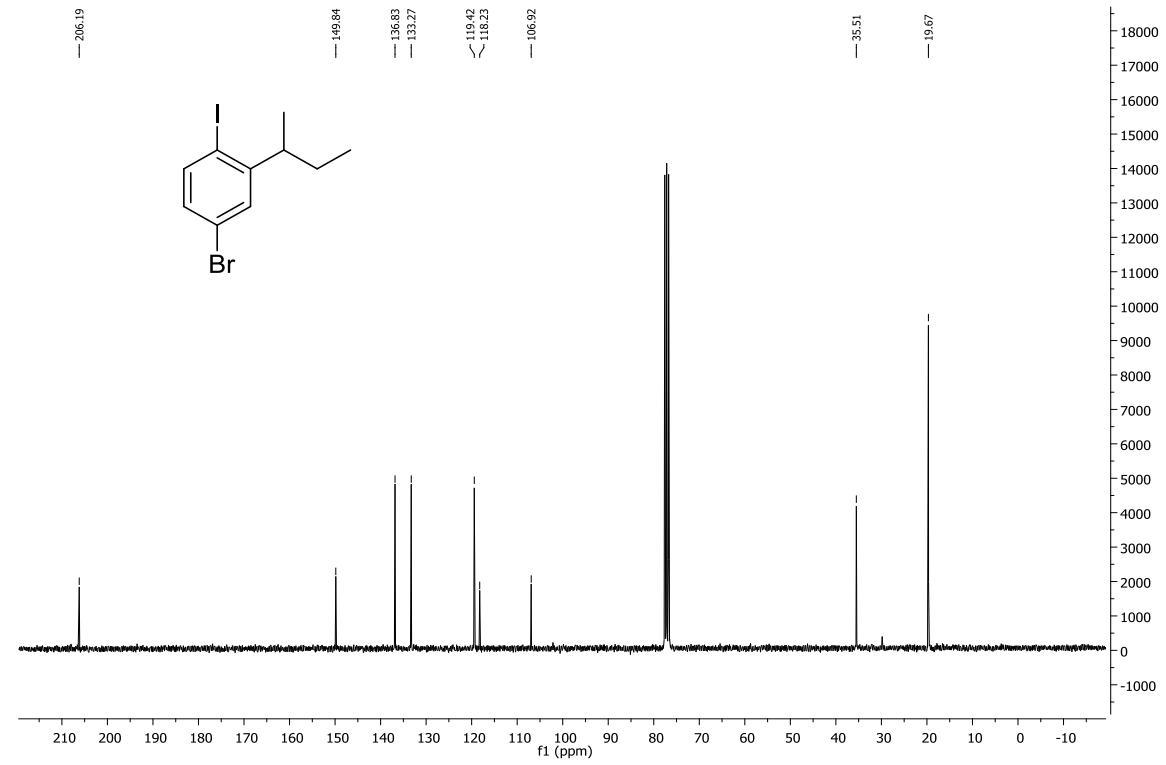

Figure 76. ^{13}C-NMR of 4-bromo-2-(sec-butyl)-1-iodobenzene (**34**).

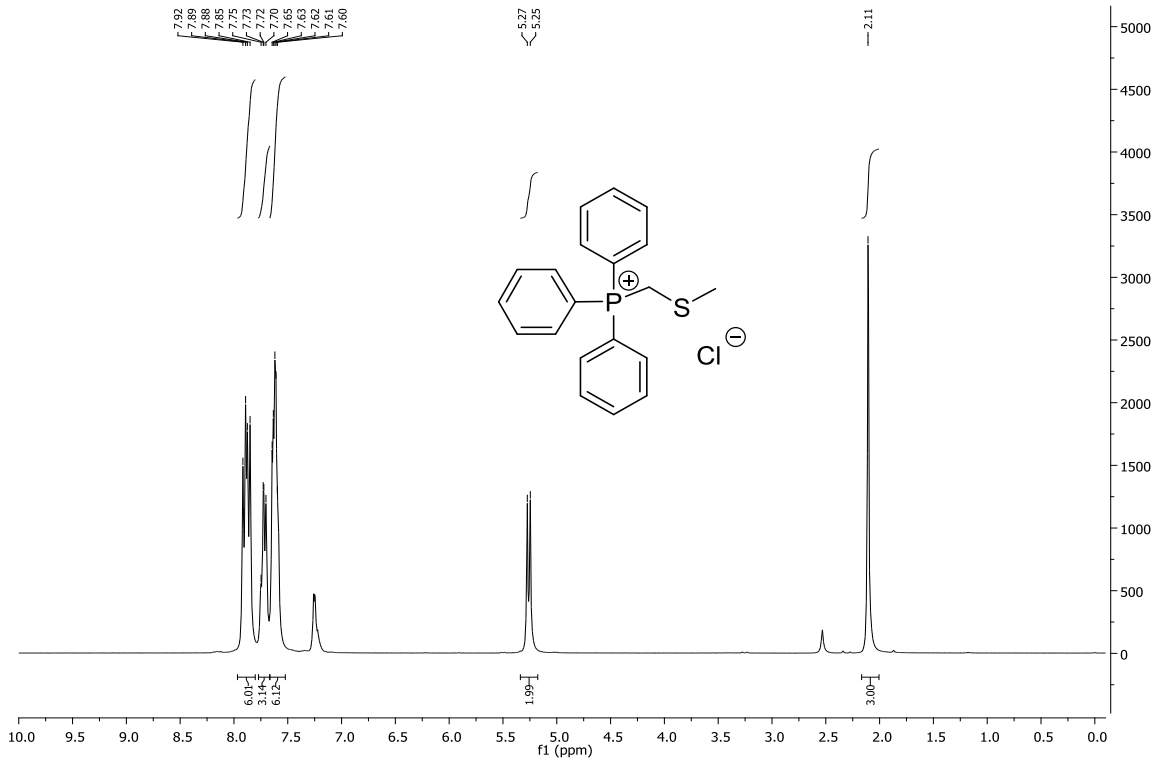

Figure 77. ^{1}H-NMR of 2-bromo-5-iodobenzoyl chloride (**37**).

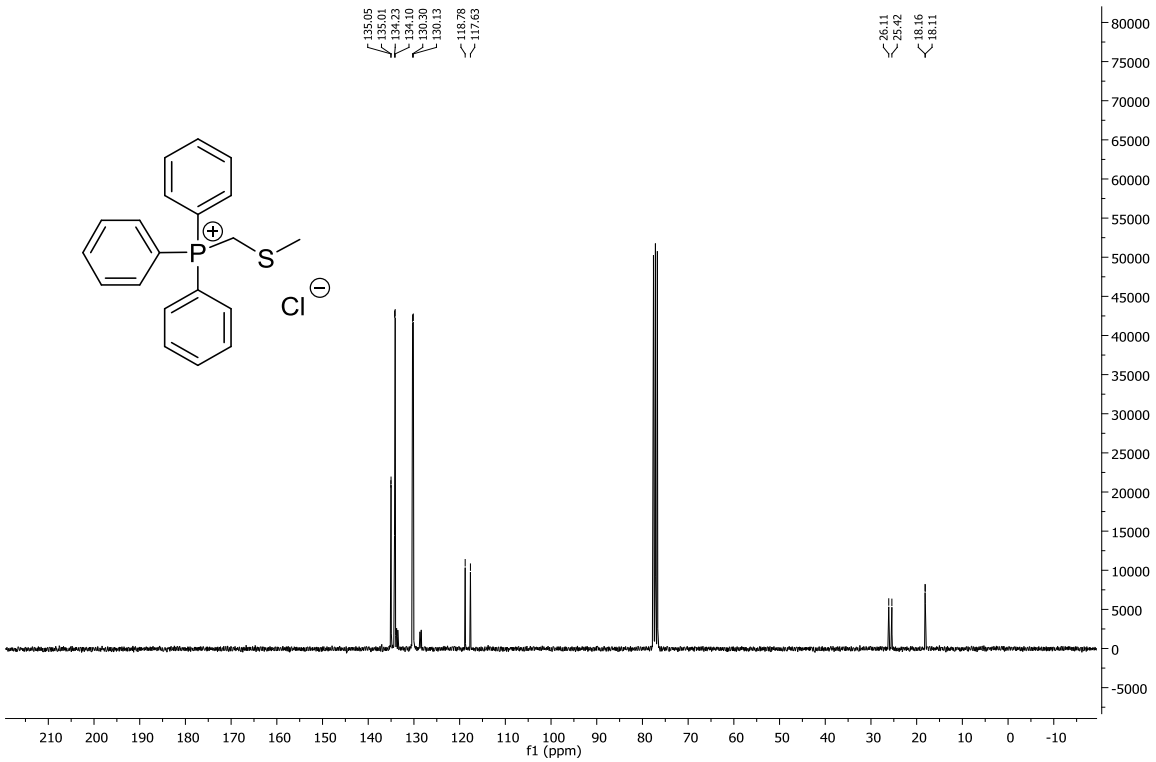

Figure 78. ^{13}C-NMR of 2-bromo-5-iodobenzoyl chloride (**37**).

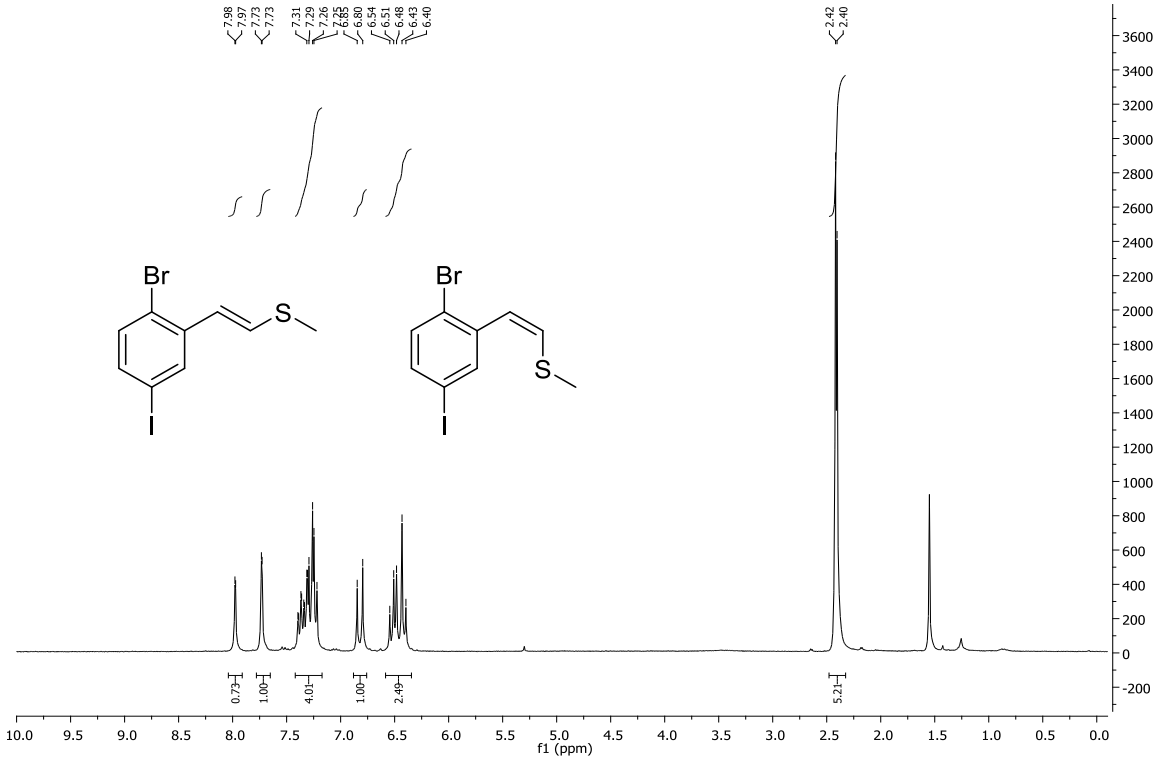

Figure 79. ^{1}H-NMR of (*E*/*Z*)-(2-bromo-5-iodostyryl)(methyl)sulfane (**38**).

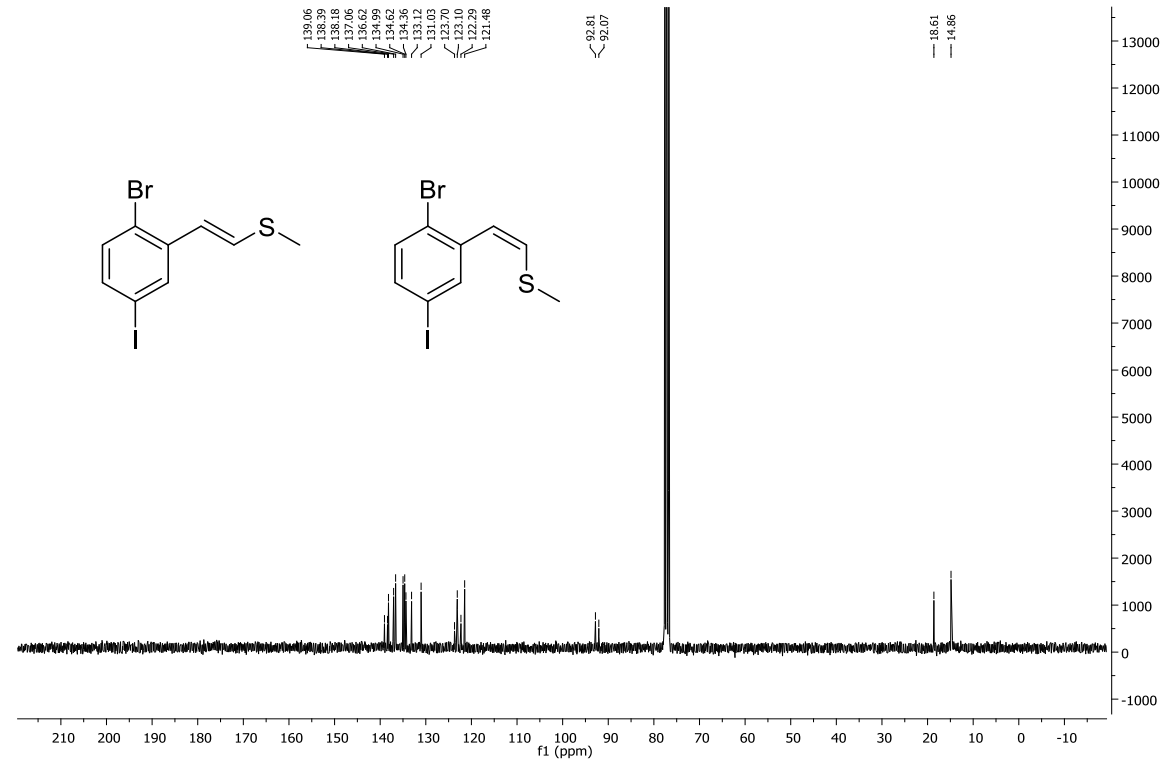

Figure 80. ^{13}C-NMR of (*E*/*Z*)-(2-bromo-5-iodostyryl)(methyl)sulfane (**38**).

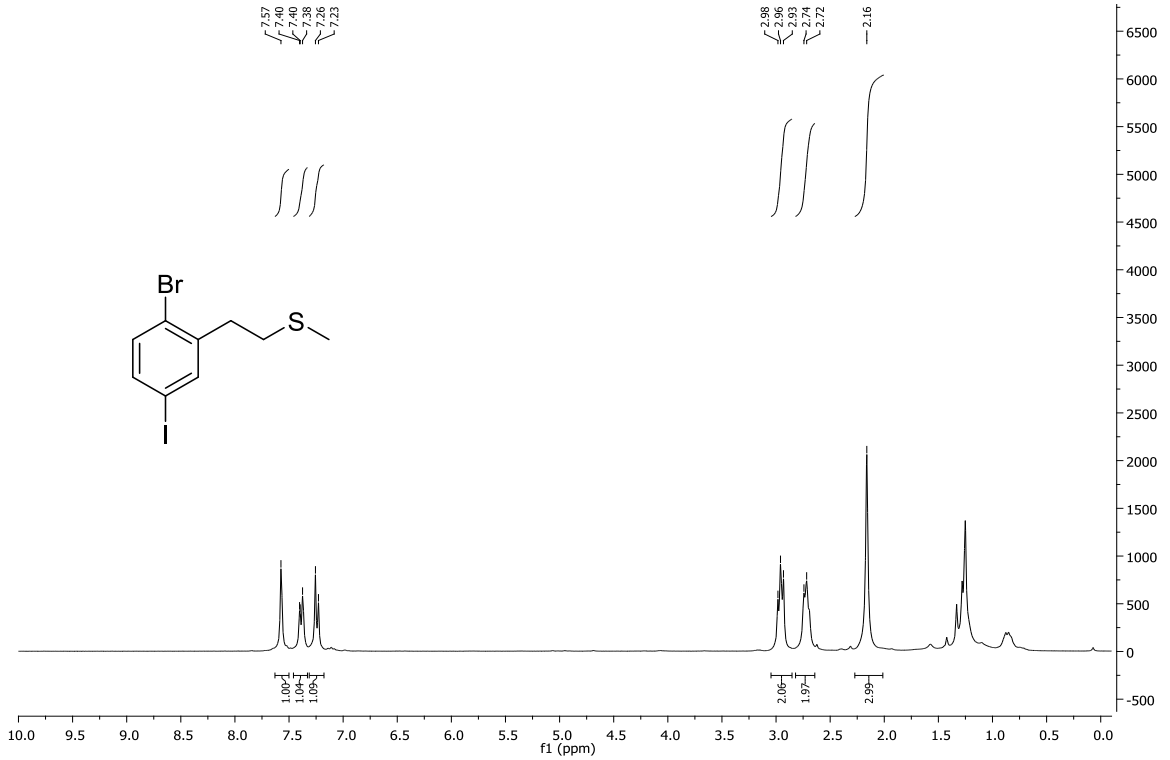

Figure 81. ^{1}H-NMR of (2-bromo-5-iodophenethyl)(methyl)sulfane (**39**).

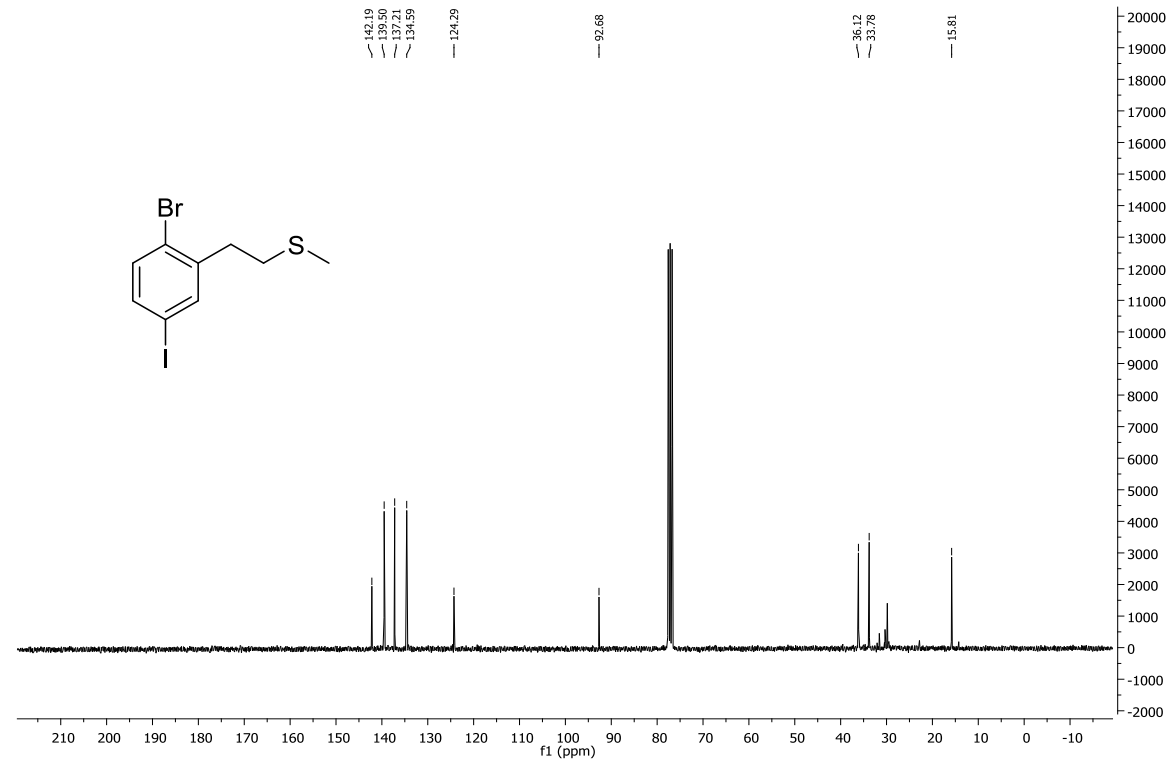

Figure 82. ^{13}C-NMR of (2-bromo-5-iodophenethyl)(methyl)sulfane (**39**).

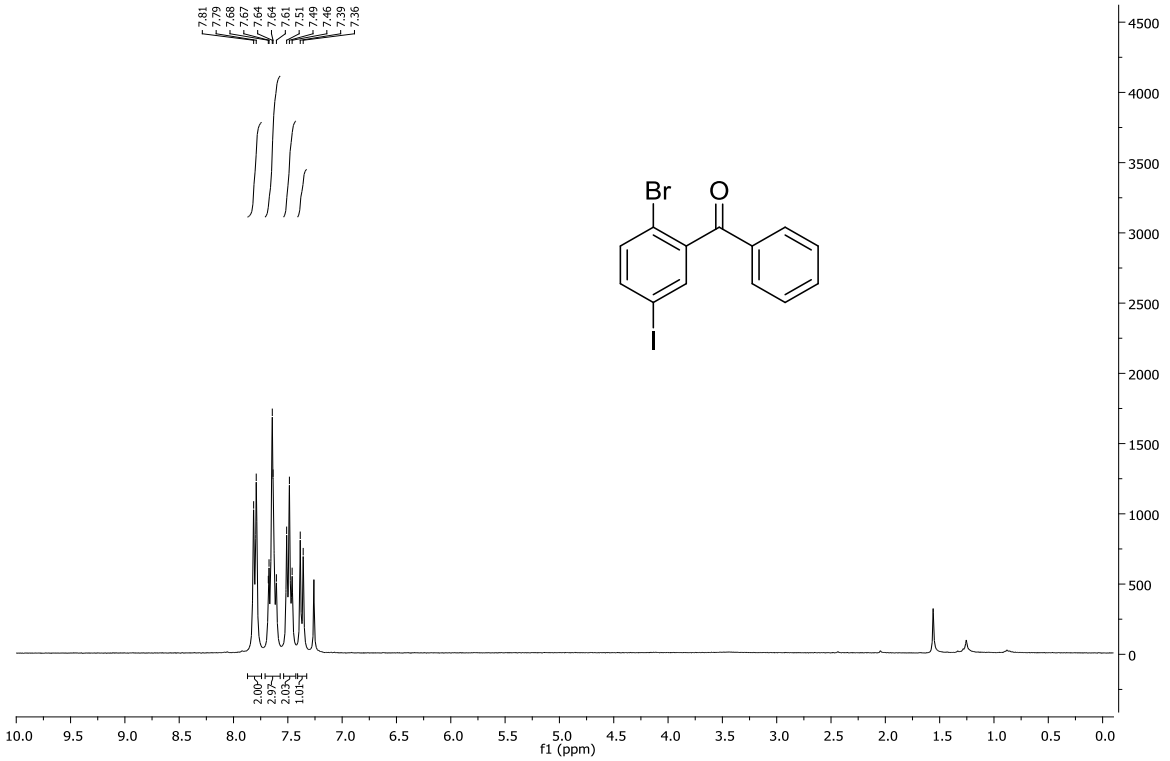

Figure 83. ^{1}H-NMR of (2-bromo-5-iodophenyl)(phenyl)methanone (**42**).

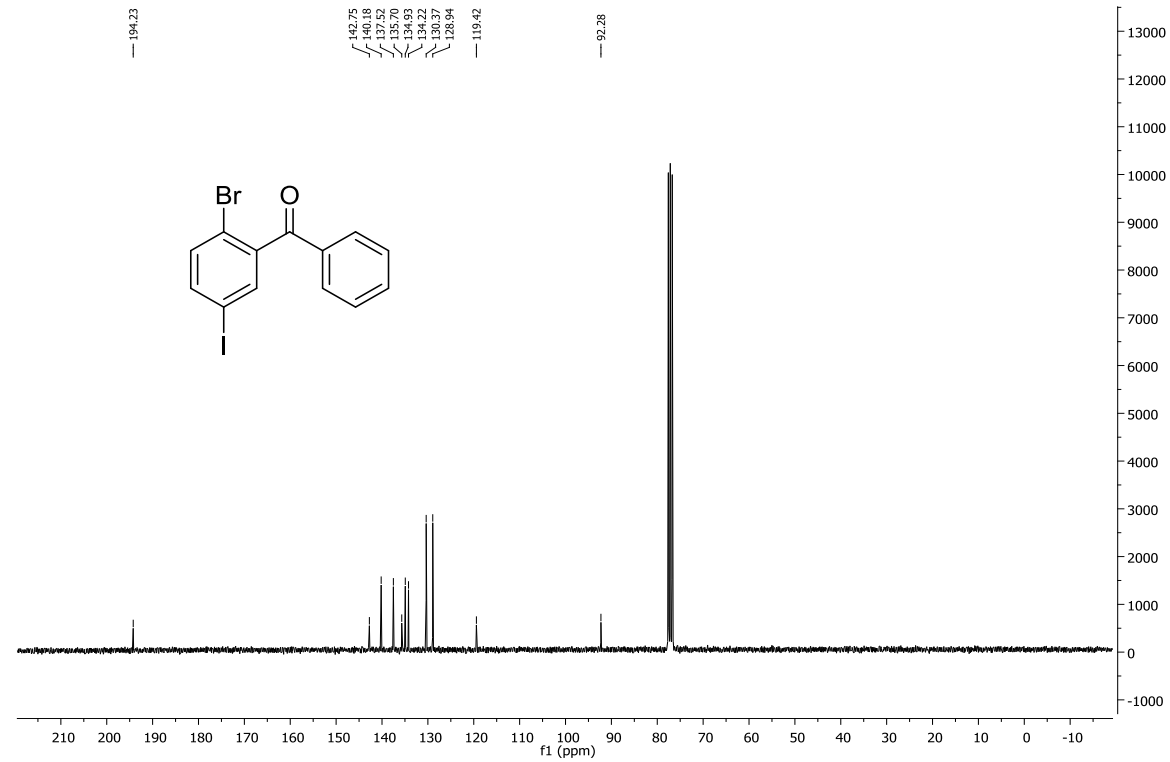

Figure 84. ^{13}C-NMR of (2-bromo-5-iodophenyl)(phenyl)methanone (**42**).

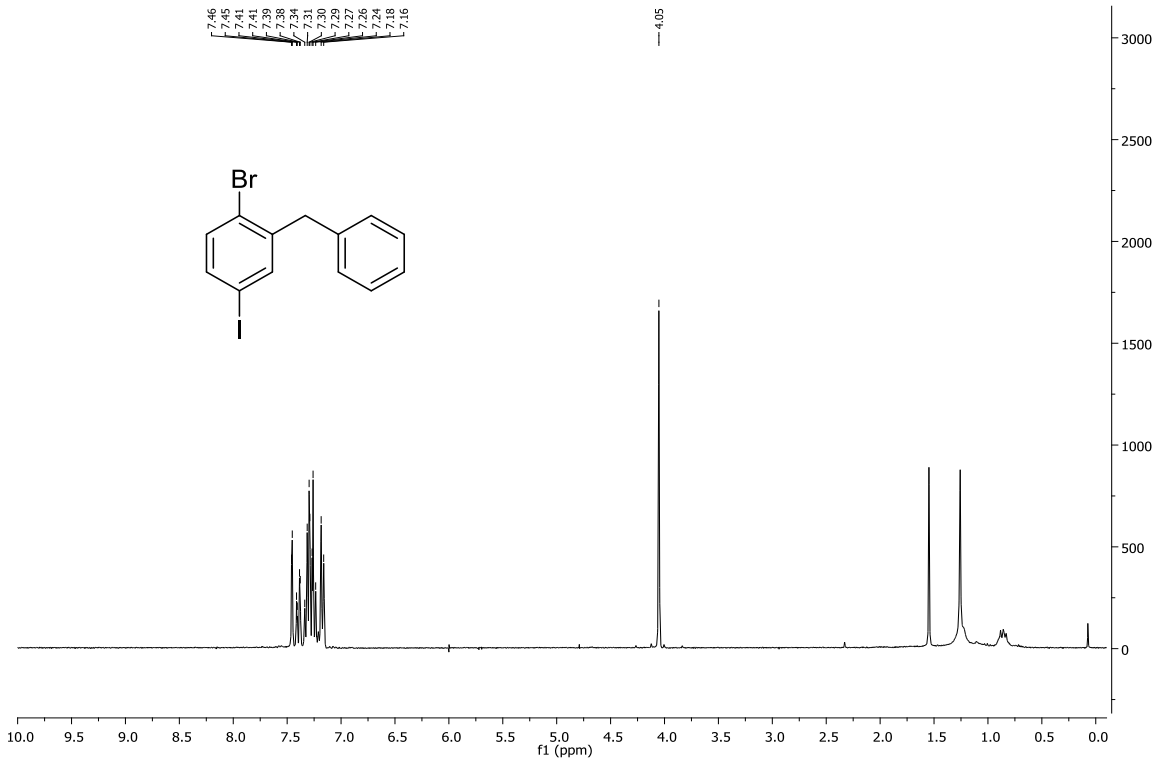

Figure 85. ^{1}H-NMR of (2-benzyl-1-bromo-4-iodobenzene (**43**).

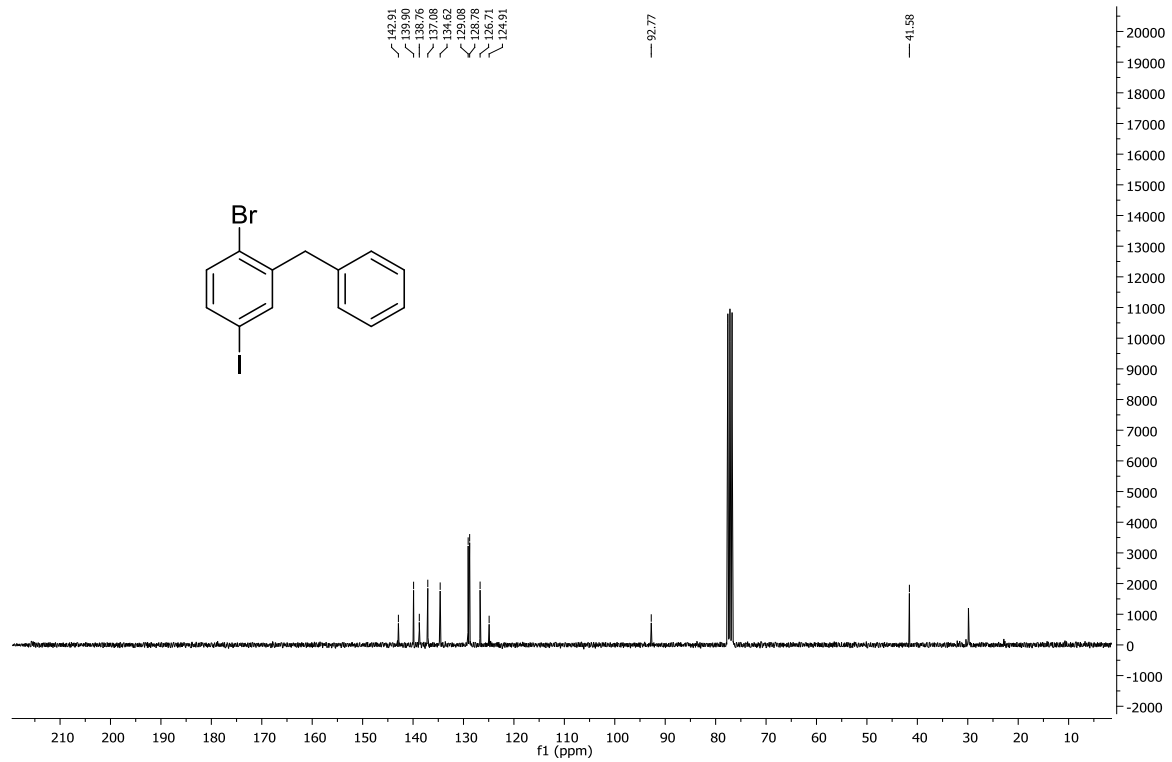

Figure 86. ^{13}C-NMR of (2-benzyl-1-bromo-4-iodobenzene (**43**).

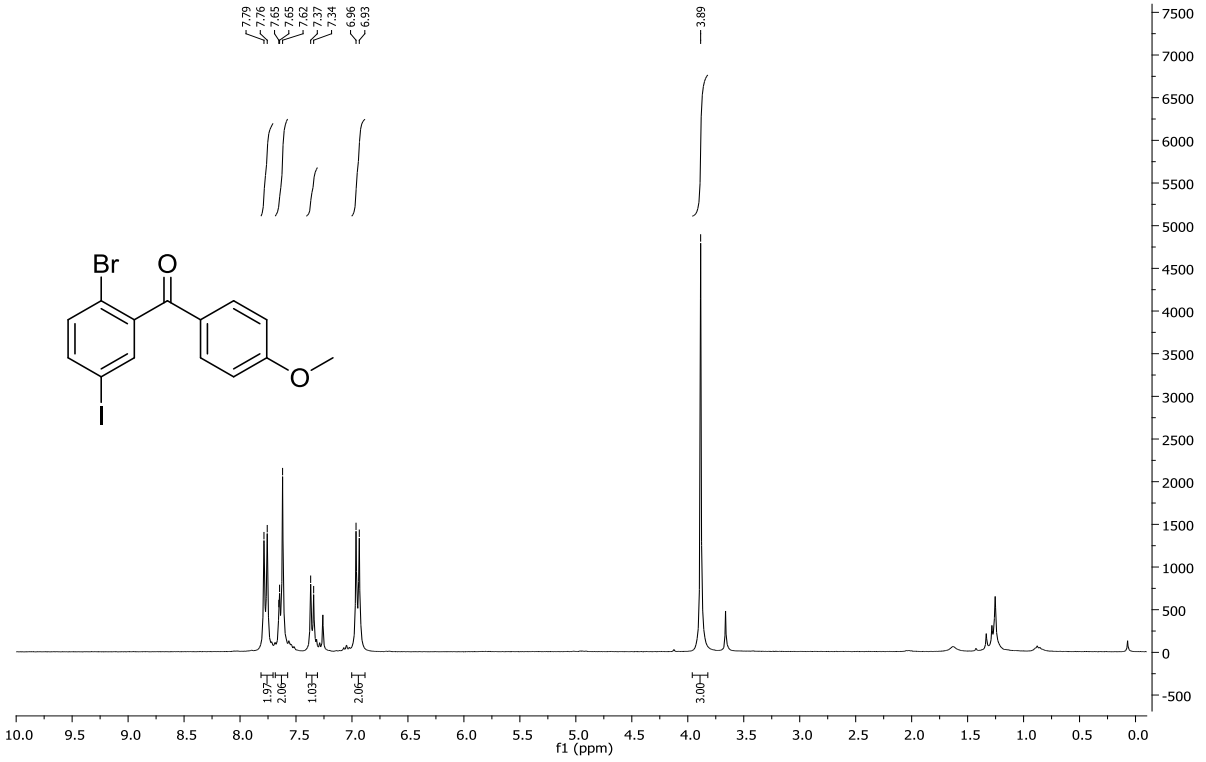

Figure 87. ^{1}H-NMR of (2-bromo-5-iodophenyl)(4-methoxyphenyl)methanone (**45**).

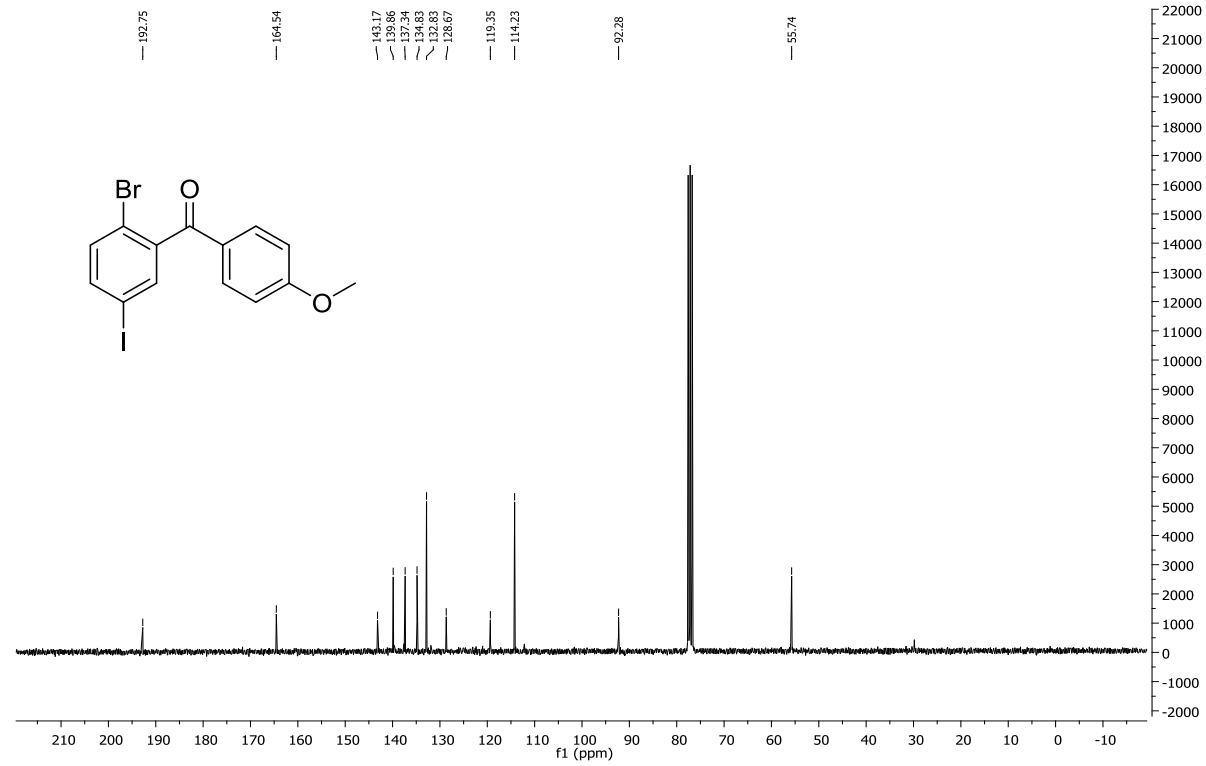

Figure 88. ^{13}C-NMR of (2-bromo-5-iodophenyl)(4-methoxyphenyl)methanone (**45**).

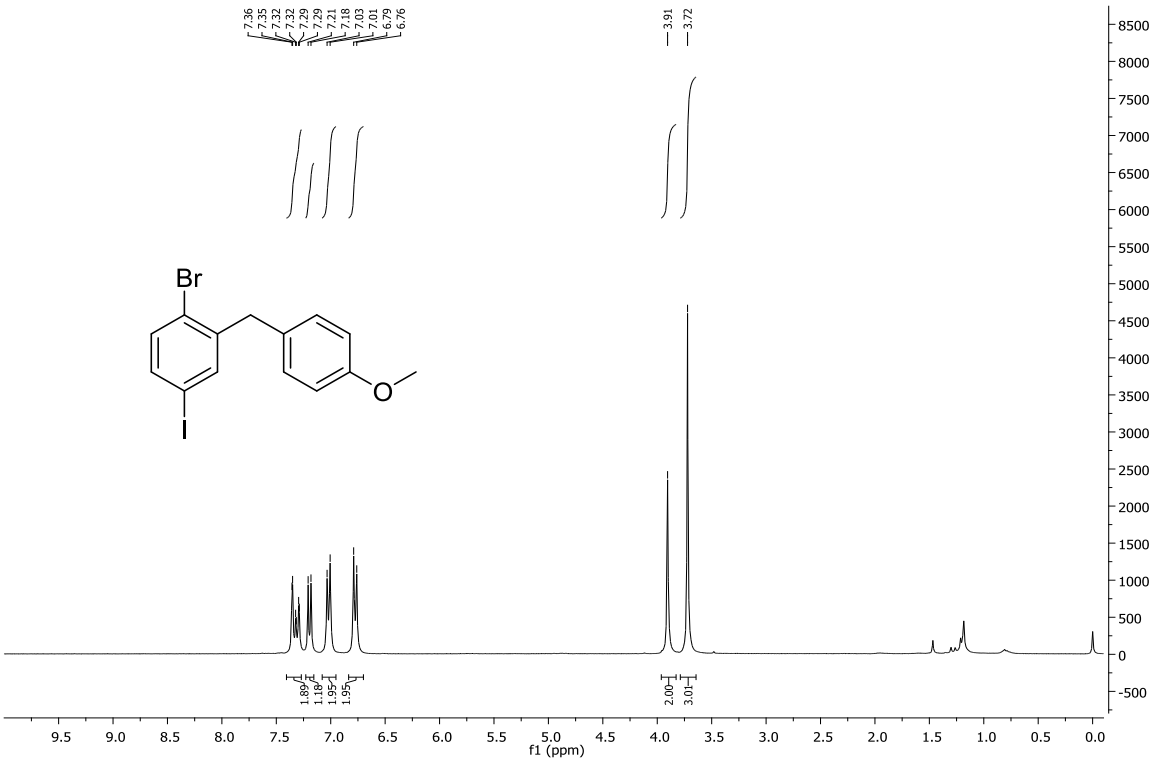

Figure 89. ^{1}H-NMR of 1-bromo-4-iodo-2-(4-methoxybenzyl)benzene (**46**).

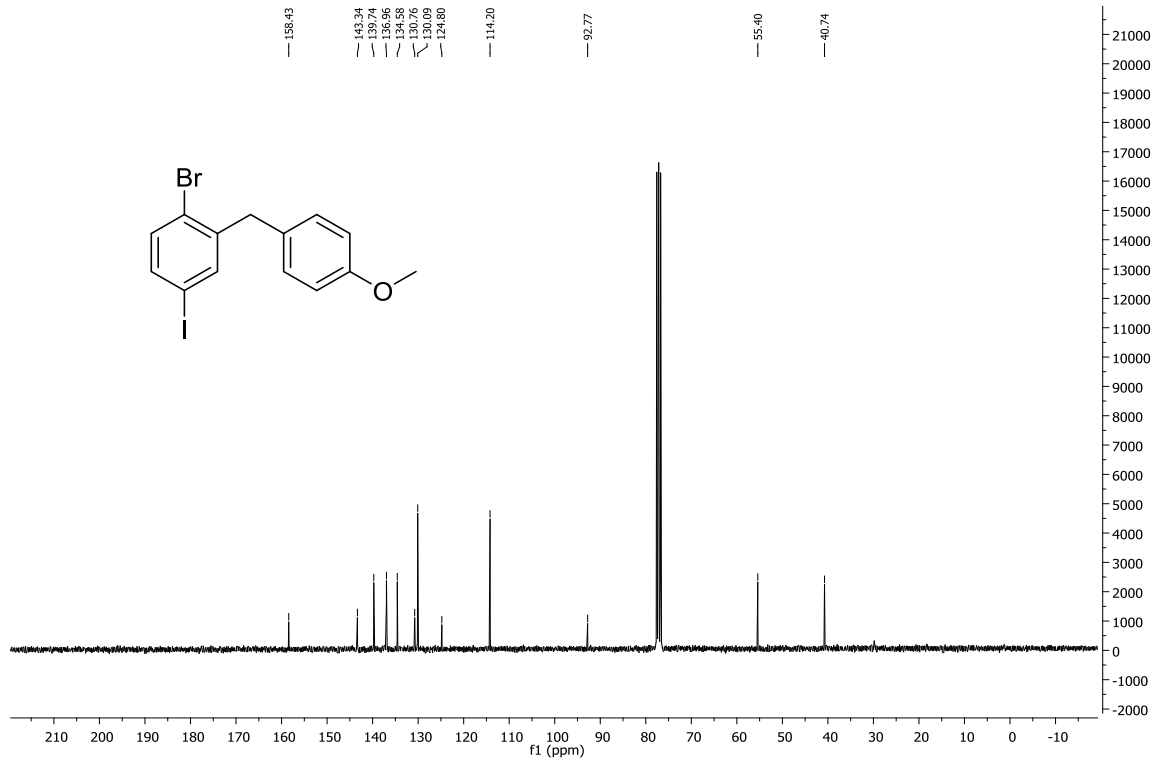

Figure 90. ^{13}C-NMR of 1-bromo-4-iodo-2-(4-methoxybenzyl)benzene (**46**).

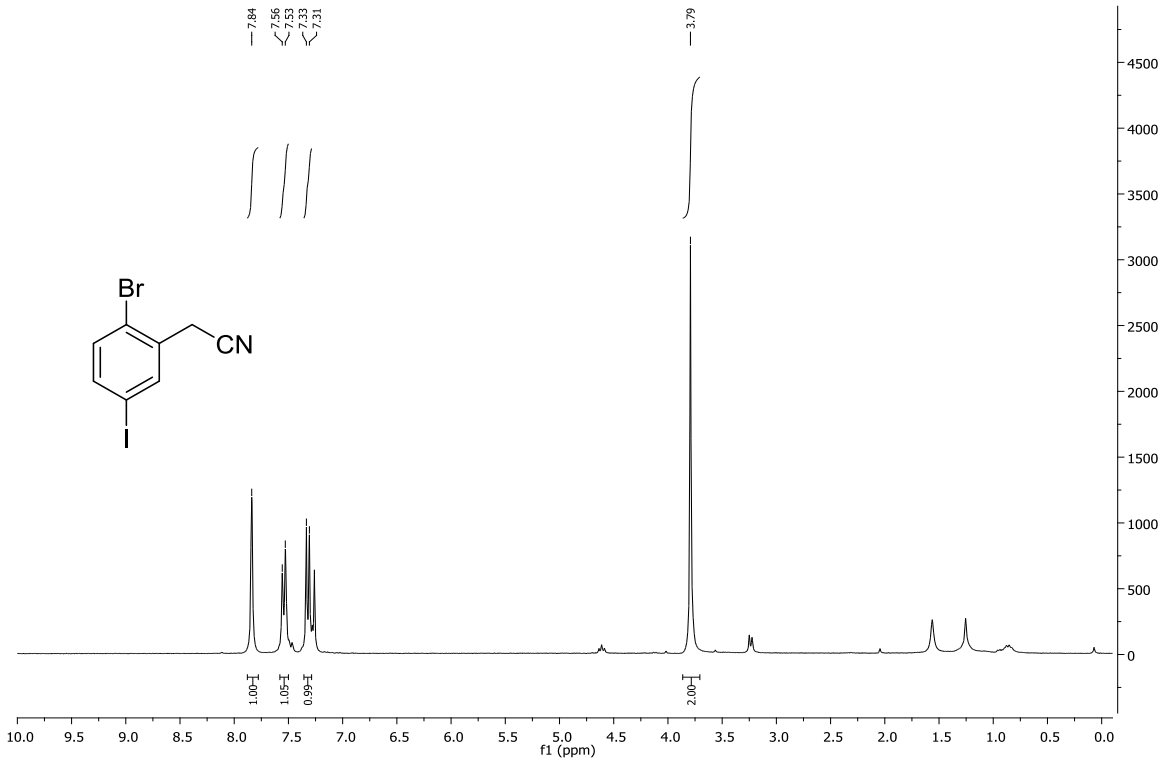

Figure 91. ^{1}H-NMR of 2-(2-bromo-5-iodophenyl)acetonitrile (**48**).

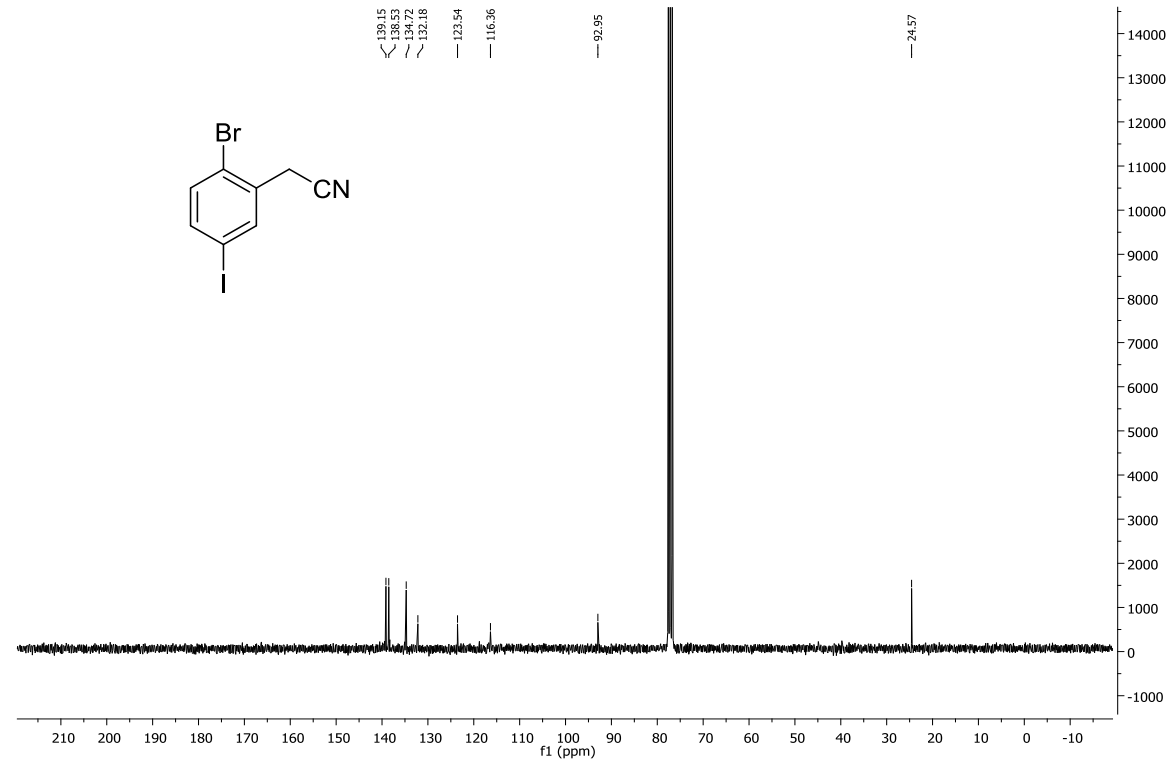

Figure 92. ^{13}C-NMR of 2-(2-bromo-5-iodophenyl)acetonitrile (**48**).

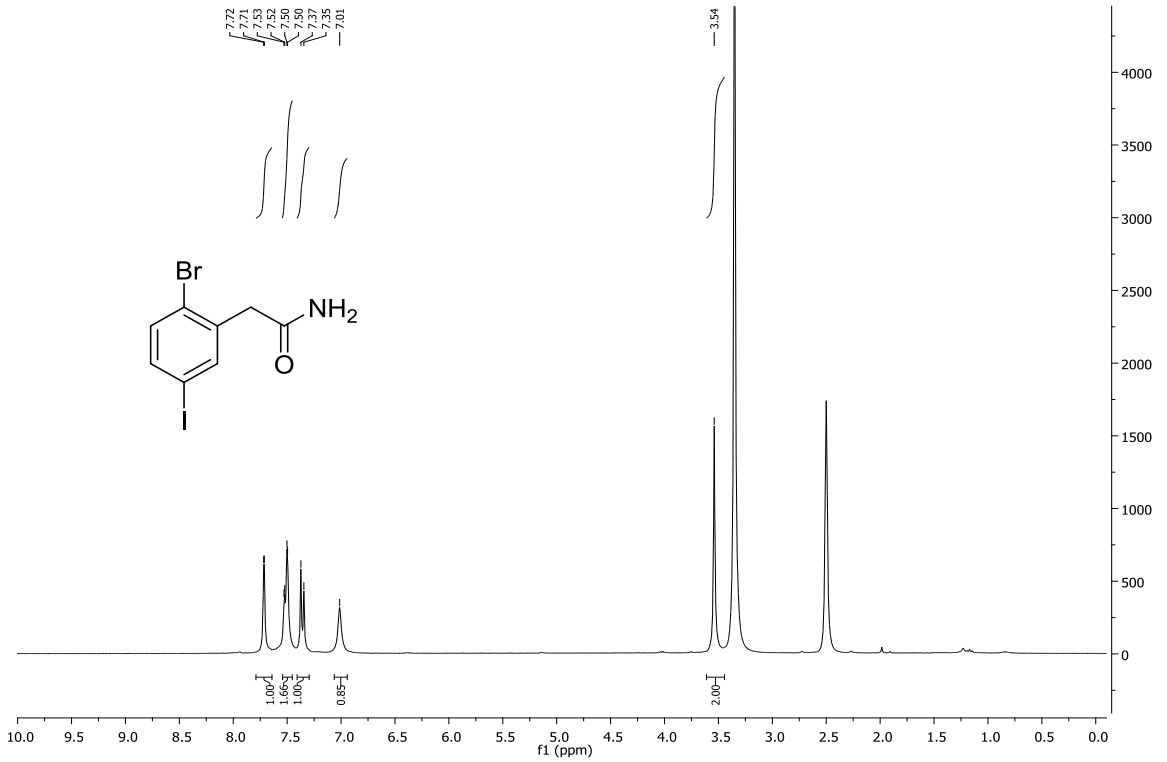

Figure 93. ^{1}H-NMR of 2-(2-bromo-5-iodophenyl)acetamide (**49**).

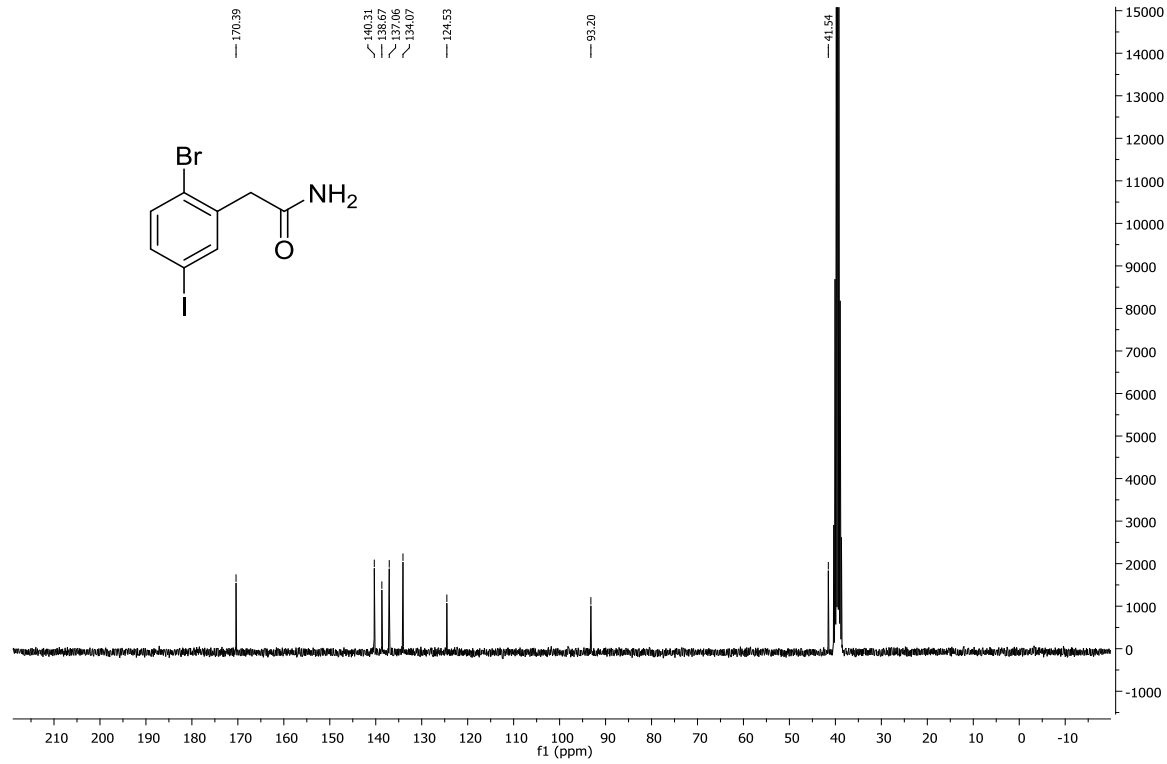

Figure 94. ^{13}C-NMR of 2-(2-bromo-5-iodophenyl)acetamide (**49**).

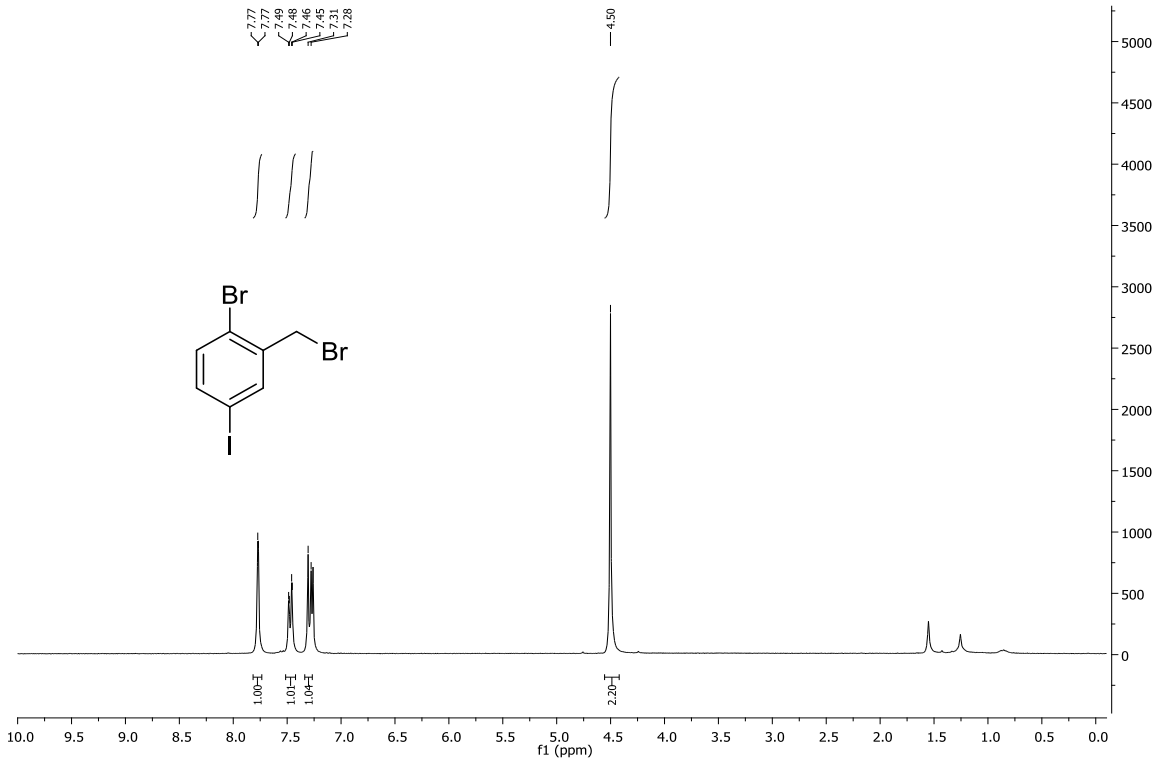

Figure 95. ^{1}H-NMR of 1-bromo-2-(bromomethyl)-4-iodobenzene (**50**).

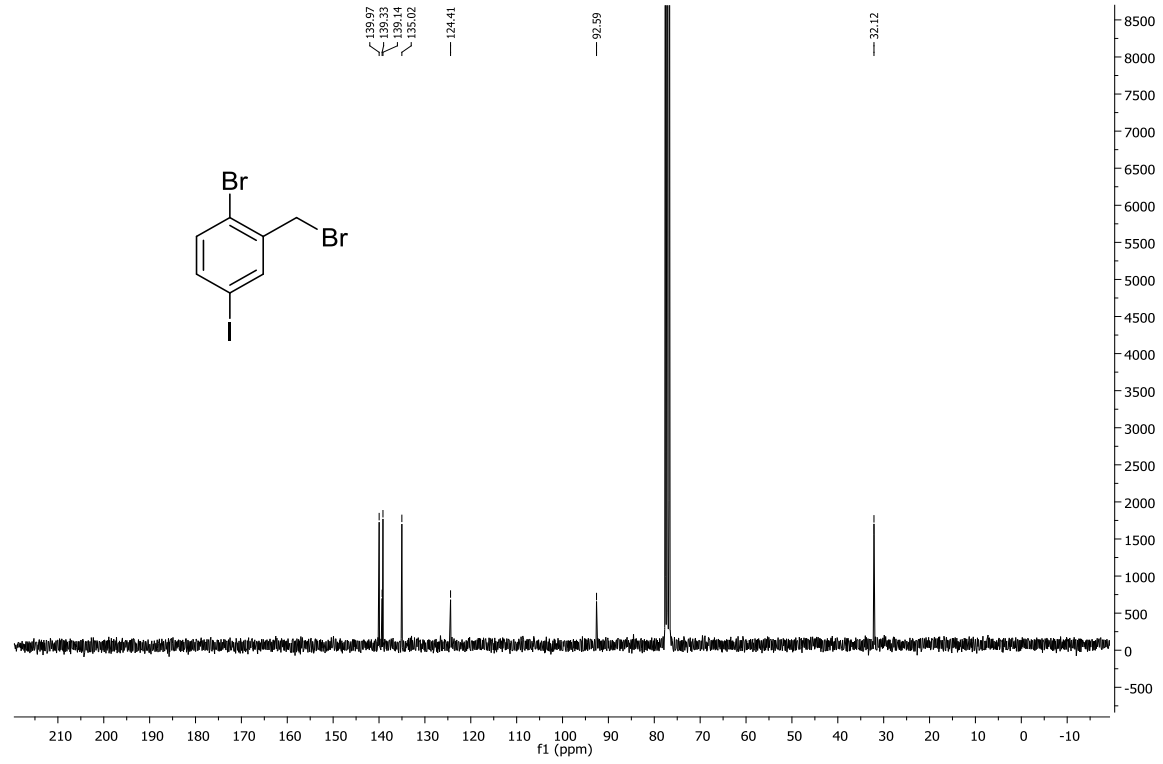

Figure 96. ^{13}C-NMR of 1-bromo-2-(bromomethyl)-4-iodobenzene (**50**).

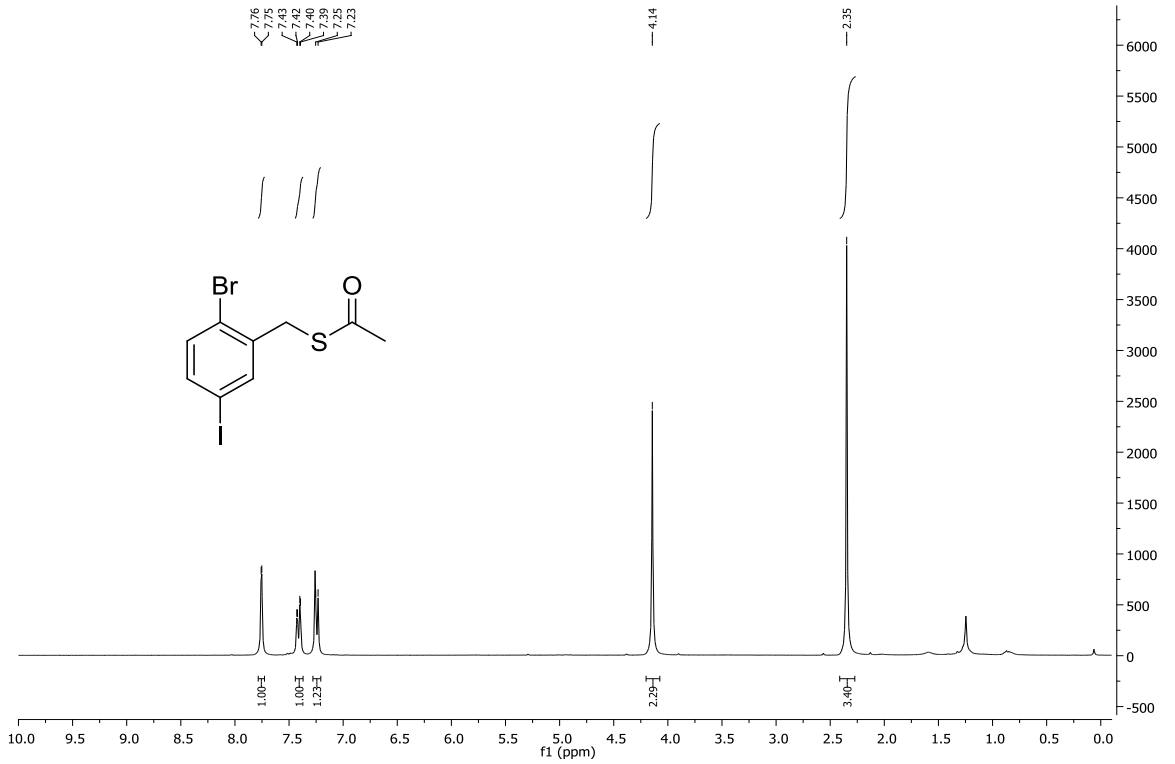

Figure 97. ^{1}H-NMR of (2-bromo-5-iodobenzyl) ethanethioate (**51**).

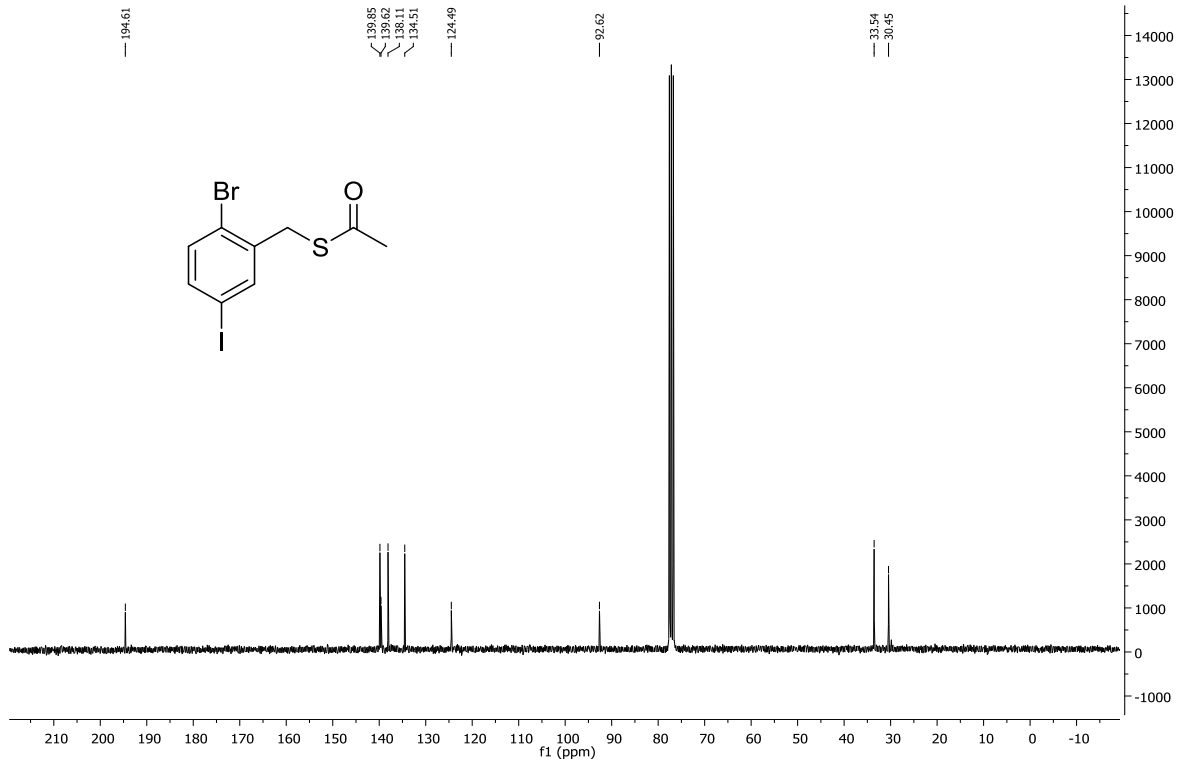

Figure 98. ^{13}C-NMR of (2-bromo-5-iodobenzyl) ethanethioate (**51**).

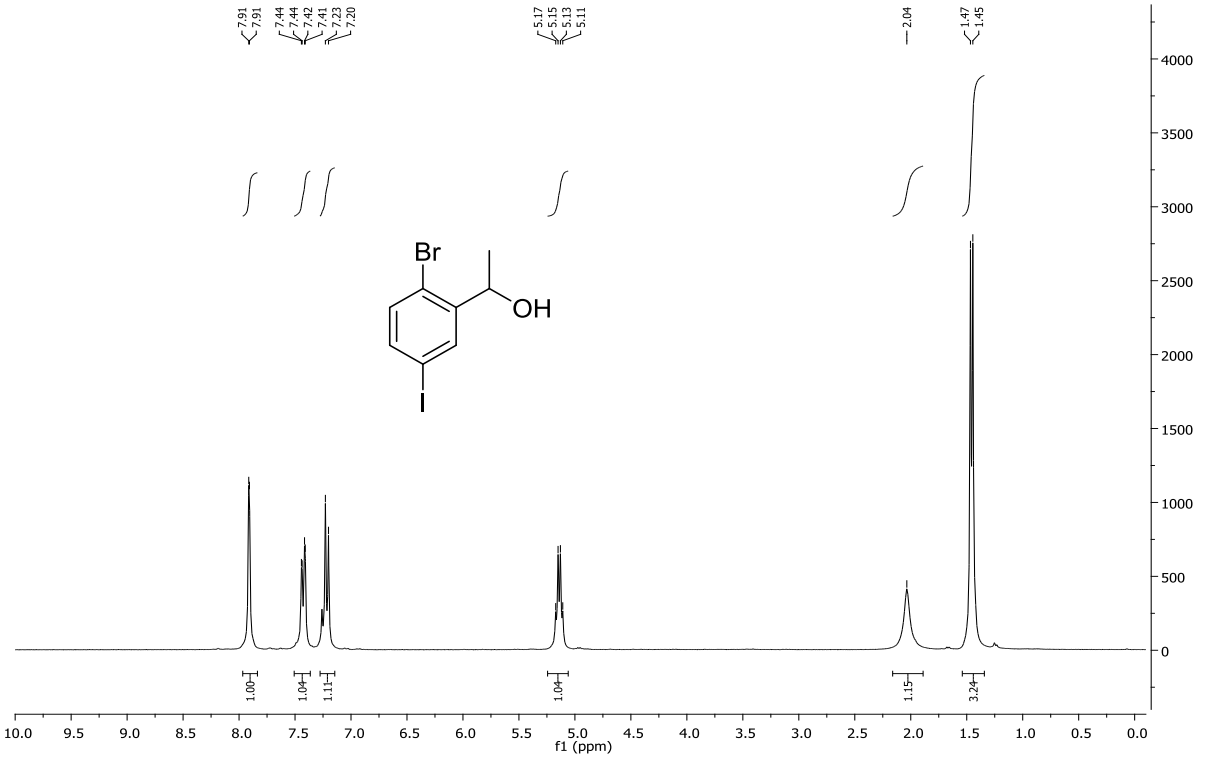

Figure 99. [1]H-NMR of 2-(2-bromo-5-iodophenyl)acetamide (**52**).

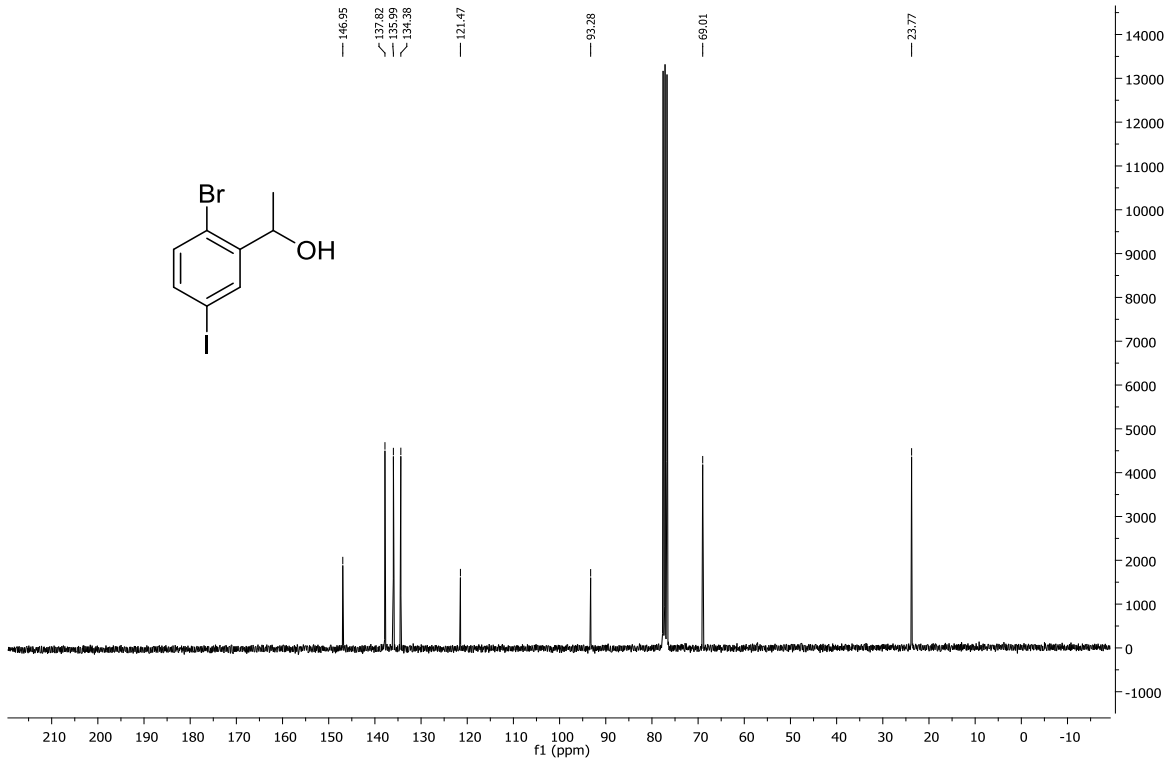

Figure 100. [13]C-NMR of 2-(2-bromo-5-iodophenyl)acetamide (**52**).

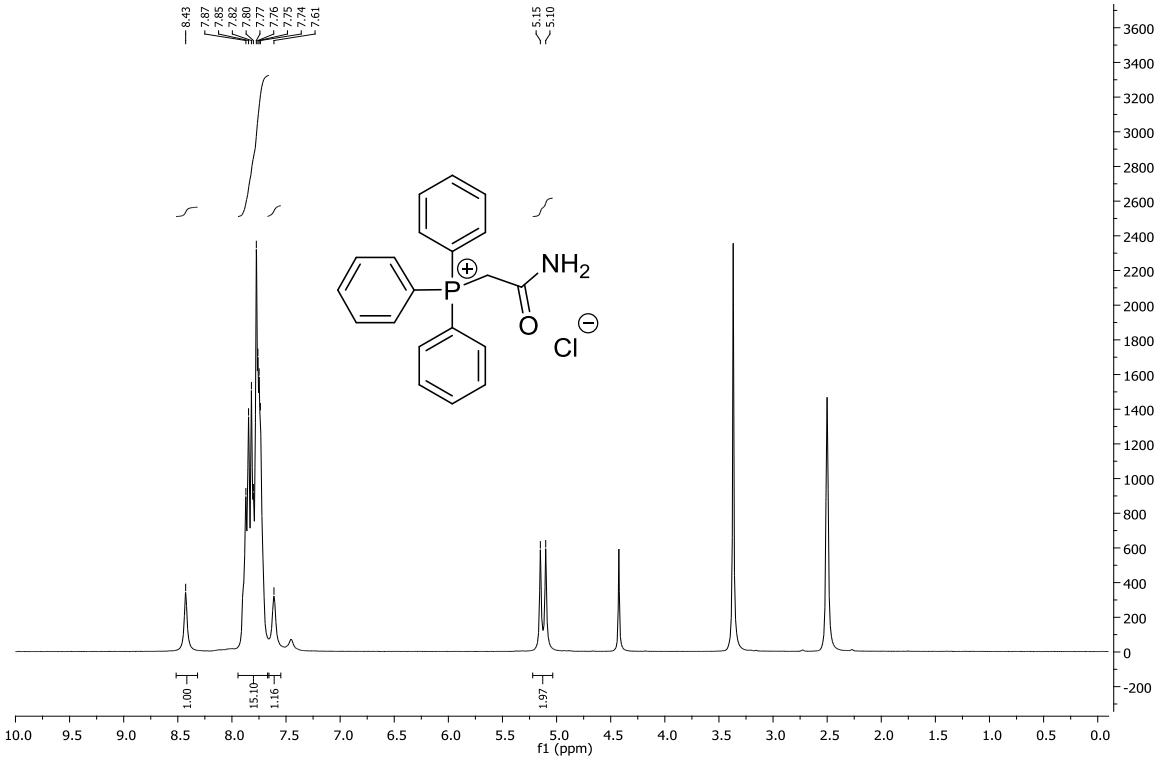

Figure 101. ^{1}H-NMR of (2-amino-2-oxoethyl)triphenylphosphonium chloride (**54**).

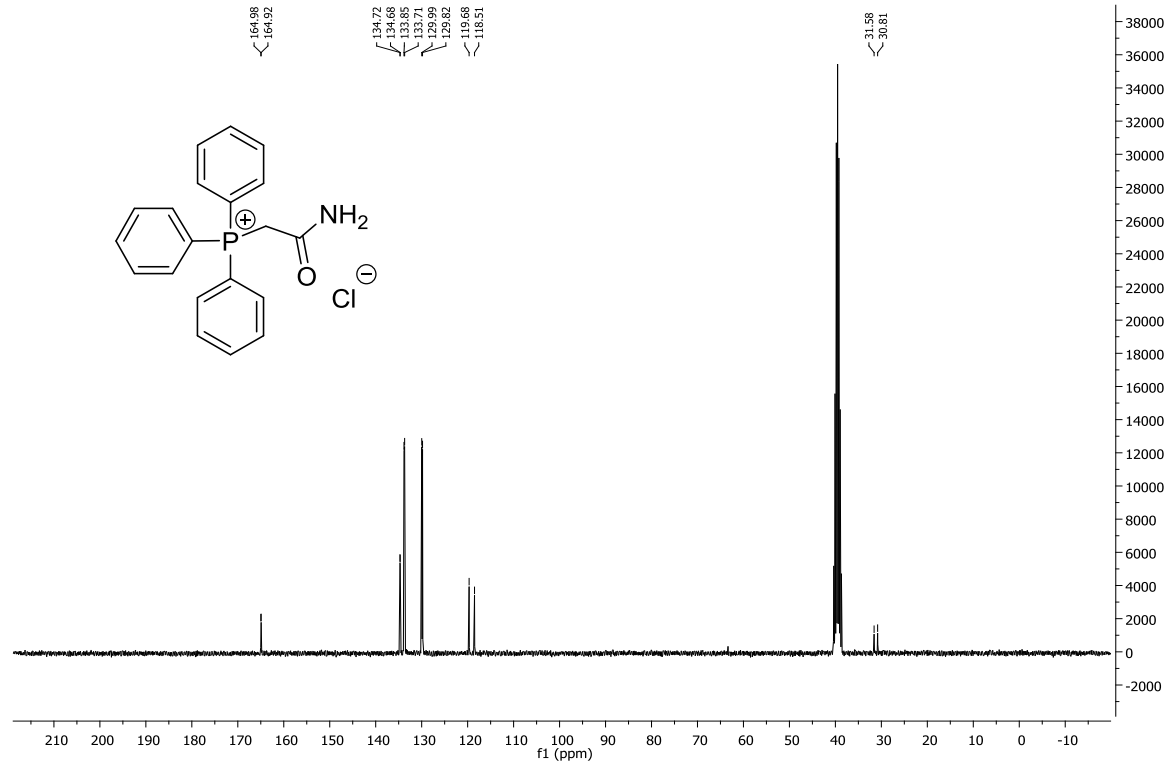

Figure 102. ^{13}C-NMR of (2-amino-2-oxoethyl)triphenylphosphonium chloride (**54**).

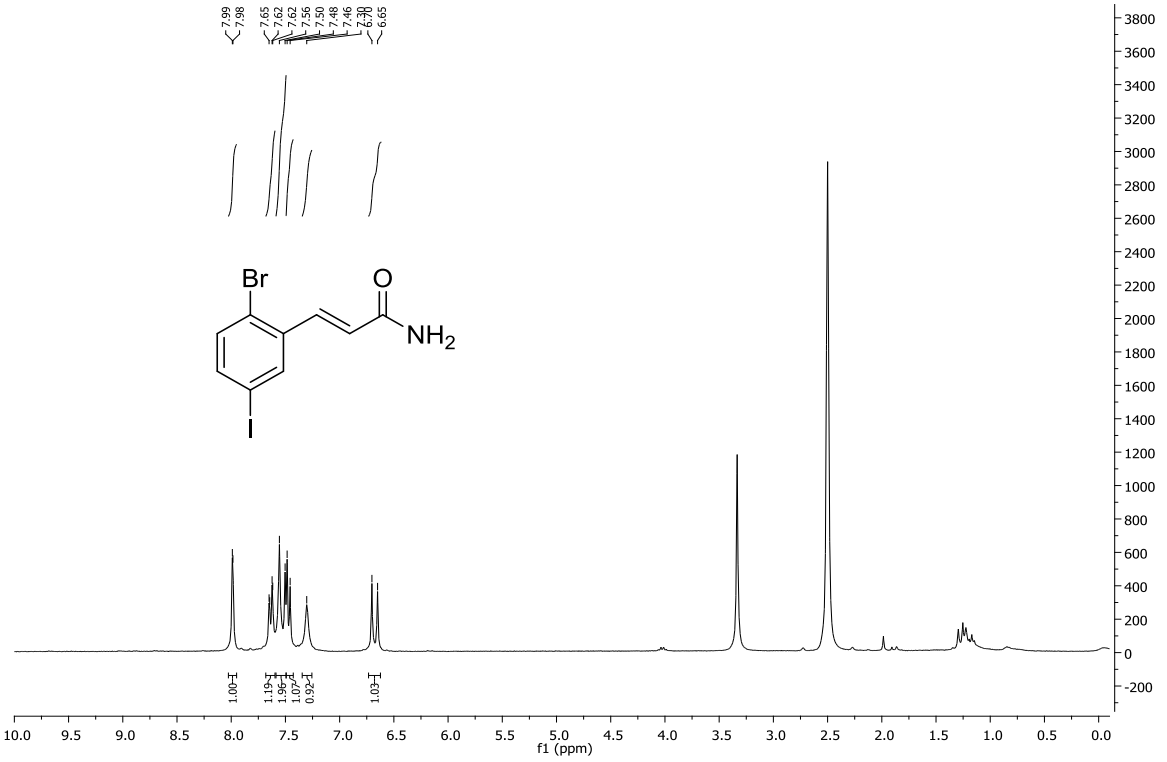

Figure 103. [1]H-NMR of 3-(2-bromo-5-iodophenyl)-propanamide (**55**).

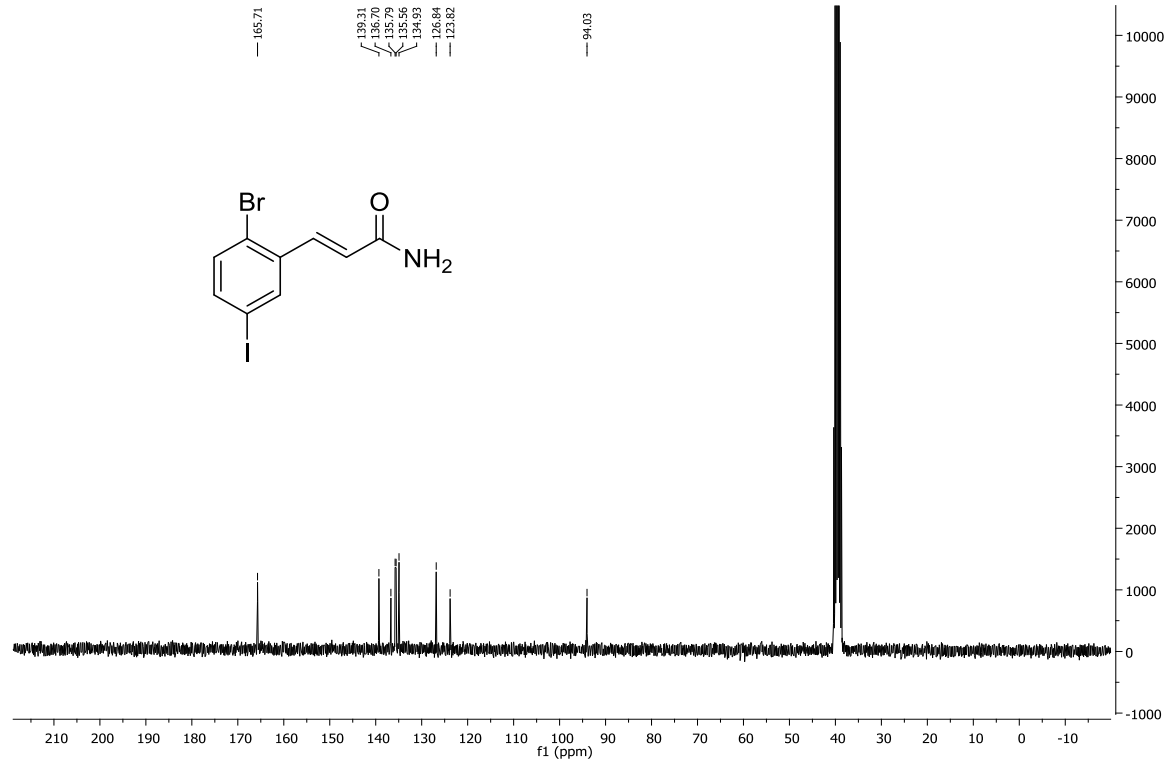

Figure 104. [13]C-NMR of 3-(2-bromo-5-iodophenyl)-propanamide (**55**).

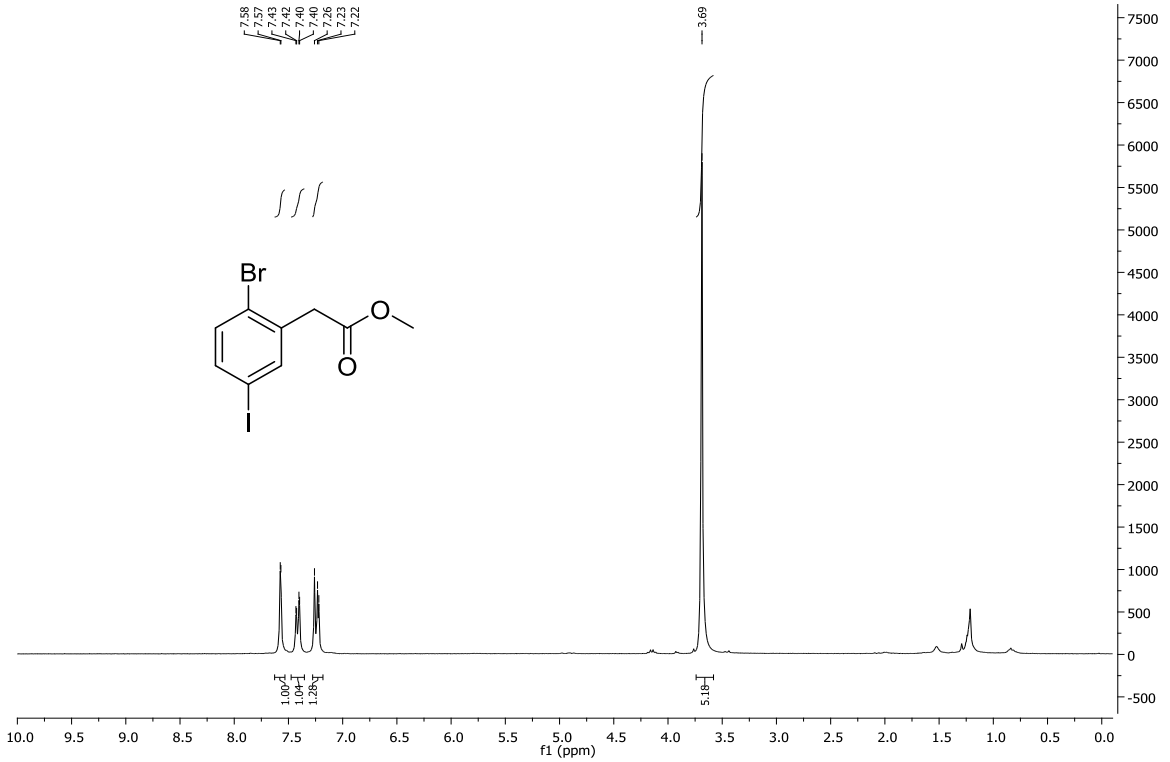

Figure 105. ^{1}H-NMR of methyl 2-(2-bromo-5-iodophenyl)acetate (**58**).

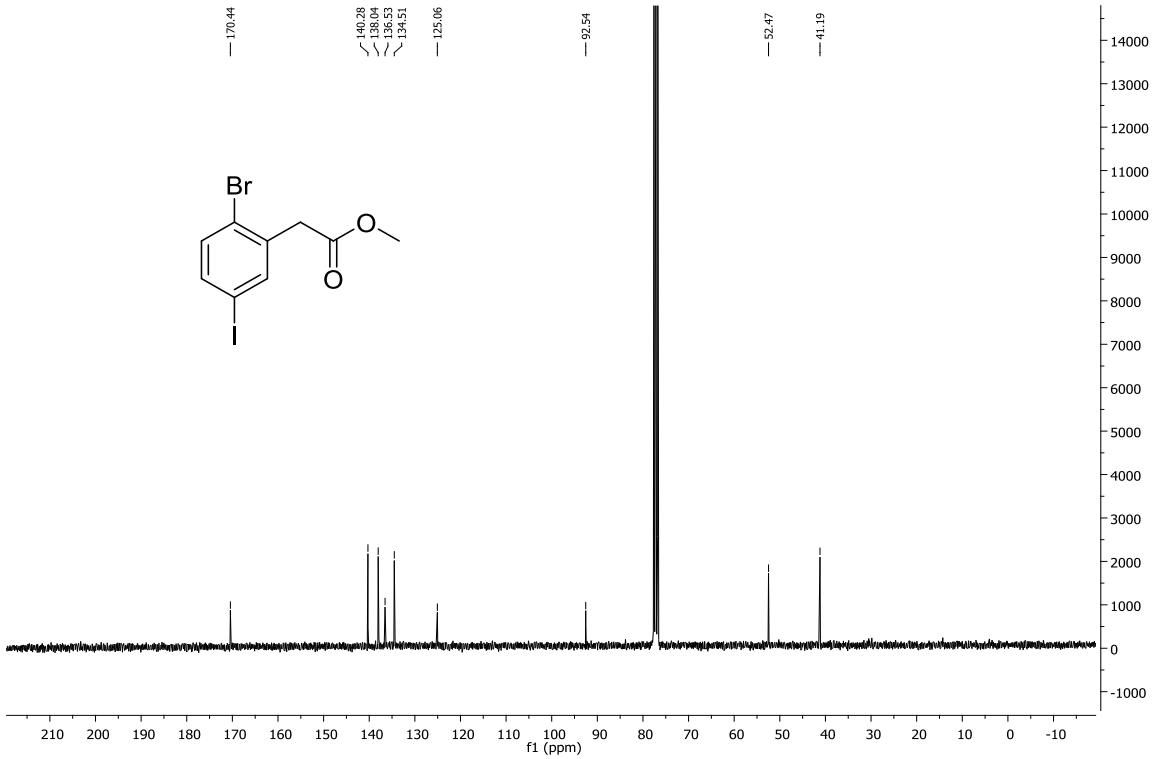

Figure 106. ^{13}C-NMR of methyl 2-(2-bromo-5-iodophenyl)acetate (**58**).

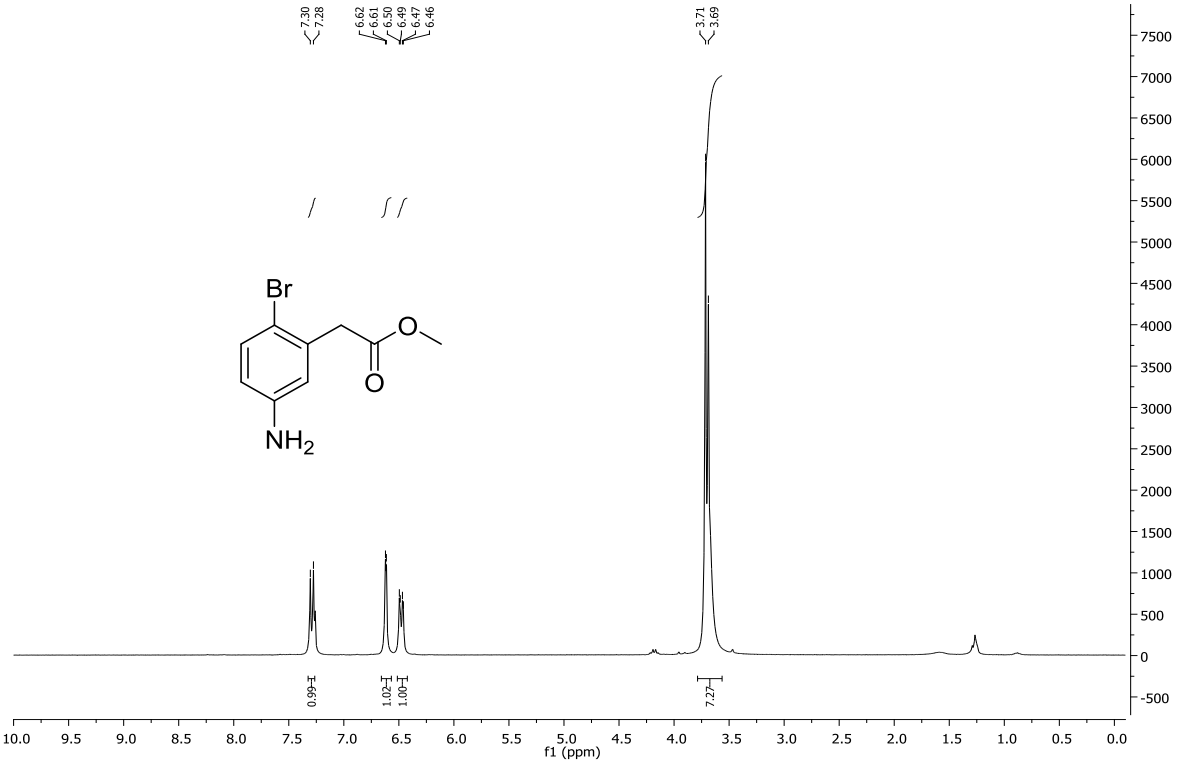

Figure 107. ^{1}H-NMR of methyl 2-(5-amino-2-bromophenyl)acetate (**63**).

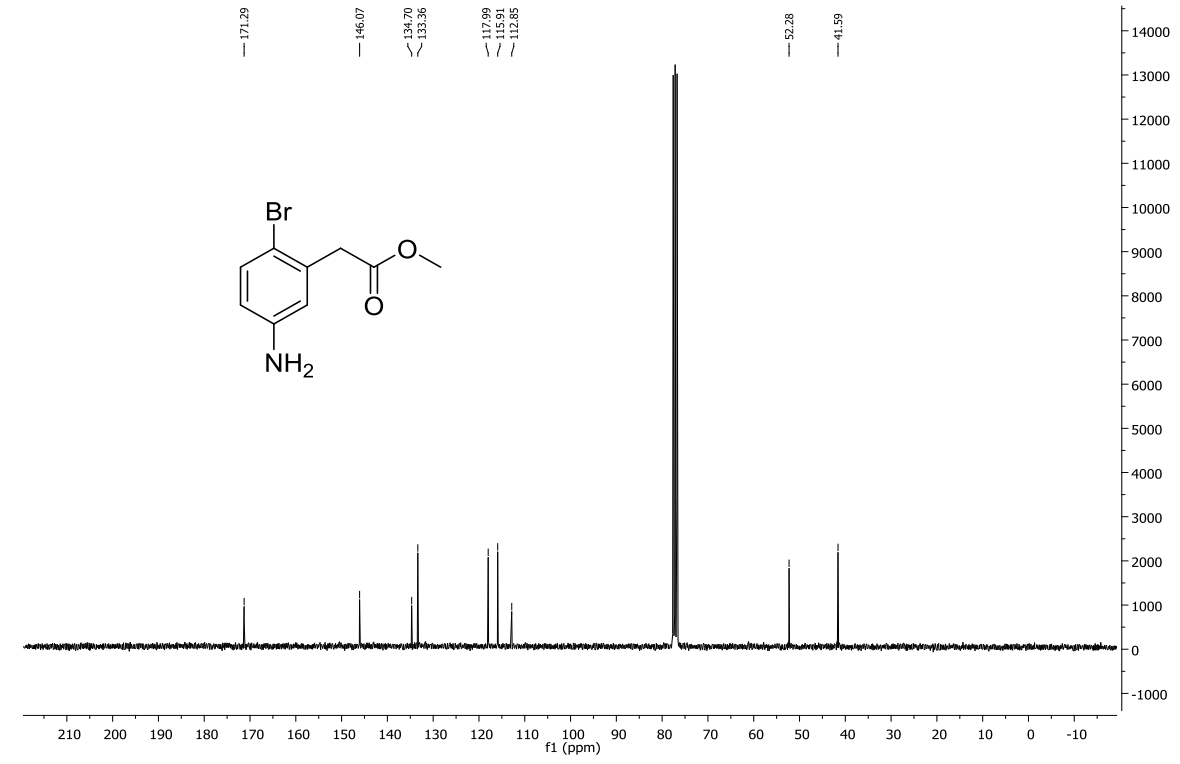

Figure 108. ^{13}C-NMR of methyl 2-(5-amino-2-bromophenyl)acetate (**63**).

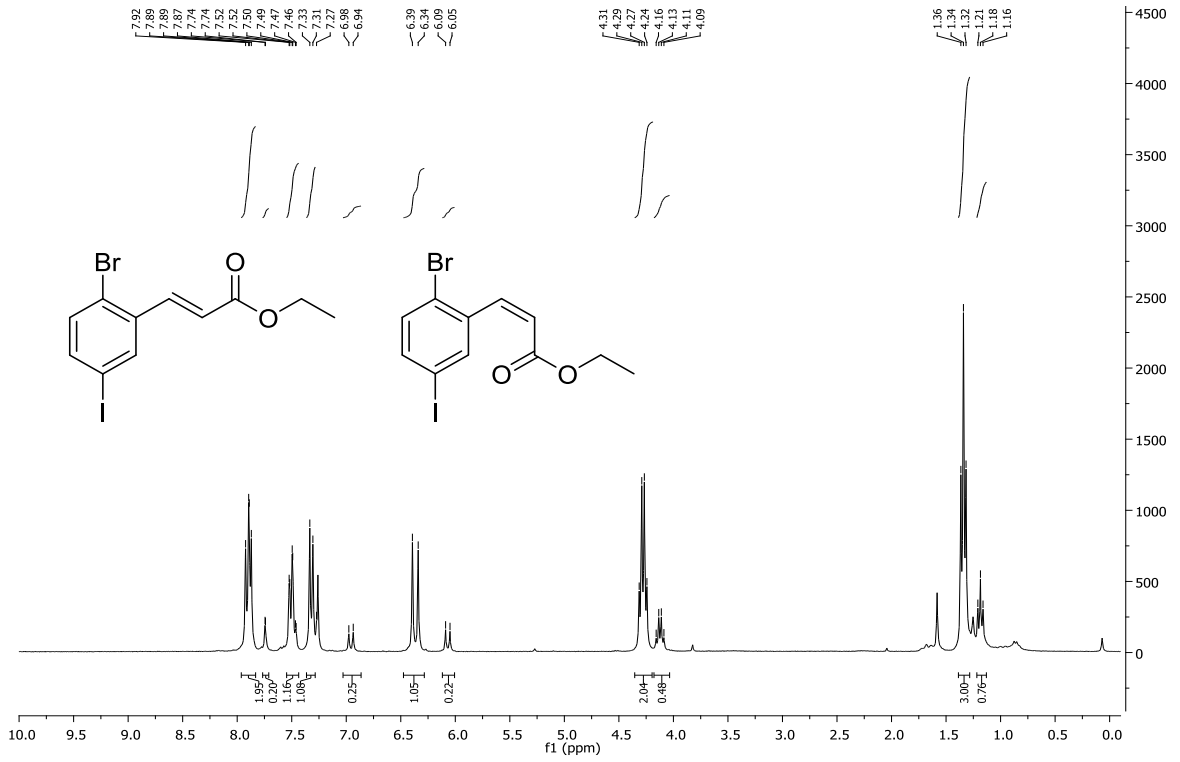

Figure 109. ^{1}H-NMR of ethyl (*E*/*Z*)-3-(2-bromo-5-iodophenyl)acrylate (**66**).

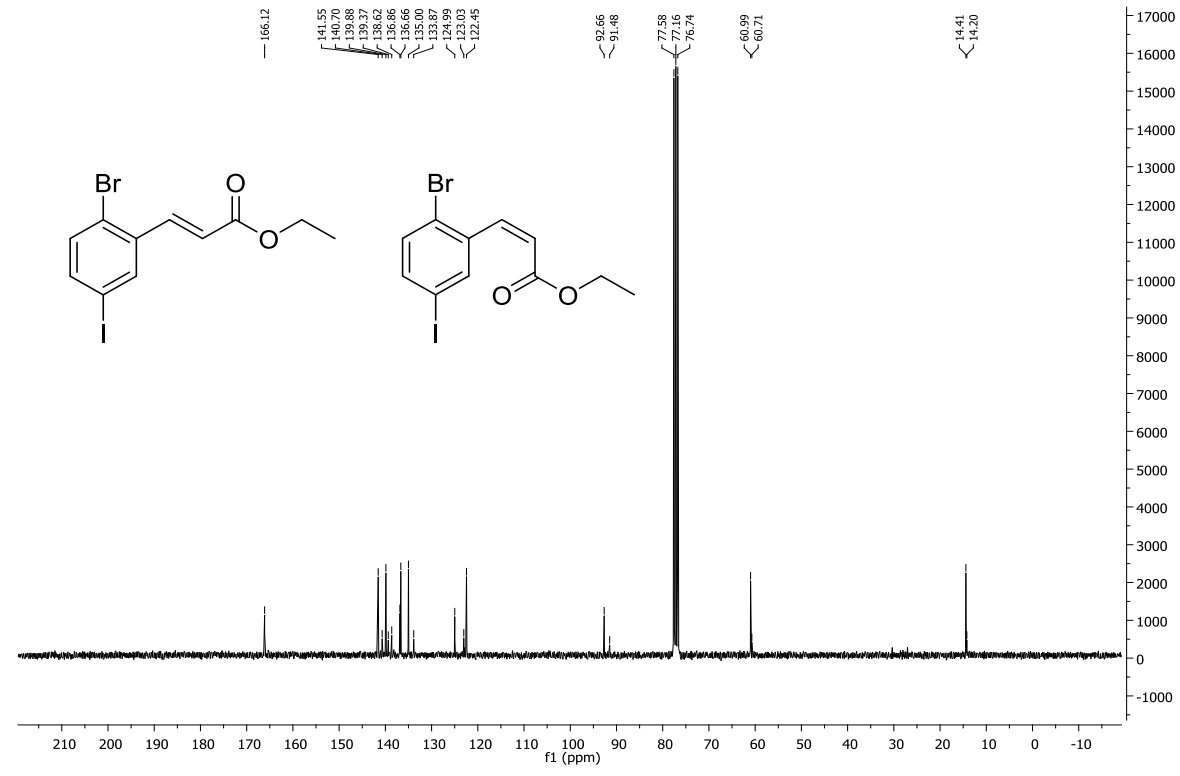

Figure 110. ^{13}C-NMR of ethyl (*E*/*Z*)-3-(2-bromo-5-iodophenyl)acrylate (**66**).

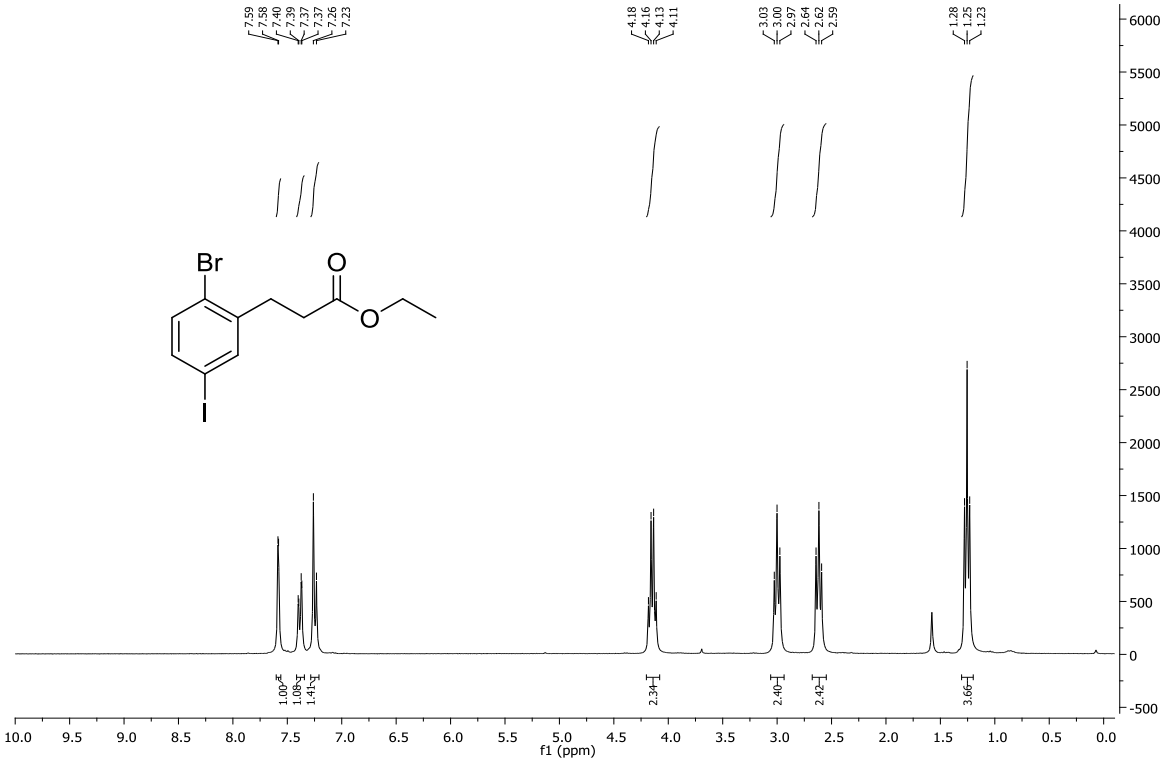

Figure 111. [1]H-NMR of ethyl 3-(2-bromo-5-iodophenyl)propanoate (**67**).

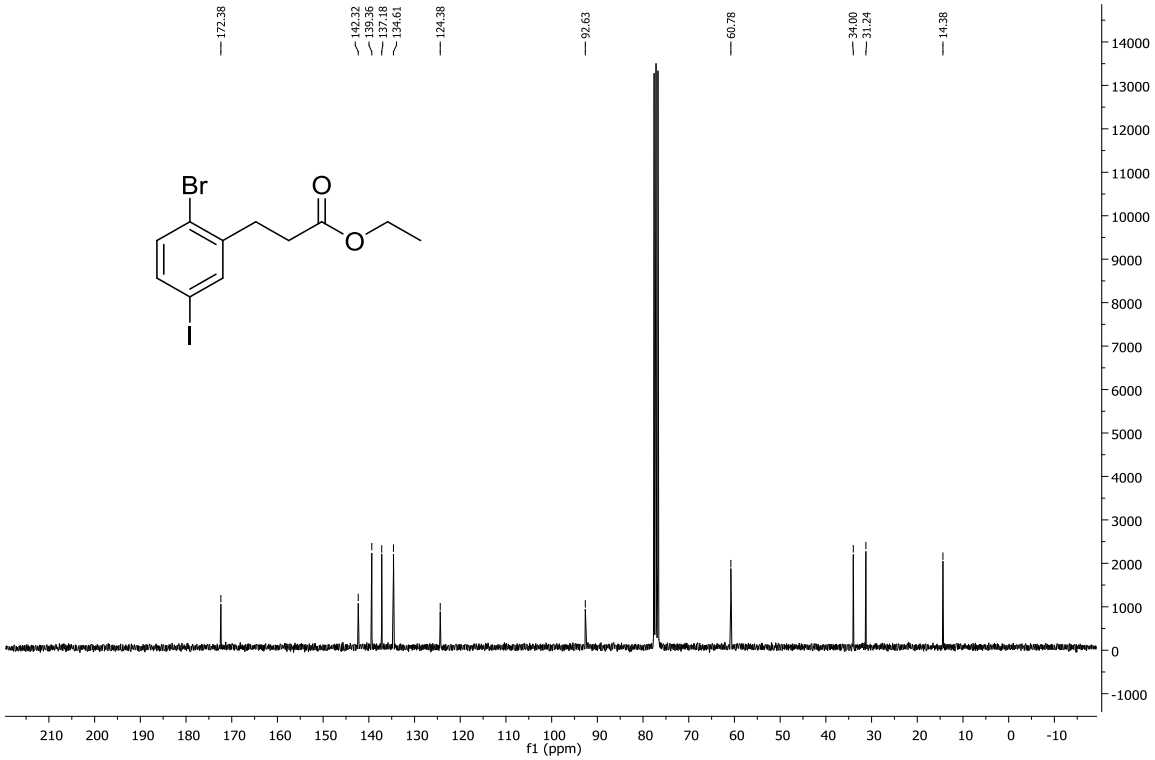

Figure 112. [13]C-NMR of ethyl 3-(2-bromo-5-iodophenyl)propanoate (**67**).

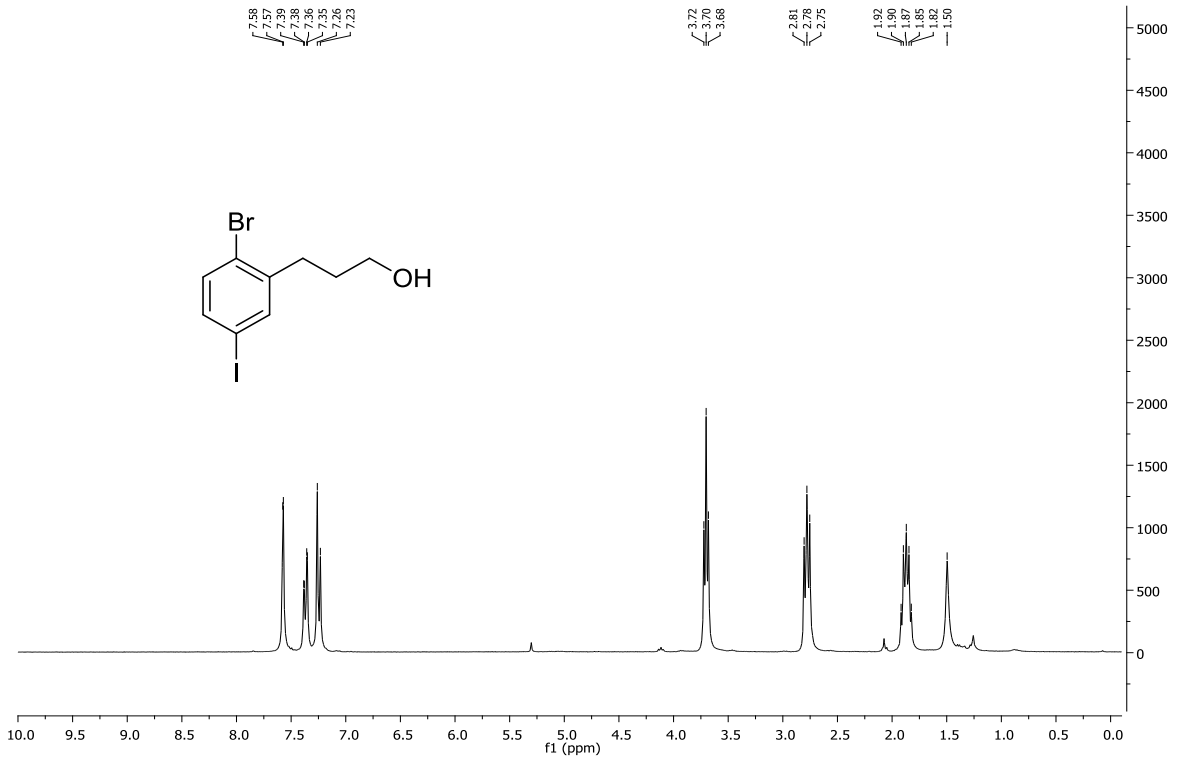

Figure 113. ^{1}H-NMR of 3-(2-bromo-5-iodophenyl)propan-1-ol (**68**).

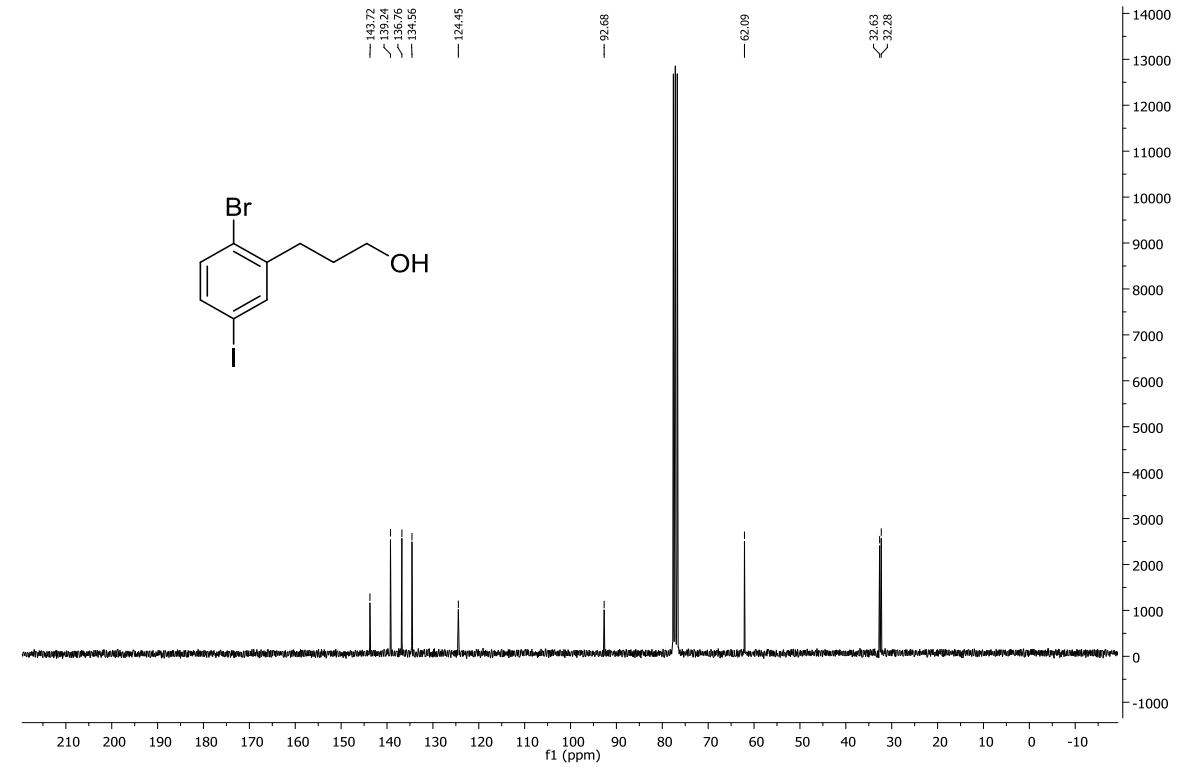

Figure 114. ^{13}C-NMR of 3-(2-bromo-5-iodophenyl)propan-1-ol (**68**).

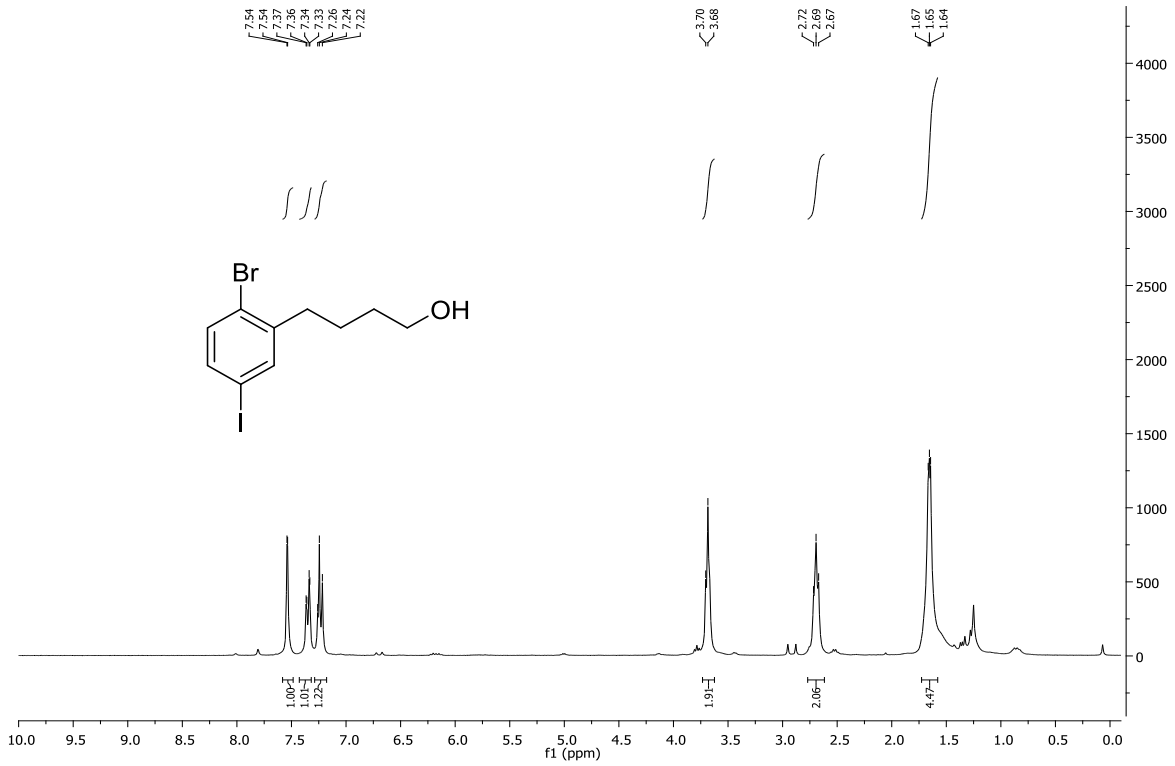

Figure 115. ^{1}H-NMR of 4-(2-bromo-5-iodophenyl)butan-1-ol (**70**).

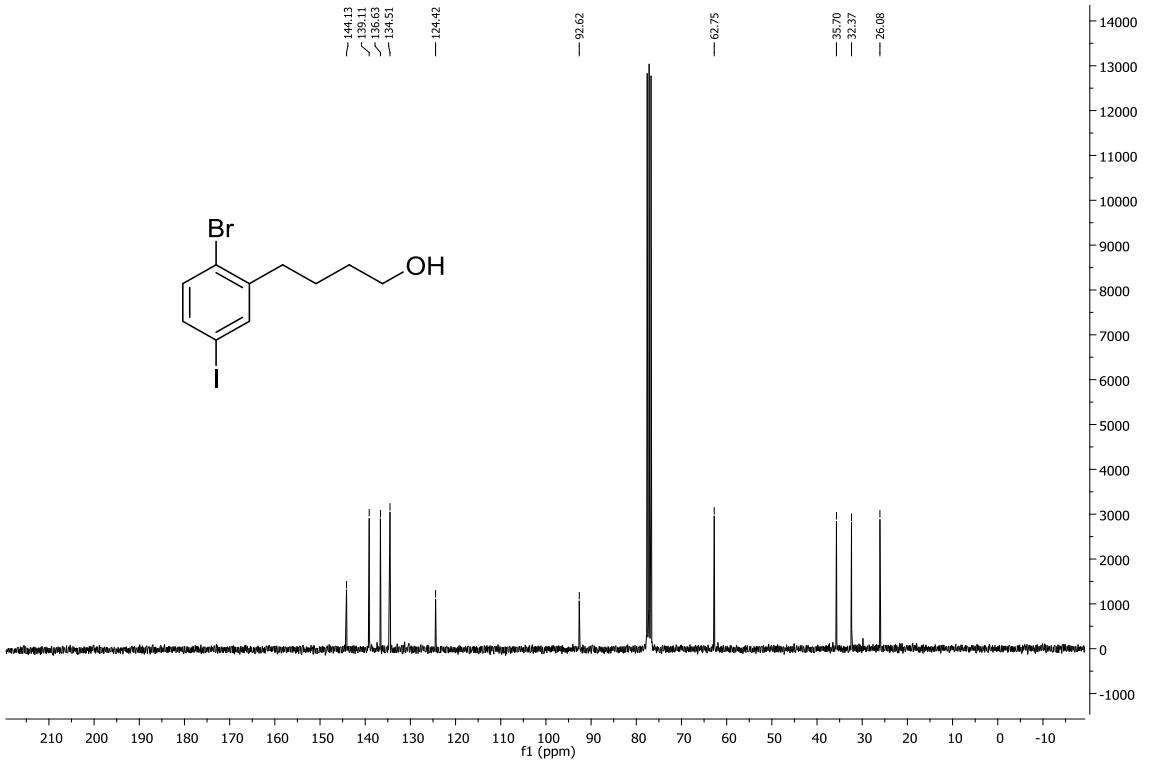

Figure 116. ^{13}C-NMR of 4-(2-bromo-5-iodophenyl)butan-1-ol (**70**).

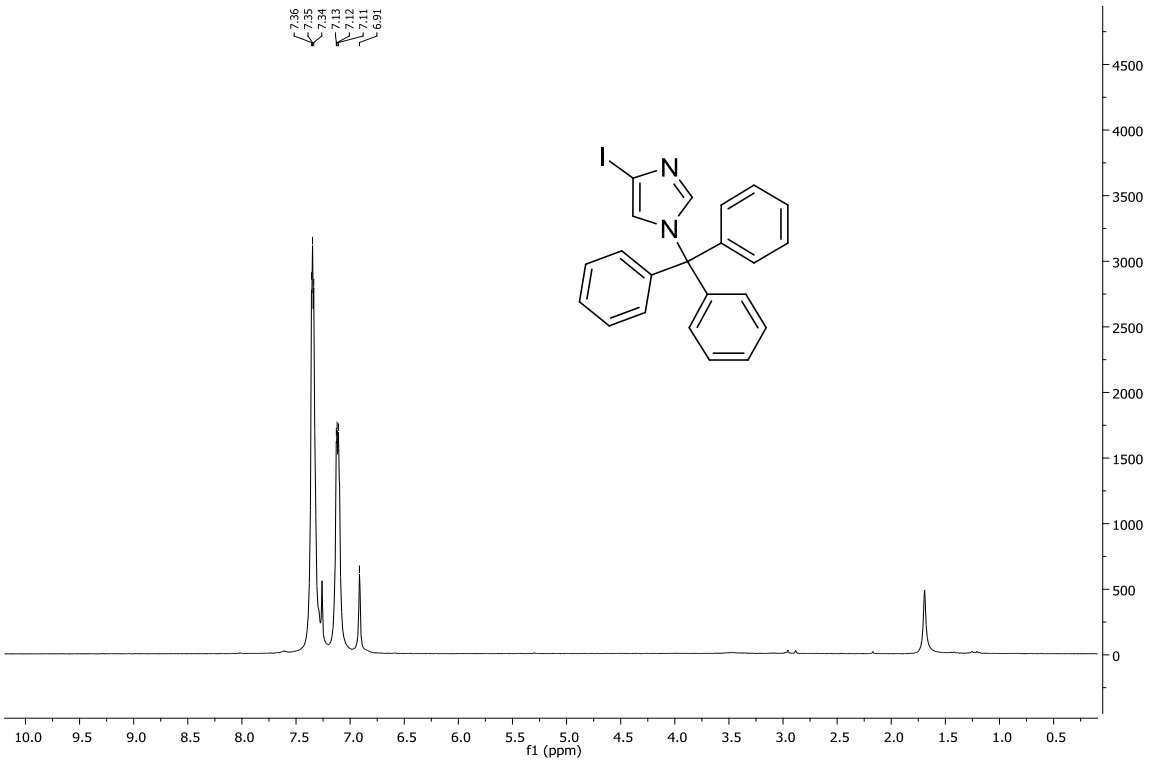

Figure 117. ^{1}H-NMR of 4-iodo-1-trityl-1*H*-imidazole (**73**).

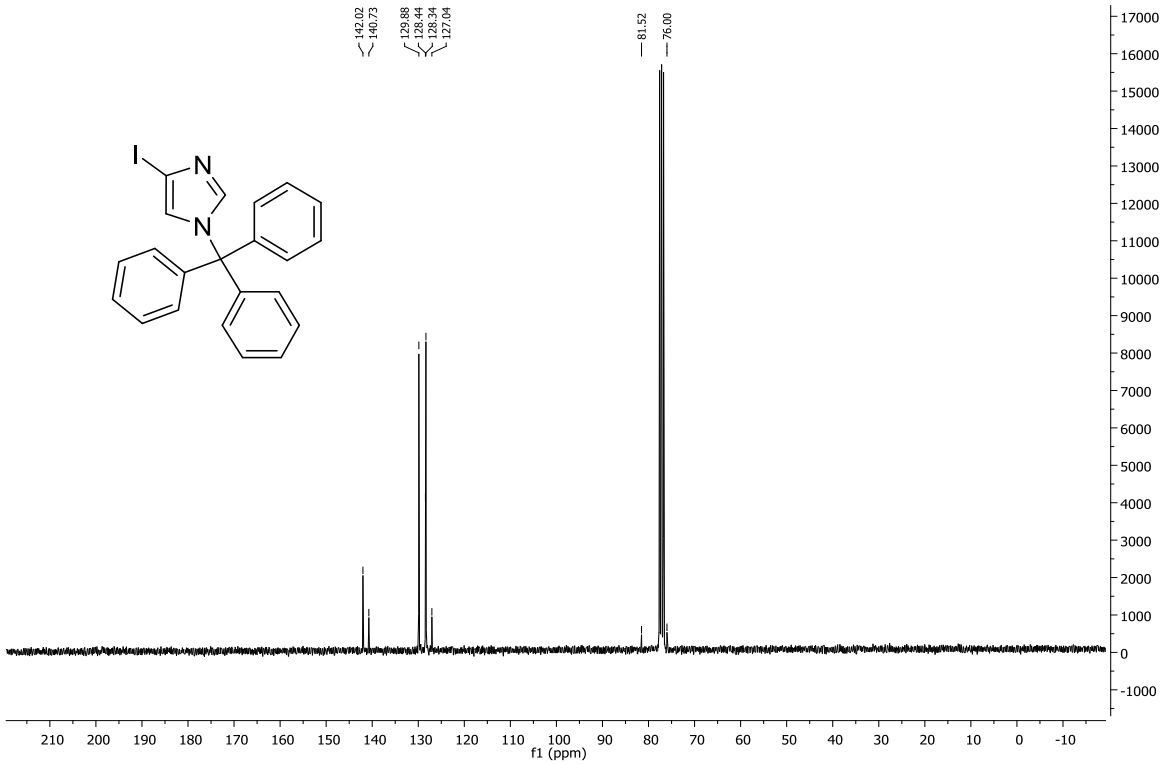

Figure 118. ^{13}C-NMR of 4-iodo-1-trityl-1*H*-imidazole (**73**).

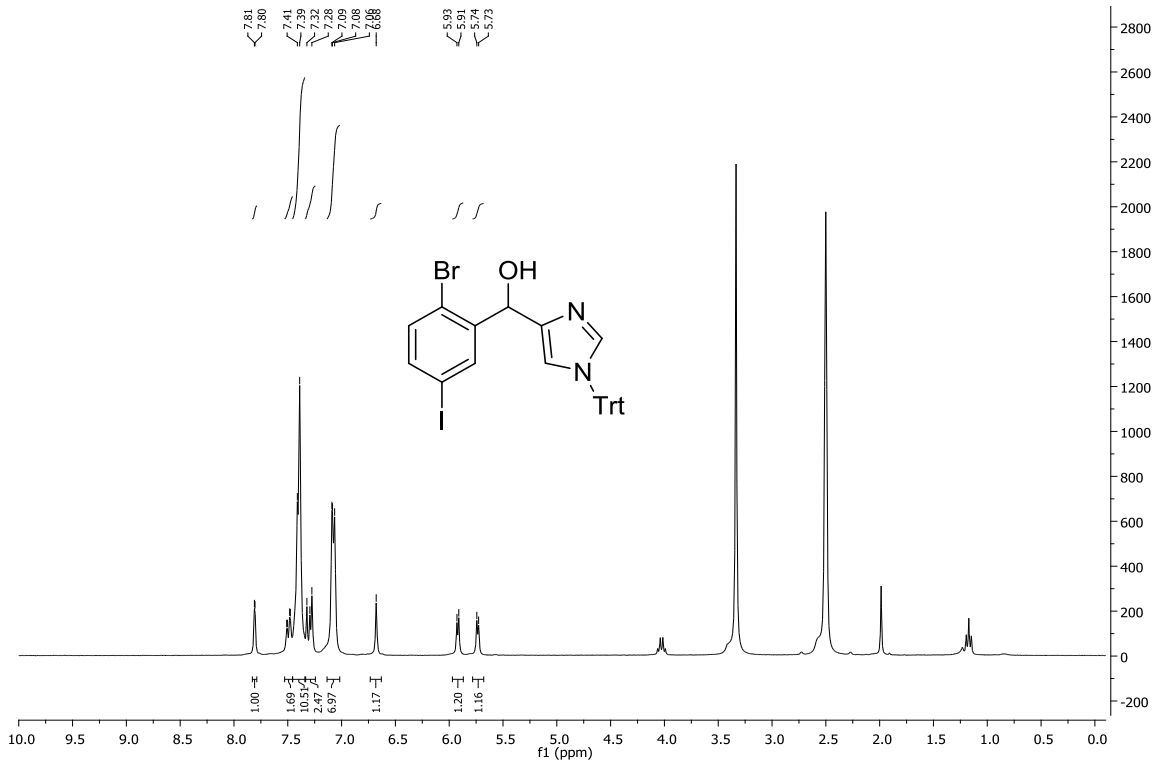

Figure 119. [1]H-NMR of (2-bromo-5-iodophenyl)(1-trityl-1*H*-imidazol-4-yl)methanol (**74**).

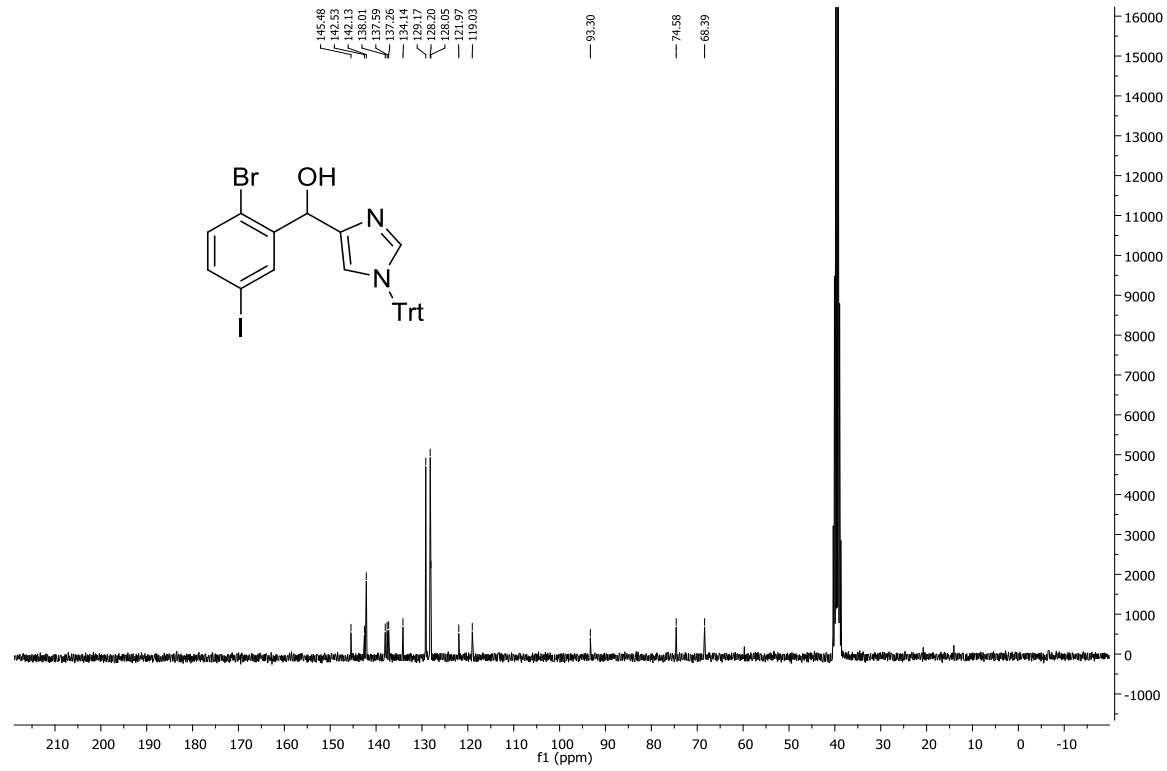

Figure 120. [13]C-NMR of (2-bromo-5-iodophenyl)(1-trityl-1*H*-imidazol-4-yl)methanol (**74**).

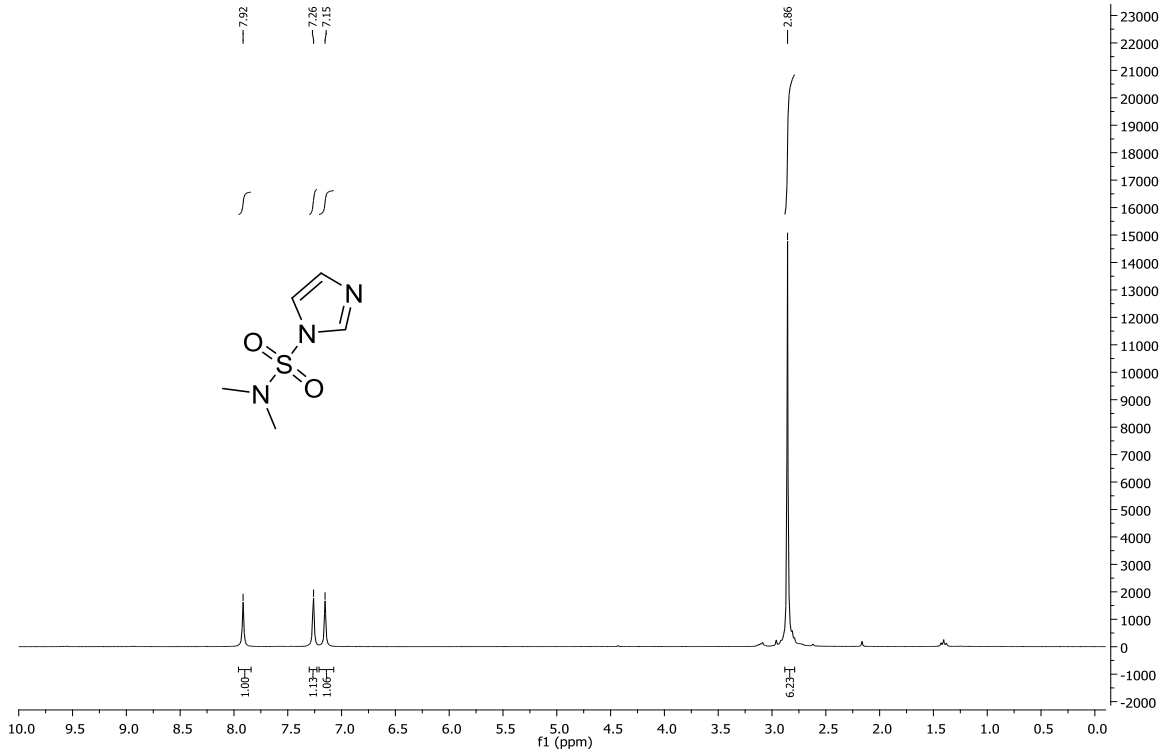

Figure 121. ^{1}H-NMR of *N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (**79**).

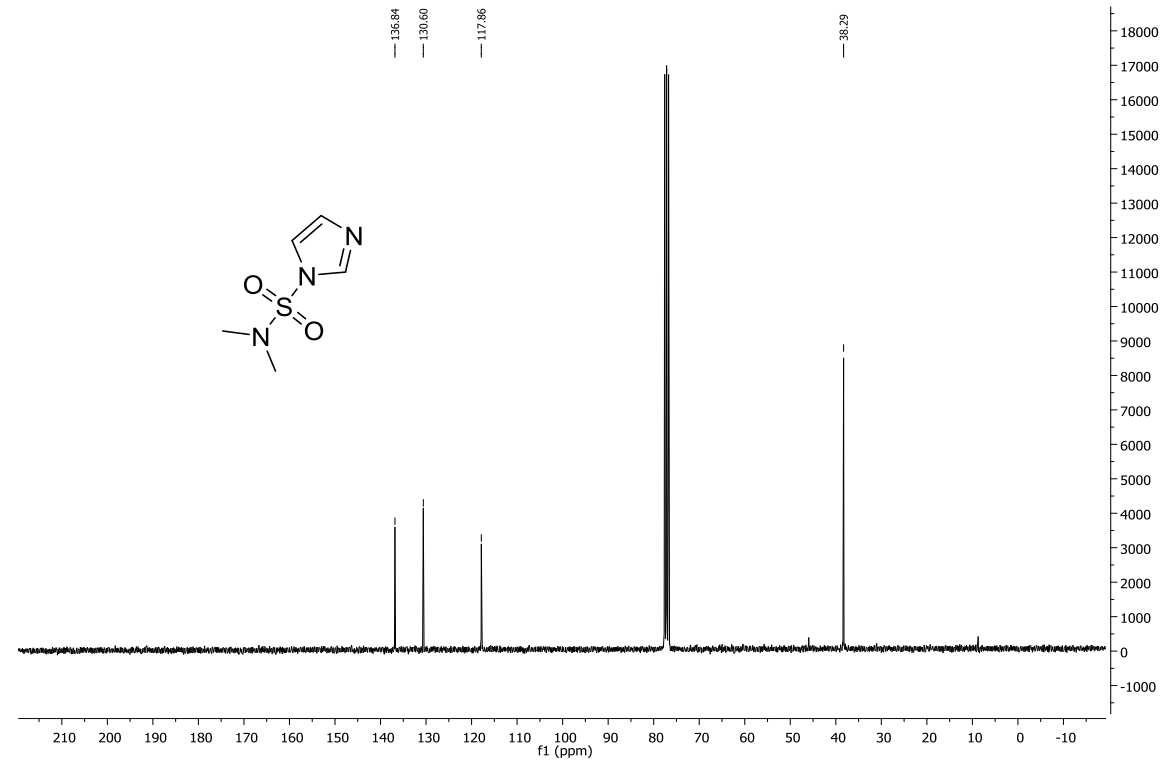

Figure 122. ^{13}C-NMR of *N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (**79**).

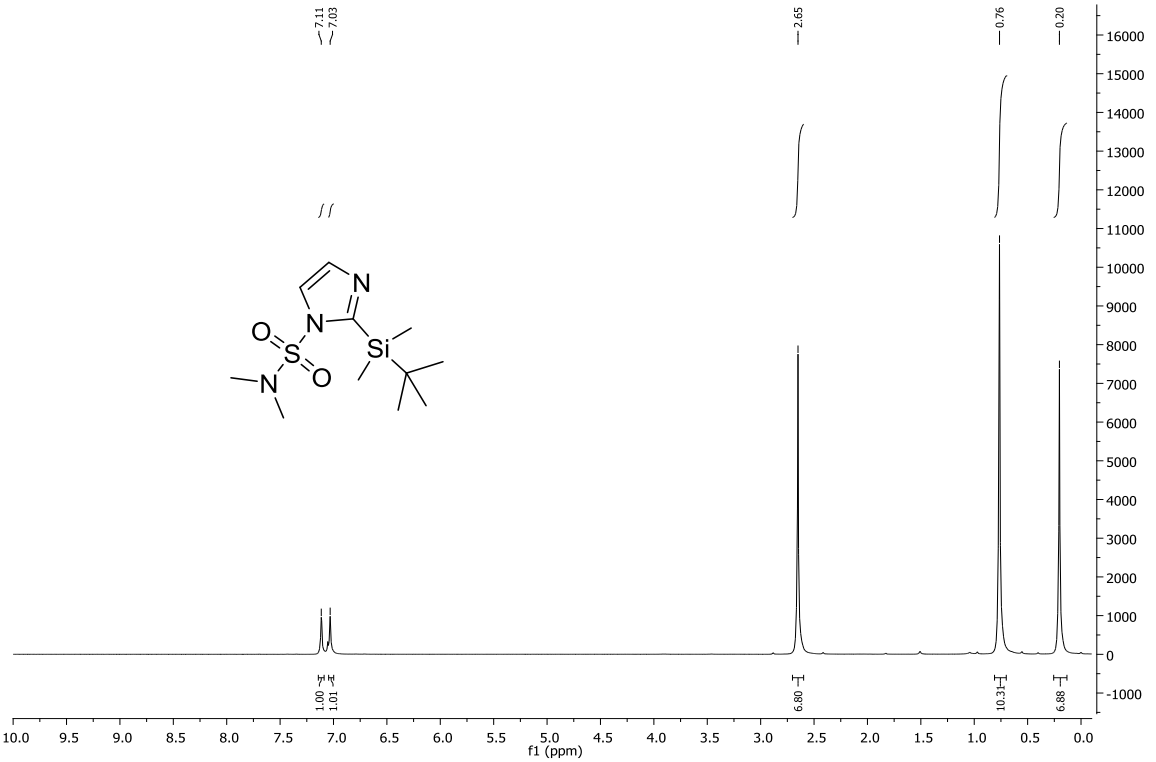

Figure 123. [1]H-NMR of 2-(tert-butyldimethylsilyl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (**81**).

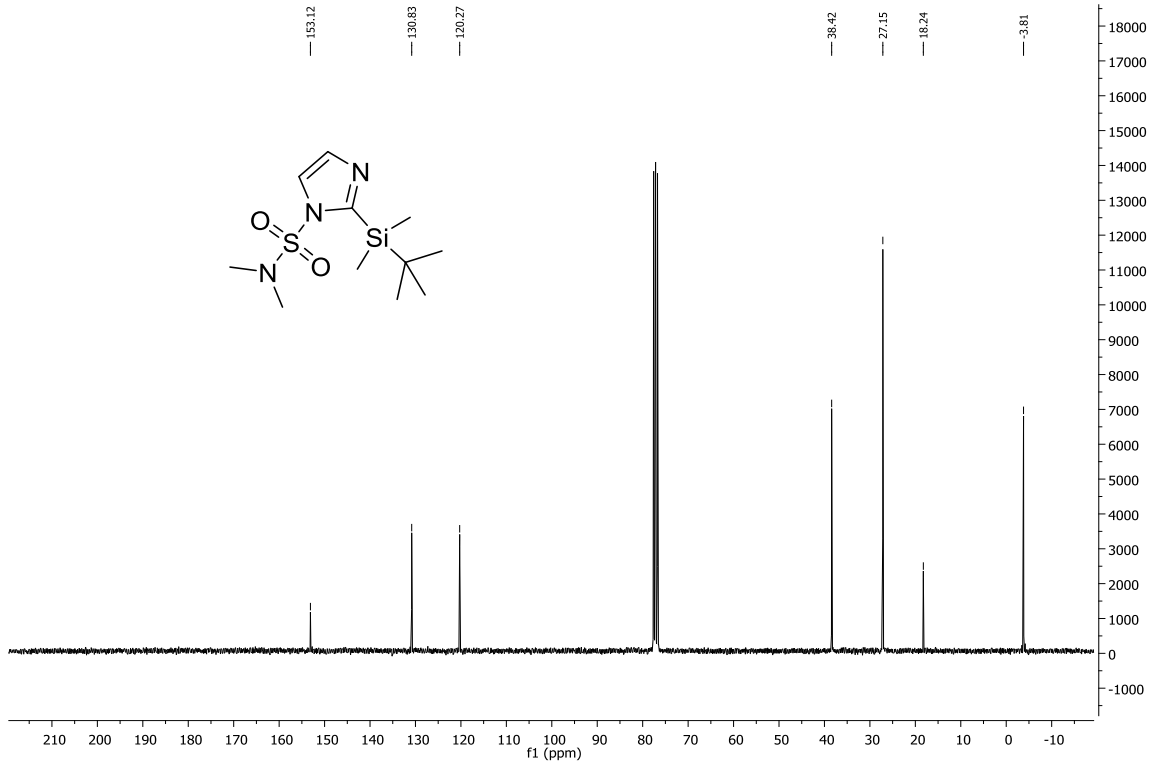

Figure 124. [13]C-NMR of 2-(tert-butyldimethylsilyl)-*N*,*N*-dimethyl-1H-imidazole-1-sulfonamide (**81**).

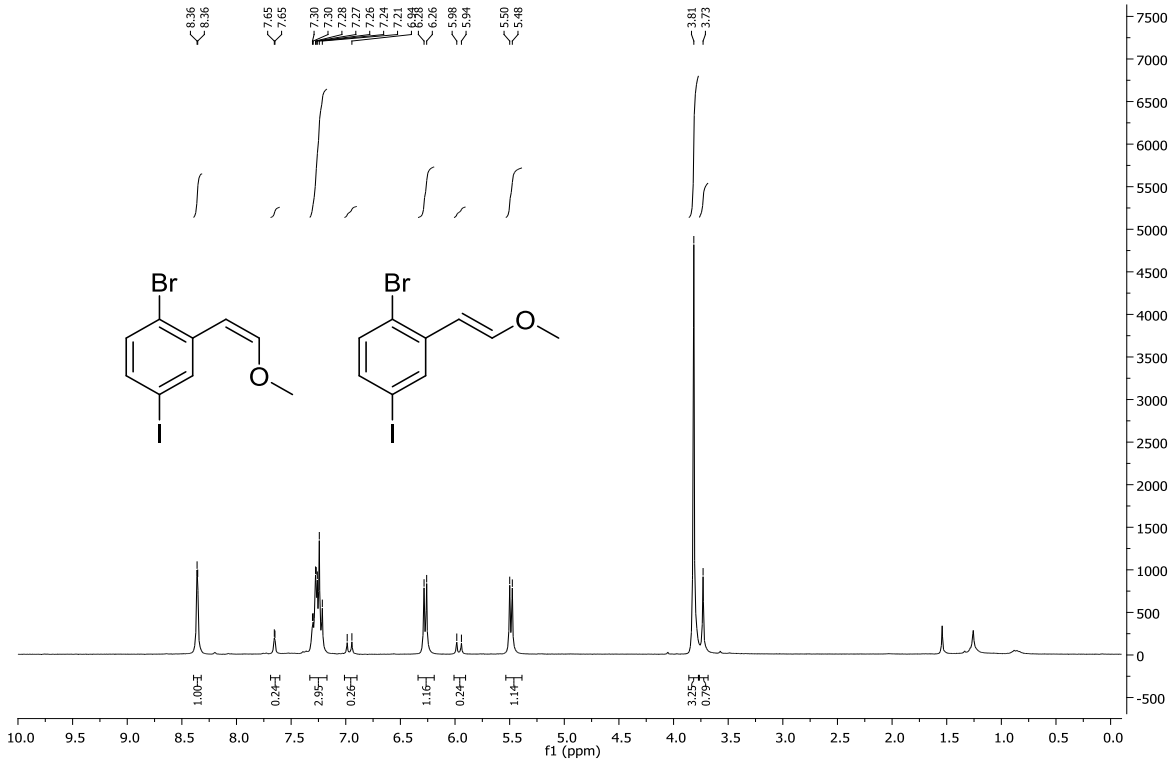

Figure 125. ^{1}H-NMR of (*E*/*Z*)-1-bromo-4-iodo-2-(2-methoxyvinyl)benzene (**83**).

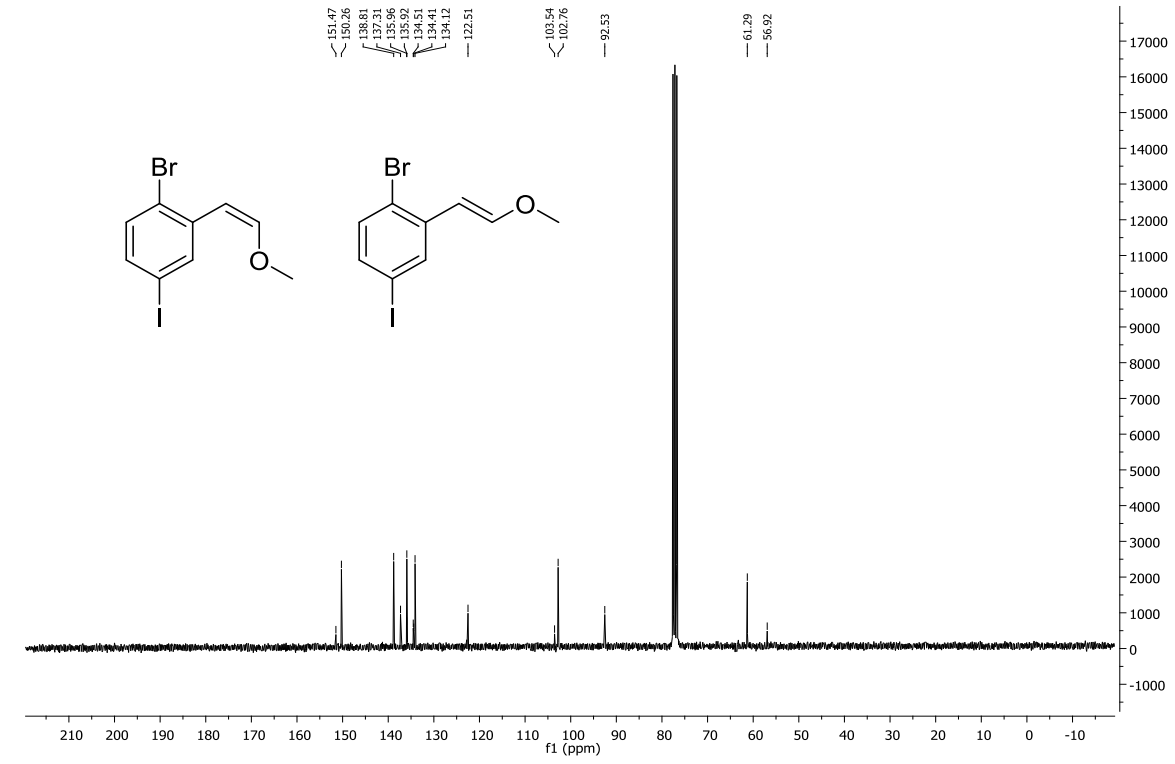

Figure 126. ^{13}C-NMR of (*E*/*Z*)-1-bromo-4-iodo-2-(2-methoxyvinyl)benzene (**83**).

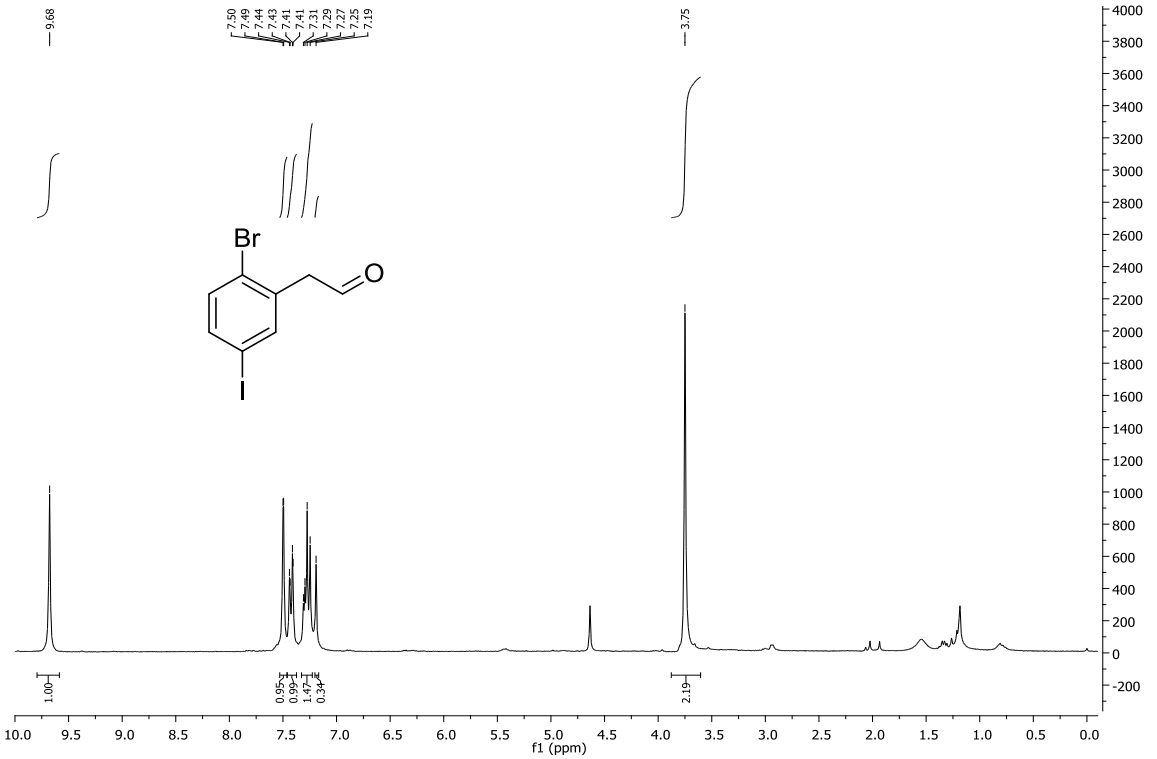

Figure 127. ^{1}H-NMR of 2-(2-bromo-5-iodophenyl)acetaldehyde (**84**).

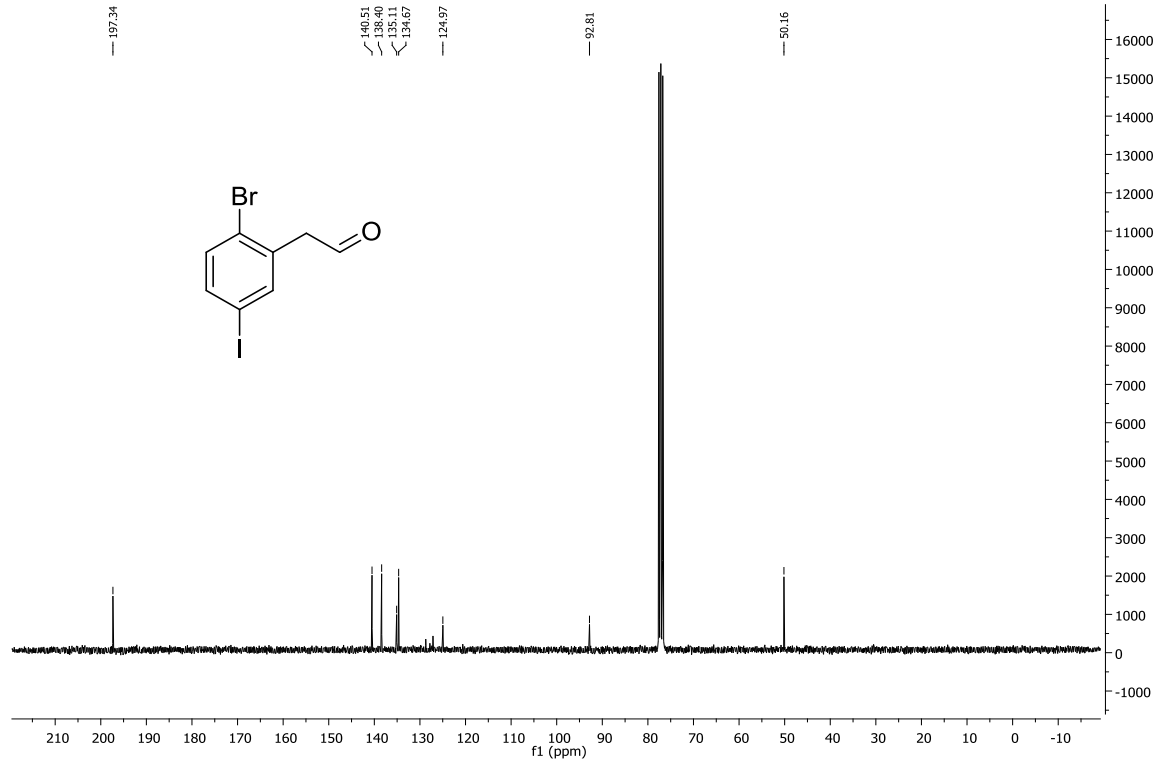

Figure 128. ^{13}C-NMR of 2-(2-bromo-5-iodophenyl)acetaldehyde (**84**).

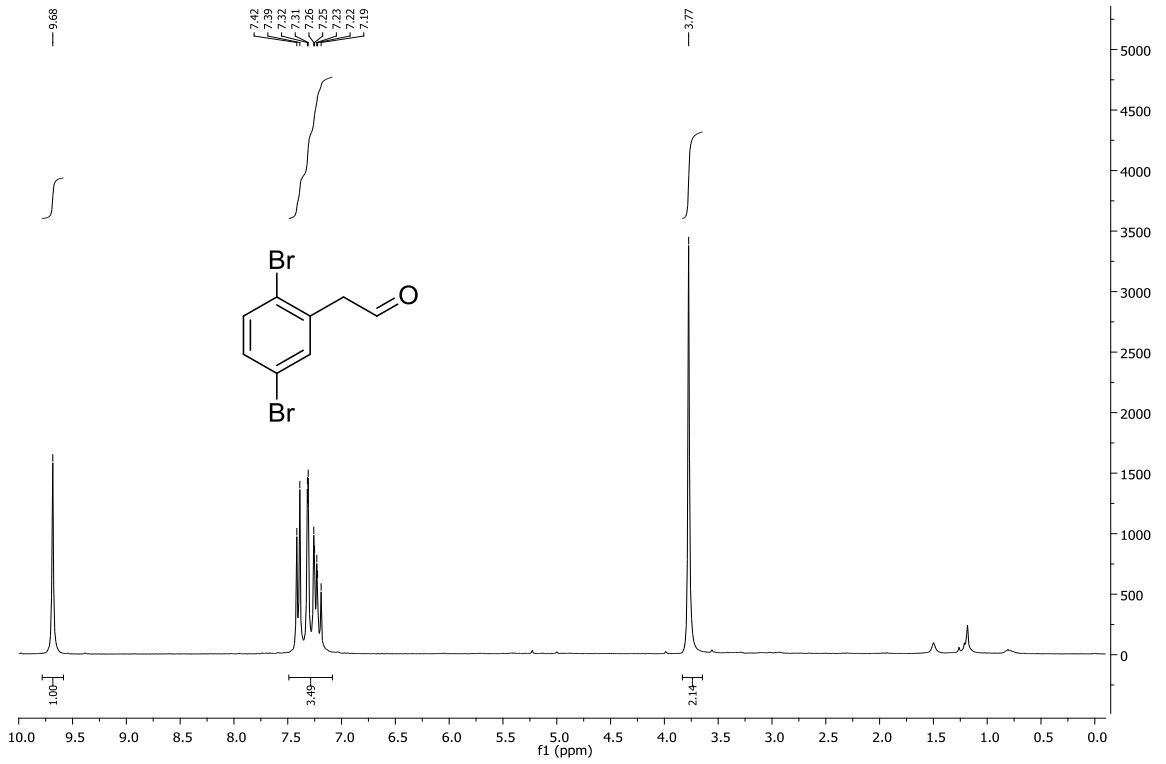

Figure 129. ^{1}H-NMR of 2-(2,5-dibromophenyl)acetaldehyde (**87**).

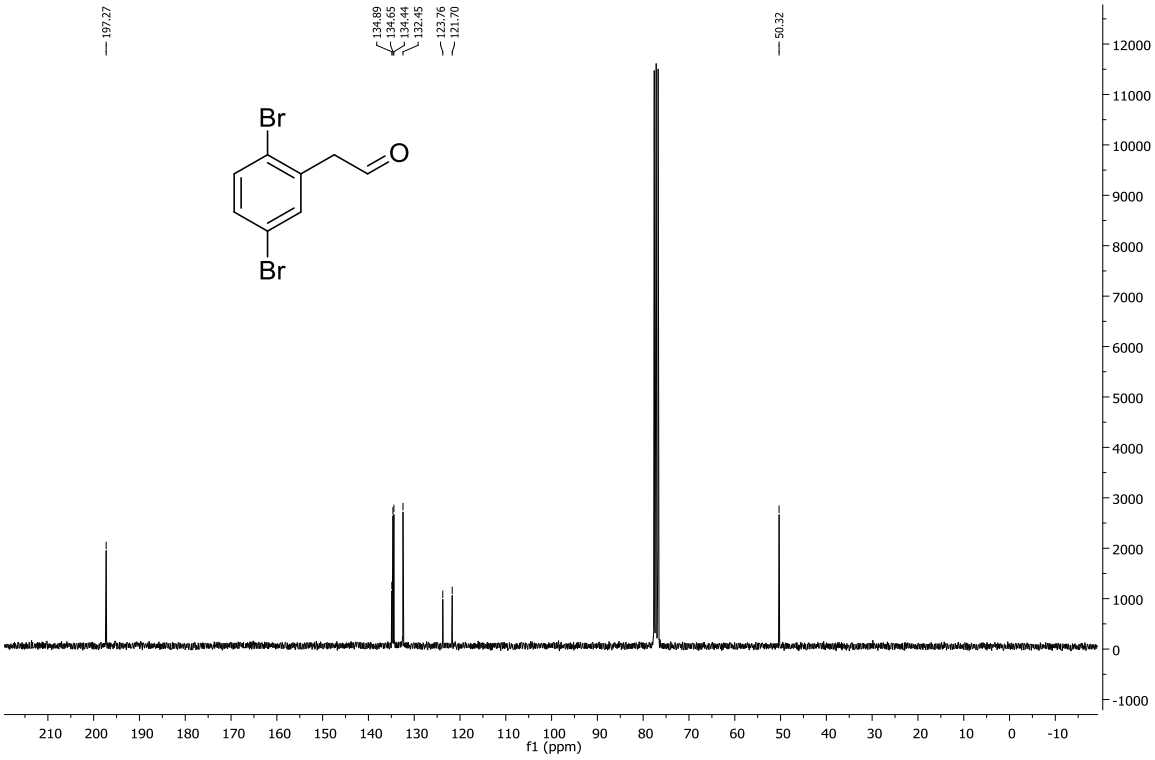

Figure 130. ^{13}C-NMR of 2-(2,5-dibromophenyl)acetaldehyde (**87**).

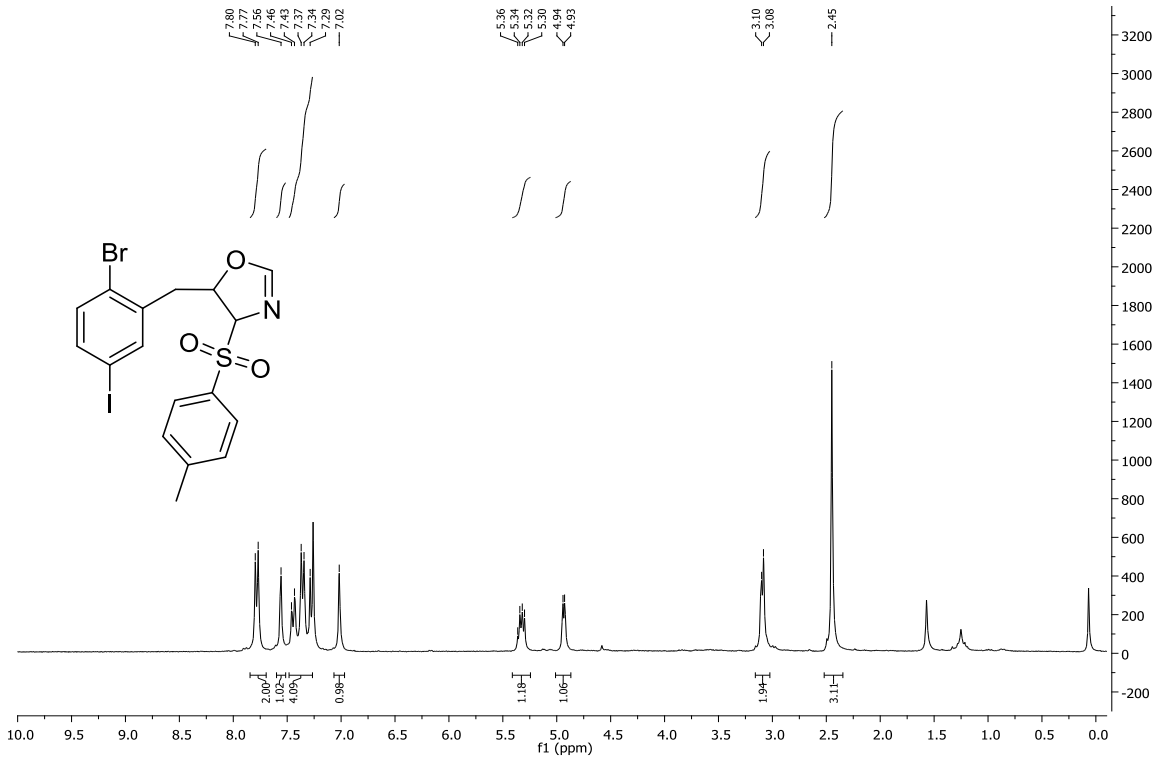

Figure 131. [1]H-NMR of 5-(2-bromo-5-iodobenzyl)-4-tosyl-4,5-dihydrooxazole (**88**).

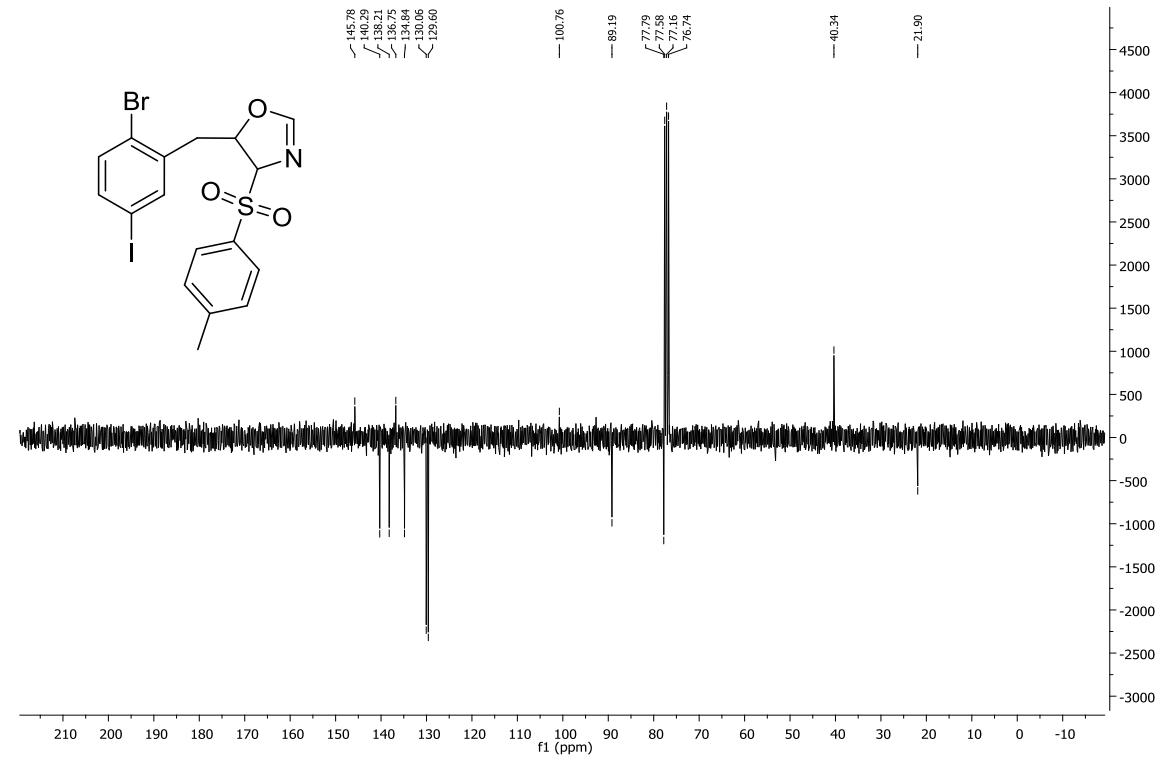

Figure 132. APT of 5-(2-bromo-5-iodobenzyl)-4-tosyl-4,5-dihydrooxazole (**88**).

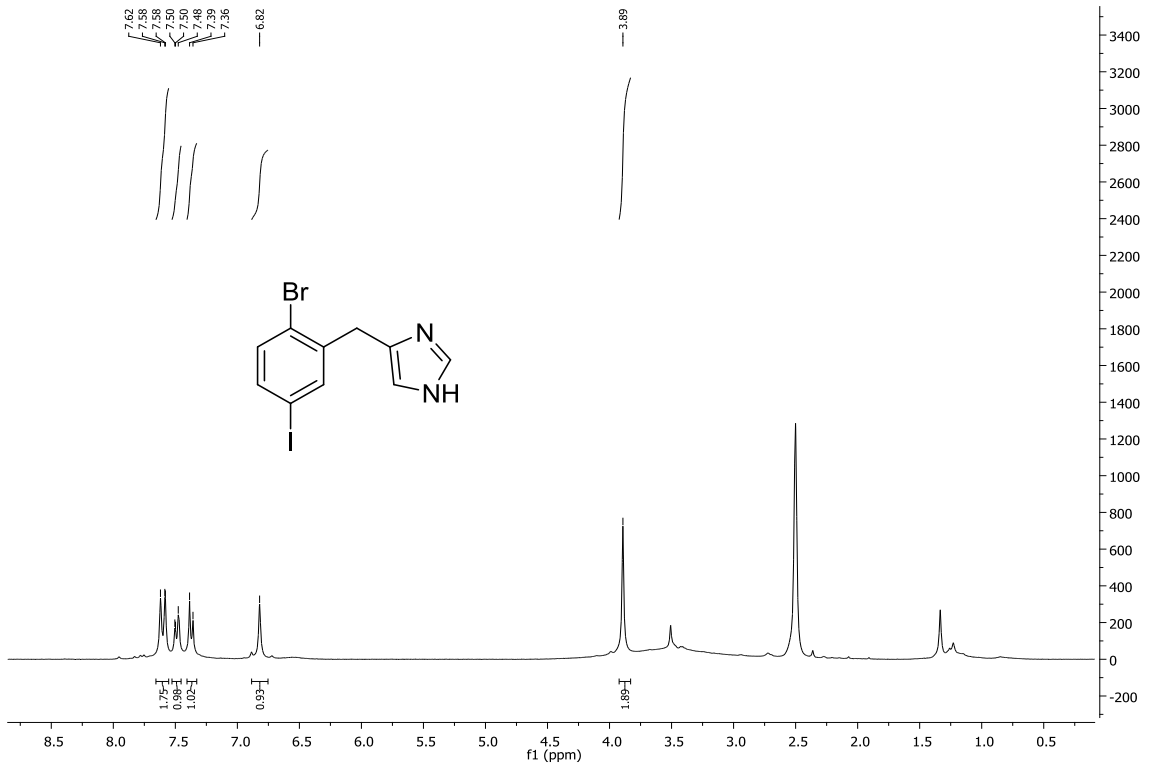

Figure 133. [1]H-NMR of 4-(2-bromo-5-iodobenzyl)-1*H*-imidazole (**75**).

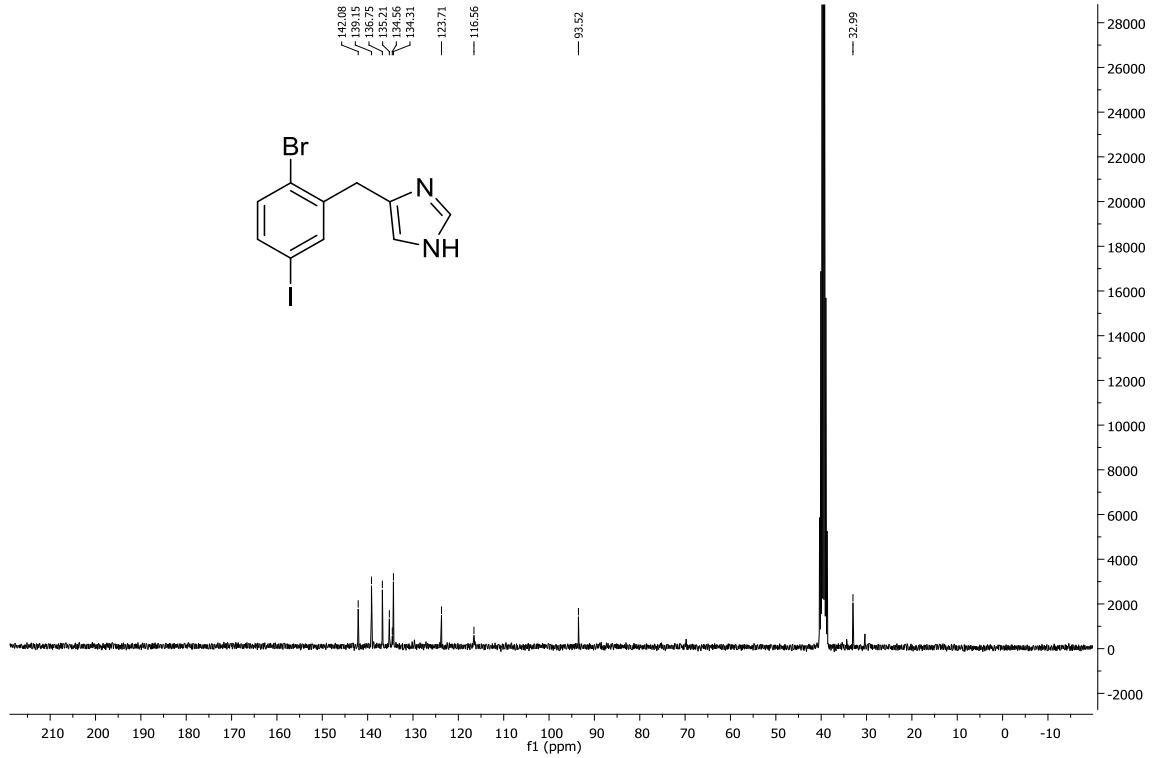

Figure 134. [13]C-NMR of 4-(2-bromo-5-iodobenzyl)-1*H*-imidazole (**75**).

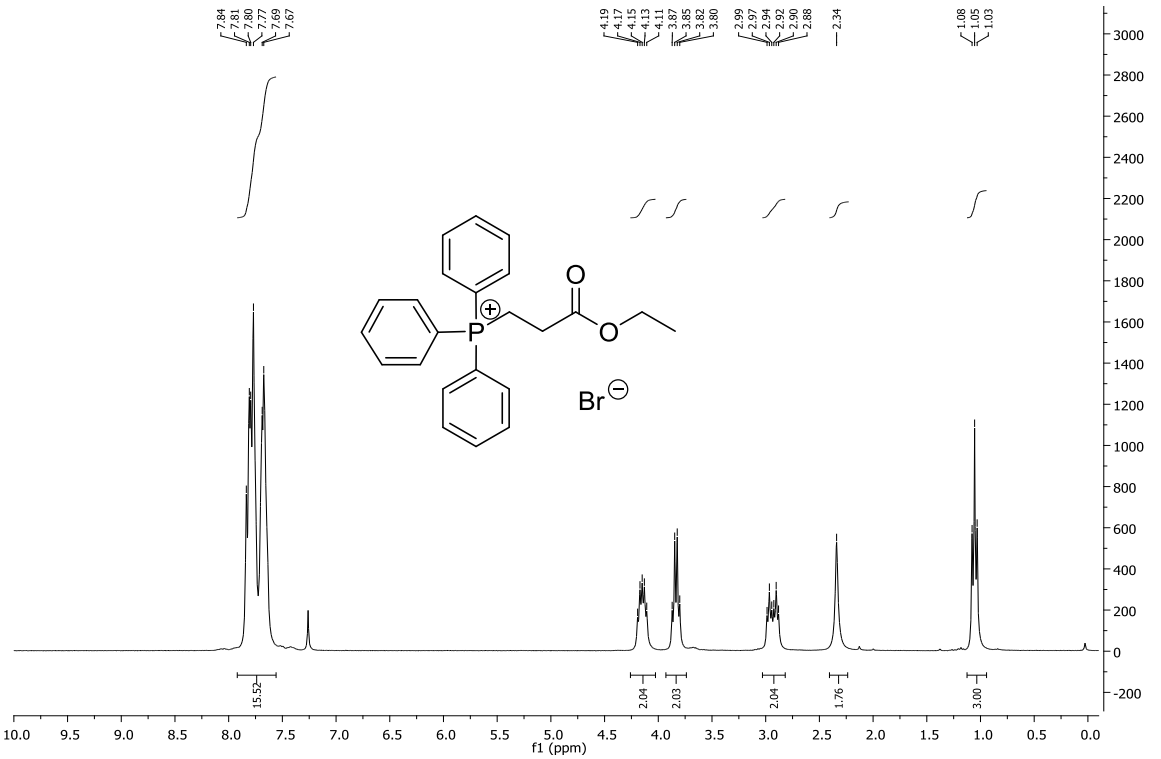

Figure 135. [1]H-NMR of (3-ethoxy-3-oxopropyl)triphenylphosphonium bromide (**92**).

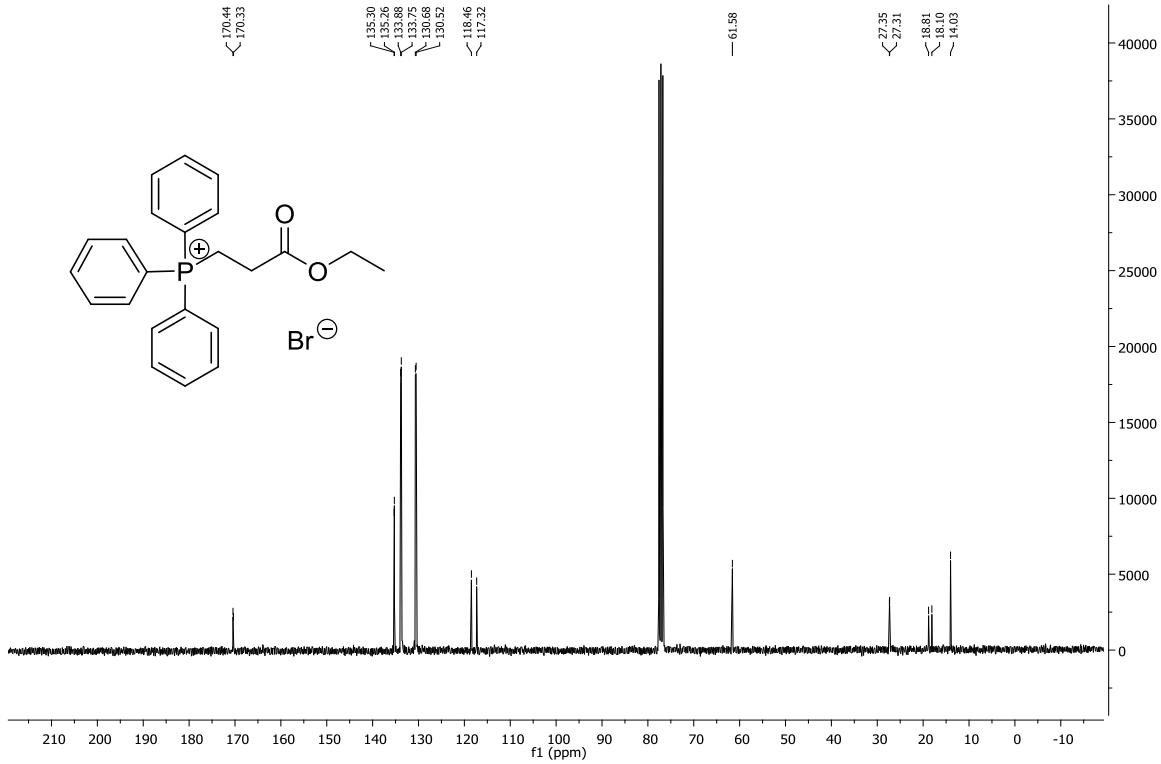

Figure 136. [13]C-NMR of (3-ethoxy-3-oxopropyl)triphenylphosphonium bromide (**92**).

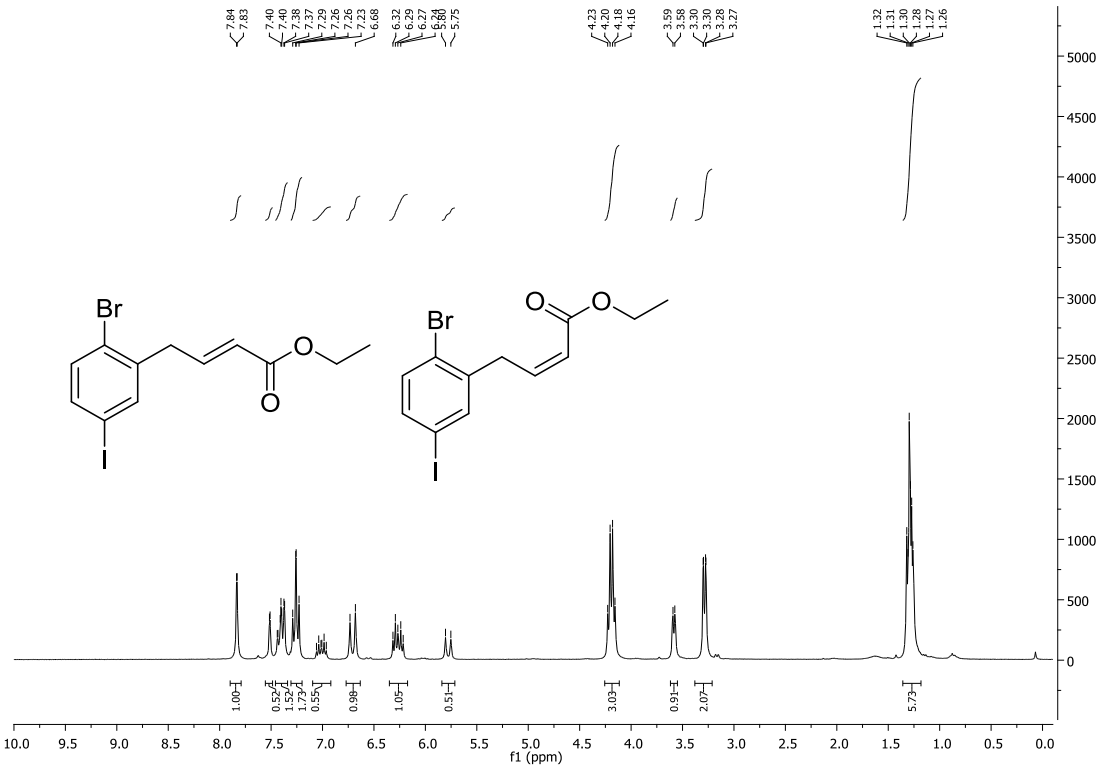

Figure 137. ^{1}H-NMR of (*E*/*Z*)-Ethyl 4-(2-bromo-5-iodophenyl)butanoate (**95**).

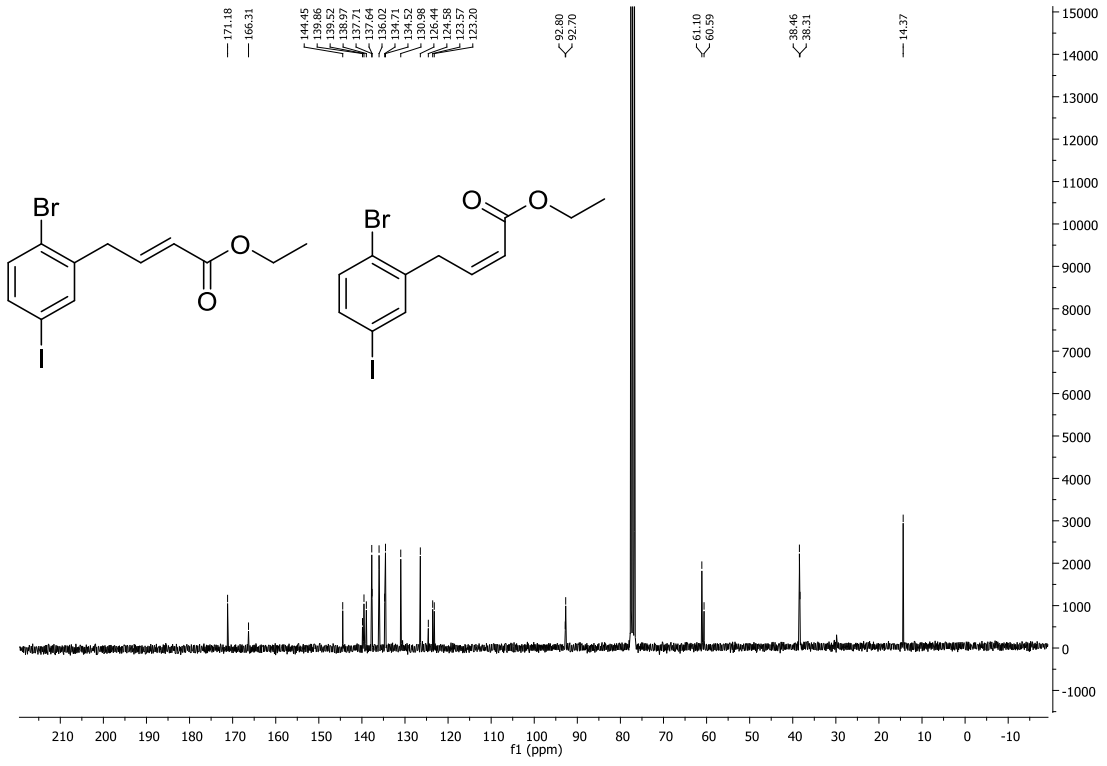

Figure 138. ^{13}C-NMR of (*E*/*Z*)-Ethyl 4-(2-bromo-5-iodophenyl)butanoate (**95**).

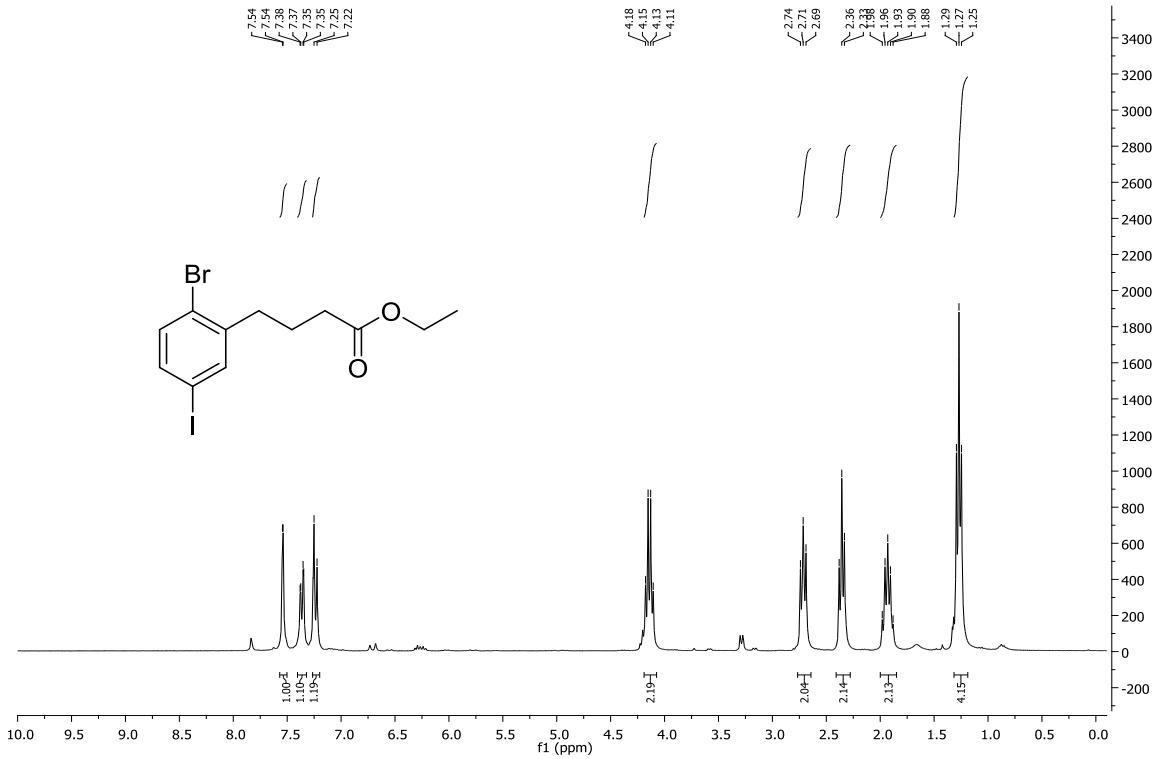

Figure 139. ^{1}H-NMR of ethyl 4-(2-bromo-5-iodophenyl)butanoate (**94**).

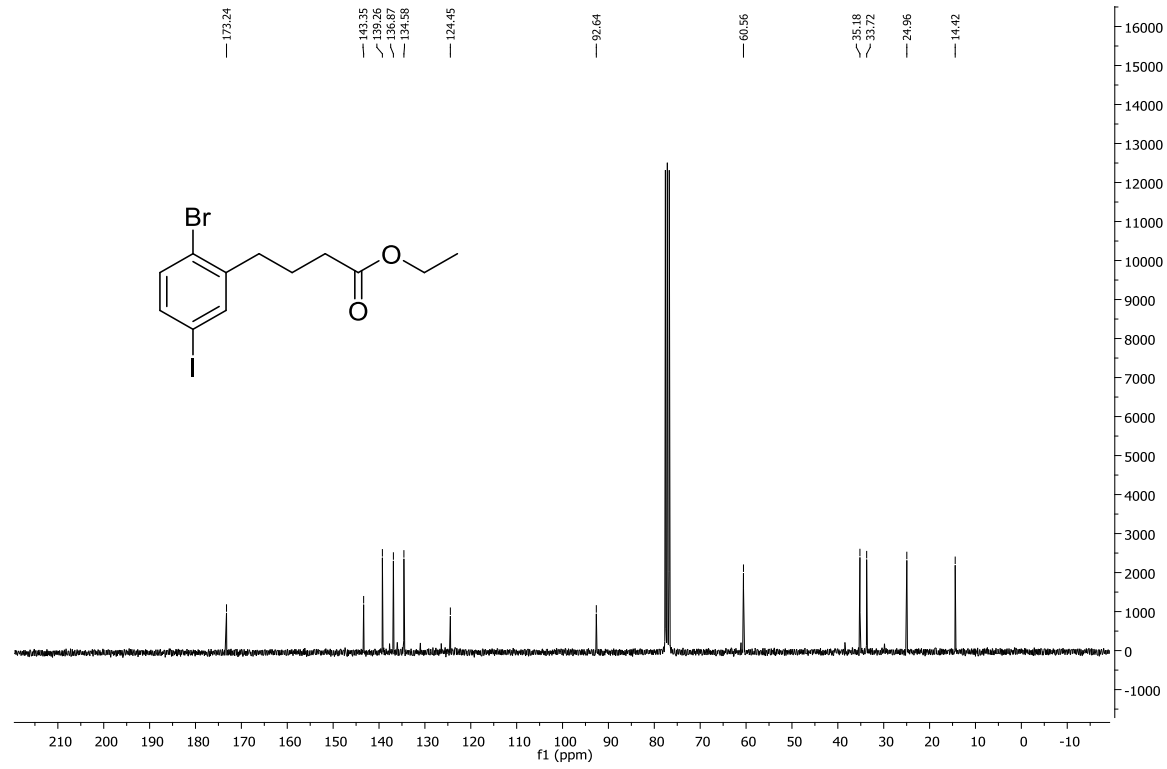

Figure 140. ^{13}C-NMR of ethyl 4-(2-bromo-5-iodophenyl)butanoate (**94**).

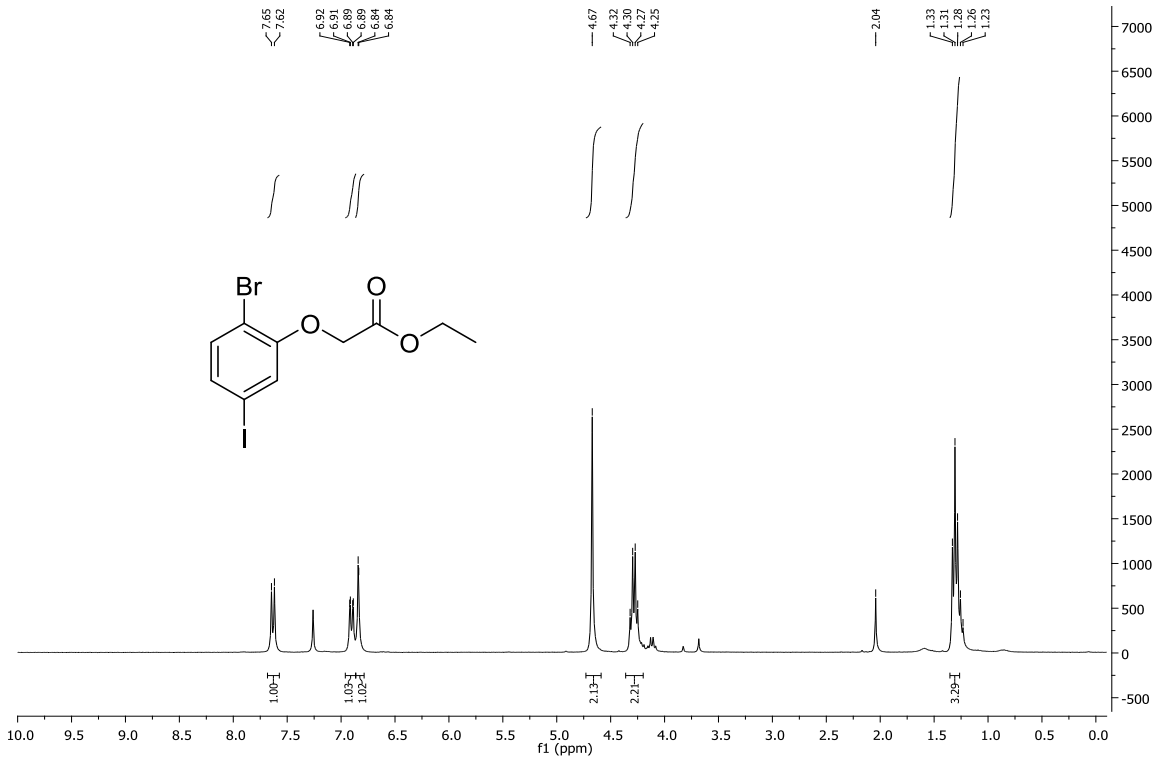

Figure 141. ^{1}H-NMR of ethyl 2-(2-bromo-5-iodophenoxy)acetate (**98**).

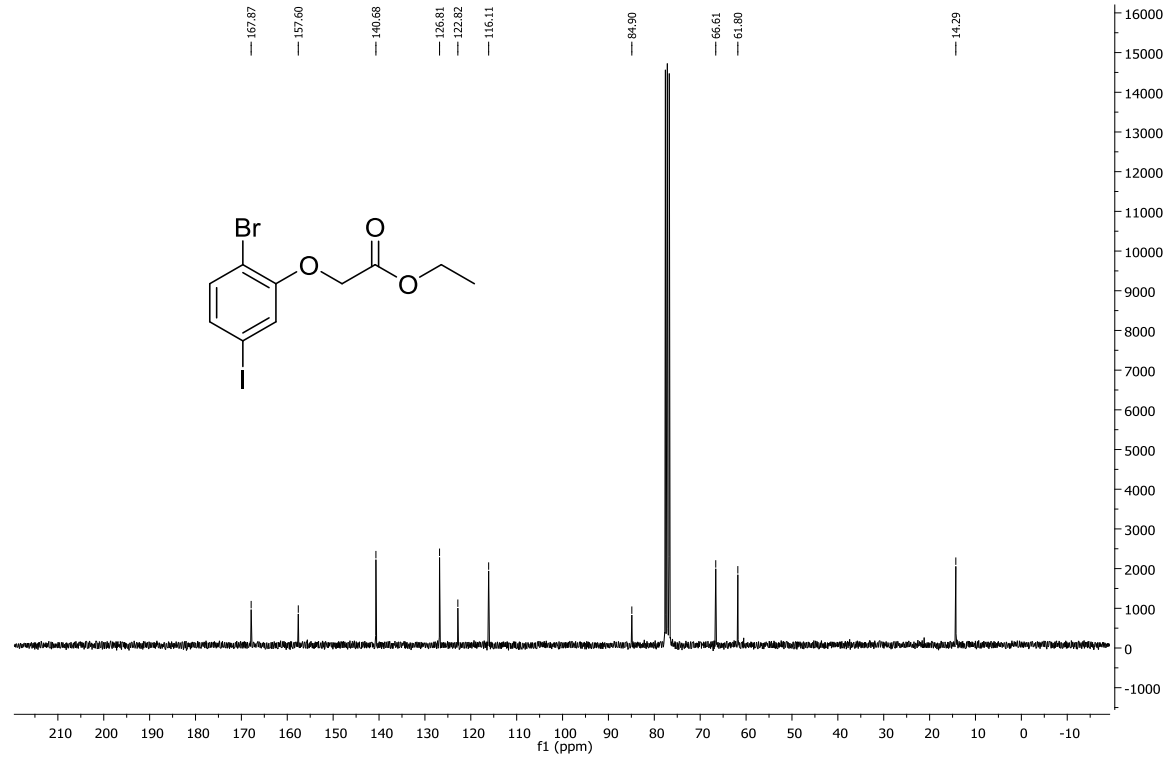

Figure 142. ^{13}C-NMR of ethyl 2-(2-bromo-5-iodophenoxy)acetate (**98**).

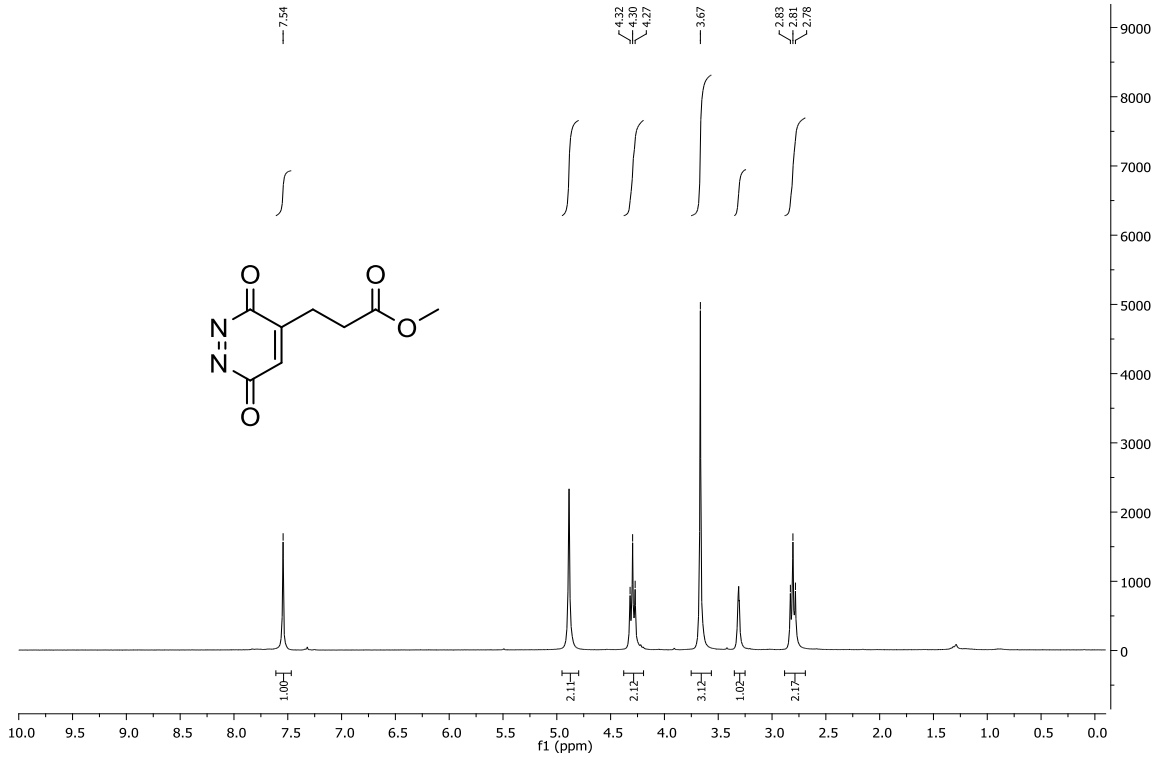

Figure 143. ^{1}H-NMR of methyl 3-(3,6-dioxo-3,6-dihydropyridazin-4-yl)propanoate (**105**).

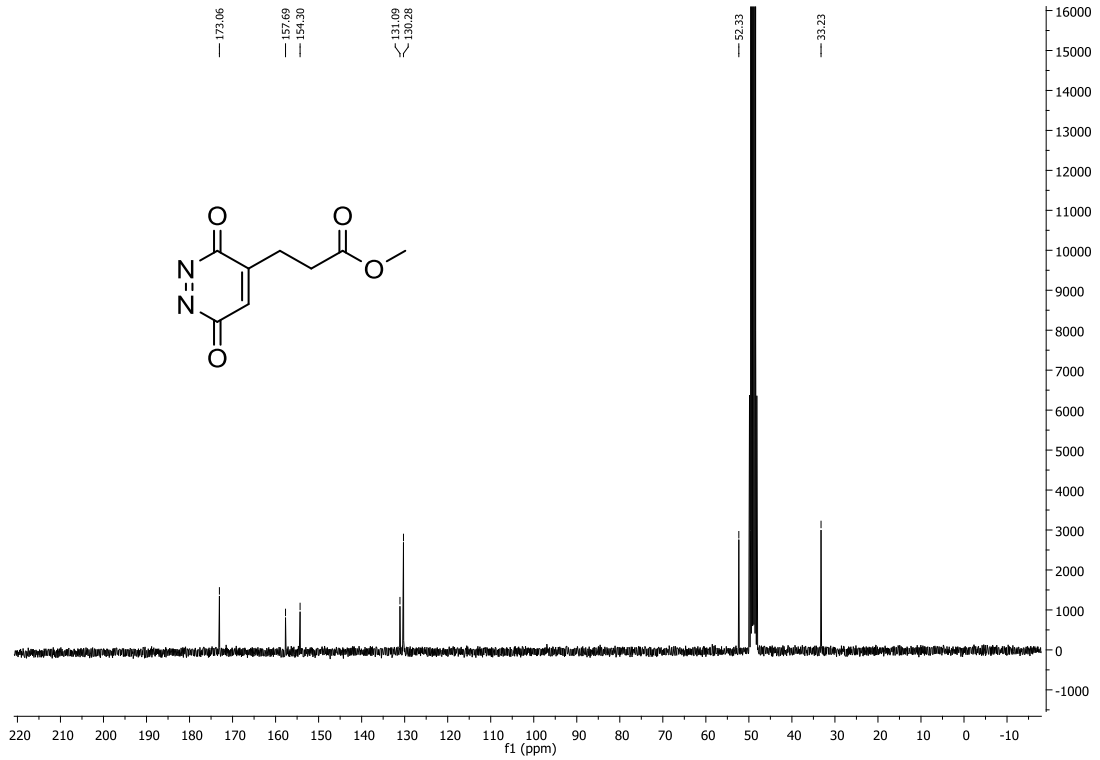

Figure 144. ^{13}C-NMR of methyl 3-(3,6-dioxo-3,6-dihydropyridazin-4-yl)propanoate (**105**).

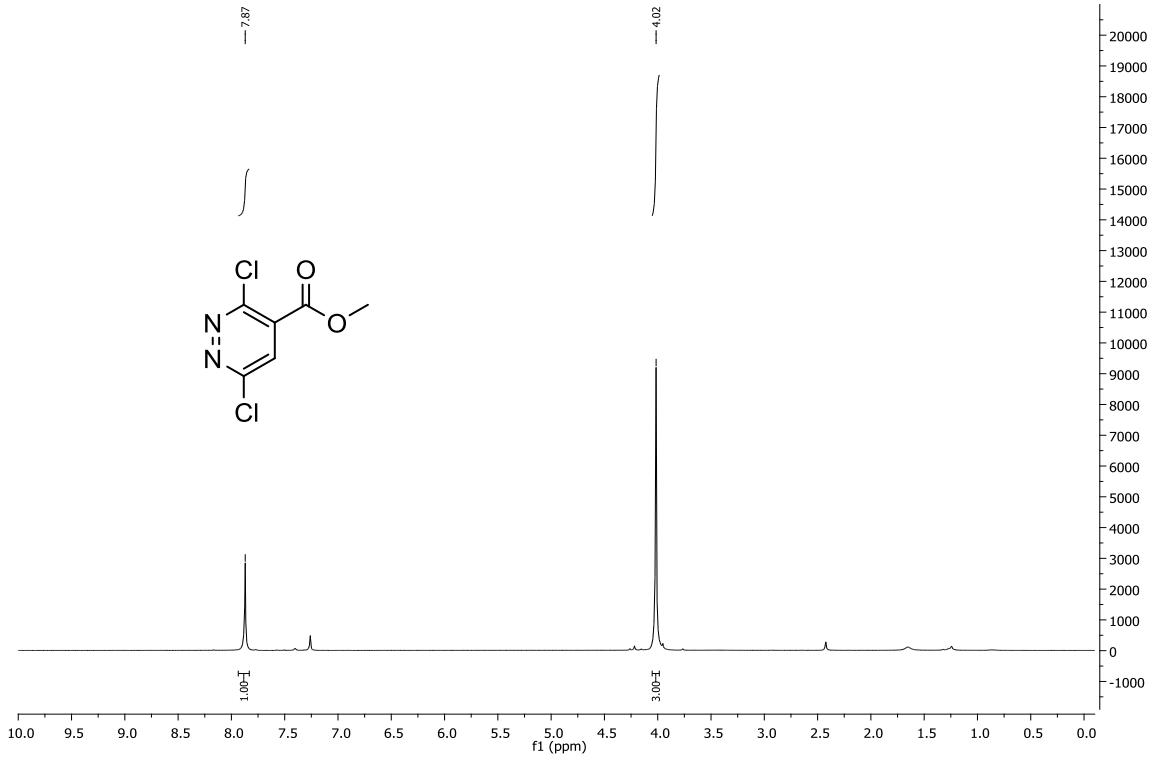

Figure 145. [1]H-NMR of methyl 3,6-dichloropyridazine-4-carboxylate (**108**).

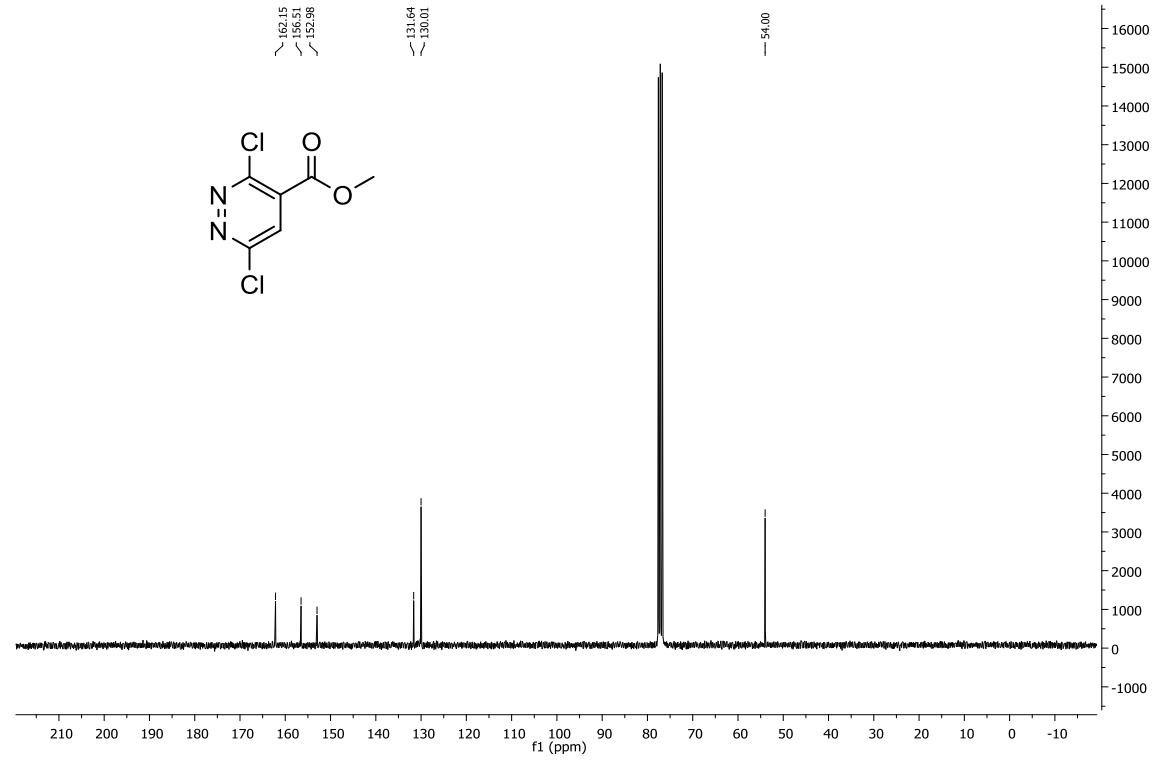

Figure 146. [13]C-NMR of methyl 3,6-dichloropyridazine-4-carboxylate (**108**).

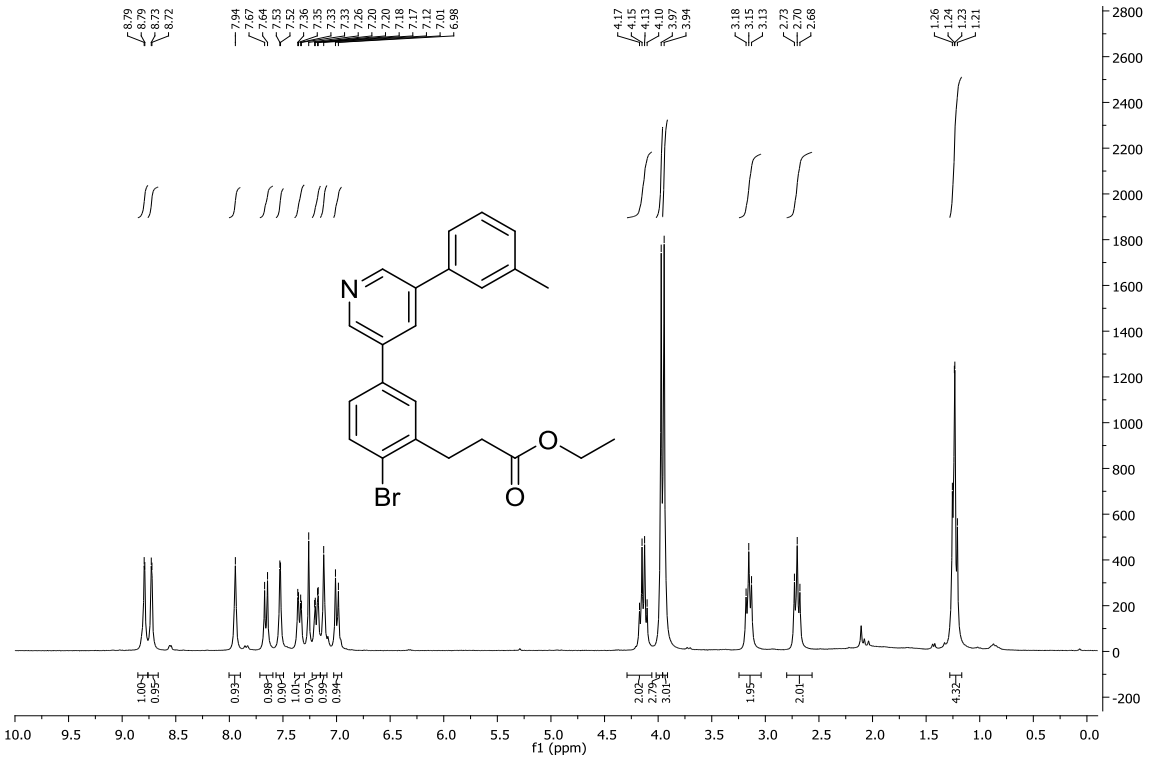

Figure 147. [1]H-NMR of ethyl 3-(2-bromo-5-(5-(m-tolyl)pyridin-3-yl)phenyl)propanoate (**110**).

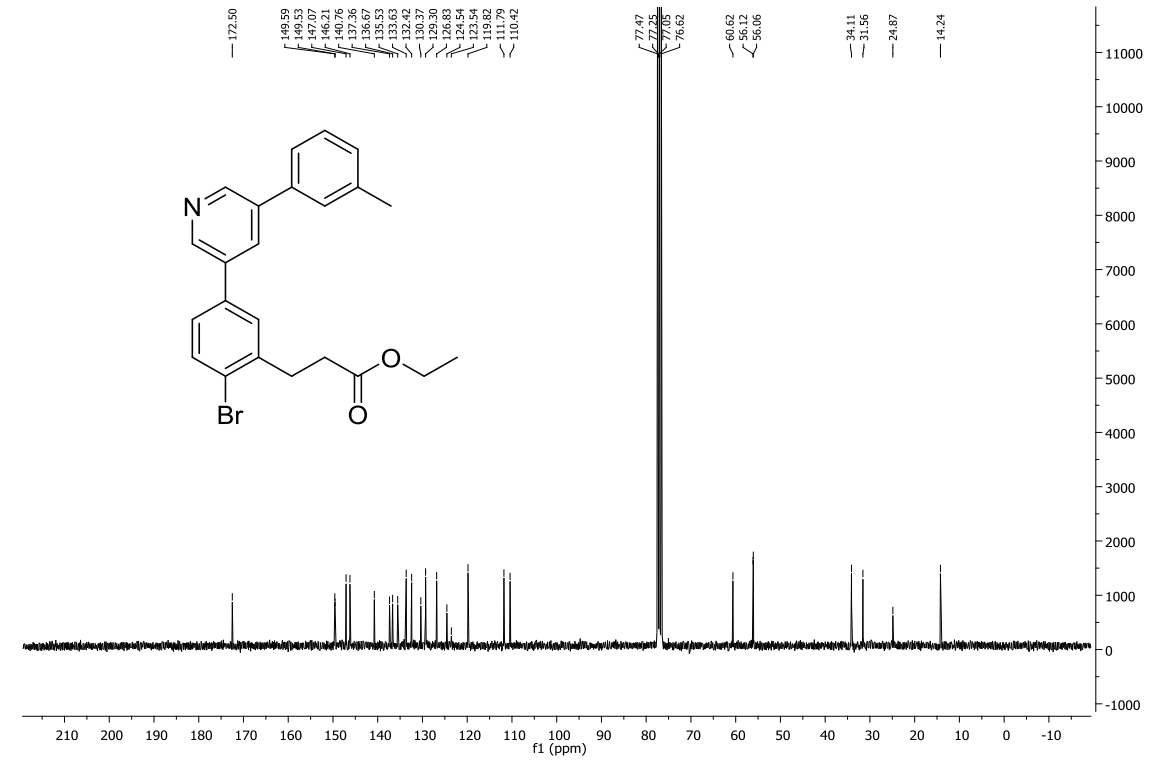

Figure 148. [13]C-NMR of ethyl 3-(2-bromo-5-(5-(m-tolyl)pyridin-3-yl)phenyl)propanoate (**110**).

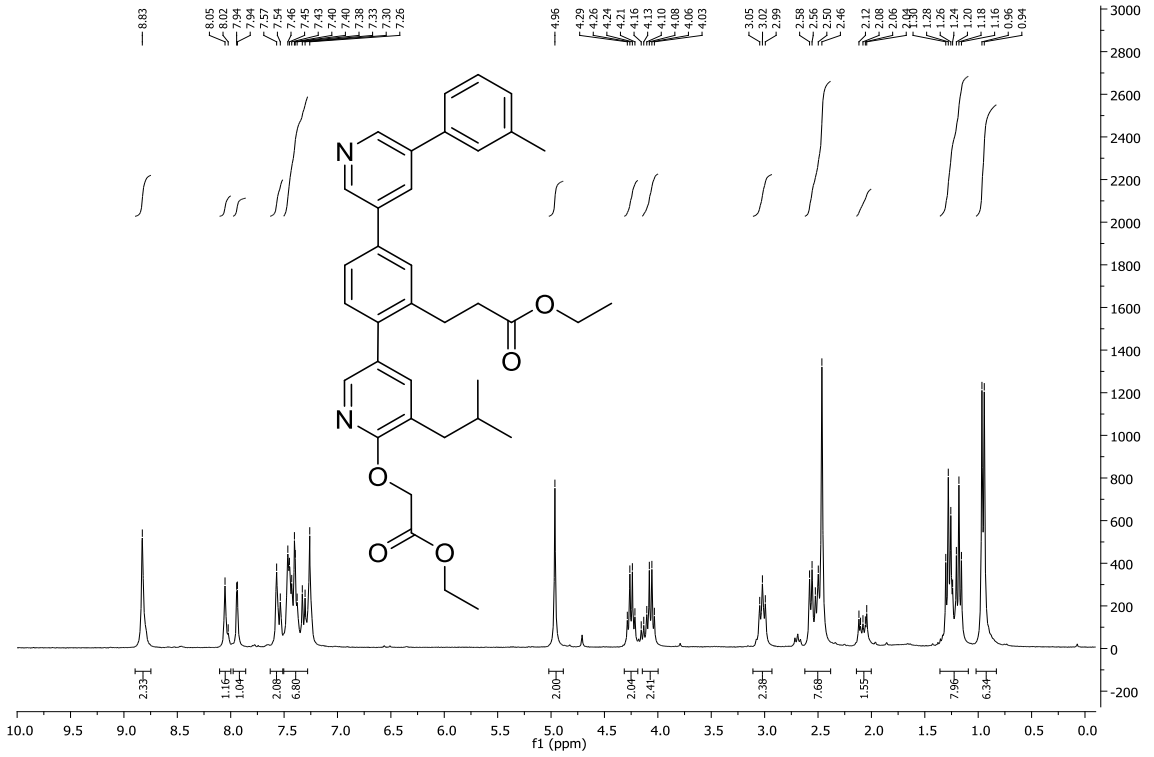

Figure 149. [1]H-NMR of ethyl 3-(2-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-5-(5-(m-tolyl)-pyridin-3-yl)phenyl)propanoate (**115**).

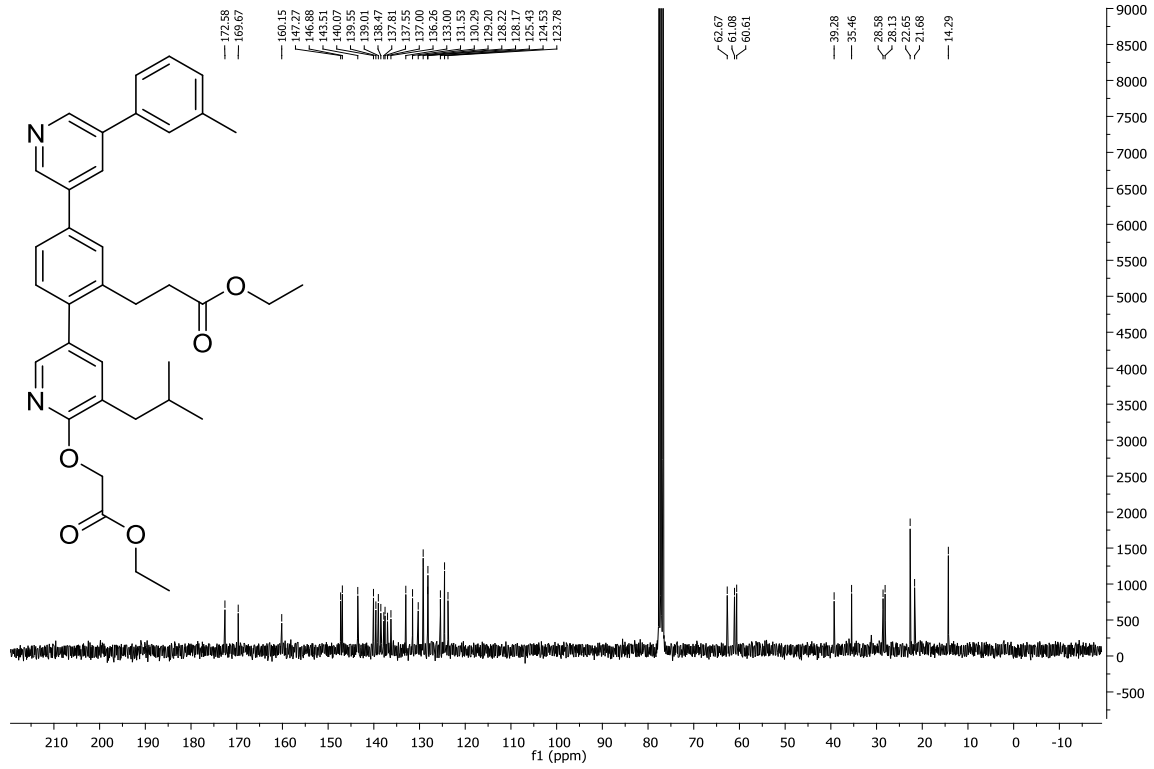

Figure 150. [13]C-NMR of ethyl 3-(2-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-5-(5-(m-tolyl)-pyridin-3-yl)phenyl)propanoate (**115**).

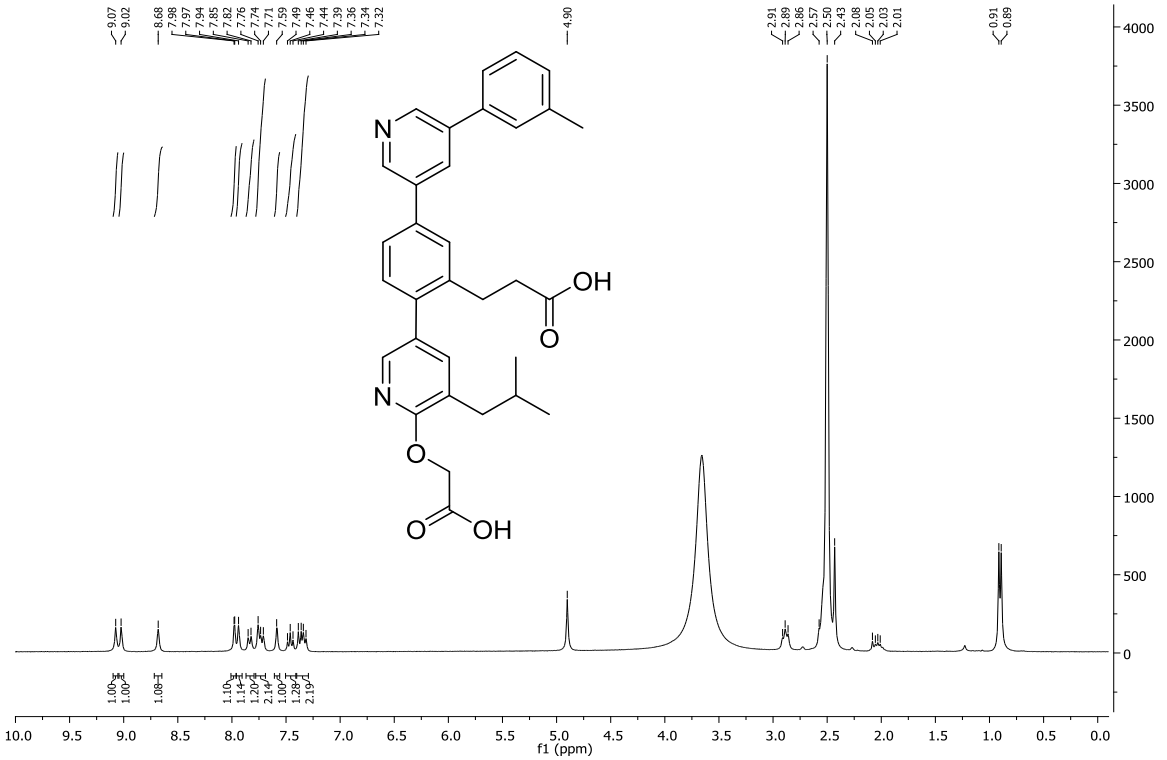

Figure 151. [1]H-NMR of ethyl 3-(2-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-5-(5-(m-tolyl) pyridin-3-yl)phenyl)propanoate (**118**).

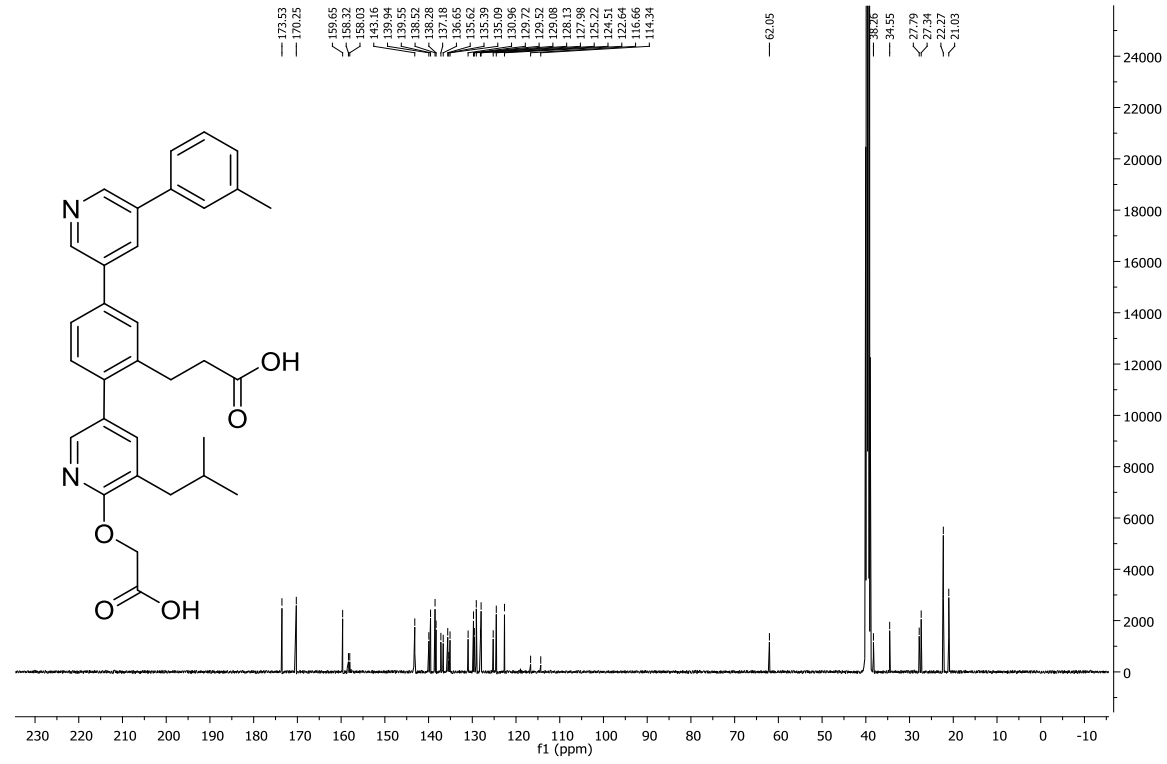

Figure 152. [13]C-NMR of ethyl 3-(2-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-5-(5-(m-tolyl) pyridin-3-yl)phenyl)propanoate (**118**).

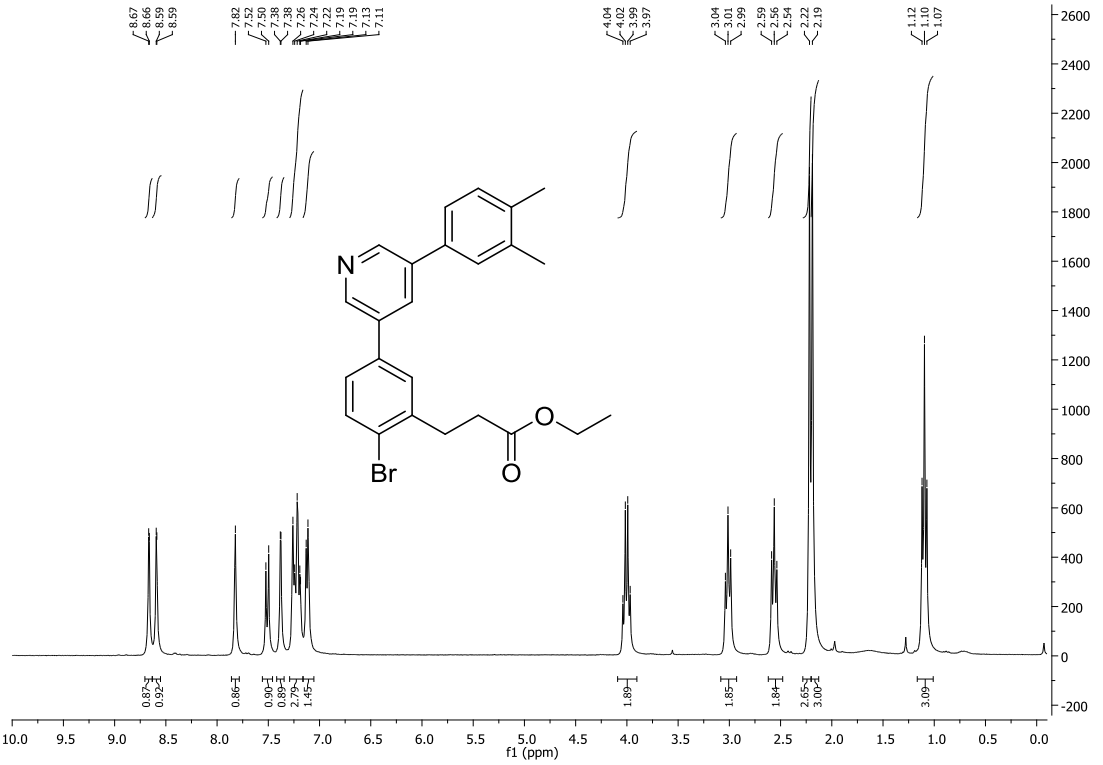

Figure 153. [1]H-NMR of ethyl 3-(2-bromo-5-(5-(3,4-dimethylphenyl)pyridin-3-yl)phenyl)propanoate (**111**).

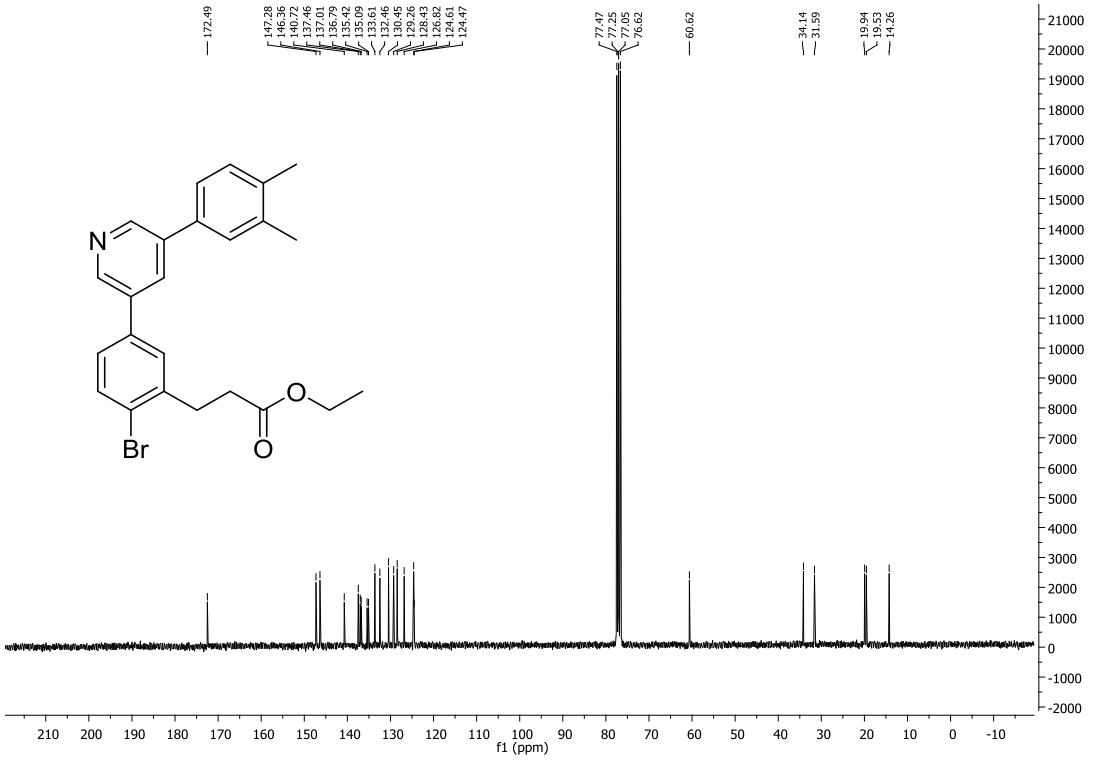

Figure 154. [13]C-NMR of ethyl 3-(2-bromo-5-(5-(3,4-dimethylphenyl)pyridin-3-yl)phenyl)propanoate (**111**).

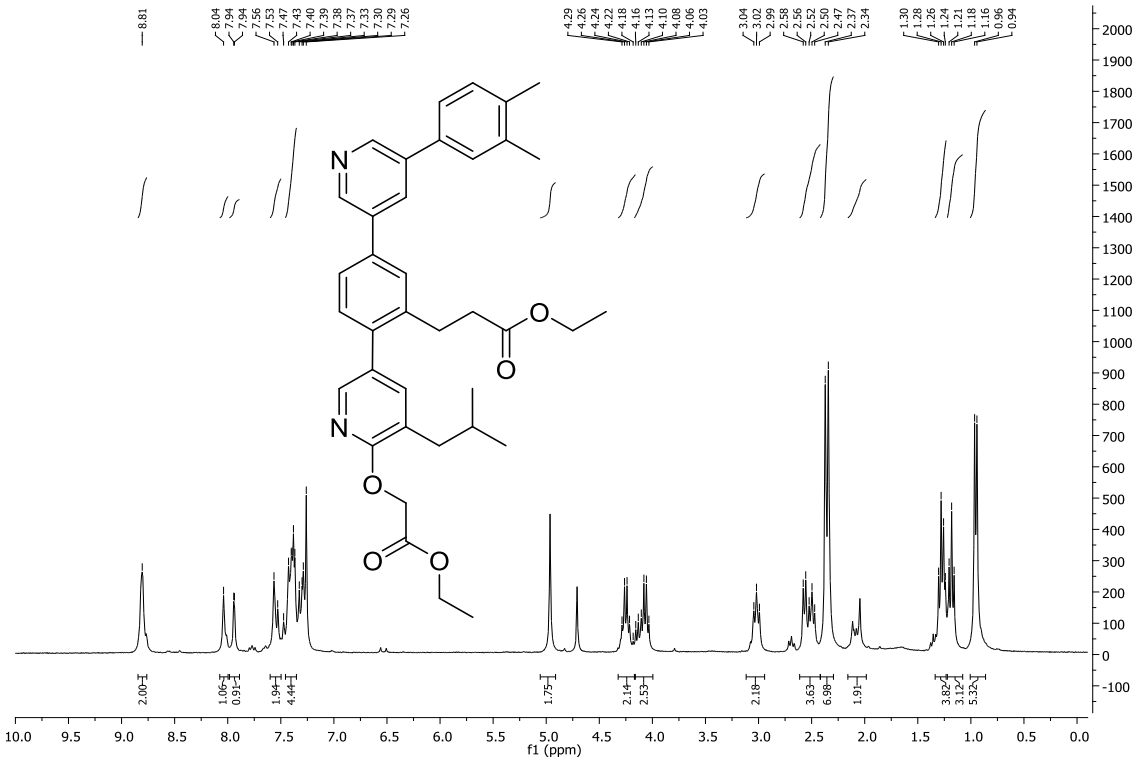

Figure 155. [1]H-NMR of ethyl 3-(4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-3",4"-dimethyl-[1,1':3',1"-terphenyl]-3-yl)propanoate (**116**).

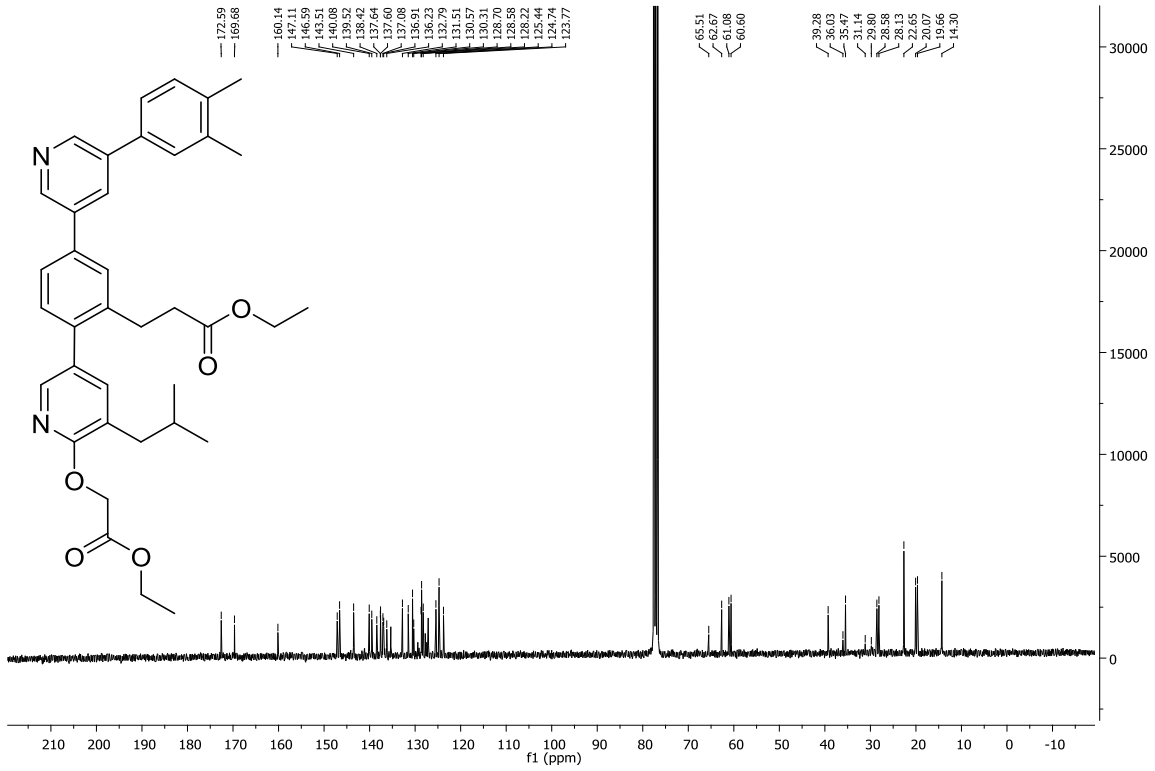

Figure 156. [13]C-NMR of ethyl 3-(4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-3",4"-dimethyl-[1,1':3',1"-terphenyl]-3-yl)propanoate (**116**).

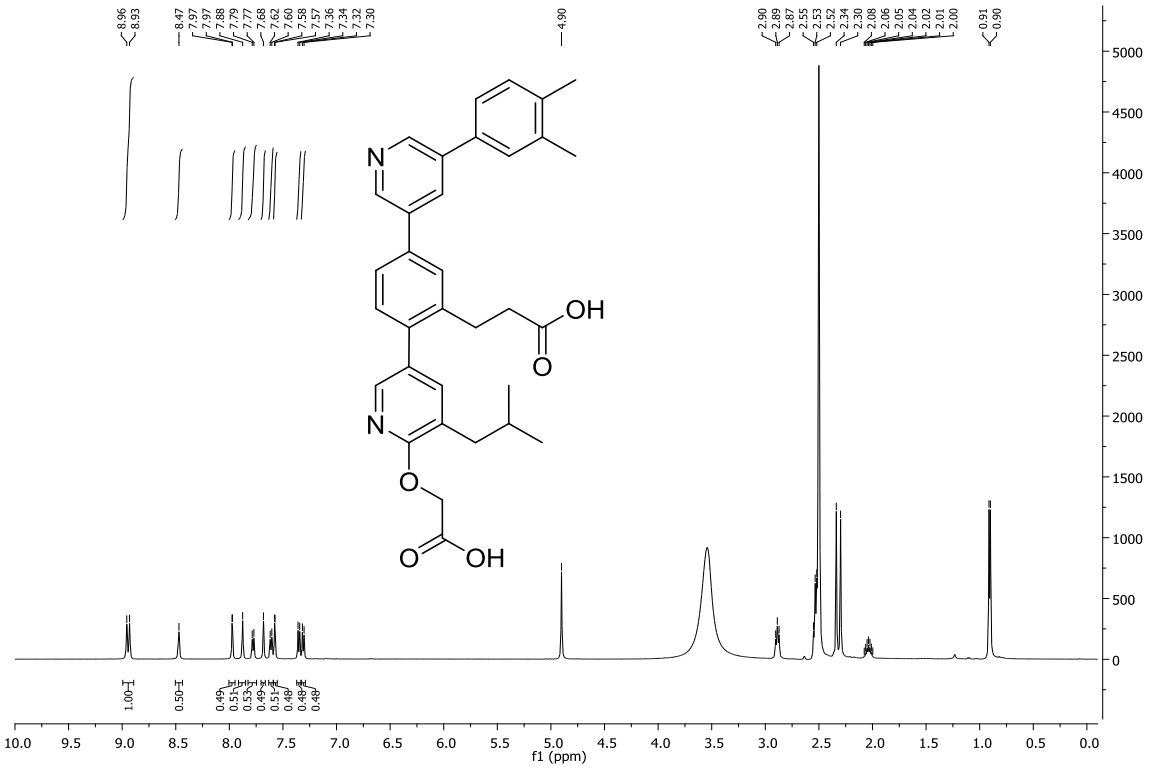

Figure 157. ^{1}H-NMR of ethyl 3-(4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-3",4"-dimethyl-[1,1':3',1"-terphenyl]-3-yl)propanoate (**120**).

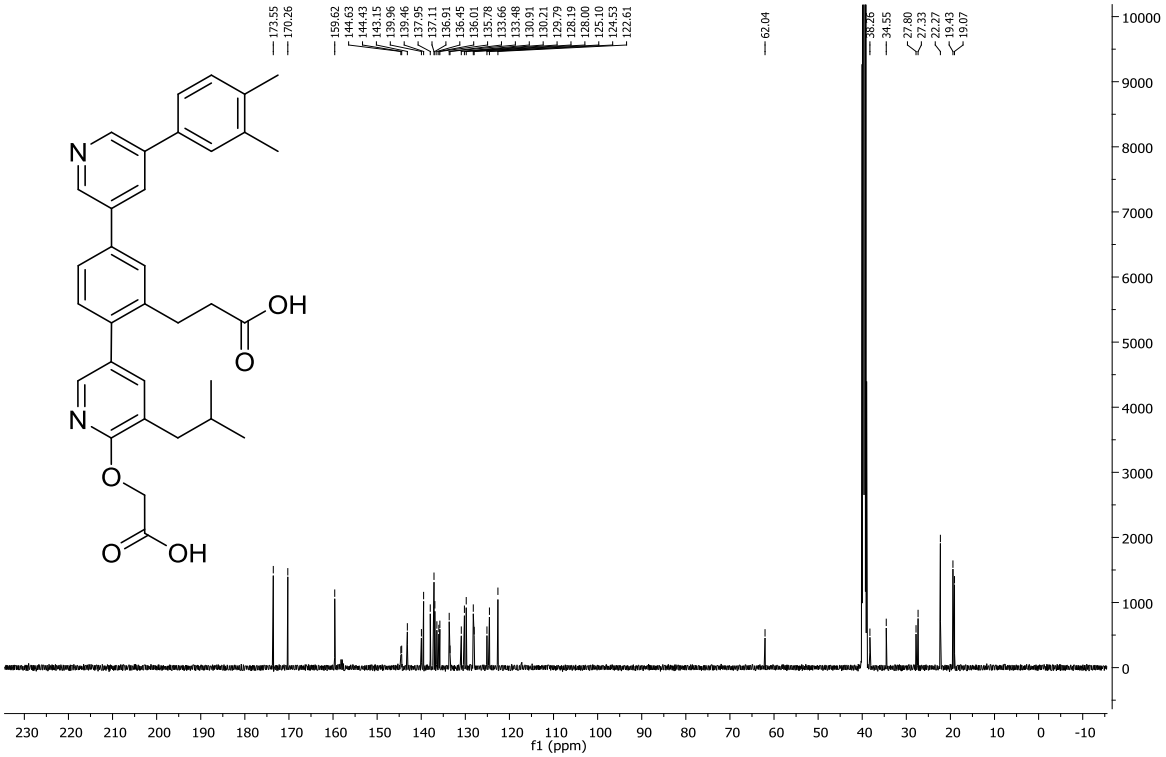

Figure 158. ^{13}C-NMR of ethyl 3-(4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-3",4"-dimethyl-[1,1':3',1"-terphenyl]-3-yl)propanoate (**120**).

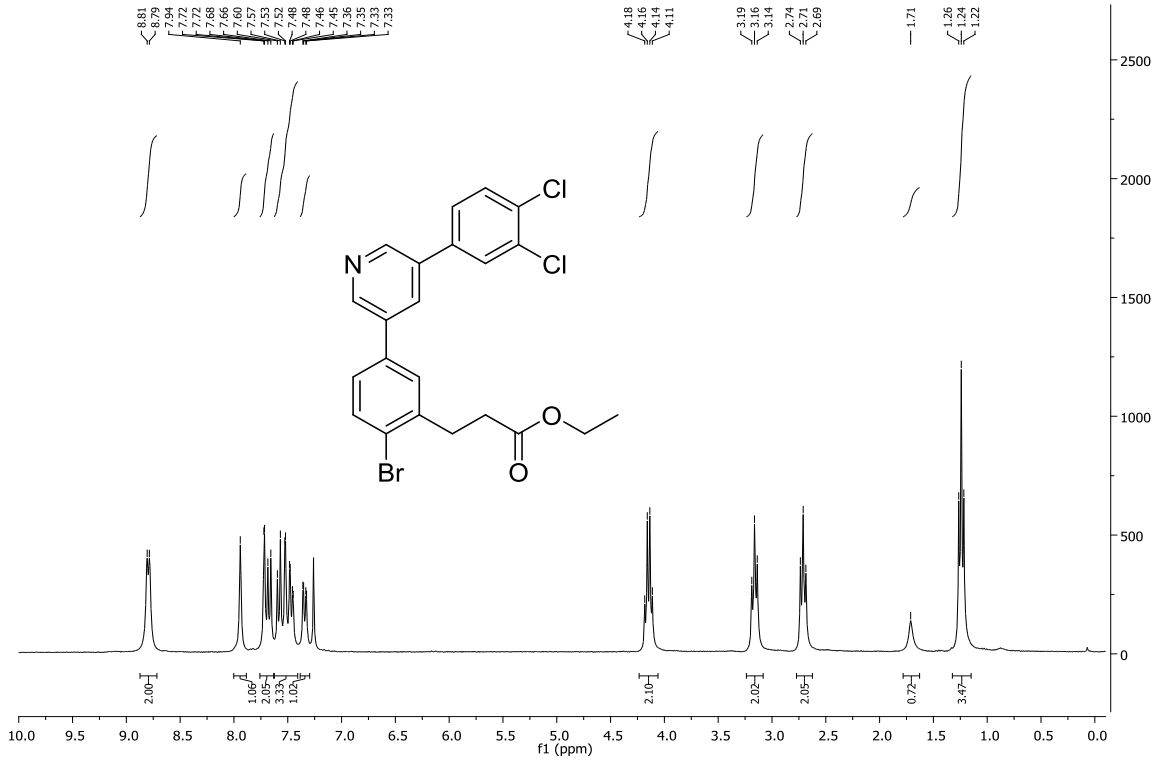

Figure 159. [1]H-NMR of ethyl 3-(2-bromo-5-(5-(3,4-dichlorophenyl)pyridin-3-yl)phenyl)propanoate (**112**).

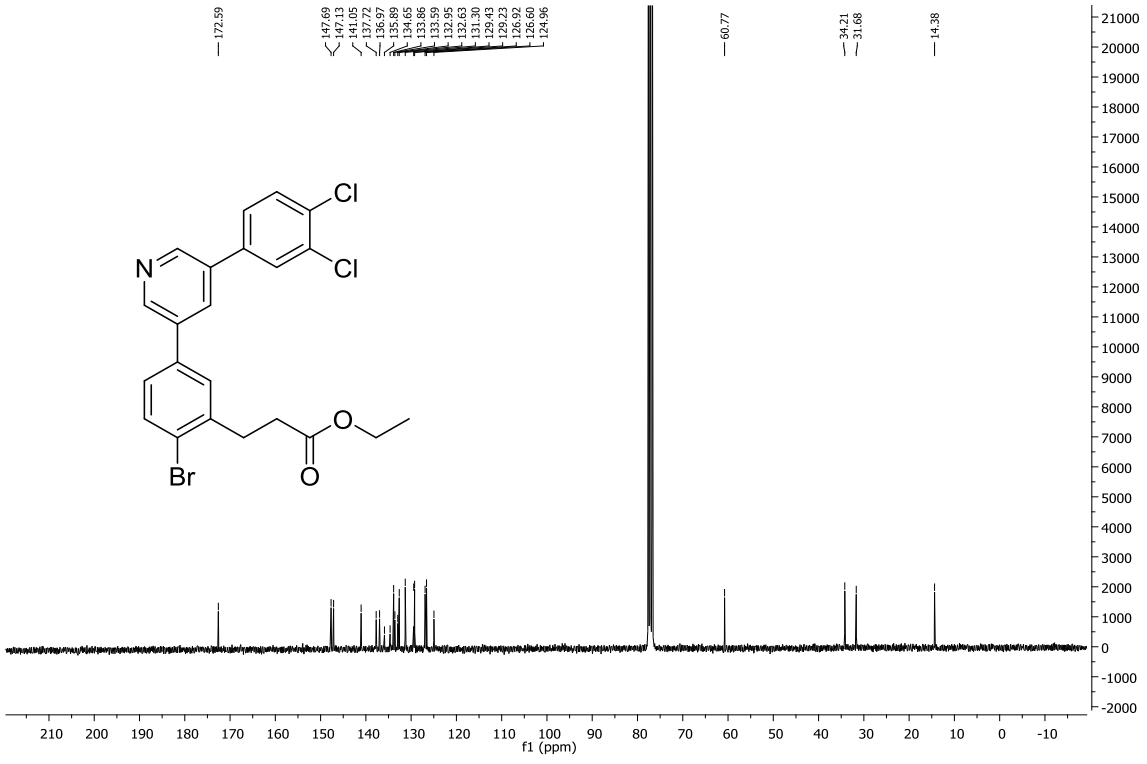

Figure 160. [13]C-NMR of ethyl 3-(2-bromo-5-(5-(3,4-dichlorophenyl)pyridin-3-yl)phenyl)propanoate (**112**).

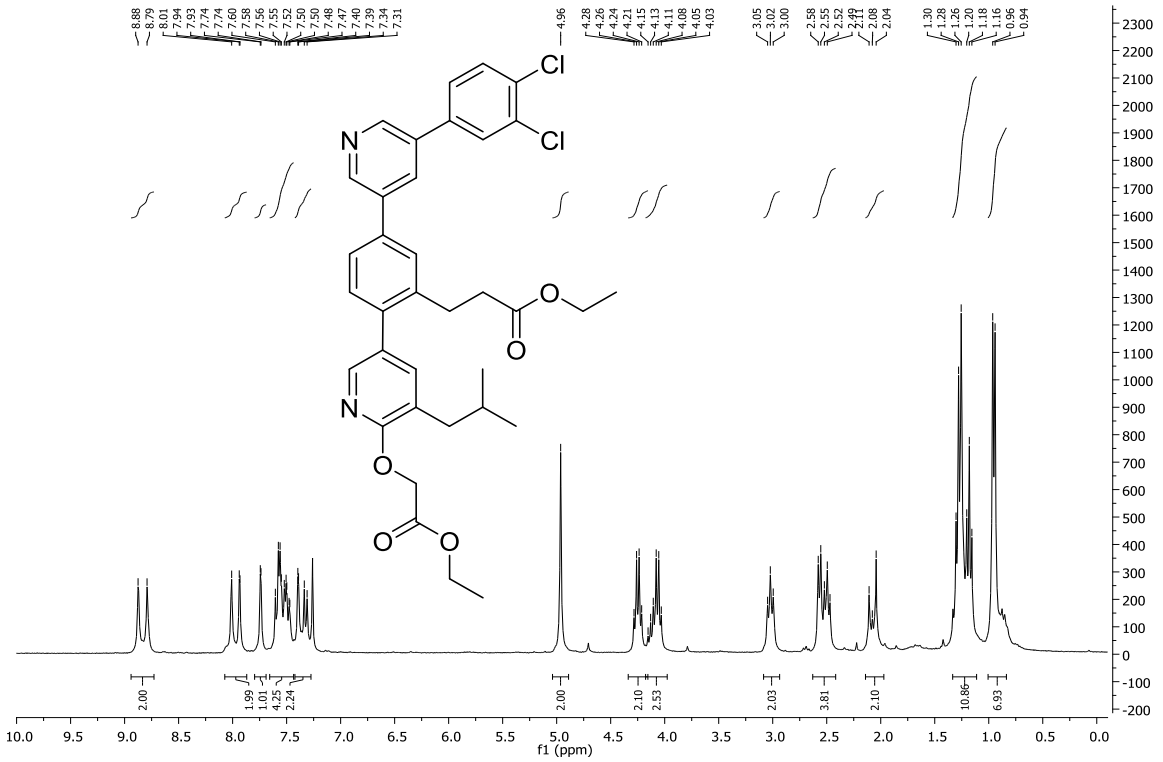

Figure 161. [1]H-NMR of ethyl 3-(3",4"-dichloro-4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-[1,1':3',1"-terphenyl]-3-yl)propanoate (**117**).

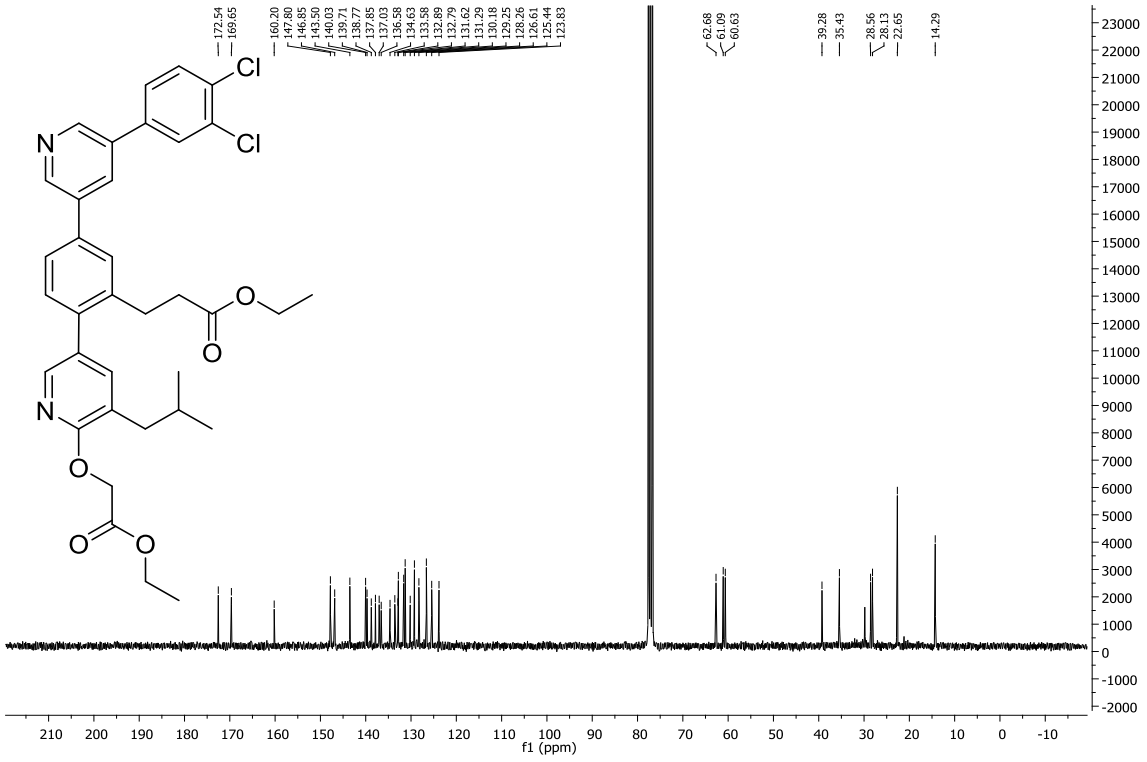

Figure 162. [13]C-NMR of thyl 3-(3",4"-dichloro-4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-[1,1':3',1"-terphenyl]-3-yl)propanoate (**117**).

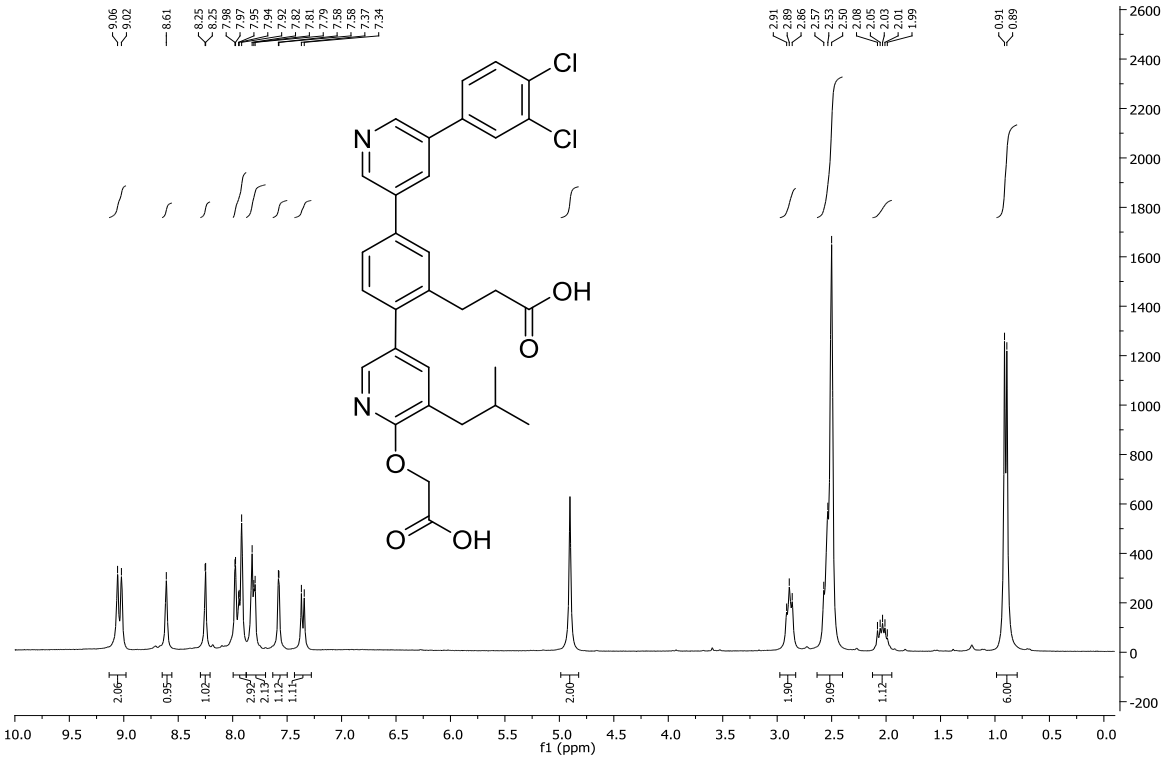

Figure 163. [1]H-NMR of ethyl 3-(3",4"-dichloro-4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-[1,1':3',1"-terphenyl]-3-yl)propanoate (**121**).

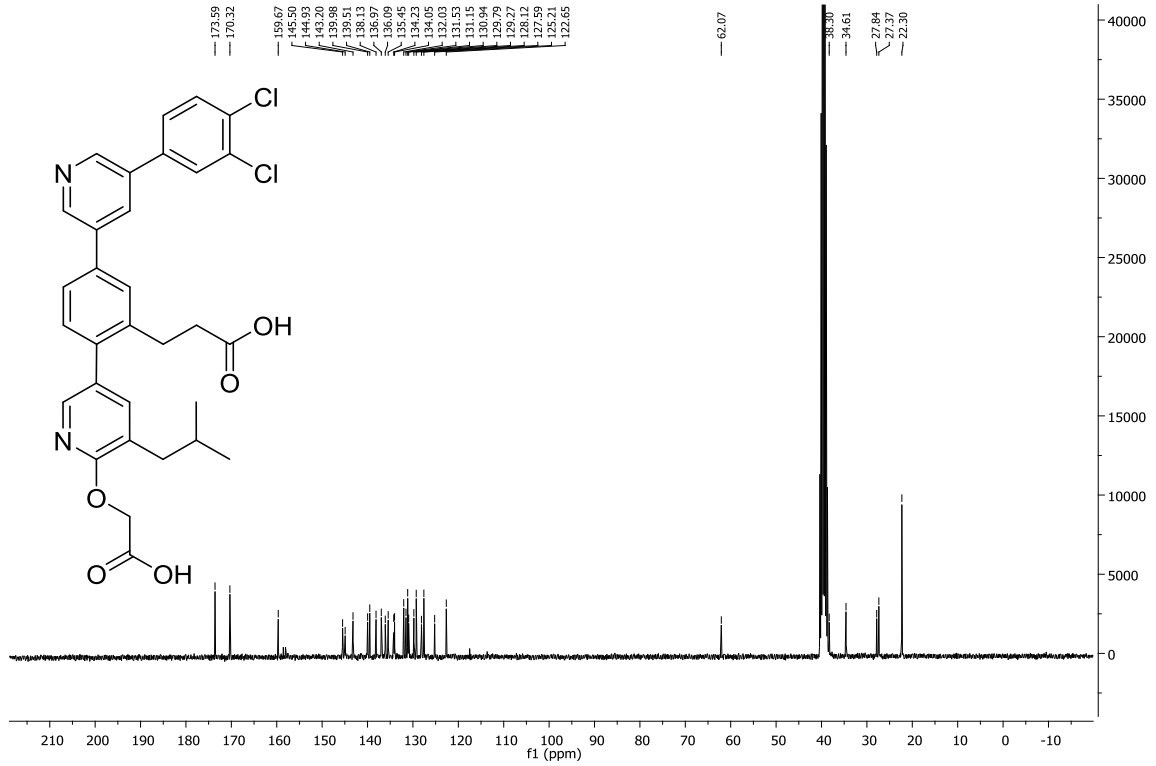

Figure 164. [13]C-NMR of ethyl 3-(3",4"-dichloro-4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-[1,1':3',1"-terphenyl]-3-yl)propanoate (**121**).

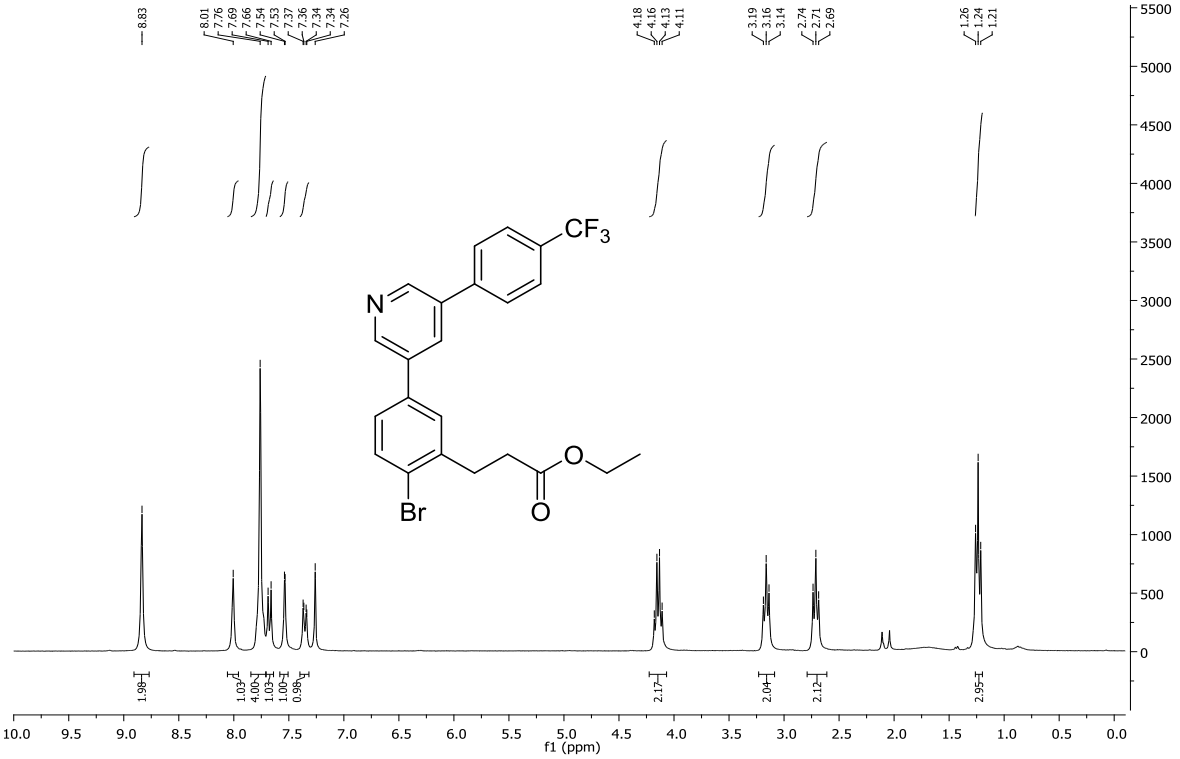

Figure 165. [1]H-NMR of ethyl 3-(2-bromo-5-(5-(4-(trifluoromethyl)phenyl)pyridin-3-yl)phenyl) propanoate (**113**).

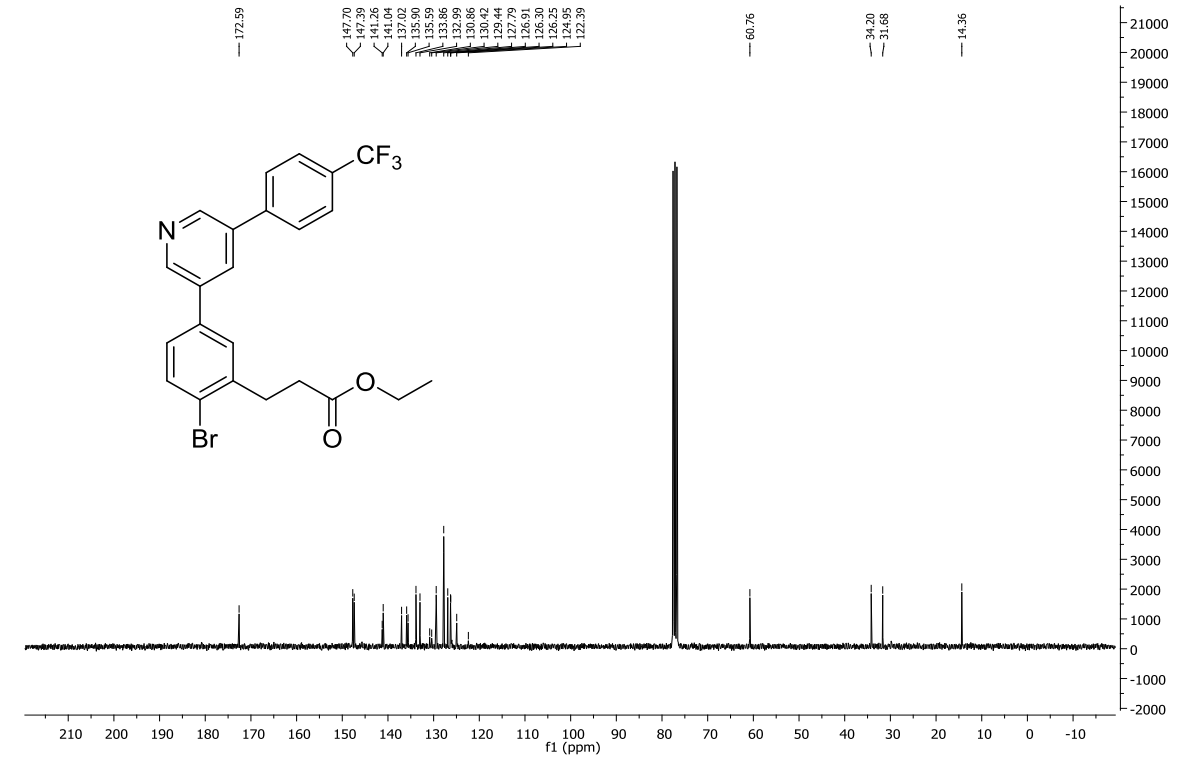

Figure 166. [13]C-NMR of ethyl 3-(2-bromo-5-(5-(4-(trifluoromethyl)phenyl)pyridin-3-yl)phenyl) propanoate (**113**).

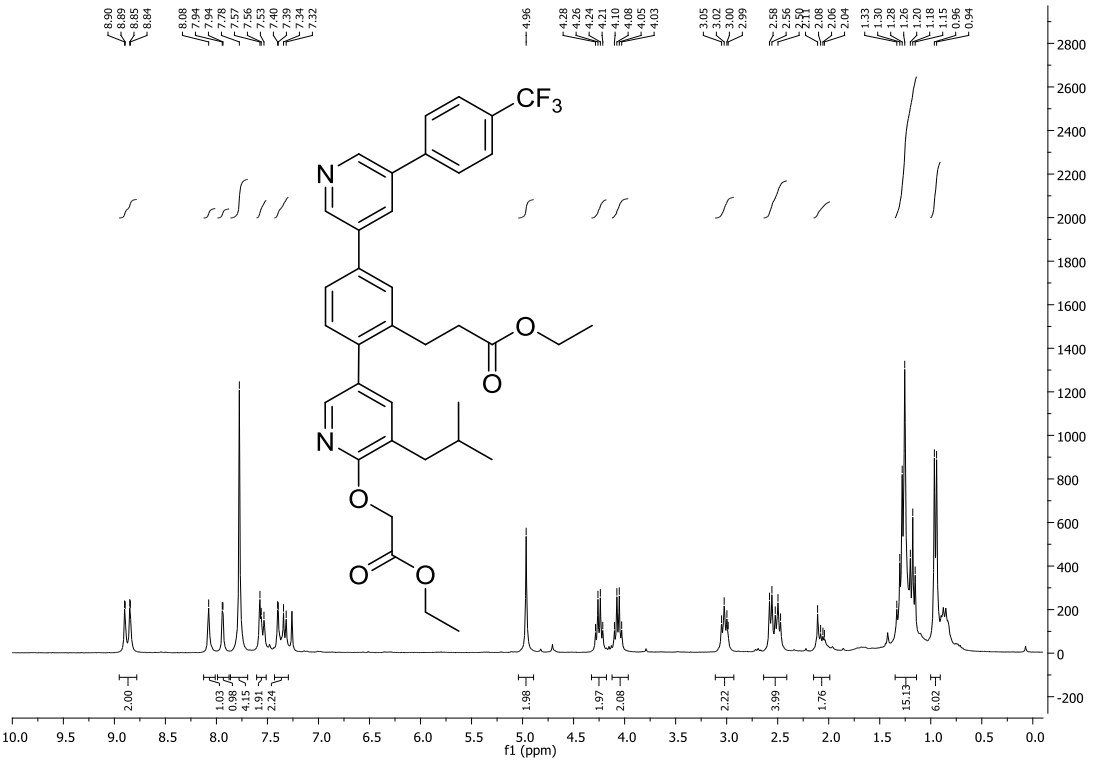

Figure 167. [1]H-NMR of ethyl 3-(4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-4"-(trifluoro methyl)-[1,1':3',1"-terphenyl]-3-yl)propanoate (**118**).

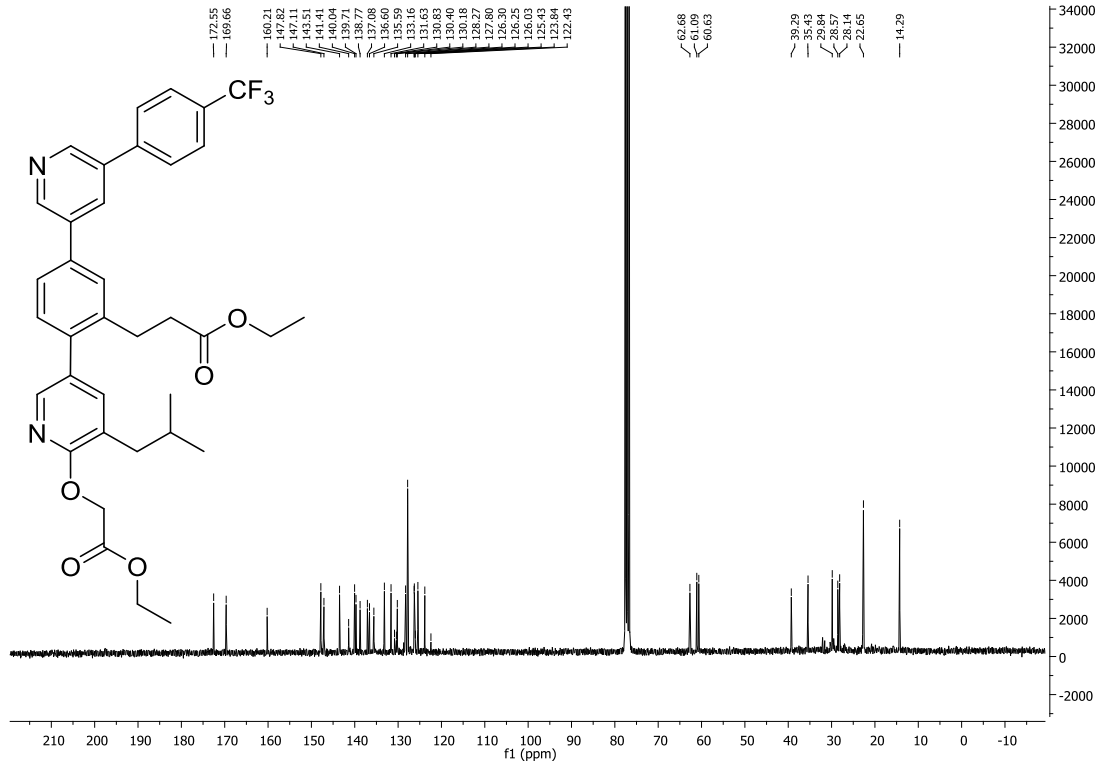

Figure 168. [13]C-NMR of ethyl 3-(4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-4"-(trifluoro methyl)-[1,1':3',1"-terphenyl]-3-yl)propanoate (**118**).

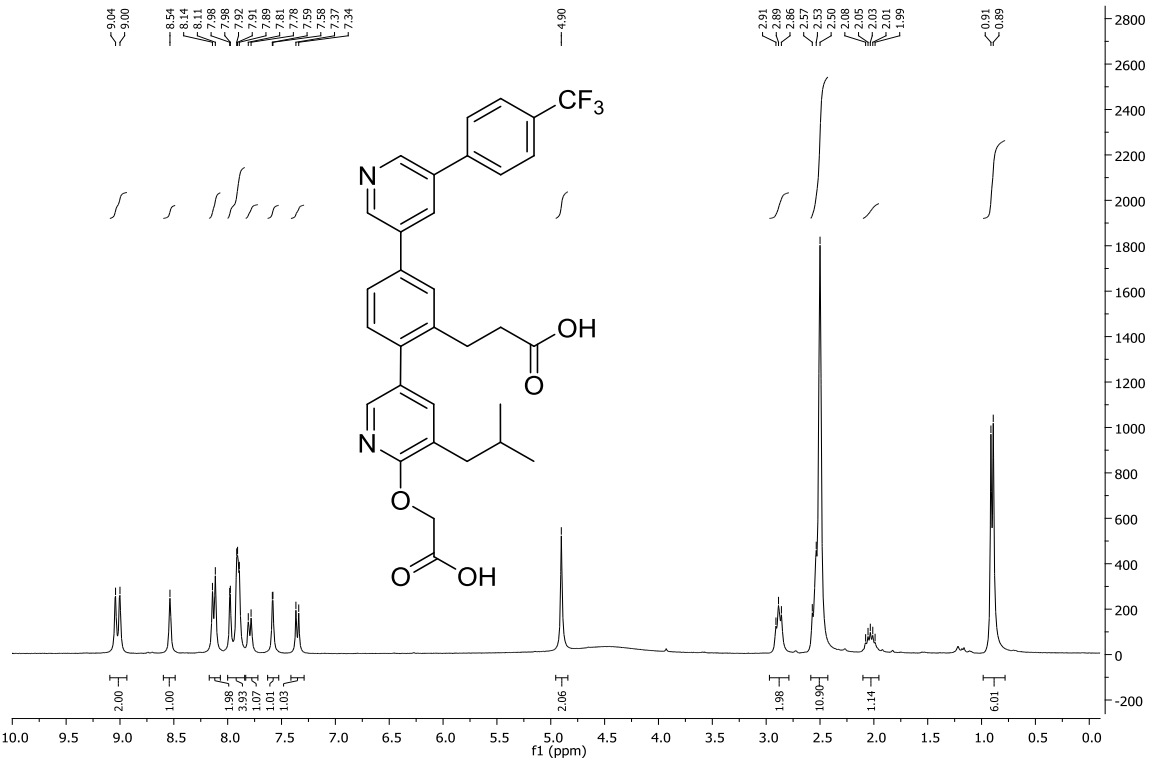

Figure 169. [1]H-NMR of ethyl 3-(4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-4"-(trifluoro methyl)-[1,1':3',1"-terphenyl]-3-yl)propanoate (**122**).

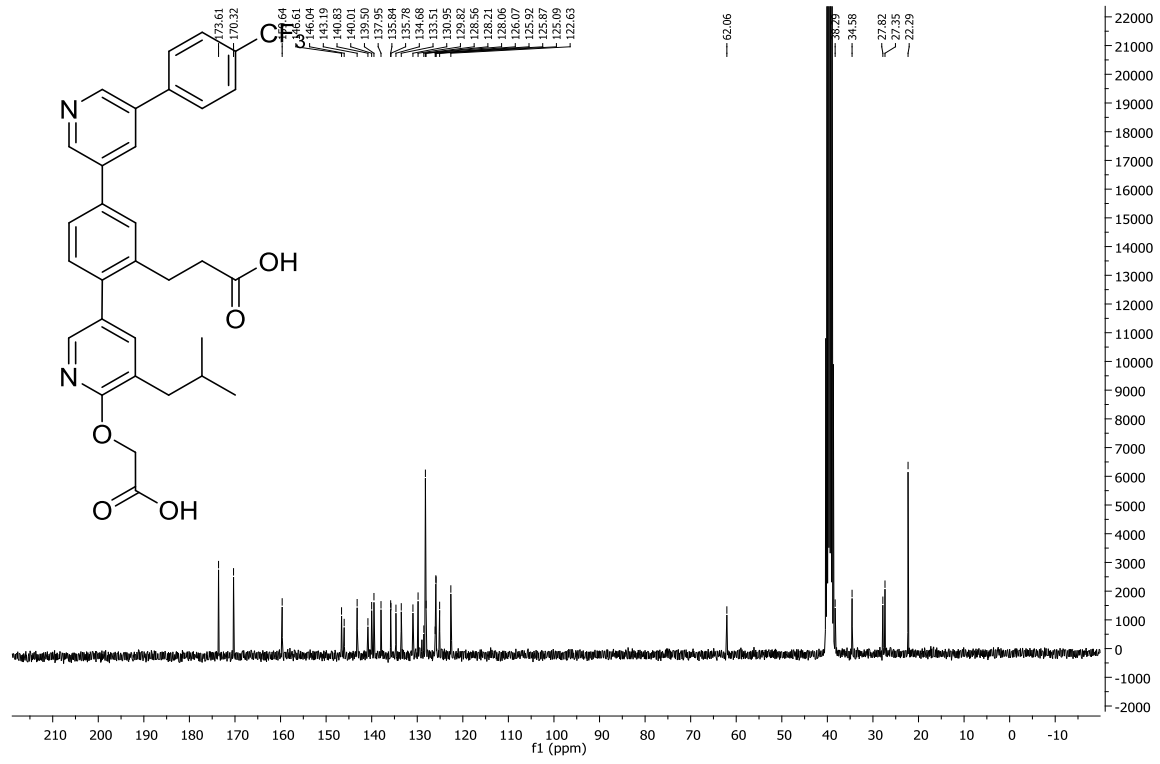

Figure 170. [13]C-NMR of ethyl 3-(4-(6-(2-ethoxy-2-oxoethoxy)-5-isobutylpyridin-3-yl)-4"-(trifluoro methyl)-[1,1':3',1"-terphenyl]-3-yl)propanoate (**122**).

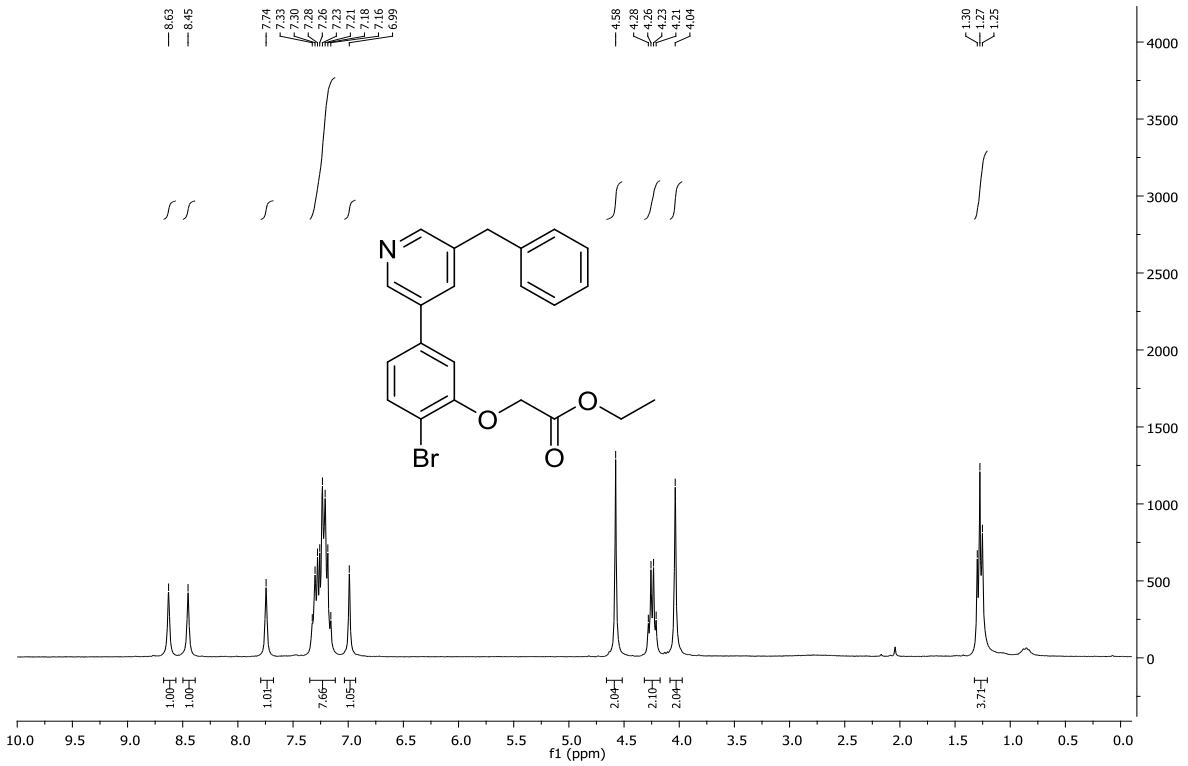

Figure 171. [1]H-NMR of ethyl 2-(5-(5-benzylpyridin-3-yl)-2-bromophenoxy)acetate (**124**).

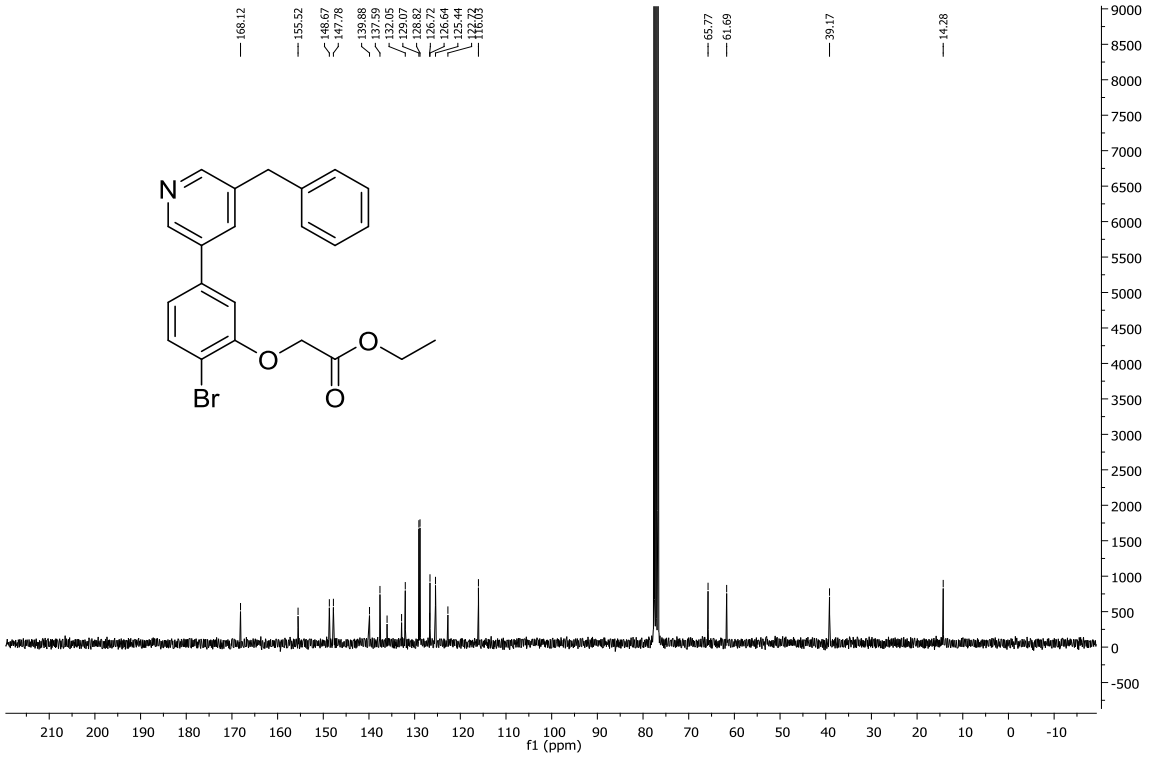

Figure 172. [13]C-NMR of ethyl 2-(5-(5-benzylpyridin-3-yl)-2-bromophenoxy)acetate (**124**).

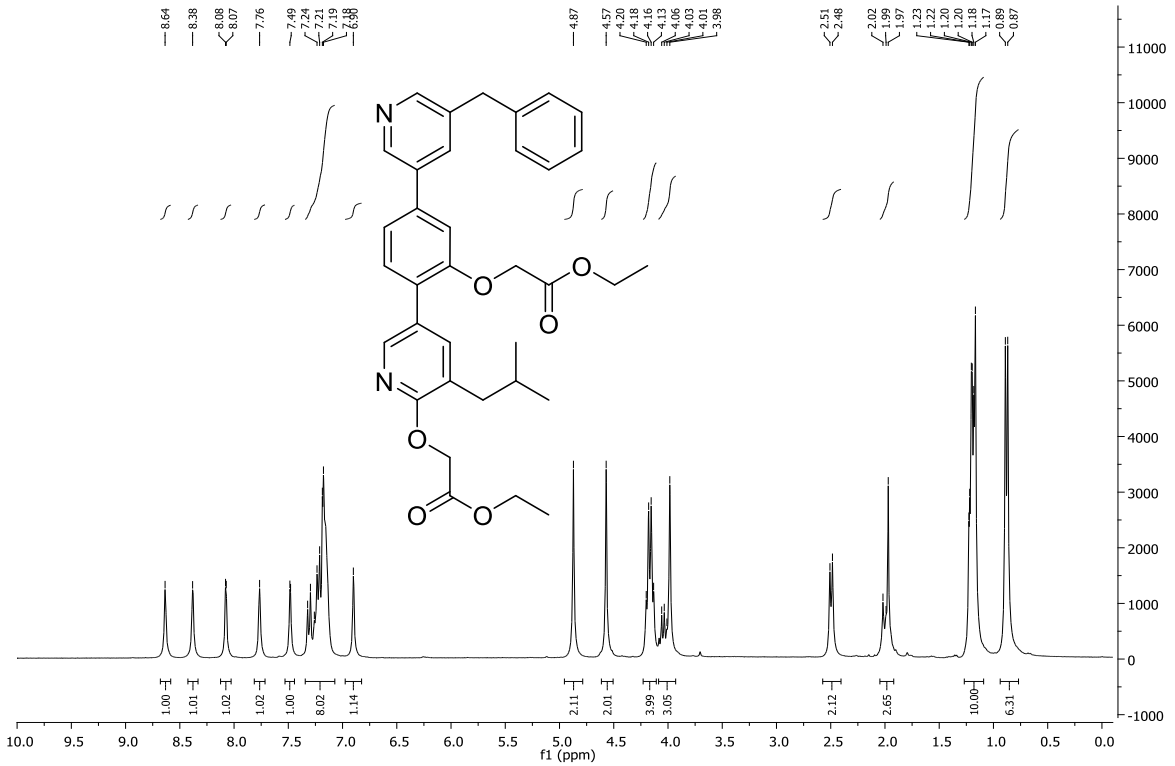

Figure 173. [1]H-NMR of ethyl-2-((5-(4-(5-benzylpyridin-3-yl)-2-(2-ethoxy-2-oxoethoxy)phenyl)-3-isobutylpyridin-2-yl)oxy)acetate (**125**).

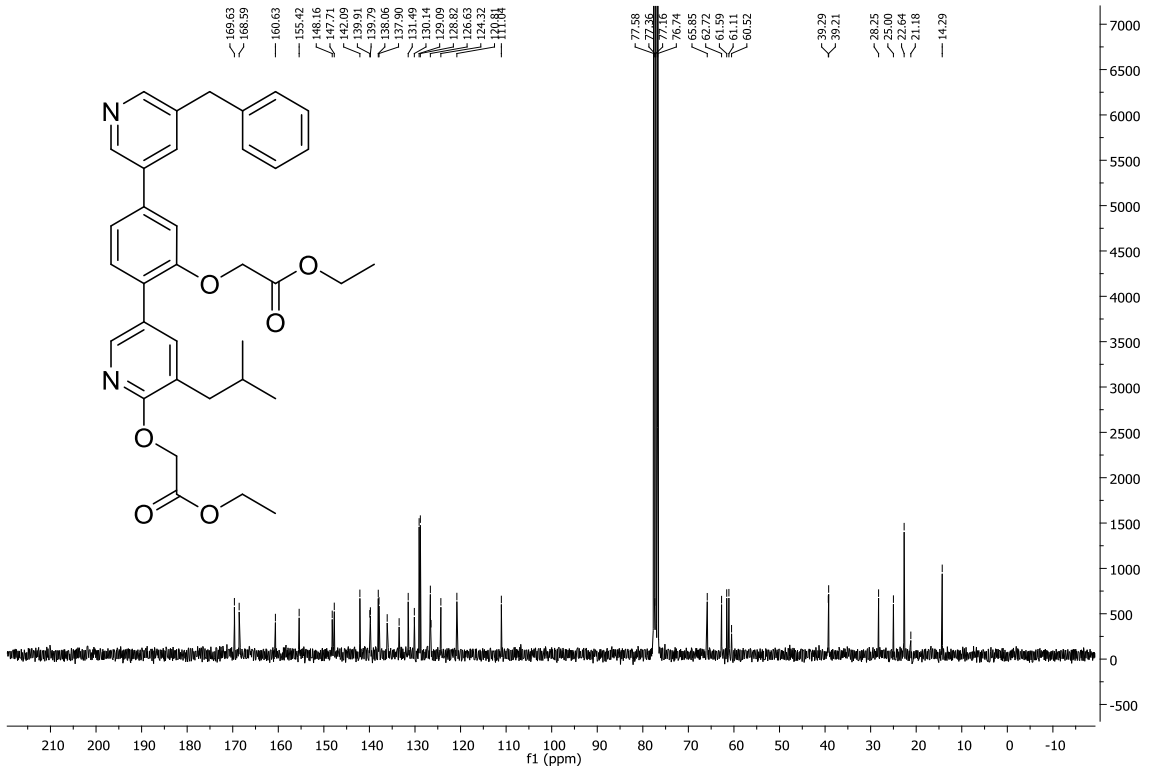

Figure 174. [13]C-NMR of ethyl-2-((5-(4-(5-benzylpyridin-3-yl)-2-(2-ethoxy-2-oxoethoxy)phenyl)-3-isobutylpyridin-2-yl)oxy)acetate (**125**).

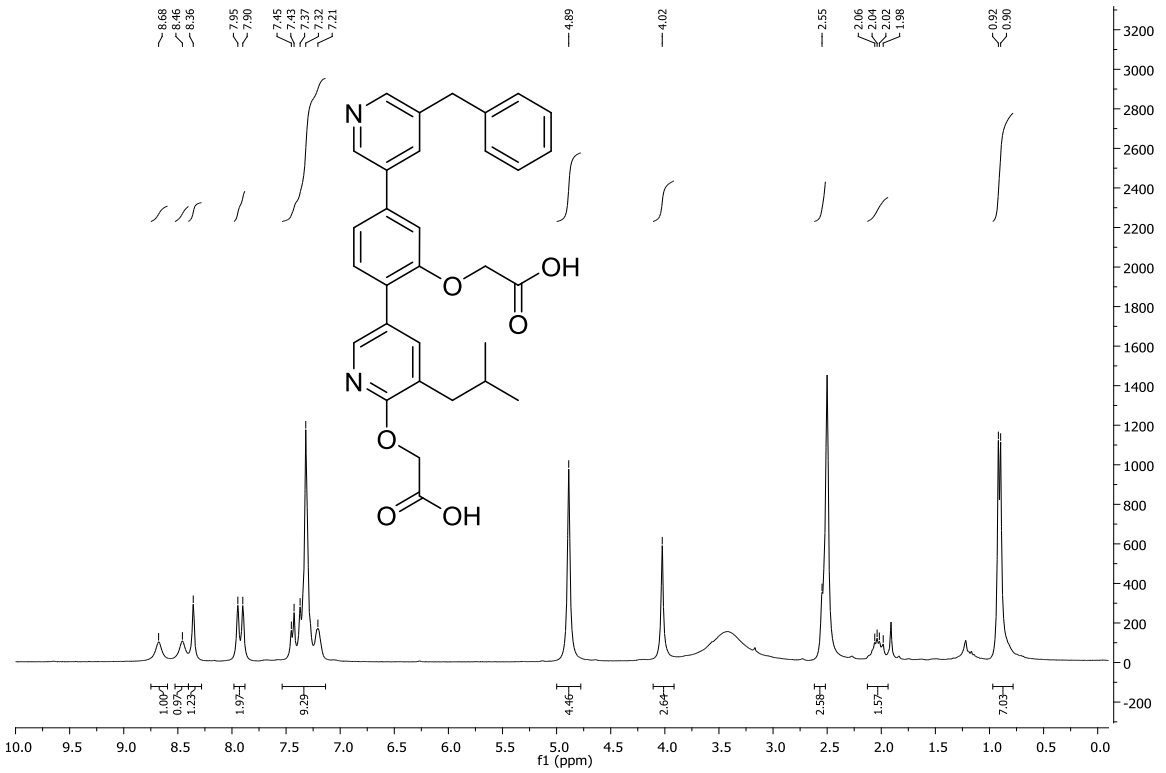

Figure 175. [1]H-NMR of 2-(5-(5-benzylpyridin-3-yl)-2-(6-(carboxymethoxy)-5-isobutylpyridin-3-yl)phenoxy) acetic acid (**126**).

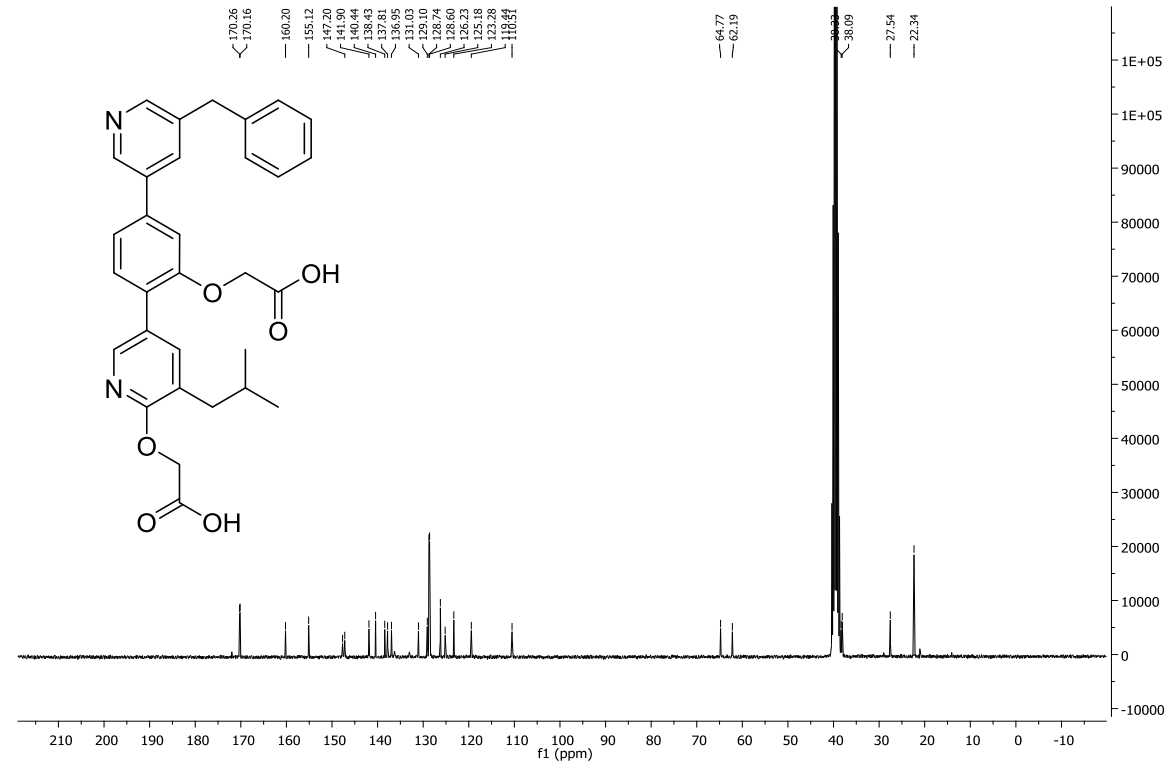

Figure 176. [13]C-NMR of 2-(5-(5-benzylpyridin-3-yl)-2-(6-(carboxymethoxy)-5-isobutylpyridin-3-yl)phenoxy) acetic acid (**126**).

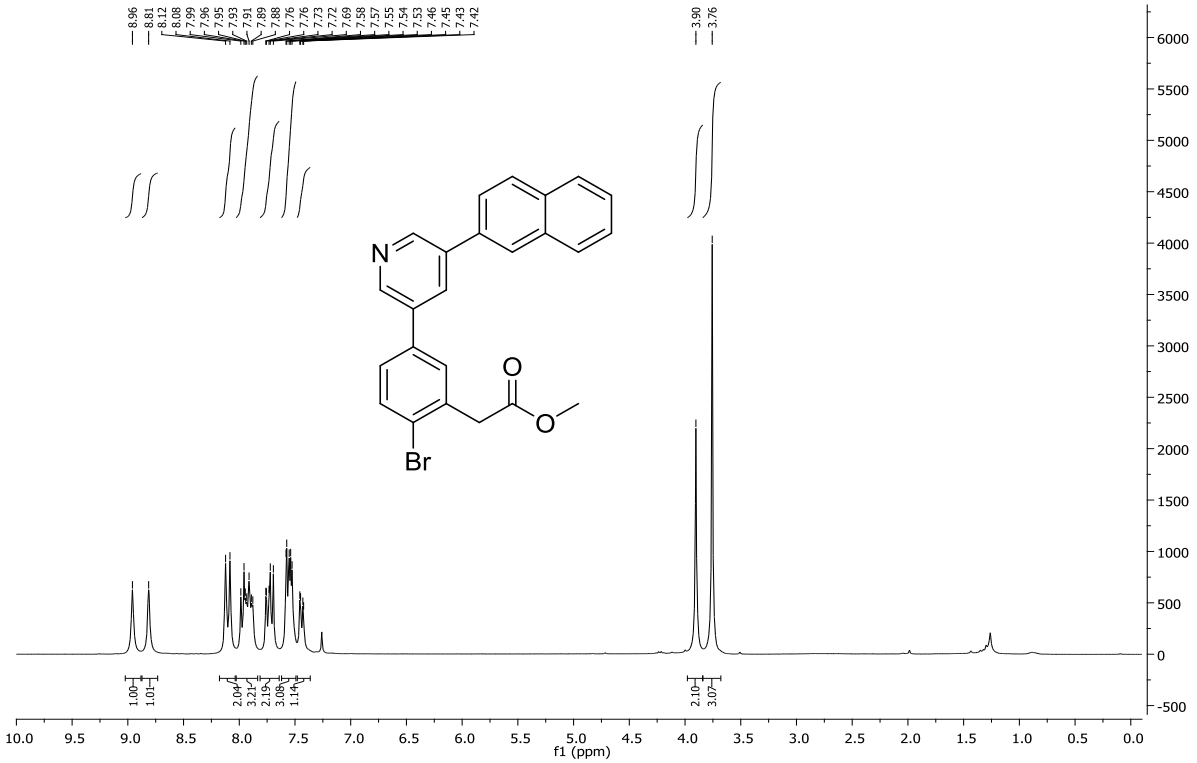

Figure 177. [1]H-NMR of methyl 2-(2-bromo-5-(5-(naphthalen-2-yl)pyridin-3-yl)phenyl)acetate (**128**).

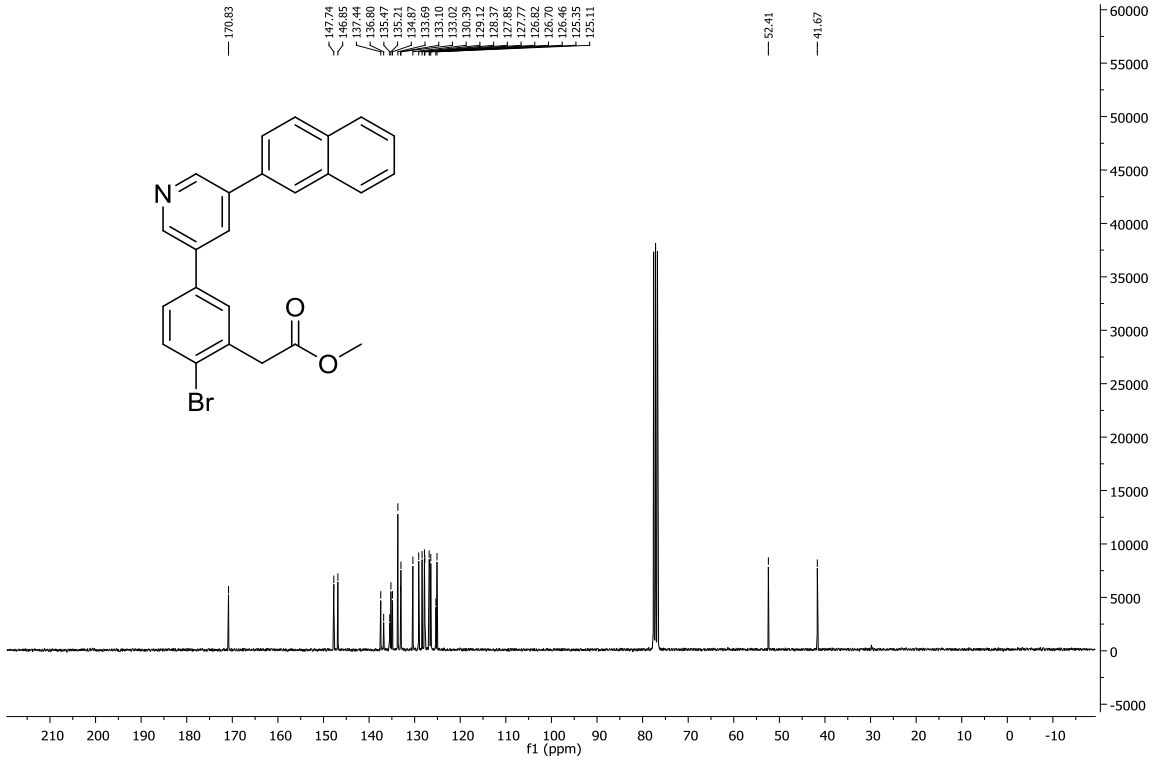

Figure 178. [13]C-NMR of methyl 2-(2-bromo-5-(5-(naphthalen-2-yl)pyridin-3-yl)phenyl)acetate (**128**).

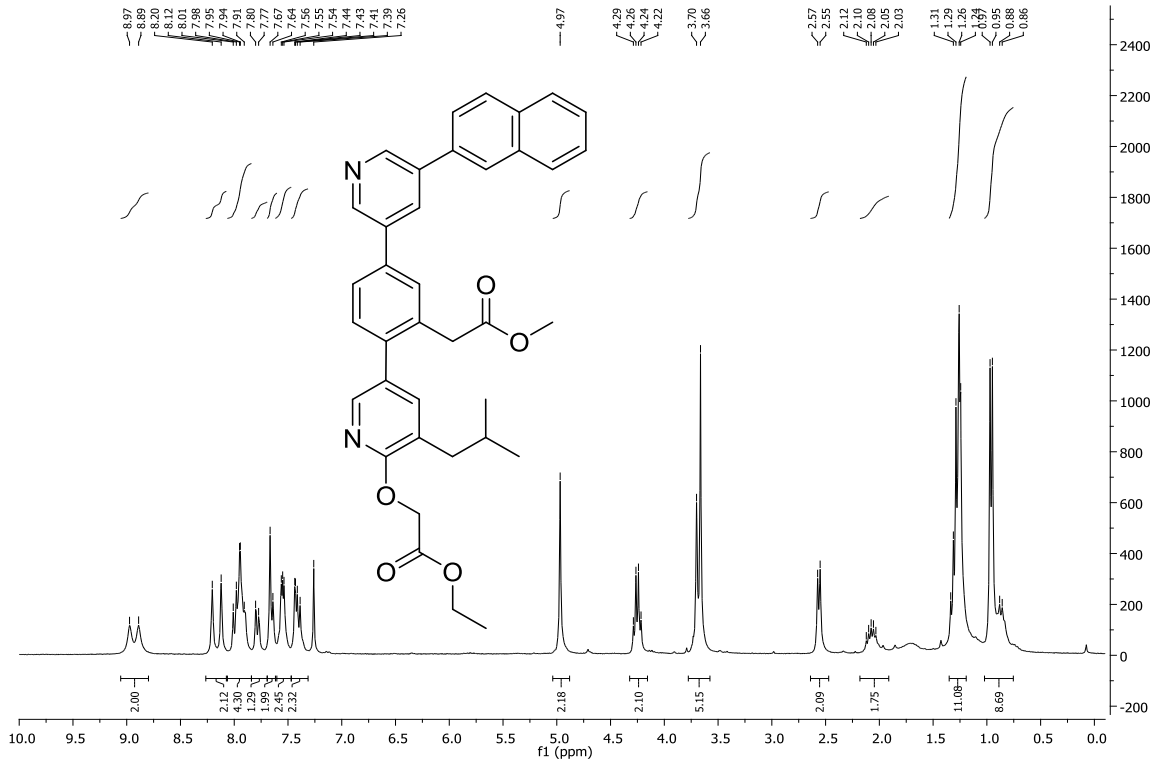

Figure 179. [1]H-NMR of ethyl 2-((3-isobutyl-5-(2-(2-methoxy-2-oxoethyl)-4-(5-(naphthalen-2-yl)pyridin-3-yl)phenyl)pyridin-2-yl)oxy)acetate (**129**).

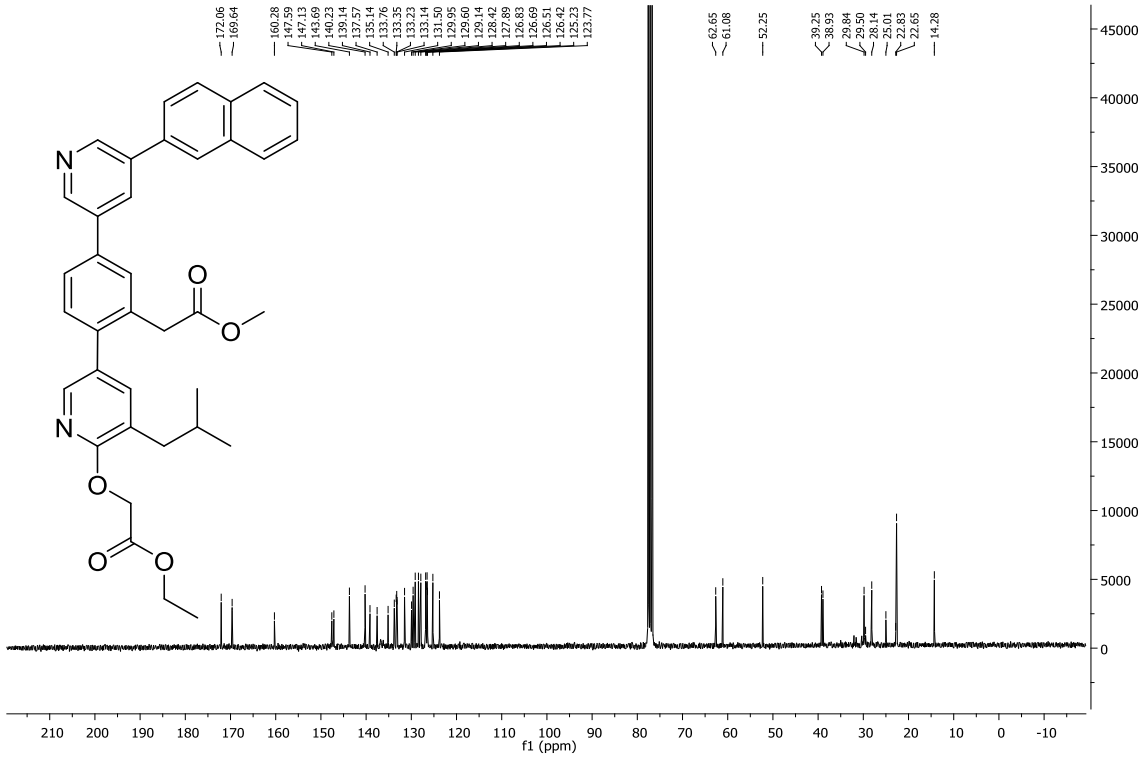

Figure 180. [13]C-NMR of ethyl 2-((3-isobutyl-5-(2-(2-methoxy-2-oxoethyl)-4-(5-(naphthalen-2-yl)pyridin-3-yl)phenyl)pyridin-2-yl)oxy)acetate (**129**).

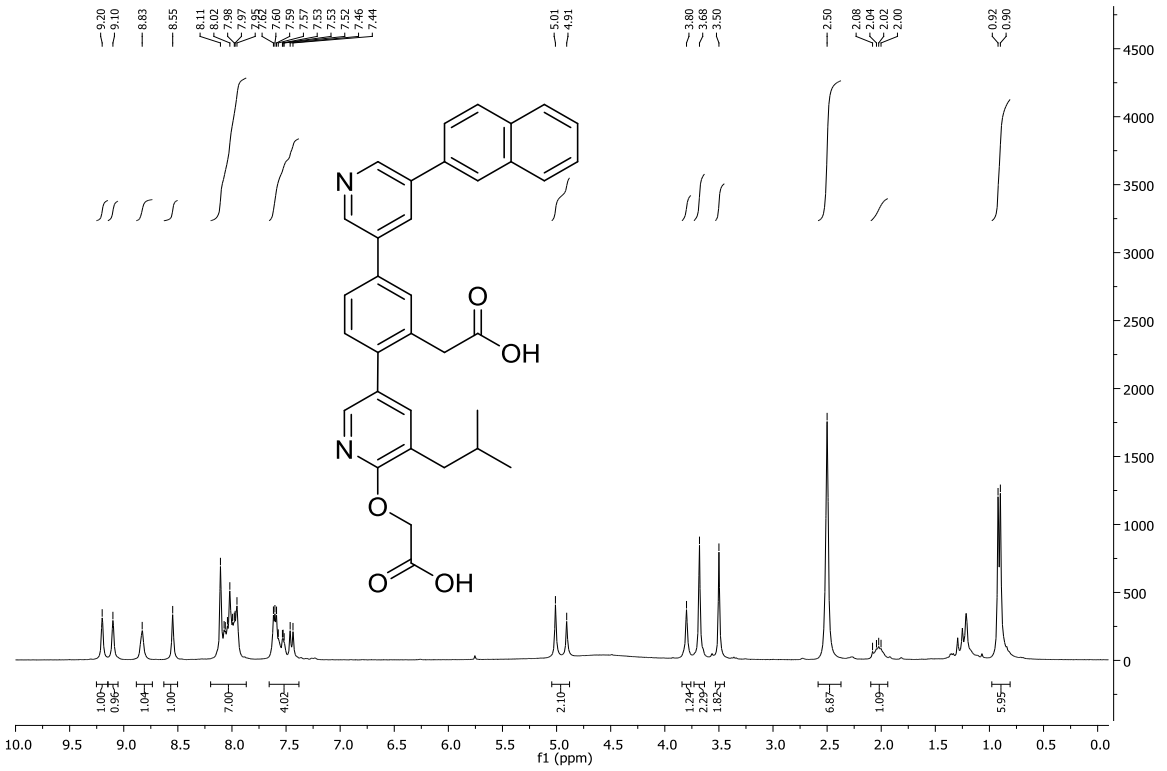

Figure 181. [1]H-NMR of 2-(2-(6-(carboxymethoxy)-5-isobutylpyridin-3-yl)-5-(5-(naphthalen-2-yl)pyridin-3-yl)phenyl)acetic acid (**130**).

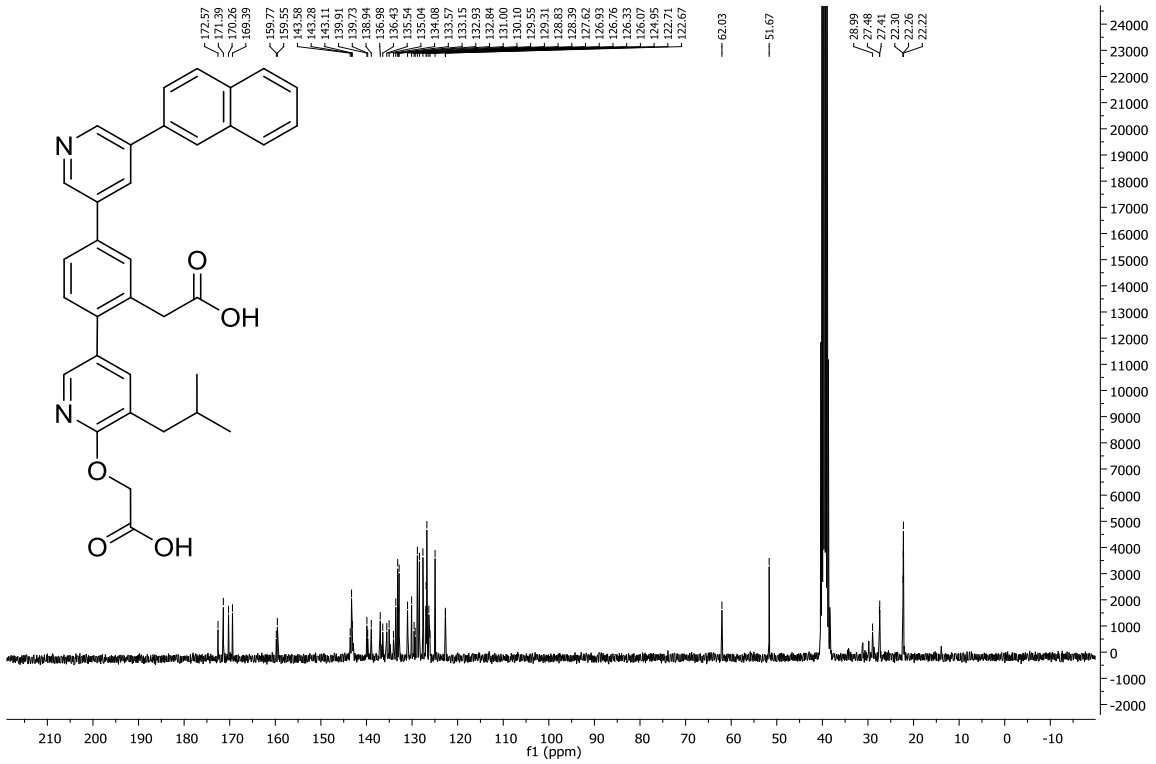

Figure 182. [13]C-NMR of 2-(2-(6-(carboxymethoxy)-5-isobutylpyridin-3-yl)-5-(5-(naphthalen-2-yl)pyridin-3-yl)phenyl)acetic acid (**130**).

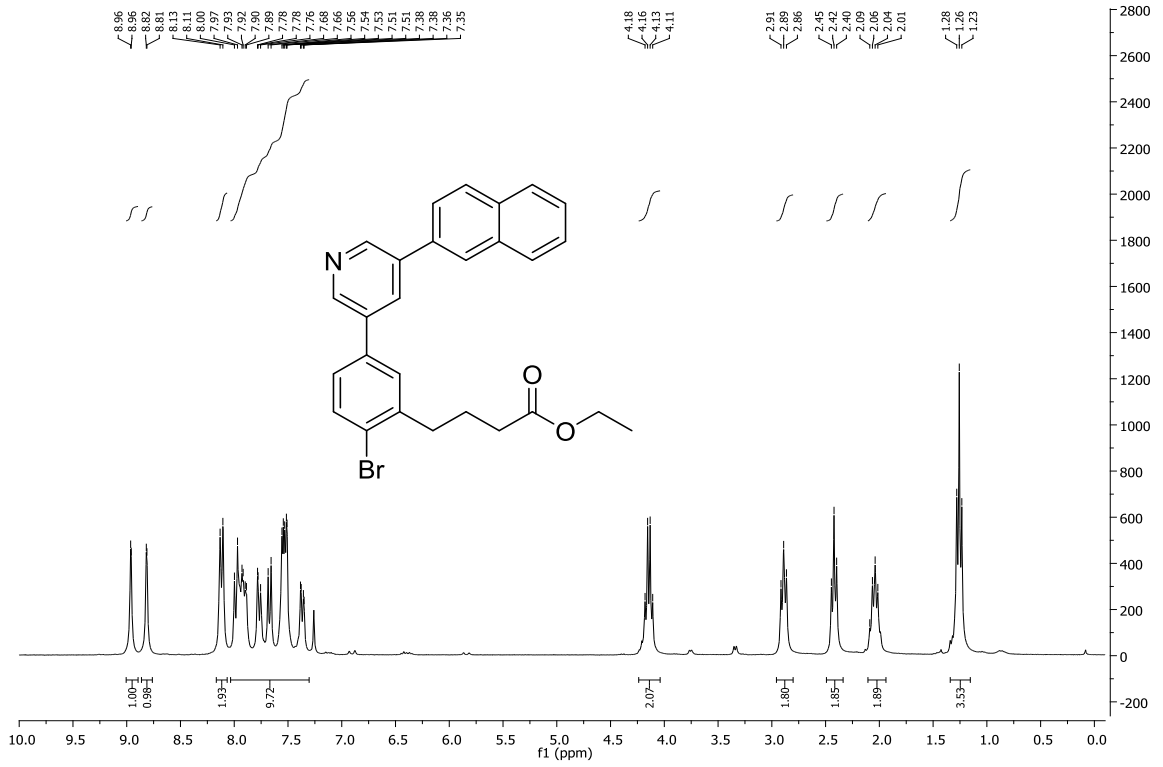

Figure 183. [1]H-NMR of ethyl 4-(2-bromo-5-(5-(naphthalen-2-yl)pyridin-3-yl)phenyl)butanoate (**131**).

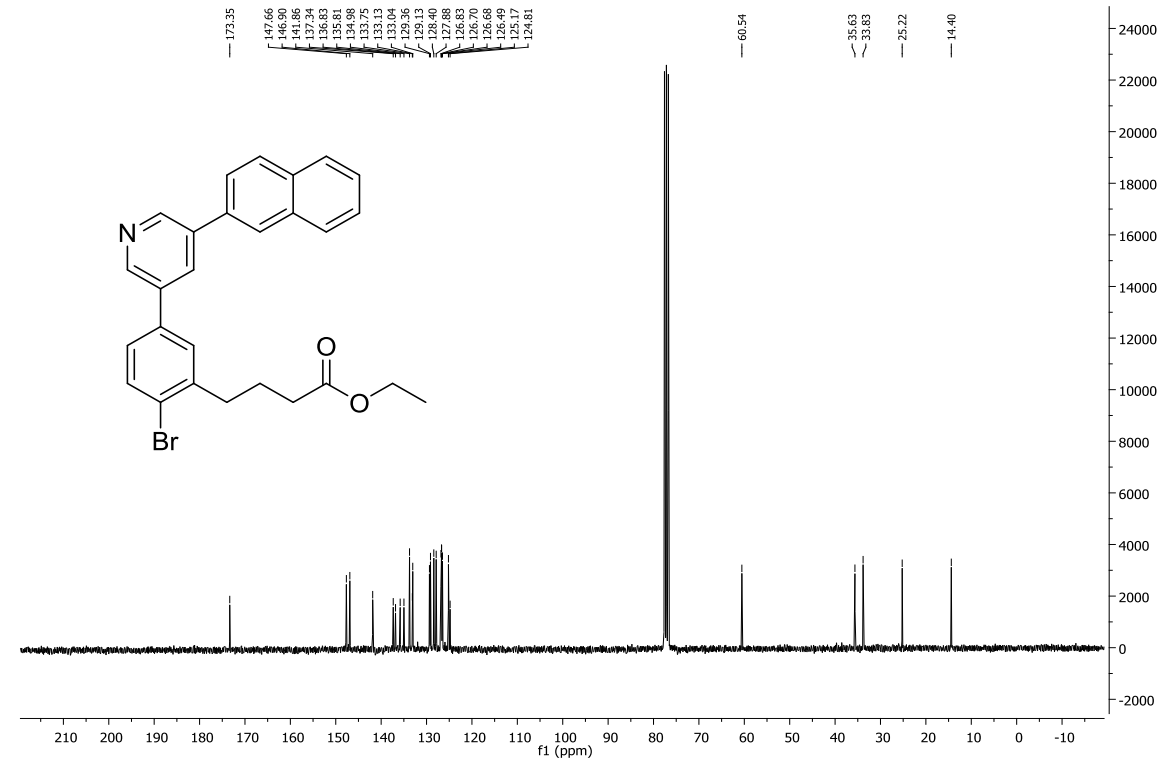

Figure 184. [13]C-NMR of ethyl 4-(2-bromo-5-(5-(naphthalen-2-yl)pyridin-3-yl)phenyl)butanoate (**131**).

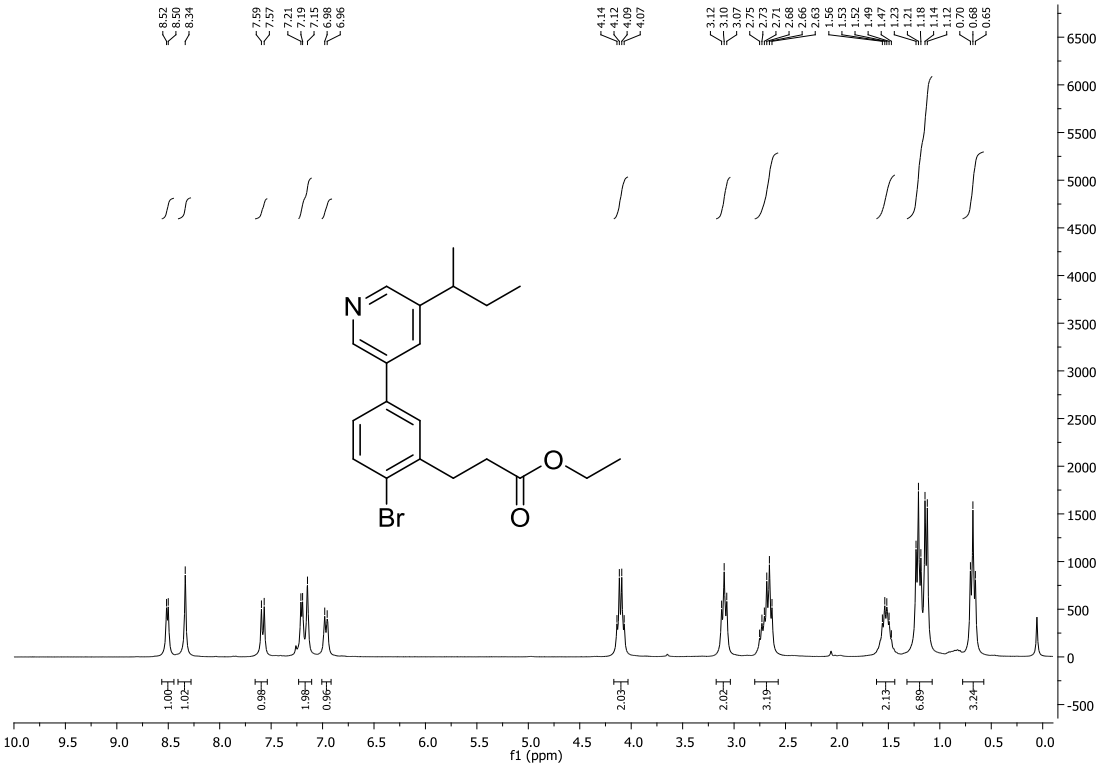

Figure 185. [1]H-NMR of ethyl 3-(2-bromo-5-(5-(sec-butyl)pyridin-3-yl)phenyl)propanoate (**133**).

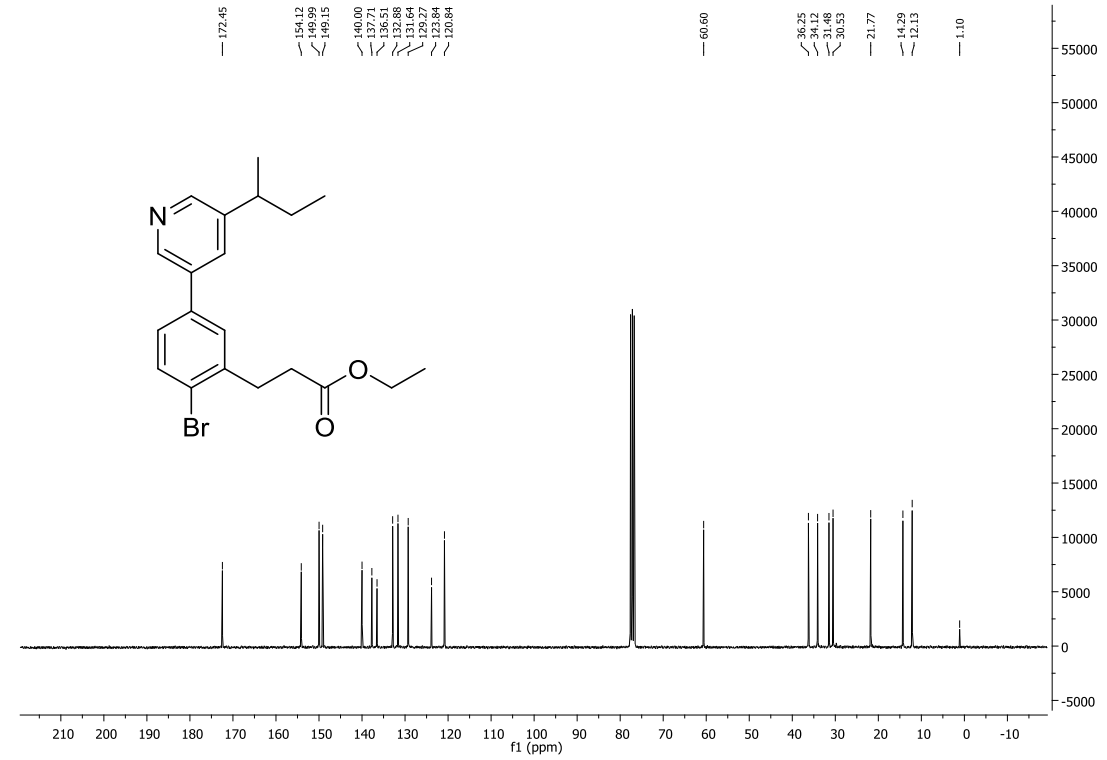

Figure 186. [13]C-NMR of ethyl 3-(2-bromo-5-(5-(sec-butyl)pyridin-3-yl)phenyl)propanoate (**133**).

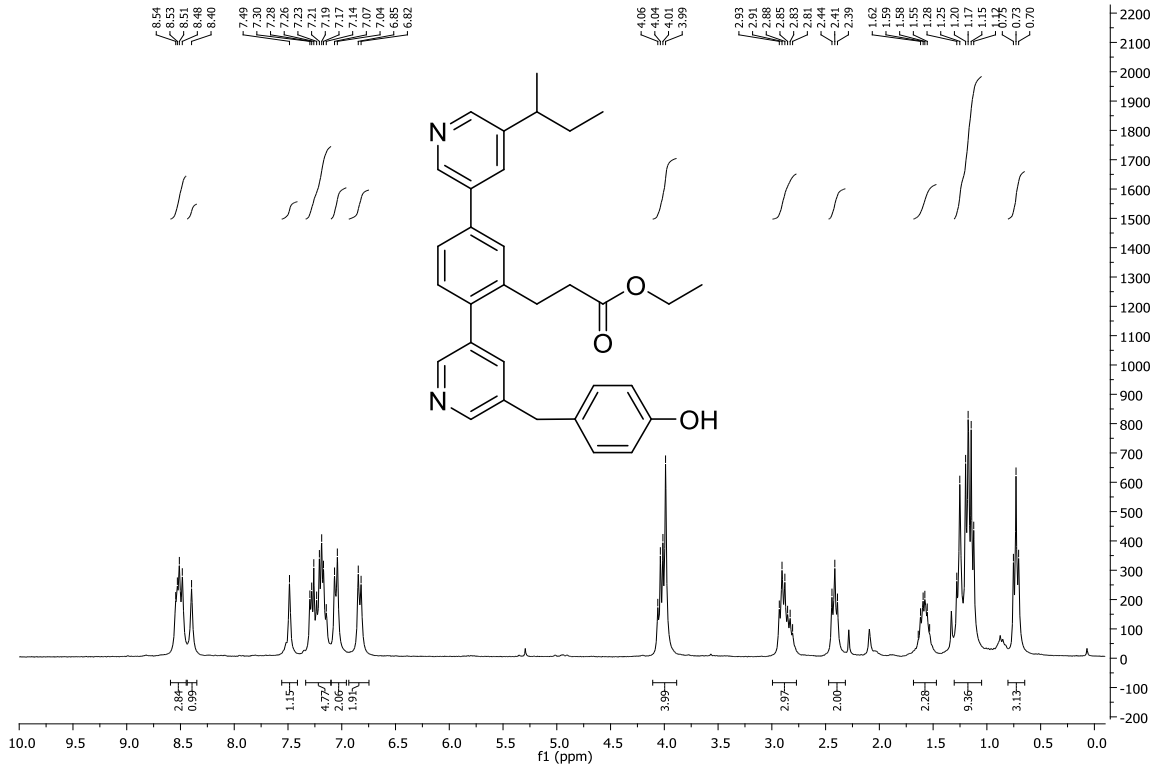

Figure 187. [1]H-NMR of ethyl 3-(2-bromo-5-(5-(sec-butyl)pyridin-3-yl)phenyl)propanoate (**134**).

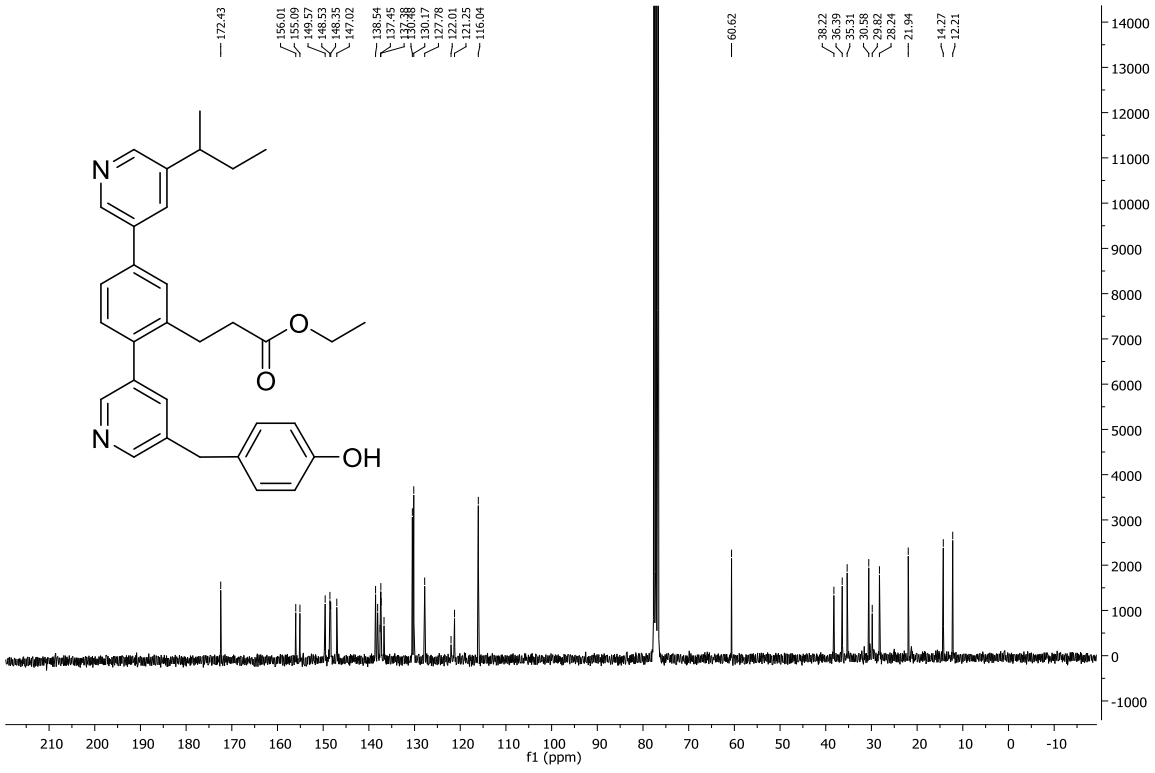

Figure 188. [13]C-NMR of ethyl 3-(2-bromo-5-(5-(sec-butyl)pyridin-3-yl)phenyl)propanoate (**134**).

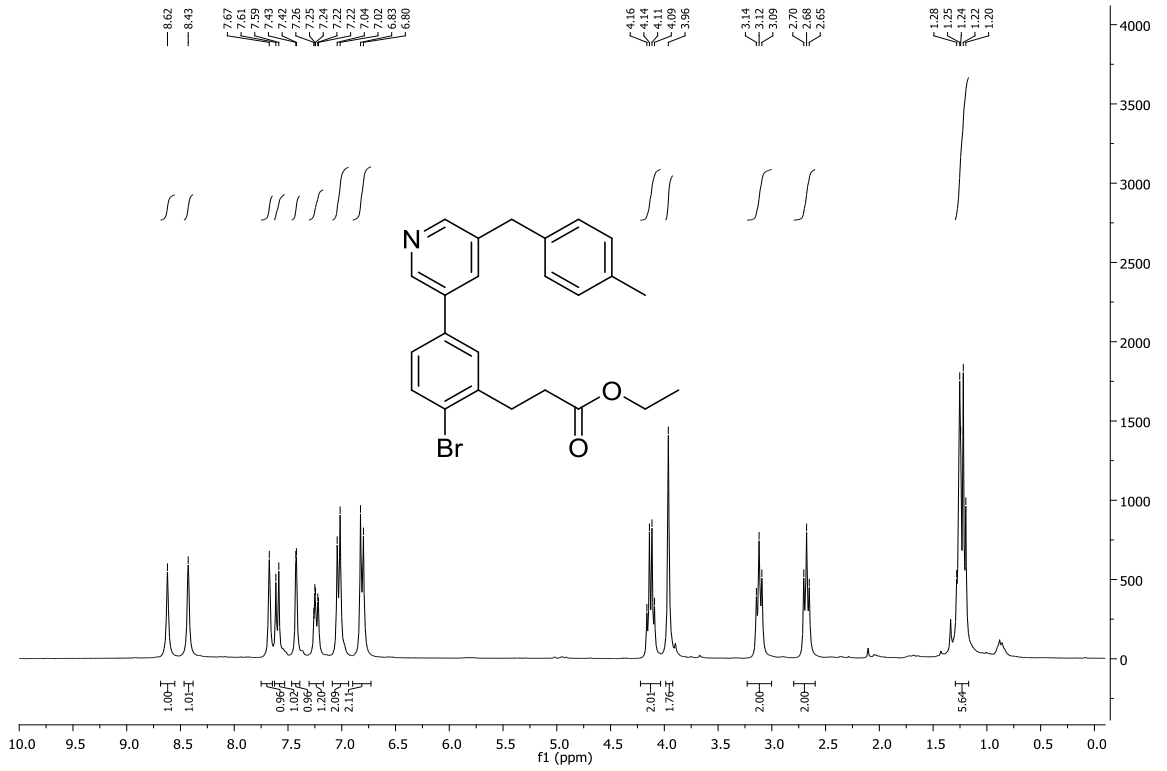

Figure 189. [1]H-NMR of ethyl 3-(2-bromo-5-(5-(4-((tert-butyldimethylsilyl)oxy)benzyl)pyridin-3 yl)phenyl)propanoate (**135**).

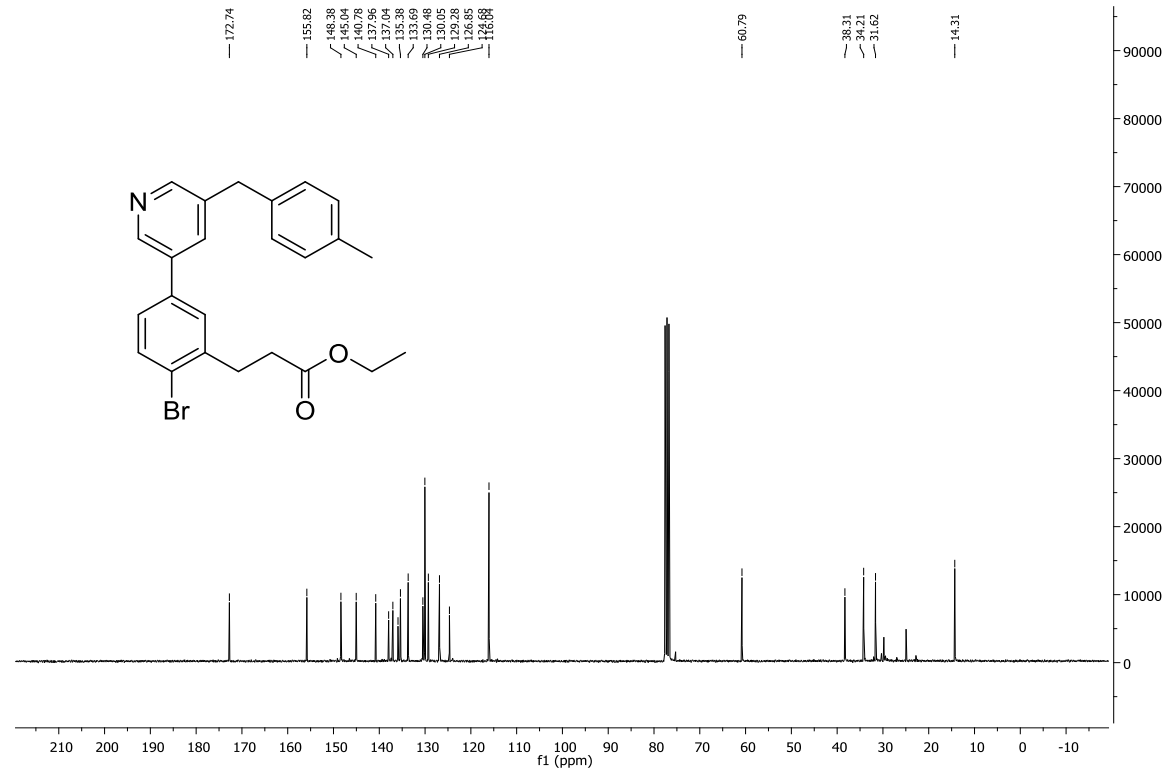

Figure 190. [13]C-NMR of ethyl 3-(2-bromo-5-(5-(4-((tert-butyldimethylsilyl)oxy)benzyl)pyridin-3 yl)phenyl)propanoate (**135**).