Suberone-based type I½ p38α MAPK-inhibitors with improved properties to treat colorectal cancer

Dissertation

der Mathematisch-Naturwissenschaftlichen Fakultät

der Eberhard Karls Universität Tübingen

zur Erlangung des Grades eines

Doktors der Naturwissenschaften

(Dr. rer. nat.)

vorgelegt von

Vanessa Haller

aus Bretten

Tübingen

2021

Gedruckt mit Genehmigung der Mathematisch-Naturwissenschaftlichen Fakultät der Eberhard Karls Universität Tübingen.

Tag der mündlichen Qualifikation:	21.05.2021
Dekan:	Prof. Dr. Thilo Stehle
1. Berichterstatter:	Prof. Dr. Stefan A. Laufer
2. Berichterstatter:	Prof. Dr. Antti Poso

»Glaube« heißt Nicht-wissen-wollen, was wahr ist."

Friedrich Nietzsche, der Antichrist

Gewidmet meiner Oma Else & meiner Mutter <3

meinem Onkel Bernd, meinem Bruder und meinem Stiefvater

Danksagung

Mein herzlicher Dank geht an:

Prof. Dr. Antti Poso für das zeitnahe Erstellen des Zweitgutachtens, seiner Funktion als Prüfer und seiner Unterstützung und Aufmunterung.

Prof. Thilo Stehle für seine Unterstützung als Ombudsperson und ebenfalls für die Teilnahme als Prüfer bei meiner Disputation.

Tatu Pantsar für die tolle Zusammenarbeit und Unterstützung während der Promotion, das Korrigieren der Arbeit und für das immer ein „offenes Ohr“ haben.

Meiner ehemaligen Masterstudentin Larissa Pünnel für die gute Zusammenarbeit und viele lustige Gespräche über Gott und die Welt.

Juliander Reiner für philosophische und kulturelle Gespräche, synthetische Ratschläge und das Bereitstellen der Oxadiazol-Linker.

Mark Kudolo, Katharina Bauer und Jens Strohbach für die biologische Testung meiner Daten. Vor allem bei Jens Strohbach noch zusätzlich für interessante und tiefgreifende Gespräche, die mir so manchen Tag versüßt haben.

Gerd Helms für das messen von NMR-Spektren und seine Hilfsbereitschaft.

Julia Liang für Ihre liebenswerte Art, großartige Gespräche und natürlich für das Mitbringen von unheimlich leckeren Kuchen ☺. Ich hoffe wir treffen uns auch in Zukunft noch regelmäßig auf einen Kaffee.

Der „Mädels-Mittagsessen-Runde“ (Theresa Kircher, Juila G., Julia L., Lisa Haarer) für eine großartige Zeit, viele lustige Gespräche und viele Süßigkeiten.

Thales Kronenberger für seine aufmunterten Worte und seine humorvolle Art.

Meinen Laborkollegen Gregor Schmidberger, Valentin Wydra, Gernot Haase, Teo Dimitrov, Stanislav Andreev, Carine Abdelmalek, Florian Wittlinger & Peter Weißhaupt.

Mechtild Seyboldt und Birgit Kailer für das Besorgen von Chemikalien sowie für nette Gespräche.

Kristine Schmidt für die Hilfestellung bei vielen bürokratischen Problemen.

Christoph Wagner für die viele Unterstützung und das Korrekturlesen meiner Arbeit.

In besonderen Maßen möchte ich mich bei meiner Familie bedanken, ihr seid mein Rückgrat und habt mich stets unterstützt, ohne Euch wäre das nicht möglich gewesen!

Summary of the thesis

The aim of this thesis was the design and synthesis of novel p38α MAPK inhibitors to gain a better understanding of the SAR and the interaction of the type I ½ residues with the R-spine. Another aim was the optimization of the ADME-properties, particularly solubility and metabolism.

Within the scope of this thesis, 74 novel p38α MAPK inhibitors were synthesized. Many inhibitors demonstrate excellent inhibitory activity against the isolated kinase with IC_{50}-values in the single-digit nanomolar or even picomolar range. Moreover, new concepts to optimize the metabolic stability were established. Thus, the major drawback of the amide-based inhibitors is the metabolic cleavage of the type 1 ½ amide residues resulting in a type I inhibitor. The replacement of the amide bond through a metabolically more stable functional group enabled the prevention of the type I ½ residue cleavage. As new functional groups inter alia ketones, imides and oxadiazoles were used. Concepts to improve the solubility were also utilized. Therefore, heteroatoms to reduce the lipophilicity were introduced and the number of C-sp^3 atoms were increased to enhance the complexity of the compounds. The success of the solubility concept still needs to be proven by test data.

Additionally, the synthesis of the dibenzosuberone scaffold was optimized. By utilizing an alkyl-Suzuki coupling reaction a two-step synthetic route with an improved overall yield of 85% instead of 66% was developed.

Furthermore, a new class of p38α MAPK inhibitors with an additional nitrogen attached to the B-ring of the tricyclic dibenzosuberone scaffold were designed. The aim thereof was the optimization of the kinase interaction and to improve the solubility. The azadibenzosuberones show high activity against the isolated p38α MAP kinase with IC_{50}-values up to 40 picomolar (compound 161). Unfortunately, the extraordinarily high activity could not be confirmed in the whole blood assay

Zusammenfassung der Arbeit

Das Ziel dieser Arbeit war die Entwicklung und Synthese neuer p38α MAPK Inhibitoren, um ein verbessertes Verständnis der SAR-Beziehungen und der Interaktion des Typ I ½ Restes mit der R-Spine zu erhalten. Ein weiteres Ziel war die Optimierung der ADME-Eigenschaften der Inhibitoren, vor allem im Hinblick auf Löslichkeit und Metabolismus.

Im Rahmen dieser Arbeit wurden insgesamt 74 neue p38α MAPK Inhibitoren synthetisiert. Viele der Inhibitoren zeigen an der isolierten Kinase ausgezeichnete Hemmwerte mit IC_{50}-Werten im einstellig nanomolaren oder sogar pikomolaren Bereich. Außerdem wurden neue Konzepte zur Steigerung der metabolischen Stabilität etabliert. Das Hauptproblem der Amid-basierten Verbindungen ist die metabolische Spaltung des Typ I½ Amid-Rests zu Typ I Inhibitoren. Der Austausch des Amids durch metabolisch stabilere funktionelle Gruppen ermöglichte es erfolgreich die Spaltung der Typ I½ Reste zu unterbinden. Als neue funktionelle Gruppen wurden unter anderem Ketone, Imide und Oxadiazole verwendet. Auch Konzepte zur Verbesserung der Löslichkeit wurden umgesetzt. Hierfür wurde versucht durch Einführen von Heteroatomen die Lipophilie zu reduzieren oder durch Erhöhung des C-sp^3-Anteils die Komplexität der Verbindungen zu steigern. Der Erfolg dieser Strategien muss noch durch Tests evaluiert werden.

Zusätzlich wurden die Synthese des Dibenzosuberon Grundgerüstes optimiert. Durch Verwendung einer Alkyl-Suzuki Reaktion gelang es einen Zwei-Stufen Prozess mit einer Erhöhung der Gesamtausbeute von ursprünglich 66% auf 85% zu entwickeln.

Außerdem gelang es eine neue Strukturklasse von p38α MAPK Inhibitoren mit einem zusätzlichen Stickstoff im trizyklischen Dibenzosuberon Grundgerüst zu entwickeln. Dies verfolgt das Ziel einer optimierten Interaktion mit der Kinase und einer verbesserten Löslichkeit der Inhibitoren. Die Azadibenzosuberone haben ein Stickstoff-Atom im B-Ring und weißen eine sehr hohe Aktivität gegen die p38α MAPK auf mit Hemmwerten von bis zu 40 picomolar (Verbindung 161). Leider konnte die außerordentlich hohe Aktivität im Vollblut Assay nicht bestätigt werden.

Abbreviation

A-loop	Activation loop / activation segment
ATF-2	Activation transcription factor 2
ATP	Adenosine triphosphate
CAMK	Calcium/calmodulin-dependent protein kinase
CDI	1,1′-carbonyldiimidazole
C-Spine	Catalytic spine
CRC	Colorectal cancer
DCM	Dichloromethane
DIPEA	Diisopropylethylamine
DMF	N, N-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
Eq.	Equivalent
ERK	Extracellular-signal-regulated kinase
ESI	Electronic spray ionisation
EtOAc	Ethyl acetate
EtOH	Ethanol
HPLC	High Performance Liquid Chromatography
HRI	Hydrophobic region I
HRII	Hydrophobic region II
JNK	Jun amino-terminal kinase
MAPK	Mitogen activated protein kinase
MeOH	Methanol
MD	Molecular dynamic
nM	Nanomolar
NMR	Nuclear magnetic resonance
PD	Pharmacodynamic
PDB	Protein data bank
PK	Pharmacokinetic
R-Spine	Regulatory spine
RT	Room temperature

RLM	Rat liver microsome
SAPK	Stress-activated protein kinases
SAR	Structure activity relationship
TRT	Target residence time
TBTU	O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate
THF	Tetrahydrofuran
TNFα	Tumor necrosis-factor-α
TK	tyrosine kinase
tR	Retention time

Table of contents

1. Introduction

1.1. Protein kinases

Protein kinases are crucial enzymes for regulating cellular functions and signalling pathways by phosphorylation of various substrates including lipids, sugars, and amino acids.[1] Phosphorylation is the transfer of a gamma phosphate of ATP to the hydroxyl group of a substrate like the amino acids serine, threonine and tyrosine.[2] The phosphorylation leads to a conformational change of the secondary structure of the substrate effecting the activity and function of the substrate.[3] It is a sensitive and crucial homeostasis for physiological functions.[4] Thus, dysregulation of kinase function through mutations, loss of negative regulators or excess of activation signals is a hallmark of many diseases such as cancer, inflammatory or neurodegenerative diseases.[5] Because of the fundamental role of protein kinases, they have become attractive medicinal drug targets.[6]

There are 518 protein kinases encoded in the human genome, so called kinome, which represents almost 2% of the human genome.[7] As a consequence of splicing and mutation variants, the number of different kinases is even higher.[8, 9] The majority of the 518 protein kinases are classified as typical kinases.[1] Based on the hydroxyamino acid phosphorylated in their protein substrates, typical protein kinases can be divided into two broad classes: tyrosine kinases (90 kinases) or serine/threonine kinases (388).[10] A more differentiated classification system depending on sequence similarity of the catalytic domain and the biochemical function, further dived the typical protein kinases into seven super families such as TK (tyrosine kinase), CAMK (calcium/calmodulin-dependent protein kinase) or CMGC (containing CDK, MAPK, GSK3, CLK families).[11, 12] These families are shown in the kinase dendrogram (Figure 1). The distance of the branches illustrates the sequence similarity of the different kinase families. In contrast to typical kinases, atypical kinases (around 40) accomplish kinase activity but have insufficient sequence homology to classical eukaryotic kinases.[10]

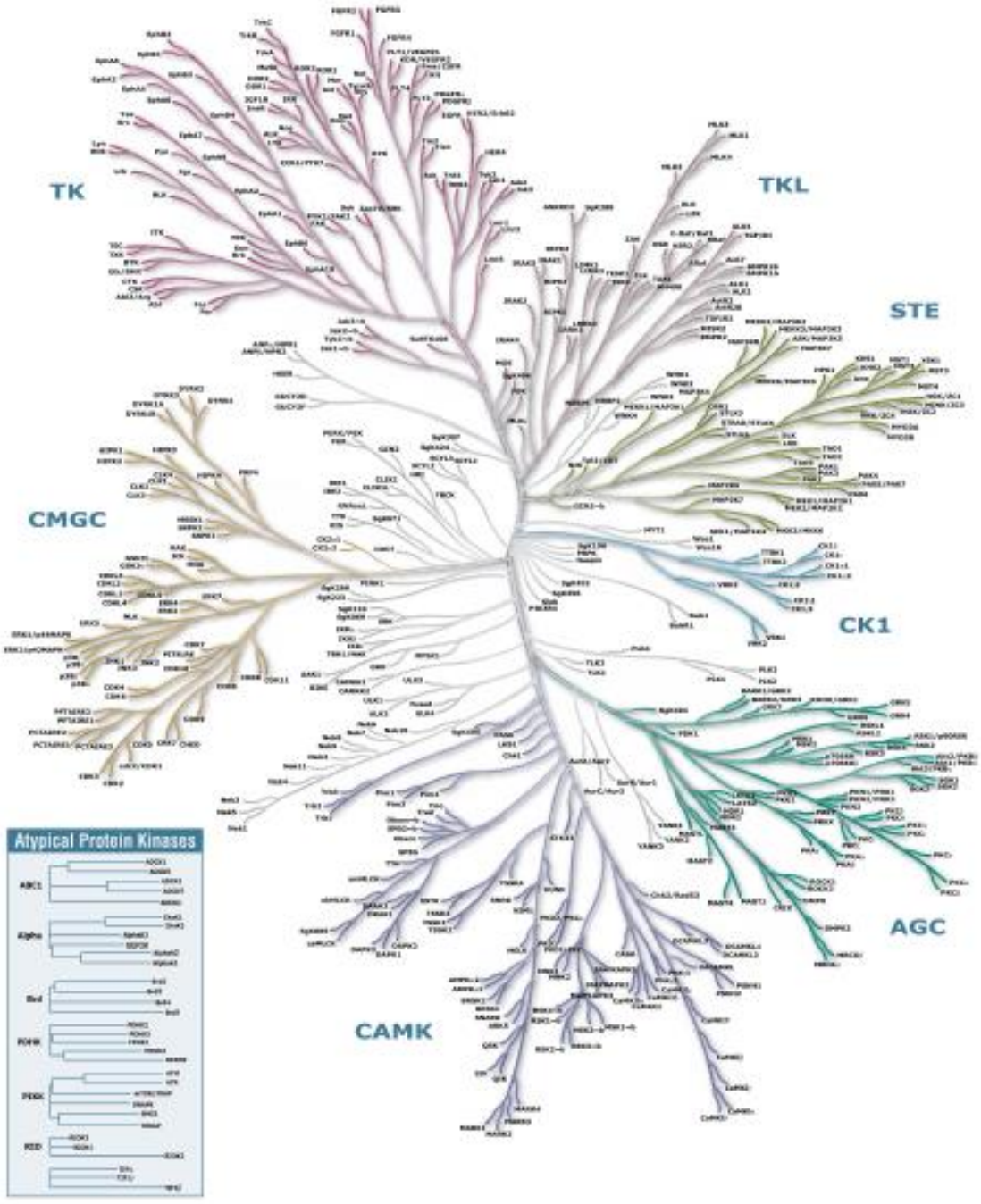


Figure 1: The human Kinome. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

1.2. The p38 MAP kinase

MAPKs (mitogen-activated protein kinases) are serine-threonine kinases that regulate a wide variety of cellular functions including proliferation, gene expression, differentiation, mitosis, cell survival, and apoptosis.[13] Three main groups belong to the MAPK family: ERKs (extracellular-signal-regulated kinases), JNKs (Jun amino-terminal kinases) and p38/SAPKs (stress-activated protein kinases).[14]

The p38 MAPK families are responsive to stress stimuli including UV irradiation, heat shock, osmotic stress, proinflammatory cytokines (such as IL-1 and TNF-Alpha), and certain

mitogens.[15] They are involved in cell differentiation, apoptosis, and autophagy.[16] Four isoforms of the p38 MAPK family (α, β, γ, δ) have been identified.[17] The α-isoform is the best characterized enzyme thereof, it is ubiquitously expressed and have inter alia a key function in the signalling pathway of inflammatory processes. The vital role of p38α is further emphasised by the fact that the knockout of p38α is embryonically lethal.[18] At present, the biological function of the other isoforms has not been finally clarified, but they appear to be pleiotropic.[19] They are particularly expressed in certain tissues, p38β is primarily expressed in the brain, p38γ is mainly found in skeletal muscles and p38δ is present in the pancreas, testis, kidneys, and small intestine.[20] Whereby, the β-isoform exhibits the highest sequence homology of around 74% to the α-isoform, whereas p38γ and p38δ are 62% and 61% identical to p38α, respectively. [19, 21]

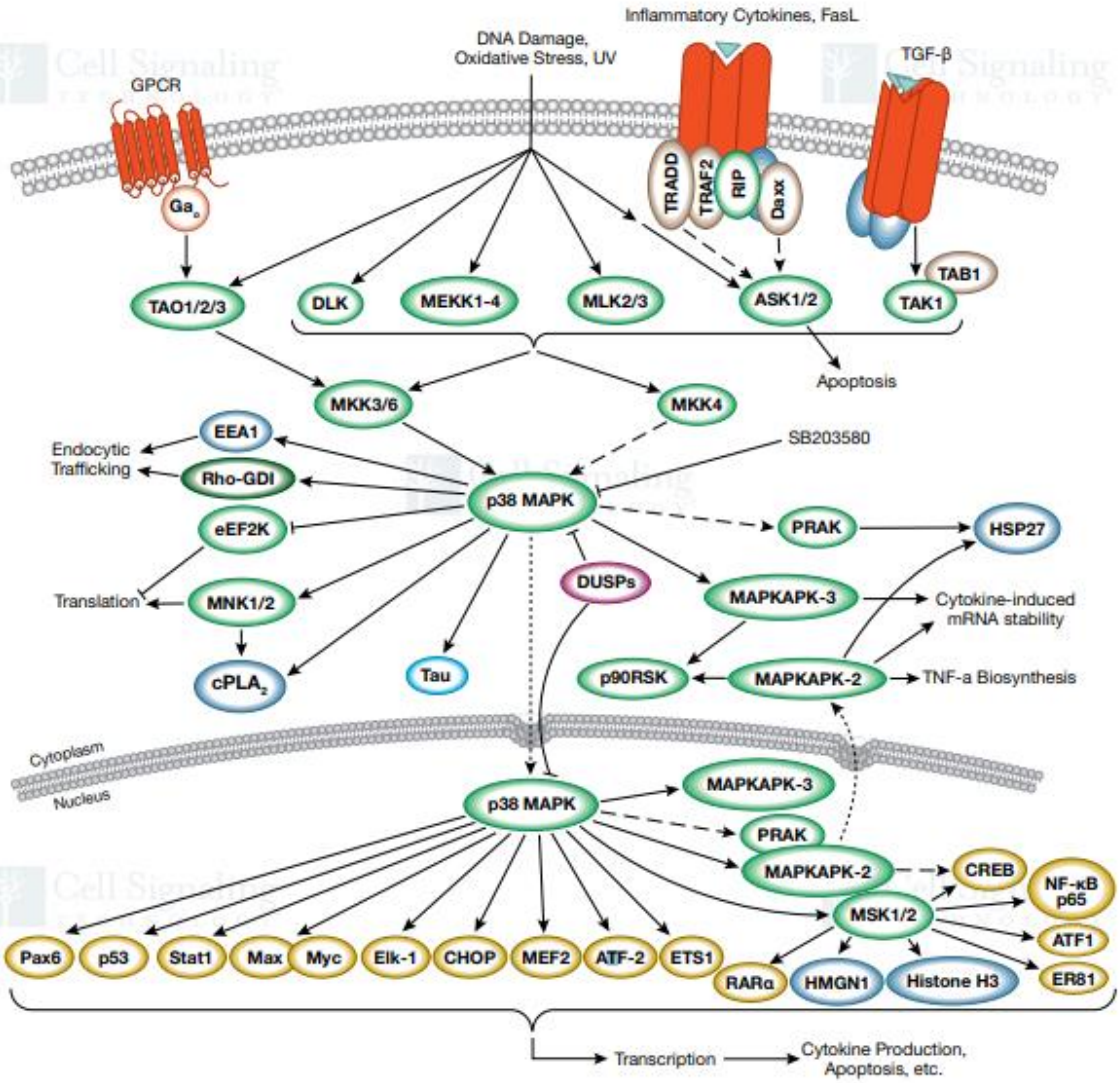


Figure 2: p38 MAPK activation and signalling pathway. The activation of p38, the most important substrates and their effects are shown. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

All isoforms of p38 are activated by MAPKKs, especially MKK3 and MKK6, by dual phosphorylation at Thr180 and Tyr182 residues at a Thr-Gly-Tyr motif located in the activation loop.[22] Followed by a conformational change leading to an increased kinase activity by

enhanced accessibility of the substrate at the catalytic site.[23] p38 is located in the cytoplasm as well as in the nucleus and thus regulates the activation of both cytoplasmic and nuclear substrates by phosphorylation.[24] The substrate binds to the active kinase and the activation itself is accomplished by phosphorylation through the p38 MAP kinase.[25] Around 100 proteins including kinases and transcription factors are directly phosphorylated by p38 and besides many transcription factors are targeted by downstream substrates of p38.[19] A more detailed overview of the p38 MAPK signalling pathway is shown in Figure2. The role of p38 MAPK in colorectal cancer is described in the next chapter (1.3.) of the thesis.

Inactivation of p38 is achieved by either dephosphorylation of the activation sites via phosphatases (DUSP, MKP1, PP2) or by downregulation of the p38 expression via miRNAs (miR-200-3-P, miR-124, miR-128).[19]

1.3. The role of p38 MAPK in colorectal cancer

The biosynthesis of pro-inflammatory mediators (IL-8, IL-1, IL-6, TNFα, COX-2) is positively regulated by p38 MAPK.[21] Due to its central role in inflammatory processes, p38 MAPK inhibitors like the pyridinylimidazol compound SB 203580 were initially developed for the treatment of inflammatory diseases such as rheumatoid arthritis (RA).[26] In recent years it has been shown that inflammation plays a crucial role in tumorigenesis and tumor progression.[27] For example gastric or colorectal cancer (CRC) are often originated from chronic inflammatory diseases such as gastritis, stomach ulcers or Inflammatory Bowel Diseases (IBD), respectively.[23] CRC is the fourth most prevalent cause of cancer death with limit therapeutical options and a dismal prognosis.[28] The cornerstone for CRC treatment are surgeries and chemotherapy using 5-fluoruracil (5-FU), oxaliplatin or irinotecan.[29] Currently, the median overall survival for patients with metastatic CRC is approximately 30 months and therefore novel therapeutic options are urgently needed.[30, 31]

In the last years, kinases have become an attractive target for cancer treatment.[32] Numerus studies indicate the role of p38 MAPK in cancer development by enhancing survival, migration, or resistance to stress and chemotherapeutic agents in tumor cells.[33] Another important function of p38 MAPK is the regulation of checkpoint controls and cell cycle at G0, G1/S and G2/M transitions via the regulation of specific cyclin (A, D1) levels.[34] The activity of p38 triggers the downregulation of cyclin D1, which is crucial for S phase transition.[35] This downregulation is achieved by stimulating ubiquitin-dependent degradation of cyclin D1 and via the inhibition of cyclin D1 gene transcription.[33] The phosphorylation of the p53 tumor suppressor, controlling the G1/S checkpoint and its activation, is also promoted by p38.[23] Furthermore, recent studies demonstrated that genetic ablation of p38α in CRC mouse models leads to tumor remissions and prolongated survival of mice.[36, 37]

However, several studies provide experimental evidence of an antitumorigenic role of p38 by promoting cell cycle arrest and differentiation.[33] Recently, Gupta *et.al.*[38] showed the importance of p38α for CRC protection by its crucial role for the epithelial barrier function and intestinal homeostasis. The epithelial barrier is important for the gastrointestinal tract protection. Defects in epithelial barrier are associated with CRC.[38]

The simultaneous promotion of both anti-tumor and pro-survival effects demonstrate the pleiotropic role of p38 MAPK signalling. This fact is also represented by disappointing study results for the use of p38 MAPK inhibitors in combination with chemotherapy for CRC treatment.[33] The previous unsatisfactory clinical results underline the urgent need for novel, highly selective and extremely active p38α MAPK inhibitors with a long target residence time.

1.4. Structure of the p38 MAP kinase

The major structural and functional features are broadly conserved in all protein kinases.[39] Like most other kinases, the p38 MAP kinase comprising two lobes, the small N-terminal subdomain (N-lobe) and the larger C-terminal lobe (C-lobe) with a hinge region between the lobes.[40] The lager C-lobe is predominantly a-helical and is mainly related to peptide binding and catalysis.[40] While the N-lobe consists of a five-stranded β-sheet (β1–β5) with a single α-helix and is primarily related to ATP binding.[40] Located between the β1 and β2 strands is a Glycine-rich loop (P-loop) containing a hydrophobic residue which is essential for the coordination of the phosphates of ATP.[3] The flexible P-loop brings the γ-phosphate of ATP in the right position for catalysis by fold over the nucleotide.[3] The hinge region provides the catalytic machinery of the kinase and is crucial for the ATP-binding by forming hydrogen bonding with the adenine ring.[41] Another important regulatory structure for the kinase is the activation loop (A-loop).[40] The A-loop can mainly have two different conformations; an open, active ATP-bound form or a closed conformations displaying the inactive state of the kinase by blocking the access of the protein substrate site.[42]

Based on the pharmacophore model introduced by Traxler, the ATP-binding site can be divided into five regions, shown in figure 3.[43]

- Adenine region: The adenine group of ATP forms two hydrogen bonds to the hinge region and the nucleotide also interacts with the glycine-rich, phosphate binding loop (P-loop).
- Sugar pocket: Hydrophilic region addressed by the ribose of ATP.
- Phosphate binding region: High solvent exposed region occupied by the phosphate group of ATP.
- Hydrophobic region I (HR I): This pocket is extended in the direction of the lone pair of the N7 nitrogen of adenine and not occupied by ATP.
- Hydrophobic region II (HR II): Solvent exposed region which is not addressed by ATP.

As shown in figure 3, Gly110 is part of the hinge region of p38α MAPK and is able to undergo rotation. Thereby, the position of the L-glycine carbonyl oxygen change with the L-glycine NH-group, resulting in the possibility that inhibitors can form two hydrogen bonds instead of one.[44] The so called “glycine-flip” increases the kinome selectivity of the inhibitor since only 46 of the 518 kinases are able to undergo this rotation in the hinge region.[43] Inhibitors addressing the glycine–flip, dramatically lose their potency when the L-glycine is replaced by L-aspartate.[45, 46] The first N-terminal amino acid residual of the hinge region connecting the C- and N-terminal lobes is commonly referred to as the “gatekeeper” residue.[41] This amino acid is different between kinases and is an important determinant of the size of the hydrophobic region I.[47] In case of p38α and p38β the relatively small amino acid Thr106 is the gatekeeper, making the hydrophobic pocket I addressable by inhibitors like SB203580.[48] In contrast, p38γ and p38δ are not inhibited by SB203580, due to a large Met residual, at the Thr106 equivalent position in the hinge region preventing the binding of the inhibitor.[47, 49] In comparison to the HR I, the HR II is oriented towards the solvent and thus allows a high variety of residuals which can be used to adapt the physicochemical properties of the inhibitor.[3]

The magnesium ions play a crucial role in stabilization and orientation of the phosphate groups of ATP and thus to the transfer of the γ-phosphate on the hydroxyl group of the substrate (s. Figure *3*).[50] Additionally, an Asp side chain from the DFG motif coordinates to the magnesium ion which interacts with the phosphate group.[3] The DFG (Asp-Phe-Gly) motif is part of the activation loop and consists of Phe169 and the amino acids Asp168 and Gly170.[51] It can have two different positions in the kinase, the inactive DFG-out and the active DFG-in position. In

the catalytically inactive conformation Asp of the DFG motif flips and change the position with Phe.[52] As a result, the Asp moves away from the ATP binding site and this opens the access to a new allosteric pocket, the so called “deep pocket”, which is adjacent to the hydrophobic region I.[53] The diphosphorylation at Thr180 and Tyr182 through their upstream MAPKK results in a difference of charge of p38α leading to conformational changes. The activation loop and Phe169 turn in opposite directions and move the DFG motif from the “out” state to the “in” state.[54] During the DFG-in conformation, the Asp pointing into the ATP binding site and coordinates two Mg^{2+} ions.[55]

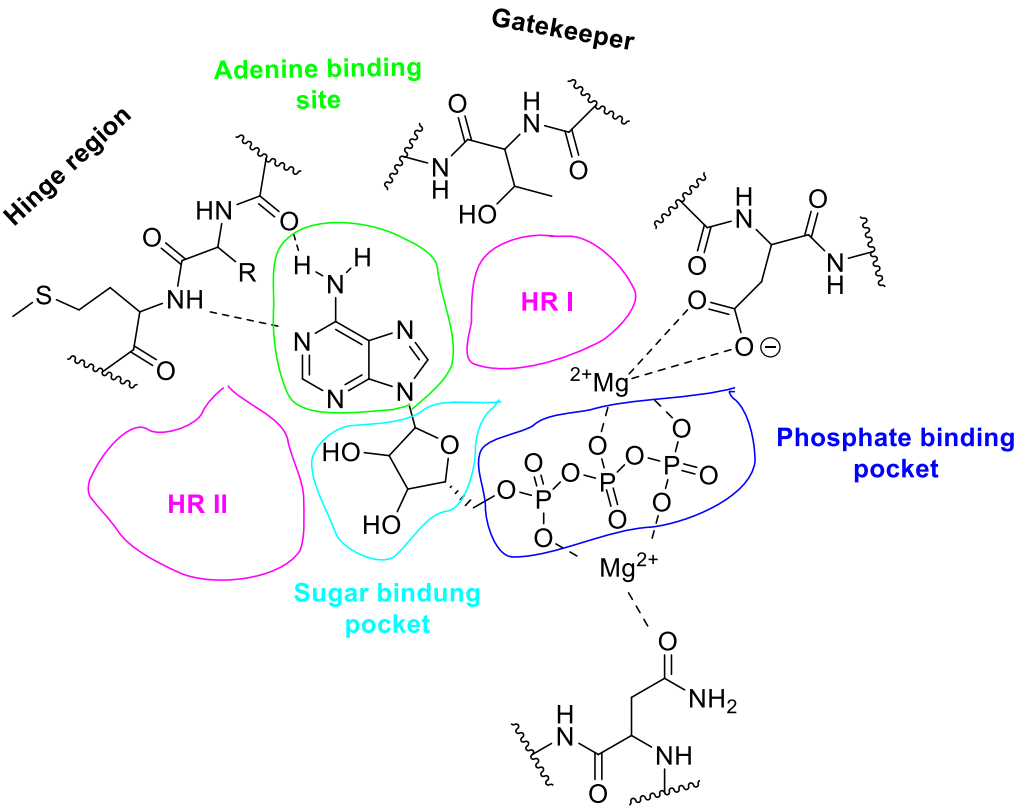


Figure 3: The ATP-binding pocket of p38α MAPK. The binding mode is based on the “Traxler-paragdigma”.[43]

Furthermore, all kinases comprise two conserved hydrophobic structural motifs known as spines. They are connecting the N-lobe with the C-lobe by bridging hydrophobic residues in the N- and C-lobes.[56] The catalytic spine (C-spine) consists of two residues from the N-lobe and six from the C-lobe. The binding of ATP triggers the assembly of the C-spine allowing the two lobes of the kinase to close making the kinase ready for catalysis.[57] The regulatory spine (R-spine) is composed of two residuals from the C-lobe and two from the N-lobe.[56, 58] In detail for p38α MAP kinase, the R-spine consists of the histidine residue (His148) which is part of the catalytic loop, the phenylalanine (Phe169) from the DFG motif and two leucine. Namely, Leu75 from the αC-helix, and Leu86 from the β4-strand.[59] In general, assembly of the R-spine results in the formation of the active conformation of all kinases.[56, 60] Phe169 is essential for the function of the p38α MAPK kinase, every mutation of this amino acid results in a complete loss of activity of the kinase.[33] The dual role of Phe169 as part of the R-Spine and the DFG motif is from utmost importance and is used for the design and binding of type 1 ½ inhibitors which is described in detail in the following chapter of the thesis.

1.5. Classification of protein kinase inhibitors

Kinase inhibitors exhibit different modes of binding to kinases. In general, inhibitors can be divided into those that bind covalently or reversibly to the kinase.[61] Most of the inhibitors show a reversible binding mode to the kinase and according to their binding site, they can be further classified into different types (type I – IV).

1.5.1. Type I inhibitors

Most type I inhibitors bind to the active DFG-in conformation of the kinase occupying the adenine- binding pocket of the kinase by forming hydrogen bonds to the hinge region and mimicking the cosubstrate adenine structure.[62] Thus, type I inhibitors are ATP competitive. Due to high sequence homology of the ATP binding region within the kinases additional sites close to the ATP binding site, like the HR I & II, are addressed by the inhibitor to gain selectivity.[3] Potency may further enhanced by displacing water molecules with suitable residues from the solvent exposed area near the binding site of the kinase by increasing of entropy.[63] Besides selectivity improvement, the occupation of the solvent- exposed area or HR II can be used to improve the physicochemical properties of kinase inhibitors by placing polar residues in this area.[3] A mutation in the ATP binding site preventing the inhibitors binding would most likely also result in a dysfunction of the kinase.[47] Thus, a loss of potency via mutations of the kinase are not observed for type I inhibitors.

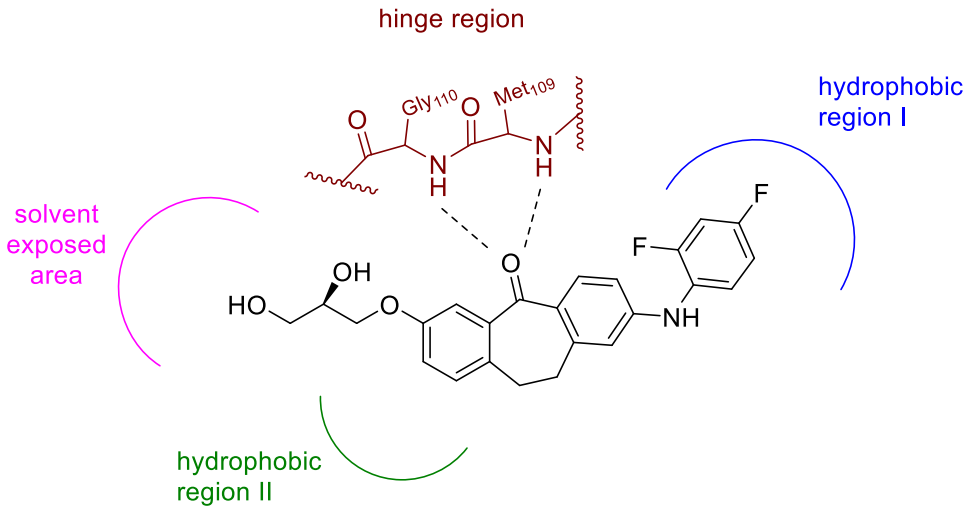


Figure 4: Binding mode of Skepinone-L, a typical type I inhibitor (PDB-Code: 3QUE). Skepinone-L forms two hydrogen bonds to the hinge region of the kinase by inducing a glycine-flip and addresses the HR I.

Skepinone-L is a selective and potent type I inhibitor which was developed in our group. The selectivity of Skepinone-L is achieved by inducing a glycine-flip at the hinge region and occupying hydrophobic regions I. The carbonyl group of the dibenzosuberone core forms two hydrogen bonds with the amide nitrogens of the hinge region of Met109 and via induced glycine-flip with Gly110. HR I is addressed by the hydrophobic 2,4-difluorophenyl moiety while the polar diol groups are oriented towards the solvent exposed area. Moreover, an additional hydrogen bond is formed between the terminal hydroxyl-group of the 2,3-dihydroxypropoxy moiety and the backbone carbonyl of Gly110.[64]

1.5.2. Type II inhibitors

Type II inhibitors can be seen as prolonged type I inhibitors. They also target the ATP-binding pocket, the hydrophobic regions and additional the deep pocket. Thus, the deep pocket is only accessible in DFG-out conformation, type II inhibitors bind to the inactive kinase and stabilising the kinase in the inactive conformation.[65] In this conformation, the Phe side chain is forced in the direction of the ATP-binding pocket, resulting in a hindered access of ATP to the catalytic binding site and simultaneously the deep pocket becomes accessible for the inhibitor. The ATP affinity of kinases is reduced in the inactive conformation, making type II inhibitors less ATP competitive.[3] In theory type II inhibitors are more selective than type I inhibitors because the deep pocket is not highly conserved like the ATP-binding pocket and more interactions with the kinase are formed but there are also examples of type II inhibitors, like BIRB-796, showing an unfavourable selectivity profile.[66] Most type II inhibitors exhibit slow dissociation rates and thus longer target residence time.[67] As additional disadvantage, a mutation in the deep pocket domain can result in the loss of activity of the inhibitor because the mutation does not lead to dysfunction of the kinase.[47]

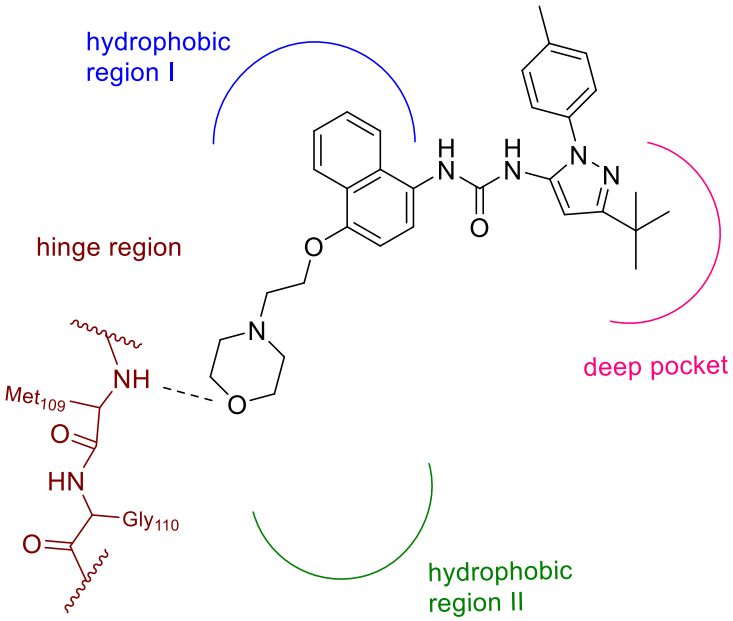


Figure 5: Binding mode of BIRB-796, a typical type II inhibitor which was invented by Boehringer (PDB-Code: 1KV2). The inhibitor interacts with the hinge region and occupies the hydrophobic region I and the deep pocket.

The binding mode of BIRB-796 is shown in Figure 5. The morpholine-moiety of BIRB-796 binds via hydrogen bonding with MET109 to the hinge region of p38 and the naphthalene residual occupies the HR I, while the HR II is not addressed. The urea linker forms hydrogen bonding to Glu71 from αC-helix and to Asp168 of the DFG-motive. The deep pocket is occupied by a bulky *tert*-butyl residual.

1.5.3. Type I ½ inhibitors

Type I ½ inhibitors combine the beneficial characteristics of type I and type II inhibitors and can be seen as a hybrid. Like type I inhibitors they interact with the hinge and can interact with both hydrophobic regions, beyond that they additionally bind to the DFG-motif and stabilize the R-Spine of the kinase.[68] In contrast to type II inhibitors, type I ½ inhibitors do not penetrate the deep pocket of the kinase and are consequently not inducing the DFG-out conformation. They bind to the active kinase and stabilize the DFG-in conformation by interaction with Phe169 of the DFG motif.[69] Although binding to the active conformation, type I ½ inhibitors do not lose potency in the presence of high ATP concentration, assuming high affinity and long TRT towards the kinase.[47, 69] A mutation of Phe169 of the DFG motif results in a complete dysfunction of the kinase, thus resistance due to mutations are rarely described.

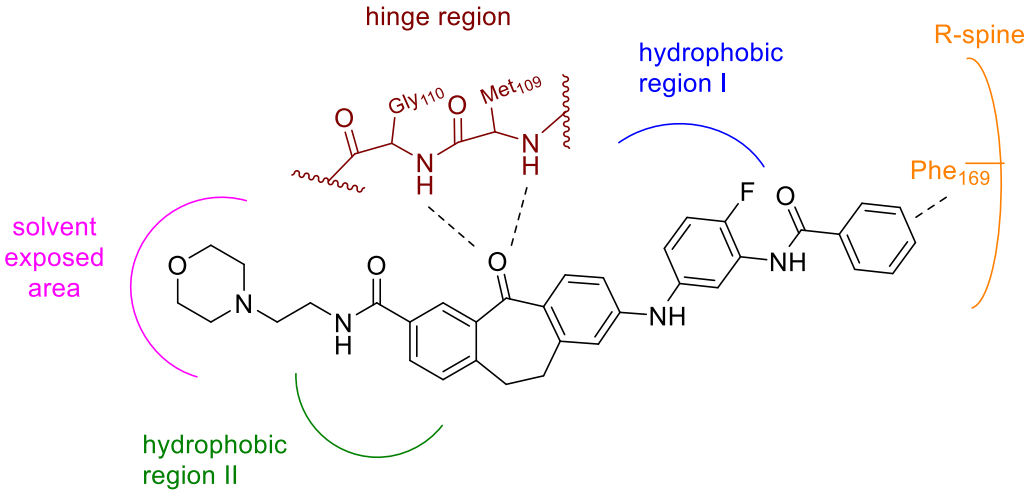


Figure 6: Binding mode of a type 1 ½ inhibitor (PDB-Code: 3UVQ). The inhibitor binds to the hinge region by induced glycine-flip and it occupies the hydrophobic region I. The terminal benzamide interacts with Phe169 of the R-spine via edge-to-face Ar-Ar interaction and stabilizes the DFG-in conformation. The morpholino ethyl amide residue is located in the solvent exposed area.

The carbonyl group of the dibenzosuberone core of the type I ½ inhibitor, shown in Figure 6, forms two hydrogen bonds with the amide nitrogens of the hinge region of Met109 and via induced glycine-flip with Gly110. HR I is addressed by the hydrophobic 2-fluorophenyl moiety while the polar morpholine group is located in the solvent exposed area. The inhibitor binds to the active DFG-in conformation of the kinase while the terminal benzamide moiety of the inhibitor stabilises the R-spine by edge-to-face Ar-Ar interaction with Phe169 of the DFG-motif.[70]

The different properties of type I, type II and type I ½ inhibitors are summarized in Table 1.

Table 1: Comparison of type I, type I ½ and type II inhibitors.

Properties	type I	type I½	type II
Binding side	ATP-binding pocket (HRI / HRII)	ATP-binding pocket R-spine (HRI / HRII)	ATP-binding pocket deep pocket (HRI / HRII)
Activation	Active	Variable	Inactive
DFG-motif	In	In	Out
ATP competitive	Yes	Yes (less)	Yes (less)

1.5.4. Type III inhibitors

Type III inhibitors are not ATP competitive and interact with an allosteric binding site next to the ATP-binding pocket. In contrast to type II inhibitors, they can for example interact with the deep pocket, but they do not bind to the hinge region of the kinase. Due to the unique structure of allosteric binding sites, type III inhibitors are highly selective. The great disadvantage of allosteric inhibitors is, that they are most likely developed by serendipity.[69]

1.5.5. Type IV inhibitors

Type IV inhibitors are also allosteric, non ATP competitive inhibitors, but in comparison to type III inhibitors, they interact with sites distant from the catalytic centrum of the kinase.[69]

1.5.6. Covalent inhibitors (Type VI inhibitors)

In most cases covalent inhibitors comprises of a binding module and a so called “warhead” that is connected via a linker. The “warhead” is an electrophilic moiety used to react with a nucleophilic amino acid of the target kinase. Usually, the ATP binding site is reversible addressed via the binding module, additionally the “warhead” covalently targets a Lys or a Cys in or around the ATP binding site. The Cys is not crucial for the kinase structure and activity, thus mutation of the Cys can prevent the covalent binding.[3]

1.6. p38 MAP kinase inhibitors in Industry

Due to the centrale role of p38 MAPK in cellular processes of inflammation, cancer and other dysfunctions, many attempts to develop an approved kinase inhibitor have been pursued in the last years. Many approaches to establish a p38 MAPK inhibitor for inflammatory diseases such as rheumatoid arthritis failed in clinical trials, mostly because of selectivity or toxicity issues. There is still no approved p38 inhibitor available on the market and apparently big pharma companies have terminated their attempts.[6]

Nevertheless, smaller pharma companies like Chiesi Farmaceutici and TopiVert Pharma Ltd started clinical trials for chronic inflammatory disorders, like chronic obstructive pulmonary disease (COPD), asthma or ulcerative colitis. Their compounds are analogues of the well-known type II inhibitor BIRB-796 and are based on the 1,2,3,4-tetrahydronaphthalen-1-yl-urea structure. Side effects are tried to be minimized by local application of the inhibitors. Considering the prior failure of systemically used p38 MAPK inhibitors for chronic diseases, this approach seems more promising.[6, 71, 72] There is also ongoing patent activity for known p38 inhibitors in new indications with great attention to orphan diseases.[6] For example, Fulcrum Therapeutics has claimed the utilization of p38 MAPK inhibitors to reduce the DUX4 expression for the treatment of facioscapulohumeral muscular dystrophy (FSHD).[73]

Furthermore, novel approaches to selectively inhibit the activation of a single p38 downstream effectors, like MK2, have been done. The aim of these approaches is to avoid side-effects mediated by the global inhibition of p38 MAPK.[6] The clinical candidate from Aclaris Therapeutics ATI-450 is claimed to selectively inhibit the p38α-MK2 dimer by interaction with a region near the ATP-binding site of p38α and simultaneously by binding to the surface of

MK-2 preventing the MK2 activation.[74] The benzooxadiazole-based p38 MAPK inhibitors from Allinky Biopharma are also claimed to inhibit the p38-MK2 heterodimer by binding to an novel allosteric binding site.[75] The success of these new approaches will be investigated by clinical trials.

2. Chemistry

2.1. Introduction

Due to the crucial role of p38α MAPK in cellular and inflammatory processes, many approaches to design selective inhibitors have been conducted. Inter alia, LEO-Pharma published a series of benzophenone based p38 MAPK inhibitors in 2003.[76] Based on their structure, the dibenzosuberone lead structure was previously developed in our group by utilizing a rigidization concept. Therefore, the two aromatic rings of the benzophenone were cyclized by the introduction of an ethylene linker to form the tricyclic dibenzosuberone.[46] Protein kinases are quite flexible structures and undergo conformational changes during activation. Flexible inhibitors can interact with several kinases by induced fit. Rigidization of kinase inhibitors can reduce induced fit and thereof selectivity can be improved.[77] Furthermore, it could be shown by crystallographic studies that the dibenzosuberone scaffold forms two hydrogen bonding to the hinge region via introduction of the glycine-flip.[77] For better orientation, the aromatic rings of the dibenzosuberone scaffold are numbered with A-C, details are shown in Figure 7.

Substitution of the A-ring of the dibenzosuberone core structure led to a gain of activity and selectivity. Resulting in the development of Skepinone-L, a highly active and selective p38α MAPK inhibitor, which is used in combination with Sorafinib for the treatment of cancer to overcome resistance.[77, 78]

For the second generation of dibenzosuberone, the A ring was substituted via amide or ester residues (R_1) instead of ether to simplify the synthetic route. Moreover, ring C was further prolonged with hydrophobic moieties via amide or urea linker (R_2). The original idea behind this prolongation was to develop type II inhibitors by occupying the deep pocket. However, subsequent investigations showed that the residues were too short to penetrate the deep pocket. They interact with the R-spine and stabilizes the DFG-in conformation of the kinase, which is the hallmark of type I ½ inhibitors.[70]

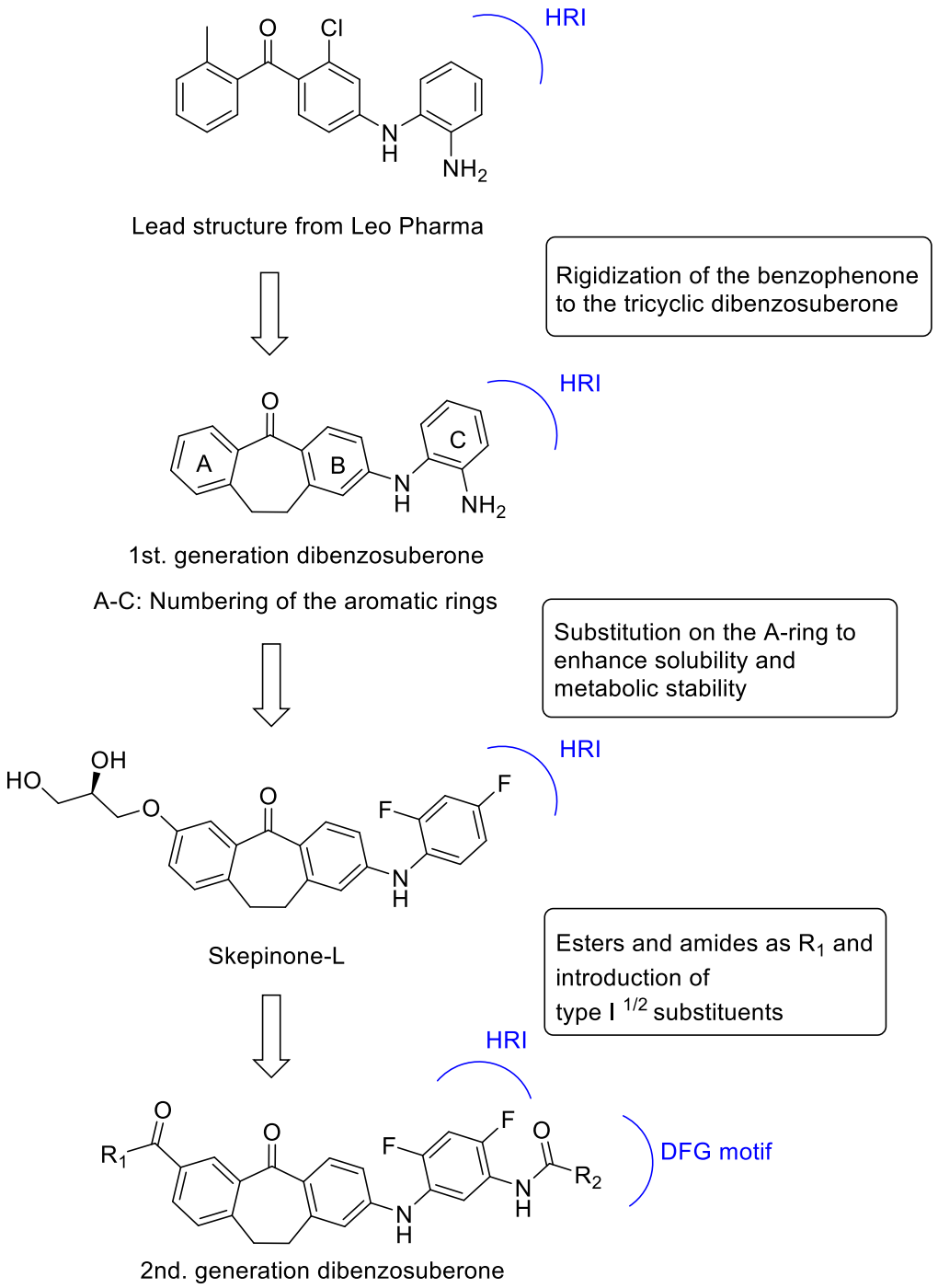


Figure 7: Overview of the most important development steps of p38α MAPK inhibitors in the group of Prof. Laufer. The aromatic rings are numbered with A, B and C for better orientation. The residue R_1 is located in the solvent exposed area and residue R_2 interacts with the R-spine. Examples for R_1 and R_2 are displayed in Figure 8.

Criteria for the efficacy of inhibitors are inter alia the IC_{50} values, the target residence time, and the metabolic stability. Another important factor is the pharmacokinetic of the inhibitor. The most potent inhibitor is of no use if it does not reach the kinase.

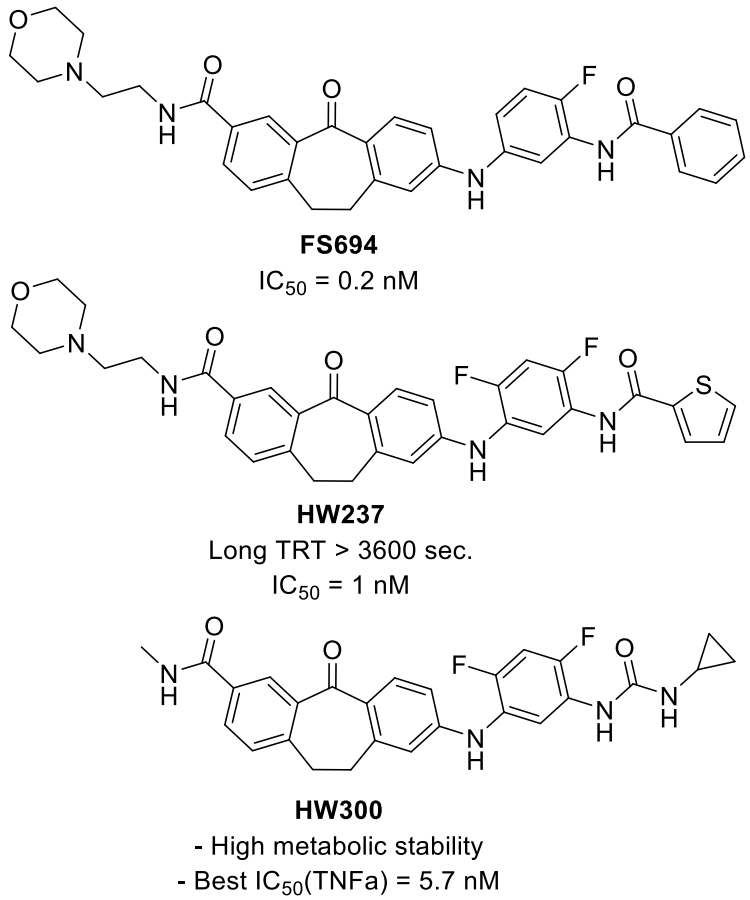


Figure 8: Examples for optimized dibenzosuberone based type I ½ inhibitors from previous work.[79]

The introduction of the type I ½ residues increased the interactions of the inhibitors with the kinase leading to improved inhibitory efficacy. As a result, inhibitors with sub-nanomolar IC_{50} values, some even below the detection limit (3 nM) of the assay system, could be achieved.[70, 80] Furthermore, by introduction of thiophen (**HW237**) as bioisosteric replacement of phenyl (**FS694**), an inhibitor with a long TRT of 3600 seconds was synthesized.[81] One major drawback of the amide-based type I ½ residues is the lack of metabolic stability. The amides are cleaved quickly under physiological conditions by enzymes. In comparison to amide bond, the urea bond is much more stable under physiological conditions. By introduction of urea-based type I ½ residues (**HW300**), the metabolic stability of the inhibitors was improved.[79] The major issue of the urea-based type I ½ residues is the poor aqueous solubility of the inhibitors.[79, 82] As a part of this thesis this issue is addressed and is described in detail with the other aims in the following chapter.

2.2. Aims and objectives of the study

The focus of this thesis is the synthesis of novel dibenzosuberone-based p38α MAPK type I ½ inhibitors. The optimization of the interaction of the type I ½ residues with the R-spine of the kinase is one of the main goals. The future aim of the optimized inhibitors is the selection of a clinical candidate for the treatment of colorectal cancer which will be tested in a phase I/II trial. Therefore, the best inhibitors will be first tested in CRC mouse models.

Novel inhibitors are also designed for investigations of the SAR limitations of the residues. Furthermore, this data is used for patent reasons. Therefore, different bioisosteric replacements are synthesized and the IC_{50} values of the inhibitors are determined.

As already described, one of the major drawbacks of the amide-based type I ½ residues is the lack of metabolic stability due to enzymatic cleaving. After cleaving of the amide bonds, the resulting metabolites are still type I inhibitors, but they do not longer have the beneficial effects of type I ½ inhibitors. Therefore, on the one hand it is tried to lower the metabolism of the amides by steric protection of the amide group with bulky residues like methyl moieties. On the other hand, amides were replaced by different functional groups as alternative linkers. In previous work this strategy was tried by replacing the amide linker through a urea linker.[79] Urea bonds are metabolically more stable than amide bonds, but they suffer from poor solubility leading to potentially bad pharmacokinetic profiles. To address this issue, novel functional groups as bioisosteric replacement for the amide respectively urea groups preventing the metabolism of the type I ½ residues are tested. Furthermore, a strategy to increase the urea solubility by masking the terminal hydrogen is also applied. For the compatibility of the results, morpholino ethylamine is used as standard residue attached to the A-ring for inhibitor synthesis. This moiety is not stable during metabolism, but initial results indicated that the metabolites do not lose activity. To proof the results, some of the metabolites are as well synthesized and tested.

Another important parameter for pharmacokinetic is the absorption of the inhibitor. Due to the complexity and required instruments for the determination of the drug absorption, we are focussing on the physicochemical properties such as solubility which directly effects the absorption. Because of the huge aromatic structure of the inhibitors, the solubility in physiological medium is not optimal. To increase the solubility of the inhibitors, several approaches are tested to optimize the physicochemical properties by attaching heteroatoms or heteroaromatic systems and by increasing the sp^3-amounth of the residues.

Additionally, novel synthetic approaches to further optimize the yield of the dibenzosuberone synthesis are tested. This is required for an efficient synthetic process of the dibenzosuberone scaffold to enable a fast and reliable inhibitor synthesis.

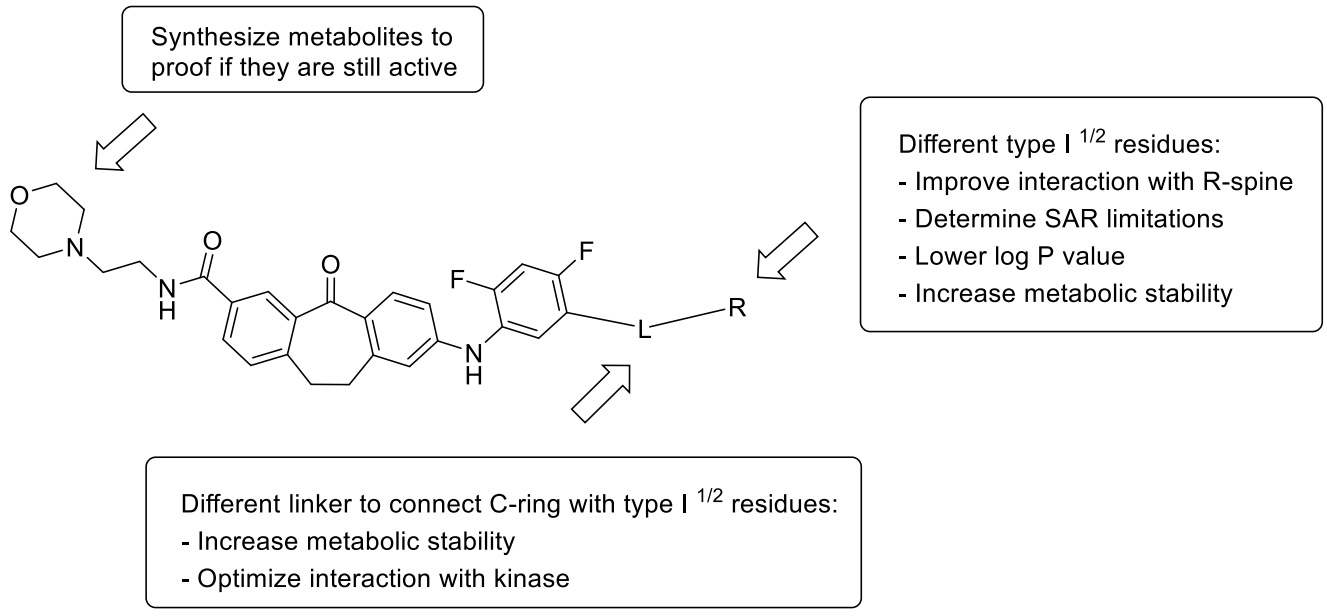


Figure 9: Summary of the aims of the thesis. The main goal is to optimize the interaction with the R-spine and increase ADME-properties of the inhibitors.

In close cooperation with Dr. Tatu Pantsar from the group of Prof. Antti Poso, computational methods are also used for the optimization of the interactions with the kinase. For better understanding of the interactions, computer simulations based on crystal structures of the inhibitor targeting the kinase, were used. The study aims to design novel inhibitors.

2.3. Synthesis of the dibenzosuberone core structure

For the synthesis of the novel inhibitors, a reliable, fast, and high yielded synthesis route for the dibenzosuberone scaffold (methyl 8-chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate) was needed.

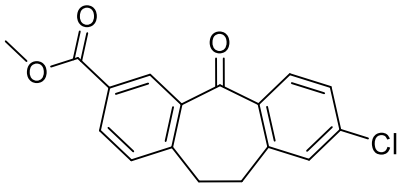
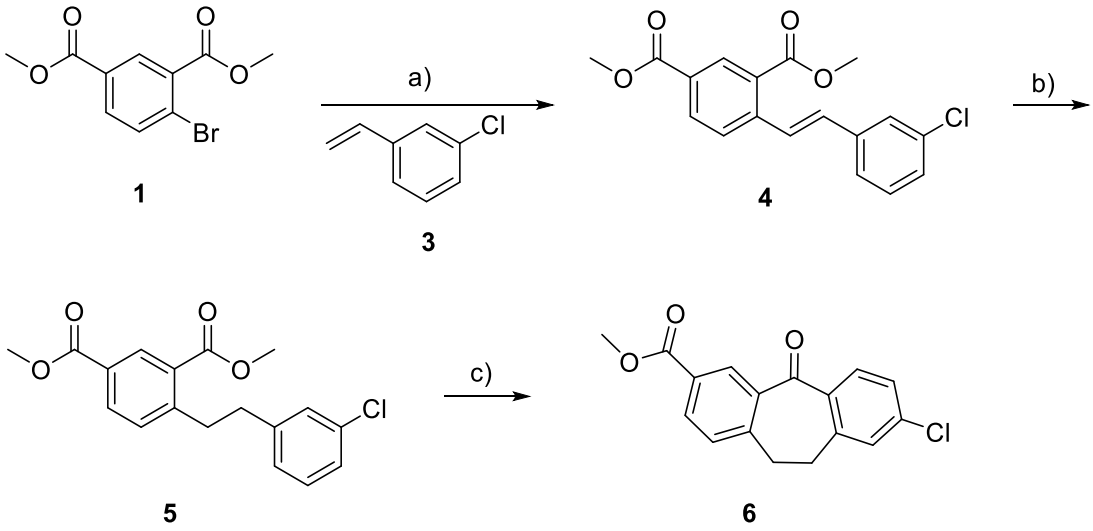


Figure 10: Methyl 8-chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate is the core structure for the dibenzosuberone based type I ½ inhibitors.

In previous work the core structure synthesis was performed via a three-step process involving Heck coupling, reduction of the double bond and consequently cyclisation via Eaton's reagent resulting in an overall yield of only 66%.[79]

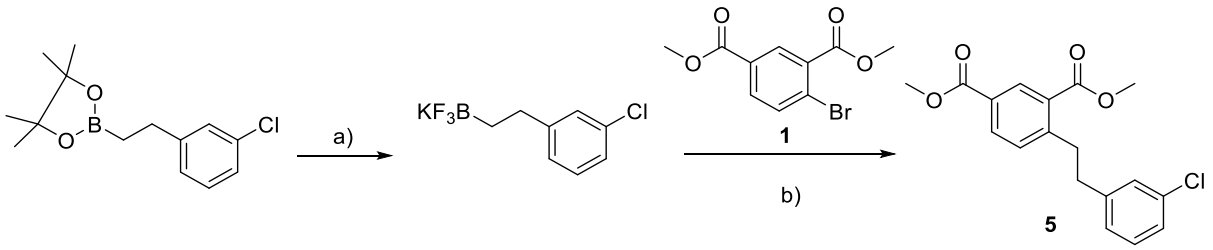


Scheme 1. Synthesis route A, including Heck reaction. Reagents and conditions: a) $Pd_2(dba)_3$, $[(tBu)_3PH]BF_4$, TBAB, N,N-Dicyclohexylmethylamine, Dioxane, 80°C (80%) b) Pd/C, H_2, EtOAc, 5°C (94%) c) Eaton´s reagent, 70°C (88%). This synthetic route was developed by Heike Wentsch.[79]

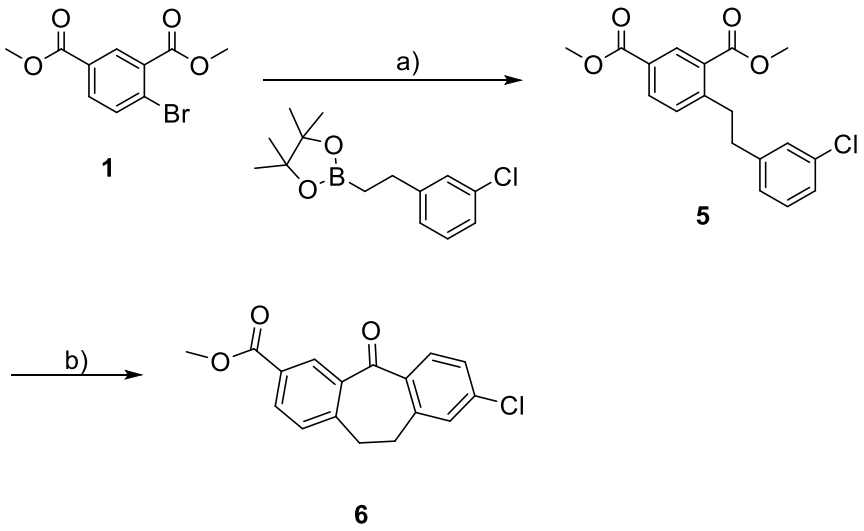
The synthesis route starts with dimethyl 4-bromoisophthalate (**1**) which reacts rapidly with 1-chloro-3-vinylbenzene (**3**) under Heck cross coupling conditions to generate dimethyl (E)-4-(3-chlorostyryl)isophthalate (**4**). For subsequent reduction of the double bond, mild reaction conditions are required to avoid dehalogenation of the chloro-moiety. Therefore, ethyl acetate as solvent and ice bath cooling is demanded for the reaction. This suffers from the poor solubility of the starting material in ethyl acetate and the long reaction time. Using Eaton´s reagent for the cyclization, dimethyl 4-(3-chlorophenethyl)isophthalate (**5**) could be directly

transformed into methyl 8-chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate (**6**) without previous saponification of the ester.[79] For the ring closure Eaton's reagent (7.7 wt% phosphorus pentoxide solution in methane sulfonic acid) is used to promote the acylation reaction. It is an alternative to polyphosphoric acid with the benefit of lower viscosity which makes the handling more convenient. Due to the reduction handling problems and the moderate overall yield of 66%, further improvements of the dibenzosuberone synthesis were required.

The novel synthesis route is based on the idea to avoid the formation of the undesired double bond via direct synthesis of dimethyl 4-(3-chlorophenethyl)isophthalate by utilizing a Suzuki cross coupling reaction instead of Heck reaction. New synthetic strategies enable the use of Suzuki-Miyaura reaction conditions for sp^2-sp^3 coupling. Based on the results of Molander *et.al.*[83], 2-(3-Chlorophenyl) ethylboronic acid pinacol ester was converted to the corresponding potassium alkyltrifluoroborate by adding a sat. solution of potassium bifluoride. The potassium alkyltrifluoroborate were described to be more stable and more reactive compared to the pinacol boronic esters. The reaction was carried out, using $PdCl_2$(dppf) (15 mol %) as catalyst with 3 equiv of Cs_2CO_3 as base in THF/H2O (10:1) heated at reflux temperature for 4 hours. TLC-MS and HPLC analytic indicated the formation of a complex mixture of desired product and dehalogenated or deboronated byproducts as well as homocoupling of the chlorine substrate. By variation of the reaction time and temperature, the ratio of desired product could be increased. However, there was still side product formation complicating the purification step.



Scheme 2: Synthesis of dimethyl 4-(3-chlorophenethyl)isophthalate by utilizing potassium alkyltrifluoroborate for Suzuki-Miyaura reaction. Reagents and conditions: a) KHF2 (4.5 M), MeOH, r.t. b) $PdCl_2$(dppf)*CH_2Cl_2; Cs_2CO_3; THF/H_2O (10:1), 70°C.



Scheme 3: Synthesis route B, including Alkyl Suzuki-Miyaura cross-coupling. Reagents and conditions: a) $PdCl_2$(dppf)*CH_2Cl_2; Cs_2CO_3; THF/H_2O (10:1), 70°C (97%) b) Eaton´s reagent, 70°C (88%).

Motivated by the initial results, the reaction was directly performed with the commercially available pinacol boronic ester. Surprisingly, a complete conversion of the starting material to the desired product without side-product formation was observed. This results in the two-step synthesis route B with improved overall yield of 85%. Instead of 1-chloro-3-vinylbenzene the commercially available corresponding pinacol boronic ester was used under standard Alkyl Suzuki-Miyaura cross-coupling reaction conditions to afford dimethyl 4-(3-chlorophenethyl)isophthalate with 97% yield.[83] Subsequent cyclisation via Eaton´s reagent give the desired dibenzosuberone core structure with 88% yield.

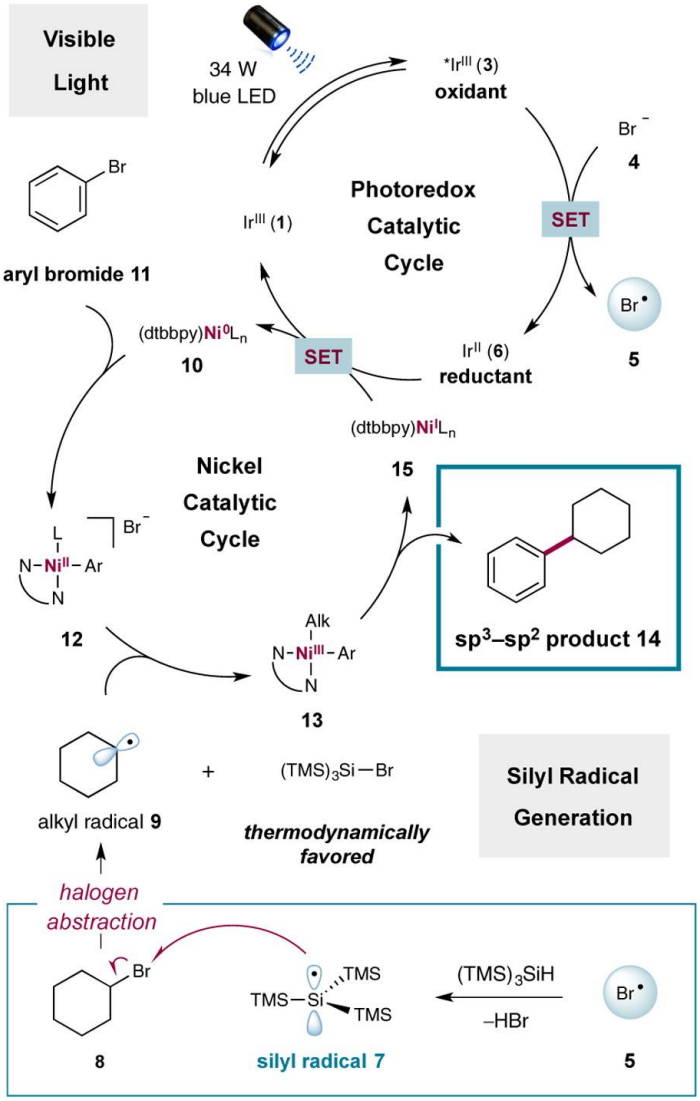
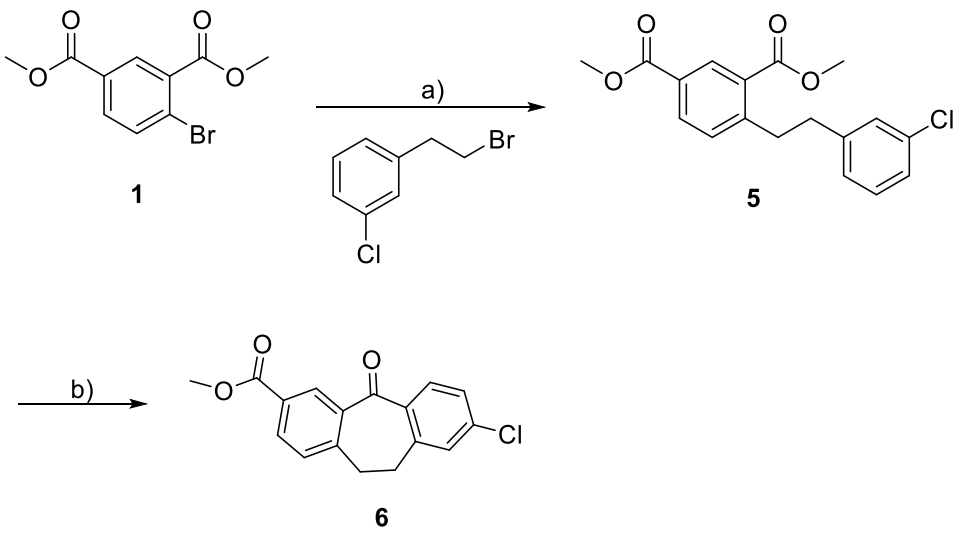


Figure 11: Proposed mechanism of the photoredox reaction for silyl radical mediated Csp^3–Csp^2 bond formation to couple alkyl bromides with aryl bromide. The figure was copied from J. Am. Chem. Soc. 2016, 138, 26, 8084-8087.

In parallel to the development of synthesis route B, another synthetic route was tested. In literature photoredox catalysis is described as a mild and robust method to construct Csp^3–Csp^2 bonds with excellent yields. MacMillan described a protocol to couple alkyl bromides with aryl bromides by the use of commercially available tris(trimethylsilyl)silane with dual nickel / iridium catalysis.[84] The proposed reaction mechanism is that Ni^0 complex undergo oxidative addition into aryl bromide. While, under blue light irritation, the photoexcited iridium catalyst generates a bromine radical which abstracts a hydrogen bond from tris(trimethysilyl)silane to produce a silyl radical intermediate. Subsequent halogen-atom abstraction from the alkyl

bromide to generate the nucleophilic radical species. This radical reacts with the aryl-Ni^{II}complex to produce the corresponding alkyl–Ni^{III} species. Consequent reductive elimination affords the desired C_{sp}^3–C_{sp}^2 product and Ni^{I} catalyst, which is regenerated to Ni^0 by the iridium photoredox catalyst.[84]

The described photoredox procedure was successfully tested, using dimethyl 4-bromoisophthalate as aryl bromide (**1**) and 1-(2-bromoethyl)-3-chlorobenzene as alkyl bromide to generate dimethyl 4-(3-chlorophenethyl)isophthalate (**5**) as desired product with 86% yield.



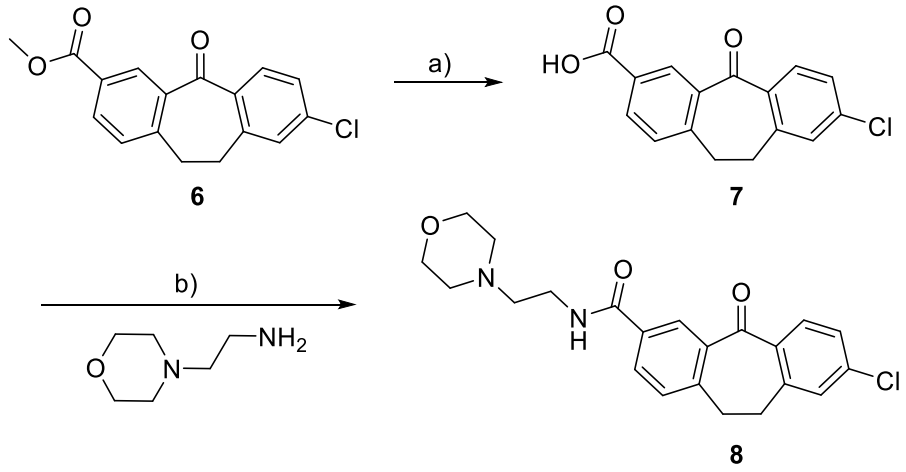
Scheme 4: Synthesis route C, including Photoredox reaction. Reagents and conditions: a) $NiCl_2$*dtbppy, $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$, $(Me_3Si)_3SiH$, Na_2CO_3, DME 20°C [84] b) Eaton´s reagent, 70°C.

In summary, two new high yield two-step synthetic routes for the synthesis of the dibenzosuberone scaffold (**6**) have been successfully established. The overall yield could be improved from 66% to 85%. However, it must be considered that different amount of starting material was used for both reaction ways.

2.4. Introduction of the residue located in the solvent exposed area

The next step to generate a final type I ½ inhibitor is the introduction of a residue for PK adjustment by interaction with the solvent exposed area. The ester group of the dibenzosuberone scaffold does not show optimal pharmacokinetic parameters due to metabolic instability. In biological systems, esters are cleaved quickly by esterase to the corresponding free carboxylic acid. The pKa value of most carboxylic acids is around 3.5 to 4.5 and thus these compounds are ionized under physiological conditions effecting the bioavailability. Crystal structures of pamapimod (a p38 MAPK inhibitor) in complex with the p38 MAPK showed an interaction of the hydrophilic hydroxy groups with conserved water in the solvent exposed area.[85] Thus, several hydrophilic groups have been introduced for the interaction with the solvent exposed area in previous work. Especially, the amides show good solubility, high IC_{50} values and a reliable, high yield synthesis.[70] Several amide residues have been evaluated with only slight difference in the IC_{50} values between the final test compounds.[86] Therefore, all compounds have been synthesized with the same residue,

morpholino ethyl amide, to predict the differences in the inhibitory activity based on the influence of novel type I ½ residues.



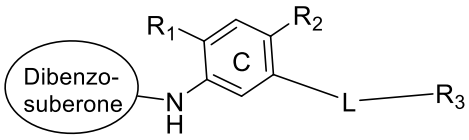
Scheme 5: Synthesis of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide. Reagents and conditions: a) KOH, MeOH, reflux; b) TBTU, TEA, DMF.

To introduce residues for interaction with the solvent exposed area to the dibenzosuberone scaffold, the ester group is cleaved to obtain the free carboxylic acid derivate (**7**). Subsequent amide coupling using 2-morpholinoethan-1-amine and TBTU as activator, affords 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (**8**) as product. With TBTU as coupling reagent a complete conversion of the starting material to the desired product was achieved. The reaction was also possible with other peptide coupling reagents like CDI, but side product formation took place resulting in an additional purification step and lower yields.

The 2-morpholinoethan-1-amine substituted dibenzosuberone scaffold (**8**) was synthesized in big scale as starting material for subsequent synthesis of several novel test compounds. Therefore, the different type I ½ residues are synthesised as the next step.

2.5. Synthesis of type I$^{1/2}$ residues for the dibenzosuberone scaffold

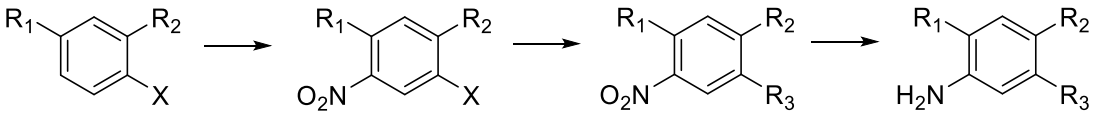
The general structure of a type I ½ residue is shown in figure 12. The C-ring is connected to a residue R_3 (e.g., heterocycle) for addressing the R-spine via different functional groups (e.g., amide) as linker.



R_1/ R_2= F, CH_3, H R_3= type $1^{1/2}$ residue L = linker

Figure 12: General structure of type I ½ residues. They comprise of moieties R_1 and R_2 (F, CH_3, H) for the interaction with the HR I, linked via L (e.g., amide) to a residue for the interaction with the R-spine (e.g., thiophene).

The type I ½ residues are all connected to the dibenzosuberone scaffold via an amine group formed by Buchwald-Hartwig amination. The type I ½ residue comprise of the aromatic C-ring bearing hydrophobic moieties like fluorine for the interaction with the HR I.



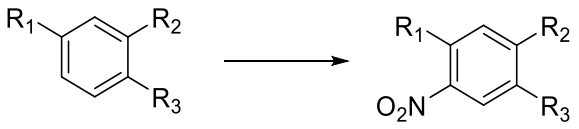
X = NH_2, CH_2COOH R_1/ R_2= F, CH_3, H R_3= type $1^{1/2}$ residual

Scheme 6: General design concept for the synthesis of the type I ½ residues.

In general, the synthesis of the type I ½ linker starts with the nitration of the different C-ring components. Afterwards the residue for the R-spine is attached and the nitro-group is reduced to an amine which is required for the Buchwald-Hartwig reaction in the next step of the final inhibitor synthesis. To prevent side reactions, a nitro-group instead of an amine was used for the first step of the type I ½ residue synthesis which was subsequently converted to the corresponding amine. The aromatic nitration as first step of the type I ½ residue synthesis is described in the next chapter.

2.5.1. Aromatic nitration

First, the aromatic nitro-containing C-ring building block was synthesised via nitration of the corresponding fluor-aniline or fluor-phenylacetic acid derivates using nitrating acid (scheme 7). Nitrating acid is a mixture of concentrated nitric acid and sulfuric acids producing nitronium ion (NO_2^+), as the active species for aromatic nitration.[87] Due to electronic and sterically effects, a selective nitration in *meta*-position to obtain the 5-nitroanaline derivate was observed. It was required to keep the temperature during the reaction and the work up below -10 °C to minimize side product formation. At higher temperature nucleophilic aromatic substitution reactions (SNAr) of the fluorine-substituents to the corresponding phenol derivates were observed. This was especially an issue for the 2,4-difluor aniline (**11**). All synthesized compounds (**11-15**) are summarized in Table 2.



R_1 / R_2 = F, H, CH3 R_3 = NH_2, CH_2COOH

Scheme 7: Aromatic nitration of the different C-ring building blocks. Reagents and conditions: a) H_2SO_4, HNO_3, ice bath.

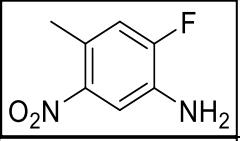
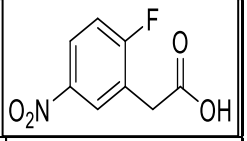
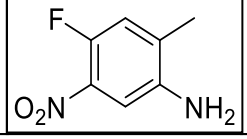
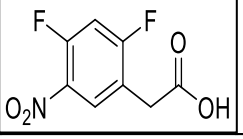
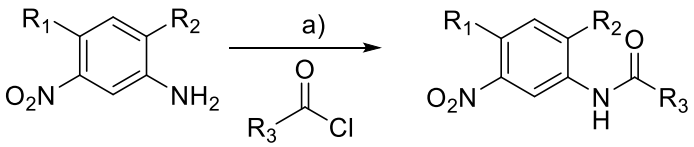
No.	Structure	No.	Structure	No.	Structure
11		**13**		**15**	
12		**14**			

Table 2: Overview of all synthesized aromatic nitro-derivates via nitration.

2.5.2. Amide linker

2.5.2.1. Aromatic amide linker

To complete SAR studies, different residues (R_3) for the interaction with the R-spine linked via amide groups to the aromatic C-ring, were synthesized. Additionally, also for SAR reasons, several residues (R1, R2) addressing the HR I were tested.



R_1/ R_2= F, CH_3, H

Scheme 8: Synthesis of type I$^{1/2}$ aromatic amide linker via amide coupling of an aniline and an acetyl chloride. Reagents and conditions: a) NaH, THF, r.t. or reflux.

The amide coupling starts with the deprotonation of the corresponding nitroaniline with sodium hydride to increase the nucleophilicity of the aniline. The need for these harsh reaction conditions has already been shown in previous work.[79, 86] The reason for this is the weak nucleophilicity of aniline itself which is further enhanced by the electronic withdrawing effect and the inductively deactivation of the nitro and fluorine substituents.

After deprotonation of the aniline derivative, the corresponding acyl chloride was added dropwise. If the carbonyl chloride was not commercially available, the carboxylic acid was refluxed in thionyl chloride for two hours and the excess thionyl chloride was removed via vacuum distillation. The yields of the amide coupling are only moderate because of side reactions based on the harsh reaction conditions. Mainly nucleophilic aromatic substitution (SNAr) reactions of the fluorine substituents take place.

Most of the type I ½ aromatic amide linker shown in Table 3 comprises of two aromatic systems linked via amide group. Heterocyclic five- or six-membered rings (**16-32**), disubstituted phenyl derivates (**33-35**) as well as an adamantly (**36**) or tertbutyl residue (**37**) are used for the interaction with the R-spine.

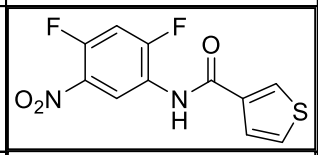
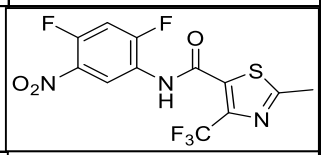
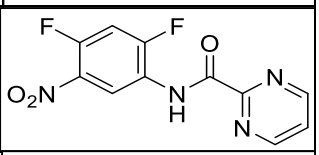
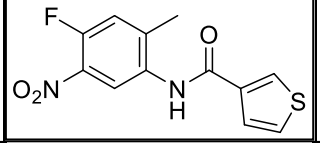
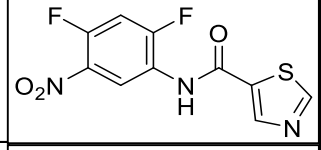
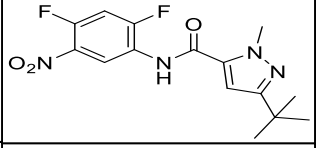
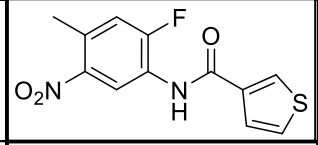
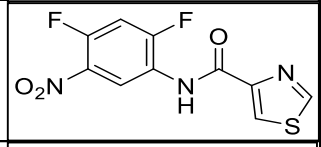
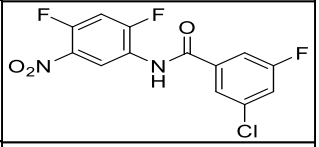
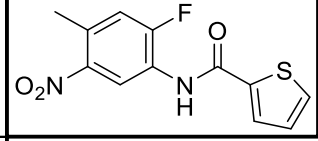
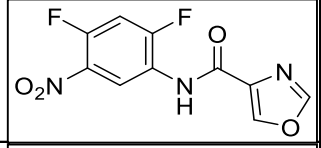
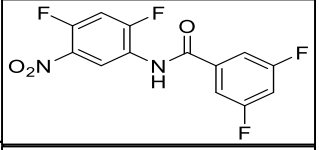
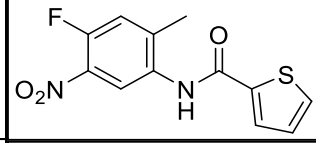
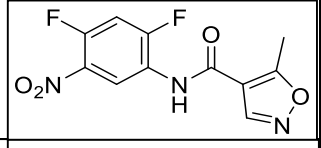
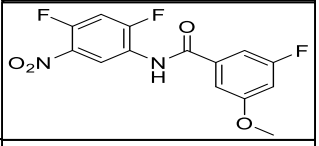
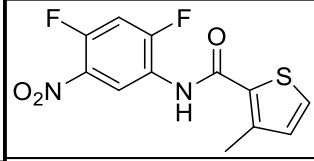
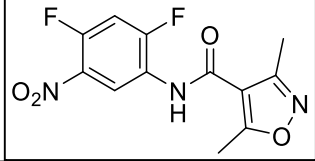
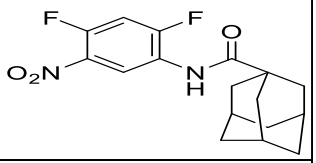
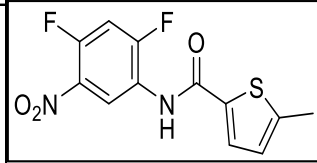
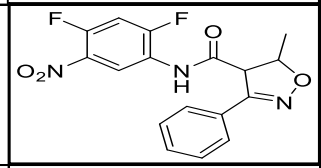
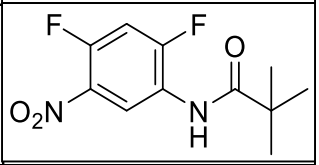
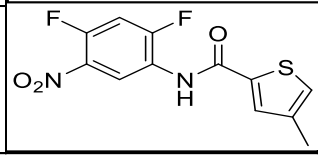
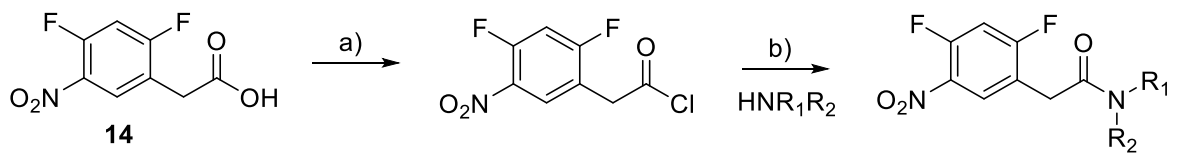
No.	Structure	No.	Structure	No.	Structure
16		**24**		**31**	
17		**25**		**32**	
18		**26**		**33**	
19		**27**		**34**	
20		**28**		**35**	
21		**29**		**36**	
22		**30**		**37**	
23					

Table 3: Overview of all synthesized aromatic amide linker.

2.5.2.2. Aliphatic amide linker



Scheme 9: Synthesis of type I[1/2] aliphatic amide linker. Reagents and conditions: a) $SOCl_2$, reflux; b) TEA, THF, r.t., R_1 / R_2 = residues for R-spine interaction.

Thionyl chloride is used to increase the carbonyl activity of the acid by converting it to 2-(2,4-difluoro-5-nitrophenyl)acetic acid chloride. A mixture of the corresponding amine and triethylamine is added dropwise to the carbonyl chloride. Subsequent attacking of the amine at the carbonyl carbon to give a tetrahedral intermediate result in the desired amide formation

by liberation of a chloride ion.[88] Triethylamine as base is used to drive the equilibrium to the product side by neutralization of the acid which is produced during the reaction and would form an unreactive salt with free amine. In contrast to the aromatic amide linker, harsh reaction conditions are not required because the nucleophilicity of the amine is not reduced by electron withdrawing groups. Furthermore, mainly aliphatic amines (**38-42**), which are better nucleophiles as anilines (**43**), were used.

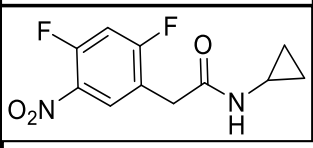
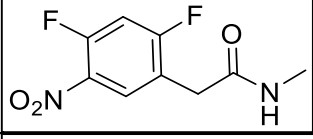
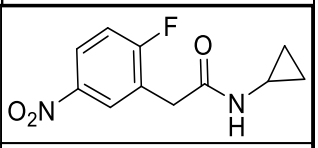
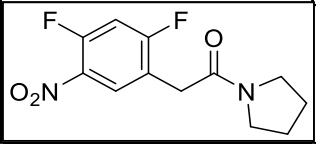
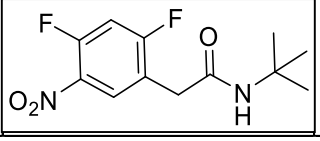
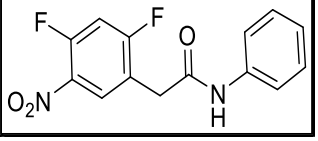
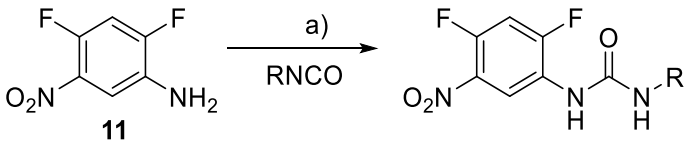
No.	Structure	No.	Structure	No.	Structure
38		**40**		**42**	
39		**41**		**43**	

Table 4: Overview of all synthesized aliphatic amide linker.

2.5.3. Urea linker

2.5.3.1. Urea linker via isocyanates



Scheme 10: Synthesis of type I$^{1/2}$ urea linker. Reagents and conditions: a) Toluene, reflux. R = desired residue for R-spine interaction.

In previous work it could be shown that urea linkers are metabolically more stable compared to the amide analogues.[79] In general, ureas are easily accessible by the reaction of isocyanates with amines by electrophilic addition, without the need of a base or catalyst. Therefore, 2,4-difluor-5-nitroaniline (**11**) as amine component and an isocyanate bearing the desired residue for R-spine interaction (e.g., phenyl), was used for the synthesis of the type I ½ urea linkers. Non commercially available isocyanates were synthesized via Curtius rearrangement using the corresponding carboxylic acid (e.g., cyclopropanecarboxylic acid) and diphenylphosphoryl azide (DPPA).[89]

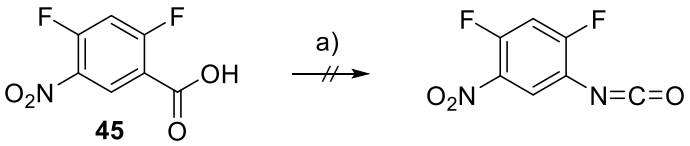
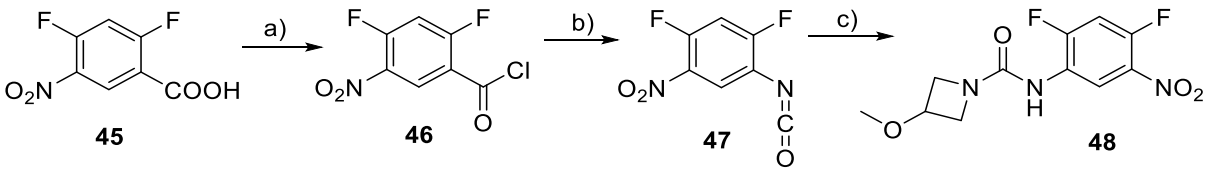


Figure 13: Failed synthesis route for type I$^{1/2}$ urea linker. It was tried to generate isocyanates by treating 2,4-difluoro-5-nitrobenzoic acid with DDPA. Reagents and conditions: a) DPPA, TEA, toluene, reflux.

For the synthesis of the cyclic urea derivates the above strategy could not be used, due to structural limitations of isocyanates. It was first tried to introduce the isocyanate function to the

difluoro-phenyl moiety and to use an amine bearing the residue for R-spine interaction. Therefore, 2,4-difluoro-5-nitrobenzoic acid (**45**) was treated with DPPA to form the isocyanate, but unfortunately without success (Figure 13). Probably due to strong electron withdrawing effects. Hence, a different method to synthesize isocyanates was used. Therefore, the carboxylic acid (**45**) was first activated via thionyl chloride and the resulting carbonyl chloride (**46**) was treated with trimethylsilyl azide to generate the isocyanate (**47**), which was further treated with 3-methoxyazetidine to yield the desired urea compound (**48**).[90]



Scheme 11: Synthesis of type I$^{1/2}$ urea linker via isocyanate formation with trimethylsilyl azide. Reagents and conditions: a) $SOCl_2$, reflux ; b) trimethylsilyl azide ; c) 3-methoxyazetidine, TEA.

2.5.3.2. Urea linker via carbamoyl chloride

The formation of 1,5-difluoro-2-isocyanato-4-nitrobenzene using trimethylsilyl azide did not work reliably. Thus, alternative synthesis strategies were needed. Different synthetic approaches for urea synthesis are reported in the literature.[91] The most classical methods are the use of isocyanates or phosgene, which are both harmful and dangerous. In the last few years, these reagents have been substituted by inherently safer compounds which can be stored and handled without special precautions.

Several test reactions with different reagents have been used to generate the desired urea compound. It was tried to treat pyrrolidine with phenyl chloroformate to produce the intermediate phenyl carbamate. As alternatives for phosgene, CDI and triphosgene were utilised to activate the pyrrolidine by formation of an isocyanate in situ. Additionally, the commercially available 1-pyrrolidinecarbonyl chloride was used.

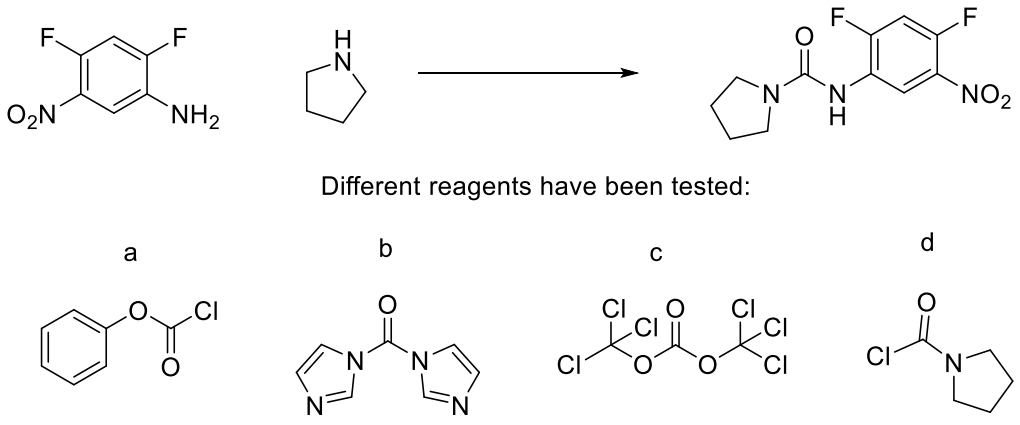
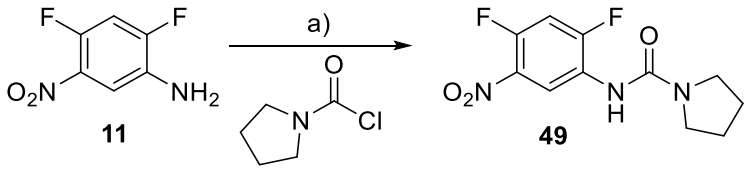


Figure 14: Failed synthesis routes for type I$^{1/2}$ cyclic urea linker. The reagents a-d were used in separate reactions. The conversion of the starting material was monitored by TLC-MS. a = phenyl chloroformate; b = CDI; c = triphosgene; d = 1-pyrrolidinecarbonyl chloride.

The different test reactions were monitored by TLC-MS. A conversion of the starting material to the desired product was only achieved using the carbamoyl chloride. For the other reaction conditions, no conversion or side product formation and only traces of desired product were observed but not further analysed.



Scheme 12: Synthesis of type I$^{1/2}$ cyclic urea linker. Here, exemplarily the synthesis of a pyrrolidine derivate is shown. *Reagents and conditions: a) NaH, THF.*

For the synthesis of the cyclic urea linker, 2,4-difluor-5-nitroaniline (**11**) was first deprotonated using sodium hydride to increase the nucleophilicity of the aniline. Afterwards, the corresponding carbamoyl chloride was added dropwise. Mechanistically it comes to a nucleophilic attack of the activated aniline on the carbonyl to form a tetrahedral intermediate, followed by the removing of the chloride anion as leaving group and the formation of the desired urea compound.[92]

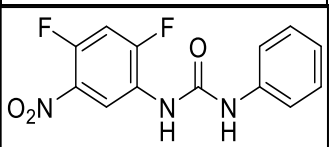
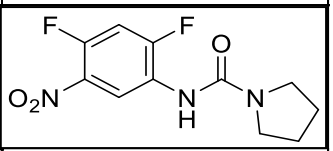
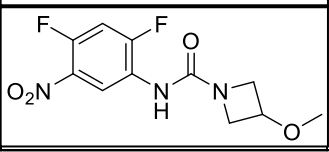
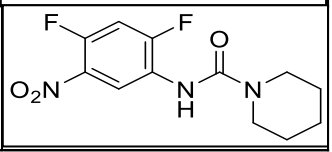
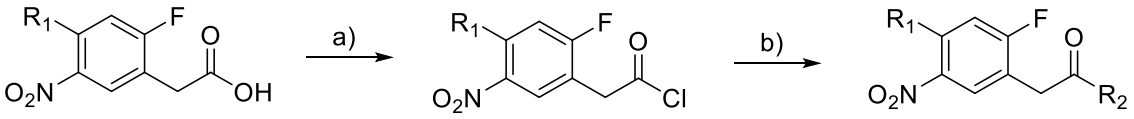
No.	Structure	No.	Structure
44		**49**	
48		**50**	

Table 5: Overview of all synthesized cyclic urea linker.

2.5.4. Ketone and Weinreb amide linker

As novel functional groups, ketones and the Weinreb amide were synthesized as alternative linkers to connect the aromatic C-ring and the residue for the R-spine interaction.



R_1 = F, H

Scheme 13: Synthesis route A of Ketone type I$^{1/2}$ linker via Friedel-Crafts acylation. Reagents and conditions: a) $SOCl_2$, reflux; b) $AlCl_3$, R (aromatic system) as solvent, ice cooling. R_2 = residue for R-spine interaction.

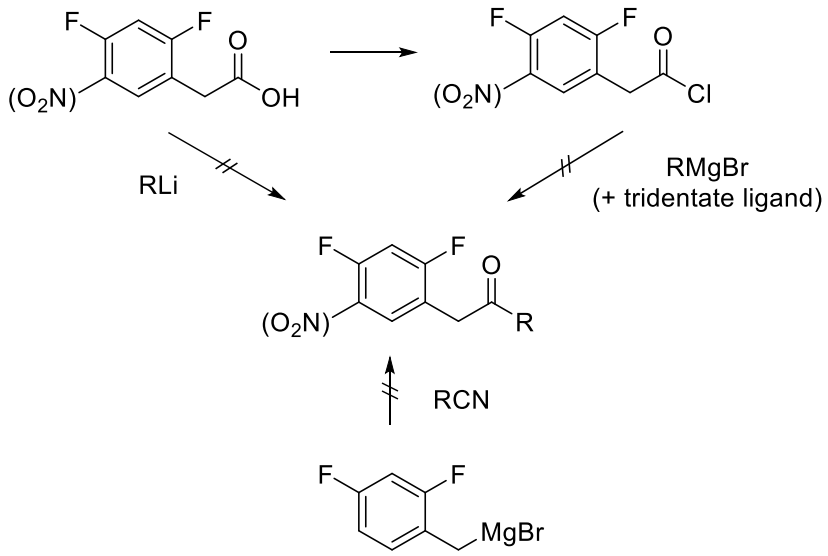
If the desired residue is an aromatic system, accessible to Friedel-Crafts acylation, synthesis route A is chosen for the ketone synthesis (Scheme 13). The synthesis via Friedel-Crafts

acylation starts with the activation of the acetyl acid derivative with thionyl chloride to afford the acetyl chloride. The arene is used as solvent and acetyl chloride is added dropwise.[93] Quantitative conversion of the starting material was observed for benzene (**51, 55**) as solvent. The reaction of fluorobenzene (**52, 56**), toluene (**53**) and isopropyl benzene (**54**) was slower and side product formation occurred. There was no product formation using thiophene or thiazole as a solvent, due to polymerisation.[94] Especially, thiophene reacts heavily by contact with acids like aluminium chloride to form a black, solid polymer with strong odour.

Different synthetic strategies were tested to get access to residues which could not be synthesized via Friedel-Crafts acylation like thiophene or aliphatic moieties. According to the literature, carboxylic acids produce ketones by treatment with organolithium compounds.[95] 2,4-difluoro-5-nitrophenylacetic acid (**14**) was treated with cyclopropyl lithium at -78°C. After 2 hours there was no conversion of the starting material. Therefore, the reaction was slowly heated to room temperature and monitored by TLC-MS. The desired product was not formed, but a decompensation of the starting material was observed. Thus, other methods were tested.

In theory, ketones can be synthesized via different variations of Grignard reactions. In parallel, the addition of the Grignard reagents to a carbonyl chloride and to a nitrile were tested.[96, 97] Grignard reagents added to nitriles form imines as intermediates, which give ketones after subsequent hydrolysis with aqueous acid.[98] Unfortunately, there was no product formation observed for the reaction of (2,4-difluorobenzyl)magnesium bromide with cyclopropane carbonitrile. The same for the other test reaction using 2,4-difluoro-5-nitrobenzoyl chloride and 2-thienylmagnesium bromide. One reason for the failure could be that ketones are still highly reactive toward organometallic reagents and can further react with an additional organometallic reagent to a tertiary alcohol.[99] In the literature, bis[2-(N,N-dimethylamino)ethyl] ether is described as a tridentate ligand, which lowers the reactivity of Grignard reagents and thus preventing the ketone from nucleophilic addition by Grignard reagents.[100] Nevertheless, a product formation was not achieved by adding of the tridentate ligand to the reaction. Another reason for the failure of these attempts could be a side reaction of the Grignard reagents with the nitro-groups providing the N-oxides.[101]

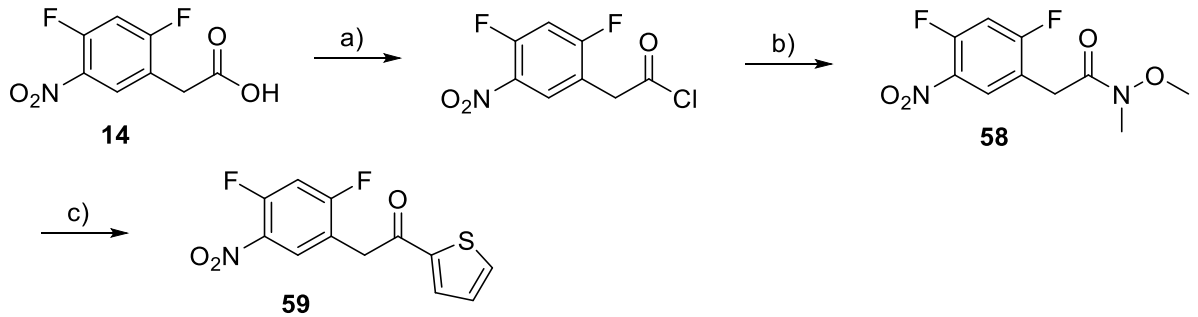
To avoid this limitation, the reaction was tested with 2-(2,4-difluorophenyl)acetyl chloride. It was planned to introduce the nitro-group in the next step. With aromatic residues for R-spine interaction, a late-stage nitration is not possible due to side product formation (nitration of both aromatic rings). Therefore, the reaction was tested using cyclopropyl magnesium bromide, but no conversion of the starting material was observed.



Scheme 14: Different, failed attempts for ketone type I ½ linker synthesis. Several variations of organometallic mediated reactions have been tried to synthesis the desired ketone.

The last idea was the Weinreb-ketone synthesis. Therefore, the carboxylic acid (**14**) is activated to the acid chloride, followed by nucleophilic acyl substitution to convert the acid chloride with N,O-Dimethylhydroxylamine to the Weinreb amide (**58**). Subsequent treatment of this species with an organometallic reagent such as a Grignard reagent give the desired ketone as product. The benefit of this method is the avoiding of over-addition of two organometallic reagents to form an alcohol. After adding of the organometallic reagent to the Weinreb amide, the tetrahedral intermediate is able to form stable chelates and this prevents further reactions.[102]

Only via Weinreb ketone synthesis (**Scheme *15***) the desired product with a thiophen residue (**59**) could be synthesized. The yields of the last step were quite low (9%) due to side reaction of the addition of the Grignard reagent to the nitro-group. Especially, thiophene was from utmost interest due to previous results indication thiophene as residue with the longest TRT.[79]



Scheme 15: Synthesis route B of Ketone type I$^{1/2}$ linker via Weinreb ketone synthesis. *Reagents and conditions: a) $SOCl_2$, reflux b) N,O-dimethyl hydroxylamine, TEA, DCM, r.t.; c) RMgBr, THF, r.t.*

The intermediate Weinreb amide (**58**) was also used for test compound synthesis. In Table 6 an overview of all ketone-based type I ½ residues are shown.

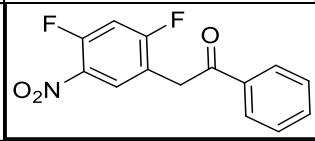
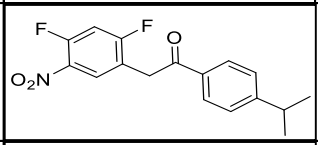
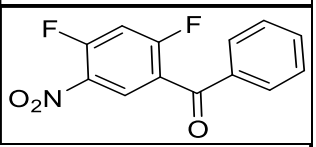
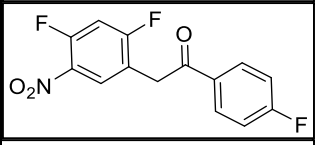
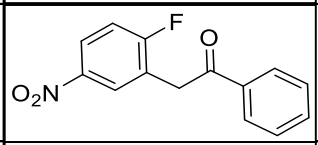
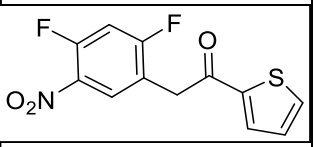
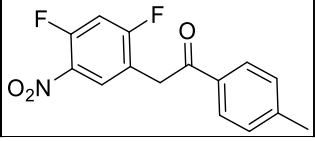
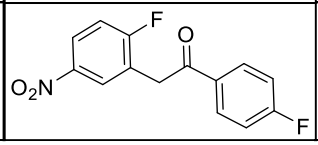
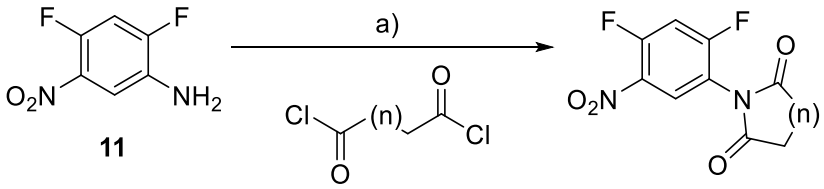
No.	Structure	No.	Structure	No.	Structure
51		**54**		**57**	
52		**55**		**59**	
53		**56**			

Table 6: Overview of all synthesized ketone linker.

2.5.5. Imide linker

Imides were also used as alternative linkers to prevent metabolism.



Scheme 16: Synthesis of Imide type I ½ linker. The procedure was used to synthesis a 5 or 6 membered ring and also for the phthalimide analogous (n = 1, 2). Reagents and conditions: a) NaH, THF.

For the synthesis of the imide linker, 2,4-difluoro-5-nitroaniline (**11**), a carbonyl dichloride derivate and sodium hydride as base are used. Similar to the amides, the synthesis of the imides starts with the deprotonation of the aniline in order to increase the nucleophilicity. Here, two equivalents of the base are used to ensure the reaction of both carbonyl chlorides, which is required for the imide formation. The synthesis is shown in Scheme 16.

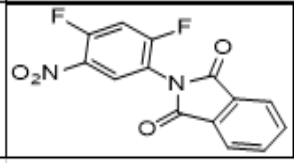
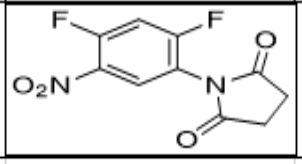
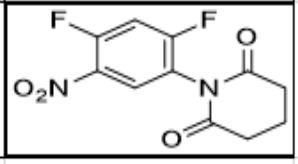
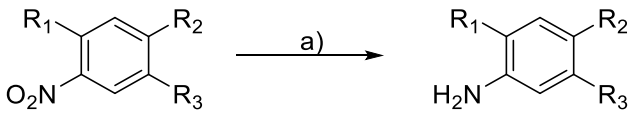
No.	Structure	No.	Structure	No.	Structure
57		**58**		**59**	

Table 7: Overview of all synthesized imide linker.

Table 7 summarizes all imide-based type 1 ½ linker. A phthalimide derivate **57** and two aliphatic derivates (**58, 59**) were synthesized.

2.6. Reduction of the nitro-group

To connect the type $I^{1/2}$ residue to the dibenzosuberone scaffold via Buchwald-Hartwig amination, the nitro group was converted to an amine. The subsequent reduction of the nitro-group was performed with tin chloride in ethanol at room temperature overnight.[103] Using these mild reaction condition, no side product formation is observed. An excess of sodium bicarbonate is used for the work up process to entirely remove tin from the product causing in some cases a separation problem of the product resulting in lower yields. Despite the work up problems, this reduction method was still the method of choice because harsher reaction conditions often lead to decompensation of the product.



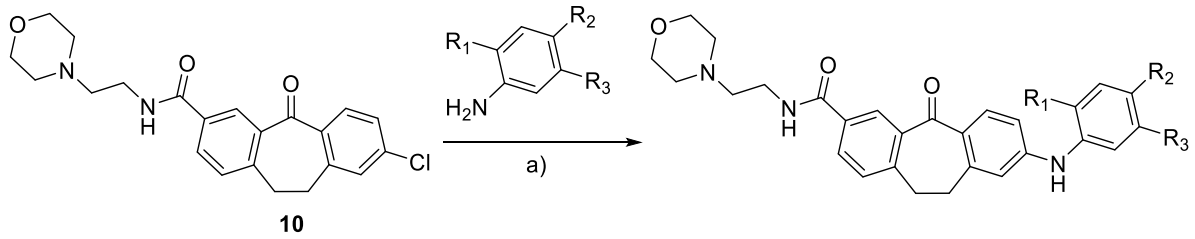
R_1/ R_2= F, CH_3, H R_3= type $1^{1/2}$ residual

Scheme 17: Reduction of the nitro-group. Reagents and conditions: a) $SnCl_2$, EtOH.

These mild reaction conditions enable the successful reduction of the nitro-groups of all above-described type I ½ residues.

2.7. Connection of the type I ½ residues with the dibenzosuberone scaffold

The Buchwald-Hartwig amination[102] is the last step to obtain novel dibenzosuberone based p38α MAPK inhibitors. It connects the morpholino ethyl amide substituted dibenzosuberone scaffold with the type I ½ residues. The reaction is shown in Scheme 18.



R_1/ R_2= F, CH_3, H R_3= type $1^{1/2}$ residue

Scheme 18: Buchwald-Hartwig amination to connect the morpholinoethan amine substituted dibenzosuberone scaffold with the type I ½ residues. Reagents and conditions: a) BrettPhos Pd G3, K_2CO_3, dioxane, argon atmosphere, 100°C.

The Buchwald-Hartwig amination is a palladium catalysed cross coupling reaction for the synthesis of aryl amines using aryl halides (or pseudohalides) and amines for the formation of a new C-N bond.[102] Previous optimization studies showed BrettPhos Pd G3 as catalyst/ ligand, potassium carbonate as base and dioxane as solvent as best reaction conditions with highest yields.[79] BrettPhos Pd G3 is a precatalyst featuring an air and moisture stable catalyst with an accurate palladium: ligand ratio.[104]

The yields of the Buchwald-Hartwig reaction for the different final compounds are widely varying between poor (11%) and excellent (94%). One reason for this is the ability of side reactions based on the different structure of the type I ½ residues depending on the attached moieties. For example, if the final type I ½ residues has halogen groups attached for interaction with the R-spine, homo coupling can occur as side reaction. All synthesised inhibitors are further described and shown in the results and discussion section.

2.8. Synthesis of the Azadibenzosuberone core structure

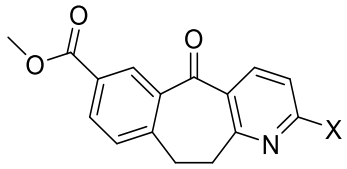
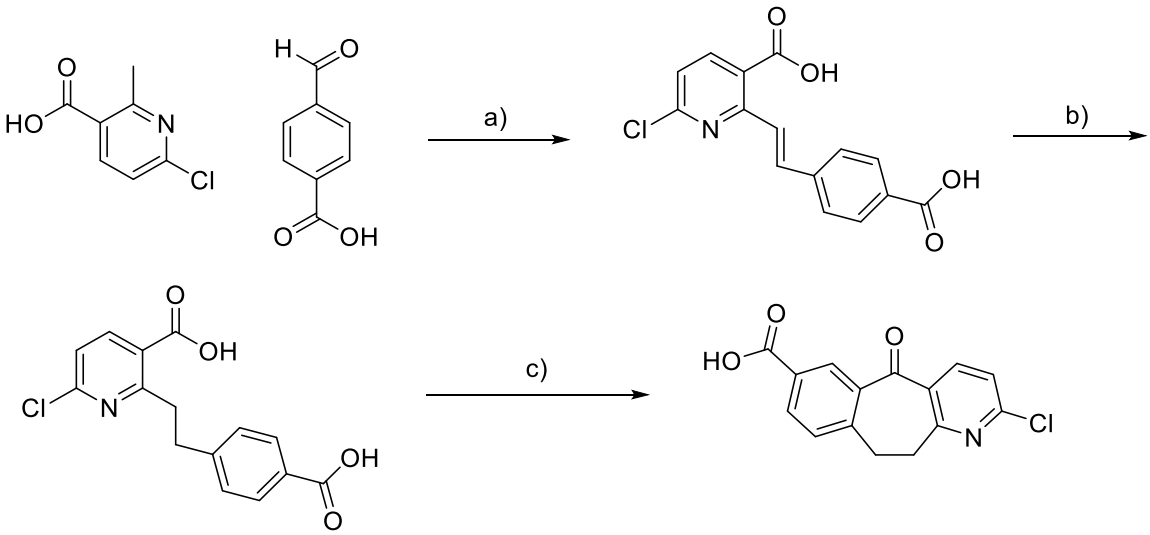


Figure 15: Methyl 5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate is the core structure of the azadibenzosuberone scaffold.

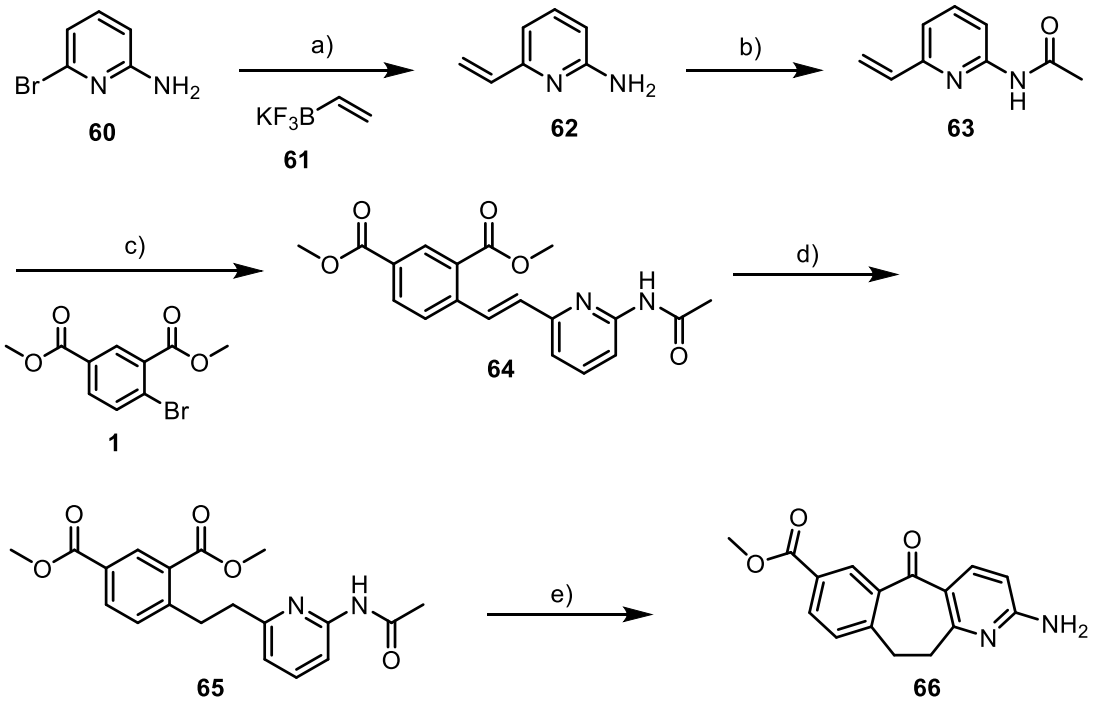
Based on computational studies, a nitrogen in the B-ring of the dibenzosuberone scaffold should favour the bioactive conformation of the inhibitor, displace water molecule from the binding pocket and lower the log-P value. The resulting azadibenzosuberone scaffold is shown in Figure 15.

The synthesis of the core structure was first tried via a three-step process. As first step, a C-C bond formation via carbanion was planned, followed by reduction of the double bond and consequent cyclization using polyphosphoric acid.



Scheme 19: First synthetic approach for the azadibenzosuberone core structure. Reagents and conditions: a) KOt-Bu, THF, 0°C; b) H_2, Pd-C; c) polyphosphoric acid, 200°C.

Unfortunately, this approach (Scheme 19) failed at the first step, because only traces of the desired product could be isolated. Despite all efforts, no significant improvement of the yield was achieved. Therefore, another synthesis route was planned. Several approaches have been tried and finally a five-step synthesis route afforded the desired azadibenzosuberone core structure with an overall yield of 34%.

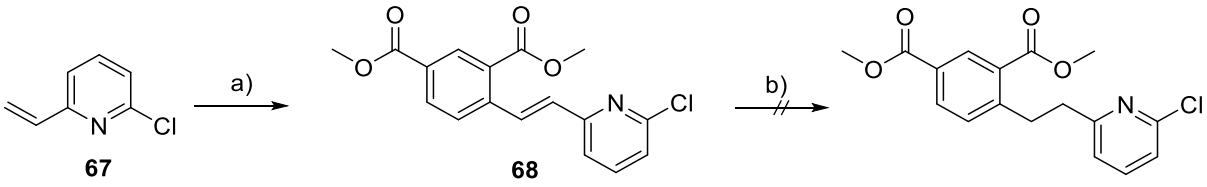


Scheme 20: Azadibenzosuberone synthesis. Reagents and conditions: a) $PdCl_2(dppf)_2$, Et_3N, iProp/H_2O (2:1), 80°C (88%); b) acetyl chloride, TEA, rt (73%); c) $Pd_2(dba)_3$, $[(tBu)_3PH]BF_4$, TBAB, N,N-Dicyclohexylmethylamine, Dioxane, 80°C (73%); b) Pd/C, H_2, MeOH, r.t. (91%); e) 1. Eaton´s reagent, 2. H_2O, 3. MeOH, H^+ (79%). The idea for this synthesis route was given by Dr. Michael Forster.

For the final, successful azadibenzosuberone sythesis, 6-bromopyridin-2-amine (**60**) reacts with potassium vinyltrifluoroborate (**61**) under Suzuki-Miyaura cross coupling conditions to generate 6-vinylpyridin-2-amine (**63**) in very good yield.[13] After purification via flash column chromatography, the product was obtained as colourless oil which slowly starts to polymerize. To avoid polymerisation, 4-*tert*-Butylcatechol (0.5%) as stabilizer was added to the product and it was stored under inert gas atmosphere. Polymerisation was particularly a problem when acetic anhydride in excess and consequent neutralization via dil. ammonia solution was used for protection of the amine. Therefore, milder reaction conditions for example stochiometric amounts of acetyl chloride, are required to avoid polymerisation. Protection of the amine is required for the next step to avoid side reaction like Buchwald-Hartwig coupling. The protected N-(6-vinylpyridin-2-yl)acetamide (**63**) reacts rapidly with Dimethyl 4-bromoisophthalate (**1**) under Heck cross coupling conditions to generate dimethyl (E)-4-(2-(6-acetamidopyridin-2-yl)vinyl)isophthalate (**64**). In contrast to the dibenzosuberone synthesis, the reduction of the double bond is performed in Methanol at room temperature within 2 hours to obtain dimethyl 4-(2-(6-acetamidopyridin-2-yl)ethyl)isophthalate (**65**) in excellent yield. Due to the structure, dehalogenation is not an issue hence harsher conditions are tolerated. Using Eaton´s reagent for cyclisation, a mixture of the desired product (**66**) and the free carboxylic acid was obtained. Due to the amphiphilic character of the structure, it cannot be separated from the water phase, resulting in poor yields. To address this, water was added to the reaction mixture and it was stirred at 70°C for 5 hours, to cleave all protecting groups. Afterwards, water was removed, and the mixture was dissolved in methanol for Fischer esterification to obtain methyl 2-amino-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate (**66**) in good yield.

In comparison to dibenzosuberone, where the halogen moiety is attached to the B-ring of the core structure and the amine function is part of the C-ring of the type $I^{1/2}$ residue, these functionalities are switched for the azadibenzosuberone synthesis. Because the reduction of the double bond of the chloropyridine derivate did not work, due to fast dehalogenation of the

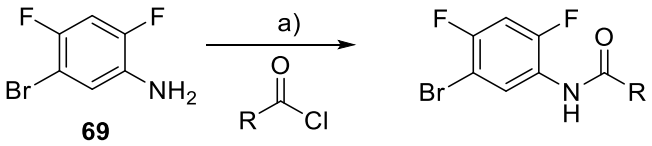
starting material even at mild reaction conditions. The reason for this, is the increased activity of the pyridine ring compared to the phenyl ring of the dibenzosuberone.



Scheme 21: Failed synthesis route for the Azadibenzosuberone scaffold. Reagents and conditions: a) dimethyl 4-bromoisophthalate, $Pd_2(dba)_3$, $[(tBu)_3PH]BF_4$, TBAB, N,N-Dicyclohexylmethylamine, Dioxane, 80°C (19%); b) Pd/C, H_2, ethyl acetate, -5°C.

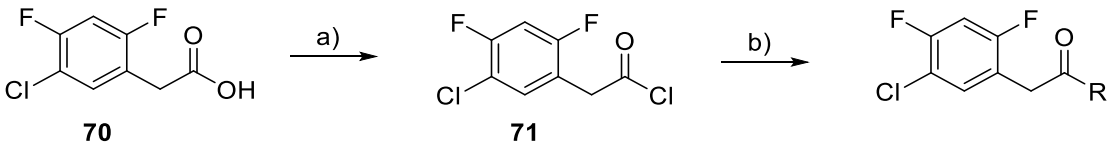
2.9. Synthesis of type I$^{1/2}$ residues for the azadibenzosuberone scaffold

The synthesis of the type I ½ linker for the azadibenzosuberone scaffold was performed similarly to those for the dibenzosuberone scaffold. The only difference is the used 2,4-difluorophenyl derivative. While an amine-group was required for Buchwald-Hartwig coupling of the dibenzosuberone linker, a halogen moiety was needed for the azadibenzosuberone derivates due to different synthetic strategies for the core scaffold. Therefore, 5-bromo-2,4-difluoroaniline (**69**) was used instead of 2,4-difluoro-5-nitroaniline (**11**) and 2-(5-chloro-2,4-difluorophenyl)acetic acid (**70**) was used instead of 2-(2,4-difluoro-5-nitrophenyl)acetic acid (**14**).



Scheme 22: Synthesis of type 1$^{1/2}$ amide linker. Reagents and conditions: a) NaH, THF. R = residues for R-spine interaction.

In most of the cases, a complete conversion of the starting material to the desired product, without any side product formation, could be observed. A reason for this could be the exchange of the strong deactivating nitro-group to a halogen.



Scheme 23: Synthesis of Ketone type 1$^{1/2}$ linker via Friedel-Crafts acylation. Reagents and conditions: a) SOCl2, reflux; b) AlCl3, R (aromatic system) as solvent, ice cooling. R = residues for R-spine interaction.

The synthesized type I ½ inhibitors for the azadibenzosuberone scaffold are summarized in *Table 8*.

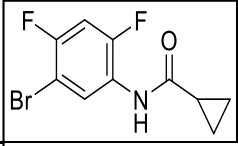
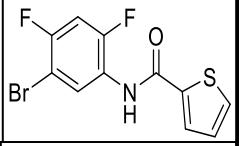
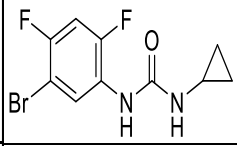
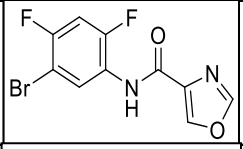
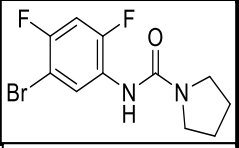
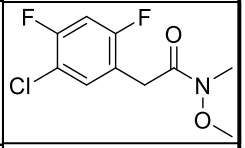
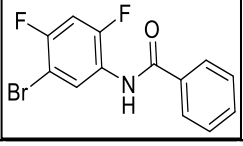
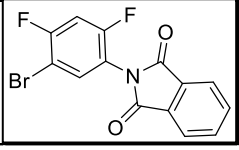
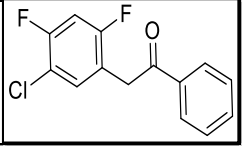
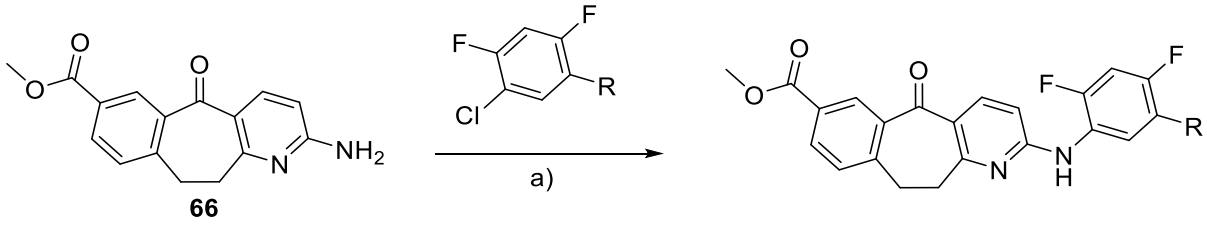
No.	Structure	No.	Structure	No.	Structure
72		**75**		**78**	
73		**76**		**79**	
74		**77**		**80**	

Table 8: Overview of all synthesized type I ½ residues for the azadibenzosuberone scaffold.

2.10. Connection of the type I ½ residues with the azadibenzosuberone scaffold

In comparison to the dibenzosuberone synthesis, the introduction of the morpholino ethyl residue to the azadibenzosuberone scaffold would lead to side product formation due to the attached aromatic amine group. In order to prevent additional steps for amine protection, the Buchwald-Hartwig amination was done as the next step. Here, the azadibenzosuberone scaffold bears the amine moiety while the type I ½ residue bears the halogen moiety which is required for the Buchwald-Hartwig amination to connect both parts via amine linker.

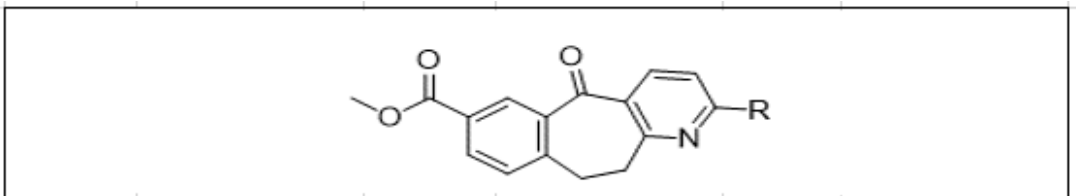


R = type $1^{1/2}$ residue

Scheme 24: Buchwald-Hartwig reaction of the azadibenzosuberone and a type I ½ residue. Reagents and conditions: a) BrettPhos Pd G3, K_2CO_3, dioxane, argon atmosphere, 100°C.

The Buchwald-Hartwig reaction of the azadibenzosuberones is the critical step for the final compound synthesis. The yields of the reactions are varying between no conversion of starting material and poor (38%, compound **81**). Compared to the average yields for the Buchwald-Hartwig amination of the dibenzosuberones, the yields of the azadibenzosuberones were lower. A reason for this could be the chelation effect of the pyridine ring on the palladium catalysts.[105]

There was no conversion of starting material for residues **78-80**. Different reaction conditions (Pd-source, ligand, base, solvent) have been tested, without conversion of the starting material or no formation of the desired product.



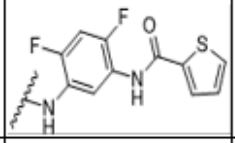
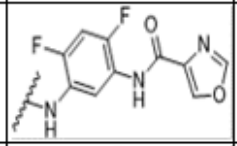
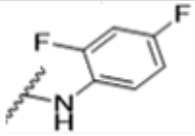
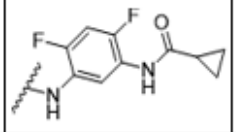
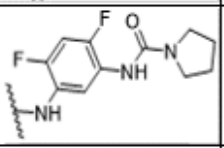
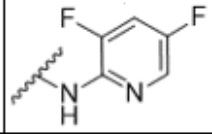
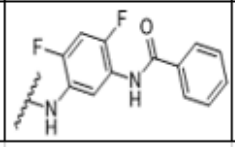
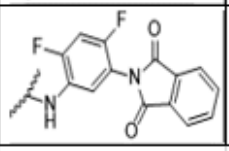
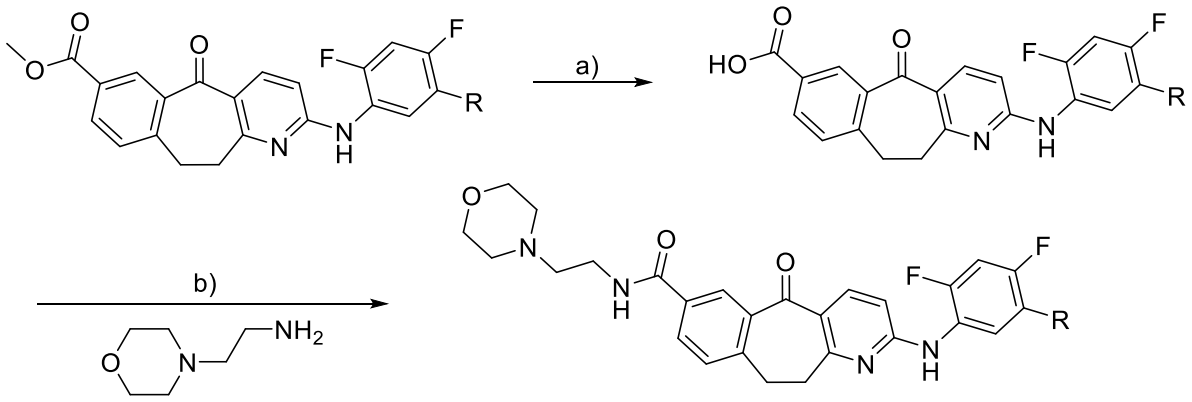
No.	Structure	No.	Structure	No.	Structure
81		84		87	
82		85		88	
83		86			

Table 9: Overview of all synthesized azadibenzosuberone-based inhibitors via Buchwald-Hartwig amination.

2.11. Introduction of the Morpholino ethyl amide residue

After successful Buchwald-Hartwig amination, the last step to get a final azadibenzosuberone compound is the introduction of the morpholino ethyl residue via amide coupling. Therefore, the methyl ester is first cleaved to obtain the free carboxylic acid which is further activated by TBTU. It activates carboxylic acids by forming an active ester via introduction of a stabilized Hydroxybenzotriazole leaving group. The intermediate active ester is attacked by a nucleophile, in this case the morpholino ethan amine, to form an amide bond.



Scheme 25: Introduction of an morpholinoethan amine residue to the azadibenzosuberone compound for HR II interaction. Reagents and conditions: a) KOH, MeOH, reflux; b) TBTU, TEA, DMF.

Both steps are quantitative with excellent yields (> 95%).

All synthesised inhibitors are further described and shown in the results and discussion section.

3. Results and discussion

3.1. Introduction

The synthesized inhibitors were tested in several in vitro assay systems. The half-maximal inhibitory concentration (IC_{50}), as parameter for the inhibitory efficacy of the drugs, were determined. The standard procedure is to determine the IC_{50} value for the isolated kinase. For selected compounds, the IC_{50} value in a whole blood system and the metabolism was also tested. Additionally, the TRT values should have been investigated, but it was unfortunately not possible due to technical issues. The assays related to the described IC_{50} values and metabolic stability data are briefly described here:

3.1.1. Isolated kinase assays

The IC_{50} values of compounds made by former PhD students were determined utilizing an ELISA-based test assay. Due to the reason that the antibody for the ELISA assay is no longer commercially available, this test system could not be used for the novel compounds. Thus, the new test results cannot be compared 1:1 to the old results. Therefore, some of the old compounds have been also tested with the new test system.

Most of the novel compounds were send to ReactionBiology and tested with the radiometric HotSpot™ assay. Due to high cost of the commercial assay, a TR-FRET-based assay was validated for in-house testing. The validation was quite time-consuming (three years); thus, this assay was not available for the evaluation of most compounds. Again, the IC_{50} values resulting from the different assay systems cannot be compared 1:1.

The procedure of the two different assay systems used to determine the IC_{50} value on the isolated kinase were shortly described:

3.1.1.1. Radiometric HotSpot™ assay

The compounds inhibitory activity was tested in an isolated kinase assay by Reaction Biology via a radiometric HotSpot™ assay using MBP (Myelin Basic Protein), ATP and radioactive labelled ATP ([γ ^{33}P]-ATP) as substrates.[106] The lower detection limit of the assay is 10 nM and the upper is 1000 nM. In some cases, values below the detection limit have been determined from Reaction Biology. However, values below the detection limit were still mentioned due to nice curve fitting.

3.1.1.2. HTRF® KinEASE™ assay

The compounds inhibitory activity was determined using an isolated kinase assay in house by utilizing a TR-FRET-based method. This method is based on the commercially available HTRF® KinEASE™ assay from cisbio assays[107], using Anti-phospho-ATF2 (Thr69/71) antibody and MAb Anti GST-d2 antibody with ATF2 as kinase substrate.

3.1.2. Whole blood TNFα-release assay

Selected inhibitors were also tested in a human whole blood TNFα-release assay. Here, the inhibition of lipopolysaccharide (LPS)-stimulated TNF-α release in whole blood is determined.[108] Due to various factors, such as inter alia solubility, absorption, plasma protein binding and ATP concentration, the resulting IC_{50} values are not comparable to those from

the isolated enzyme assay. In general, the results of this assay system display more the situation in vivo. Moreover, the results depend on individual blood variations of the different donors. Therefore, as a reference compound SB203580 is included in every assay. Since this assay is based on biological material, certain fluctuations are commonly observed. The observed reference IC_{50} value is usually between 1 and 2,5 µM.

3.1.3. Target residence time (TRT)

The TRT describes the binding time of the drug to the enzyme to form a drug-target-complex. Previous studies demonstrated that the stabilization of the R-spine greatly affects the TRT of the inhibitor.[81] Improvements of the stabilization results in a prolonged TRT which is discussed to achieve beneficial effects like improved PK or increased in vivo efficacy and thus is an important factor for the inhibitor optimization.[109]

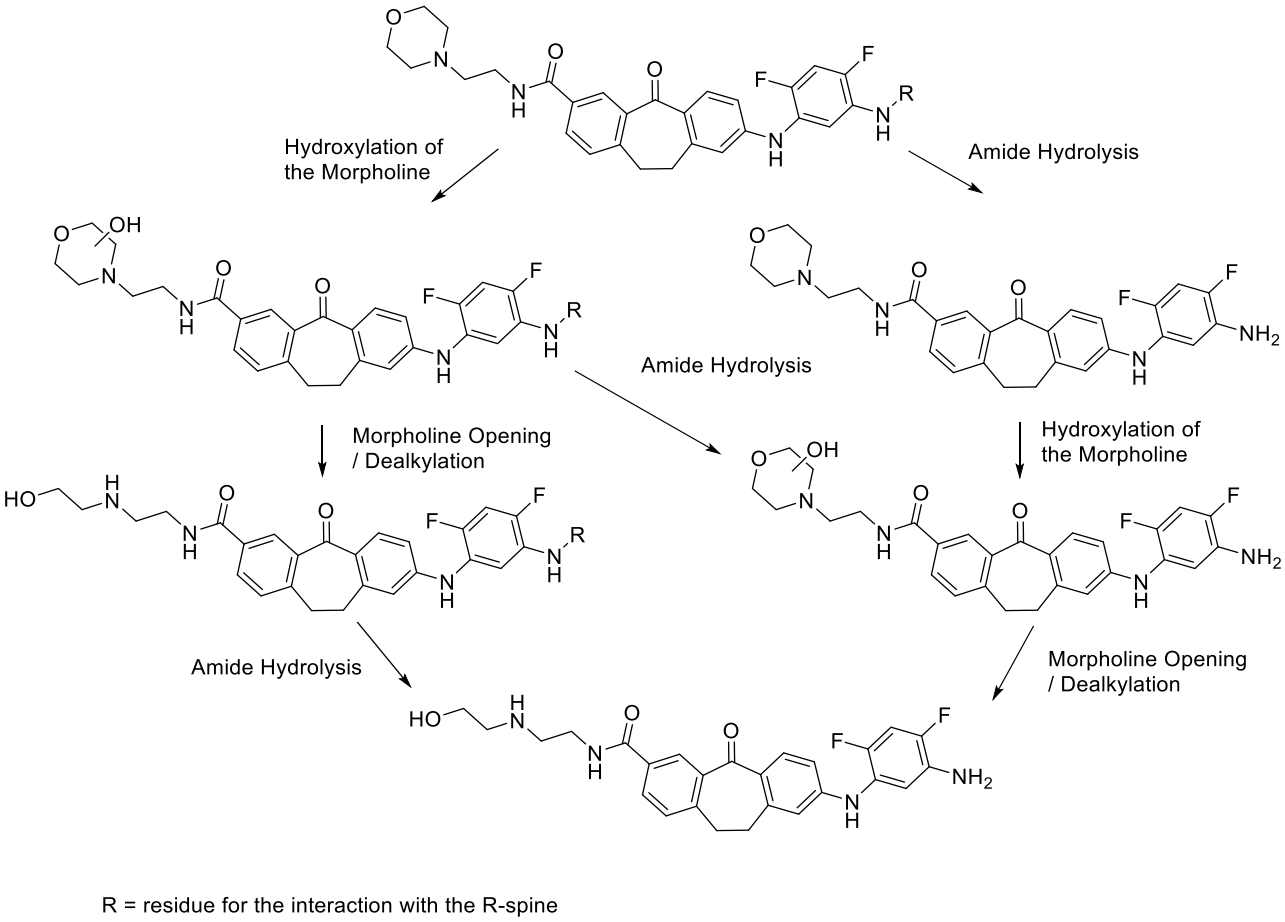
3.1.4. In vitro metabolism

After absorption into the body, the drug is metabolized by liver enzymes. The metabolism is divided into three phases: modification (oxidation, reduction, hydrolysis by CYP-enzymes), conjugation with an endogenous substance (eg, glucuronic acid), and finally excretion.[110] The aim of the biotransformation of pharmaceutical substances is to increase the hydrophilicity of the compounds to eliminate them easier from the body. Metabolism typically inactivates drugs, but some drug metabolites are still or even more pharmacologically active. Thus, the metabolism is an important parameter for the drug development. The metabolism of selected compounds was determined in vitro using rat liver microsomes (RLM) and the assay was performed by Mark Kudolo. Microsomes express phase-I CYP enzymes and thus are used for metabolism studies.[111, 112]

The procedure of the metabolism assay related to the described compound concentrations after incubation with RML are briefly described here.

The compound, a NADPH regenerating system and $MgCl_2$ x 6 H_2O in 0.1 M Tris buffer (pH 7.4) were pre-incubated for 5 min. The reaction was started by addition of RLM. To follow the course of metabolism, the reaction was quenched at selected time points (0-60 min) and analysed by LC-MS analysis. All incubations were conducted in triplicates. The results are given in percentage of the analysed m/z concentration. It is a semiquantitative analysis because it is just an estimation of their approximate concentrations. Due to the fact that the metabolites have a differently ability to be ionized, the total percentage of all metabolites can be more or less than 100%.

The metabolism of amide-based type I ½ inhibitor with an morpholino ethyl moiety has been previously investigated in our group.[79] The morpholino ethyl moiety gets hydroxylated by CYP-enzymes followed by ring opening and dealkylation. Additionally, the amide bond of the type I ½ residues is cleaved resulting in a type I inhibitor. The resulting metabolites are still active but do no longer have the beneficial effects of type I ½ inhibitors after amide hydrolysis. [70, 79] The metabolites of the morpholino ethyl moiety do not lose activity (see Table 16) and thus, it is still used as residue for PK-adjustment due to good solubilizing effects.[86]



Scheme 26: Typical metabolism of an amide-based type I ½ inhibitor with an morpholino ethyl moiety. During the metabolism, the amide of the type I ½ residues is cleaved. The morpholine ring is first hydroxylated followed by ring opening and dealkylation. These steps can happen in different order resulting in the same final metabolite. The metabolism was investigated by Eva Döring.

3.2. Test results and discussion

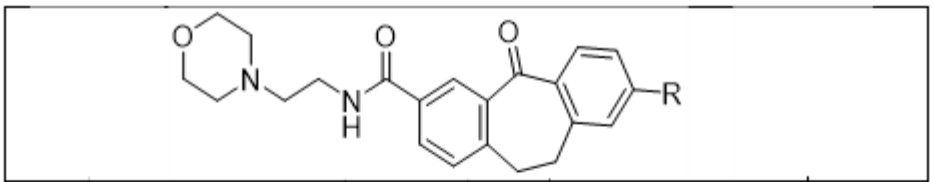
The biological test results of the inhibitors are discussed in the following section of the thesis. The dibenzosuberone based inhibitors are sorted by the utilized functional group of the type I ½ residue linker, starting with aromatic amides.

3.2.1. Aromatic amides

Most of the previously synthesized type I ½ aromatic amide-based inhibitors show excellent IC_{50} values in the low single-digit nM range and thus are attractive residues. Some of them were used as references. All compounds named with HW and a number were synthesized by Heike Wentsch[79] and FS compounds are made by Stefan Fischer[80].

For a better understanding and to further optimize the interaction with the R-spine, novel R-spine interacting residues were designed and tested. To achieve this, the concept of bioisosteric replacement was used. Therefore, the previous utilized thiophene (**HW237**) and phenyl (**HW299, FS694**) rings were replaced by several heterocycles containing two heteroatoms. The IC_{50} values of the reference compounds **HW237** and **HW299** shown in Table 10 are 1.8 nM and 1.54 nM, respectively. For the replacement of the phenyl or

thiophen moiety, an oxazole (**89**), thiazoles (**90, 91**) and a pyrimidine (**92**) derivatives were used, and the results are summarized in Table 10.



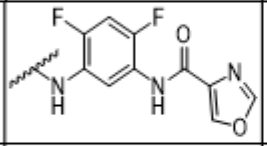
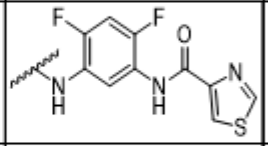
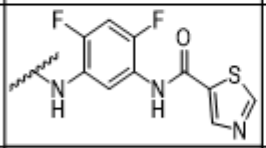
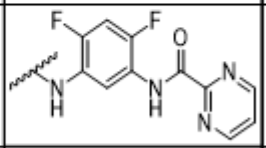
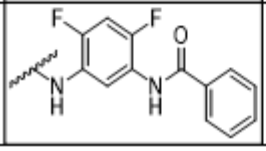
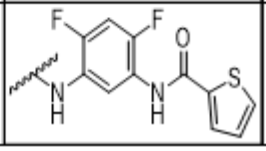
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
89		0.087	90		0.086
91		0.22	92		0.11
HW 299		1.53	HW 237		1.8

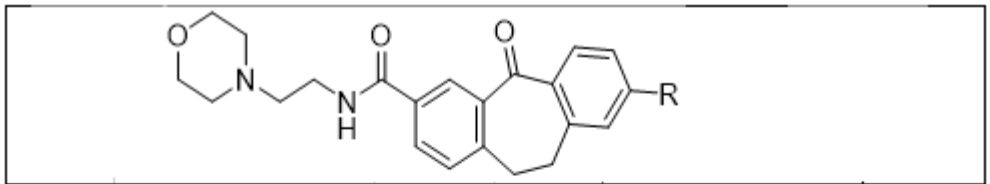
Table 10: Test results of the radiometric HotSpot™ assay for heterocyclic amide-based type I ½ inhibitors.

All compounds from table 10 show excellent potencies on the isolated enzyme. The IC_{50} values of all compounds are in a picomolar range and lower compared to the reference compounds. Based on these results, it can be assumed that heterocyclic compounds with two heteroatoms have a stronger interaction with the R-spine compared to phenyl or thiophene derivates. Additionally, these results show a great tolerance of several five- and six- membered heterocyclic aromatic rings, without a discrimination between the orientation of different heteroatoms. The IC_{50} values are below the detection limit of the assay, thus further analysis based on these IC_{50} values cannot be done.

Beyond the increased potency, the strategy of bioisosteric replacement might have additional benefits. Previous test results showed an increased TRT from **FS694** (259 sec.) to **HW237** (3663 sec.) which is presumably caused by the higher electron density of thiophene compared to phenyl leading to an enhanced edge-to-face π–π interaction with the Phe169 residue of the R-spine.[81] To further investigate the influence of the electron density to the TRT, thiazole and oxazole derivates were synthesized within this work. The introduction of an additional heteroatom effects the electron density of the molecule. Thiazole is more electron-deficient than thiophene due to a limitation of the contribution of electrons to the molecules π-system.[113, 114] This is caused by the electronegative nitrogen atom pulling the electron density from the π-system. Thiazoles are characterized by larger π-electron delocalization of a lone pair of sulphur electrons than the corresponding oxazoles.[115] Unfortunately, the TRT values were not available up to this date due to technical issues. Therefore, the influence of the electron density to the TRT could yet not be further evaluated.

Furthermore, the influence of different substituents to a phenyl-ring was determined. Therefore, the steric tolerance of a bulky methoxy-group as well as the influence of halogens attached to the phenyl-ring in *meta*-position were tested and the results are summarized in Table 11. Fluorine is often used as bioisosteric replacement for hydrogens and to reduce the drug metabolism. The size of fluorine is approximately 20% larger than those of hydrogen

based on the van der Waals radii.[116] Compared to the other halogens such as chlorine, fluorine has still a small size and is not engaged in halogen bonding.[117] While the substitution of two hydrogens with fluorine (**93**) resulted in a slight improvement of the inhibitory activity compared to the unsubstituted phenyl derivate **HW299**. The introduction of the bulky methoxy-substituent **94** resulted in a decline of the inhibitory activity. Also, for compound **95** with the chlorine-moiety, a higher IC_{50} value compared to the reference was obtained. Hence, for six-membered rings bulky substituents in *meta*-position are not tolerated and diminish the inhibitory activity of the compound.



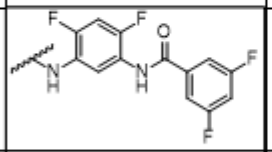
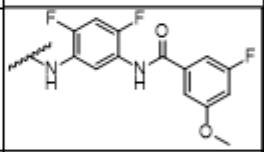
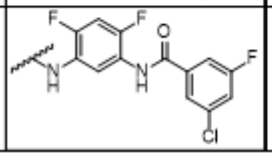
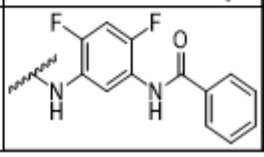
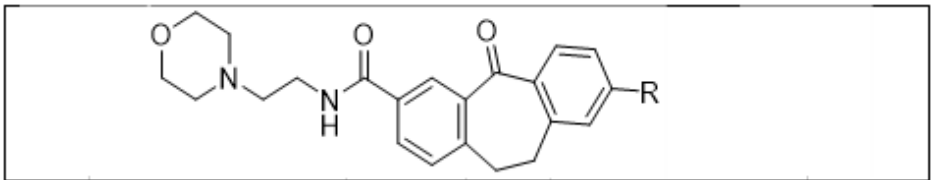
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
93		0.551	94		2.53
95		4.71	HW 299		1.53

Table 11: Test results of the radiometric HotSpot™ assay for substituted phenyl derivates for the R-spine interaction as type I ½ inhibitors.

To further investigate the influence of bulky substituents, compounds summarized in Table 12 were synthesized. Compounds **96** and **97** were synthesized to test if bulky residues are tolerated for five-membered rings. The IC_{50} values of **96** and **97** are 44 nM and 212 nM, respectively. This is a significant reduction of the potency compared to compounds with type I ½ residues bearing five-membered rings without bulky substituents which demonstrate IC_{50} values in a low single-digit nanomolar range or even below the detection limit. Additionally, compound **98** bearing an adamantyl substituent as bulky sp^3-rich component was designed. Adamantane as residue have gained attraction in medicinal chemistry due to its three-dimensional structure which is discussed to enhance pharmacokinetic properties.[118] The IC_{50} value of compound **98** is over the detection limit of the assay which suggest that this compound has no inhibitory activity against the kinase. These results show a limitation in the size of the residue fitting into the kinase pocket. Large, bulky substituents are not tolerated by the kinase and leading to a dramatic reduction of the inhibitory activity of the inhibitors.

To proof if bulky but small aliphatic residues are generally accessible for the kinase, compound **99** utilizing a *tert*-butyl group, were synthesised. The *t*-butyl group is a bioisosteric replacement for the already utilized cyclopropyl group[70, 81] which is an aromatic-alike structure. Compound **99** shows excellent inhibitory activity with an IC_{50} value of 0.133 nM which is in a similar range compared to the IC_{50} value of the corresponding cyclopropyl-substituted compound shown in Table 14.



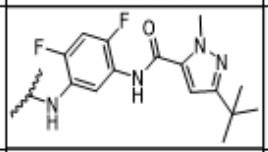
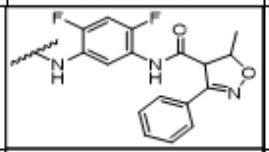
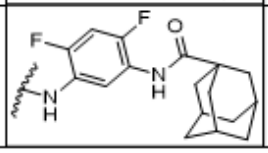
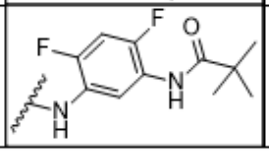
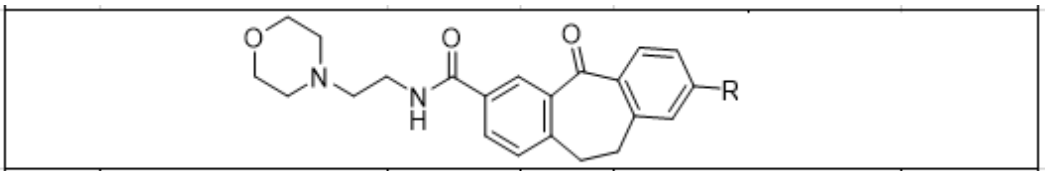
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
96		44 [a]	97		211.7 [b]
98		> d.l. [a]	99		0.133 [a]

Table 12: Test results for five-membered rings with bulky substituents and for aliphatic residues for the R-spine interaction as type I ½ inhibitors. The IC50 value were determined as follows: a) using the radiometric HotSpot™ assay; b) using the TR-FRET-based assay.

In summary, the test results confirm the presumption that an aromatic or an aromatic-alike structure is required for interaction with Phe169 of the DFG-motif via charge transfer or π−π-interactions. Furthermore, it could be shown that a broad variety of small aromatic and aliphatic residues for the interaction with the R-spine of the kinase are tolerated without further discrimination. On the other hand, bulky residues with high molecular size, decrease the inhibitory activity.

Another aim of the inhibitors was to increase solubility by introduction of heteroatoms (compounds **89-92**) and saturated, sp^3-rich residues (compound **99**).[119] The solubility is an important impact factor for the bioavailability of a compound and effects the ADME (absorption, distribution, penetration, metabolism, and excretion) properties. For the absorption of a drug into the body, the compound needs to be soluble in water. The partition coefficient P describes the distribution of a substance in a two-phase system, usually octanol and water and describes the solubility. The logarithm of this ratio is known as log P value and is a measure of lipophilicity.[120] The lower the log P value of a compound, the better is the aqueous solubility and the lower is the lipophilicity. These considerations were used by Lipinski to predict the drug-likeness of a compound and describe the relationship between pharmacokinetic and physicochemical parameters. This so called “Rule of five” define that drugs should have a log P value less than 5, a molecular weight less than 500 Dalton as well as less than 5 hydrogen bond donors and less than 10 acceptors to be orally bioavailable.[121] The number of hydrogen bond donors is limited because a too hydrophilic drug cannot penetrate the amphiphilic cell membrane to reach the inside of the cell. Since Lipinski announced the “Rule of five” many advances on drug-likeness prediction have been done and new properties such as polar surface area (PSA) or number of aromatic rings (AROM) have been defined.[122] Moreover, the amount of sp^3 hybridized carbons is considered to enhance the molecular complexity which is supposed to correlate with solubility.[119, 123] However, simple rules and calculation models are not always reliable, and some approved drugs have properties causing a low score on drug-likeness indices.[122, 124] Moreover, the toxicological safety profile of a drug cannot be ensured by these models. Therefore, we were focusing on the enhancement of the aqueous solubility by decreasing the log P value as main parameter. Due to a high amount of aromatic carbon cycles, the dibenzosuberone-based p38α MAPK inhibitors are quite lipophilic structures. The introduction of heteroatoms

enhances polarity and thus decreases the log P value of the compound and this is supposed to result in an optimization of the ADME properties of lipophilic drugs. This can be demonstrated by the comparison of the log P values of thiophene (1.95) with thiazole (0.44) or benzene (2.18) with pyridine (0.84) and pyrimidine (0.26). The log P values were calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02. However, if the goal of enhanced aqueous solubility was successfully achieved, still needs to be proven by test data and thus cannot be evaluated yet.



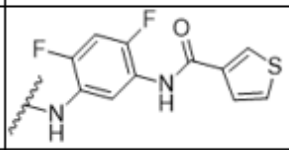
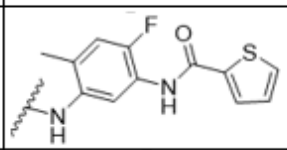
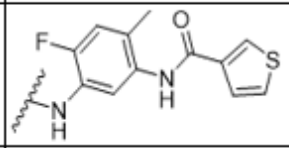
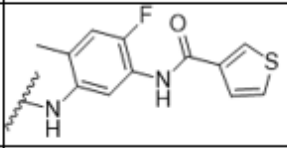
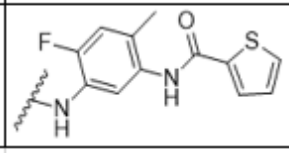
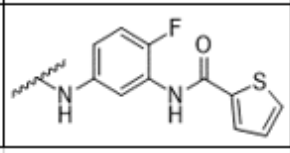
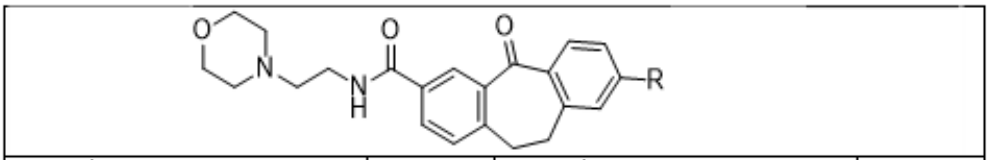
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
100		0.065	101		2.62
102		0.283	103		2.28
104		0.653	HW 225		0.5

Table 13: Test results of the radiometric HotSpot™ assay for thiophen-based type I ½ residues with different substituent patterns on the C-ring for SAR study.

One goal of this thesis was the completion of the SAR study of the different substituent patterns (-F, -CH_3, -H) on the C-ring. Therefore, 2-thiophenecarboxamide derivates with 2,4-difluoro (**HW237**, shown in Table 10) or 2-fluor (**HW225**) substitution at the C-ring are used as reference compounds. Compared to **HW237** (IC_{50} = 1.8 nM), the 3-thiophencarboxamide derivate **100** has a higher potency indicating an improved interaction with the R-spine of these isomer. The substituent pattern of the C-ring addressing the HR I, seems to be important when using a methyl residue. The methyl group in 2-position (**102**, **104**) resulted in an increased inhibitory activity compared to the substituted compound in 4-position (**101**,**103**). For a well-founded consideration of the influence of the substituents of the C-ring, additional compounds were synthesized. Under my supervision, compounds **105-122** were synthesized by the master student Larissa Pünnel. A morpholino ethyl moiety is attached at compounds **105-112** shown in Table 14.



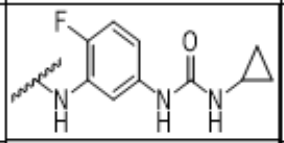
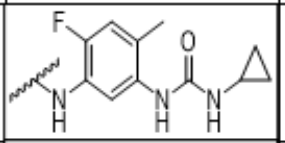
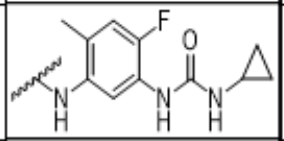
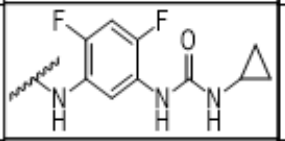
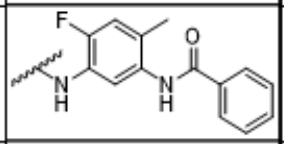
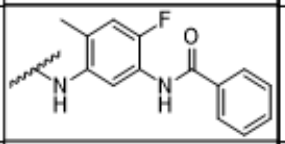
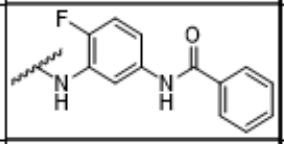
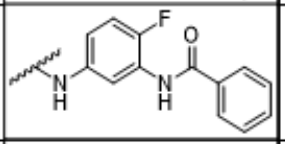
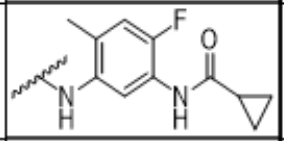
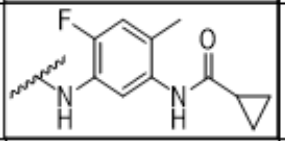
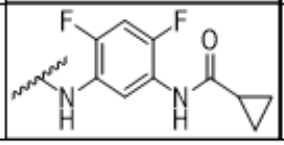
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
105		1.84	106		4.11
107		1.75	HW 306		1.7
108		0.3	109		2.28
110		1.89	FS 694		0.689
111		1.42	112		4.11
HW 307		1.53			

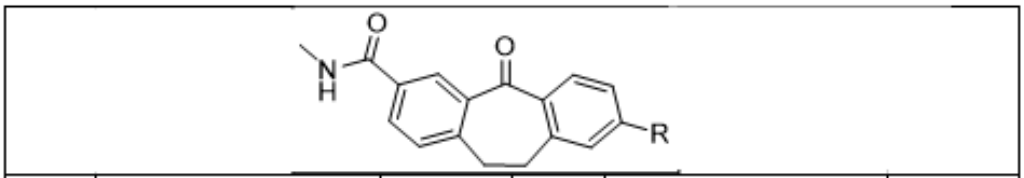
Table 14: Test results of the radiometric HotSpot™ assay for type I ½ residues with different substituent patterns on the C-ring and a morpholino ethylamine moiety.

A cyclopropyl urea as R-spine interacting residue is utilized for compounds **105-107** and reference **HW306**. There is only a marginal difference in the potency of the monofluoro compound **105** (1.84 nM) and the difluoro reference **HW306** (1.7 nM). In contrast to the above results, for the cyclopropyl derivates a methyl group in 4-position (**107**) demonstrate higher inhibitory activity than those with methyl in 2-position (**106**). While, for the phenyl containing compounds **108** and **109** and the cyclopropyl containing compounds **111** and **112** it is again vice versa. In summary, for most compounds a methyl group in 2-position of the C-ring results in higher potency compared to inhibitors with a methyl group in 4-position. The IC_{50} value of the cyclopropyl amide compound **111** is 1.42 nM. The potency of the 4-methyl-2-fluor derivate is lower compared to the difluoro reference **HW307** (0.3 nM). A comparison of the IC_{50} values of the different substitution patterns of the C-ring demonstrates the mainly disadvantageous role of a methyl substitution. In most cases, the difluoro derivates demonstrated the highest potencies of the different substituent patterns of the C-ring. Therefore, all novel inhibitors are synthesized with the 2,4-difluoro substituent motif on the C-ring.

For a better understanding of the interaction with the kinase and to complete SAR studies, inhibitors with previously utilized R-spine interacting residues like thiophene, cyclopropyl or phenyl combined with different substituents (e.g., methylamine) for addressing the solvent exposed area were synthesized. Previous results indicated in most cases similar potency for compounds with the same type I ½ residue but different moieties addressing the solvent exposed area.[86] To further investigate the influence of these moieties, the compounds

summarized in Table 15 were synthesized. Here, methylamine was utilized as moiety instead of morpholino ethylamine.

The IC_{50} value of the phenyl derivates with a morpholino ethyl amide (**108**, **109**, **FS694**) as well as with a methyl amide residue (**114**, **116**, **117**) are all in a single-digit nM range. The potencies of the cyclopropyl compounds **118** and **109** are almost the same with 2.02 nM and 2.28 nM, respectively. There is only a slight difference in the inhibitory activity of **115** (11.5 nM) compared to **112** (4.11 nM). Based on these results, the assumption that a broad variety of residues addressing the solvent exposed area are tolerated without effecting the potency of the inhibitors can be confirmed. To verify this, also 2-aminoethylaminoethanol as moiety is synthesized and tested. Another reason to use 2-aminoethylaminoethanol as moiety is the fact that this is the metabolite of the mainly utilized morpholino ethyl moiety. Hence, this result can be also used to evaluate if the metabolites are still active inhibitors of the p38α MAP kinase, which was another aim of this thesis.



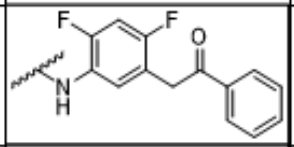
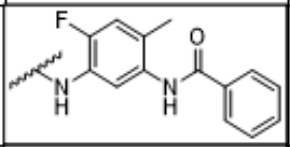
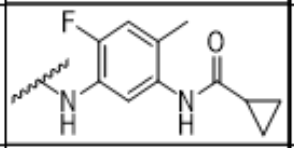
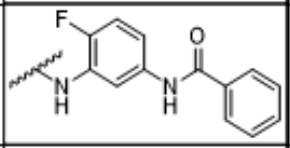
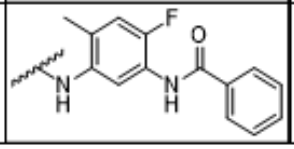
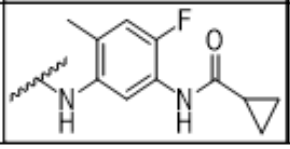
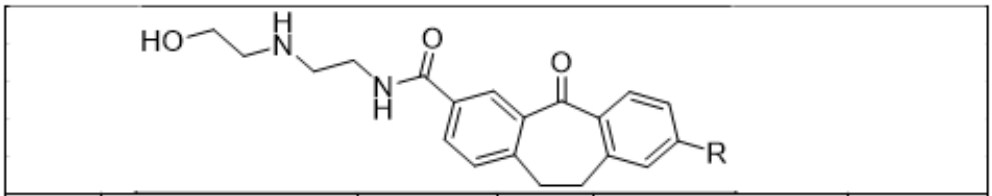
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
113		61.7	114		1.81
115		11.5	116		2.18
117		3.65	118		2.02

Table 15: Test results of the radiometric HotSpot™ assay for type I ½ residues with different substituent patterns on the C-ring and a methyl amide moiety.

All inhibitors utilizing the metabolised amino ethyl moiety are summarized in Table 16. According to the biological test results, compounds **119**-**122** are potent inhibitors of the p38α MAP kinase. The IC_{50} values are in a single-digit nM range or for compound **122** even under the detection limit of the assay. For example, the IC_{50} values of **110** and **121** are almost identical with 1.89 nM and 1.84 nM, respectively. This results consequently show that the metabolites of the morpholino ethylamine-based compounds are still potent inhibitors. Presumably, the metabolism leads to an improvement of the biochemical properties of the inhibitors due to the increased polarity and the resulting enhanced solubility. However, this needs to be proven by biological data in the future.



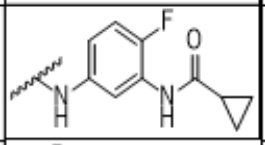
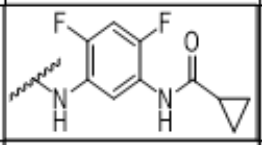
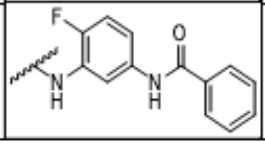
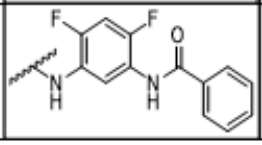
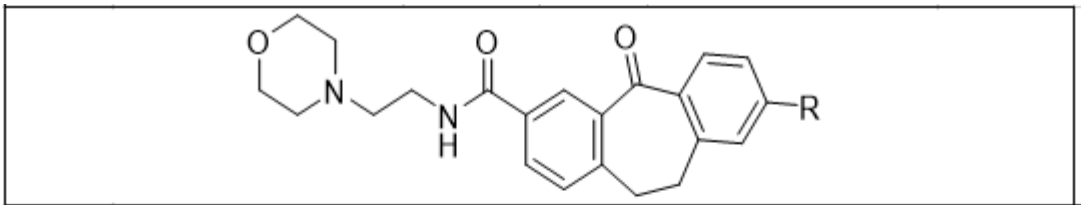
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
119		2.3	120		2.58
121		1.84	122		0.699

Table 16: Test results of the radiometric HotSpot™ assay for type I ½ residues with different substituent patterns on the C-ring and a 2-aminoethylaminoethanol moiety.

Another issue related to metabolism is the enzymatically cleavage of the amide-based type I ½ inhibitors resulting in a type I inhibitor. The aim of inhibitors **123** - **128** (Table 17) with methyl-groups attached to the heterocycle, is the steric protection of the amide bond to prevent enzymatic cleavage of the amide bond during metabolism and thus increase the metabolic stability without losing potency. The thiophene compounds **123** - **125** were designed to evaluate which position of the methyl-group is the most effective one to prevent cleavage. To evaluate if one or two methyl-groups are required, the methylisoxazole compound **127** compared to the dimethylisoxazole derivate **128** were synthesized. The aim of compound **126** is to figure out if trifluoromethyl is an appropriate replacement for the methyl-group or if it works even better due to electronic effects. The compounds metabolic stability is not determined yet. However, a loss of potency compared to the inhibitors without methyl-groups was observed for all compounds. Especially, the attachment of the trifluoromethyl group for compound **126** is not tolerated by the kinase. For the thiophene compounds, the introduction of the methyl-substituent at position 2 results in an almost 70-fold decreased inhibitory activity. The result indicates a structural limitation in this direction. The methyl-substitution at position 3 is the best derivate according to the IC_{50} values. **123** is still a good inhibitor of the isolated p38α MAPK with an IC_{50} value of 16.4 nM. Unfortunately, the inhibitors lose their inhibitory activity in whole blood assay. Thus, the aim to prevent metabolic cleavage without losing potency was not achieved. Another strategy to increase the metabolic stability is to replace the amide bond by different functional groups. This concept is used in the following section of the thesis.



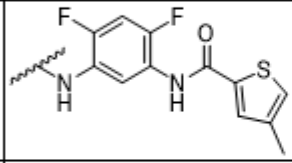
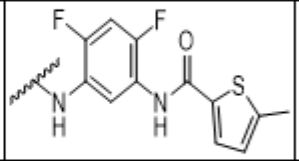
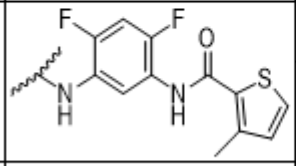
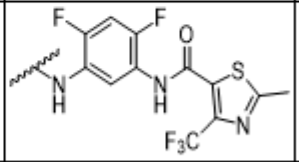
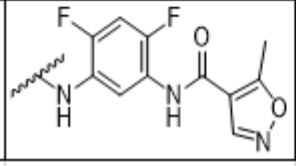
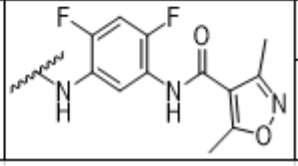
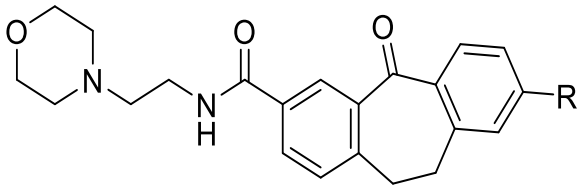
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
123		16.4 455 (TNFα)	124		115.2
125		40.7 490 (TNFα)	126		290.1
127		269.3	128		31.2 156 (TNFα)

Table 17: Test results of the TR-FRET-based assay for inhibitors with methyl-groups attached to the heterocycle for steric protection of the amide bond aiming to prevent metabolism. The IC50 values for TNFα-release were measured in human whole blood.

3.2.2. Ketones and Weinreb amide

Molecular dynamic (MD) simulations conducted by Tatu Pantsar, indicated that the NH-group of the amides from the type I ½ residue is not perhaps crucial for the interaction with the kinase. Furthermore, the amides are not metabolically stable. Therefore, we proposed the concept to replace the NH-group of the amide by a methyl-group to obtain a benzyl methyl ketone derivate aiming to evaluate how crucial the NH-group is for the activity of the compounds and how the replacement influence the IC_{50} values. All ketone and Weinreb amide derivates are summarized in Table 18. The ketone derivate **129** shows similar IC_{50} values to the corresponding amide derivate **HW299**, with excellent potency of 0.23 nM compared to 0.3 nM. Additionally, **129** is a potent inhibitor of TNFα-release in human whole blood with an IC_{50} value of 52 nM (n = 2). Moreover, the determined activity of the thiophene-based derivate **130** and the reference compound **HW237** is exactly the same IC_{50} value with 1.8 nM. Thus, the observations from the MD simulations proved to be right.



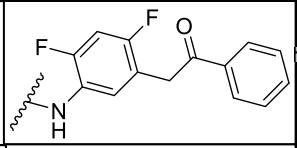
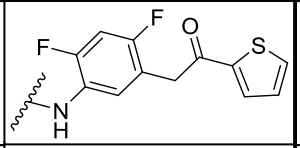
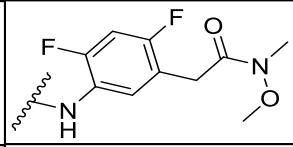
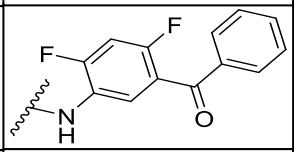
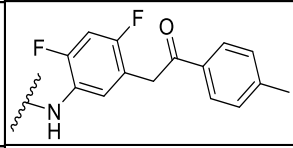
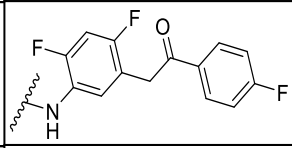
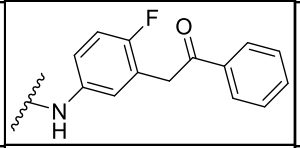
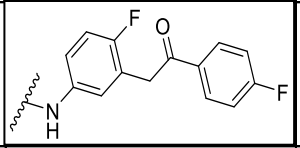
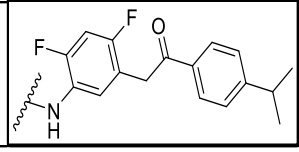
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
129		**0.23** **52** **(TNFα)**	**130**		**1.8**
131		**1.69**	**132**		**95.7**
133		**59.3**	**134**		**835.5** **152** **(TNFα)**
135		**36.6**	**136**		**186**
137		**551**			

Table 18: Test results of the radiometric HotSpot™ assay for ketone- and Weinreb amide-based type I ½ inhibitors. The IC50 value of compound 129 for TNFα-release was measured in human whole blood.

The synthesis of the thiophene derivate was accomplished utilizing Weinreb amide ketone synthesis. Thus, the inhibitory activity of the Weinreb amide intermediate **131** was also tested and showed excellent activity with an IC_{50} value of 1.69 nM. Compound **132** was designed as negative probe to evaluate the hypothesis that the methylene-group in between the aromatic C-ring and the carbonyl-group is required for the potency of the inhibitors. As we assumed, the direct connection of the carbonyl group to the C-ring resulted in a 400-fold decreased activity compared to **129**. These initial results for the activity of the ketone compounds confirmed our hypothesis that the NH-group of the amide bond from the type I ½ residue is not crucial for the interaction with the kinase and therefore, further derivates have been synthesized.

The in vitro metabolism study of **129** shown in Figure 16 demonstrated that after incubation with microsomes for 180 min, only 32% of the initial concentration is left. As expected, the open morpholine ethyl derivate was identified as main metabolite A (m/z 584, 10%). Furthermore, a metabolite with one additional hydroxyl group (m/z 626, 3%) was also present after incubation. This could be the first intermediate metabolite of the morpholine ethyl residue metabolism (B3), or it is also possible that it comes to *para*-hydroxylation (B2) of the phenyl-moiety or *beta*-hydroxylation (B1) of the methylene-group. With our instruments it is not possible to clarify the position of the hydroxyl-group based on mass analysis. However, a cleavage of the type I ½ residue was not observed.

To further investigate the metabolism of **129**, compounds **133** and **134** were synthesized. To prevent the potential hydroxylation of the phenyl-ring, the hydrogen in para-position is replacing with a methyl- or fluorine-moiety. The analysed results of the in vitro metabolism study of **133** and **134** are summarized in Figure 17.

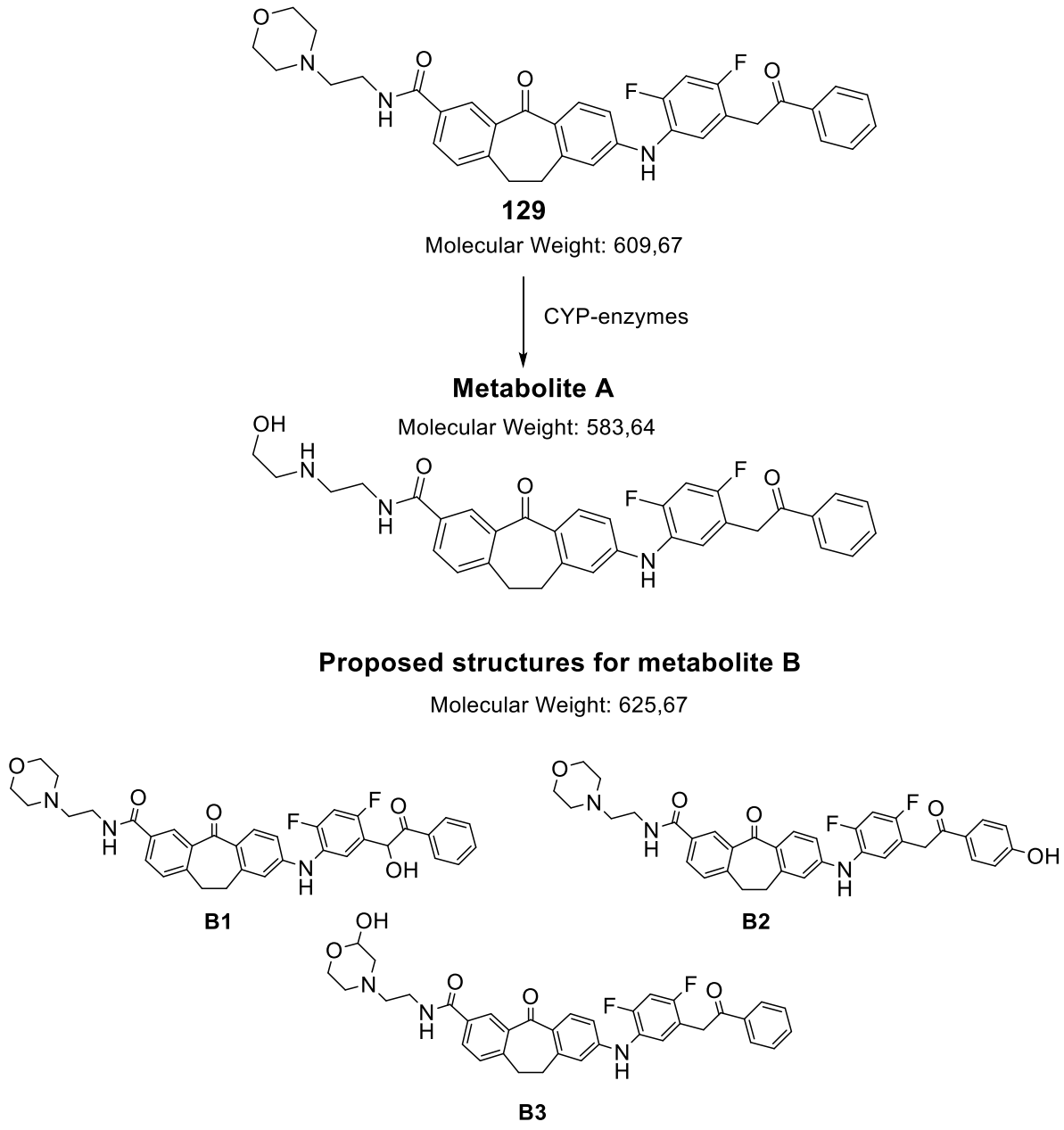
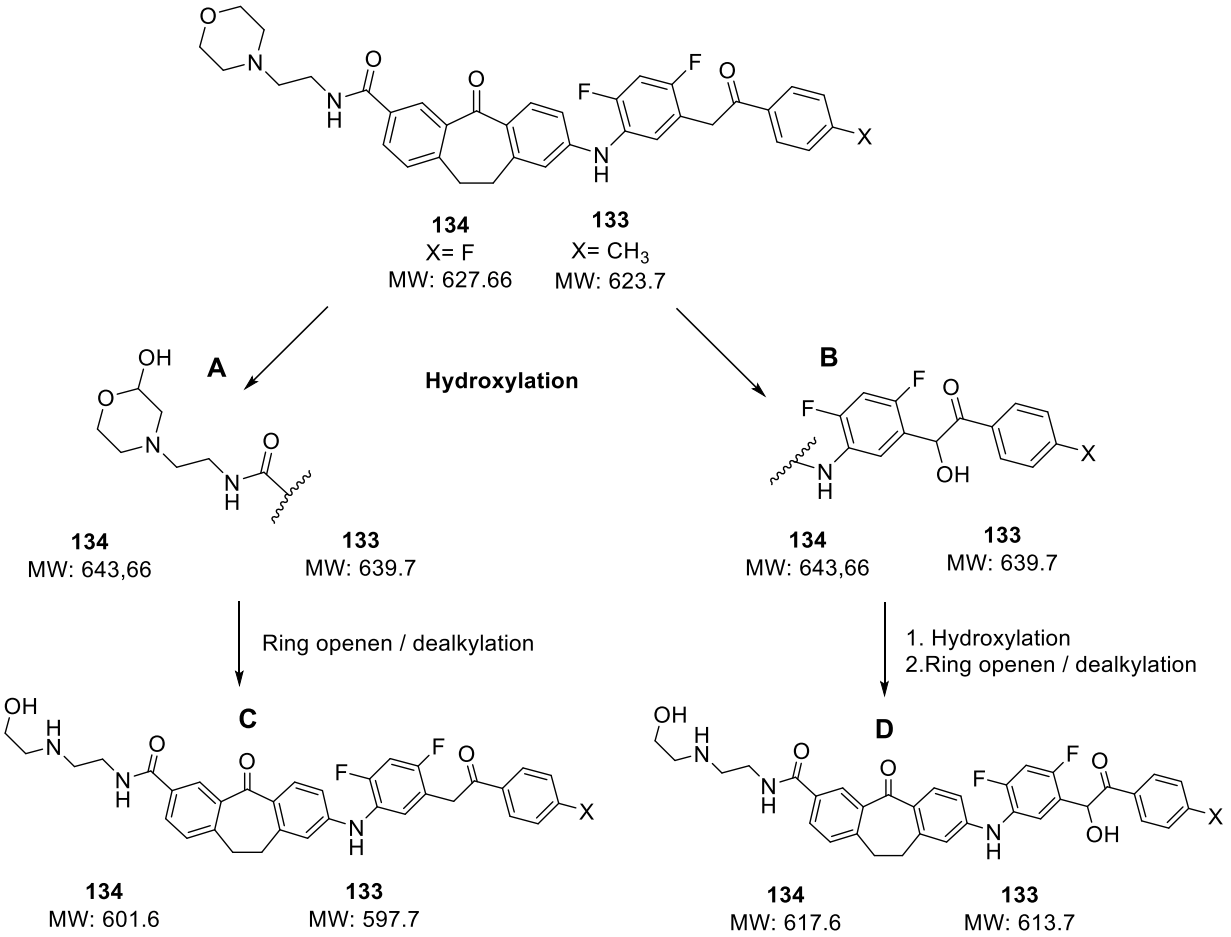


Figure 16: Results of the in-vitro metabolism study of compound 129 after 60 min incubation with RLM and the proposed metabolites A-B3.

Compound **134** demonstrated a good metabolic stability of 78% after incubation with RLM for 180 min. The main metabolite C is the ring-opened, dealkylated morpholino ethyl derivate (m/z 602). Moreover, there is one metabolite (A or B) with an additional hydroxy group (m/z 644) and traces of a ring-opened, dealkylated morpholino ethyl metabolite D with an additional hydroxy-group attached (m/z 618). The determined metabolite D support the assumption of *beta*-hydroxylation of the benzyl methyl ketone derivates.

Compound **133** shows an excellent metabolic stability of 90% after incubation with RLM for 180 min. It is much more stable than the amide derivates **FS694** and **HW237** with a metabolic stability of 41% and 67%, respectively.[79] Thus, by the introduction of a methyl-substituent, the metabolic stability was further enhanced. Comparable to the metabolism of **129** and **134**, the main metabolite here is also the ring-opened, dealkylated morpholino ethyl derivate.



Time [min]	134 m/z 628 [%]	m/z: 602 [%]	m/z: 644 [%]	m/z: 618 [%]
0	100	0.5	1.8	0
10	81.5	1	3.2	0
20	81	1.8	3.3	0.1
30	75.1	2.6	3.2	0.3
60	79.3	4.8	2.8	0.6
120	78.7	7.8	2.2	1.3
180	78.4	8.7	2.1	0.9

Time	133 m/z 624 [%]	m/z 640 [%]	m/z 614 [%]	m/z 598 [%]
0	100	0.5	0	0
10	92	0.5	0.1	0.3
20	85.2	0.6	0.2	0.5
30	89.4	0.7	0.2	0.8
60	90.7	1	0.4	1.6
120	84.3	2	0.6	3
180	90.2	2.7	0.7	3.8

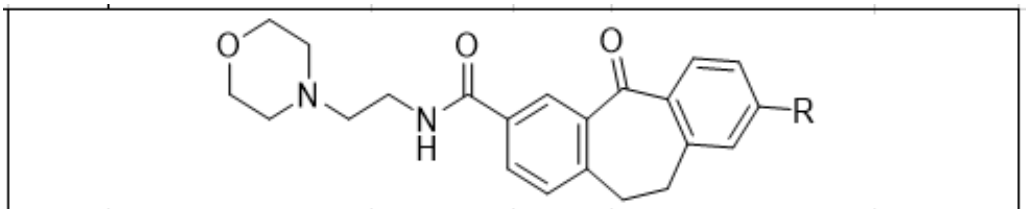
Figure 17: Results of the in-vitro metabolism study of compounds 133 and 134 after 180 min incubation with RLM and the proposed metabolites A-D.

In summary, compound **129** is metabolised by microsomes but the aim to prevent the type I ½ residue cleavage was achieved. In general, inhibitors with the morpholino ethyl moiety are metabolically less stable than those with a methyl amide moiety and thus cannot be directly

compared. The introduction of a fluorine- or methyl- substituent in para-position of the phenyl moiety is an appropriate method to reduce the metabolism of the ketone compounds. By introduction of a methyl-substituent in para-position, the metabolic stability could be enhanced to 90%. Unfortunately, the introduction resulted in a decreased potency.

3.2.3. Urea derivatives

Besides the searching for new replacements of the amide bond, one of the goals of this thesis is the optimization of the PK-properties of the urea bond. The reasons for this are the promising results of the cyclopropyl urea reference compound **HW300** and because ureas are well-known metabolically stable bioisosteric replacements for amide bonds. To address the solubility issue, the idea was to improve the solubility of the inhibitors by masking the terminal hydrogen to may prevent intermolecular stacking. This approach was successfully applied for HIV-1 protease inhibitors to achieve an improved oral bioavailability of the inhibitors.[125]



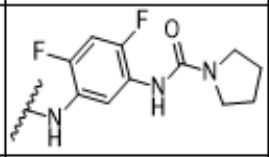
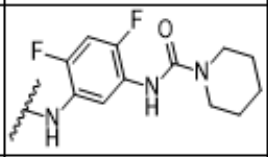
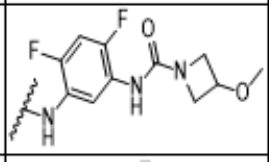
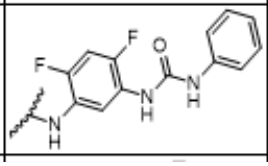
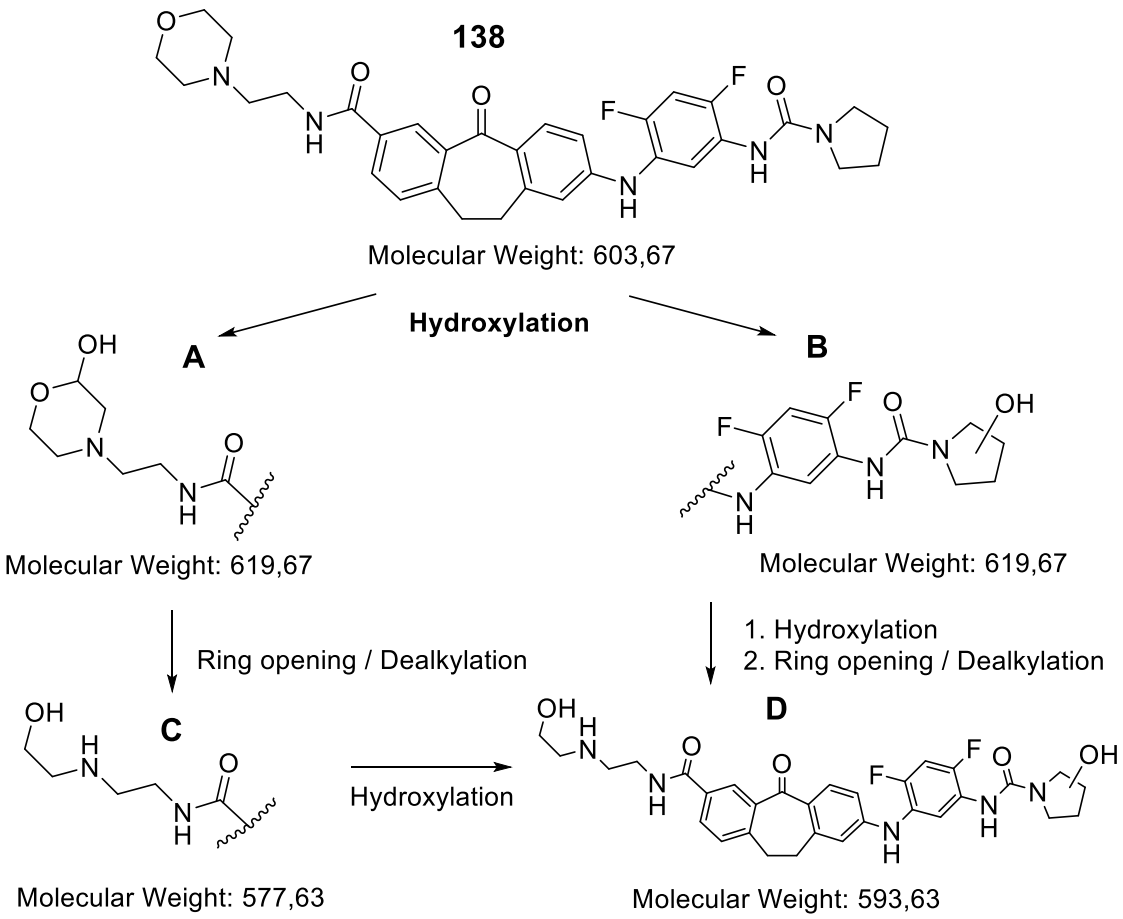
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
138		0.1 31,1 (TNFα)	139		2.08
140		24	141		51.4

Table 19: Test results of the radiometric HotSpot™ assay for urea-based type I ½ inhibitors. The IC_{50} value of compound 138 for TNFα-release was measured in human whole blood (n = 2).

Several cyclic urea compounds with different ring sizes have been synthesized and are summarized in Table 19. Due to the fact that aziridine rings are quite reactive and widely used as DNA alkylating agents, they were not used for the design of novel inhibitors.[120, 126] The pyrrolidine derivate **138** demonstrates high potency against the isolated kinase (0.1 nM) and also a good inhibition of the TNFα-release in human whole blood (31.1 nM, n = 2). Furthermore, the in vitro metabolism study (Figure 18) showed a good metabolic stability of 79%. The main metabolite C is the ring-opened, dealkylated morpholino ethyl derivate (m/z 578). Moreover, there are three different metabolites, recognizable by different retention times, with an additional hydroxy group (m/z 620). The hydroxy group is attached either to the morpholino ethyl group (A) or in position 2 or 3 of the pyrrolidine ring (B). Traces of a ring-opened, dealkylated morpholino ethyl metabolite D with an additional hydroxy-group on the pyrrolidine ring (m/z 594) was also detected. A metabolite with two hydroxy-groups attached, was not determined during the in-vitro measurements. This indicates the preferred metabolism of the morpholino ethyl moiety and subsequent hydroxylation thereof.

The urea derivate **HW300** also demonstrated high metabolic stability (97%).[81] Due to the fact that for **HW300** a methyl amide residue for addressing the solvent exposed area is attached,

the metabolism cannot be compared. Due to the fact that the methyl amide residue is in general metabolically more stable than the utilized morpholine ethyl amide residue.



Time [min]	Analyte corrected for control [%]	m/z: 620; RT: 9.8 [%]	m/z: 620; RT: 10.5 [%]	m/z: 620; RT: 11.72 [%]	m/z: 594 [%]	m/z: 578 [%]
0	100	0.1	0.1	0.1	0	0.2
10	95.8	0.3	0.3	0.1	0	0.9
20	92.4	0.3	0.3	0.1	0	0.9
30	91	0.5	0.6	0.1	0	2.4
60	80.4	0.9	1.2	0.1	0	4.3
120	77.4	0.4	3.1	0.2	0.1	8.6
180	78.5	0.5	3.8	0.2	0.1	9

Figure 18: Results of the in-vitro metabolism study of compound 138 after 180 min incubation with RLM and the proposed metabolites A-D.

Compounds **139** and **140** show a decreased potency compared to **138**, presumably due to a bigger size of the type I ½ residue. These results indicate a five-membered ring as optimum ring size for the cyclic urea compounds. Furthermore, the introduction of an additional hydrogen-bond acceptor by the methoxy group of **140** may also negatively affect the interaction with the kinase. While compound **141** was designed for SAR reasons to compare the phenyl urea moiety with the other functional group phenyl derivates. The loss of activity is presumable due to the bigger size of the phenyl residue which is not tolerated in combination

with the longer urea linker or due to an unfavourable structural orientation of the phenyl residue.

In summary, compound **138** showed excellent potency on the isolated kinase as well as in whole blood assay and additionally the type I ½ residue is not cleaved during metabolism. Therefore, the PK-properties of this compound should be tested in the future.

3.2.4. Aliphatic amides

Due to the excellent results for the ketone derivate **129** and the reference compound **HW300**, the idea was a structural combination of the urea and the ketone compounds.

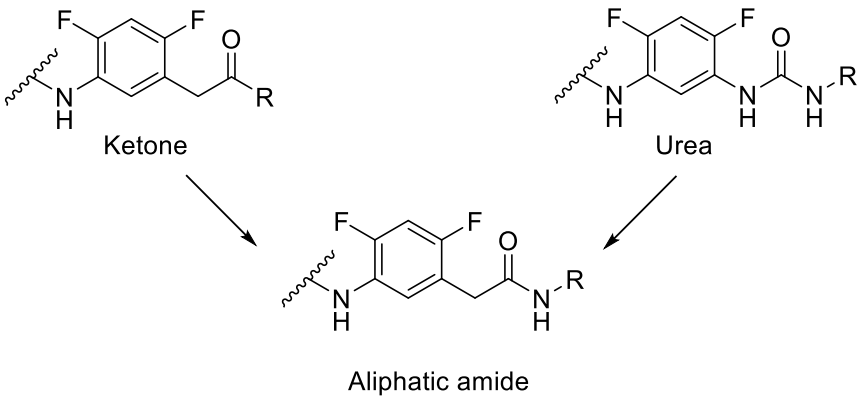
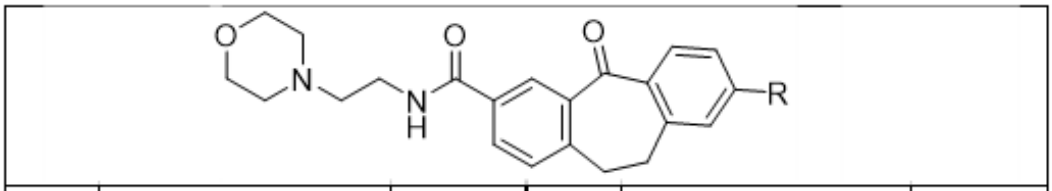


Figure 19: Idea for the aliphatic amide-based type I ½ inhibitors was a combination of the urea and the ketone compounds.

The introduction of the acetamide moiety resulted in compounds **142**-**147** (shown Table 20) with decreased biological activity on the isolated enzyme compared to corresponding ketones and ureas. In comparison to the urea reference compound **HW306** (1.7 nM), the introduction of the acetamide structure of compound **142** results in a 10-fold loss of activity. Moreover, compound **144** shows a 550-fold decrease in activity compared to **138**. A decreased activity is also observed for the fluorine compound **145** compared to the difluoro compound **142**. The best results with the lowest IC_{50} value were observed utilizing cyclopropyl, an aromatic-alike structure or an aromatic phenyl residue. This may explain the ability to form charge transfer or π−π-interactions with Phe169 of the DFG-motif.



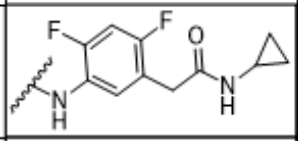
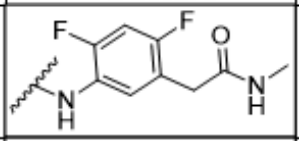
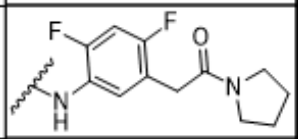
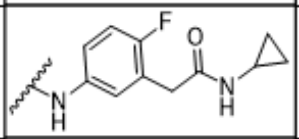
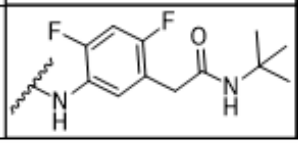
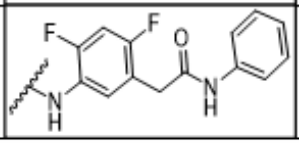
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
142		17.8	143		50.8
144		55.1	145		29.7
146		64.6	147		24.8

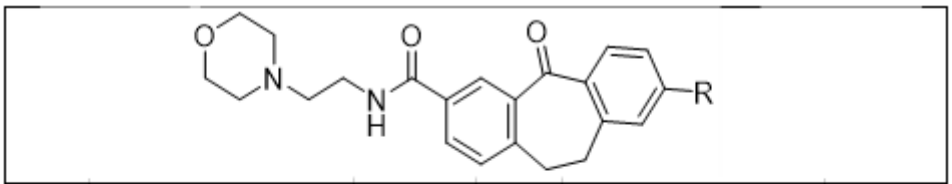
Table 20: Test results of the radiometric HotSpot™ assay for urea-based type I ½ inhibitors.

In summary, the acetamide moiety is inappropriate for the design of novel p38α MAPK type I ½ inhibitors.

3.2.5. Imides

The results of **129** brought evidence that the N-H hydrogen bond donor of the amide group is not required for a good interaction with the kinase. Based on these results, another idea to replace the amide by a metabolically more stable group was to introduce an N-substituted imide function. Especially, Phthalimide-based derivatives gained great popularity as attractive molecules for drug discovery. Due to the potential biological activity, the phthalimide scaffold is used for drug design in versatile therapeutic treatments, including for example the use as antimalarial cytochrome bc1 inhibitor[127] and as anti-inflammatory drug by the inhibition of soluble epoxide hydrolase[128].

All imide-based inhibitors are summarized in Table 21. The N-substituted phthalimide derivate **148** demonstrated high potency against the isolated kinase (0.049 nM) and also a good inhibition of the TNFα-release in human whole blood (30.3 nM). The analysed results of the in-vitro metabolism study of **148** are shown in Figure 20 demonstrate a metabolic stability of 73% after incubation with microsomes for 60 min. The results of the mass spectroscopy analysis verify that the type I ½ residue is not cleaved (m/z 506), only the previous described metabolism of the morpholino ethyl moiety was observed. The hydroxylated morpholino ethyl metabolite A (m/z 637) and the ring opened, dealkylated metabolite B (m/z 611) were determined. By changing the HR II residue to a metabolically stable group like methyl amide, the number of metabolites could be further reduced. In summary, the replacement of the amide bond by an imide bond led to an increased metabolic stability compared to the reference compound **FS694** which demonstrated a metabolic stability of 41% in previous study.[70]



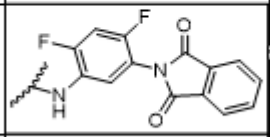
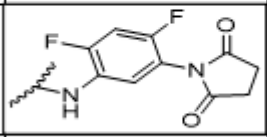
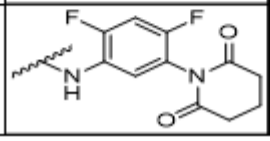
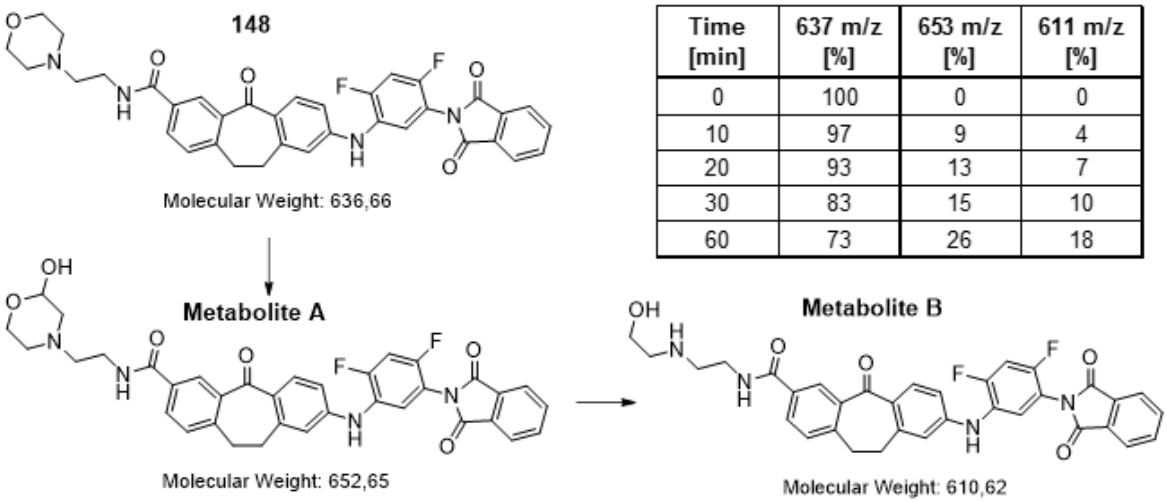
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
148		0.049 [a] 30,3 (TNFα)	149		677.4 [b]
150		85.3 [b]			

Table 21: Test results for imide-based type I ½ inhibitors. The IC50 value were determined as follows: a) using the radiometric HotSpot™ assay; b) using the TR-FRET-based assay. The IC50 value of TNFα-release was measured in human whole blood for compound 148 (n = 2).



Time [min]	637 m/z [%]	653 m/z [%]	611 m/z [%]
0	100	0	0
10	97	9	4
20	93	13	7
30	83	15	10
60	73	26	18

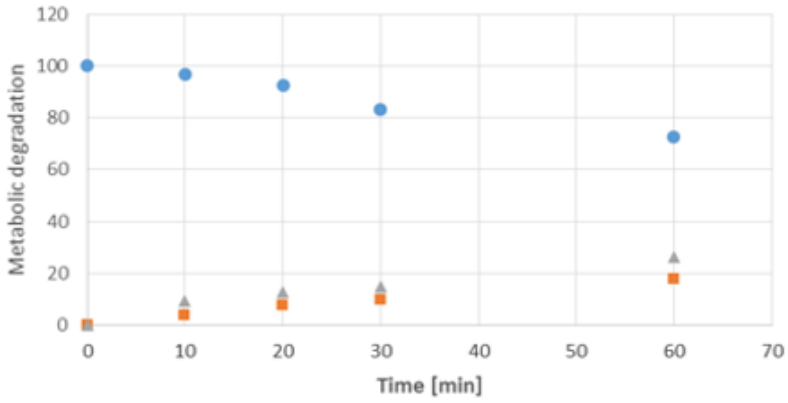


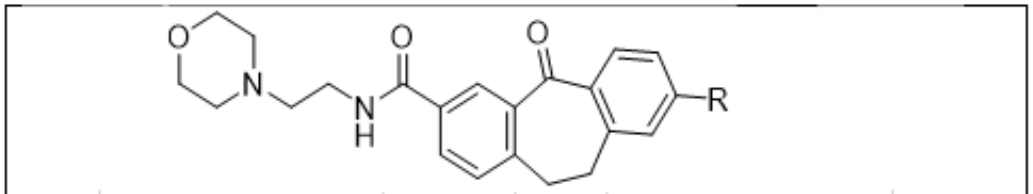
Figure 20: Results of the in-vitro metabolism study of compound 148 after 60 min incubation with RLM and the proposed metabolites. Legend: Blue circle = 148; grey triangle = metabolite A; orange square: metabolite B

Based on the excellent results for **148**, the succinimide (**149**) and glutarimide (**150**) derivates were designed for ADME optimization due to a lower molecular weight of the compounds and enhanced amount of saturated sp^3-hybridized carbons.[119] This approach resulted in the loss of potency of the inhibitors. Especially, the IC_{50} value of the five-membered ring derivate **149** is decreased compared to the phthalimide derivate **148**. This may explain by the small ring size and the loss of aromatic-based charge transfer or π−π-interactions with the Phe167 of the DFG-motif.

3.2.6. Oxadiazoles

Another approach to replace the enzymatically labile amide group is the use of bioisosteric replacements. Oxadiazoles are one of the known atypical amide bioisosteres which are widely used to improved metabolic stability, membrane permeability, and bioavailability.[129, 130] Mostly the 1,2,4-isomer and 1,3,4-isomer are used for the replacement. The regioisomers are able to mimic the molecular planarity and dipole moment of an amide. However, a difference in aromatic, electrostatic, and hydrogen bonding character is observed. There are many examples in the literature where the oxadiazoles were successfully applied as amide surrogates with enhanced properties.[130, 131]

To evaluate if this strategy could be also applied for our project, three novel inhibitors **151**-**153** shown in Table 22 utilizing an oxadiazole as replacement for the amide bond, were synthesized. The type I ½ residues were previously used for another project and kindly provided by Juliander Reiner. Compound **151** and **152** containing the 1,2,4- or 1,3,4-isomer of oxadiazole utilising a phenyl moiety for R-spine interactions were made to test if both regioisomers are having the same activity or which is better. Additionally, compound **153** comprises of a thiophene moiety for R-spine interaction. Unfortunately, all tested compounds demonstrate a dramatically loss of potency compared to the amide analogues. This results clearly show the failure of this approach. For our inhibitors, oxadiazoles are not an appropriate bioisosteric replacement of the amide bond.



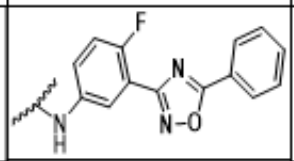
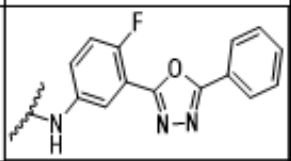
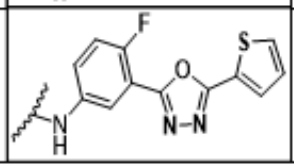
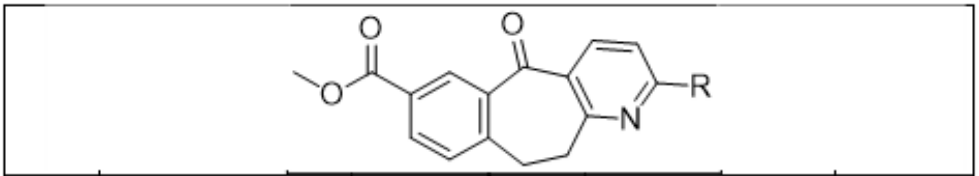
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
151		> 1000	152		n.t.
153		934.8			

Table 22: Test results of the TR-FRET assay for oxadiazole-based type I ½ inhibitors. N.t. = not tested.

3.2.7. Azadibenzosuberones

As already described, there is an urgent need for highly potent and selective p38 MAPK inhibitors with long TRT and optimized ADME-properties which could be tested for the treatment of CRC. Therefore, a novel suberone based core scaffold was designed. Based on QM Conformer & Tautomer Predictor (Schrodinger LLC) studies by Tatu Pantsar, a nitrogen in the B-ring of the dibenzosuberone scaffold should favour the bioactive conformation of the inhibitor. Moreover, the position where the nitrogen is attached, is solvent exposed. Thus, MD simulations done by Tatu Pantsar suggested a beneficial additional water-mediated interaction from the nitrogen atom with water. Furthermore, the attachment of the nitrogen atom results in a decreased log P value which probably enhance the compounds solubility.



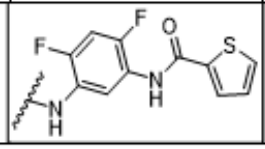
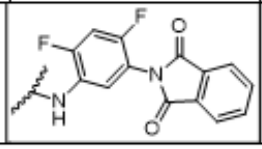
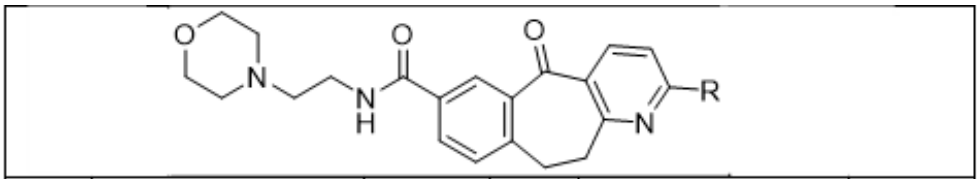
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
154		1.56	155		3.25

Table 23: Test results of the radiometric HotSpot™ assay for azadibenzosuberone-based type I ½ inhibitors with a methyl ester moiety.

The azadibenzosuberone-based inhibitors shown in Table 23 were synthesized with a methyl ester moiety due to faster synthetic availability and to gain initial results. As already shown, the moiety located in the solvent exposed area has only a slight influence on the inhibitory activity. Compounds **154** and **155** demonstrate high potency against the p38α MAPK in the isolated kinase assay. Based on these initial results, more azadibenzosuberone-based inhibitors were synthesized. The introduction of the morpholino ethyl residue resulted in a 2-fold gain of activity on the isolated kinase for the thiophene-based R-spine interacting residue.

Compounds **156**-**158** (Table 24) show excellent potency, with values below the detection limit of the assay. The inhibitory activity of all three inhibitors is better compared to the dibenzosuberone reference compounds. For example, the activity of **158** is 4-fold higher than the activity of the reference compound **HW299** (1.53 nM). These results indicate the success of the approach. However, the oxazole-based inhibitor **159** and the pyrrolidine urea based **160** show a 100-fold loss of potency in comparison to the dibenzosuberone-based analogues. The type I inhibitor **161** demonstrated the lowest IC_{50} value of all tested compounds with 40 picomolar (< detection limit). This result match to the simulation data indicating an increased solvent exposure of the Type-I inhibitor compared to Type I ½. In comparison to **161**, the activity of **162** utilizing difluoro-pyrimidine as C-ring, is dramatically lower. One reason for the loss of activity may results from a chelating ability of the three nitrogen in close vicinity interfering with the test assay. Another reason could be the formation of an additional hinge-binder lowering the potency and enhancing promiscuity.

Unfortunately, a loss of potency in whole blood assay was observed. Compound **156** is the only azadibenzosuberone-based inhibitor demonstrating a good inhibition of lipopolysaccharide (LPS)-stimulated TNF-α release in whole blood.



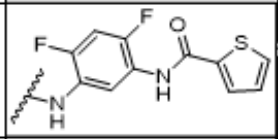
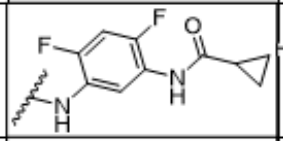
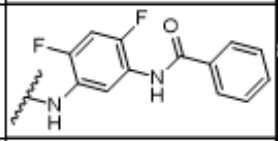
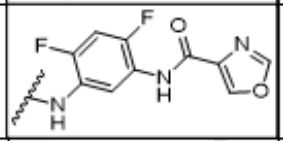
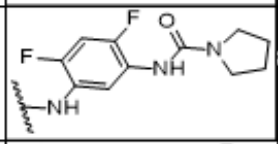
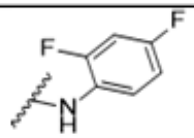
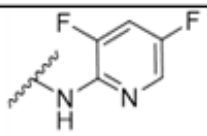
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
156		0.796 70 (TNFα)	157		0.121 159 (TNFα)
158		0.349 170 (TNFα)	159		10.5
160		10.4 465 (TNFα)	161		0.04 181 (TNFα)
162		364			

Table 24: Test results of the radiometric HotSpot™ assay for azadibenzosuberone-based type I ½ inhibitors with a morpholino ethyl moiety. The IC50 value of compounds 156, 157, 158 and 160 for TNFα-release were measured in human whole blood (n = 3).

In summary, most azadibenzosuberones show excellent potency on the isolated kinase, but not in whole blood system. The influence of the nitrogen to the TRT, metabolism and ADME-properties still needs to be evaluated by test results.

3.2.8. Pyrimidine-based type I inhibitor

Based on the promising results for the azadibenzosuberones, the influence of an additional nitrogen in the C-ring was analysed. Therefore, the pyrimidine-based inhibitor **163** shown in Table 25 was synthesized. By utilizing a difluoro-pyrimidine as C-ring building block, a 60-fold decreased potency compared to the difluoro-phenyl analogue **FS365** was observed.

In summary, the introduction of a pyrimidine-based C-ring negatively affect the inhibitory activity of the dibenzosuberones and the azadibenzosuberones.

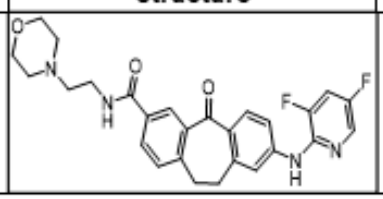
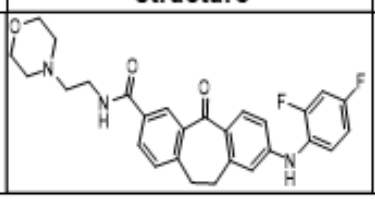
No.	Structure	IC_{50} [nM]	No.	Structure	IC_{50} [nM]
163		48.7	FS365		0.8

Table 25: Test results of the radiometric HotSpot™ assay for type I inhibitors.

4. Summary and outlook

As part of this thesis 74 novel inhibitors of p38α MAP kinase were synthesized. Many inhibitors display low nanomolar or even picomolar IC_{50} values.

First of all, by further optimization of the dibenzosuberone synthesis, a two-step synthetic strategy utilizing B-alkyl-Suzuki-reaction was established. With this approach the overall yield was improved from 66% to 85%. This optimized synthetic route facilitated a fast, reliable, and high yield synthesis of the dibenzosuberone scaffold which was required for the final inhibitor synthesis. The final inhibitors enable a deeper insight of the SAR and the influence on the R-spine interaction. On the one hand, previous SAR could be confirmed; a difluoro phenyl moiety as C-ring demonstrate the best potencies, the residues located into the solvent exposed area are mostly interchangeable and the metabolite of the morpholino ethyl residue is still an active inhibitor. On the other hand, it could be shown that for the amide-based inhibitors, five- or six-membered heterocycles (**89-92**) and small aliphatic residues (**99**) are good for the R-spine interaction. The concept of bioisosteric replacement was successfully applied. Especially, five- or six-membered aromatic heterocycles demonstrating high potency without a further discrimination between the type and position of the two heteroatoms. While large, bulky R-spine interacting residues like adamantane lower the potency.

Inhibitors comprising of novel functional classes as linker for the type I ½ residues were synthesized and synthetic strategies thereof were established. The metabolically instable amide bond could be successfully replaced by ketones, Weinreb amide and Imides. Especially, the ketone derivate **129**, the phthalimide derivate **148** and the cyclic urea derivate **138** demonstrated high potency on the isolated kinase as well in the whole blood test system. Furthermore, compounds **138**, **148** and the ketone derivate **133** are metabolically more stable than the previous amide derivates **FS694** and **HW237** which are also having a morpholine ethyl moiety attached. Whereas oxadiazole (**151-153**) and acetamide-based compounds (**142-147)** are not appropriate bioisosteric replacements for amide linker as dibenzosuberone-based p38α MAP kinase inhibitors due to the observed decreased biological activity on the isolated enzyme. An overview of the best dibenzosuberone-based compounds is shown in Figure 21.

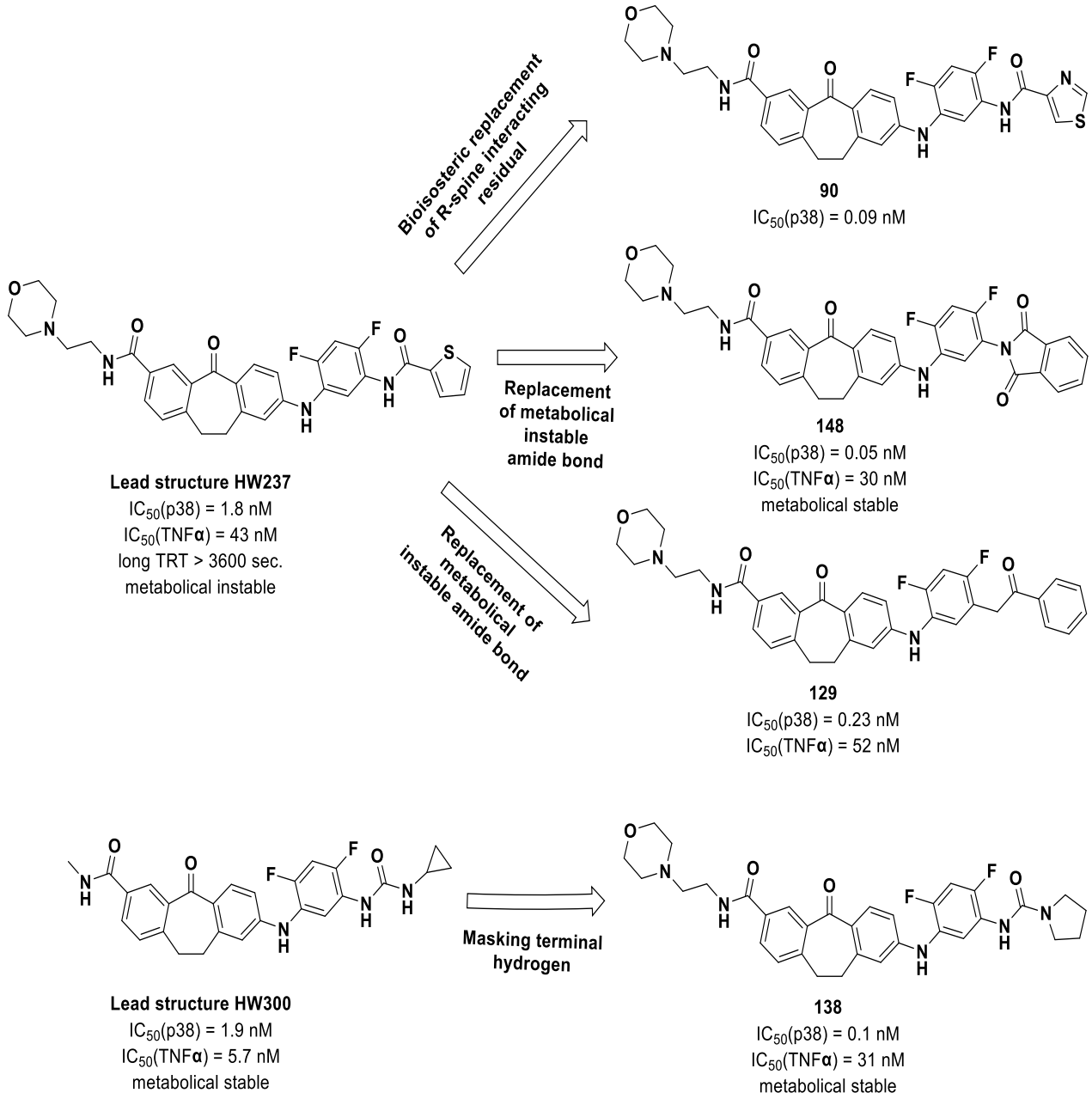


Figure 21: Overview of the best compounds and strategies.

To address the aim of finding a clinical candidate for CRC treatment, a novel suberone-based scaffold containing an additional nitrogen was developed. This approach should enable the synthesis of highly active and selective p38 MAPK inhibitors with long TRT and optimized PK-properties. The so called azadibenzosuberones are highlighted in Figure 22. The initial results of the obtained inhibitors look quite promising by demonstrating high potency on the isolated kinase. Unfortunately, this promising result could not be confirmed in the whole blood assay. In this assay, the azadibenzosuberone based inhibitors are not as active as the dibenzosuberone analogues.

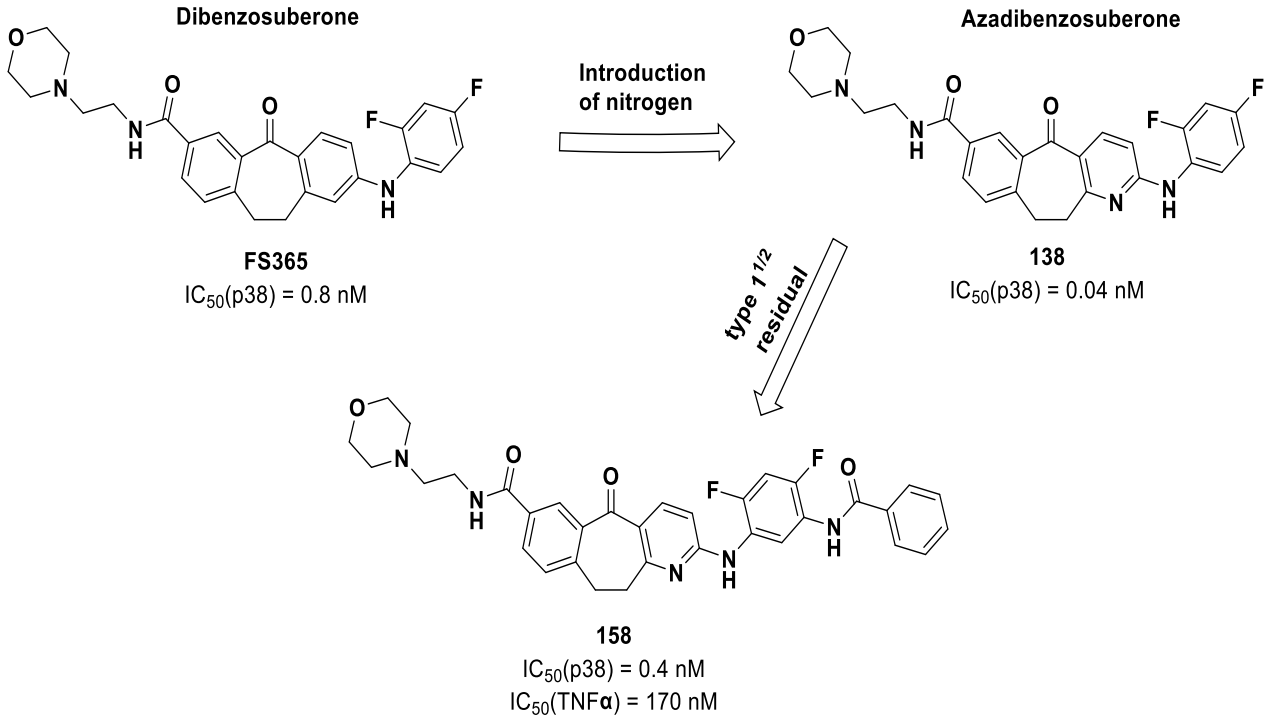


Figure 22: Introduction of an additional nitrogen to the B-ring of the dibenzosuberone scaffold resulted in the development of the azadibenzosuberones.

The TRT and the PK-properties of the most promising compounds should be determined in the future. These results are required to evaluate the success of some utilized approaches for example to optimize PK-properties by the introduction of heteroatoms. The success of the TRT and the PK-properties optimization is important for the selection of a clinical candidate for the treatment of colorectal cancer. As soon as the TRT and PK results are available, the best inhibitors should be tested in CRC mouse models and based on this outcome a clinical candidate can be selected.

5. Experimental procedures

5.1. General experimental procedures

The following instruments, methods and materials were used for the synthesis, purification and analytic of the synthesized compounds.

All reagents were purchased from commercial suppliers and used without further purification.

NMR

^{1}H- and ^{13}C-NMR spectra were recorded on Bruker Avance 200 MHz or Bruker Ultra Shield 400 MHz spectrometer. Chemical shifts (δ) values are presented in parts per million (ppm), referenced to the solvent peak ($CDCl_3$, defined at δ 7.26 for ^{1}H, δ 77.0 for ^{13}C; CD_3OD: δ 3.31 for ^{1}H, δ 49.0 for ^{13}C; $(CD_3)_2SO$: δ 2.50 for ^{1}H, δ 39.5 for 13C). ^{19}F chemical shifts are reported in ppm relative to CFCl3 (0 ppm). The peak multiplicity is reported as singlet (s), doublet(d), triplet(t), quartet(q), pentet(p), doublet of doublets (dd), doublet of triplets (dt), triplet of triplets (tt) and broad signal (br). All multiplets that do not fit into one of the above categories are reported as multiplet (m). The coupling constants J is mentioned in Herz (Hz).

Mass spectrometry (MS)

TLC-MS Plate Express system from Advion with electronic spray ionisation (ESI) technique was used to obtain mass spectra. This system is suitable for a mass to charge ratio of 10-1200 m/z and the detection could be in positive [$m+H^+$; $m+Na^+$] and in negative [$m-H^-$] mode.

Ionisation energy:	3.50 kV
Capillary voltage:	187 V
Source voltage:	44 V
Capillary temp.:	250 °C
Gas temp.:	250 °C
Flow rate:	5 l/min (N2)

HPLC

High performance liquid chromatography was measured on Hewlett Packard HP 1090 Series II LC equipped with a UV diode array detector (DAD, detection at 230 nm and 254 nm). The chromatographic separation was performed on a reverse phase Phenomenex Luna 5u C8 column (150 mm x 4.6 mm, 5 µm) at 35 °C. The injection volume was 5 µL and the gradient of the method was as followed:

Mobile phase A:	0.01 M KH_2PO_3 pH 2.30
Mobile phase B:	Methanol
Flow rate:	1.5 ml/min
Gradient:	40% B to 85% B in 8 min, 85% B for 5 min, 85% B to 40 % B in 5 min, 40 % B for 2 min, stop time 16 min.

The purity of all test compounds was determined via HPLC and is > 95 %.

TLC

For TLC, fluorescent silica gel 60 F254 plates (Merck) were used and the spots were visualized under UV illumination at 254 nm and 366 nm.

Melting points

The melting points of the test compounds were determined with a Büchi Melting Point B-545 apparatus with thermodynamic correction.

IR spectrum

IR spectra were measured with an Agilent Cary 630 FT-IR (ATR) spectrometer.

Column chromatography

Davisil® 60Å (20-45 µm particle size) chromatography silica from Grace and an Interchim puriFlash XS 420 plus automated flash chromatography system were used for column chromatography.

5.2. General synthetic procedures

1: Buchwald-Hartwig amination

Aryl chloride (1.0 eq.) Potassium carbonate (3 eq., dried in oven at 150°C overnight), Brettphos Pd G3 (0.02 eq.) and the corresponding amine (1.2 eq.) were added into a 10 mL screw cap vial containing a magnetic stir bar and flushed with argon. Degassed, dry 1,4-Dioxane (0.5 M) was added, and the reaction mixture was stirred at 100 °C overnight.

Work up: Upon completion of the reaction 1 mL DCM was added to the reaction mixture and the mixture was transferred to a round bottom flask. The screw cap vial was washed 3 x DCM (in total ca. 15 mL). Celite® was added and the mixture was concentrated in vacuo. The residual was purified by automated flash column chromatography (silica gel, gradient 0-5% DCM/MeOH, 20 min).

2: Amide coupling

1). Using acyl chloride and NaH

After adding of amine (1 eq.) to a solution of NaH (1 eq.) in dry THF (0.2 M), the reaction mixture was allowed to stir until there was no more gas formation (ca. 20 min). The reaction mixture was cooled to 0°C in an ice bath and the acyl chloride (1 eq.) was carefully added. The reaction mixture was stirred at room temperature (or at reflux temperature, if needed) until TLC indicated complete conversion of the starting material.

Work up: Upon full consumption of the amine starting material, the reaction was quenched with water, extracted with ethyl acetate (3x 10 ml), washed with aq. NH_4Cl, sat. KCO_2 and brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo.

2). Using TBTU

To a mixture of TBTU (1.5 eq.) and DIPEA (3 eq.) in THF (0.1 M), the carboxylic acid was added, and the mixture was stirred for 10 min. The amine (1.1 eq.) was added dropwise, and the reaction mixture was stirred at 50°C until TLC indicated complete conversion of the starting material.

Work up: The reaction was quenched with water. The resulting mixture was extracted with ethyl acetate (3x 10 ml), washed with aq. NH_4Cl, sat. KCO_2 and brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo.

3). Using CDI

The carboxylic acid (1 eq.) was added to a mixture of CDI (1,1 eq.) in dry THF (0.1 M) and stirred for 10 min. The amine (2 eq.) was added dropwise and it was stirred at 40°C until TLC indicated complete conversion of the starting material.

Work up: The reaction was quenched with water. The resulting mixture was extracted with ethyl acetate (3x 10 ml), washed with aq. NH_4Cl, sat. KCO_2 and brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo.

3: Esterification

To a cold solution of the carboxylic acid in the corresponding alcohol (0.5 M), sulfuric acid (0.2 eq.) was added, and the reaction mixture was stirred at reflux temperature overnight.

Work up: The reaction was quenched with water. The resulting mixture was extracted with ethyl acetate (3x). The combined organic layers were washed with saturated $NaHCO_3$ solution, brine and dried in vacuo.

4: Saponification

Carboxylic acid (1 eq.) was added to a mixture of KOH (4 eq.) in MeOH (0.05M) and stirred at reflux temperature until TLC indicated complete conversion of the starting material.

Work up: Water (5 ml) was added to the reaction mixture and the aqueous layer was acidified to pH 2 with 6N HCl. The organic layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo.

5: Nitration

In a three-neck round bottom flask, equipped with a drop funnel and thermometer, sulfuric acid (1 M) was cooled down to -10°C in an acetone ice bath. The aryl derivative (1 eq.) was slowly added dropwise, and the reaction mixture was cooled down to -10°C. HNO3 conc. (1 eq.) was carefully added dropwise, keeping the temperature below 0°C and the solution was stirred for 2h.

Work up: The mixture was poured onto ice (200 ml) and it was adjusted to pH 13 using conc. NaOH solution. The precipitate was filtered, washed with water and dried in vacuo.

6: Reduction of nitro-group

The nitro derivative was dissolved in dry ethanol (0.1 M), tin (II) chloride dihydrate (5 eq.) was added and it was stirred at room temperature (or reflux temperature if required) until TLC indicated complete conversion.

Work up: Ethanol was removed in vacuum and the residual was dissolved in ethyl acetate. Sodium bicarbonate (10 eq.) was added to the reaction mixture, filtered through Celite and dried in vacuum.

7: Reduction of double bond

The starting material was dissolved in ethyl acetate (0.02 M), Palladium on activated charcoal (10 wt%) was added and it was cooled down to -5°C in an acetone/ice bath. The reaction mixture was flushed with hydrogen for 30 min and stirred under saturated hydrogen atmosphere and ice bath cooling until HPLC indicated complete conversion of the starting material.

Work up: The mixture was filtered throw Celite and the solvent was evaporated under reduced pressure and dried under vacuo.

8: Acyl chloride synthesis

The carboxylic acid was treated with excess of thionyl chloride (2M) and heated to reflux temperature for 2h. Thionyl chloride was removed in vacuo.

The product was used without further purification for the next step (e.g., Friedel-Crafts acylating, amide coupling).

9: Friedel-Crafts acylation

1). Using liquid arenes

In a Schlenk flask under argon atmosphere aluminium chloride (1.5 eq.) was dissolved in the corresponding arene (0.4 M). The reaction mixture was cooled down to -10°C in an ice/acetone bath and the acetyl chloride was carefully added dropwise. It was stirred at room temperature overnight.

Work up: The reaction mixture was put on ice, 6M HCl was added and it was extracted with DCM (3x 10 ml). The combined organic layers were washed with water and brine, prior to drying and evaporating.

2). Using solid arenes

In a Schlenk flask under argon atmosphere aluminium chloride (1.5 eq.) was dissolved in dry DCM (0.4 M). The reaction mixture was cooled down to -10°C in an ice/acetone bath and the acetyl chloride was carefully added. A mixture of the arene (1.2 eq.) in DCM was slowly added to the reaction mixture. It was stirred at room temperature overnight.

Work up: The reaction mixture was put on ice, 6M HCl was added and it was extracted with DCM (3x). The combined organic layers were washed with water and brine, prior to drying and evaporating.

10: Isocyanate synthesis using DPPA

To a cold solution of the carboxylic acid (1 eq.) in dry toluene (0.25 M), triethylamine (1 eq.) and diphenyl phosphoryl azide was added dropwise and it was first stirred at room temperature for 30 min and then at reflux temperature for 2h.

The product was used without further purification for the next step (11: urea synthesis).

11: Urea synthesis

1). Using Isocyanate

To a solution of isocyanate (1.2 eq.) in dry toluene (0.25 M), a mixture of aniline derivative (1 eq.) in dry toluene was added and it was stirred at reflux temperature overnight.

The reaction was quenched with water. The resulting mixture was extracted with ethyl acetate (3x). The combined organic layers were washed with saturated $NaHCO_3$ solution, brine and dried in vacuo. The residual was purified by automated flash column chromatography (silica gel, gradient 10-50% petroleum ether/ ethyl acetate, 20 min).

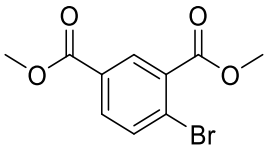
2). Using carbamoyl chloride

The aniline derivative (1 eq.) was dissolved in dry THF (0.5 M) under ice bath cooling, NaH was added and it was stirred for 20 min. The carbamoyl chloride (1.1 eq.) was carefully added dropwise, and the reaction mixture was stirred at room temperature until TLC indicated a complete conversion of the starting material.

Work up: Celite® was added and the mixture was concentrated in vacuo. The residual was purified by automated flash column chromatography (silica gel, gradient 10-50% petroleum ether/ ethyl acetate, 20 min).

5.3. Synthetic procedures

Dimethyl 4-bromoisophthalate (1)

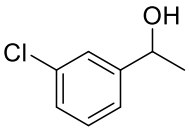


Compound 1 was synthesized according to the general procedure **3** for esterification, using 4-bromoisophtalic acid (102 mmol, 25 g), sulfuric acid (40.8 mmol, 4 g) and methanol (40 ml) to yield the product (25.8 g) as white crystals.

$C_{10}H_9BrO_4$ (Mr = 273.08)

Yield	93%
HPLC	> 99% (t_R= 7.04 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.19 (d, J = 2.0 Hz, 1H), 7.75 (dd, J = 8.4, 2.1 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H)

1-(3-Chlorophenyl)ethan-1-ol (2)



Compound 2 was synthesised according to the literature (Org. Synth.1984,28,28).

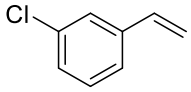
In a dry 100 ml three-necked round-bottomed flask equipped with a stirrer, a dropping funnel and a reflux condenser with calcium chloride tube attached, magnesium turnings (1.2 eq., 3 g), a crystal of iodine, and 10 ml dry ether were placed. A mixture of m-bromochlorobenzene (1 eq., 25 g) in 20 ml dry ether was added dropwise over ca. 1h. The reaction mixture was stirred at reflux temperature for 1.5 hours. A solution of freshly distilled acetaldehyde (1.1 eq., 6.5 g) was added and the mixture was stirred at reflux overnight.

Work up: The reaction mixture was put on ice, ammonium chloride (25%, aq.) was added and it was extracted with diethyl ether (3x 25 ml). The combined organic layers were dried over anhydrous sodium sulfate, the ether was evaporated, and the crude product was distilled under reduced pressure to give 14.32 g of m-chlorophenylmethylcarbinol.

C_8H_9ClO (M_r = 156.61)

Yield	70%
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 7.34 (d, J = 5.8 Hz, 1H), 7.32 – 7.16 (m, 3H), 4.79 (q, J = 6.5 Hz, 1H), 3.64 (bs, 1H), 1.43 (d, J = 6.5 Hz, 3H)
^{13}C NMR (50 MHz, $CDCl_3$)	δ 147.77, 134.31, 129.71, 127.46, 125.55, 123.44, 69.80, 25.11

1-Chloro-3-vinylbenzene (3)



Compound 3 was synthesised according to the literature (Org. Synth. 1948, 28, 31).

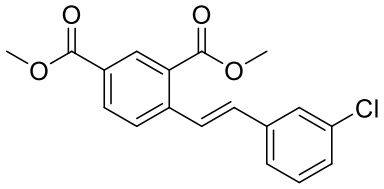
In a 25 ml three-necked round-bottomed flask with dropping funnel, a Vigreux column and a water condenser attached, 8 g of potassium acid sulfate and 20 mg of p-tert-butylcatechol were added. The flask was heated to 200°C under reduced pressure and a mixture of 14.3 g of m-chlorophenylmethylcarbinol and 20 mg of p-tert-butylcatechol was slowly added dropwise. The m-chlorostyrene and water were collected by distillation in a collector.

Work up: The mixture is extracted with ether and the combined organic layers were separated, dried over anhydrous sodium sulfate, filtered, p-tert-butylcatechol was added and the ether was removed in vacuo to achieve 7.3 g of m-chlorostyrene.

C_8H_7Cl (Mr = 138.59)

Yield	59%
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 7.40 (s, 5H), 7.31 – 7.19 (m, 15H), 6.66 (dd, J = 17.6, 10.9 Hz, 4H), 5.76 (d, J = 17.6 Hz, 4H), 5.31 (d, J = 10.9 Hz, 4H)
^{13}C NMR (50 MHz, $CDCl_3$)	δ 139.33, 135.53, 134.43, 129.66, 127.67, 126.09, 124.37, 115.25

Dimethyl (E)-4-(3-chlorostyryl)isophthalate (4)



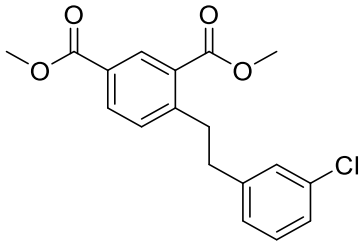
Dimethyl-4-bromoisophtalate (1) (1 eq., 4.9 g), $Pd_2(dba)_3$ (1 mol%, 0.17 g), tetrabutylammonium chloride (0.1 eq., 0.5 g) and tri-tertbutylphoshonium tetrafluoroborate (6 mol%, 0.31 g) were added to a 50 ml flask under argon atmosphere. A mixture of 1-chlor-3-vinylbenzene (3) (1.1 eq., 2.8 g) and N, N-dicyclohexyl methylamine (1.5 eq., 5.2 g) in dry, degassed Dioxane (5 ml) was added to the reaction mixture and stirred at 85 °C for 2h.

Work up: 20 ml 2M $KHSO_4$ solution was added to the mixture and it was extracted with ethyl acetate (3x 15 ml). The combined organic phases were washed with brine, dried over $NaSO_4$ and evaporated to dryness to give 7.51 g yellow solid. The crude product was recrystallized with EA/MeOH (1:4) to achieve 5.4 g white solid.

$C_{18}H_{15}ClO_4$ (Mr = 330.76)

Yield	91%
HPLC	98% (t_R = 10.189 min)
^{1}H-NMR (200 MHz, $CDCl_3$):	δ 8.60 (d, J = 1.5 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.29 (d, 1H), 7.21 (d, J = 5.9 Hz, 1H), 7.09 (s, 1H), 3.95 (s, 6H), 3.32 (t, 2H), 2.91 (t, 2H)

Dimethyl 4-(3-chlorophenethyl)isophthalate (5)



The key intermediate **5** was synthesized in 3 different ways:

1) Reduction of the double bond:

Compound **5** was synthesized according to the general procedure 7 reduction of the double bond, starting from dimethyl (E)-4-(3-chlorostyryl)isophthalate (3.5 g) to yield the title compound (3.1 g, 84%) as yellow oil.

2) Suzuki-reaction

Based on the following literature: J. Org. Chem., 2003, 68 (14), pp 5534–5539; DOI: 10.1021/jo0343331

2-(3-Chlorophenyl)ethylboronic acid pinacol ester (1 eq., 1 g), Cs_2CO_3 (3 eq., 3.7 g), $PdCl_2(dppf)\cdot CH_2Cl_2$ (15mol%, 0.5 g) and 4-bromoisophtalic acid dimethylester (1 eq., 1 g) were dissolved in THF:H_2O (10:1, 20 mL) under an argon atmosphere in a screw cap vial and stirred at 70°C overnight. The reaction mixture was filtered through Celite to yield the title compound (1.2 g, 97%) as colourless oil.

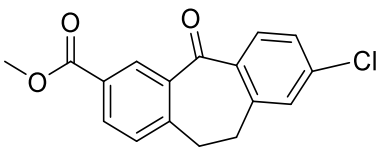
3) Photoredox reaction

In a dried microwave vial, 4-bromoisophtalic acid dimethylester (1 eq., 123 mg), $[Ir\{DF(CF_3)PPY]_2(DTBPY)]PF_6$ (1 mol%, 5.6 mg), $NiCl_2$*dtbppy (5 mol%, 1 mg) and sodium carbonate (2eq., 106 mg) were placed in the glovebox. A mixture of 1-(2-bromoethyl)-3-chlorobenzene (1.5 eq., 138.8 mg), $(TMS)_3SiBr$ (1.1 eq., 137 mg) and dry DME (5ml) were added to the reaction vessel and it was stirred under blue light irradiation overnight at ca. 20°C. The reaction mixture was filtered through Celite and purified via automatic flush chromatography with hexane/ ethyl acetate 0-30% over 20min to yield the product as colourless oil (143 mg, 86%).

$C_{18}H_{17}ClO_4$ (Mr = 332.78)

HPLC	>99% (t_R = 10.160 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.58 (d, J = 1.8 Hz, 1H), 8.06 (dd, J = 8.0, 1.9 Hz, 1H), 7.27 (t, J = 3.9 Hz, 1H), 7.23 – 7.16 (m, 3H), 7.09 – 7.02 (m, J = 3.9 Hz, 1H), 3.93 (s, 6H), 3.30 (dd, J = 9.5, 6.6 Hz, 2H), 2.89 (dd, J = 9.4, 6.5 Hz, 2H)

Methyl 8-chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate (6)



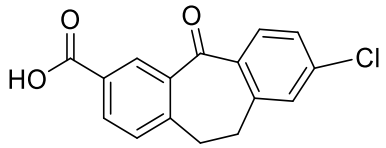
Dimethyl 4-(3-Chlorophenethyl)isophtalat (600 mg) was stirred in 4 ml Eaton´s reagent at 70°C under argon atmosphere in a 50 ml flask overnight.

Work up: The reaction mixture was cooled down to 5°C and sat. Na_2CO_3 solution with ice was carefully added. The mixture was extracted with ethyl acetate (3x) and dried over Na_2SO_4. The crude product was dried under reduced pressure and recrystallized in methanol to afford 527 mg of the product (dibenzosuberone) as brown solid.

$C_{17}H_{13}ClO_3$ (Mr = 300.74)

HPLC	94% (t_R = 9.196 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.69 (d, J = 1.5 Hz, 1H), 8.13 (dd, J = 7.9, 1.7 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 7.8 Hz, 2H), 7.28 (s, 1H), 3.97 (s, 3H), 3.25 (q, J = 9.1Hz, 4H)

8-Chloro-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylic acid (7)

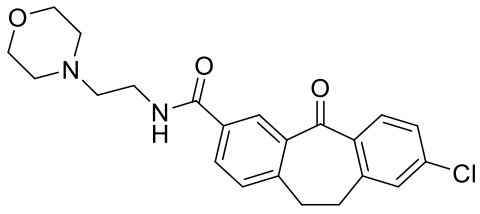


The title compound was synthesized according to the general procedure **4** for saponification of esters, starting with 1.3 g dibenzosuberone to yield 1.2 g of product as brown solid.

$C_{16}H_{11}ClO_3$ (Mr = 286.71)

Yield	95%
HPLC	97% (t_r = 8.617 min)
ESI-MS	m/z 284.9 $[M-H]^-$
^{1}H-NMR (400 MHz, MeOD)	δ 8.59 (d, J = 3.5 Hz, 1H), 8.11 (dd, 1H), 8.02 – 7.98 (m, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.40 – 7.37 (m, 2H), 3.31 – 3.21 (m, J = 9.1, 5.0, 2.4 Hz, 4H)
^{13}C NMR (100 MHz, MeOD)	δ 194.53, 168.91, 148.35, 145.69, 139.86, 139.53, 137.74, 134.44, 133.55, 133.14, 131.09, 130.80, 130.45, 128.04, 35.64, 35.36

8-Chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (8)



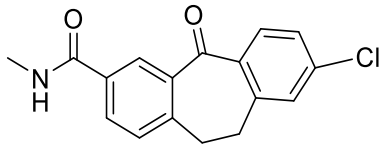
The title compound was synthesized according to the general procedure **2.2** amide coupling using TBTU, starting from 1.1 g dibenzosuberone carboxylic acid and 0.5 g 4-(2-aminoethyl)morpholine to yield 1.15 g product as yellow solid.

$C_{22}H_{23}ClN_2O_3$ (Mr = 398.89)

Yield	79%

HPLC	97% (t_r = 5.125 min)
ESI-MS	m/z 397.1 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.36 (d, *J* = 1.2 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.07 (s, 1H), 3.75 (t, 4H), 3.59 (q, *J* = 11.5, 5.8 Hz, 2H), 3.21 (q, *J* = 9.3 Hz, 4H), 2.64 (t, *J* = 6.1 Hz, 2H), 2.54 (t, 4H)

8-Chloro-N-methyl-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (9)

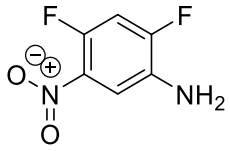


The title compound was synthesized according to the general procedure **2.3** amide coupling using CDI, starting from 970 mg dibenzosuberone carboxylic acid and methylamine solution (33% in ethanol) to yield 648 mg product as yellow solid.

$C_{17}H_{14}ClNO_2$ (Mr = 299.75)

Yield	64%
HPLC	96% (t_r = 7.705 min)
ESI-MS	m/z 298.0 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	8.30 (s, 4H), 8.04 – 7.92 (m, J = 8.3 Hz, 8H), 7.33 (dd, J = 7.5, 3.1 Hz, 8H), 7.27 – 7.23 (m, J = 2.7, 2.0 Hz, 9H), 6.28 (s, 3H), 3.21 (q, J = 9.0 Hz, 16H), 3.06 – 2.99 (m, J = 4.2 Hz, 12H)

2,4-Difluoro-5-nitroaniline (11)

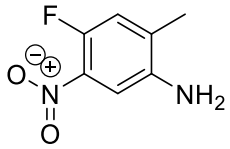


The title compound was synthesized according to the general procedure **5** nitration of arenes, starting from 5g 2,4-difluoroaniline to afford 6.5 g of product as orange crystals.

$C_6H_4F_2N_2O_2$ (Mr = 174.11)

Yield	96%
HPLC	95% (t_r = 3,932 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 7.50 (dd, 3H), 6.97 (t, 3H), 3.83 (s, 5H)

4-Fluoro-2-methyl-5-nitroaniline (12)

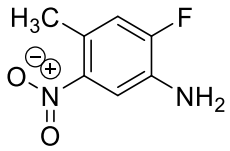


The title compound was synthesized according to the general procedure **5** nitration of arenes, starting from 3 g 4-fluoro-2-methylaniline to afford 3 g of product as brown solid.

$C_7H_7FN_2O_2$ (Mr = 170.05)

Yield	74%
HPLC	96% (t_r = 4.199 min)
ESI-MS	m/z 169.1 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 7.32 (d, J = 6.3 Hz, 1H), 6.98 (d, J = 11.4 Hz, 1H), 3.71 (bs, 2H), 2.22 (s, 3H)
^{13}C NMR (50 MHz, $CDCl_3$)	δ 148.98, 144.14, 131.67, 131.53, 119.48, 119.05, 108.38, 17.90

2-Fluoro-4-methyl-5-nitroaniline (13)

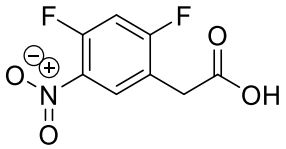


The title compound was synthesized according to the general procedure **5** nitration of arenes, starting from 5 g 2-fluoro-4-methylaniline to afford 3.8 g of product as brown solid.

$C_7H_7FN_2O_2$ (Mr = 170.05)

Yield	56%
HPLC	93% (t_r = 5.128 min)
^{1}H-NMR (200 MHz, DMSO-d_6)	δ 7.44 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 11.9 Hz, 1H), 5.61 (s, 2H), 2.35 (s, 3H)

2-(2,4-Difluoro-5-nitrophenyl)acetic acid (14)

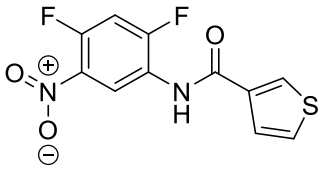


The title compound was synthesized based on the general procedure **5** nitration of arenes, but the pH value during the work up was only adjusted to pH 4. The reaction was started with 2 g 2,4-Difluorophenylacetic acid to afford 1.9 g of product as pale solid.

$C_8H_5F_2NO_4$ (Mr = 217.13)

Yield	75%
HPLC	100% (t_r = 4.287 min)
ESI-MS	m/z 217.0
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.14 (t, J = 7.7 Hz, 1H), 7.07 (t, J = 9.8 Hz, 1H), 3.68 (s, 2H)
^{13}C NMR (101 MHz, DMSO)	δ δ 170.94, 165.03 (d, *J* = 11.7 Hz), 162.47 (d, *J* = 11.8 Hz), 154.9 (d, J = 252.3 Hz), 153.63 (d, *J* = 14.0 Hz), 133.43 – 133.23 (m), 129.57 (dd, *J* = 7.5, 1.8 Hz), 120.57 (dd, *J* = 18.4, 4.1 Hz), 106.64 (dd, *J* = 28.2, 25.1 Hz), 33.32

N-(2,4-difluoro-5-nitrophenyl)thiophene-3-carboxamide (16)

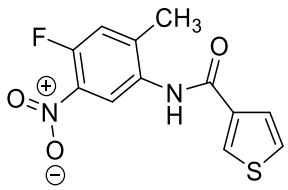


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 100 mg of 2,4-difluoro-5-nitroaniline and 84 mg thiophen-3-carbonyl chloride was used to obtain 160 mg of the product as brown solid.

$C_{11}H_6F_2N_2O_3S$ (Mr = 284.24)

Yield	99%
HPLC	89% (t_r = 6.025 min)
ESI-MS	m/z 348.4 $[M+ACN+Na]^+$
^{1}H NMR (400 MHz, DMSO)	δ 9.73 (s, 1H), 8.31 (s, 1H), 7.63 (s, 1H), 7.59 (s, 1H), 7.11 (t, *J* = 10.6 Hz, 1H), 6.92 (t, *J* = 8.6 Hz, 1H), 5.06 (bs, 2H)
^{13}C NMR (101 MHz, DMSO)	δ 160.84, 148.09, 145.73, 137.12, 132.66, 129.93, 121.15, 113.73, 103.69

N-(4-Fluoro-2-methyl-5-nitrophenyl)thiophene-3-carboxamide (17)



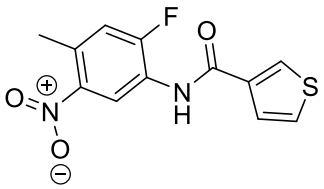
The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 350 mg of 4-fluoro-2-methyl-5-nitroaniline and 302 mg thiophen-3-carbonyl chloride was used to obtain 342 mg of the product as yellow solid.

$C_{12}H_9FN_2O_3S$ (Mr = 280.27)

Yield	60%

HPLC	98% (t_r = 5.817 min)
ESI-MS	m/z 303.3 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.67 (d, J = 7.2 Hz, 1H), 8.06 – 8.00 (m, 1H), 7.53 – 7.41 (m, J = 4.1 Hz, 3H), 7.17 (d, J = 11.2 Hz, 1H), 2.42 (s, 3H)
^{13}C NMR (101 MHz, DMSO)	δ 161.20, 153.39, 150.81, 144.14 (d, *J* = 248.9 Hz), 136.79, 134.23, 132.92, 130.40, 127.19 (d, *J* = 13.0 Hz), 123.17, 119.70 (d, *J* = 21.5 Hz), 18.24

N-(2-fluoro-4-methyl-5-nitrophenyl)thiophene-3-carboxamide (18)

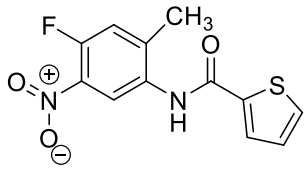


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 347 mg of 2-fluoro-4-methyl-5-nitroaniline and 300 mg thiophen-3-carbonyl chloride was used to obtain 571 mg of the product as white solid.

$C_{12}H_9FN_2O_3S$ (Mr = 280.27)

Yield	100%
HPLC	100% (t_r = 6.539 min)
ESI-MS	m/z 303.0 $[M+Na]^+$
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 9.17 (d, J = 7.4 Hz, 1H), 8.04 (dd, J = 2.9, 1.3 Hz, 1H), 7.84 (bs, J = 20.4 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.10 (d, J = 11.1 Hz, 1H), 2.58 (s, 3H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 160.78, 155.29, 152.78, 136.72, 130.94, 129.89, 127.57, 126.04, 125.12, 118.74, 118.52, 20.47

N-(4-Fluoro-2-methyl-5-nitrophenyl)thiophene-2-carboxamide (19)



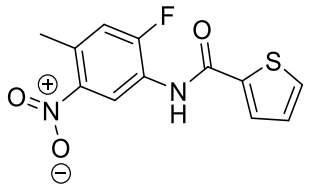
The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 350 mg of 4-fluoro-2-methyl-5-nitroaniline and 302 mg thiophen-2-carbonyl chloride was used to obtain 120 mg of the product as beige solid.

$C_{12}H_9FN_2O_3S$ (Mr = 280.27)

Yield	21%
HPLC	93% (t_r = 5.890 min)
ESI-MS	m/z 303.2 $[M+Na]^+$

^{1}H NMR (400 MHz, DMSO)	δ 10.17 (s, 1H), 8.17 (d, 1H), 8.00 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.89 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.57 (d, *J* = 12.4 Hz, 1H), 7.25 (dd, *J* = 5.0, 3.8 Hz, 1H), 2.35 (s, 3H)
^{13}C NMR (101 MHz, DMSO)	δ 160.29, 153.46, 150.87, 144.24, 138.66, 132.61, 132.20, 129.76, 128.16, 123.33, 119.70, 18.16

N-(2-fluoro-4-methyl-5-nitrophenyl)thiophene-2-carboxamide (20)

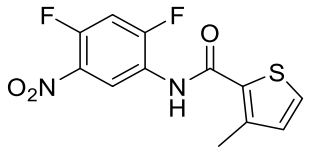


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 350 mg of 2-fluoro-4-methyl-5-nitroaniline and 284 mg thiophen-2-carbonyl chloride was used to obtain 248 mg of the product as yellow solid.

$C_{12}H_9FN_2O_3S$ (Mr = 280.27)

Yield	50%
HPLC	93% (t_r = 6.699 min)
ESI-MS	m/z 280.9 $[M+H]^+$
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 9.12 (d, J = 7.4 Hz, 1H), 7.90 (s, 1H), 7.67 (dd, J = 3.8, 1.1 Hz, 1H), 7.61 (dd, J = 5.0, 1.1 Hz, 1H), 7.16 (dd, J = 5.0, 3.8 Hz, 1H), 7.10 (d, J = 11.1 Hz, 1H), 2.58 (s, 3H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 159.76, 155.28, 152.77, 138.02, 134.35, 132.12, 131.07, 128.79, 124.94, 118.77, 118.57, 20.47

N-(2,4-difluoro-5-nitrophenyl)-3-methylthiophene-2-carboxamide (21)



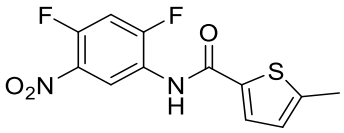
First, 3-methylthiophene-2-carbonyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis. The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 350 mg of 2,4-difluoro-5-nitroaniline and 386 mg 3-methylthiophene-2-carbonyl chloride were used to obtain 589 mg of the product as brown solid.

$C_{12}H_8F_2N_2O_3S$ (Mr =298.3)

Yield	99%
HPLC	98% (t_r = 7.037 min)
ESI-MS	m/z 321.5 $[M+Na]^+$

^{1}H NMR (400 MHz, $CDCl_3$)	δ 9.27 (td, *J* = 8.0, 3.3 Hz, 1H), 7.75 (bs, 1H), 7.42 (d, *J* = 5.0 Hz, 1H), 7.13 (t, *J* = 10.1 Hz, 1H), 6.99 (d, *J* = 5.0 Hz, 1H), 2.61 (s, 3H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 160.90, 156.21 (d, *J* = 210.3 Hz), 153.66 (d, *J* = 210.1 Hz), 153.19 (d, *J* = 12.6 Hz), 149.1 (d, J = 255.8 Hz), 143.84, 132.87, 129.64, 128.59, 119.17 (t, *J* = 2.8 Hz), 106.12 (t, *J* = 25.4 Hz), 16.13

N-(2,4-difluoro-5-nitrophenyl)-5-methylthiophene-2-carboxamide (22)

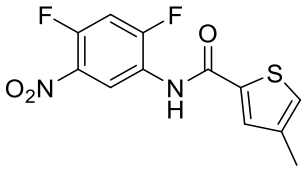


First, 5-methylthiophene-2-carbonyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis. The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 350 mg of 2,4-difluoro-5-nitroaniline and 386 mg 5-methylthiophene-2-carbonyl chloride were used to obtain 249 mg of the product as brown solid.

$C_{12}H_8F_2N_2O_3S$ (Mr =298.3)

Yield	42%
HPLC	98% (t_r = 6.815 min)
ESI-MS	m/z 297.3 $[M-H]^-$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 9.25 (t, *J* = 8.0, 2.8 Hz, 1H), 7.76 (bs, 1H), 7.49 (d, *J* = 3.7 Hz, 1H), 7.12 (t, *J* = 10.1 Hz, 1H), 6.84 – 6.82 (m, 1H), 2.56 (d, *J* = 0.8 Hz, 3H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 159.77, 146.4 (dd, J = 141.4, 10.6 Hz),144.0 (dd, J = 140.3, 10.5 Hz), 148.26, 134.78, 130.08, 126.84, 119.18 (t, *J* = 2.9 Hz), 106.11 (t, *J* = 25.4 Hz), 15.98

N-(2,4-difluoro-5-nitrophenyl)-4-methylthiophene-2-carboxamide (23)



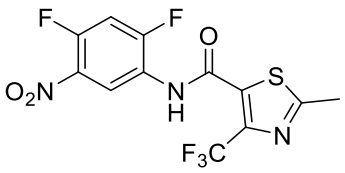
First, 4-methylthiophene-2-carbonyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis. The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 297 mg of 2,4-difluoro-5-nitroaniline and 300 mg 4-methylthiophene-2-carbonyl chloride were used to obtain 235 mg of the product as brown solid.

$C_{12}H_8F_2N_2O_3S$ (Mr =298.3)

Yield	46%

HPLC	92% (t_r = 7.152 min)
ESI-MS	m/z 297.3 $[M-H]^-$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 9.27 (t, *J* = 9.3, 6.7 Hz, 1H), 7.79 (bs, 1H), 7.48 (d, *J* = 1.2 Hz, 1H), 7.23 – 7.21 (m, 1H), 7.13 (t, *J* = 10.1 Hz, 1H), 2.33 (d, *J* = 0.7 Hz, 3H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 159.85, 157.17, 156.79, 154.87, 139.22, 136.94, 131.72, 128.00, 119.31 – 119.19 (m), 106.15, 15.79

N-(2,4-difluoro-5-nitrophenyl)-2-methyl-4-(trifluoromethyl)thiazole-5-carboxamide (24)

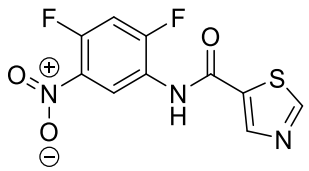


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 158 mg of 2,4-difluoro-5-nitroaniline and 250 mg 3-methylthiophene-2-carbonyl chloride were used to obtain 297 mg of the product as brown solid.

$C_{12}H_6F_5N_3O_3S$ (Mr =367.25)

Yield	89%
HPLC	100% (t_r = 7.015 min)
ESI-MS	m/z 366.4 $[M-H]^-$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 9.20 (t, *J* = 7.9, 3.1 Hz, 1H), 8.12 (bs, 1H), 7.17 (t, 1H), 2.79 (s, 3H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 170.11, 156.84, , 153.96 (t, *J* = 14.2 Hz), 151.38 (d, *J* = 213.1 Hz), 141.43 (d, *J* = 236.7 Hz), 134.46 (d, *J* = 2.0 Hz), 122.60 (dd, *J* = 11.5, 4.3 Hz), 121.65, 119.57 (t, *J* = 2.9 Hz), 118.95, 106.51 (t), 19.56

N-(2,4-difluoro-5-nitrophenyl)thiazole-5-carboxamide (25)

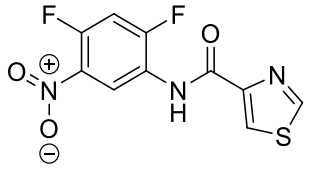


First, thiazole-5-carbonyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis. The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 455 mg of 2,4-difluoro-5-nitroaniline and 500 mg thiazole-5-carbonyl chloride was used to obtain 465 mg of the product as yellow solid.

$C_{10}H_5F_2N_3O_3S$ (Mr =285.22)

Yield	53%
HPLC	100% (t_r = 5.177 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 9.20 (t, J = 7.9 Hz, 1H), 9.02 (s, 1H), 8.44 (s, 1H), 7.91 (s, 1H), 7.17 (t, J = 9.9 Hz, 1H)

N-(2,4-Difluoro-5-nitrophenyl)thiazole-4-carboxamide (26)

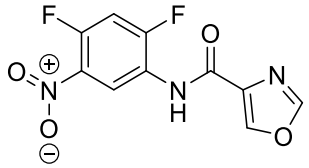


First, thiazole-4-carbonyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis. The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 455 mg of 2,4-difluoro-5-nitroaniline and 500 mg thiazole-4-carbonyl chloride was used to obtain 447 mg of the product as orange needles.

$C_{10}H_5F_2N_3O_3S$ (Mr =285.22)

Yield	51%
HPLC	96% (t_r = 6.185 min)
ESI-MS	283,7 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 9.54 (s, 1H), 9.36 (t, J = 8.0 Hz, 1H), 8.85 (d, J = 1.8 Hz, 1H), 8.34 (d, J = 2.0 Hz, 1H), 7.17 (t, J = 22.1, 12.0 Hz, 1H)

N-(2,4-difluoro-5-nitrophenyl)oxazole-4-carboxamide (27)

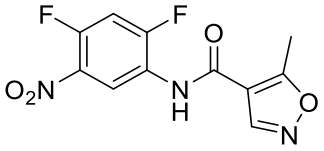


First, oxazole-4-carbonyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis. The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 542 mg of 2,4-difluoro-5-nitroaniline and 500 mg oxazole-4-carbonyl chloride were used to obtain 428 mg of the product as red-brown solid.

$C_{11}H_{12}F_2N_2O_3$ (Mr =258.22)

Yield	62%
HPLC	100% (t_r = 6.271 min)
ESI-MS	m/z 280.3 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 9.20 (t, J = 8.0 Hz, 1H), 7.58 (bs, 1H), 7.09 (t, J = 10.2 Hz, 1H), 1.34 (s, 9H)

N-(2,4-difluoro-5-nitrophenyl)-5-methylisoxazole-4-carboxamide (28)

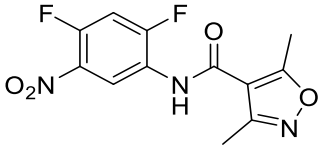


First, 5-methylisoxazole-4-carbonyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis. The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 397 mg of 2,4-difluoro-5-nitroaniline and 400 mg 5-methylisoxazole-4-carbonyl chloride were used to obtain 220 mg of the product as brown crystals.

$C_{11}H_7F_2N_3O_4$ (Mr =283.19)

Yield	34%
HPLC	100% (t_r = 6.015 min)
ESI-MS	m/z 282.2 $[M-H]^-$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 9.22 – 9.17 (m, 1H), 8.49 (d, J = 0.4 Hz, 1H), 7.53 (bs, J = 11.8 Hz, 1H), 7.16 (t, J = 10.0 Hz, 1H), 2.80 (d, J = 0.5 Hz, 3H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 174.61, 159.04, 156.38, 153.89, 153.62, 150.97, 147.42, 119.70, 106.36, 12.88

N-(2,4-difluoro-5-nitrophenyl)-3,5-dimethylisoxazole-4-carboxamide (29)

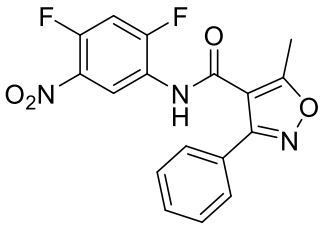


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 250 mg of 2,4-difluoro-5-nitroaniline and 252 mg 3,5-dimethylisoxazole-4-carbonyl chloride were used to obtain 346 mg of the product as brown crystals.

$C_{12}H_9F_2N_3O_4$ (Mr =297.2)

Yield	81%
HPLC	100% (t_r = 5.650 min)
ESI-MS	m/z 296.2 $[M-H]^-$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 9.22 – 9.17 (m, 1H), 8.49 (d, J = 0.4 Hz, 1H), 7.53 (bs, J = 11.8 Hz, 1H), 7.16 (t, J = 10.0 Hz, 1H), 2.80 (d, J = 0.5 Hz, 3H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 173.76, 159.91, 157.24, 156.17 (d, *J* = 212.1 Hz), 153.52 (dd, *J* = 19.0, 12.6 Hz), 150.77 (d, *J* = 213.2 Hz), 123.16 (dd, *J* = 11.3, 4.1 Hz), 119.26 (t, *J* = 3.1 Hz), 111.53, 106.24 (t, *J* = 25.4 Hz), 13.39, 11.91

N-(2,4-difluoro-5-nitrophenyl)-5-methyl-3-phenylisoxazole-4-carboxamide (30)

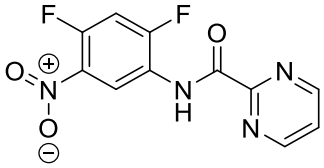


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 250 mg of 2,4-difluoro-5-nitroaniline and 350 mg 5-methyl-3-phenylisoxazole-4-carbonyl chloride were used to obtain 227 mg of the product as brown crystals.

$C_{17}H_{11}F_2N_3O_4$ (Mr =359.3)

Yield	44%
HPLC	99% (t_r = 7.617 min)
ESI-MS	m/z 358.5 $[M-H]^-$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 9.22 (t, *J* = 7.9 Hz, 1H), 7.64 – 7.57 (m, 5H), 7.40 (bs, *J* = 11.4 Hz, 1H), 6.93 (t, *J* = 10.0 Hz, 1H), 2.84 (s, 3H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 176.86, 159.76, 159.31, 155.68 (d, *J* = 247.4 Hz), 153.03 (d, *J* = 8.6 Hz), 150.41 (d, *J* = 12.5 Hz), 131.12, 129.74, 129.16, 127.40, 122.96 (dd, *J* = 12.0, 4.1 Hz), 118.77, 110.37, 105.83 (t, *J* = 25.2 Hz), 13.51

N-(2,4-difluoro-5-nitrophenyl)pyrimidine-2-carboxamide (31)

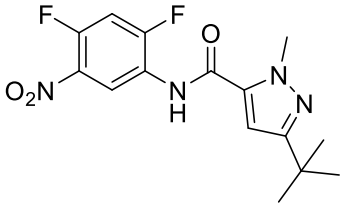


First, pyrimidine-2-carbonyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis. The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 455 mg of 2,4-difluoro-5-nitroaniline and 485 mg pyrimidine-2-carbonyl chloride were used to obtain 76 mg of the product as yellow solid.

$C_{11}H_6F_2N_4O_3$ (Mr =280.19)

Yield	9%
HPLC	95% (t_r = 4.832 min)
ESI-MS	m/z 302.8 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 10.28 (s, 1H), 9.45 (t, J = 7.7 Hz, 1H), 8.99 (d, J = 4.7 Hz, 2H), 7.58 (t, J = 4.3 Hz, 1H), 7.17 (t, J = 10.5 Hz, 1H)

3-(tert-butyl)-N-(2,4-difluoro-5-nitrophenyl)-1-methyl-1H-pyrazole-5-carboxamide (32)

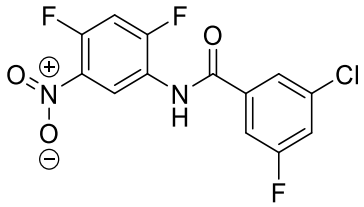


First, 3-(tert-butyl)-1-methyl-1H-pyrazole-5-carbonyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis. The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 237 mg of 2,4-difluoro-5-nitroaniline and 300 mg 3-(tert-butyl)-1-methyl-1H-pyrazole-5-carbonyl chloride were used to obtain 412 mg of the product as yellow needles.

$C_{15}H_{16}F_2N_4O_2$ (Mr =338.31)

Yield	90%
HPLC	93% (t_r = 8.564 min)
^{1}H NMR (400 MHz, $CDCl_3$)	δ 9.22 (t, *J* = 7.8 Hz, 1H), 7.82 (s, 1H), 7.16 (t, *J* = 10.0 Hz, 1H), 6.53 (s, 1H), 4.18 (s, 3H), 3.50 (bs, *J* = 131.6 Hz, 1H), 1.34 (s, 9H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 160.77, 157.86, 156.34, 153.63, 150.83, 134.13, 123.12, 119.29, 106.33, 103.46, 39.47, 32.24, 30.59

3-Chloro-N-(2,4-difluoro-5-nitrophenyl)-5-fluorobenzamide (33)

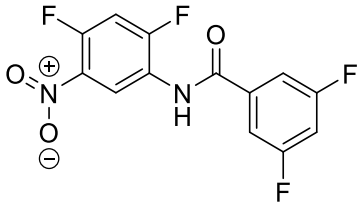


First, 3-chloro-5-fluorobenzoyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis. The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 300 mg of 2,4-difluoro-5-nitroaniline and 193 mg 3-chloro-5-fluorobenzoyl chloride was used to obtain 257 mg of the product as orange solid.

$C_{13}H_6ClF_3N_2O_3$ (Mr = 330.56)

Yield	46%
HPLC	>99% (t_r = 8.199 min)
ESI-MS	m/z 385.1 $[M+Na+MeOH]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 9.30 (t, J = 7.9 Hz, 1H), 7.95 (s, 1H), 7.73 – 7.62 (m, 1H), 7.60 – 7.49 (m, J = 7.6 Hz, 1H), 7.45 – 7.33 (m, 1H), 7.22 (t, J = 10.0 Hz, 1H)
^{13}C NMR (50 MHz, $CDCl_3$)	δ 165.30, 163.04, 160.29, 137.83, 137.70, 136.10, 123.32, 120.14, 119.65, 113.41, 112.96, 104.09, 103.61, 103.13

N-(2,4-difluoro-5-nitrophenyl)-3,5-difluorobenzamide (34)

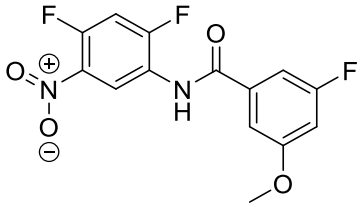


First, 3,5-difluorobenzoyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis. The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 700 mg of 2,4-difluoro-5-nitroaniline and 702 mg 3,5-difluorobenzoyl chloride was used to obtain 832 mg of the product as yellow solid.

$C_{13}H_6F_4N_2O_3$ (Mr = 314.20)

Yield	66%
HPLC	94% (t_r = 6.945 min)
ESI-MS	m/z 369.3 $[M+Na+MeOH]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 9.26 (t, J = 8.0 Hz, 1H), 7.92 (s, 1H), 7.40 (dt, J = 11.4, 3.8 Hz, 2H), 7.17 (t, J = 10.2 Hz, 1H), 7.12 – 6.99 (m, J = 8.5, 5.4, 3.1 Hz, 1H
^{13}C NMR (50 MHz, $CDCl_3$)	δ 165.65 (d, J = 12.0 Hz), 162.85 (t), 160.63 (d, J = 11.9 Hz), 157.58 (d, J = 211.0 Hz), 154.83 (d, J = 213.2 Hz), 152.46 (d, J = 10.7 Hz), 149.51 (d, J = 13.6 Hz), 136.41 (t, J = 8.4 Hz), 122.80 (dd, J = 11.3, 4.2 Hz), 119.53 – 119.35 (m), 110.80 – 110.15 (m), 108.19 (t, J = 25.2 Hz), 106.15 (t, J = 25.3 Hz)

N-(2,4-difluoro-5-nitrophenyl)-3-fluoro-5-methoxybenzamide (35)

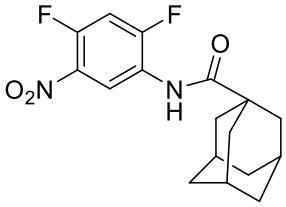


First, 3-fluoro-5-methoxybenzoyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis. The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 700 mg of 2,4-difluoro-5-nitroaniline and 979 mg 3-fluoro-5-methoxybenzoyl chloride was used to obtain 727 mg of the product as yellow solid.

$C_{14}H_9F_3N_2O_4$ (Mr = 326.23)

Yield	56%
HPLC	99% (t_r = 7.499 min)
ESI-MS	m/z 349.3 $[M+Na]^+$
^{1}H-NMR (200 MHz, DMSO-d_6)	δ 10.51 (s, 1H), 8.51 (t, 1H), 7.86 (t, 1H), 7.50 – 7.30 (m, 2H), 7.12 (d, 1H), 3.85 (s, 3H)

(3r,5r,7r)-N-(2,4-difluoro-5-nitrophenyl)adamantane-1-carboxamide (36)

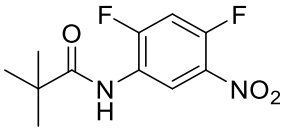


First, (3r,5r,7r)-adamantane-1-carbonyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis. The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 200 mg of 2,4-difluoro-5-nitroaniline and 188 mg adamantylcarbonyl chloride were used to obtain 281 mg of the product as brown solid.

$C_{17}H_{18}F_2N_2O_3$ (Mr =336.36)

Yield	98%
HPLC	98% (t_r = 9.216 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 9.23 (t, J = 8.1 Hz, 1H), 7.53 (bs, 1H), 7.08 (t, J = 10.1 Hz, 1H), 2.15 – 2.10 (m, J = 12.4 Hz, 3H), 1.97 (s, 3H), 1.91 (s, 2H), 1.84 – 1.80 (m, J = 7.8 Hz, 1H), 1.80 – 1.78 (m, 2H), 1.71 (t, J = 7.2 Hz, 4H)

N-(2,4-difluoro-5-nitrophenyl)pivalamide (37)

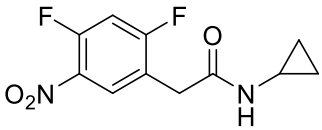


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 657 mg of 2,4-difluoro-5-nitroaniline and 500 mg pivaloyl chloride were used to obtain 603 mg of the product as orange solid.

$C_{10}H_5F_2N_3O_4$ (Mr =269.16)

Yield	62%
HPLC	97% (t_r = 5.161 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 9.28 (t, J = 8.0 Hz, 1H), 8.97 (s, 1H), 8.38 (d, J = 0.9 Hz, 1H), 7.97 (d, J = 0.8 Hz, 1H), 7.14 (t, J = 10.1 Hz, 1H)

N-cyclopropyl-2-(2,4-difluoro-5-nitrophenyl)acetamide (38)



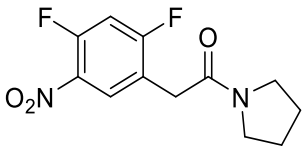
To a stirred solution of cyclopropylamine (1.1 eq., 80 mg) and triethylamine (1.1 eq., 110 mg) in dry THF (5 ml), 300 mg of 2-(2,4-difluoro-5-nitrophenyl)acetyl chloride was added dropwise. The mixture was stirred for 5 min at room temperature.

Work up: Water was added, and it was extracted with ethyl acetate, washed with brine, and dried under reduced pressure to obtain 309 mg of the product as yellow solid.

$C_{14}H_{10}F_2N_2O_3$ (Mr =292.23)

Yield	89%
HPLC	96% (t_r = 3.351 min)
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.16 (t, *J* = 7.8 Hz, 1H), 7.03 (dd, 1H), 5.85 (s, 1H), 3.52 (s, 2H), 2.74 – 2.67 (m, 1H), 0.82 – 0.75 (m, 2H), 0.55 – 0.48 (m, 2H)

2-(2,4-difluoro-5-nitrophenyl)-1-(pyrrolidin-1-yl)ethan-1-one (39)



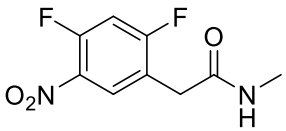
To a stirred solution of pyrrolidine (1.1 eq., 100 mg) and triethylamine (1.1 eq., 140 mg) in dry THF (5 ml), 300 mg of 2-(2,4-difluoro-5-nitrophenyl)acetyl chloride was added dropwise. The mixture was stirred for 5 min at room temperature.

Work up: Water was added, and it was extracted with ethyl acetate, washed with brine, and dried under reduced pressure to obtain 124 mg of the product as yellow solid.

$C_{12}H_{12}F_2N_2O_3$ (Mr =270.24)

Yield	36%
HPLC	96% (t_r = 5.076 min)
ESI-MS	m/z 271.2 $[M+H]^+$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.13 (t, *J* = 7.8 Hz, 1H), 7.02 (dd, *J* = 10.4, 9.0 Hz, 1H), 3.66 (s, 2H), 3.52 (q, *J* = 13.8, 6.8 Hz, 4H), 2.03 (q, 2H), 1.91 (q, 2H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 166.54, 165.26, 162.68, 157.08, 154.42, 129.77, 106.34, 46.97, 46.30, 33.91, 26.29, 24.51

2-(2,4-difluoro-5-nitrophenyl)-N-methylacetamide (40)



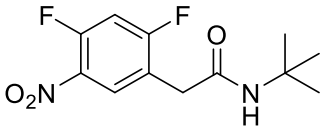
To a stirred solution of methyamine (1.1 eq., 44 mg) and triethylamine (1.1 eq., 140 mg) in dry THF (5 ml), 300 mg of 2-(2,4-difluoro-5-nitrophenyl)acetyl chloride was added dropwise. The mixture was stirred for 5 min at room temperature.

Work up: Water was added, and it was extracted with ethyl acetate, washed with brine, and dried under reduced pressure to obtain 230 mg of the product as white solid.

$C_9H_8F_2N_2O_3$ (Mr =230.17)

Yield	62%
HPLC	99% (t_r = 6.561 min)
ESI-MS	m/z 253.1 $[M+Na]^+$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.17 (t, *J* = 7.8 Hz, 1H), 7.04 (dd, *J* = 10.3, 9.1 Hz, 1H), 5.59 (s, 1H), 3.57 (s, 2H), 2.85 (d, *J* = 4.8 Hz, 3H)

N-(tert-butyl)-2-(2,4-difluoro-5-nitrophenyl)acetamide (41)



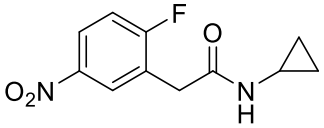
To a stirred solution of tert-butylamine (1.1 eq., 103 mg) and triethylamine (1.1 eq., 140 mg) in dry THF (5 ml), 300 mg of 2-(2,4-difluoro-5-nitrophenyl)acetyl chloride was added dropwise. The mixture was stirred for 5 min at room temperature.

Work up: Water was added, and it was extracted with ethyl acetate, washed with brine, and dried under reduced pressure to obtain 186 mg of the product as brown solid.

$C_{12}H_{14}F_2N_2O_3$ (Mr =272.25)

Yield	54%
HPLC	89% (t_r = 6.390 min)
ESI-MS	m/z 295.3 $[M+Na]^+$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.14 (t, *J* = 7.8 Hz, 1H), 7.03 (dd, *J* = 10.3, 9.1 Hz, 1H), 5.43 (bs, 1H), 3.49 (s, 2H), 1.35 (s, 9H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 167.15, 165.16, 162.59, 28.84, 154.58 – 154.39 (m), 129.58, 120.35, 106.52, 52.11, 36.47, 28.84

N-cyclopropyl-2-(2-fluoro-5-nitrophenyl)acetamide (42)



To a stirred solution of cyclopropylamine (1.1 eq., 143 mg) and triethylamine (1.1 eq., 253 mg) in dry THF (5 ml), 500 mg of 2-fluoro-5-nitrophenylacetyl chloride was added dropwise. The mixture was stirred for 5 min at room temperature.

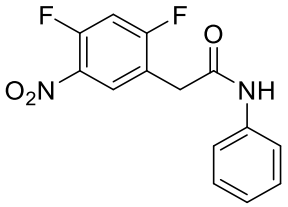
Work up: Water was added, and it was extracted with ethyl acetate, washed with brine, and dried under reduced pressure to obtain 554 mg of the product as pale solid.

$C_{11}H_{11}FN_2O_2$ (Mr =238.22)

Yield	69%

HPLC	100% (t_r = 4.339 min)
ESI-MS	m/z 261.1 $[M+Na]^+$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.28 – 8.24 (m, *J* = 6.3, 2.8 Hz, 1H), 8.17 (ddd, *J* = 9.0, 4.4, 2.9 Hz, 1H), 7.20 (t, *J* = 8.8 Hz, 1H), 5.85 (s, 1H), 3.57 (d, *J* = 0.9 Hz, 2H), 2.75 – 2.68 (m, 1H), 0.81 – 0.74 (m, 2H), 0.54 – 0.48 (m, 2H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 169.60, 165.86, 163.30, 127.75, 125.13, 124.19, 116.47, 36.22, 23.14, 8.62, 6.78

2-(2,4-difluoro-5-nitrophenyl)-N-phenylacetamide (43)

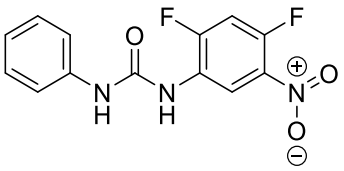


The title compound was synthesized according to the general procedure **2.1** for amide coupling using carboxylic acid chlorids. For the reaction, 200 mg of 2-(2,4-difluoro-5-nitrophenyl)acetyl chloride and 60 mg of aniline were used to obtain 168 mg of the product as yellow solid.

$C_{14}H_{10}F_2N_2O_3$ (Mr =292.23)

Yield	68%
HPLC	97% (t_r = 6.655 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 7.46 (s, 1H), 7.45 (s, 1H), 7.30 (t, J = 7.9 Hz, 2H), 7.22 (bs, 1H), 7.10 (t, J = 7.4 Hz, 1H), 6.83 (t, 1H), 6.77 (dd, J = 9.3, 7.6 Hz, 1H), 3.88 – 3.40 (m, 4H)

1-(2,4-difluoro-5-nitrophenyl)-3-phenylurea (44)



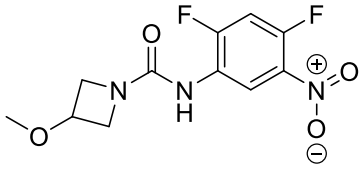
2,4-difluoro-5-nitroaniline (1 eq., 250 mg) was dissolved in 5 ml dry toluene and phenyl isocyanate (1.1 eq., 189 mg) was added dropwise. The reaction mixture was stirred at reflux temperature overnight.

Work up: The reaction mixture was put on Celite and purified via flash chromatography with petroleum ether/ ethyl acetate (0-50%) as solvent to obtain 103 mg product as brown solid.

$C_{13}H_9F_2N_3O_3$ (Mr =293.1)

Yield	24%
HPLC	100% (t_r = 7.802 min)
ESI-MS	m/z 316.1 $[M+Na]^+$

N-(2,4-difluoro-5-nitrophenyl)-3-methoxyazetidine-1-carboxamide (48)



Trimethylsilyl azide (1.2 eq., 313 mg) was dissolved in 5 ml dry dioxane. 2,4-Difluoro-5-nitrobenzoyl chloride (1 eq., 500 mg) was added dropwise and it was stirred at 70°C for 30 min. It was stirred at reflux temperature for 5 min.

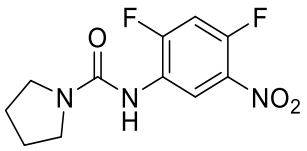
To a solution of 3-methoxyazetidine*HCl (1 eq., 242 mg) in 2 ml dioxane was added triethylamine (1.05 eq., 240 mg) and it was stirred for 30 min before adding to the reaction mixture. The reaction mixture was stirred at reflux temperature overnight.

Work up: The reaction mixture was put on Celite and purified via flash chromatography with petroleum ether/ ethyl acetate (0-50%) as solvent to obtain 305 mg product as yellow solid.

$C_{11}H_{11}F_2N_3O_4$ (Mr =287.22)

Yield	47%
HPLC	100% (t_r = 4.329 min)
ESI-MS	m/z 309.8 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.93 (t, J = 8.1 Hz, 1H), 7.02 (t, J = 10.2 Hz, 1H), 6.32 (s, 1H), 4.32 – 4.17 (m, 3H), 4.05 – 3.88 (m, J = 5.0 Hz, 2H), 3.30 (s, 3H)

N-(2,4-difluoro-5-nitrophenyl)pyrrolidine-1-carboxamide (49)

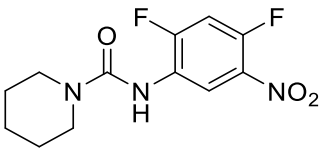


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 500 mg of 2,4-difluoro-5-nitroaniline and 429 mg pyrrolidine-1-carbonyl chloride were used to obtain 111 mg of the product as brown solid.

$C_{11}H_{11}F_2N_3O_3$ (Mr =271.22)

Yield	14%
HPLC	86% (t_r = 5.060 min)
ESI-MS	m/z 293.8 $[M+Na]^+$
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.94 (t, J = 8.1 Hz, 1H), 7.00 (t, J = 13.5, 7.0 Hz, 1H), 6.48 (s, 1H), 3.46 (t, J = 6.6 Hz, 4H), 1.98 (t, J = 6.4 Hz, 4H)

N-(2,4-difluoro-5-nitrophenyl)piperidine-1-carboxamide (50)

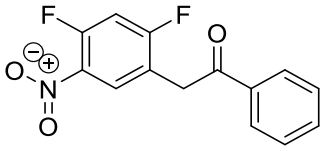


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 300 mg of 2,4-difluoro-5-nitroaniline and 284 mg piperidine-1-carbonyl chloride were used to obtain 73 mg of the product as orange solid.

$C_{12}H_{13}F_2N_3O_3$ (Mr =285.25)

Yield	15%
HPLC	95% (t_r = 6.347 min)
ESI-MS	m/z 286.4 $[M+H]^+$
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.86 (t, J = 8.1 Hz, 1H), 7.01 (t, J = 10.2 Hz, 1H), 6.71 (s, 1H), 3.46 (s, 4H), 1.64 (s, 6H)
^{13}C NMR (50 MHz, $CDCl_3$)	δ 153.51, 148.05, 133.70, 125.28, 125.05, 118.93, 105.65, 45.39, 25.68, 24.24

2-(2,4-difluoro-5-nitrophenyl)-1-phenylethan-1-one (51)

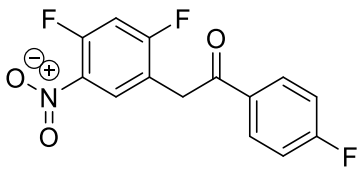


The title compound was synthesized according to the general procedure **9** for Friedel's-Craft acylation. For the reaction, 1.5 g of 2-(2,4-difluoro-5-nitrophenyl) acetyl chloride and benzene as solvent were used to obtain 1.24 g of the product as yellow crystals.

$C_{14}H_9F_2NO_3$ (Mr =277.06)

Yield	83%
HPLC	97% (t_r = 7.292 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.12 – 8.04 (m, 5H), 7.75 – 7.44 (m, 8H), 7.11 (dd, J = 10.3, 9.0 Hz, 2H), 4.43 (s, 4H)

2-(2,4-difluoro-5-nitrophenyl)-1-(4-fluorophenyl)ethan-1-one (52)



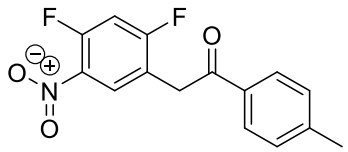
First, 2-(2,4-difluoro-5-nitrophenyl)acetyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis.

The title compound was synthesized according to the general procedure **9** for Friedel's-Craft acylation. For the reaction, 250 mg of 2-(2,4-difluoro-5-nitrophenyl) acetyl chloride and fluorobenzene as solvent were used to obtain 317 mg of the product as yellow crystals.

$C_{14}H_8F_3NO_3$ (Mr =295.22)

Yield	100%
HPLC	100% (t_r = 7.966 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.12 – 8.00 (m, 3H), 7.19 (t, J = 8.6 Hz, 2H), 7.06 (dd, J = 10.3, 9.1 Hz, 1H), 4.36 (s, 2H)

2-(2,4-difluoro-5-nitrophenyl)-1-(p-tolyl)ethan-1-one (53)



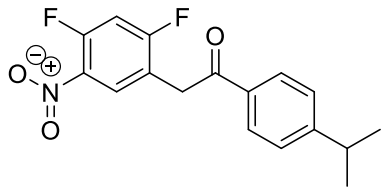
First, 2-(2,4-difluoro-5-nitrophenyl)acetyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis.

The title compound was synthesized according to the general procedure **9** for Friedel's-Craft acylation. For the reaction, 250 mg of 2-(2,4-difluoro-5-nitrophenyl) acetyl chloride and toluene as solvent were used to obtain 167 mg of the product as yellow oil.

$C_{15}H_{11}F_2NO_3$ (Mr =291.25)

Yield	67%
HPLC	99% (t_r = 8.298 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.07 (t, J = 7.7 Hz, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.06 (t, 1H), 4.36 (s, 2H), 2.45 (s, 3H)

2-(2,4-difluoro-5-nitrophenyl)-1-(4-isopropylphenyl)ethan-1-one (54)



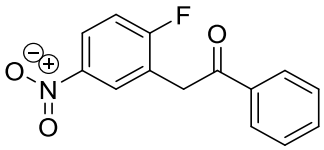
First, 2-(2,4-difluoro-5-nitrophenyl)acetyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis.

The title compound was synthesized according to the general procedure **9** for Friedel's-Craft acylation. For the reaction, 200 mg of 2-(2,4-difluoro-5-nitrophenyl) acetyl chloride and cumene as solvent were used to obtain 147 mg of the product as white crystals.

$C_{17}H_{15}F_2NO_3$ (Mr =319.31)

Yield	54%
HPLC	100% (t_r = 9.473 min)
ESI-MS	m/z 318.2 $[M-H]^-$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.07 (t, *J* = 7.7 Hz, 1H), 7.96 (d, *J* = 7.5 Hz, 2H), 7.37 (d, *J* = 7.5 Hz, 2H), 7.06 (t, *J* = 9.7 Hz, 1H), 4.36 (s, 2H), 3.06 – 2.94 (m, 1H), 1.30 (s, 3H), 1.28 (s, 3H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 193.80, 165.31 (d, *J* = 11.0 Hz), 162.73 (d, *J* = 11.0 Hz), 157.14 (d, *J* = 13.3 Hz), 155.67, 154.48 (d, *J* = 13.3 Hz), 133.68, 129.69 (dd, *J* = 7.4, 2.0 Hz), 128.57, 127.04, 119.85 (d, *J* = 4.3 Hz), 119.67 (d, *J* = 4.4 Hz), 106.41 (dd, *J* = 27.6, 24.5 Hz), 37.81, 34.34, 23.63

2-(2-fluoro-5-nitrophenyl)-1-phenylethan-1-one (55)



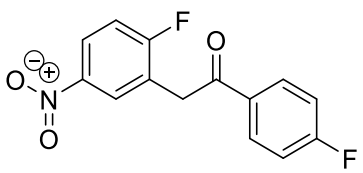
First, 2-(2-fluoro-5-nitrophenyl)acetyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis.

The title compound was synthesized according to the general procedure **9** for Friedel's-Craft acylation. For the reaction, 300 mg of 2-(2-fluoro-5-nitrophenyl) acetyl chloride and benzene as solvent were used to obtain 390 mg of the product as yellow crystals.

$C_{14}H_{10}FNO_3$ (Mr =259.24)

Yield	100%
HPLC	100% (t_r = 7.529 min)
ESI-MS	m/z 238.9 $[M-H]^-$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.15 – 8.08 (m, *J* = 3.8, 2.8 Hz, 5H), 7.97 – 7.92 (m, *J* = 8.5, 1.6 Hz, 5H), 7.54 (tt, 3H), 7.45 – 7.40 (m, 5H), 7.16 – 7.12 (m, *J* = 8.9, 3.7 Hz, 3H), 4.34 (d, *J* = 0.8 Hz, 5H)

2-(2-fluoro-5-nitrophenyl)-1-(4-fluorophenyl)ethan-1-one (56)



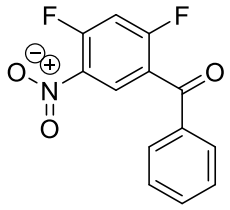
First, 2-(2-fluoro-5-nitrophenyl)acetyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis.

The title compound was synthesized according to the general procedure **9** for Friedel's-Craft acylation. For the reaction, 300 mg of 2-(2-fluoro-5-nitrophenyl) acetyl chloride and fluorobenzene as solvent were used to obtain 353 mg of the product as yellow crystals.

$C_{14}H_9F_2NO_3$ (Mr =277.23)

Yield	84%
HPLC	100% (t_r = 7.703 min)
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.25 – 8.18 (m, 2H), 8.10 – 8.05 (m, 2H), 7.27 – 7.24 (m, J = 4.3 Hz, 1H), 7.23 – 7.17 (m, 2H), 4.40 (d, J = 0.8 Hz, 2H)

(2,4-difluoro-5-nitrophenyl)(phenyl)methanone (57)

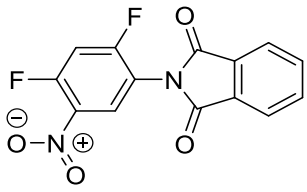


First, 2,4-difluoro-5-nitrobenzoyl chloride was synthesized according to the general procedure **8** for acyl chloride synthesis. The product was directly used for the next step without analytical analysis. The title compound was synthesized according to the general procedure **9** for Friedel's-Craft acylation. For the reaction, 300 mg of 2,4-difluoro-5-nitrobenzoyl chloride and benzene as solvent were used to yield 325 mg of the product as yellow crystals.

$C_{13}H_7F_2NO_3$ (Mr =263.20)

Yield	91%
HPLC	90% (t_r = 7.856 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.86 (t, J = 7.7 Hz, 1H), 8.30 (dd, J = 8.1, 6.9 Hz, 2H), 7.73 (s, 2H), 7.69 (s, 2H), 7.58 (t, J = 7.3 Hz, 2H), 7.43 (t, J = 7.5 Hz, 4H), 7.10 (dd, J = 18.7, 9.4 Hz, 4H)

2-(2,4-Difluoro-5-nitrophenyl)isoindoline-1,3-dione (57)

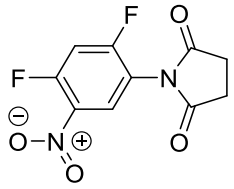


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 250 mg of 2,4-difluoro-5-nitroaniline and 376 mg phthaloyl dichloride was used to obtain 433 mg of the product as yellow solid.

$C_{14}H_6F_2N_2O_4$ (Mr = 304.21)

Yield	100%
HPLC	97% (t_r = 6.925 min)
ESI-MS	m/z 359.3 $[M+Na+MeOH]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.25 (t, J = 7.5 Hz, 1H), 8.00 (dt, J = 6.7, 3.4 Hz, 2H), 7.87 (dt, 2H), 7.26 (t, 1H)

1-(2,4-difluoro-5-nitrophenyl)pyrrolidine-2,5-dione (58)

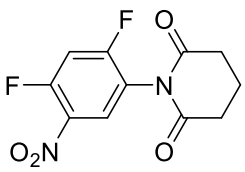


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 250 mg of 2,4-difluoro-5-nitroaniline and 286 mg succinyl chloride were used to obtain 155 mg of the product as white solid.

$C_{10}H_6F_2N_2O_4$ (Mr =256.16)

Yield	42%
HPLC	98% (t_r = 3.659 min)
ESI-MS	m/z 255.4 $[M-H]^-$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.13 (t, *J* = 7.4 Hz, 1H), 7.22 (dd, *J* = 9.9, 9.2 Hz, 1H), 2.99 (s, 4H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 174.42, 162.15 (d, *J* = 11.5 Hz), 159.50 (d, *J* = 11.6 Hz), 158.05 (d, *J* = 12.6 Hz), 155.35 (d, *J* = 12.7 Hz), 127.91 (dd, *J* = 3.3, 1.5 Hz), 108.06 (t, *J* = 25.2 Hz), 28.73

1-(2,4-difluoro-5-nitrophenyl)piperidine-2,6-dione (59)

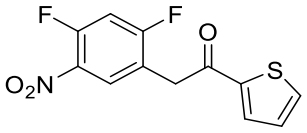


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 250 mg of 2,4-difluoro-5-nitroaniline and 254 mg glutaryl chloride were used to obtain 189 mg of the product as brown solid.

$C_{11}H_8F_2N_2O_4$ (Mr =270.19)

Yield	49%
HPLC	92% (t_r = 4.224 min)
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.03 (t, *J* = 7.5 Hz, 1H), 7.16 (dd, 1H), 2.88 – 2.84 (m, 4H), 2.15 (p, *J* = 6.6 Hz, 2H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 171.43, 162.65 (d, *J* = 11.6 Hz), 160.03 (d, *J* = 11.6 Hz), 157.96 (d, *J* = 12.6 Hz), 155.27 (d, *J* = 12.6 Hz), 129.15 (dd, *J* = 3.5, 1.7 Hz), 119.80 (dd, *J* = 15.4, 4.5 Hz), 107.56 (t, *J* = 25.4 Hz), 32.76, 17.15

2-(2,4-difluoro-5-nitrophenyl)-1-(thiophen-2-yl)ethan-1-one (60)



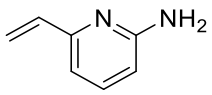
In a three-necked flask magnesium (2 eq., 130 mg) was activated by sublimation of iodine under argon atmosphere. 8 ml dry THF was added and it was stirred at room temperature. 2-Bromothiopene (2 eq., 867 mg) was dissolved in 2 ml dry THF and approximately. 10% of the solution was added to the reaction mixture. It was stirred until the solvent became cloudy. The residual 2-bromothiophene solution was slowly added dropwise and the reaction mixture was stirred at reflux temperature for 1 hour. The reaction mixture was cooled down in an ice bath and a solution of 2-(2,4-difluoro-5-nitrophenyl)-N-methoxy-N-methylacetamide (1 eq., 700 mg) in THF was added dropwise. It was stirred at ambient temperature.

Work up: Ammonium chloride solution was added to the reaction mixture, and it was extracted with DCM (3x 20 ml). Celite was added to the combined organic layers and the solvent was evaporated. The reaction mixture was purified via automatic flash chromatography on silica with petroleum ether/ ethyl acetate (10-50% over 20 min) to yield 67 mg as yellow solid.

$C_{12}H_7F_2NO_3S$ (Mr = 283.25)

Yield	9%
HPLC	85% (t_r = 6.690 min)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.12 (t, J = 7.8 Hz, 1H), 7.85 (dd, J = 3.8, 1.1 Hz, 1H), 7.73 (dd, J = 5.0, 1.1 Hz, 1H), 7.20 (dd, J = 4.9, 3.9 Hz, 1H), 7.07 (dd, J = 10.3, 9.0 Hz, 1H), 4.30 (s, 2H)

6-vinylpyridin-2-amine (62)



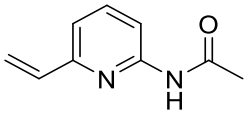
In a 10 ml screw cap vial under argon atmosphere 2-Bromo-6-amino pyridine (1 eq., 1.2 g), potassium trifluoro vinylborate (1.2 eq., 1.2 g) and $PdCl_2(dppf)_2$ were placed. A mixture of triethylamine (3 eq., 0.12 g) in *i*PrOH/H_2O (2:1) was degassed and added to the reaction mixture. It was stirred at 80°C for 22 hours.

Work up: The reaction mixture was extracted with ethyl acetate (3x 10 ml) and purified via flash column using petroleum ether/ ethyl acetate (7:3) as solvent. TBCA (1 mol%) was added to the product to prevent polymerization.

$C_7H_8N_2$ (Mr = 120.16)

Yield	89%
HPLC	100% (t_R = 1.160 min)
ESI-MS	m/z 121.1 $[M+H]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 7.39 (t, J = 7.8 Hz, 1H), 6.75 – 6.53 (m, 2H), 6.39 (d, J = 8.1 Hz, 1H), 6.13 (dd, J = 17.4, 1.5 Hz, 1H), 5.37 (dd, J = 10.6, 1.4 Hz, 1H), 4.44 (s, 2H)
^{13}C NMR (50 MHz, $CDCl_3$)	δ 138.23, 136.96, 134.94, 117.41, 112.43, 112.35, 107.91

N-(6-vinylpyridin-2-yl)acetamide (63)

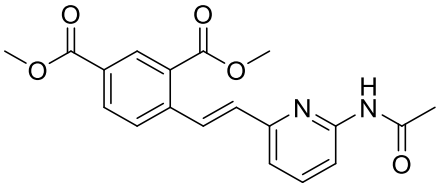


For the synthesis of the title compound, 6-vinylpyridin-2-amine (1 eq., 650 mg) was dissolved in acetic anhydride (5 ml). To this solution, catalytic amount of DMAP was added and the mixture was stirred at 70°C overnight. Upon cooling to room temperature, ice water was added to the reaction mixture and the pH was adjusted to pH 8 with NH_4OH. The product was extracted with ethyl acetate (3x 15 ml), TBCA (1 mol%) was added to the mixture and it was dried in vacuum overnight to yield the title compound (637 mg) as a grey-brown solid.

$C_9H_{10}N_2O$ (Mr = 162.19)

Yield	73%
HPLC	94% (t_R = 2.968 min)
ESI-MS	m/z 184.9 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.40 (s, 1H), 8.08 (d, J = 8.1 Hz, 1H), 7.66 (t, J = 7.9 Hz, 1H), 7.07 (d, J = 7.5 Hz, 1H), 6.69 (dd, J = 17.4, 10.8 Hz, 1H), 6.24 – 6.06 (m, J = 17.4 Hz, 1H), 5.53 – 5.41 (m, J = 10.6 Hz, 1H), 2.18 (s, 3H)
^{13}C NMR (50 MHz, $CDCl_3$)	δ 168.80, 153.80, 150.90, 138.94, 135.90, 118.51, 117.22, 112.78, 24.55

Dimethyl (E)-4-(2-(6-acetamidopyridin-2-yl)vinyl)isophthalate (64)



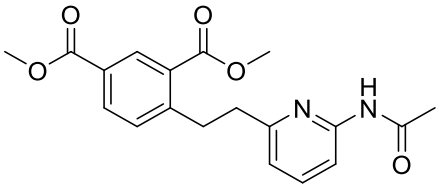
Dimethyl-4-bromoisophtalat (1 eq., 770 mg), $Pd_2(dba)_3$ (1 mol%, 26 mg), N-(6-vinylpyridin-2-yl)acetamide (1.1 eq., 500 mg) and tri-tertbutylphoshonium tetrafluoroborat (6 mol%, 49 mg) were added to a 25 ml Schlenk flask and flushed with argon. A mixture of N,N-Dicyclohexyl methylamine (1.5 eq., 820 mg) and dry dioxan (10 ml) were added and the mixture was stirred at 85 °C for 4h.

Work up: The reaction mixture was put on Celite and purified via flash chromatography on silica with petroleum ether/ ethyl acetate (15-60%) as solvent to achieve 727 mg of the product as white solid.

$C_{19}H_{18}N_2O_5$ (Mr = 354.12)

Yield	73%
HPLC	93% (t_R = 7.932 min)
ESI-MS	m/z 377.0 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.58 (d, J = 1.6 Hz, 1H), 8.39 (d, J = 16.0 Hz, 1H), 8.27 – 8.00 (m, J = 16.9, 8.6 Hz, 3H), 7.76 (d, J = 8.2 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 16.0 Hz, 1H), 3.93 (d, J = 0.7 Hz, 6H), 2.20 (s, 3H)
^{13}C NMR (50 MHz, $CDCl_3$)	δ 166.94, 166.10, 153.41, 151.28, 142.93, 139.02, 132.94, 132.25, 130.62, 129.44, 129.03, 127.48, 118.85, 113.22 52.51, 52.47, 32.89, 30.24, 26.21, 24.85

Dimethyl 4-(2-(6-acetamidopyridin-2-yl)ethyl)isophthalate (65)



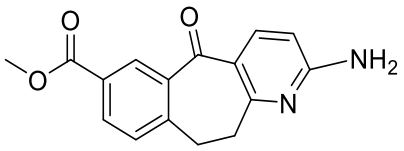
Compound 10 was synthesized according to the general procedure 7 reduction of the double bond, starting from Dimethyl (E)-4-(2-(6-acetamidopyridin-2-yl)vinyl)isophthalate (700 mg) to yield the product (567 mg) as colourless oil.

$C_{19}H_{20}N_2O_5$ (Mr = 356.38 min)

Yield	81%
HPLC	>99% (t_R = 7.395 min)
ESI-MS	m/z 379.0 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.54 (d, J = 1.7 Hz, 1H), 8.15 (s, 1H), 8.05 – 7.94 (m, 2H), 7.56 (t, J = 7.9 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 6.83 (d, J =

	7.5 Hz, 1H), 3.91 (s, 6H), 3.44 – 3.30 (m, 2H), 3.03 – 2.91 (m, 2H), 2.19 (s, 3H)
^{13}C NMR (50 MHz, $CDCl_3$)	δ 167.26, 166.34, 159.33, 150.91, 148.65, 138.84, 132.78, 132.20, 131.45, 129.87, 128.39, 119.01, 111.36, 52.34, 39.19, 34.39, 25.83, 24.82

Methyl 2-amino-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate (66)



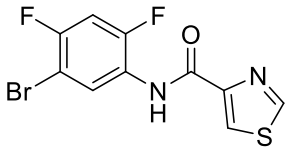
Dimethyl 4-(2-(6-acetamidopyridin-2-yl)ethyl)isophthalate (550 mg) was stirred in 10 ml Eaton´s reagent at 70°C under argon atmosphere overnight. Water was added and it was refluxed for 4 hours. The water was removed under reduced pressure and methanol was added, it was stirred at reflux temperature overnight.

Work up: Water was added, and it was extracted with ethyl acetate (3x). The combined organic layers were washed with saturated $NaHCO_3$ solution, brine and dried in vacuo.

$C_{16}H_{14}N_2O_3$ (Mr = 282.30)

Yield	73%
HPLC	89% (t_r = 1.736 min)
ESI-MS	m/z 305.4 $[M+Na]^+$
^{1}H-NMR (400 MHz, DMSO-d_6)	δ 8.34 (d, J = 1.9 Hz, 1H), 8.15 (d, J = 8.9 Hz, 1H), 8.01 (dd, J = 7.9, 1.9 Hz, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.10 (s, 2H), 6.49 (d, J = 8.9 Hz, 1H), 3.86 (s, 3H), 3.12 (ddd, J = 10.9, 6.3, 2.8 Hz, 4H)
^{13}C NMR (100 MHz, DMSO-d_6)	δ 188.28, 165.73, 163.46, 160.83, 146.32, 140.68, 139.19, 132.05, 130.96, 129.34, 128.14, 120.55, 107.20, 52.28, 37.89, 32.12

N-(5-bromo-2,4-difluorophenyl)thiazole-4-carboxamide (69)



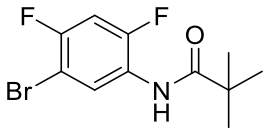
The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 400 mg of 5-bromo-2,4-difluoroaniline and 500 mg thiazole-4-carbonyl chloride were used to obtain 558 mg of the product as white solid.

$C_{10}H_5BrF_2N_2OS$ (Mr =319.12)

Yield	91%
HPLC	99% (t_r = 7.980 min)
ESI-MS	m/z 317.1 $[M-H]^-$

^{1}H NMR (400 MHz, $CDCl_3$)	δ 9.43 (s, 1H), 8.83 (d, *J* = 1.6 Hz, 1H), 8.80 (t, 1H), 8.30 (d, *J* = 2.1 Hz, 1H), 7.00 (dd, 1H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 158.72,156.16 (d, *J* = 243.6 Hz), 153.71 (d, *J* = 251.5 Hz), 152.91 (d, *J* = 10.1 Hz), 125.27 (d, *J* = 1.7 Hz), 123.75 (dd, *J* = 11.1, 4.1 Hz), 104.63 (dd, *J* = 27.4, 24.3 Hz), 104.03 (dd, *J* = 21.4, 4.3 Hz)

N-(5-bromo-2,4-difluorophenyl)pivalamide (70)

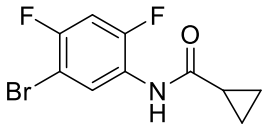


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 300 mg of 5-bromo-2,4-difluoroaniline and 174 mg pivaloyl chloride were used to obtain 421 mg of the product as orange crystals.

$C_{11}H_{12}BrF_2NO$ (Mr =292.12)

Yield	100%
HPLC	100% (t_r = 7.961 min)
ESI-MS	m/z 290.2 $[M-H]^-$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.66 (dd, *J* = 13.7, 5.9 Hz, 1H), 7.50 (bs, *J* = 14.5 Hz, 1H), 6.94 (dd, 1H), 1.32 (s, 9H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 176.65, 155.75, 153.30, 152.65, 150.21, 125.57, 104.15, 39.97, 27.46

N-(5-bromo-2,4-difluorophenyl)cyclopropanecarboxamide (72)

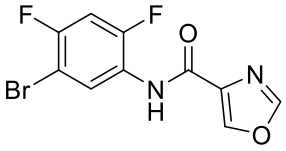


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 500 mg of 5-bromo-2,4-difluoro-aniline and 251 mg cyclopropylcarbonyl chloride were used to obtain 537 mg of the product as pink solid.

$C_{10}H_8BrF_2NO$ (Mr =276.08)

Yield	81%
HPLC	100% (t_r = 7.251 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.59 (t, J = 7.8 Hz, 1H), 7.48 (bs, 1H), 6.94 (dd, J = 10.7, 8.0 Hz, 1H), 1.61 – 1.48 (m, 1H), 1.16 – 1.05 (m, 2H), 0.96 – 0.85 (m, 2H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 172.08, 125.79, 124.09, 123.99, 104.34, 104.03, 103.81, 15.86, 8.59

N-(5-bromo-2,4-difluorophenyl)oxazole-4-carboxamide (73)

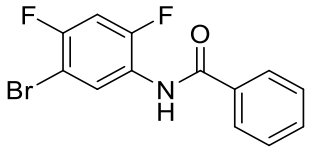


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 361 mg of 5-bromo-2,4-difluoro-aniline and 300 mg oxazole-4-carbonyl chloride were used to obtain 618 mg of the product as pink solid.

$C_{10}H_5BrF_2N_2O_2$ (Mr =303.06)

Yield	99%
HPLC	100% (t_r = 7.142 min)
ESI-MS	m/z 327.2 $[M+Na]^+$
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.86 (bs, 1H), 8.74 (t, J = 7.8 Hz, 1H), 8.35 (s, 1H), 7.94 (s, 1H), 7.00 (dd, J = 10.5, 7.9 Hz, 1H)
^{13}C NMR (101 MHz, MeOD)	δ 160.78, 158.54 (d, *J* = 11.9 Hz), 156.09 (d, *J* = 248.7 Hz), 153.94 (d, *J* = 250.5 Hz), 153.48, 144.20, 136.44, 129.10, 106.09 (dd), 104.12 (dd, *J* = 21.8, 3.9 Hz)

N-(5-bromo-2,4-difluorophenyl)benzamide (74)

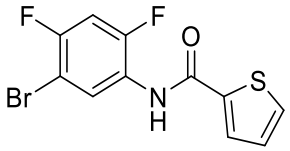


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 500 mg of 5-bromo-2,4-difluoro-aniline and 337 mg benzoyl chloride were used to obtain 599 mg of the product as pink solid.

$C_{13}H_8BrF_2NO$ (Mr =312.11)

Yield	80%
HPLC	91% (t_r = 7.900 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.74 (t, J = 7.8 Hz, 1H), 7.97 (s, 1H), 7.89–7.82 (m, J = 8.0, 1.4 Hz, 2H), 7.60–7.45 (m, 3H), 6.99 (dd, J = 10.6, 7.9 Hz, 1H)
^{13}C NMR (101 MHz, MeOD)	δ 168.96, 159.08 (d, J = 11.3 Hz), 157.80 (d, J = 10.5 Hz), 156.62 (d, J = 241.4 Hz), 155.31 (d, J = 246.4 Hz), 135.01, 133.39, 131.30, 130.19, 129.73, 128.83, 106.51 – 105.88 (t), 103.91 (dd, J = 22.1, 4.2 Hz)

N-(5-bromo-2,4-difluorophenyl)thiophene-2-carboxamide (75)

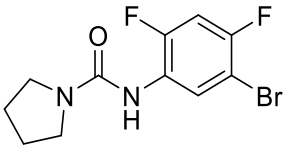


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 500 mg of 5-bromo-2,4-difluoro-aniline and 352 mg thiophene-2-carbonyl chloride were used to obtain 552 mg of the product as pink solid.

$C_{11}H_6BrF_2NOS$ (Mr =318.93)

Yield	73%
HPLC	97% (t_r = 7.393 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.65 (t, J = 7.8 Hz, 1H), 7.81 (s, 1H), 7.71 – 7.55 (m, 2H), 7.22 – 7.10 (m, 1H), 6.98 (dd, J = 10.6, 7.9 Hz, 1H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 159.80, 156.30, 153.84, 138.25, 131.79, 129.20, 128.16, 126.04, 123.61, 104.53, 104.04

N-(5-bromo-2,4-difluorophenyl)pyrrolidine-1-carboxamide (76)

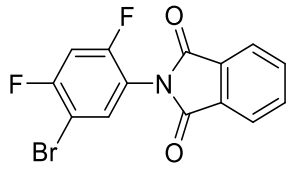


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 300 mg of 5-bromo-2,4-difluoroaniline and 211 mg pyrrolidine-1-carbonyl chloride were used to obtain 145 mg of the product as white solid.

$C_{11}H_{11}BrF_2N_2O$ (Mr =305.12)

Yield	33%
HPLC	98% (t_r = 6.799 min)
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.48 (t, J = 8.0 Hz, 1H), 6.89 (dd, J = 10.8, 8.0 Hz, 1H), 6.27 (s, 1H), 3.46 (t, J = 6.7 Hz, 4H), 2.04 – 1.92 (m, 4H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 154.93, 154.82, 152.38, 152.26, 149.88, 125.17, 124.98, 104.01, 45.92, 25.66

2-(5-bromo-2,4-difluorophenyl)isoindoline-1,3-dione (77)

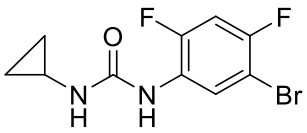


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 298 mg of 5-bromo-2,4-difluoro-aniline and 376 mg phthaloyl dichloride were used to obtain 439 mg of the product as pink solid.

$C_{13}H_8BrF_2NO$ (Mr =312.11)

Yield	91%
HPLC	85% (t_r = 8.401 min)
ESI-MS	m/z 336.1 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.01 – 7.92 (m, J = 5.1, 2.0 Hz, 2H), 7.87 – 7.78 (m, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.11 (dd, J = 9.2, 8.2 Hz, 1H)

1-(5-bromo-2,4-difluorophenyl)-3-cyclopropylurea (78)

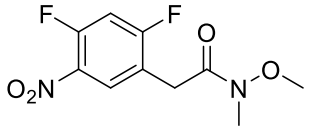


The title compound was synthesized according to the general procedure **10** for isocyanate synthesis using DPPA, followed by general procedure **11.1** for urea synthesis using isocyanates. For the reaction, 1.15 g of 5-bromo-2,4-difluoroaniline and 500 mg cyclopropancarboxylic acid were used to obtain 903 mg of the product as white solid.

$C_{10}H_9BrF_2N_2O$ (Mr =291.12)

Yield	54%
HPLC	90% (t_r = 7.335 min)
ESI-MS	m/z 312.2 $[M+Na]^+$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.43 (t, *J* = 7.7 Hz, 1H), 7.23 (s, 1H), 6.96 – 6.86 (m, 1H), 5.40 (s, 1H), 2.60 (s, 1H), 0.85 (d, *J* = 5.5 Hz, 2H), 0.66 (s, 2H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 155.95, 155.24 (d, J = 11.7 Hz), 152.80 (d, J = 12.0 Hz), 152.61 (d, J = 10.0 Hz), 150.18 (d, J = 10.2 Hz), 125.10, 104.22 (t), 22.68, 7.61

2-(2,4-difluoro-5-nitrophenyl)-N-methoxy-N-methylacetamide (79)



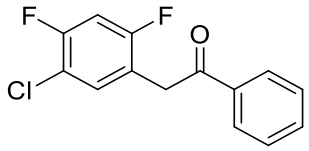
To a solution of N,O-dimethylhydroxylamine*HCl (1.1 eq., 91 mg) in dry DCM (5ml), triethylamine (2 eq., 172 mg) was added and it was stirred for 5 min in an ice-bath. 2-(2,4-difluoro-5-nitrophenyl) acetyl chloride (1 eq., 200 mg) was carefully added dropwise and the reaction mixture was stirred at room temperature for 5 hours.

Work up: Water was added, and it was extracted with DCM (3x 15 ml), washed with brine and evaporated to dryness to achieve 200 mg product as yellow solid.

$C_{10}H_{10}F_2N_2O_4$ (Mr =260.20)

Yield	90%
HPLC	92% (t_r = 5.373 min)
ESI-MS	m/z 282.9 $[M+Na]^+$
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.10 (t, J = 7.8 Hz, 1H), 7.03 (dd, J = 10.4, 9.0 Hz, 1H), 3.84 (s, 2H), 3.77 (s, 3H), 3.23 (s, 3H)

2-(5-chloro-2,4-difluorophenyl)-1-phenylethan-1-one (80)

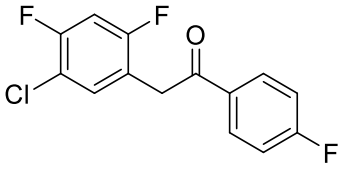


The title compound was synthesized according to the general procedure **9** for Friedel's-Craft acylation. For the reaction, 270 mg of 2-(2,4-difluoro-5-chlorophenyl) acetyl chloride and benzene as solvent were used to obtain 188 mg of the product as orange solid.

$C_{14}H_9ClF_2O$ (Mr =266.67)

Yield	70%
HPLC	91% (t_r = 8.999 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.10 – 8.03 (m, 2H), 7.67 – 7.59 (m, 1H), 7.60 – 7.50 (m, J = 8.1, 6.5 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 6.98 (t, J = 9.0 Hz, 1H), 4.32 (s, 2H)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ 195.30, 161.91 (d, J = 10.2 Hz), 159.83 (d, J = 12.3 Hz), 156.97 (d, J = 249.3 Hz), 154.86 (d, J = 250.4 Hz), 136.17, 133.75, 132.69 (d, J = 5.6 Hz), 128.93, 128.41, 119.17 (dd, J = 17.7, 4.3 Hz), 116.43 (dd, J = 17.8, 4.2 Hz), 105.10 (dd, J = 27.6, 24.8 Hz), 37.91

2-(5-chloro-2,4-difluorophenyl)-1-(4-fluorophenyl)ethan-1-one

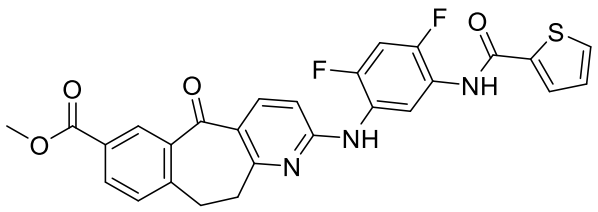


The title compound was synthesized according to the general procedure **9** for Friedel's-Craft acylation. For the reaction, 270 mg of 2-(2,4-difluoro-5-chlorophenyl) acetyl chloride and fluorobenzene as solvent were used to obtain 62 mg of the product as orange oil.

$C_{14}H_9ClF_2O$ (Mr =266.67)

Yield	23%
HPLC	73% (t_r = 9.186 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.18 – 8.09 (m, 2H), 7.38 (t, J = 6.8 Hz, 1H), 7.28 (t, J = 8.5 Hz, 2H), 7.04 (t, J = 9.0 Hz, 1H), 4.34 (s, 2H)

Methyl 2-((2,4-difluoro-5-(thiophene-2-carboxamido)phenyl)amino)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate (81)

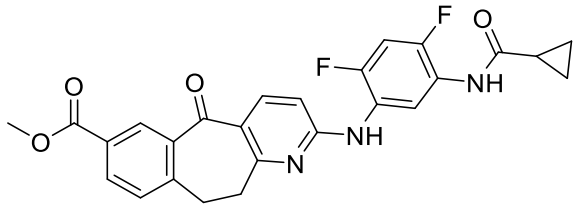


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 70 mg azadibenzosuberone and 79 mg of N-(5-bromo-2,4-difluorophenyl)thiophene-2-carboxamide were used to obtain 50 mg of the product as yellow solid.

$C_{27}H_{19}F_2N_3O_4S$ (Mr =519.52)

Yield	38%
HPLC	100% (t_r = 8.522 min)
ESI-MS	m/z 518.9 $[M-H]^-$
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 9.15 (t, *J* = 8.3 Hz, 1H), 8.57 (d, *J* = 1.8 Hz, 1H), 8.46 (d, *J* = 9.2 Hz, 1H), 8.09 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.86 (bs, 1H), 7.67 (dd, *J* = 3.7, 0.9 Hz, 1H), 7.59 (dd, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.15 (dd, *J* = 4.9, 3.8 Hz, 1H), 7.00 (t, *J* = 10.2 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 3.92 (s, 3H), 3.41 – 3.36 (m, 2H), 3.25 – 3.20 (m, 2H)

Methyl 2-((5-(cyclopropanecarboxamido)-2,4-difluorophenyl)amino)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate (82)

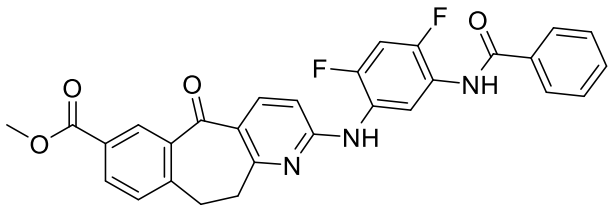


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 70 mg azadibenzosuberone and 69 mg of N-(5-bromo-2,4-difluorophenyl)cyclopropanecarboxamide were used to obtain 30 mg of the product as yellow solid.

$C_{26}H_{21}F_2N_3O_4$ (Mr =477.47)

Yield	25%
HPLC	100% (t_r = 8.341 min)
ESI-MS	m/z 476.4 $[M-H]^-$
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 9.00 (t, J = 8.8 Hz, 1H), 8.56 (d, J = 1.5 Hz, 1H), 8.42 (d, J = 8.7 Hz, 1H), 8.09 (dd, J = 7.7, 1.8 Hz, 1H), 7.54 (s, 1H), 7.33 (d, J = 7.9 Hz, 1H), 6.95 (t, J = 10.3 Hz, 2H), 6.71 (d, J = 8.9 Hz, 1H), 3.92 (s, 3H), 3.39 – 3.15 (m, J = 22.4, 8.4 Hz, 4H), 1.62 – 1.53 (m, J = 8.1, 4.0 Hz, 1H), 1.15 – 1.06 (m, J = 7.3, 3.2 Hz, 2H), 0.92 – 0.86 (m, J = 7.7, 2.8 Hz, 2H)

Methyl 2-((5-benzamido-2,4-difluorophenyl)amino)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate (83)



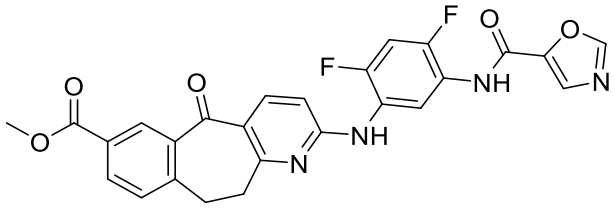
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 100 mg azadibenzosuberone and 122 mg of N-(5-bromo-2,4-difluorophenyl)phenylcarboxamide were used to obtain 30 mg of the product as yellow solid.

$C_{29}H_{21}F_2N_3O_4$ (Mr =513.50)

Yield	16%
HPLC	98% (t_r = 8.707 min)
ESI-MS	m/z 512.3 $[M-H]^-$
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 9.31 (t, J = 8.6 Hz, 1H), 8.57 (d, J = 1.6 Hz, 1H), 8.47 (d, J = 8.8 Hz, 1H), 8.09 (dd, J = 7.8, 1.8 Hz, 1H), 7.99 (s, 1H), 7.93 – 7.85 (m, 2H), 7.61 – 7.49 (m, J = 9.4, 7.0 Hz, 3H), 7.33 (d, J =

7.9 Hz, 1H), 7.02 (t, J = 10.3 Hz, 1H), 6.77 (d, J = 9.0 Hz, 1H), 3.92 (s, 3H), 3.48 – 3.18 (m, J = 21.1, 16.1 Hz, 4H)

Methyl 2-((2,4-difluoro-5-(oxazole-5-carboxamido)phenyl)amino)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate (84)

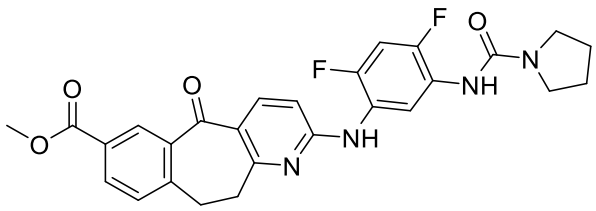


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 70 mg azadibenzosuberone and 76 mg of N-(5-bromo-2,4-difluorophenyl)oxazole-5-carboxamide were used to obtain 10 mg of the product as yellow solid.

$C_{26}H_{18}F_2N_4O_5$ (Mr =504.45)

Yield	8%
HPLC	92% (t_r = 8.364 min)
ESI-MS	m/z 503.2 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 9.32 (t, J = 8.6 Hz, 1H), 8.91 (s, 1H), 8.56 (d, J = 1.8 Hz, 1H), 8.43 (d, J = 8.8 Hz, 1H), 8.36 (d, J = 1.0 Hz, 1H), 8.08 (dd, J = 7.8, 1.9 Hz, 1H), 7.95 (d, J = 1.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 6.99 (qi, 2H), 6.75 (d, J = 8.7 Hz, 1H), 3.91 (s, 3H), 3.41 – 3.34 (m, 3H), 3.28 – 3.16 (m, 2H)

Methyl 2-((2,4-difluoro-5-(pyrrolidine-1-carboxamido)phenyl)amino)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate (85)



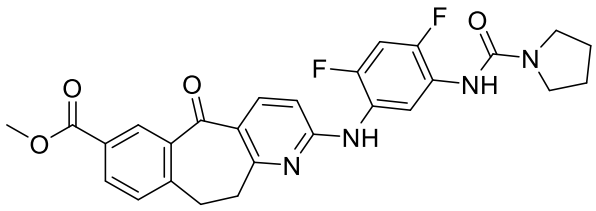
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 70 mg azadibenzosuberone and 76 mg of N-(5-bromo-2,4-difluorophenyl)pyrrolidine-1-carboxamide were used to obtain 48 mg of the product as yellow solid.

$C_{27}H_{24}F_2N_4O_4$ (Mr = 505,5)

Yield	30%
HPLC	95% (t_r = 8.065 min)
ESI-MS	m/z 505.2 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.70 (t, J = 8.6 Hz, 1H), 8.55 (d, J = 1.9 Hz, 1H), 8.39 (d, J = 8.9 Hz, 1H), 8.07 (dd, J = 7.8, 1.9 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.06 – 6.81 (m, J = 10.3 Hz, 2H), 6.73 (d, J = 8.8 Hz, 1H), 6.31 (d, J = 3.1 Hz, 1H), 3.91 (s, 3H), 3.52 – 3.40 (m, J = 6.6

Hz, 4H), 3.34 – 3.14 (m, J = 19.9, 8.3 Hz, 4H), 2.04 – 1.94 (m, J = 12.1, 5.5 Hz, 4H)

Methyl 2-((2,4-difluoro-5-(pyrrolidine-1-carboxamido)phenyl)amino)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate (85)

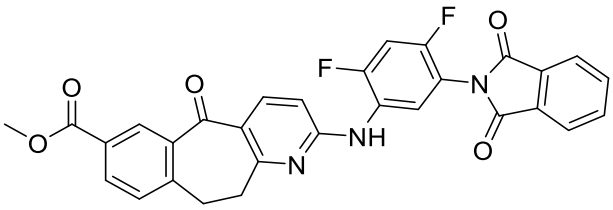


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 70 mg azadibenzosuberone and 76 mg of N-(5-bromo-2,4-difluorophenyl)pyrrolidine-1-carboxamide were used to obtain 48 mg of the product as yellow solid.

$C_{27}H_{24}F_2N_4O_4$ (Mr =506.51)

Yield	38%
HPLC	94% (t_r = 8.065 min)
ESI-MS	m/z 505.2 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.70 (t, J = 8.6 Hz, 1H), 8.55 (d, J = 1.9 Hz, 1H), 8.39 (d, J = 8.9 Hz, 1H), 8.07 (dd, J = 7.8, 1.9 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.06 – 6.81 (m, J = 10.3 Hz, 2H), 6.73 (d, J = 8.8 Hz, 1H), 6.31 (d, J = 3.1 Hz, 1H), 3.91 (s, 3H), 3.52 – 3.40 (m, J = 6.6 Hz, 4H), 3.34 – 3.14 (m, J = 19.9, 8.3 Hz, 4H), 2.04 – 1.94 (m, J = 12.1, 5.5 Hz, 4H)

Methyl 2-((5-(1,3-dioxoisoindolin-2-yl)-2,4-difluorophenyl)amino)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate (86)



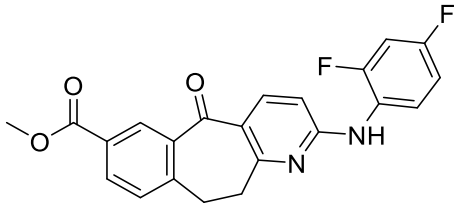
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 100 mg azadibenzosuberone and 132 mg of 2-(5-bromo-2,4-difluorophenyl)isoindoline-1,3-dione were used to obtain 45 mg of the product as yellow solid.

$C_{30}H_{19}F_2N_3O_5$ (Mr =539.49)

Yield	24%
HPLC	98% (t_r = 9.321 min)

IR (ATR)	[cm^{-1}] 1710, 1584, 1525, 1491, 1437, 1343, 1309, 1247, 1177, 1157, 1102, 1065, 879, 839, 795, 758, 718, 695, 652
ESI-MS	m/z 538.3 $[M-H]^-$
^{1}H-NMR (600 MHz, $CDCl_3$)	δ 8.56 (s, 1H), 8.46 (d, J = 8.6 Hz, 1H), 8.32 (s, 1H), 8.09 (d, J = 7.4 Hz, 1H), 8.02 – 7.94 (m, 2H), 7.87 – 7.80 (m, 2H), 7.31 (d, J = 7.7 Hz, 1H), 7.11 (t, J = 9.5 Hz, 1H), 6.76 (d, J = 8.7 Hz, 1H), 3.92 (s, 3H), 3.36 – 3.16 (m, 4H)

Methyl 2-((2,4-difluorophenyl)amino)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate (87)

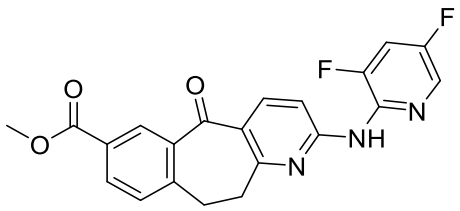


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 70 mg azadibenzosuberone and 52 mg of 1-bromo-2,4-difluorobenzene were used to obtain 35 mg of the product as yellow solid.

$C_{22}H_{16}F_2N_2O_3$ (Mr =394.38)

Yield	36%
HPLC	100% (t_r = 9.482 min)
ESI-MS	m/z 393.4 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.57 (d, J = 1.7 Hz, 1H), 8.40 (d, J = 8.8 Hz, 1H), 8.08 (dd, J = 7.8, 1.8 Hz, 1H), 8.05 – 7.93 (m, J = 12.0, 6.1 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.06 – 6.80 (m, J = 13.2, 5.1 Hz, 3H), 6.64 (d, J = 8.8 Hz, 1H), 3.91 (s, 3H), 3.37 – 3.15 (m, J = 10.9, 2.4 Hz, 4H)

Methyl 2-((3,5-difluoropyridin-2-yl)amino)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate (88)

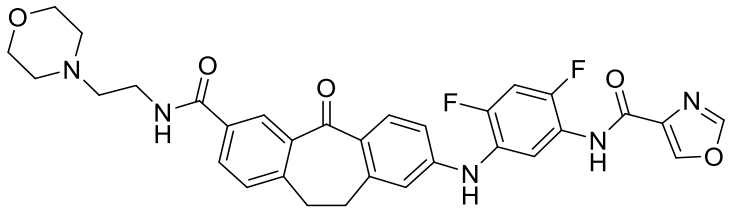


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 70 mg azadibenzosuberone and 52 mg of 1-bromo-2,4-difluoropyridine were used to obtain 25 mg of the product as yellow solid.

$C_{21}H_{15}F_2N_3O_3$ (Mr =395.4)

Yield	25%
HPLC	100% (t_r = 8.893 min)
ESI-MS	m/z 393.9 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.61 – 8.49 (m, J = 7.9, 5.2 Hz, 2H), 8.35 (d, J = 8.9 Hz, 1H), 8.14 – 8.04 (m, J = 10.2, 2.1 Hz, 2H), 7.65 (s, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.27 – 7.21 (m, 1H), 3.93 (s, 3H), 3.27 (q, J = 9.1 Hz, 4H)

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)oxazole-4-carboxamide (89)

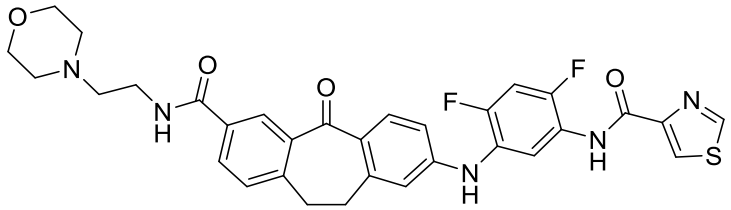


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 37 mg of N-(5-amino-2,4-difluorophenyl)-oxazole-4-carboxamide were used to obtain 54 mg of the product as yellow solid.

$C_{32}H_{29}F_2N_5O_5$ (Mr =601.61)

Yield	69%
HPLC	100% (t_r = 5.577 min)
ESI-MS	m/z 599.9 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1635, 1581, 1533, 1511, 1436, 1399, 1352, 1310, 1259, 1188, 1141, 1112, 1087, 911, 858, 785, 755
MP	171.2°C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.88 (s, 1H), 8.57 (t, 1H), 8.32 (d, J = 0.8 Hz, 1H), 8.30 (d, J = 1.8 Hz, 1H), 8.16 (d, J = 8.7 Hz, 1H), 7.98 – 7.91 (m, J = 8.1, 1.4 Hz, 2H), 7.28 (d, 1H), 7.00 (t, J = 13.5, 6.8 Hz, 1H), 6.92 (dd, J = 8.8, 2.3 Hz, 1H), 6.89 (t, J = 4.7 Hz, 1H), 6.79 (d, J = 2.1 Hz, 1H), 6.14 (s, 1H), 3.73 (t, 4H), 3.56 (dd, J = 11.3, 5.7 Hz, 2H), 3.15 (q, J = 9.2 Hz, 4H), 2.60 (t, J = 6.0 Hz, 2H), 2.54 – 2.47 (m, J = 13.2 Hz, 4H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.65, 166.88, 158.20, 150.82, 150.18 (dd, J = 237.8, 7.8 Hz), 148.11 (dd, J = 236.7, 7.8 Hz), 147.46, 145.47, 145.20, 142.34, 139.17, 135.79, 134.28, 133.15, 131.41, 129.48, 129.46, 128.57, 125.06 (dd, J = 12.0, 3.5 Hz), 122.31 (dd), 115.19, 115.07, 113.83, 104.42 (t, J = 24.5 Hz), 77.36, 67.07, 57.14, 53.51, 36.38, 35.95, 34.78, 28.55

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)thiazole-4-carboxamide (90)

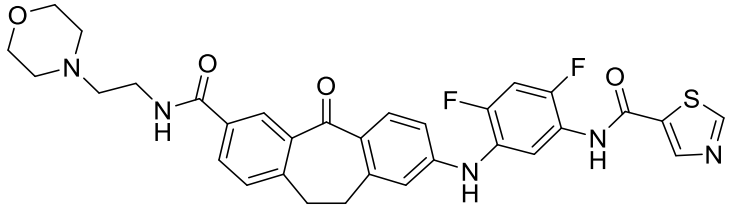


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 38 mg of N-(5-amino-2,4-difluorophenyl)-thiazole-4-carboxamide were used to obtain 21 mg of the product as yellow solid.

$C_{32}H_{29}F_2N_5O_4S$ (Mr =617.67)

Yield	28%
HPLC	98% (t_r = 6.204 min)
ESI-MS	m/z 616.0 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1634, 1600, 1576, 1533, 1472, 1436, 1419, 1399, 1352, 1308, 1258, 1191, 1141, 1111, 1068, 913, 854, 785, 754, 724, 651
MP	212.3°C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 9.42 (s, 1H), 8.81 (d, J = 1.8 Hz, 1H), 8.58 (t, J = 8.3 Hz, 1H), 8.30 (s, 1H), 8.24 (d, J = 1.8 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 7.04 (s, 1H), 6.98 (t, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.77 (s, 1H), 6.32 (s, 1H), 3.73 (s, 4H), 3.58 (s, 2H), 3.19 – 3.04 (m, J = 9.1 Hz, 4H), 2.68 – 2.60 (m, 2H), 2.53 (s, 4H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 191.56, 166.91, 158.77, 153.19, 151.77, 150.7 (dd, J =243.9, 11.5 Hz), 148.3 (dd, J = 245.9, 9.7 Hz), 147.64, 147.60, 147.01 (d, J = 10.8 Hz), 145.41, 145.19, 139.21, 134.24, 133.13, 131.28, 129.40, 128.72, 125.06 (dd, J = 11.7, 3.1 Hz), 124.56, 122.70 (dd, J = 10.5, 3.0 Hz), 115.17, 113.78, 104.35 (t, J = 24.5 Hz), 66.88, 57.26, 53.51, 36.35, 35.94, 34.78

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)thiazole-5-carboxamide (91)

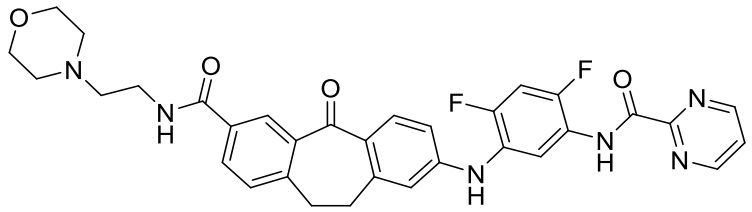


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 100 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 77 mg of N-(5-amino-2,4-difluorophenyl)-thiazole-5-carboxamide were used to obtain 74 mg of the product as yellow solid.

$C_{32}H_{29}F_2N_5O_4S$ (Mr =617.67)

Yield	48%
HPLC	100% (t_r = 4.763 min)
ESI-MS	m/z 616.1 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1636, 1602, 1580, 1522, 1490, 1437, 1400, 1374, 1353, 1261, 1197, 1169, 1142, 1112, 1064, 914, 858, 785, 756, 727, 681, 652
MP	203.1°C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.93 (s, 1H), 8.58 (s, 1H), 8.51 (s, 1H), 8.26 (s, 1H), 8.16 – 8.02 (m, 2H), 7.85 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 7.9 Hz, 1H), 7.07 – 6.99 (m, 1H), 6.92 (t, J = 10.0 Hz, 1H), 6.82 (d, J = 8.7 Hz, 1H), 6.70 (s, 1H), 6.44 (s, 1H), 3.70 (t, J = 3.9 Hz, 4H), 3.54 (q, J = 5.3 Hz, 2H), 3.14 – 2.99 (m, 4H), 2.57 (t, J = 5.9 Hz, 2H), 2.52 – 2.36 (m, 4H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 191.65, 167.07, 158.80, 157.46, 151.38 (dd, *J* = 235.8, 14.3 Hz), 149.04 (dd, *J* = 236.4, 8.4 Hz), 147.54, 145.41, 145.20, 144.63, 139.16, 134.78, 134.18, 133.18, 131.12, 129.41, 128.78, 125.25 (d, J = 13.9 Hz), 121.84 (d, J = 13.1 Hz), 117.07, 115.25, 113.75, 104.55 (t, J = 24.3 Hz), 67.03, 57.14, 53.51, 36.51, 35.88, 34.72

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)pyrimidine-2-carboxamide (92)



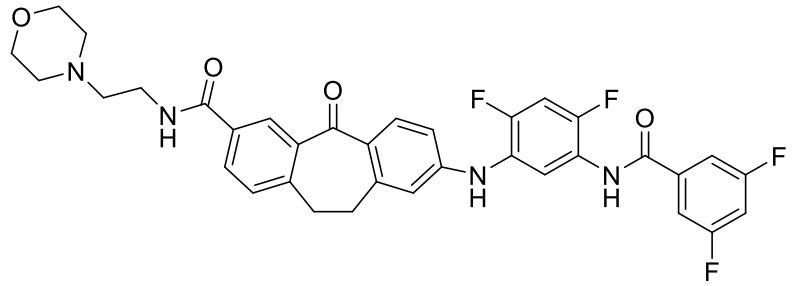
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 38 mg of N-(5-amino-2,4-difluorophenyl)-pyrimidine-2-carboxamide were used to obtain 24 mg of the product as yellow solid.

$C_{33}H_{30}F_2N_6O_4$ (Mr =612.67)

Yield	31%
HPLC	100% (t_r = 5.291 min)
ESI-MS	m/z 611.1 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1600, 1559, 1528, 1489, 1436, 1404, 1353, 1307, 1257, 1209, 1188, 1141, 1110, 929, 856, 831, 784, 757, 723, 667
MP	197.9°C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 10.15 (s, 1H), 8.94 (d, J = 4.8 Hz, 2H), 8.72 (t, J = 8.3 Hz, 1H), 8.28 (s, 1H), 8.11 (d, J = 9.2 Hz, 1H), 7.94 (d, 1H), 7.51 (t, J = 4.8 Hz, 1H), 7.26 (t, J = 3.9 Hz, 1H), 7.05 – 6.95 (m,

	2H), 6.94 – 6.82 (m, J = 5.9 Hz, 2H), 6.32 (s, 1H), 3.77 – 3.68 (m, 4H), 3.57 (dd, J = 10.9, 5.5 Hz, 2H), 3.20 – 3.05 (m, 4H), 2.61 (t, J = 5.9 Hz, 2H), 2.51 (s, 4H)
^{19}F NMR (376 MHz, $CDCl_3$)	δ -127.20 (t, *J* = 9.2 Hz), -132.73 (t, *J* = 9.1 Hz)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 191.62, 166.85, 159.76, 157.75, 157.09, 152.7 (dd, J =246.9, 11.2 Hz), 151.6 (dd, J = 245.6, 9.9 Hz), 147.24, 146.73 (d, J = 11.2 Hz), 145.46, 145.07, 139.12, 134.05, 132.99, 131.22, 129.31, 129.23, 128.47, 125.18 (dd, J = 11.8, 3.3 Hz), 123.02, 122.38 (t, J = 3.6 Hz), 122.26 (d, J = 3.1 Hz), 114.80, 114.57, 113.99, 104.24 (t, J = 24.5 Hz), 66.89, 57.09, 53.40, 36.28, 35.88, 34.63

8-((5-(3,5-difluorobenzamido)-2,4-difluorophenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (93)

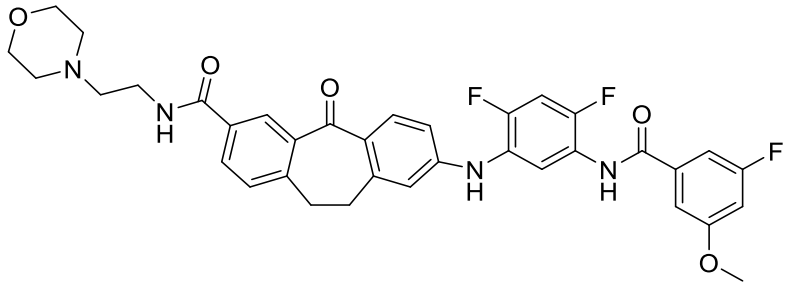


The title compound was synthesized according to the general procedure **2** for amide coupling using TBTU. For the reaction, 70 mg of compound **143** and 17 mg of 2-morpholinoethan-1-amine were used to obtain 30 mg of the product as yellow solid.

$C_{35}H_{30}F_4N_4O_4$ (Mr =646.64)

Yield	35%
HPLC	100% (t_r = 6.375 min)
ESI-MS	m/z 645.3 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1635, 1593, 1522, 1437, 1400, 1354, 1323, 1259, 1196, 1166, 1112, 988, 857, 786, 755, 719, 668
MP	212.6°C
^{1}H-NMR (700 MHz, $CDCl_3$)	δ 8.34 – 8.28 (m, J = 10.4, 4.9 Hz, 2H), 8.21 (s, 1H), 8.11 (d, J = 8.7 Hz, 1H), 7.95 – 7.90 (m, 1H), 7.42 (d, J = 5.2 Hz, 2H), 7.25 (d, J = 7.9 Hz, 1H), 7.16 (bs, 1H), 7.02 – 6.96 (m, J = 19.9, 6.1 Hz, 2H), 6.88 (dd, J = 8.7, 2.1 Hz, 1H), 6.78 (s, 1H), 6.22 (s, 1H), 3.79 – 3.74 (m, 4H), 3.60 (dd, J = 11.0, 5.5 Hz, 2H), 3.16 – 3.08 (m, 4H), 2.68 (s, 2H), 2.59 (s, 4H)
^{19}F NMR (659 MHz, $CDCl_3$)	δ -107.16, -126.50, -130.95
^{13}C NMR (176 MHz, $CDCl_3$)	δ 191.73, 167.04, 163.88 (d, J = 12.0 Hz), 163.30, 162.46 (d, J = 12.1 Hz), 151.01 (dd, J = 246.4, 11.1 Hz), 148.81 (dd, J = 244.5, 10.8 Hz), 147.38, 145.49, 145.25, 139.18, 137.42 (t, J = 8.3 Hz), 134.22, 132.94, 131.20, 129.43, 128.89, 125.21 (d, J = 12.1 Hz), 122.12 (d, J = 8.1 Hz), 116.31, 115.21, 113.83, 110.73 (dd, J = 21.5, 5.2 Hz), 107.77 (t, J = 25.3 Hz), 104.51 (t, J = 24.5 Hz), 66.62, 57.28, 53.42, 36.11, 35.90, 34.71.

8-((2,4-difluoro-5-(3-fluoro-5-methoxybenzamido)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (94)

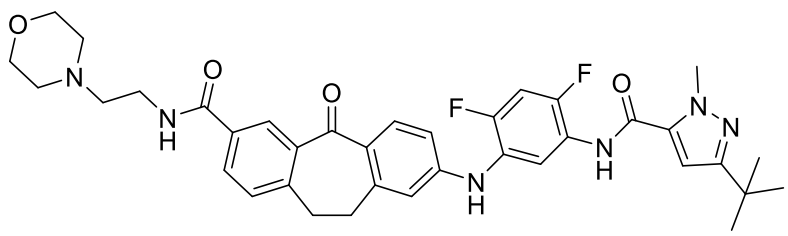


The title compound was synthesized according to the general procedure **2** for amide coupling using TBTU. For the reaction, 75 mg of compound **164** and 21 mg of 2-morpholinoethan-1-amine were used to obtain 35 mg of the product as yellow solid.

$C_{36}H_{33}F_3N_4O_5$ (Mr =658.24)

Yield	40%
HPLC	98% (t_r = 6.056 min)
ESI-MS	m/z 657.5 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1635, 1576, 1525, 1499, 1456, 1429, 1399, 1352, 1307, 1260, 1141, 1111, 1048, 974, 912, 858, 785, 755, 667
MP	208.4°C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.39 (t, *J* = 8.2 Hz, 1H), 8.32 (s, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 8.07 (s, 1H), 7.94 (d, *J* = 7.4 Hz, 1H), 7.26 – 7.17 (m, 3H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.98 (t, *J* = 10.1 Hz, 1H), 6.89 (d, *J* = 7.3 Hz, 1H), 6.83 – 6.73 (m, *J* = 8.0 Hz, 2H), 6.20 (s, 1H), 3.84 (s, 3H), 3.82 – 3.74 (m, 4H), 3.65 – 3.58 (m, *J* = 5.1 Hz, 2H), 3.12 (dd, *J* = 16.3, 8.3 Hz, 4H), 2.78 – 2.69 (m, 2H), 2.63 (s, 4H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.59, 166.86, 164.75, 164.31 (d, J = 3.0 Hz), 162.29, 161.34 (d, J = 11.0 Hz), 150.78 (d, J = 210.9 Hz), 147.33, 145.37, 145.15, 139.09, 136.70 (d, J = 8.7 Hz), 134.12, 132.78, 131.12, 129.31, 128.81, 125.03 (dd, J = 11.8, 3.4 Hz), 122.37 (dd, J = 11.6, 3.1 Hz), 115.89, 115.09, 113.71, 109.04, 106.36 (d, J = 23.6 Hz), 105.44 (d, J = 24.8 Hz), 104.28 (t, J = 24.4 Hz), 66.38, 57.24, 55.92, 53.30, 35.92, 35.80, 34.62, 22.34, 14.07

3-(tert-butyl)-N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)-1-methyl-1H-pyrazole-5-carboxamide (96)

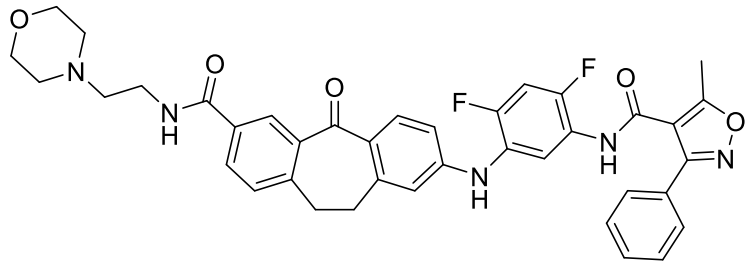


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 43 mg N-(5-amino-2,4-difluorophenyl)-3-(tert-butyl)-1-methyl-1H-pyrazole-5-carboxamide were used to obtain 82 mg of the product as yellow solid.

$C_{37}H_{40}F_2N_6O_4$ (Mr =670.76)

Yield	94%
HPLC	100% (t_r = 7.389 min)
ESI-MS	m/z 670.1 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1603, 1580, 1525, 1456, 1400, 1353, 1256, 1206, 1170, 1113, 1078, 859, 760, 718
MP	192,1 °C
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.36 – 8.29 (m, *J* = 10.3 Hz, 2H), 8.14 (d, *J* = 8.7 Hz, 1H), 7.94 (d, *J* = 7.2 Hz, 2H), 7.27 (d, *J* = 5.7 Hz, 1H), 7.09 (bs, 1H), 6.99 (t, *J* = 10.1 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 6.76 (s, 1H), 6.56 (s, 1H), 6.26 (s, 1H), 4.12 (s, 3H), 3.78 – 3.73 (m, 4H), 3.59 (d, *J* = 5.1 Hz, 2H), 3.13 (dd, *J* = 20.4, 8.8 Hz, 4H), 2.65 (t, *J* = 5.3 Hz, 2H), 2.55 (s, 4H), 1.32 (s, 9H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.64, 166.96, 160.61, 158.22, 152.11, 150.97 (dd, J = 229.9, 11.0 Hz), 148.53 (dd, J = 227.9, 11.1 Hz), 147.35, 145.43, 145.23, 139.13, 134.76, 134.23, 133.02, 131.24, 129.44, 129.37, 128.85, 125.05 (dd, *J* = 12.1, 3.4 Hz), 122.18 (dd, *J* = 11.4, 3.7 Hz), 116.21, 115.12, 113.68, 104.45 (t, *J* = 24.6 Hz), 66.76, 57.23, 53.44, 39.25, 36.22, 35.88, 34.75, 32.13, 30.60

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)-5-methyl-3-phenylisoxazole-4-carboxamide (97)



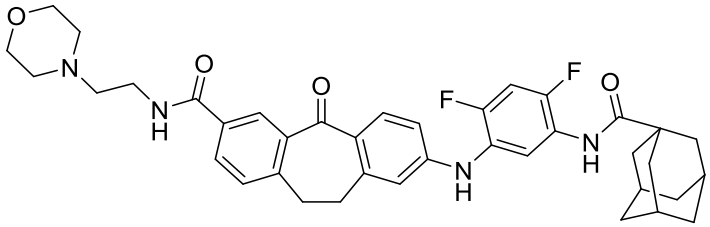
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-5-carboxamide and 46 mg N-(5-amino-2,4-difluorophenyl)-5-methyl-3-phenylisoxazole-4-carboxamide were used to obtain 24 mg of the product as yellow solid.

$C_{39}H_{35}F_2N_5O_5$ (Mr =615.64)

Yield	27%
HPLC	100% (t_r = 6.479 min)
ESI-MS	m/z 690.0 $[M-H]^-$

IR (ATR)	[cm^{-1}] 1636, 1601, 1577, 1528, 1437, 1400, 1353, 1307, 1261, 1142, 1113, 1069, 914, 860, 763, 695
MP	187,3 °C
^{1}H NMR (400 MHz, MeOD)	δ 8.36 (d, *J* = 1.9 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.96 (t, *J* = 8.1 Hz, 1H), 7.86 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.72 – 7.65 (m, *J* = 4.4 Hz, 2H), 7.47 – 7.40 (m, *J* = 9.2, 5.4 Hz, 3H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 10.2 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 6.75 (s, 1H), 3.70 (t, 4H), 3.54 (t, *J* = 6.7 Hz, 2H), 3.14 – 3.02 (m, *J* = 26.3, 9.6 Hz, 4H), 2.66 – 2.54 (m, 9H)
^{13}C NMR (101 MHz, MeOD)	δ 193.12, 173.16, 169.33, 162.93, 162.07, 152.7 (dd, J =246.9, 11.2 Hz), 151.6 (dd, J = 245.6, 9.9 Hz), 147.07, 146.82, 140.65, 134.84, 133.98, 131.66, 131.37, 130.51, 130.20, 129.92, 129.41, 129.32, 129.25, 126.42 (dd, *J* = 12.5, 3.1 Hz), 122.69 (dd, *J* = 12.7, 3.5 Hz), 120.48, 115.57, 114.18, 113.43, 105.72 (t, *J* = 25.0 Hz), 67.64, 58.61, 54.66, 37.67, 36.92, 35.51, 12.29

(3r,5r,7r)-N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)adamantane-1-carboxamide (98)



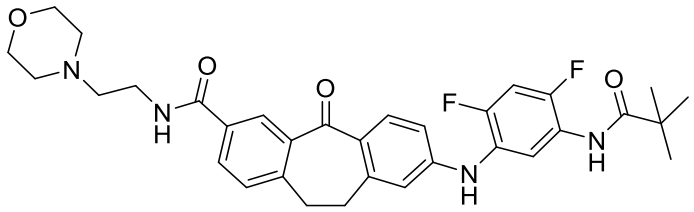
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 40 mg of (3r,5r,7r)-N-(5-amino-2,4-difluorophenyl)adamantane-1-carboxamide were used to obtain 44 mg of the product as yellow solid.

$C_{39}H_{42}F_2N_4O_4$ (Mr =668.87)

Yield	52%
HPLC	100% (t_r = 7.618 min)
ESI-MS	m/z 669.9 $[M+H]^+$
IR (ATR)	[cm^{-1}] 1636, 1602, 1581, 1522, 14371. 1400, 1353, 1258, 1143, 1112, 1069, 860, 837, 785, 754
MP	185,2 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.40 (t, J = 8.5 Hz, 1H), 8.30 (d, J = 6.3 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.94 (dd, J = 7.8, 1.9 Hz, 1H), 7.51 (d, J = 2.6 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 6.99 – 6.91 (m, J = 10.2 Hz, 2H), 6.86 (dd, J = 8.8, 2.3 Hz, 1H), 6.72 (d, J = 2.2 Hz, 1H), 6.10 (s, 1H), 3.76 – 3.71 (m, 4H), 3.57 (dd, J = 11.3, 5.7 Hz, 2H), 3.18 – 3.07 (m, 4H), 2.61 (t, J = 6.0 Hz, 2H), 2.56 – 2.48 (m, 4H), 2.12 – 2.06 (m, 3H), 1.95 (d, J = 2.5 Hz, 6H), 1.75 (q, J = 12.4 Hz, 6H)

^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.64, 176.25, 166.91, 150.57 (dd, J = 207.9, 11.0 Hz), 148.14 (dd, J = 205.2, 11.1 Hz), 147.75, 147.12 (d, J = 10.7 Hz), 145.45, 145.19, 139.22, 134.27, 133.09, 131.34, 129.41, 129.20, 128.61, 124.76 (dd, J = 11.8, 3.0 Hz), 123.07 (dd, J = 10.9, 3.4 Hz), 116.05, 115.09, 113.56, 104.04 (t, J = 24.7 Hz), 67.19, 66.97, 57.20, 53.50, 41.96, 39.28, 36.44, 36.34, 35.93, 34.75, 28.14

8-((2,4-difluoro-5-pivalamidophenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (99)

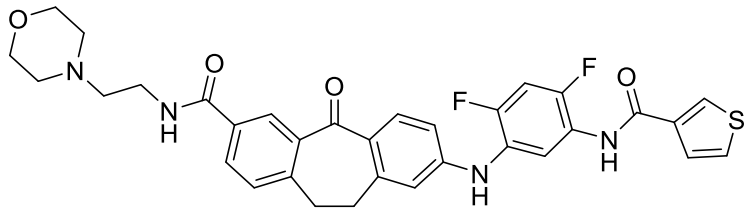


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 60 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 36 mg of N-(5-amino-2,4-difluorophenyl)pivalamide were used to obtain 48 mg of the product as yellow solid.

$C_{33}H_{36}F_2N_4O_4$ (Mr =590.67)

Yield	54%
HPLC	100% (t_r = 5.728 min)
ESI-MS	m/z 589.7 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1635, 1601, 1580, 1522, 1437, 1400, 1354, 1260, 1190, 1112, 860, 786, 761
MP	187,5 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.38 (t, J = 8.5 Hz, 1H), 8.31 (d, J = 1.8 Hz, 1H), 8.14 (d, J = 8.7 Hz, 1H), 7.95 (dd, J = 7.8, 1.9 Hz, 1H), 7.53 (t, J = 5.2 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H), 7.00 (bs, J = 14.3 Hz, 1H), 6.95 (t, J = 10.2 Hz, 1H), 6.88 (dd, J = 8.8, 2.3 Hz, 1H), 6.72 (d, J = 2.1 Hz, 1H), 6.07 (s, 1H), 3.75 (t, 4H), 3.58 (dd, J = 11.3, 5.7 Hz, 2H), 3.22 – 3.04 (m, 4H), 2.64 (t, J = 6.0 Hz, 2H), 2.61 – 2.47 (m, 4H), 1.31 (s, 9H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 191.68, 176.81, 166.94, 150.60 (dd, J = 213.2, 11.1 Hz), 148.18 (dd, J = 210.4, 11.3 Hz), 147.72, 145.47, 145.24, 139.21, 134.29, 133.05, 131.34, 129.45, 129.29, 128.71, 124.81 (dd, J = 11.9, 3.2 Hz), 123.05 (dd, J = 10.8, 3.6 Hz), 116.03, 115.14, 113.60, 104.09 (t, J = 24.7 Hz), 66.88, 57.26, 53.49, 40.06, 36.27, 35.93, 34.77, 27.64

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)thiophene-3-carboxamide (100)

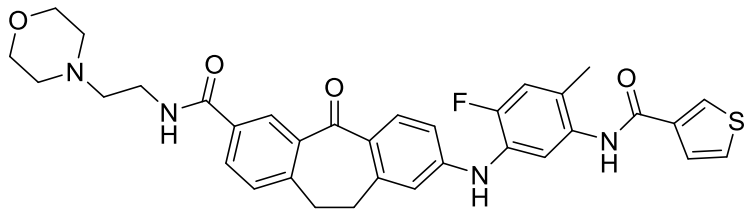


The title compound was synthesized according to the general procedure **2** for amide coupling using TBTU. For the reaction, 50 mg of compound **159** and 13 mg of 2-morpholinoethan-1-amine were used to obtain 39 mg of the product as yellow solid.

$C_{33}H_{30}F_2N_4O_4S$ (Mr =616.20)

Yield	63%
HPLC	100% (t_r = 5.003 min)
ESI-MS	m/z 639.7 $[M+Na]^+$
IR (ATR)	[cm^{-1}] 1635, 1601, 1577, 1522, 1437, 1400, 1353, 1257, 1197, 1168, 1112, 860, 786, 740, 696
MP	222.7°C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.37 (t, J = 8.5 Hz, 1H), 8.28 (s, 1H), 8.11 (d, J = 8.7 Hz, 1H), 8.02 (s, 2H), 7.91 (d, J = 8.1 Hz, 1H), 7.55 – 7.44 (m, J = 4.7 Hz, 1H), 7.43 – 7.33 (m, 1H), 7.24 (d, J = 7.2 Hz, 2H), 7.04 – 6.81 (m, 3H), 6.75 (s, 1H), 6.25 (s, 1H), 3.80 – 3.65 (m, J = 4.2 Hz, 4H), 3.63 – 3.48 (m, J = 5.3 Hz, 2H), 3.25 – 2.96 (m, 4H), 2.60 (t, J = 6.0 Hz, 2H), 2.55 – 2.38 (m, 4H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 191.63, 166.97, 161.08, 152.9 (dd, J =246.7, 10.3 Hz), 151.1 (dd, J = 243.2, 9.5 Hz), 147.64, 145.42, 145.23, 139.23, 137.16, 134.23, 133.17, 131.25, 129.50, 129.44, 128.75, 127.21, 126.24, 125.13 (d, J = 11.0 Hz), 122.74 (d, J = 11.1 Hz), 116.29, 115.19, 113.83, 104.29 (t, J = 24.6 Hz), 77.48, 77.36, 77.16, 76.84, 66.96, 57.26, 53.54, 36.42, 35.94, 34.80

N-(4-fluoro-2-methyl-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)thiophene-3-carboxamide (101)

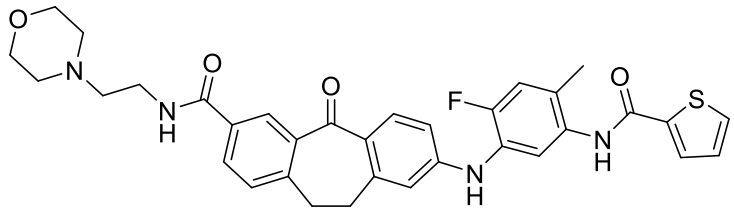


The title compound was synthesized according to the general procedure **2** for amide coupling using TBTU. For the reaction, 45 mg of compound **161** and 12 mg of 2-morpholinoethan-1-amine were used to obtain 27 mg of the product as yellow solid.

$C_{33}H_{30}F_2N_4O_4S$ (Mr =612.72)

Yield	49%
HPLC	95% (t_r = 5.014 min)
ESI-MS	m/z 635.5 $[M+Na]^+$
IR (ATR)	[cm^{-1}] 1635,1602, 1521, 1448, 1400, 1353, 1258, 1196, 1112, 1035, 1007, 860, 828, 786, 744
MP	182.0°C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.34 – 8.12 (m, 2H), 8.00 (d, J = 8.8 Hz, 2H), 7.88 – 7.77 (m, J = 7.8 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 5.1 Hz, 1H), 7.37 – 7.27 (m, J = 5.1, 3.0 Hz, 1H), 7.22 – 7.00 (m, J = 10.2, 6.3 Hz, 2H), 6.89 (d, J = 11.3 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 6.68 (s, 1H), 6.43 (s, 1H), 3.77 – 3.60 (m, 4H), 3.51 (q, J = 5.3 Hz, 2H), 3.14 – 2.89 (m, 4H), 2.56 (t, J = 6.0 Hz, 2H), 2.53 – 2.36 (m, J = 4.1 Hz, 4H), 2.22 (s, 3H)
^{13}C-NMR (101 MHz, DMSO-d_6)	δ 190.42, 165.73 (d, J = 3.6 Hz), 152.7 (dd, J =246.9, 11.2 Hz), 151.6 (dd, J = 245.6, 9.9 Hz), 149.13, 145.16, 144.68, 138.94, 137.37, 133.26, 132.60, 132.39 (d, J = 2.6 Hz),130.72, 130.38, 129.61, 129.08, 128.91, 127.06, 126.90, 125.53 (d, J = 13.1 Hz), 122.40 (d, J = 2.4 Hz), 117.48 (d, J = 20.3 Hz), 113.89, 112.48, 79.11, 69.90, 69.37, 35.43, 33.78, 25.86, 25.71, 25.13, 20.64, 17.30

N-(4-fluoro-2-methyl-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)thiophene-2-carboxamide (102)



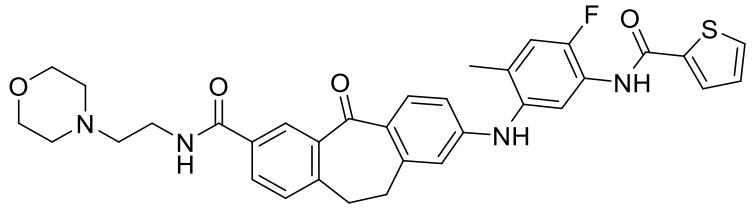
The title compound was synthesized according to the general procedure **2** for amide coupling using TBTU. For the reaction, 20 mg of compound **160** and 5 mg of 2-morpholinoethan-1-amine were used to obtain 18 mg of the product as yellow solid.

$C_{33}H_{30}F_2N_4O_4S$ (Mr =616.20)

Yield	74%
HPLC	100% (t_r = 5.504 min)
ESI-MS	m/z 635.6 $[M+Na]^+$
IR (ATR)	[cm^{-1}] 1635, 1604, 1522, 1448, 1400, 1352, 1259, 1191, 1111, 1034, 857, 786, 719, 652
MP	189.5°C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.27 (d, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.97 – 7.81 (m, J = 8.7 Hz, 2H), 7.76 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 3.2 Hz, 1H), 7.52 (d, J = 4.7 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.14 – 7.05 (m, 1H), 6.94 (d, J = 11.2 Hz, 2H), 6.85 (d, J = 8.6 Hz, 1H), 6.76 (s, 1H), 6.27 (s, 1H), 3.77 – 3.65 (m, 4H), 3.56 (q, 2H),

	3.20 – 2.92 (m, J = 10.2 Hz, 4H), 2.59 (t, J = 5.9 Hz, 2H), 2.53 – 2.42 (m, 4H), 2.26 (s, 3H)
^{13}C-NMR (151 MHz, $CDCl_3$)	δ 191.79, 167.41, 160.70, 152.21 (d, J = 243.6 Hz), 147.89, 145.50, 145.42, 139.26, 138.78, 134.05, 132.49, 131.41, 130.95, 129.27, 129.21, 129.10, 128.78, 127.96, 126.62 (d, J = 10.1 Hz), 118.84 (d, J = 12.2 Hz), 117.62 (d, J = 20.7 Hz), 115.07, 113.64, 65.86, 57.43, 53.25, 35.84, 34.66, 30.88, 17.40

N-(2-fluoro-4-methyl-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)thiophene-2-carboxamide (103)

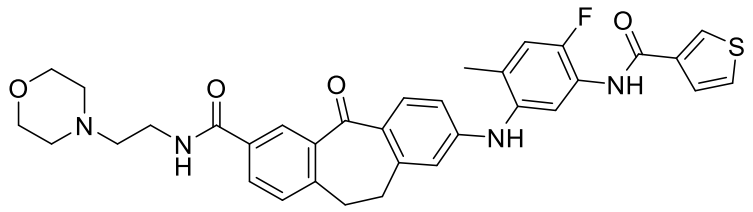


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 70 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 46 mg of N-(5-amino-4-methyl-2-fluorophenyl)-thiophene-2-carboxamide were used to obtain 59 mg of the product as yellow solid.

$C_{34}H_{33}FN_4O_4S$ (Mr =612.72)

Yield	55%
HPLC	95% (t_r = 5.763 min)
ESI-MS	m/z 635.2 $[M+Na]^+$
IR (ATR)	[cm^{-1}] 1636, 1600, 1577, 1522, 1448, 14500, 1352, 1308, 1257, 1195, 1141, 1111, 1067, 858, 832, 756, 714
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.30 (d, J = 2.4 Hz, 1H), 8.28 (d, J = 7.5 Hz, 1H), 8.14 (d, J = 8.8, 2.6 Hz, 1H), 7.96 – 7.88 (m, 2H), 7.64 (dd, J = 3.8, 1.1 Hz, 1H), 7.56 (dd, 1H), 7.27 (dd, J = 6.9, 2.6 Hz, 1H), 7.13 (dd, J = 5.0, 3.8 Hz, 1H), 7.03 (d, J = 11.4 Hz, 1H), 6.89 (t, J = 11.1, 6.4 Hz, 1H), 6.67 (dd, J = 8.8, 2.4 Hz, 1H), 6.51 (d, J = 2.3 Hz, 1H), 5.87 (s, 1H), 3.75 – 3.71 (m, 4H), 3.56 (dd, J = 11.3, 5.7 Hz, 2H), 3.18 – 3.04 (m, J = 9.8, 4.1 Hz, 4H), 2.60 (t, J = 6.1 Hz, 2H), 2.53 – 2.46 (m, J = 4.1 Hz, 4H), 2.20 (s, 3H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 191.43, 166.97, 159.80, 151.30, 150.09 (d, J = 242.2 Hz), 148.89, 145.71, 145.27, 139.34, 138.79, 134.64 (d, J = 2.3 Hz), 134.47, 133.08, 131.47, 131.29, 130.11 (d, J = 7.1 Hz), 129.39, 128.88, 128.60, 128.14, 128.08, 124.53 (d, J = 11.3 Hz), 118.54, 117.08 (d, J = 19.8 Hz), 113.92, 112.90, 67.04, 57.17, 53.51, 36.37, 36.08, 34.82, 17.85

N-(2-fluoro-4-methyl-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)thiophene-3-carboxamide (104)

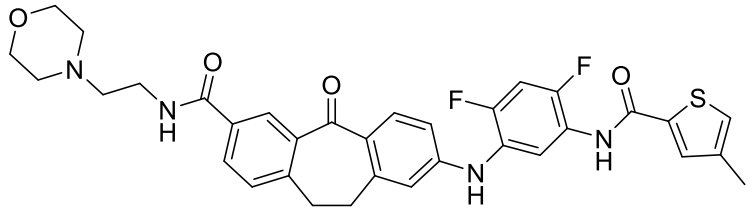


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 70 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 46 mg of N-(5-amino-4-methyl-2-fluorophenyl)-thiophene-3-carboxamide were used to obtain 50 mg of the product as yellow solid.

$C_{34}H_{33}FN_4O_4S$ (Mr =612.72)

Yield	46%
HPLC	99% (t_r = 5.437 min)
ESI-MS	m/z 635.2 $[M+Na]^+$
IR (ATR)	[cm^{-1}] 1636, 1601, 1577, 1522, 1448, 1400, 1352, 1352, 1255, 1196, 1171, 1143, 1112, 860, 785, 742
MP	189,1 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.29 (d, J = 8.3 Hz, 2H), 8.13 (d, J = 8.7 Hz, 1H), 8.00 (d, J = 1.4 Hz, 1H), 7.97 – 7.86 (m, 2H), 7.48 (d, J = 4.6 Hz, 1H), 7.43 – 7.36 (m, 1H), 7.27 (d, J = 6.1 Hz, 1H), 7.02 (d, J = 11.3 Hz, 1H), 6.93 (s, 1H), 6.71 – 6.61 (m, 1H), 6.51 (s, 1H), 5.91 (s, 1H), 3.74 (s, 4H), 3.57 (d, J = 5.2 Hz, 2H), 3.18 – 3.02 (m, 4H), 2.62 (t, J = 5.6 Hz, 2H), 2.52 (s, 4H), 2.19 (s, 3H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 191.42, 166.98, 160.91, 151.38, 150.18 (d, J = 241.7 Hz), 148.98, 145.69, 145.26, 139.36, 137.34, 134.59 (d, J = 1.6 Hz), 134.45, 133.04, 131.23, 130.08 (d, J = 7.1 Hz), 129.35, 128.67, 128.09, 127.23, 126.16, 124.68 (d, J = 11.1 Hz), 118.63, 117.06 (d, J = 19.9 Hz), 113.89, 112.85, 66.94, 57.21, 53.49, 36.30, 36.08, 34.81, 17.84

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)-4-methylthiophene-2-carboxamide (123)

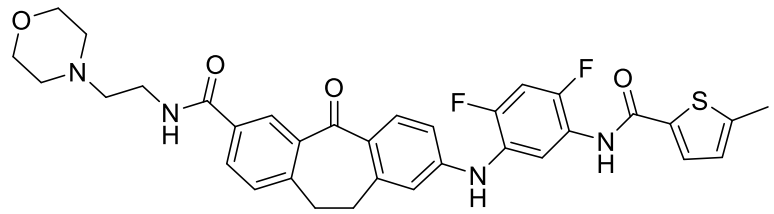


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-5-carboxamide and 38 mg N-(5-amino-2,4-difluorophenyl)-4-methylthiophene-2-carboxamide were used to obtain 53 mg of the product as yellow solid.

$C_{34}H_{32}F_2N_4O_4S$ (Mr =630.71)

Yield	65%
HPLC	98% (t_r = 5.791 min)
ESI-MS	m/z 629.9 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1635, 1603, 1581, 1522, 1420, 1400, 1353, 1260, 1169, 1113, 856, 786, 760
^{1}H NMR (400 MHz, MeOD)	δ 8.36 (d, *J* = 2.0 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.86 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.74 (t, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 1.1 Hz, 1H), 7.33 – 7.29 (m, *J* = 4.9 Hz, 2H), 7.16 (t, *J* = 10.2 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.75 (d, *J* = 2.2 Hz, 1H), 3.72 – 3.68 (m, 4H), 3.55 (t, *J* = 6.7 Hz, 2H), 3.14 – 3.03 (m, 4H), 2.63 (t, *J* = 6.7 Hz, 2H), 2.59 – 2.52 (m, 4H), 2.29 (d, *J* = 0.6 Hz, 3H)
^{13}C NMR (101 MHz, MeOD)	δ 193.11, 169.37, 163.09, 155.42 (d, *J* = 10.9 Hz), 154.11 (d, *J* = 11.0 Hz), 152.96 (d, *J* = 10.8 Hz), 151.66 (d, *J* = 11.3 Hz), 150.55, 148.85 (d, J = 241.8 Hz), 146.85, 140.66, 139.99, 139.05, 134.89, 133.96, 132.78, 131.64, 130.53, 130.17, 129.15, 128.52, 126.27 (dd, *J* = 12.9, 3.5 Hz), 122.77 (dd, *J* = 12.9, 3.6 Hz), 122.24, 115.39, 114.06, 105.79 (t, *J* = 25.1 Hz), 67.62, 58.61, 54.65, 37.66, 36.94, 35.52, 15.62

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)-5-methylthiophene-2-carboxamide (124)



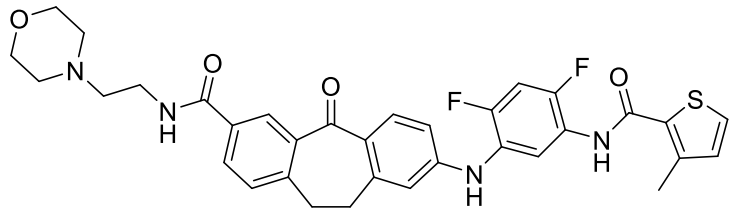
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-5-carboxamide and 38 mg N-(5-amino-2,4-difluorophenyl)-5-methylthiophene-2-carboxamide were used to obtain 63 mg of the product as yellow solid.

$C_{34}H_{32}F_2N_4O_4S$ (Mr =630.71)

Yield	77%
HPLC	98% (t_r = 5.988 min)
ESI-MS	m/z 629.8 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1636, 1601, 1581, 1522, 1457, 1437, 1400, 1261, 1207, 1168, 1113, 1077, 858
MP	188,1 °C
^{1}H NMR (400 MHz, MeOD)	δ 8.37 (s, 1H), 8.07 – 8.03 (m, 1H), 7.89 – 7.84 (m, *J* = 7.9, 1.3 Hz, 1H), 7.71 (t, *J* = 13.0, 4.7 Hz, 1H), 7.69 (d, *J* = 3.8 Hz, 1H), 7.37 – 7.30 (m, 1H), 7.19 – 7.12 (m, 1H), 6.88 – 6.84 (m, 2H), 6.75 (s, 1H), 3.73 – 3.67 (m, 4H), 3.55 (t, *J* = 6.7 Hz, 2H),

	3.16 – 3.04 (m, 4H), 2.63 (t, *J* = 6.7 Hz, 2H), 2.60 – 2.54 (m, *J* = 10.2 Hz, 4H), 2.52 (s, 3H)
^{13}C NMR (101 MHz, MeOD)	δ 193.15, 169.39, 163.07, 154.83 (dd, J = 126.3, 10.3 Hz), 152.39 (dd, J = 124.6, 9.9 Hz), 150.61, 148.52, 147.17, 146.87, 140.68, 136.93, 134.90, 133.98, 131.65, 131.31, 130.52, 130.19, 129.14, 127.69, 126.25 (dd, *J* = 12.8, 3.2 Hz), 122.82 (dd, *J* = 12.9, 3.4 Hz), 122.39, 115.36, 114.04, 105.79 (t, *J* = 25.1 Hz), 67.64, 58.62, 54.67, 37.68, 36.95, 35.53, 15.53

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)-3-methylthiophene-2-carboxamide (125)

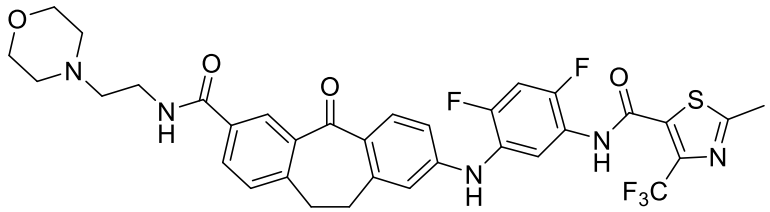


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-5-carboxamide and 38 mg N-(5-amino-2,4-difluorophenyl)-3-methylthiophene-2-carboxamide were used to obtain 65 mg of the product as yellow solid.

$C_{34}H_{32}F_2N_4O_4S$ (Mr =630.71)

Yield	79%
HPLC	100% (t_r = 5.876 min)
ESI-MS	m/z 629.7 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1636, 1601, 1581, 1523, 1437, 1405, 1353, 1261, 1169, 1141, 1112, 1068, 856, 786, 757
MP	180,7 °C
^{1}H NMR (400 MHz, MeOD)	δ 8.38 (d, *J* = 2.0 Hz, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.88 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.82 (t, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 5.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 10.3 Hz, 1H), 6.99 (d, *J* = 4.9 Hz, 1H), 6.87 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.77 (d, *J* = 2.2 Hz, 1H), 3.71 (t, 4H), 3.56 (t, *J* = 6.7 Hz, 2H), 3.17 – 3.07 (m, 4H), 2.63 (t, *J* = 6.7 Hz, 2H), 2.60 – 2.55 (m, *J* = 9.1, 4.8 Hz, 4H), 2.54 (s, 3H)
^{13}C NMR (101 MHz, MeOD)	δ 193.16, 169.40, 164.30, 154.70 (dd, J = 141.5, 10.9 Hz), 152.25 (dd, J = 141.2, 10.8 Hz), 126.29 (dd, J = 12.7, 3.3 Hz), 123.10 (dd, J = 12.9, 3.5 Hz), 150.67, 147.17, 146.89, 143.75, 140.69, 134.89, 134.00, 132.87, 131.66, 131.47, 130.53, 130.20, 129.23, 129.15, 126.29 (dd, *J* = 12.7, 3.3 Hz), 123.10 (dd, *J* = 12.9, 3.5 Hz), 121.88, 115.37, 114.07, 105.76 (t, *J* = 25.2 Hz), 67.64, 58.62, 54.67, 37.67, 36.96, 35.55, 15.78

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)-2-methyl-4-(trifluoromethyl)thiazole-5-carboxamide (126)

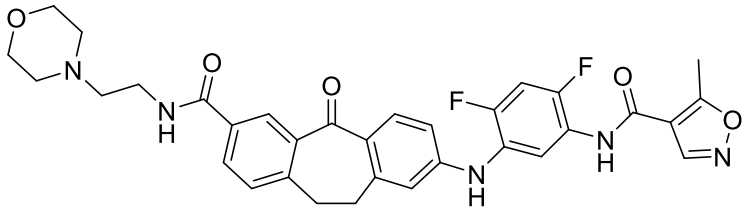


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-5-carboxamide and 47 mg N-(5-amino-2,4-difluorophenyl)-2-methyl-4-(trifluoromethyl)thiazole-5-carboxamide were used to yield 18 mg of the product as yellow solid.

$C_{34}H_{30}F_5N_5O_4S$ (Mr =699.7)

Yield	20%
HPLC	99% (t_r = 5.895 min)
ESI-MS	m/z 699.2 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1601, 1581, 1528, 1490, 1437, 1354, 1261, 1197, 1167, 1136, 1114, 908, 862, 757, 728
MP	193,4 °C
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.37 (t, *J* = 8.1 Hz, 1H), 8.32 (d, *J* = 1.9 Hz, 1H), 8.17 (bs, *J* = 7.2 Hz, 1H), 8.14 (d, *J* = 8.7 Hz, 1H), 7.94 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.27 (d, 1H), 7.09 (bs, *J* = 23.9 Hz, 1H), 7.00 (t, *J* = 10.1 Hz, 1H), 6.90 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.80 (d, *J* = 2.2 Hz, 1H), 6.17 (s, 1H), 3.77 (t, 4H), 3.59 (dd, *J* = 11.2, 5.6 Hz, 2H), 3.19 – 3.09 (m, *J* = 19.6, 9.2 Hz, 4H), 2.75 (s, 3H), 2.68 (t, *J* = 5.9 Hz, 2H), 2.63 – 2.54 (m, 4H)
^{19}F NMR (376 MHz, $CDCl_3$)	δ -59.42, -126.12 (t, *J* = 8.3 Hz), -131.94 (t)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.75, 169.19, 166.95, 156.91, 152.33 (d, *J* = 11.2 Hz), 151.10 (dd, J = 247.0, 11.2 Hz), 149.57 (d, *J* = 11.8 Hz), 147.22, 145.47, 145.27, 141.28, 140.91, 139.15, 134.92, 134.24, 132.98, 131.29, 129.67, 129.50, 128.88, 125.44, 125.36 (dd, *J* = 12.0, 3.1 Hz), 121.90 – 121.62 (m), 118.95, 115.60, 115.32, 113.96, 104.57 (t, *J* = 24.5 Hz), 66.66, 57.31, 53.45, 36.12, 35.89, 34.75, 19.44

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)-5-methylisoxazole-4-carboxamide (127)

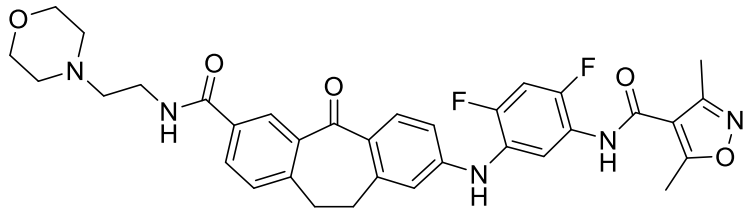


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-5-carboxamide and 35 mg N-(5-amino-2,4-difluorophenyl)-5-methylisoxazole-4-carboxamide were used to obtain 37 mg of the product as yellow solid.

$C_{33}H_{31}F_2N_5O_5$ (Mr =615.64)

Yield	47%
HPLC	96% (t_r = 5.901 min)
ESI-MS	m/z 614.9 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1628, 1601, 1577, 1522, 1430, 1380, 1353, 1312, 1256, 1188, 1109, 971, 861, 831, 760
MP	173,7 °C
^{1}H NMR (400 MHz, MeOD)	δ 8.45 (t, *J* = 8.5 Hz, 1H), 8.38 (d, *J* = 1.9 Hz, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.92 – 7.80 (m, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.07 (t, *J* = 10.5 Hz, 1H), 6.86 – 6.81 (m, 1H), 6.72 (s, 1H), 3.75 – 3.71 (m, 4H), 3.58 (t, *J* = 6.6 Hz, 2H), 3.20 – 3.06 (m, 4H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.62 (s, 4H), 2.21 (s, 3H)
^{13}C NMR (101 MHz, MeOD)	δ 193.19, 192.21, 191.97, 169.49, 169.37, 163.43 (d, J= 269.5 Hz), 158.97, 152.78 (d, *J* = 10.4 Hz), 151.20, 147.28, 146.93, 140.83, 134.91, 133.91, 131.57, 130.52, 130.12, 128.63, 125.83 (dd), 125.46 (dd, *J* = 9.8, 5.3 Hz), 117.96, 115.02, 113.91, 111.00, 104.81 (t, *J* = 24.9 Hz), 103.53 (d, *J* = 24.9 Hz), 67.52, 58.62, 54.62, 37.57, 37.02, 35.55, 27.00

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)-3,5-dimethylisoxazole-4-carboxamide (128)



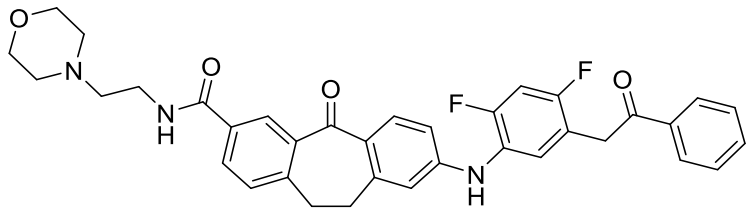
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 37 mg N-(5-amino-2,4-difluorophenyl)-3,5-dimethylisoxazole-4-carboxamide were used to obtain 28 mg of the product as yellow solid.

$C_{34}H_{33}F_2N_5O_5$ (Mr =629.66)

Yield	35%
HPLC	96% (t_r = 5.606 min)
ESI-MS	m/z 630.9 $[M+H]^+$
IR (ATR)	[cm^{-1}] 1636, 1600, 1577, 1522, 1420, 1401, 1353, 1262, 1170, 1142, 1113, 915, 861, 785, 757
MP	178,3 °C

^{1}H NMR (400 MHz, MeOD)	δ 8.38 (d, *J* = 2.0 Hz, 1H), 8.05 (d, *J* = 8.5, 6.2 Hz, 1H), 7.96 (t, *J* = 17.1, 8.8 Hz, 1H), 7.87 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 10.3 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.78 (d, *J* = 3.3 Hz, 1H), 3.73 – 3.69 (m, 4H), 3.56 (t, *J* = 6.7 Hz, 2H), 3.33 (dt, *J* = 3.3, 1.6 Hz, 1H), 3.16 – 3.06 (m, 4H), 2.66 – 2.60 (m, 5H), 2.59 – 2.54 (m, 4H), 2.41 (s, 3H)
^{13}C NMR (101 MHz, MeOD)	δ 193.08, 172.50, 169.34, 163.00, 160.02, 155.13 (d, *J* = 11.0 Hz), 152.5 (dd, J = 246.5, 2.6 Hz), 151.8 (dd, J =247.3, 2.2 Hz), 150.90 (d, *J* = 11.0 Hz), 150.56, 146.99 (d, *J* = 25.4 Hz), 140.64, 134.88, 133.98, 131.65, 130.54, 130.20, 129.20, 126.34 (dd, *J* = 12.6, 3.2 Hz), 122.96 (dd, *J* = 12.7, 3.3 Hz), 121.08, 115.51, 114.04, 105.73 (t, *J* = 25.0 Hz), 67.62, 58.62, 54.66, 37.66, 36.94, 35.54, 12.49, 10.88

8-((2,4-difluoro-5-(2-oxo-2-phenylethyl)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (129)

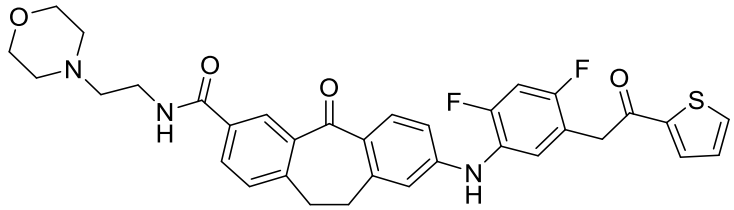


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 100 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 74 mg of 2-(5-amino-2,4-difluorophenyl)1-phenylethan-1-one were used to obtain 69 mg of the product as yellow solid.

$C_{36}H_{33}F_2N_3O_4$ (Mr =609.24)

Yield	46%
HPLC	99% (t_r = 6.705 min)
ESI-MS	m/z 608.2 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1577, 1507, 1353, 1259, 1211, 1169, 1144, 1113, 988, 859, 752, 689
MP	218.8°C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.33 (s, 1H), 8.19 – 7.90 (m, 4H), 7.67 – 7.44 (m, J = 14.3, 7.0 Hz, 3H), 7.36 – 7.20 (m, J = 6.7 Hz, 2H), 7.06 (s, 1H), 6.93 (t, J = 9.7 Hz, 1H), 6.81 (d, J = 8.9 Hz, 1H), 6.66 (s, 1H), 6.12 (s, 1H), 4.29 (s, 2H), 3.85 – 3.70 (m, 4H), 3.67 – 3.50 (m, 2H), 3.27 – 2.99 (m, J = 6.4 Hz, 4H), 2.80 – 2.48 (m, 6H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 195.94, 191.44, 166.90, 156.86 (dd, J = 226.2, 11.3 Hz), 154.41 (dd, J = 228.5, 11.8 Hz), 148.18, 146.57, 145.38, 145.21, 139.14, 138.95, 136.36, 134.98, 134.22, 133.64, 133.10, 131.20, 129.98, 129.43, 129.18 (d, J = 4.5 Hz), 128.89, 128.43, 125.84 (d, J = 3.8 Hz), 124.91 (dd, J = 11.8, 3.4 Hz), 118.31 – 118.04 (m), 115.91 (d, J = 1.3 Hz), 114.80, 113.43, 104.68 (dd, J = 27.1, 24.0 Hz), 66.73, 57.26, 53.45, 38.03, 36.25, 35.90, 34.79

8-((2,4-difluoro-5-(2-oxo-2-(thiophen-2-yl)ethyl)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (130)

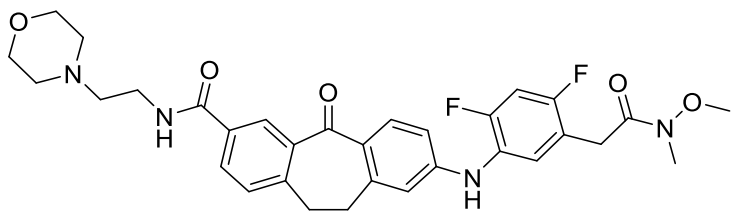


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 95 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 60 mg of 2-(5-amino-2,4-difluorophenyl)-1-(thiophen-2-yl)ethan-1-one were used to obtain 33 mg of the product as yellow solid.

$C_{34}H_{31}F_2N_3O_4S$ (Mr =615.70)

Yield	23%
HPLC	95% (t_r = 6.499 min)
ESI-MS	m/z 614.2 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1635, 1600, 1576, 1506, 1409, 1352, 1258, 1144, 1112, 1058, 858, 785, 752, 725
MP	172.8 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.34 (s, 1H), 8.14 (d, J = 8.7 Hz, 1H), 7.96 (d, J = 7.3 Hz, 1H), 7.83 (d, J = 2.8 Hz, 1H), 7.69 (d, J = 4.4 Hz, 1H), 7.31 (dt, J = 13.8, 6.8 Hz, 2H), 7.20 – 7.13 (m, 1H), 7.04 – 6.90 (m, 2H), 6.84 (d, J = 7.9 Hz, 1H), 6.68 (s, 1H), 5.96 (s, 1H), 4.22 (s, 2H), 3.76 (s, 4H), 3.59 (d, J = 4.4 Hz, 2H), 3.21 – 3.05 (m, 4H), 2.65 (s, 2H), 2.56 (s, 4H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 191.59, 188.84, 177.50, 166.92, 156.75 (dd, J = 218.3, 13.1 Hz), 154.35 (dd, J = 229.6, 11.3 Hz), 147.92, 145.51, 145.31, 143.42, 139.11, 134.65, 134.33, 133.09, 132.77, 131.39, 129.55, 129.38, 128.81, 128.49, 125.45, 124.98 (d, J = 12.0 Hz), 117.79 (d, J = 20.6 Hz), 114.87, 113.59, 104.78 (dd, J = 27.2, 23.9 Hz), 66.85, 57.25, 53.49, 38.48, 36.23, 35.95, 34.84

8-((2,4-difluoro-5-(2-(methoxy(methyl)amino)-2-oxoethyl)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (131)

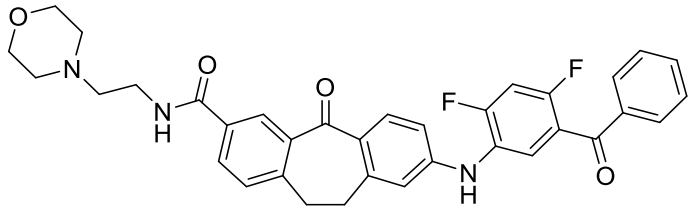


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 100 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 64 mg of 2-(5-amino-2,4-difluorophenyl)-N-methoxy-N-methylacetamide were used to obtain 65 mg of the product as yellow solid.

$C_{32}H_{34}F_2N_4O_5$ (Mr =592.64)

Yield	44%
HPLC	94% (t_r = 5.173 min)
ESI-MS	m/z 591.6 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1634, 1599, 1579, 1506, 1435, 1398, 1352, 1258, 1201, 1145, 1112, 997, 860, 785, 757, 651
MP	167.3 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.33 (s, 1H), 8.14 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 6.5 Hz, 1H), 7.30 (s, 2H), 6.91 (s, 2H), 6.83 (d, J = 7.9 Hz, 1H), 6.66 (s, 1H), 6.03 (s, 1H), 3.74 (s, 9H), 3.57 (s, 2H), 3.21 (s, 3H), 3.13 (d, J = 19.1 Hz, 4H), 2.61 (s, 2H), 2.52 (s, 4H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 191.52, 170.95, 166.88, 156.86 (dd, J = 245.8, 11.7 Hz), 154.41 (dd, J = 247.2, 11.8 Hz), 148.19, 145.48, 145.26, 139.12, 134.29, 133.14, 131.37, 129.51, 129.12, 128.72, 125.79, 124.66 (d, J = 10.9 Hz), 118.47 (d, J = 14.7 Hz), 114.76, 113.38, 104.59 (dd, J = 26.6, 24.4 Hz), 66.99, 61.52, 57.18, 53.50, 36.31, 35.96, 34.82, 32.52, 31.69

8-((5-benzoyl-2,4-difluorophenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (132)



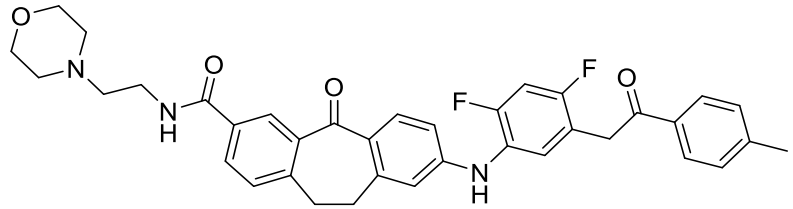
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 33 mg of N-(5-amino-2,4-difluorophenyl)(phenyl)methadone were used to obtain 36 mg of the product as yellow solid.

$C_{35}H_{31}F_2N_3O_4$ (Mr =595.65)

Yield	47%
HPLC	95% (t_r = 6.961 min)
ESI-MS	m/z 594.0 $[M-H]^-$
IR (ATR) [cm^{-1}]	1577, 1507, 1353, 1259, 1211, 1169, 1144, 1113, 988, 859, 752, 689

^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.33 (d, J = 1.5 Hz, 1H), 8.14 (d, J = 8.7 Hz, 1H), 7.95 (dd, J = 7.8, 1.7 Hz, 1H), 7.84 (d, J = 7.9 Hz, 2H), 7.61 (t, J = 11.2, 4.0 Hz, 2H), 7.54 – 7.43 (m, 2H), 7.29 (d, J = 7.9 Hz, 1H), 7.01 (t, J = 9.6 Hz, 1H), 6.90 (dd, 2H), 6.75 (s, 1H), 6.18 (s, 1H), 3.77 – 3.70 (m, 4H), 3.57 (dd, J = 11.0, 5.5 Hz, 2H), 3.21 – 3.06 (m, 4H), 2.61 (t, J = 5.9 Hz, 2H), 2.51 (s, 4H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 192.00, 191.61, 166.83, 157.48 (dd, J = 166.4, 11.4 Hz), 154.97 (dd, J = 165.7, 11.6 Hz), 146.97, 145.38, 145.20, 138.92, 137.30, 134.28, 133.80, 133.20, 131.45, 130.05, 129.85, 129.85, 129.61, 128.76, 128.70, 126.07 (d, J = 3.5 Hz), 125.95 (d, J = 3.6 Hz), 123.48 (t, J = 3.7 Hz), 123.35 (d, J = 3.9 Hz), 115.39, 114.09, 105.64 (dd, J = 27.1, 24.0 Hz), 66.99, 57.14, 53.49, 36.31, 35.87, 34.80

8-((2,4-difluoro-5-(2-oxo-2-(p-tolyl)ethyl)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (133)

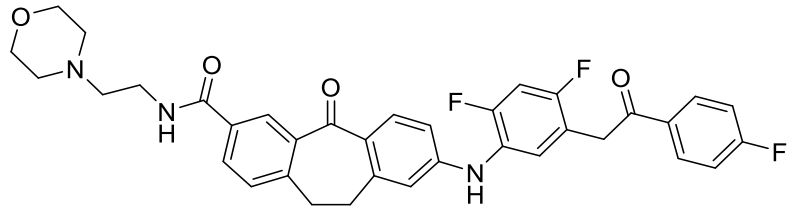


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 45 mg of 2-(5-amino-2,4-difluorophenyl)-1-(p-tolyl)ethan-1-one were used to obtain 56 mg of the product as yellow solid.

$C_{37}H_{35}F_2N_3O_4$ (Mr =623.70)

Yield	72%
HPLC	100% (t_r = 7.495 min)
ESI-MS	m/z 622.7 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1636, 1602, 1577, 1508, 1400, 1353, 1259, 1205, 1180, 1113, 981, 859, 808, 786, 757
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.34 (d, J = 4.1 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.95 (dd, J = 7.9, 1.9 Hz, 1H), 7.92 (d, J = 8.2 Hz, 2H), 7.32 – 7.26 (m, 4H), 7.00 (s, 1H), 6.93 (t, 1H), 6.81 (dd, J = 8.8, 2.3 Hz, 1H), 6.66 (d, 1H), 6.03 (s, 1H), 4.24 (d, J = 16.7 Hz, 2H), 3.75 (t, 4H), 3.58 (dd, J = 11.2, 5.6 Hz, 2H), 3.17 – 3.05 (m, 4H), 2.64 (t, J = 5.9 Hz, 2H), 2.55 (s, 4H), 2.42 (s, 3H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 195.60, 191.52, 166.90, 156.74 (dd, J = 245.5, 11.3 Hz), 152.64 (dd, J = 229.9, 8.4 Hz), 148.10, 145.47, 145.27, 144.64, 139.12, 134.29, 133.83, 133.08, 131.33, 129.61, 129.49, 129.20, 128.81, 128.60, 125.72 (d, J = 3.3 Hz), 124.79 (dd, J = 12.1, 3.3 Hz), 118.36 (dd, J = 17.1, 3.9 Hz), 114.78, 113.45, 104.71 (dd, J = 27.2, 23.9 Hz), 66.83, 57.25, 53.48, 37.92, 36.23, 35.93, 34.82, 29.81, 21.82, 14.23

8-((2,4-difluoro-5-(2-(4-fluorophenyl)-2-oxoethyl)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (134)

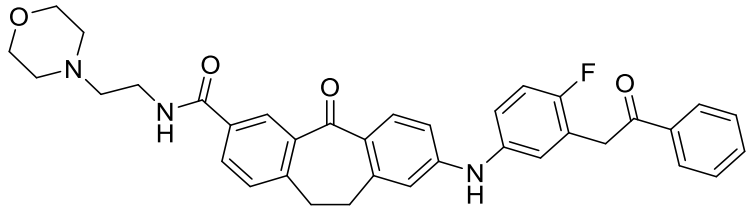


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 70 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 56 mg of 2-(5-amino-2,4-difluorophenyl)-1-(4-fluorophenyl)ethan-1-one were used to obtain 98 mg of the product as yellow solid.

$C_{36}H_{32}F_3N_3O_4$ (Mr =627.66)

Yield	90%
HPLC	99% (t_r = 6.862 min)
ESI-MS	m/z 626.7 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1636, 1577, 1507, 1400, 1353, 1259, 1210, 1155, 1112, 991, 914, 833, 786, 759
MP	181,1 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.33 (d, J = 1.6 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 8.05 (dd, J = 8.8, 5.4 Hz, 2H), 7.95 (dd, J = 7.8, 1.8 Hz, 1H), 7.30 – 7.24 (m, J = 11.6, 6.9 Hz, 2H), 7.16 (t, J = 8.6 Hz, 2H), 7.02 – 6.90 (m, J = 17.2, 7.5 Hz, 2H), 6.83 (dd, J = 8.7, 2.2 Hz, 1H), 6.66 (d, J = 1.9 Hz, 1H), 6.05 (s, 1H), 4.26 (s, 2H), 3.77 – 3.71 (m, 4H), 3.57 (dd, J = 11.1, 5.6 Hz, 2H), 3.19 – 3.05 (m, 4H), 2.63 (t, J = 5.9 Hz, 2H), 2.54 (s, 4H)
^{19}F NMR (376 MHz, $CDCl_3$)	δ -104.12, -118.50, -123.52.
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 194.36, 191.53, 167.40, 166.89, 164.86, 156.79 (dd, J = 220.1, 11.5 Hz), 154.34 (dd, J = 222.1, 11.6 Hz), 148.01, 145.46, 145.24, 139.10, 134.29, 133.12, 132.71 (d, J = 2.8 Hz), 131.33, 131.20, 131.10, 129.51, 129.29, 128.81, 125.58 (d, J = 3.1 Hz), 124.95 (dd, J = 12.0, 3.4 Hz), 117.91 (dd, J = 17.1, 3.7 Hz), 116.19, 115.98, 114.89, 113.48, 104.77 (dd, J = 27.1, 24.1 Hz), 66.87, 57.22, 53.48, 37.98, 36.25, 35.93, 34.81

8-((4-fluoro-3-(2-oxo-2-phenylethyl)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (135)

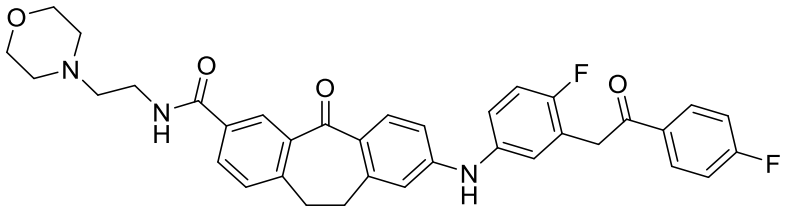


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 32 mg of 2-(5-amino-2-fluorophenyl)-1-phenylethan-1-one were used to obtain 54 mg of the product as yellow solid.

$C_{36}H_{34}FN_3O_4$ (Mr =591.25)

Yield	70%
HPLC	100% (t_r = 6.782 min)
ESI-MS	m/z 592.5 $[M+H]^+$
IR (ATR)	[cm^{-1}] 1636, 1577, 1526, 149, 1447, 1352, 1333, 1264, 1213, 1173, 1142, 1113, 1001, 860, 827, 784, 752, 687
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.34 (d, *J* = 1.2 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 8.03 (d, *J* = 7.4 Hz, 2H), 7.95 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.27 (d, 1H), 7.12 – 7.03 (m, *J* = 8.2 Hz, 3H), 6.99 (s, 1H), 6.80 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.65 (s, 1H), 6.17 (s, 1H), 4.31 (s, 2H), 3.80 – 3.71 (m, *J* = 4.0 Hz, 4H), 3.58 (dd, *J* = 10.8, 5.4 Hz, 2H), 3.20 – 3.02 (m, 4H), 2.64 (t, *J* = 5.6 Hz, 2H), 2.55 (s, 4H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 196.26, 191.32, 166.95, 157.55 (d, J = 243.0 Hz), 148.91, 145.45 (d, *J* = 33.8 Hz), 139.24, 136.52 (d, *J* = 2.5 Hz), 136.41, 134.42, 133.66, 133.07, 131.27, 129.46, 128.92, 128.83, 128.54, 125.32 (d, *J* = 3.9 Hz), 123.09 (d, *J* = 17.5 Hz), 122.44 (d, *J* = 8.1 Hz), 116.39 (d, *J* = 23.5 Hz), 114.26, 113.22, 66.83, 57.25, 53.48, 38.61, 36.23, 36.04, 34.84

8-((4-fluoro-3-(2-(4-fluorophenyl)-2-oxoethyl)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (136)

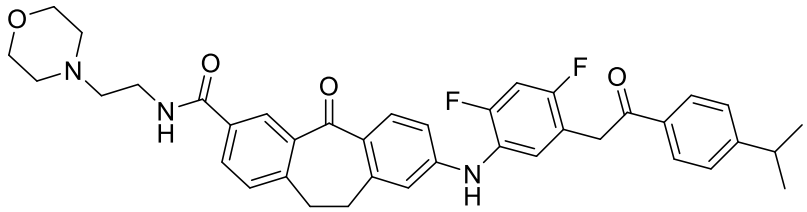


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 37 mg of 2-(5-amino-2-fluorophenyl)-1-fluorophenylethan-1-one were used to obtain 48 mg of the product as yellow solid.

$C_{36}H_{33}FN_3O_4$ (Mr =609.67)

Yield	60%
HPLC	98% (t_r = 6.992 min)
ESI-MS	m/z 610.2 $[M+H]^+$
IR (ATR)	[cm^{-1}] 1577, 1522, 1497, 1353, 1333, 1263, 1210, 1155, 1112, 1002, 859, 831, 785, 759
MP	164,6 °C
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.34 (d, *J* = 1.8 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 8.09 – 8.03 (m, 2H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 9.6 Hz, 1H), 7.15 (t, *J* = 8.5 Hz, 2H), 7.10 – 7.03 (m, 3H), 6.99 (bs, 1H), 6.80 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.64 (d, *J* = 1.8 Hz, 1H), 6.21 (bs, 1H), 4.27 (s, 2H), 3.75 (t, 4H), 3.58 (dd, *J* = 11.2, 5.6 Hz, 2H), 3.16 – 3.03 (m, 4H), 2.63 (t, *J* = 5.9 Hz, 2H), 2.58 – 2.50 (m, 4H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 194.70, 191.31, 167.37, 166.94, 164.83, 157.44 (d, J = 243.0 Hz), 156.23, 148.85, 145.60, 145.26, 139.21, 136.61 (d, *J* = 2.4 Hz), 134.40, 133.08, 132.80 (d, *J* = 2.8 Hz), 131.26, 131.17, 129.45, 128.84, 128.57, 125.17 (d, *J* = 3.8 Hz), 122.85 (d, *J* = 17.4 Hz), 122.45 (d, *J* = 8.1 Hz), 116.41 (d, *J* = 23.5 Hz), 116.05 (d, *J* = 21.9 Hz), 113.76 (d, *J* = 107.6 Hz), 66.84, 57.23, 53.47, 38.53, 36.24, 36.03, 34.82

8-((2,4-difluoro-5-(2-(4-isopropylphenyl)-2-oxoethyl)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (137)



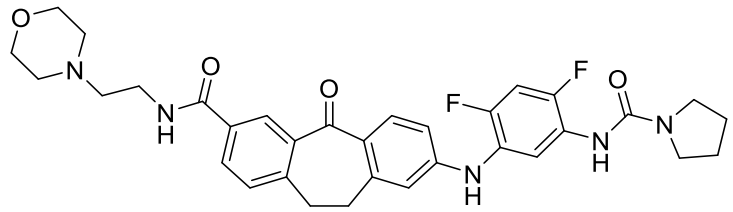
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 41 mg 2-(5-amino-2,4-difluorophenyl)-1-(4-isopropylphenyl)ethan-1-one were used to obtain 42 mg of the product as yellow solid.

$C_{39}H_{39}F_2N_3O_4$ (Mr =670.76)

Yield	49%
HPLC	96% (t_r = 8.328 min)
ESI-MS	m/z 653.1 $[M+H]^+$
IR (ATR)	[cm^{-1}] 1635, 1604, 1577, 1512, 1400, 1353, 1258, 1217, 1143, 1113, 1054, 914, 830, 786, 759
MP	188,5 °C
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.35 (d, *J* = 1.8 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 1H), 7.99 – 7.94 (m, 3H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.31 – 7.26 (m, 2H), 7.07 (bs, *J* = 2.5 Hz, 1H), 6.95 (t, *J* = 11.9, 7.5 Hz, 1H), 6.82

	(dd, *J* = 8.8, 2.4 Hz, 1H), 6.67 (d, *J* = 2.2 Hz, 1H), 5.96 (s, 1H), 4.27 (s, 2H), 3.81 – 3.76 (m, 4H), 3.61 (dd, *J* = 11.2, 5.5 Hz, 2H), 3.18 – 3.06 (m, *J* = 9.7, 3.7 Hz, 4H), 2.97 (qt, 1H), 2.68 (t, *J* = 5.7 Hz, 2H), 2.59 (s, 4H), 1.28 (s, 3H), 1.27 (s, 3H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 195.59, 191.51, 166.93, 156.74 (dd, J = 245.5, 11.3 Hz), 155.34, 153.19 (d, *J* = 11.3 Hz), 148.11, 145.46, 145.27, 139.16, 134.27, 134.16, 132.97, 131.25, 129.45, 129.15, 128.96, 128.74, 127.02, 125.89 – 125.66 (m), 124.79 (dd, *J* = 12.1, 3.6 Hz), 118.36 (dd, *J* = 17.1, 4.1 Hz), 114.75, 113.43, 104.69 (dd, *J* = 27.3, 23.9 Hz), 66.57, 57.35, 53.44, 37.95, 36.07, 35.93, 34.79, 34.40, 34.23, 23.75, 22.44, 14.17

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)pyrrolidine-1-carboxamide (138)

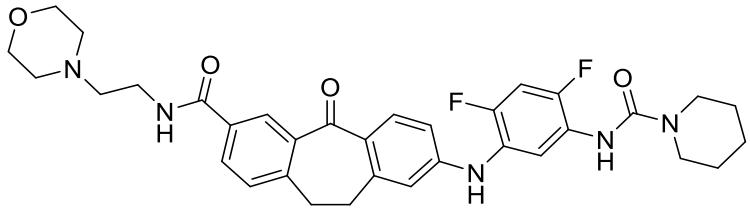


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 100 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 65 mg of N-(5-amino-2,4-difluorophenyl)-pyrrolidine-1-carboxamide were used to obtain 81 mg of the product as yellow solid.

$C_{33}H_{30}F_2N_6O_4$ (Mr =612.67)

Yield	52%
HPLC	95% (t_r = 4.986 min)
ESI-MS	m/z 602.0 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1635, 1601, 1579, 1527, 1436, 1399, 1353, 1310, 1260, 1189, 1112, 1069, 859, 785, 749, 722
MP	205.7°C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.26 (d, J = 5.7 Hz, 1H), 8.18 (t, J = 8.5 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.91 (dd, J = 7.8, 1.8 Hz, 1H), 7.24 (t, 1H), 6.98 (t, J = 4.8 Hz, 1H), 6.87 (t, J = 10.2 Hz, 1H), 6.81 (dd, J = 8.8, 2.1 Hz, 1H), 6.66 (d, J = 8.3 Hz, 1H), 6.32 (d, J = 3.0 Hz, 1H), 6.25 (d, J = 18.4 Hz, 1H), 3.70 (t, 4H), 3.54 (dd, J = 11.3, 5.8 Hz, 2H), 3.44 (t, J = 6.5 Hz, 4H), 3.07 (dd, J = 22.7, 9.2 Hz, 4H), 2.58 (t, J = 6.1 Hz, 2H), 2.48 (s, 4H), 1.95 (s, 4H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 191.53, 166.93, 153.37, 150.15 (dd, J = 169.6, 11.3 Hz), 148.13, 147.74 (dd, J = 167.5, 11.1 Hz), 145.42, 145.13, 139.23, 134.16, 133.05, 131.22, 129.28, 128.74, 128.55, 124.52 (dd, J = 12.0, 3.4 Hz), 124.14 (dd, J = 10.9, 3.6 Hz), 115.98, 114.83, 113.34, 103.79 (t, J = 24.6 Hz), 100.41, 67.00, 57.15, 53.47, 45.91, 36.39, 35.92, 34.69, 25.62, 22.40, 14.13

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)piperidine-1-carboxamide (139)

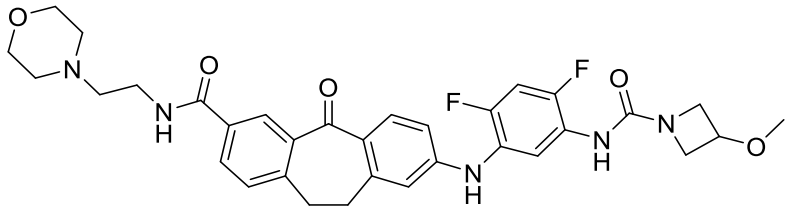


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 80 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 54 mg of N-(5-amino-2,4-difluorophenyl)piperidine-1-carboxamide were used to obtain 118 mg of the product as yellow solid.

$C_{34}H_{37}F_2N_5O_4$ (Mr =617.70)

Yield	96%
HPLC	97% (t_r = 5.124 min)
ESI-MS	m/z 616.9 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1636, 1601, 1577, 1508, 1437, 1400, 1353, 1252, 1113, 1019, 859, 753, 668
MP	203,5 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.38 (s, 1H), 8.08 – 7.86 (m, 4H), 7.20 (d, J = 7.9 Hz, 1H), 6.88 (t, J = 10.2 Hz, 1H), 6.79 (dd, J = 8.7, 1.8 Hz, 1H), 6.70 – 6.60 (m, 2H), 6.35 (s, 1H), 3.90 (s, 4H), 3.75 (d, J = 3.9 Hz, 2H), 3.46 – 3.40 (m, J = 5.3 Hz, 4H), 3.12 – 2.84 (m, 10H), 1.61 (s, 6H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 191.64, 167.22, 154.42, 150.62 (dd, J = 243.5, 11.0 Hz), 148.91 (d, J = 11.3 Hz), 148.49 (t, J = 2.6 Hz), 148.18, 147.51 (d, J = 10.8 Hz), 145.48, 145.35, 139.37, 134.14, 132.37, 131.02, 129.51, 129.23, 128.73, 124.52 (dd, J = 11.9, 2.9 Hz), 124.20 (dd, J = 11.0, 3.2 Hz), 116.80, 114.85, 113.33, 103.94 (t, J = 24.7 Hz), 65.28, 57.66, 53.16, 45.35, 35.89, 35.35, 34.66, 29.81, 25.74, 24.37

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulen-2-yl)amino)phenyl)-3-methoxyazetidine-1-carboxamide (140)



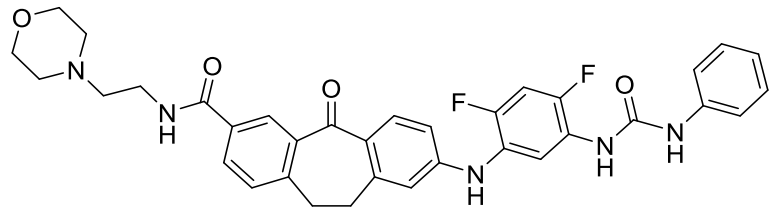
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-

dibenzo[a,d][7]annulene-3-carboxamide and 37 mg of N-(5-amino-2,4-difluorophenyl)-3-methoxyazetidine-1-carboxamide were used to obtain 18 mg of the product as yellow solid.

$C_{33}H_{35}F_2N_5O_5$ (Mr =619.67)

Yield	22%
HPLC	99% (t_r = 4.812 min)
ESI-MS	m/z 618.0 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1635, 1601, 1576, 1521, 1436, 1392, 1352, 1258, 1193, 1109, 1066, 1018, 858, 798, 753, 719, 652
MP	186.5°C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.27 (s, 1H), 8.11 (dd, J = 13.5, 8.6 Hz, 2H), 7.91 (d, J = 6.5 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.00 (s, 1H), 6.88 (t, J = 10.2 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 6.69 (s, 1H), 6.22 (d, J = 14.2 Hz, 2H), 4.21 (d, J = 5.2 Hz, 3H), 3.94 (d, J = 5.3 Hz, 2H), 3.74 – 3.68 (m, 4H), 3.55 (dd, J = 5.3 Hz, 2H), 3.29 (s, 3H), 3.08 (dd, J = 21.4, 8.8 Hz, 4H), 2.60 (t, J = 5.8 Hz, 2H), 2.50 (s, 4H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.61, 166.96, 155.60, 150.15 (dd, J = 186.9, 11.1 Hz), 148.88, 147.23 (dd, J = 184.7, 11.0 Hz), 145.44, 145.17, 139.23, 134.17, 133.04, 131.23, 129.34, 128.95, 128.61, 124.73 (dd, J = 12.0, 3.0 Hz), 123.44 (dd, J = 10.9, 3.6 Hz), 115.55, 114.92, 113.50, 103.97 (t, J = 24.5 Hz), 68.70, 66.95, 57.18, 56.39, 56.27, 53.48, 36.36, 35.92, 34.70, 31.32

8-((2,4-difluoro-5-(3-phenylureido)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (141)



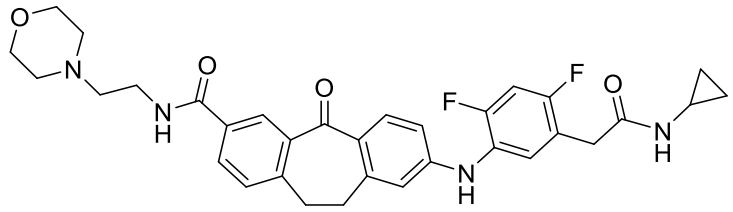
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 70 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 50 mg of 1-(5-amino-2,4-difluorophenyl)-3-phenylurea were used to obtain 59 mg of the product as yellow solid.

$C_{35}H_{33}F_2N_5O_4$ (Mr =625.3)

Yield	53%
HPLC	96% (t_r = 6.188 min)
ESI-MS	m/z 626.2 $[M+H]^+$
IR (ATR)	[cm^{-1}] 1629, 1600, 1577, 1534, 1497, 1438, 1400, 1353, 1310. 1261, 1188, 1112, 858, 749, 690
MP	209,7 °C

^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.32 (d, *J* = 1.8 Hz, 1H), 8.18 (t, *J* = 8.5 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.91 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.70 (s, 1H), 7.50 (d, *J* = 13.6 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.27 (d, *J* = 6.6 Hz, 2H), 7.25 – 7.23 (m, 1H), 7.09 – 7.00 (m, *J* = 7.2 Hz, 2H), 6.87 – 6.78 (m, 2H), 6.67 (d, *J* = 3.7 Hz, 1H), 6.01 (s, 1H), 3.73 (t, 4H), 3.60 – 3.55 (m, 2H), 3.15 – 3.04 (m, 4H), 2.62 (t, *J* = 5.9 Hz, 2H), 2.52 (s, 4H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.73, 167.44, 153.00, 152.7 (dd, J =246.9, 11.2 Hz),151.6 (dd, J = 245.6, 9.9 Hz), 149.75 (d, *J* = 10.5 Hz), 148.88 (d, *J* = 11.5 Hz), 148.01, 147.33 (d, *J* = 11.2 Hz), 145.53, 145.47, 139.37, 138.23, 134.37, 134.27, 132.95, 131.34, 131.14, 129.52, 129.34, 129.00, 128.82, 124.58 (dd, *J* = 11.9, 3.1 Hz), 124.12, 123.62 (dd, *J* = 11.1, 3.0 Hz), 120.67, 116.12, 114.93, 114.88, 113.56, 104.09 (t, *J* = 24.5 Hz), 66.99, 57.11, 53.51, 36.44, 35.94, 34.76

8-((5-(2-(cyclopropylamino)-2-oxoethyl)-2,4-difluorophenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (142)



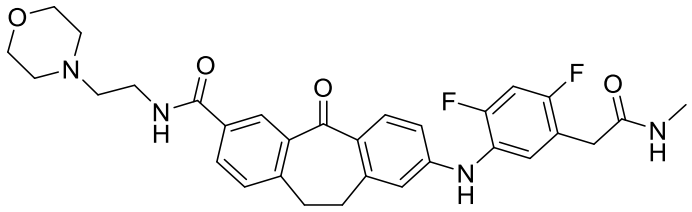
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 60 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 37 mg of 2-(5-amino-2,4-difluorophenyl)-N-cyclopropylacetamide were used to obtain 27 mg of the product as yellow solid.

$C_{33}H_{34}F_2N_4O_4$ (Mr =588.71)

Yield	31%
HPLC	99% (t_r = 4.926 min)
ESI-MS	m/z 589.2 $[M+H]^+$
IR (ATR)	[cm^{-1}] 1636, 1601, 1577, 1508, 1437, 1400, 1353, 1259, 1169, 1144, 1111, 914, 859, 834, 785, 753
MP	156,8 °C
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.33 (d, *J* = 1.9 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 1H), 7.94 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.34 (t, 1H), 7.28 (d, *J* = 7.9, 3.4 Hz, 1H), 6.99 (bs, *J* = 15.9 Hz, 1H), 6.90 (t, *J* = 12.8, 6.6 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.67 (d, *J* = 2.1 Hz, 1H), 6.10 (s, 1H), 5.91 (bs, 1H), 3.75 (t, 4H), 3.58 (dd, *J* = 11.3, 5.7 Hz, 2H), 3.46 (s, 2H), 3.18 – 3.06 (m, *J* = 9.6, 5.3 Hz, 4H), 2.71 – 2.66 (m, 1H), 2.64 (t, *J* = 6.0 Hz, 2H), 2.58 – 2.51 (m, 4H), 0.79 – 0.71 (m, 2H), 0.51 – 0.44 (m, 2H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.58, 170.82, 166.93, 156.62 (dd, J = 213.1, 11.4 Hz), 154.17 (dd, J = 215.8, 11.5 Hz), 147.89, 145.47, 145.27, 139.12, 134.27, 133.12, 131.32, 129.52, 129.33, 128.85, 125.25 (d, J = 3.3 Hz), 125.12, 118.59 (dd, J = 16.8, 3.7 Hz),

114.97, 113.55, 104.77 (dd, J = 27.0, 24.0 Hz), 77.48, 77.36, 77.16, 76.84, 66.87, 57.22, 53.49, 36.27, 36.03, 35.95, 34.82, 32.65, 24.13, 23.04, 8.55, 6.76

8-((2,4-difluoro-5-(2-(methylamino)-2-oxoethyl)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (143)

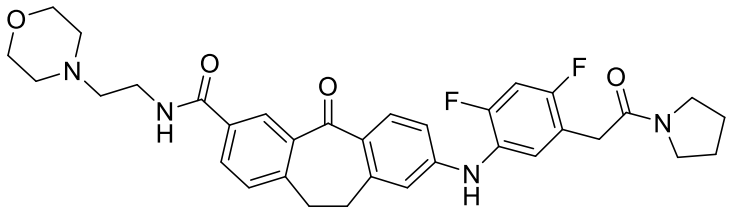


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 37 mg of 2-(5-amino-2,4-difluorophenyl)-N-methylacetamide were used to obtain 39 mg of the product as yellow solid.

$C_{31}H_{32}F_2N_4O_4$ (Mr =609.67)

Yield	53%
HPLC	99% (t_r = 4.457 min)
ESI-MS	m/z 610.2 $[M+H]^+$
IR (ATR)	[cm^{-1}] 1636, 1601, 1577, 1560, 1508, 1400, 1352, 1260, 1214, 1148, 1112, 912, 853, 784, 758, 724
MP	126,7 °C
^{1}H NMR (400 MHz, $CDCl_3$ + MeOD)	δ 8.30 (d, *J* = 1.8 Hz, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.91 – 7.85 (m, 1H), 7.27 (d, *J* = 9.5 Hz, 1H), 7.24 (s, 1H), 6.87 (t, *J* = 9.7 Hz, 1H), 6.78 – 6.73 (m, *J* = 8.7, 2.0 Hz, 1H), 6.59 (s, 1H), 3.76 – 3.68 (m, 4H), 3.54 (t, 2H), 3.44 (s, 2H), 3.08 (dd, *J* = 25.3, 9.0 Hz, 4H), 2.73 (s, 3H), 2.67 – 2.47 (m, *J* = 32.1 Hz, 6H)
^{13}C NMR (101 MHz, $CDCl_3$ + MeOD)	δ 191.90, 170.73 (d, *J* = 3.9 Hz), 167.40, 156.88 (dd, J = 202.3, 11.3 Hz), 154.44 (dd, J = 203.2, 10.7 Hz), 148.45 (d, *J* = 7.4 Hz), 145.56, 145.38, 139.15, 134.10, 132.68, 131.11, 129.37, 128.97, 128.61, 125.78, 124.98 (d, *J* = 13.0 Hz), 118.58 (d, *J* = 3.7 Hz), 118.41 (d, *J* = 3.6 Hz), 114.51, 113.21, 104.68 (dd, *J* = 26.7, 24.1 Hz), 66.55, 57.37, 53.38, 36.07, 35.87, 35.69, 34.68, 26.43

8-((2,4-difluoro-5-(2-oxo-2-(pyrrolidin-1-yl)ethyl)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (144)

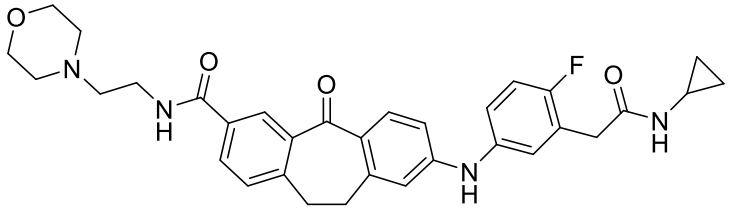


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 34 mg of 2-(5-amino-2,4-difluorophenyl)-1-(pyrrolidin-1-yl)ethan-1-one were used to obtain 12 mg of the product as yellow solid.

$C_{34}H_{36}F_2N_4O_4$ (Mr =602.68)

Yield	16%
HPLC	95% (t_r = 5.668 min)
ESI-MS	m/z 603.5 $[M+H]^+$
IR (ATR)	[cm^{-1}] 1628, 1601, 1577, 1508, 1437, 1400, 1354, 1258, 1169, 1146, 1113, 856, 786, 757
MP	140,2 °C
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.34 (d, *J* = 1.8 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 1H), 7.96 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.36 (t, *J* = 8.3 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.01 (bs, 1H), 6.90 (t, *J* = 9.7 Hz, 1H), 6.82 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.66 (d, *J* = 2.0 Hz, 1H), 6.01 (s, 1H), 3.77 (t, 4H), 3.63 – 3.58 (m, *J* = 9.7 Hz, 4H), 3.50 (p, 4H), 3.13 (td, *J* = 9.7, 5.2 Hz, 4H), 2.67 (t, *J* = 5.8 Hz, 2H), 2.58 (s, 4H), 1.99 (p, 2H), 1.88 (p, 2H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.55, 168.06, 166.95, 156.76 (dd, J = 230.4, 11.1 Hz), 154.31 (dd, J = 232.8, 11.6 Hz), 148.19, 145.49, 145.31, 139.20, 134.29, 133.04, 131.33, 129.51, 129.14, 128.86, 125.71 (d, *J* = 3.0 Hz), 124.83, 124.75 (dd, *J* = 11.8, 3.3 Hz), 124.68, 118.74 (dd, *J* = 17.0, 3.6 Hz), 116.05, 114.82, 113.41, 104.51 (dd, *J* = 27.3, 23.8 Hz), 66.76, 57.31, 53.49, 46.96, 46.23, 36.18, 35.98, 34.84, 34.07, 26.30, 24.53

8-((3-(2-(cyclopropylamino)-2-oxoethyl)-4-fluorophenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (145)

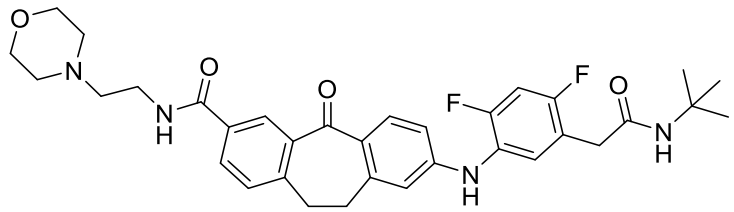


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 34 mg of 2-(5-amino-2-fluorophenyl)-N-cyclopropylacetamide were used to obtain 41 mg of the product as yellow solid.

$C_{33}H_{35}FN_4O_4$ (Mr =570.67)

Yield	55%
HPLC	100% (t_r = 3.510 min)
ESI-MS	m/z 571.7 $[M+H]^+$
IR (ATR)	[cm^{-1}] 1628, 1601, 1577, 1508, 1437, 1400, 1354, 1258, 1169, 1146, 1113, 856, 786, 757
^1H NMR (400 MHz, $CDCl_3$)	δ 8.32 (d, *J* = 3.9 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.90 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.25 (d, *J* = 5.4 Hz, 1H), 7.09 (ddd, *J* = 8.7, 4.4, 2.9 Hz, 1H), 7.03 (dd, *J* = 6.5, 2.7 Hz, 1H), 6.98 (t, *J* = 11.4, 6.5 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.65 (d, *J* = 2.3 Hz, 1H), 3.76 – 3.72 (m, 4H), 3.56 (t, *J* = 5.8 Hz, 2H), 3.13 – 3.02 (m, 4H), 2.72 (s, 4H), 2.67 – 2.61 (m, 3H), 2.58 (s, 2H), 0.75 – 0.67 (m, 2H), 0.48 – 0.41 (m, 2H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.62, 171.81, 167.40, 158.18, 156.98 (d, J = 242.1 Hz), 148.97, 145.73, 145.38, 139.25, 137.01 (d, *J* = 2.7 Hz), 134.29, 132.66, 131.08, 129.33, 129.03, 128.10, 124.41 (d, *J* = 3.6 Hz), 123.16 (d, *J* = 17.1 Hz), 121.59 (d, *J* = 8.1 Hz), 116.24, 116.00, 114.19, 113.06, 66.46, 57.39, 53.37, 36.40, 36.01, 34.72, 22.77, 6.44

8-((5-(2-(tert-butylamino)-2-oxoethyl)-2,4-difluorophenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (146)



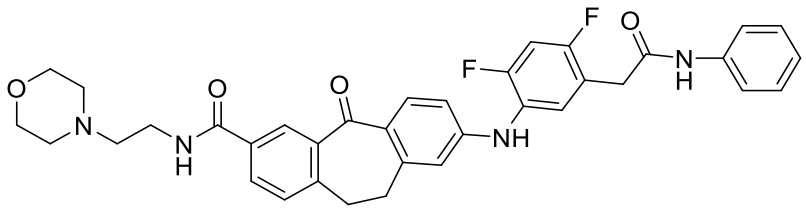
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 34 mg of 2-(5-amino-2,4-difluorophenyl)-N-(tert-butyl)acetamide were used to obtain 37 mg of the product as yellow solid.

$C_{34}H_{38}F_2N_4O_4$ (Mr =604.67)

Yield	47%
HPLC	99% (t_r = 5.950 min)
ESI-MS	m/z 605.5 $[M+H]^+$
IR (ATR)	[cm^{-1}] 1636, 1601, 1577, 1507, 1448, 1400, 1353, 1307, 1259, 1214, 1144, 1112, 860, 785, 757, 725
MP	135,9 °C
^1H NMR (400 MHz, $CDCl_3$)	δ 8.34 (d, *J* = 1.7 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 1H), 7.95 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.34 (t, *J* = 8.3 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 6.97 (bs, *J* = 12.8 Hz, 1H), 6.91 (t, *J* = 9.7 Hz, 1H), 6.83 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.07 (s, 1H), 5.48 (s, 1H), 3.75 (t, 4H), 3.58 (dd, *J* = 11.2, 5.6 Hz, 2H), 3.42

	(s, 2H), 3.12 (td, *J* = 9.5, 4.9 Hz, 4H), 2.64 (t, *J* = 5.9 Hz, 2H), 2.60 – 2.48 (m, 4H), 1.33 (s, 9H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.54, 168.65, 166.91, 157.78 (d, *J* = 10.8 Hz), 156.98 (d, J = 242.1 Hz), 153.09 (d, *J* = 11.7 Hz), 148.00, 145.47, 145.29, 139.12, 134.28, 133.11, 131.33, 129.52, 129.27, 128.84, 125.27 (d, *J* = 3.3 Hz), 125.01 (dd, *J* = 12.0, 3.3 Hz), 119.05 (dd, *J* = 16.9, 3.9 Hz), 114.89, 113.48, 104.72 (dd, *J* = 26.9, 23.9 Hz), 66.86, 57.24, 53.49, 51.71, 37.11, 36.25, 35.94, 34.84, 28.85

8-((2,4-difluoro-5-(2-oxo-2-(phenylamino)ethyl)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (147)

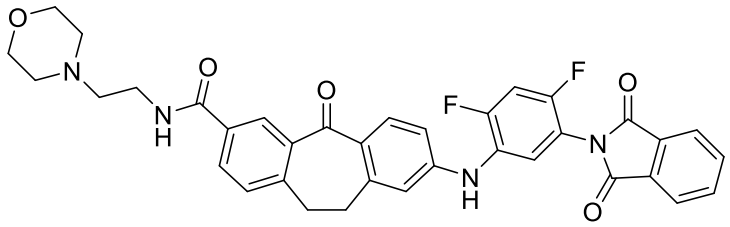


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 35 mg of 2-(5-amino-2,4-difluorophenyl)-N-phenylacetamide were used to obtain 38 mg of the product as yellow solid.

$C_{36}H_{34}F_2N_4O_4$ (Mr =624.7)

Yield	49%
HPLC	98% (t_r = 4.755 min)
ESI-MS	m/z 625.3 $[M+H]^+$
IR (ATR)	[cm^{-1}] 1630, 1600, 1577, 1534, 1497, 1400, 1353, 1310, 1261, 1188, 1112, 858, 744
MP	163,9 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.35 (d, J = 1.7 Hz, 2H), 8.15 (d, J = 8.7 Hz, 2H), 7.97 (dd, J = 7.8, 1.9 Hz, 2H), 7.51 – 7.41 (m, 8H), 7.33 – 7.28 (m, 6H), 7.11 (t, J = 7.4 Hz, 2H), 6.99 (t, J = 26.3, 16.5 Hz, 3H), 6.86 (dd, J = 8.7, 2.3 Hz, 2H), 6.71 (d, J = 2.2 Hz, 2H), 5.94 (s, 2H), 3.81 – 3.75 (m, 8H), 3.69 (s, 4H), 3.63 – 3.58 (m, 4H), 3.12 (td, J = 10.0, 3.9 Hz, 7H), 2.71 – 2.64 (m, 4H), 2.58 (bs, 8H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.64, 167.55, 166.93, 147.60 (d, J = 249.1 Hz), 145.49, 145.31, 139.12, 137.72, 134.34, 133.08, 131.37, 130.36, 129.65, 129.58, 129.21, 128.91, 125.54 (d, J = 2.7 Hz), 124.80, 120.01, 115.07, 113.83, 105.07 (dd, J = 24.3, 2.7 Hz), 66.72, 57.32, 53.48, 37.31, 36.15, 35.91, 34.84

8-((5-(1,3-dioxoisoindolin-2-yl)-2,4-difluorophenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (148)

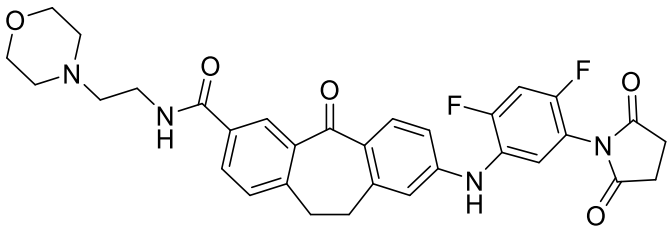


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 100 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 83 mg of 2-(5-amino-2,4-difluorophenyl)isoindoline-1,3-dione were used to obtain 62 mg of the product as yellow solid.

$C_{36}H_{30}F_2N_4O_5$ (Mr =636.22)

Yield	39%
HPLC	95% (t_r = 6.567 min)
ESI-MS	m/z 635.3 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1722, 1635, 1577, 1522, 1437, 1395, 1352, 1261, 1206, 1170, 1139, 1112, 1070, 1007, 861, 786, 757, 718
MP	228.1°C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.32 (s, 1H), 8.12 (d, J = 8.7 Hz, 1H), 8.05 – 7.88 (m, J = 5.4 Hz, 3H), 7.87 – 7.70 (m, J = 3.2 Hz, 2H), 7.41 (t, J = 7.7 Hz, 1H), 7.27 (d, J = 5.5 Hz, 1H), 7.19 – 6.99 (m, J = 9.4 Hz, 2H), 6.94 (d, J = 9.2 Hz, 1H), 6.81 (s, 1H), 6.29 (s, 1H), 3.75 (s, 4H), 3.67 – 3.48 (m, 2H), 3.25 – 3.03 (m, 4H), 2.75 – 2.61 (m, 2H), 2.56 (s, 4H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.63, 166.87, 166.42, 155.23 (dd, J = 213.4, 6.3 Hz), 152.67 (dd, J = 228.3, 11.1 Hz), 147.07, 147.03, 145.32 (d, J = 16.6 Hz), 139.07, 134.76, 134.25, 133.16, 131.94, 131.34, 130.09, 129.54, 128.87, 126.12 (dd, J = 12.7, 3.6 Hz), 124.15, 122.40, 115.70 (d, J = 3.6 Hz), 115.49 (t, J = 4.5 Hz), 114.32, 105.85 (t, J = 24.7 Hz), 66.76, 57.32, 53.50, 36.25, 35.87, 34.81

8-((5-(2,5-dioxopyrrolidin-1-yl)-2,4-difluorophenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (149)



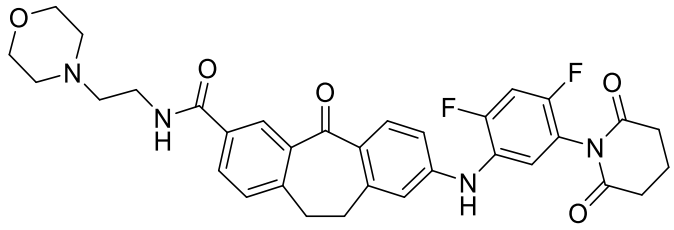
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-

dibenzo[a,d][7]annulene-5-carboxamide and 32 mg 1-(5-amino-2,4-difluorophenyl)pyrrolidine-2,5-dione were used to obtain 21 mg of the product as yellow solid.

$C_{32}H_{30}F_2N_4O_5$ (Mr =588.61)

Yield	28%
HPLC	95% (t_r = 4.312 min)
ESI-MS	m/z 587.7 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1717, 1635, 1603, 1579, 1522, 1437, 1400, 1352, 1262, 1173, 1112, 912, 859, 786
^1H NMR (400 MHz, $CDCl_3$)	δ 8.32 (d, *J* = 1.9 Hz, 1H), 8.11 (d, 1H), 7.95 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.29 – 7.25 (m, *J* = 8.7, 6.0 Hz, 2H), 7.13 – 7.02 (m, 2H), 6.90 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.77 (d, *J* = 2.2 Hz, 1H), 6.20 (s, 1H), 3.78 – 3.73 (m, 4H), 3.58 (dd, *J* = 11.3, 5.7 Hz, 2H), 3.12 (td, *J* = 9.5, 5.2 Hz, 4H), 2.94 (s, 4H), 2.65 (t, *J* = 6.0 Hz, 2H), 2.61 – 2.51 (m, 4H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.76, 175.34, 166.87, 154.84 (dd, J = 188.2, 11.4 Hz), 152.35 (dd, J = 189.9, 11.3 Hz), 151.40 (d, *J* = 11.7 Hz), 146.14 (d, J = 243.8 Hz), 145.24, 138.99, 134.19, 133.07, 131.39, 130.01, 129.57, 128.83, 126.17 (dd, *J* = 12.6, 3.4 Hz), 121.62, 115.85 (dd, *J* = 14.1, 3.8 Hz), 115.56, 114.28, 105.85 (t, *J* = 24.6 Hz), 66.75, 57.28, 53.46, 36.19, 35.82, 34.74, 28.70

8-((5-(2,6-dioxopiperidin-1-yl)-2,4-difluorophenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (150)



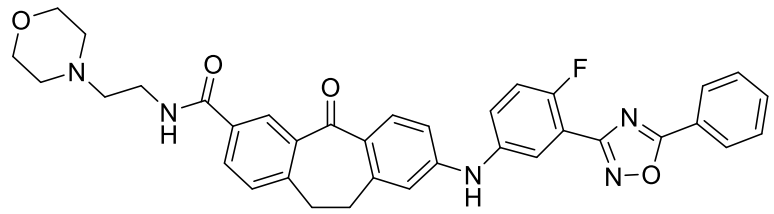
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-5-carboxamide and 34 mg 1-(5-amino-2,4-difluorophenyl)piperidine-2,6-dione were used to obtain 58 mg of the product as yellow solid.

$C_{32}H_{30}F_2N_4O_5$ (Mr =602.64)

Yield	74%
HPLC	100% (t_r = 5.036 min)
ESI-MS	m/z 602.0 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1577, 1522, 1507, 1482, 1437, 1400, 1352, 1251, 1196, 1141, 1110, 1007, 914, 854, 785, 759, 721
MP	156,8 °C

^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.35 (t, 1H), 8.33 (d, *J* = 1.6 Hz, 1H), 8.14 (d, *J* = 8.7 Hz, 1H), 7.96 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.55 (s, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 6.94 (t, *J* = 10.2 Hz, 1H), 6.87 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.75 (d, *J* = 2.0 Hz, 1H), 6.08 (s, 1H), 3.78 (t, 4H), 3.62 (dd, *J* = 11.1, 5.5 Hz, 2H), 3.19 – 3.09 (m, *J* = 20.3, 9.3 Hz, 4H), 2.70 (t, *J* = 5.6 Hz, 2H), 2.61 (s, 4H), 2.48 (t, *J* = 7.3 Hz, 2H), 2.43 (t, *J* = 7.1 Hz, 2H), 2.03 (p, *J* = 7.2 Hz, 2H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.71, 173.74, 170.70, 166.96, 150.43 (dd, J = 246.1, 9.9 Hz), 147.56, 145.47, 145.28, 139.25, 134.26, 132.96, 131.29, 129.47, 129.41, 128.87, 124.87 (dd, *J* = 11.7, 3.5 Hz), 122.71 (dd, *J* = 11.3, 3.6 Hz), 115.88, 115.08, 113.76, 104.21 (t, *J* = 24.6 Hz), 66.62, 57.38, 53.47, 51.85, 36.37, 35.95, 34.78, 32.98, 20.71

8-((4-fluoro-3-(5-phenyl-1,2,4-oxadiazol-3-yl)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (151)

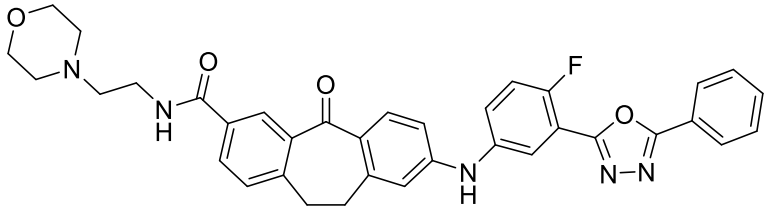


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-5-carboxamide and 35 mg 4-fluoro-3-(5-phenyl-1,2,4-oxadiazol-3-yl)aniline (kindly provided by Juliander Rainer) were used to obtain 12 mg of the product as yellow solid.

$C_{36}H_{32}FN_5O_4$ (Mr =617.68)

Yield	14%
HPLC	99% (t_r = 7.644 min)
ESI-MS	m/z 618.9 $[M+H]^+$
IR (ATR)	[cm^{-1}] 1633, 1601, 1561, 1528, 1478, 1448, 1400, 1340, 1262, 1216, 1174, 1114, 1065, 964, 915, 860, 783, 731, 690
MP	184,9 °C
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.38 (d, *J* = 1.7 Hz, 1H), 8.21 – 8.16 (m, 3H), 8.01 – 7.96 (m, *J* = 6.1, 2.4 Hz, 2H), 7.61 (dt, *J* = 2.6, 1.9 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.36 – 7.32 (m, 1H), 7.30 (s, 1H), 7.27 (d, *J* = 5.2 Hz, 1H), 7.25 – 7.22 (m, 1H), 6.92 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.73 (d, *J* = 2.2 Hz, 1H), 6.28 (s, 1H), 3.81 (t, 2H), 3.69 – 3.60 (m, *J* = 11.8, 6.2 Hz, 4H), 3.19 – 3.08 (m, 4H), 2.75 (t, 2H), 2.66 (s, 4H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.52, 175.61, 167.01, 165.62 (d, *J* = 5.8 Hz), 157.08 (d, J = 255.0 Hz), 148.36, 145.61, 145.30, 139.21, 137.13 (d, *J* = 3.0 Hz), 134.48, 133.15, 132.91, 131.26, 129.50, 129.32, 129.20, 128.37, 125.79, 125.71, 124.05, 123.59 (d, *J* = 2.3 Hz), 118.07, 117.85, 116.36, 116.22, 114.72, 113.51, 66.29, 57.49, 53.42, 36.01, 35.90, 34.83, 29.84

8-((4-fluoro-3-(5-phenyl-1,3,4-oxadiazol-2-yl)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (152)

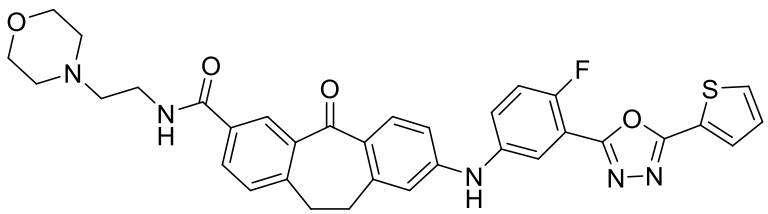


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-5-carboxamide and 35 mg 4-fluoro-3-(5-phenyl-1,3,4-oxadiazol-2-yl)aniline (kindly provided by Juliander Rainer) were used to obtain 59 mg of the product as yellow solid.

$C_{36}H_{32}FN_5O_4$ (Mr =617.68)

Yield	74%
HPLC	100% (t_r = 7.313 min)
ESI-MS	m/z 617.0 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1636, 1604, 1577, 559, 1534, 1500, 1449, 1354. 1264, 1113, 1069, 861, 823, 753, 689
MP	169,7 °C
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.35 (s, 1H), 8.16 – 8.09 (m, 3H), 8.00 – 7.92 (m, *J* = 9.5, 6.8, 2.1 Hz, 2H), 7.57 – 7.49 (m, 3H), 7.41 – 7.35 (m, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 9.4 Hz, 1H), 7.11 (bs, *J* = 22.9 Hz, 1H), 6.92 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.75 (d, *J* = 11.9 Hz, 2H), 3.80 – 3.73 (m, 4H), 3.60 (dd, *J* = 11.7, 6.2 Hz, 2H), 3.19 – 3.04 (m, 4H), 2.67 (t, *J* = 5.7 Hz, 2H), 2.66 – 2.49 (m, *J* = 33.0 Hz, 4H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.45, 166.99, 165.30 (d, *J* = 1.2 Hz), 161.36 (d, *J* = 4.9 Hz), 157.21, 155.95 (d, J = 255.1 Hz), 148.01, 145.56, 145.25, 139.10, 137.72 (d, *J* = 2.9 Hz), 134.39, 133.11, 132.14, 131.27, 129.50, 129.34, 129.27, 128.97, 127.19, 125.95 (d, *J* = 8.1 Hz), 123.69, 121.64, 118.28, 118.06, 115.01, 113.71, 113.23, 113.10, 66.79, 57.28, 53.48, 36.24, 35.96, 34.81

8-((4-fluoro-3-(5-(thiophen-2-yl)-1,3,4-oxadiazol-2-yl)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (153)



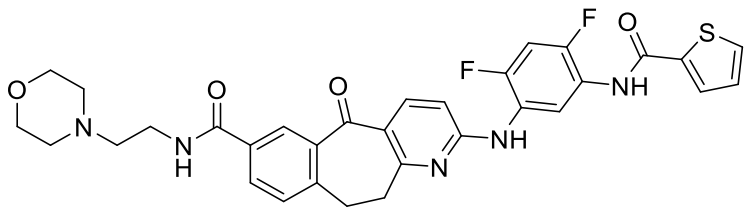
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 50 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-5-carboxamide and 46 mg 4-fluoro-3-(5-(thiophen-2-yl)-1,3,4-oxadiazol-2-

yl)aniline (kindly provided by Juliander Rainer) were used to obtain 38 mg of the product as yellow solid.

$C_{34}H_{30}FN_5O_4S$ (Mr =623.70)

Yield	35%
HPLC	98% (t_r = 6.824 min)
ESI-MS	m/z 625.0 $[M+H]^+$
IR (ATR)	[cm^{-1}] 1636, 1602, 1577, 1526, 1437, 1400, 1353, 1309, 1258, 1168, 1143, 1110, 1007, 913, 859, 756, 760, 727
MP	181,6 °C
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.34 (d, *J* = 8.7 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.87 (dd, *J* = 5.8, 2.7 Hz, 1H), 7.81 (d, *J* = 3.7 Hz, 1H), 7.57 (d, *J* = 5.0 Hz, 1H), 7.39 (bs, *J* = 3.3 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.26 – 7.14 (m, 3H), 7.08 (bs, *J* = 33.7 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 1H), 6.74 (s, 1H), 3.76 (t, 4H), 3.60 (t, *J* = 5.5 Hz, 2H), 3.16 – 3.02 (m, 4H), 2.69 (t, *J* = 5.6 Hz, 2H), 2.60 (s, 4H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 191.61, 167.19 (d, *J* = 7.3 Hz), 161.52, 160.79 (d, *J* = 5.0 Hz), 155.75 (dd, J = 254.9, 2.6 Hz), 148.09, 147.98, 145.62, 145.29, 139.09, 137.79 (dd, *J* = 8.1, 2.9 Hz), 134.33, 132.86 (d, *J* = 2.7 Hz), 131.22, 130.80, 130.47, 129.43, 129.08 (d, *J* = 2.1 Hz), 128.43, 125.75 (dd, *J* = 10.5, 8.2 Hz), 124.72, 121.27 (d, *J* = 11.2 Hz), 118.21, 117.98, 114.88 (d, *J* = 5.1 Hz), 113.61 (d, *J* = 4.8 Hz), 112.72 (d, *J* = 13.0 Hz), 66.55, 57.41, 53.43, 36.14, 36.03, 35.94, 34.74

2-((2,4-difluoro-5-(thiophene-2-carboxamido)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxamide (156)



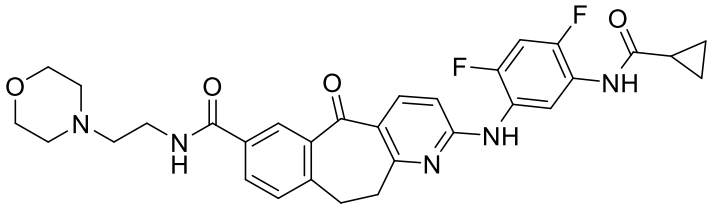
The title compound was synthesized according to the general procedure **4** for saponification of esters, followed by general procedure **2** for amide coupling using TBTU. For the reaction, 35 mg of methyl 2-((2,4-difluoro-5-(thiophene-2-carboxamido)phenyl)amino)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate and 19 mg of 2-morpholinoethan-1-amine were used to obtain 27 mg of the product as yellow solid.

$C_{32}H_{29}F_2N_5O_4S$ (Mr =617.67)

Yield	66%
HPLC	95% (t_r = 5.027 min)
ESI-MS	m/z 616.3 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1635, 1580, 1521, 1490, 1419, 1333, 1308, 1260, 1197, 1169, 1141, 1111, 1066, 839, 793, 716

MP	187.6 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 9.17 (t, J = 8.4 Hz, 1H), 8.39 (d, J = 8.6 Hz, 1H), 8.24 (s, 1H), 7.97 (d, J = 6.9 Hz, 1H), 7.92 (s, 1H), 7.68 (d, J = 3.2 Hz, 1H), 7.58 (d, J = 4.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.14 (t, 1H), 7.05 (s, 1H), 6.97 (t, J = 10.2 Hz, 2H), 6.74 (d, J = 8.6 Hz, 1H), 3.79 – 3.71 (m, 4H), 3.59 (dd, J = 10.8, 5.5 Hz, 2H), 3.37 – 3.17 (m, 4H), 2.65 (t, J = 5.7 Hz, 2H), 2.56 (s, 4H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 190.43, 166.84, 163.64, 159.86, 156.48, 150.16 (dd, J = 149.1, 11.0 Hz), 147.73 (dd, J = 147.2, 11.0 Hz), 146.99 (d, J = 11.1 Hz), 144.81, 141.84, 139.02, 138.67, 133.26, 131.51, 129.31, 129.06, 128.62, 128.10, 125.64, 124.79, 123.99 (dd, J = 10.9, 2.9 Hz), 122.39 (dd, J = 10.7, 3.1 Hz), 115.96, 107.66, 103.72 (t, J = 24.7 Hz), 66.81, 57.25, 53.47, 38.79, 36.23, 33.05, 30.44, 29.82

2-((5-(cyclopropanecarboxamido)-2,4-difluorophenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxamide (157)



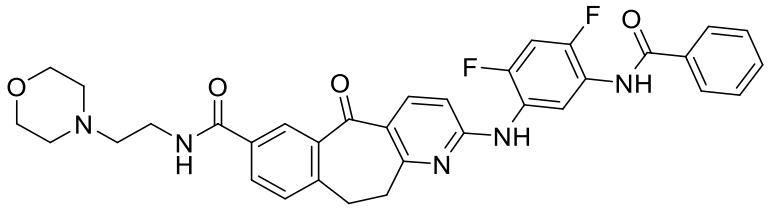
The title compound was synthesized according to the general procedure **4** for saponification of esters, followed by general procedure **2** for amide coupling using TBTU. For the reaction, 30 mg of methyl 2-((5-(cyclopropanecarboxamido)-2,4-difluorophenyl)amino)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate and 10 mg of 2-morpholinoethan-1-amine were used to obtain 29 mg of the product as yellow solid.

$C_{32}H_{29}F_2N_5O_4S$ (Mr =617.67)

Yield	79%
HPLC	100% (t_r = 1.902 min)
ESI-MS	m/z 574.4 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1636, 1581, 1521, 1425, 1334, 1310, 1260, 1191, 1112, 1027, 953, 913, 838, 794, 762
MP	194.8 °C
^{1}H-NMR (600 MHz, $CDCl_3$)	δ 9.00 (t, J = 7.6 Hz, 1H), 8.38 (d, J = 8.8 Hz, 1H), 8.25 (d, J = 1.6 Hz, 1H), 7.98 (dd, J = 7.8, 1.8 Hz, 1H), 7.60 (s, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.08 (s, 1H), 6.98 – 6.87 (m, J = 22.2, 12.0 Hz, 2H), 6.70 (d, J = 8.8 Hz, 1H), 3.76 (t, J = 4.4 Hz, 4H), 3.60 (dd, J = 11.2, 5.6 Hz, 2H), 3.33 – 3.26 (m, J = 7.0, 4.3 Hz, 2H), 3.23 – 3.16 (m, J = 7.2, 4.1 Hz, 2H), 2.67 (t, J = 5.7 Hz, 2H), 2.57 (s, 4H), 1.59 (ddd, J = 12.3, 8.0, 4.5 Hz, 1H), 1.12 – 1.08 (m, 2H), 0.90 – 0.87 (m, 2H)
^{13}C-NMR (151 MHz, $CDCl_3$)	δ 190.92, 172.61, 167.39, 164.16, 157.22, 150.11 (dd, J = 245.0, 10.8 Hz), 148.49 (dd, J = 244.8, 10.3 Hz), 145.36, 142.48, 139.57, 133.79, 132.04, 129.86, 129.21, 126.19,

125.27, 124.13 (d, J = 9.5 Hz), 123.52 (d, J = 8.3 Hz), 116.65, 107.80, 104.21 (t, J = 24.6 Hz), 67.30, 57.84, 54.02, 39.28, 36.73, 33.61, 30.99, 23.00, 16.50, 14.73, 9.03

2-((5-benzamido-2,4-difluorophenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxamide (158)

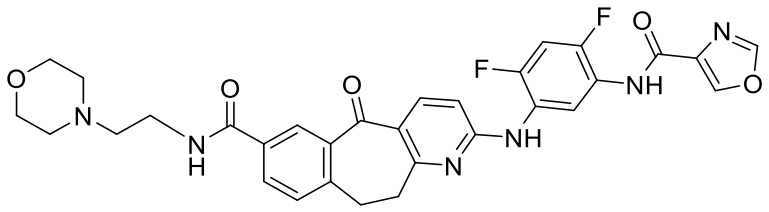


The title compound was synthesized according to the general procedure **4** for saponification of esters, followed by general procedure **2** for amide coupling using TBTU. For the reaction, 29 mg of methyl 2-((5-benzamido-2,4-difluorophenyl)amino)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylateand and 10 mg of 2-morpholinoethan-1-amine were used to obtain 29 mg of the product as yellow solid.

$C_{34}H_{31}F_2N_5O_4$ (Mr =611.65)

Yield	74%
HPLC	95% (t_r = 5.261 min)
ESI-MS	m/z 610.8 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1636, 1580, 1517, 1487, 1427, 1378, 1334, 1306, 1257, 1199, 1171, 1112, 914, 868, 839, 795, 705, 653
MP	147,3 °C
^{1}H-NMR (600 MHz, $CDCl_3$)	δ 9.29 (t, J = 8.5 Hz, 1H), 8.39 (d, J = 9.3 Hz, 1H), 8.25 (d, J = 1.4 Hz, 1H), 8.04 (d, J = 1.2 Hz, 1H), 7.96 (dd, J = 7.8, 1.6 Hz, 1H), 7.90 (d, J = 7.3 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.31 (d, J = 7.9 Hz, 1H), 7.16 – 7.00 (m, 2H), 6.97 (t, J = 10.2 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 3.78 – 3.74 (m, 4H), 3.60 (dd, J = 11.0, 5.5 Hz, 2H), 3.38 – 3.33 (m, 2H), 3.22 – 3.17 (m, 2H), 2.67 (t, J = 5.6 Hz, 2H), 2.58 (s, 4H)
^{13}C-NMR (151 MHz, $CDCl_3$)	δ 190.40, 166.87, 165.65, 163.64, 156.53, 149.75 (dd, J = 200.0, 11.1 Hz), 148.13 (dd, J = 198.0, 11.2 Hz), 144.81, 141.82, 139.01, 134.48, 133.24, 132.41, 131.50, 129.29, 129.07, 128.66, 127.26, 125.64, 124.76, 123.97 (dd, J = 10.9, 2.7 Hz), 122.73 (dd, J = 10.7, 2.9 Hz), 115.88, 107.73, 103.67 (t, J = 24.7 Hz), 66.72, 57.25, 53.44, 38.77, 36.17, 33.05, 30.44, 22.45

N-(2,4-difluoro-5-((7-((2-morpholinoethyl)carbamoyl)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridin-2-yl)amino)phenyl)oxazole-4-carboxamide (159)

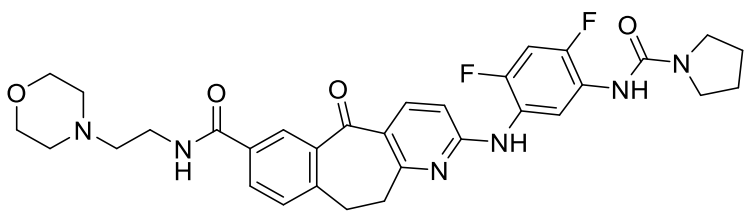


The title compound was synthesized according to the general procedure **4** for saponification of esters, followed by general procedure **2** for amide coupling using TBTU. For the reaction, 12 mg of methyl 2-((2,4-difluoro-5-(oxazole-5-carboxamido)phenyl)amino)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate and 3 mg of 2-morpholinoethan-1-amine were used to obtain 8 mg of the product as yellow solid.

$C_{27}H_{26}F_2N_4O_3$ (Mr =492.53)

Yield	60%
HPLC	93% (t_r = 5.349 min)
ESI-MS	m/z 491.8 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1636, 1582, 1522, 1425, 1374, 1335, 1310, 1257, 1177, 1142, 1112, 1068, 913, 868, 837, 794, 750
MP	160,5 °C
^{1}H-NMR (600 MHz, $CDCl_3$)	δ 9.39 (t, J = 8.5 Hz, 1H), 8.97 (s, 1H), 8.49 (d, 1H), 8.42 (s, 1H), 8.30 (d, J = 11.1 Hz, 1H), 8.06 – 8.02 (m, 1H), 8.01 (s, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.09 – 6.96 (m, J = 20.8, 10.1 Hz, 3H), 6.81 (d, J = 9.6 Hz, 1H), 3.82 (t, 4H), 3.66 (dd, J = 11.0, 5.4 Hz, 2H), 3.47 – 3.42 (m, J = 7.0, 4.3 Hz, 2H), 3.32 – 3.27 (m, 2H), 2.72 (t, 2H), 2.62 (s, 4H)
^{13}C NMR (151 MHz, $CDCl_3$)	δ 190.42, 166.80, 163.66, 158.11, 156.50, 150.79, 149.69 (d, J = 221.5 Hz), 148.07 (dd, J = 232.6, 11.5 Hz), 144.83, 142.34, 141.98, 139.02, 135.95, 133.32, 131.58, 129.36, 128.57, 124.88, 123.92 (dd, J = 10.9, 3.2 Hz), 122.28 (dd, J = 10.4, 3.0 Hz), 115.24, 107.62, 103.87 (t, J = 24.5 Hz), 66.85, 57.20, 53.47, 38.75, 36.23, 33.12

2-((2,4-difluoro-5-(pyrrolidine-1-carboxamido)phenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxamide (160)



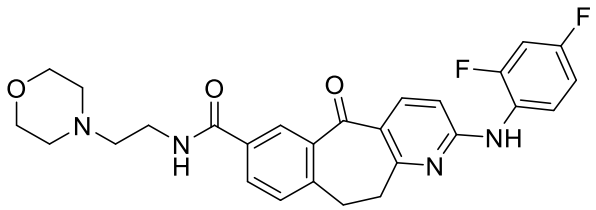
The title compound was synthesized according to the general procedure **4** for saponification of esters, followed by general procedure **2** for amide coupling using TBTU. For the reaction, 49 mg of methyl 2-((2,4-difluoro-5-(pyrrolidine-1-carboxamido)phenyl)amino)-5-oxo-10,11-dihydro-5H-

benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate and 10 mg of 2-morpholinoethan-1-amine were used to obtain 9 mg of the product as yellow solid.

$C_{32}H_{34}F_2N_6O_4$ (Mr =604.66)

Yield	16%
HPLC	100% (t_r = 4.313 min)
ESI-MS	m/z 601.1 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1636, 1582, 1522, 1425, 1374, 1335, 1310, 1257, 1177, 1142, 1112, 1068, 913, 868, 837, 794, 750
MP	153,9 °C
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.72 (t, J = 8.6 Hz, 1H), 8.38 (d, J = 8.9 Hz, 1H), 8.23 (d, J = 1.9 Hz, 1H), 7.97 (dd, J = 7.8, 1.9 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 6.99 – 6.84 (m, J = 13.8, 6.6 Hz, 3H), 6.74 (d, J = 8.8 Hz, 1H), 6.31 (d, J = 3.2 Hz, 1H), 3.73 (t, 4H), 3.57 (dd, J = 11.3, 5.7 Hz, 2H), 3.48 (t, J = 6.6 Hz, 4H), 3.33 – 3.17 (m, 4H), 2.61 (t, J = 6.0 Hz, 2H), 2.55 – 2.44 (m, 4H), 1.99 (t, J = 6.5 Hz, 4H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 190.36, 166.80, 163.63, 157.04, 153.34, 149.95 (dd, J = 104.2, 11.2 Hz), 147.54 (dd, J = 101.9, 11.0 Hz), 147.03 (d, J = 10.6 Hz), 144.77, 142.05, 139.06, 133.35, 131.54, 129.29, 128.45, 124.60, 124.21 (dd, J = 10.7, 3.4 Hz), 123.24 (dd, J = 11.4, 3.3 Hz), 116.09, 106.80, 103.53 (t, J = 24.8 Hz), 67.01, 57.18, 53.51, 45.98, 38.81, 36.34, 33.07, 25.70

2-((2,4-difluorophenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxamide (163)



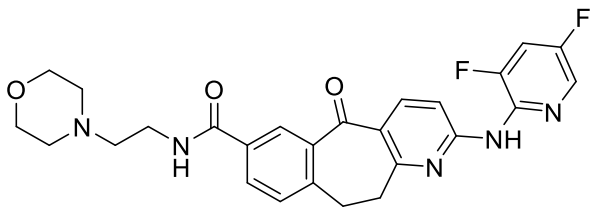
The title compound was synthesized according to the general procedure **4** for saponification of esters, followed by general procedure **2** for amide coupling using TBTU. For the reaction, 30 mg of methyl 2-((2,4-difluorophenyl)amino)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate and 12 mg of 2-morpholinoethan-1-amine were used to obtain 28 mg of the product as yellow solid.

$C_{27}H_{26}F_2N_4O_3$ (Mr =492.53)

Yield	74%
HPLC	100% (t_r = 4.923 min)
ESI-MS	m/z 491.8 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1635, 1580, 1521, 1497, 1431, 1361, 1361, 1335, 1314, 1264, 1185, 1138, 1115, 1091, 956, 848, 975, 755, 726, 706, 652

^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.37 (d, J = 8.8 Hz, 1H), 8.25 (d, J = 1.8 Hz, 1H), 8.06 – 7.98 (m, 1H), 7.96 (dd, J = 7.8, 1.9 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.03 – 6.86 (m, 4H), 6.63 (d, J = 8.8 Hz, 1H), 3.76 – 3.70 (m, 4H), 3.57 (dd, J = 11.3, 5.6 Hz, 2H), 3.30 – 3.16 (m, 4H), 2.62 (t, J = 6.0 Hz, 2H), 2.52 (s, 4H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 190.30, 166.76, 163.50, 160.04 (d, J = 11.4 Hz), 157.60 (d, J = 11.3 Hz), 156.96, 153.37 (dd, J = 252.8, 3.4 Hz), 133.37, 131.52, 129.34, 128.69, 125.64, 124.69, 124.07 (d, J = 8.9 Hz), 123.81 (dd, J = 10.9, 3.7 Hz), 111.37 (dd, J = 21.9, 3.5 Hz), 107.39, 104.35 (dd, J = 26.4, 23.7 Hz), 66.84, 57.24, 53.48, 38.91, 38.73, 36.20, 33.07, 30.44

2-((3,5-difluoropyridin-2-yl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxamide (164)

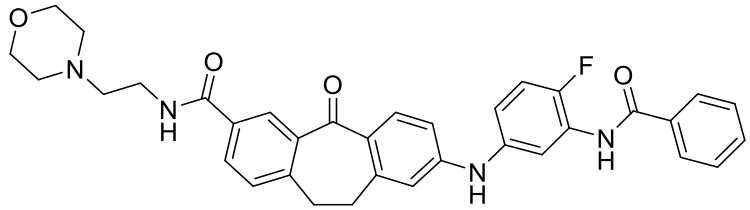


The title compound was synthesized according to the general procedure **4** for saponification of esters, followed by general procedure **2** for amide coupling using TBTU. For the reaction, 25 mg of methyl 2-((3,5-difluoropyridin-2-yl)amino)-5-oxo-10,11-dihydro-5H-benzo[4,5]cyclohepta[1,2-b]pyridine-7-carboxylate and 7 mg of 2-morpholinoethan-1-amine were used to obtain 17 mg of the product as yellow solid.

$C_{26}H_{25}F_2N_5O_3$ (Mr =493.5)

Yield	66%
HPLC	97% (t_r = 3.771 min)
ESI-MS	m/z 492.1 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1628, 1597, 1577, 1522, 1473, 1446, 1425, 1380, 1327, 1257, 1230, 1162, 1111, 983, 842, 794, 761, 731
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.51 (d, 2H), 8.33 (d, J = 12.2, 6.2 Hz, 2H), 8.28 (d, J = 1.5 Hz, 2H), 8.07 (d, J = 2.4 Hz, 2H), 7.99 (dd, J = 7.8, 1.7 Hz, 2H), 7.68 (s, 2H), 7.34 (d, J = 7.9 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.06 (s, 2H), 3.80 – 3.73 (m, 8H), 3.61 (dd, J = 11.0, 5.5 Hz, 4H), 3.31 – 3.21 (m, 8H), 2.69 (t, J = 14.9, 9.4 Hz, 4H), 2.59 (s, 8H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 190.66, 166.72, 162.38, 154.11 (dd, J = 254.3, 3.0 Hz), 154.46, 153.27 (d, J = 3.1 Hz), 146.50 (dd, J = 263.5, 5.9 Hz), 144.67, 142.65, 139.52 (d, J = 9.6 Hz), 138.90, 133.39, 131.66, 129.87, (dd, J = 24.0, 5.5 Hz), 129.46, 128.72, 126.79, 112.00 (dd, J = 23.6, 19.1 Hz), 109.56, 66.71, 57.25, 53.45, 38.54, 36.13, 33.05

8-((3-benzamido-4-fluorophenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (165)

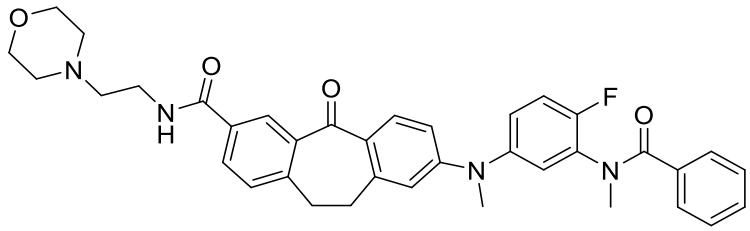


The title compound was designed by Stefan Fischer and resynthesized in big scale for animal study according to the general procedure **2** for amide coupling using TBTU. For the reaction, 900 mg of compound **162** and 244 mg of 2-morpholinoethan-1-amine were used to obtain 798 mg of the product as yellow solid.

$C_{35}H_{33}FN_4O_4$ (Mr =592.67)

Yield	72%
HPLC	95% (t_r = 5.479 min)
ESI-MS	m/z 635.5 $[M+Na]^+$
^{1}H-NMR (400 MHz, DMSO-*d6*)	δ 10.1 (s, 1H), 8.89 (s, 1H), 8.45-8.61 (m, 1H), 8.32 (d, 1H), 7.86-8.06 (m, 4H), 7.47-7.62 (m, 4H), 6.93-7.44 (m, 4H), 6.86 (s, 1H), 3.49-3.62 (m, 4H), 3.49-3.62 (m, 2H), 2.99-3.21 (m, 4H), 2.27-2.62 (m, 2H)

-((4-fluoro-3-(N-methylbenzamido)phenyl)(methyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (166)



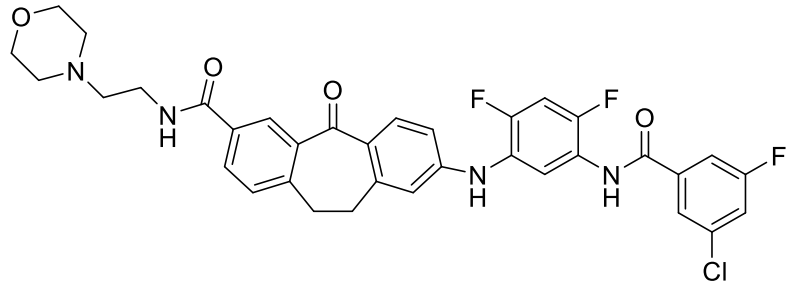
The title compound was synthesized according to the general procedure **2** for amide coupling using TBTU. For the reaction, 25 mg of compound **163** and 7 mg of 2-morpholinoethan-1-amine were used to obtain 8 mg of the product as yellow solid.

$C_{37}H_{37}FN_4O_4$ (Mr =620.28)

Yield	26%
HPLC	100% (t_r = 6.771 min)
ESI-MS	m/z 643.2 $[M+Na]^+$
IR (ATR)	[cm^{-1}] 1577, 1533, 1502, 1262, 1141, 1113, 652
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.44 (t, J = 19.2, 10.9 Hz, 1H), 8.37 (d, J = 9.5 Hz, 1H), 8.16 (d, J = 8.7 Hz, 1H), 8.01 – 7.96 (m, 2H), 7.39 – 7.28 (m, J = 10.9, 9.8, 4.8 Hz, 4H), 7.21 (s, 1H), 7.15 – 7.09 (m, 1H), 6.99 (t, J = 10.3 Hz, 1H), 6.91 (dt, J = 14.7, 7.3 Hz, 1H), 6.86 – 6.76 (m, 2H), 3.86 – 3.85 (m, J = 4.4 Hz, 2H), 3.82 (s, 4H),

	3.72 – 3.57 (m, J = 4.0 Hz, 3H), 3.43 (s, 2H), 3.18 – 3.13 (m, 4H), 2.80 – 2.74 (m, 2H), 2.73 – 2.58 (m, 5H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 194.60, 194.12, 174.01, 169.84, 167.77, 165.31, 164.37 (d, J = 11.3 Hz), 154.91, 150.22, 148.35, 148.14 (d, J = 248.2 Hz), 146.38, 142.15, 139.74 (d, J = 8.6 Hz), 138.49, 137.15, 136.82, 135.75, 134.12, 133.07, 132.31 (d, J = 5.1 Hz), 132.29, 131.05 (d, J = 5.1 Hz), 130.37, 129.59 (d, J = 7.3 Hz), 120.69, 118.63, 118.12, 116.71 (d, J = 18.3 Hz), 115.72, 112.00 (d, J = 2.6 Hz), 109.32 (d, J = 23.6 Hz), 108.60, 107.26, 69.18, 60.40, 58.93, 56.31, 43.17, 39.22, 38.82, 37.66

8-((5-(3-chloro-5-fluorobenzamido)-2,4-difluorophenyl)amino)-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide (167)

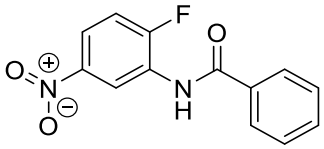


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 100 mg of 8-chloro-N-(2-morpholinoethyl)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxamide and 90 mg of N-(5-amino-2,4-difluorophenyl)-3-chloro-5-fluorobenzamide were used to obtain 18 mg of the product as yellow solid.

$C_{35}H_{30}ClF_3N_4O_4$ (Mr =663.09)

Yield	11%
HPLC	95% (t_r = 6.954 min)
ESI-MS	m/z 661.4 $[M-H]^-$
IR (ATR)	[cm^{-1}] 1582, 1522, 1430, 1400, 1354, 1261, 1197, 1166, 1114, 859, 756, 704, 663
MP	168.8°C
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.47 – 8.30 (m, 2H), 8.15 (d, J = 8.8 Hz, 1H), 8.12 – 8.02 (m, 1H), 7.97 (d, J = 7.7 Hz, 1H), 7.65 (s, 1H), 7.56 – 7.46 (m, J = 8.0 Hz, 1H), 7.39 – 7.26 (m, J = 6.1, 2.5 Hz, 2H), 7.01 (t, J = 10.2 Hz, 1H), 6.90 (dd, J = 8.9 Hz, 1H), 6.86 – 6.76 (m, 1H), 6.12 (s, 1H), 3.98 – 3.73 (m, 4H), 3.73 – 3.59 (m, 2H), 3.27 – 3.03 (m, 4H), 2.88 – 2.53 (m, J = 15.8 Hz, 6H)
^{13}C-NMR (101 MHz, $CDCl_3$)	δ 193.98, 169.68 (d, J = 7.1 Hz), 166.06, 165.58, 163.56, 152.26 (d, J = 245.9 Hz), 149.75, 147.53, 141.42, 139.44 (d, J = 8.6 Hz), 138.02 (d, J = 10.3 Hz), 136.19, 134.30, 133.05, 131.70, 131.39, 125.73, 124.02 (d, J = 10.7 Hz), 121.95 (d, J = 24.9 Hz), 119.31 (d, J = 11.9 Hz), 117.15 (d, J = 2.9 Hz), 115.82, 115.59, 115.36, 106.64 (t, J = 25.1 Hz), 67.12, 59.67, 55.21, 37.93, 36.76, 31.84

N-(2-fluoro-5-nitrophenyl)benzamide (168)

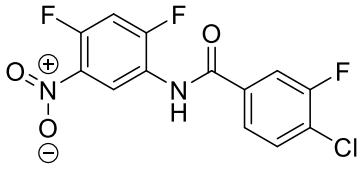


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 3 g of 2-fluoro-5-nitroaniline and 3 g benzoyl chloride was used to obtain 5 g of the product as brown solid.

$C_{13}H_9FN_2O_3$ (Mr = 260.22)

Yield	100%
HPLC	94% (t_r = 6.159 min)
ESI-MS	m/z 283.1 $[M+Na]^+$

4-Chloro-N-(2,4-difluoro-5-nitrophenyl)-3-fluorobenzamide (169)

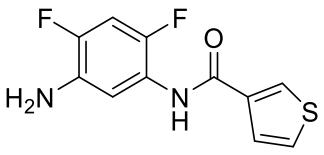


The title compound was synthesized according to the general procedure **2.1** for amide coupling by using acyl chloride and sodium hydride. For the reaction, 500 mg of 2,4-difluoro-5-nitroaniline and 726 mg 4-chloro-3-fluorobenzoyl chloride was used to obtain 623 mg of the product as yellow solid.

$C_{13}H_6ClF_3N_2O_3$ (Mr = 330.65)

Yield	66%
HPLC	94% (t_r = 6.757 min)
ESI-MS	m/z 297 $[M-H]^-$
^{1}H NMR (400 MHz, DMSO)	δ 10.10 (s, 1H), 7.95 (d, *J* = 10.1 Hz, 1H), 7.85 – 7.74 (m, 2H), 7.13 (t, *J* = 10.6 Hz, 1H), 6.94 (t, *J* = 8.6 Hz, 1H), 5.09 (s, 2H)
^{13}C NMR (101 MHz, DMSO)	δ 163.23, 158.25, 155.79, 148.70 – 147.60 (m), 145.78 (dd, *J* = 88.5, 10.9 Hz), 134.87 (d, *J* = 6.1 Hz), 132.78 (dd, *J* = 13.6, 2.6 Hz), 130.94, 125.07 (d, *J* = 3.6 Hz), 123.19 (d, *J* = 17.6 Hz), 120.96 (dd, *J* = 13.1, 3.4 Hz), 116.13 (d, *J* = 22.5 Hz), 113.50 (d, *J* = 5.2 Hz), 103.79 (t, *J* = 24.3 Hz)

N-(5-amino-2,4-difluorophenyl)thiophene-3-carboxamide (170)

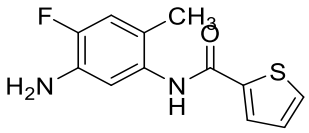


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 150 mg of N-(2,4-difluoro-5-nitrophenyl)thiophene-3-carboxamide was used to obtain 75 mg of the product as brown solid.

$C_{11}H_8F_2N_2OS$ (Mr =254.25)

Yield	56%
HPLC	89% (t_r = 3.897 min)
ESI-MS	m/z 277.2 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.05 – 7.66 (m, 3H), 7.57 – 7.28 (m, 2H), 6.82 (t, J = 10.4 Hz, 1H), 3.88 (s, 2H)

N-(5-amino-4-fluoro-2-methylphenyl)thiophene-2-carboxamide (171)

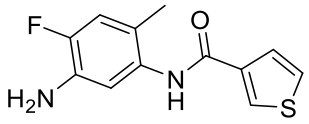


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 110 mg of N-(4-fluoro-2-methyl-5-nitrophenyl)thiophene-2-carboxamide was used to obtain 98 mg of the product as brown solid.

$C_{12}H_{11}FN_2OS$ (Mr =250.29)

Yield	98%
HPLC	97% (t_r = 3.678 min)
ESI-MS	m/z 273.2 $[M+Na]^+$
^{1}H-NMR (200 MHz, DMSO-d_6)	δ 9.73 (s, 1H), 7.92 (d, J = 3.1 Hz, 1H), 7.79 (d, J = 4.7 Hz, 1H), 7.19 (t, 1H), 6.89 (d, J = 12.1 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 2.04 (s, 3H)

N-(5-amino-4-fluoro-2-methylphenyl)thiophene-3-carboxamide (172)

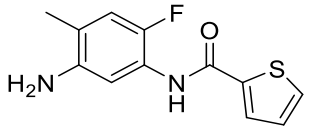


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 300 mg of N-(4-fluoro-2-methyl-5-nitrophenyl)thiophene-3-carboxamide was used to obtain 193 mg of the product as brown solid.

$C_{12}H_{11}FN_2OS$ (Mr =250.29)

Yield	77%
ESI-MS	m/z 273.2 $[M+Na]^+$
^{1}H-NMR (200 MHz, DMSO-d_6)	δ 9.73 (s, 1H), 7.92 (d, J = 3.1 Hz, 1H), 7.79 (d, J = 4.7 Hz, 1H), 7.19 (t, 1H), 6.89 (d, J = 12.1 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 2.04 (s, 3H)

N-(5-amino-2-fluoro-4-methylphenyl)thiophene-2-carboxamide (173)

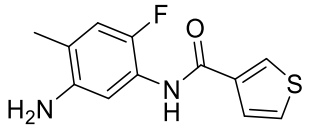


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 230 mg of N-(2,4-difluoro-5-nitrophenyl)thiophene-2-carboxamide was used to obtain 189 mg of the product as yellow solid.

$C_{12}H_{11}FN_2OS$ (Mr = 250.29)

Yield	89%
HPLC	94% (t_r = 1.814 min)
ESI-MS	m/z 251.0 $[M+H]^+$
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 9.17 (d, J = 7.4 Hz, 1H), 8.04 (dd, J = 2.9, 1.3 Hz, 1H), 7.84 (bs, J = 20.4 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.10 (d, J = 11.1 Hz, 1H), 2.58 (s, 3H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 159.67, 147.21, 144.89, 140.99, 139.32, 131.12, 128.53, 128.00, 124.34, 118.47, 116.26, 107.86, 17.22

N-(5-amino-2-fluoro-4-methylphenyl)thiophene-3-carboxamide (174)

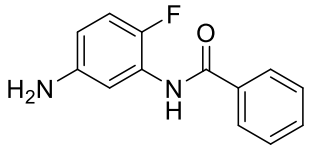


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 500 mg of N-(2,4-difluoro-5-nitrophenyl)thiophene-3-carboxamide was used to obtain 389 mg of the product as white solid.

$C_{12}H_{11}FN_2OS$ (Mr = 250.29)

Yield	89%
HPLC	100% (t_r = 1.792 min)
ESI-MS	m/z 273.0 $[M+H]^+$
^{1}H-NMR (400 MHz, DMSO-d_6)	δ 9.76 (s, 1H), 8.33 (dd, J = 2.8, 1.2 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.04 (d, J = 6.6 Hz, 1H), 6.98 (d, J = 11.1 Hz, 1H), 2.13 (s, 3H)
^{13}C NMR (101 MHz, DMSO-d_6)	δ 170.42, 160.79, 150.81, 137.17, 129.93, 127.17, 127.01, 122.95, 116.88, 114.58, 59.81, 16.95

N-(5-amino-2-fluorophenyl)benzamide (175)

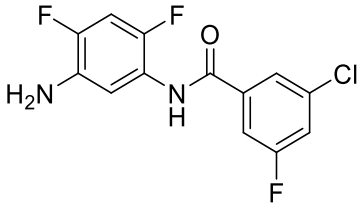


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 5 g of N-(2-fluoro-5-nitrophenyl)benzamide was used to obtain 3.5 g of the product as grey solid.

$C_{13}H_{11}FN_2O$ (Mr =230.09)

Yield	80%
HPLC	94% (t_r = 3.080 min)
ESI-MS	m/z 253.2 $[M+Na]^+$

N-(5-amino-2,4-difluorophenyl)-3-chloro-5-fluorobenzamide (176)

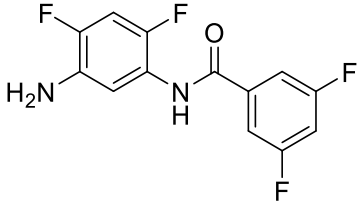


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 150 mg of 3-chloro-N-(2,4-difluoro-5-nitrophenyl)-5-fluorobenzamide was used to obtain 113 mg of the product as purple solid.

$C_{13}H_8ClF_3N2O$ (Mr =300.67)

Yield	76%
HPLC	100% (t_r = 6.925 min)
ESI-MS	m/z 299.1 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 7.93 – 7.71 (m, 5H), 7.60 (s, 3H), 7.45 (d, J = 8.6 Hz, 3H), 7.32 – 7.23 (m, J = 4.4, 2.1 Hz, 4H), 6.84 (t, J = 10.4 Hz, 3H), 3.71 (bs, J = 54.5 Hz, 6H)

N-(5-amino-2,4-difluorophenyl)-3,5-difluorobenzamide (177)

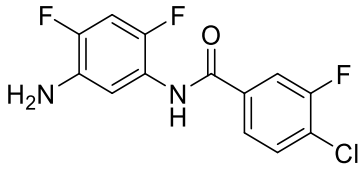


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 800 mg of N-(2,4-difluoro-5-nitrophenyl)-3,5-difluorobenzamide was used to obtain 724 mg of the product as salmon solid.

$C_{13}H_8F_4N2O$ (Mr =284.21)

Yield	100%
HPLC	90% (t_r = 5.854 min)
ESI-MS	m/z 283.0 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 7.98 – 7.86 (dd, 1H), 7.82 (bs, 1H), 7.37 (dt, J = 7.2, 3.6 Hz, 2H), 7.02 (tt, J = 8.5, 2.3 Hz, 1H), 6.87 (t, J = 10.4 Hz, 1H), 3.16 (bs, 2H)
^{19}F NMR (376 MHz, MeOD)	δ -110.31 – -110.37 (m, 2H), -135.17 (t, *J* = 10.0 Hz, 1H), -135.52 (dd, *J* = 9.9, 7.9 Hz, 1H)
^{13}C NMR (101 MHz, MeOD)	δ 165.65 (d, J = 12.3 Hz), 163.18 (d, J = 12.2 Hz), 151.35 (d, J = 249.3 Hz), 150.37 (d, J = 248.9 Hz), 148.96 (d, J = 10.9 Hz), 147.99 (d, J = 10.8 Hz), 139.01 (t, J = 8.7 Hz), 133.39 (dd, J = 13.7, 2.8 Hz), 122.06 (dd, J = 13.3, 3.3 Hz), 115.14 (d, J = 4.9 Hz), 112.33 – 111.69 (m), 108.07 (t, J = 25.8 Hz), 104.65 (t, J = 24.6 Hz)

N-(5-amino-2,4-difluorophenyl)-4-chloro-3-fluorobenzamide (178)

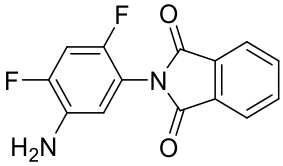


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 400 mg of 4-chloro-N-(2,4-difluoro-5-nitrophenyl)-3-fluorobenzamide was used to obtain 297 mg of the product as white solid.

$C_{13}H_8ClF_3N_2O$ (Mr =300.67)

Yield	82%
HPLC	97% (t_r = 6.757 min)
ESI-MS	m/z 299.2 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.05 – 7.80 (m, 2H), 7.67 (d, J = 8.7 Hz, 1H), 7.63 – 7.45 (m, 2H), 6.86 (t, J = 10.4 Hz, 1H), 3.43 (bs, 2H)

2-(5-amino-2,4-difluorophenyl)isoindoline-1,3-dione (179)

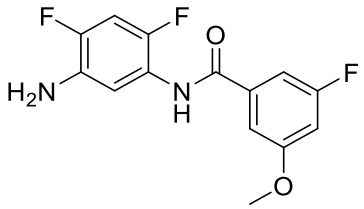


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 250 mg of 2-(2,4-difluoro-5-nitrophenyl)isoindoline-1,3-dione was used to obtain 360 mg of the product as brown solid.

$C_{14}H_8F_2N_2O_2$ (Mr =274.06)

Yield	74%
HPLC	90% (t_r = 5.528 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 7.94 (dt, J = 7.2, 3.5 Hz, 2H), 7.80 (dt, 2H), 6.96 (t, 1H), 6.74 (dd, J = 8.9, 7.1 Hz, 1H), 3.34 (s, 2H)

N-(5-amino-2,4-difluorophenyl)-3-fluoro-5-methoxybenzamide (180)

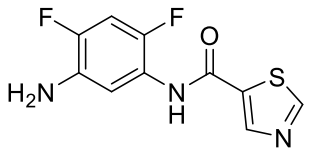


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 240 mg of N-(2,4-difluoro-5-nitrophenyl)-3-fluoro-5-methoxybenzamide was used to obtain 199 mg of the product as grey solid.

$C_{14}H_{11}F_3N_2O_2$ (Mr =296.25)

Yield	88%
HPLC	85% (t_r = 5.800 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 7.90 (t, J = 16.6, 8.1 Hz, 1H), 7.83 (s, 1H), 7.20 – 6.95 (m, 2H), 6.94 – 6.56 (m, J = 19.0, 8.7 Hz, 2H), 3.86 (s, 3H), 3.50 (s, 2H)
^{13}C-NMR (50 MHz, $CDCl_3$)	δ 166.14, 164.22 (d, J = 3.2 Hz), 161.47 (d, J = 11.0 Hz), 161.23, 137.24 (d, J = 8.8 Hz), 109.63 (d, J = 4.4 Hz), 108.99 (d, J = 2.8 Hz), 106.63, 106.17, 105.67, 105.17, 103.53 (t, J = 24.1 Hz), 56.03

N-(5-amino-2,4-difluorophenyl)thiazole-5-carboxamide (181)

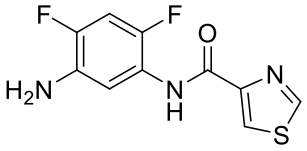


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 440 mg of N-(2,4-difluoro-5-nitrophenyl)thiazole-5-carboxamide was used to obtain 344 mg of the product as yellow solid.

$C_{10}H_7F_2N_3OS$ (Mr =255.24)

Yield	87%
HPLC	100% (t_r = 2.750 min)
ESI-MS	m/z 255.9 $[M+H]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.96 (s, 1H), 8.37 (s, 1H), 7.84 (t, 1H), 7.73 (s, 1H), 6.87 (t, J = 10.4 Hz, 1H), 3.69 (s, 2H)

N-(5-amino-2,4-difluorophenyl)thiazole-4-carboxamide (182)

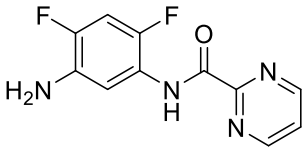


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 400 mg of N-(2,4-difluoro-5-nitrophenyl)thiazole-4-carboxamide was used to obtain 304 mg of the product as yellow solid.

$C_{10}H_7F_2N_3OS$ (Mr =255.24)

Yield	85%
HPLC	88% (t_r = 4.495 min)
ESI-MS	m/z 256.5 $[M+H]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 9.38 (bs, 1H), 8.81 (d, J = 2.1 Hz, 1H), 8.28 – 8.24 (m, 1H), 8.02 (dd, J = 9.3, 8.0 Hz, 1H), 6.86 (t, J = 10.4 Hz, 1H), 3.66 (bs, 1H)

N-(5-amino-2,4-difluorophenyl)pyrimidine-2-carboxamide (183)

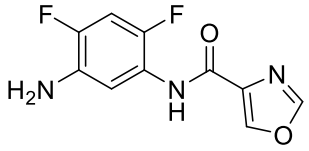


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 75 mg of N-(2,4-difluoro-5-nitrophenyl)pyrimidine-2-carboxamide was used to obtain 47 mg of the product as brown solid.

$C_{11}H_8F_2N_4O$ (Mr =250.21)

Yield	71%
HPLC	100% (t_r = 3.627 min)
ESI-MS	m/z 250.9 $[M+H]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 10.16 (s, 1H), 9.00 (s, 2H), 8.22 (s, 1H), 7.55 (s, 1H), 7.31 (s, 1H), 7.14 – 6.62 (m, 2H)
^{13}C NMR (101 MHz, DMSO)	δ 160.44, 158.03, 157.38, 147.71 (d, *J* = 251.3 Hz), 145.66 (dd, *J* = 249.5, 11.1 Hz), 143.64 (d, *J* = 11.1 Hz), 132.92 (d, *J* = 12.4 Hz), 123.50, 121.39 (dd, *J* = 11.9, 3.0 Hz), 110.52 (d, *J* = 5.1 Hz), 103.64 (t, *J* = 24.2 Hz), 103.40

N-(5-amino-2,4-difluorophenyl)oxazole-4-carboxamide (184)

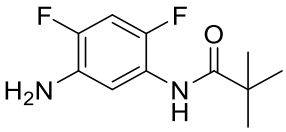


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 400 mg of N-(2,4-difluoro-5-nitrophenyl) oxazole-4-carboxamide was used to obtain 216 mg of the product as white solid.

$C_{11}H_8F_2N_4O$ (Mr =250.21)

Yield	61%
HPLC	100% (t_r = 3.454 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.83 (s, 1H), 8.33 (s, 1H), 8.14 – 7.85 (m, 2H), 6.86 (t, J = 10.4 Hz, 1H), 3.67 (s, 2H)
^{13}C NMR (101 MHz, DMSO)	δ 152.49, 148.05 (d, *J* = 10.8 Hz), 146.80 (d, *J* = 11.1 Hz), 145.68 (d, *J* = 11.2 Hz), 144.45 (d, *J* = 10.9 Hz), 142.85, 132.75 (dd, *J* = 13.5, 2.0 Hz), 120.89 (dd, *J* = 12.5, 3.3 Hz), 112.05 (d, *J* = 5.3 Hz), 103.62 (t, *J* = 24.3 Hz)

N-(5-amino-2,4-difluorophenyl)pivalamide (185)

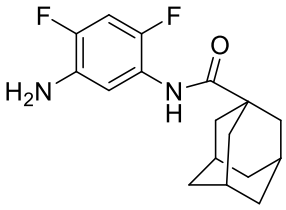


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 580 mg of N-(2,4-difluoro-5-nitrophenyl)pivalamide was used to obtain 503 mg of the product as white solid.

$C_{11}H_{14}F_2N_2O$ (Mr = 228.24)

Yield	97%
HPLC	91% (t_r = 4.173 min)
ESI-MS	m/z 229.3 $[M+H]^+$
^{1}H NMR (400 MHz, DMSO)	δ 8.86 (bs, 1H), 7.02 (t, *J* = 10.6 Hz, 1H), 6.81 (t, *J* = 8.6 Hz, 1H), 4.97 (bs, 2H), 1.19 (s, 9H)
^{13}C NMR (101 MHz, DMSO)	δ 176.64, 148.03, 145.67, 132.44, 121.77, 114.12, 103.40, 27.29

(3r,5r,7r)-N-(5-amino-2,4-difluorophenyl)adamantane-1-carboxamide (186)

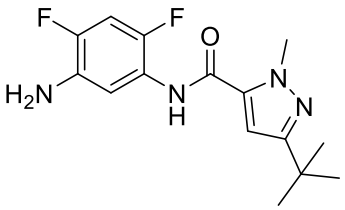


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 200 mg of (3r,5r,7r)-N-(2,4-difluoro-5-nitrophenyl)adamantane-1-carboxamide was used to obtain 110 mg of the product as brown solid.

$C_{17}H_{20}F_2N_2O$ (Mr = 306.42)

Yield	54%
HPLC	95% (t_r = 8.359 min)
ESI-MS	m/z 307.2 $[M+H]^+$
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 7.92 (dd, J = 9.4, 8.0 Hz, 1H), 7.45 (s, 1H), 6.80 (t, J = 10.5 Hz, 1H), 3.65 (bs, J = 38.3, 12.7, 5.9 Hz, 2H), 2.13 – 2.07 (m, 3H), 1.95 (d, J = 2.8 Hz, 6H), 1.80 – 1.71 (m, 6H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 176.22, 147.62 (d, J = 251.8 Hz), 146.23 (d, J = 250.4 Hz), 145.24 (d, J = 11.4 Hz), 143.88 (d, J = 10.5 Hz), 130.44 (dd), 122.91 (dd, J = 10.6, 3.4 Hz), 109.69 (d, J = 3.3 Hz), 103.24 (t, J = 24.1 Hz), 41.97, 39.31, 36.52, 28.22

N-(5-amino-2,4-difluorophenyl)-3-(tert-butyl)-1-methyl-1H-pyrazole-5-carboxamide (187)

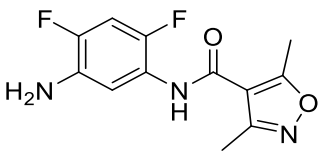


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 400 mg of 3-(tert-butyl)-N-(2,4-difluoro-5-nitrophenyl)-1-methyl-1H-pyrazole-5-carboxamide was used to obtain 344 mg of the product as yellow solid.

$C_{15}H_{18}F_2N_4O$ (Mr = 308.33)

Yield	92%
HPLC	100% (t_r = 7.159 min)
ESI-MS	m/z 309.4 $[M+H]^+$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.84 (t, *J* = 8.5 Hz, 1H), 7.67 (s, 1H), 6.86 (t, *J* = 10.4 Hz, 1H), 6.46 (s, 1H), 4.14 (s, 3H), 3.66 (s, 2H), 1.33 (s, 9H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 160.64, 158.11, 148.05, 146.16, 145.66 , 143.81, 135.10, 131.06, 122.17, 109.40, 103.60, 39.27, 32.18, 30.65

N-(5-amino-2,4-difluorophenyl)-3,5-dimethylisoxazole-4-carboxamide (188)

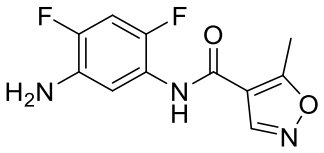


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 330 mg of N-(2,4-difluoro-5-nitrophenyl)-3,5-dimethylisoxazole-4-carboxamide was used to obtain 267 mg of the product as pink solid.

$C_{12}H_{11}F_2N_3O_2$ (Mr = 267.08)

Yield	86%
HPLC	96% (t_r = 2.703 min)
ESI-MS	m/z 268.2 $[M+H]^+$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.89 (t, *J* = 8.5 Hz, 1H), 7.40 (bs, 1H), 6.86 (t, *J* = 10.4 Hz, 1H), 3.70 (bs, 2H), 2.69 (s, 3H), 2.52 (s, 3H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 172.65, 159.90, 157.57, 147.97 (d, *J* = 11.2 Hz), 145.80 (dd, *J* = 242.6, 11.0 Hz), 143.67 (d, *J* = 10.6 Hz), 131.16 (dd, *J* = 213.2, 2.9 Hz), 122.26 (dd, *J* = 10.8, 3.6 Hz), 109.34 (d, *J* = 3.9 Hz), 103.52 (t, *J* = 24.2 Hz), 13.23, 11.83

N-(5-amino-2,4-difluorophenyl)-5-methylisoxazole-4-carboxamide (189)

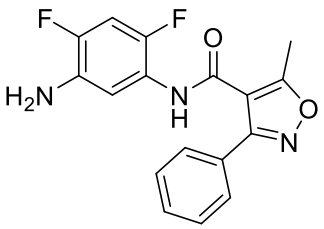


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 210 mg of N-(2,4-difluoro-5-nitrophenyl)-5-methylisoxazole-4-carboxamide was used to obtain 157 mg of the product as brown solid.

$C_{11}H_9F_2N_3O_2$ (Mr = 253,21)

Yield	84%
HPLC	100% (t_r = 2.330 min)
ESI-MS	m/z 254.3 $[M+H]^+$
^{1}H NMR (400 MHz, DMSO)	δ 9.80 (s, 3H), 9.05 (s, 3H), 7.12 (dd, 3H), 6.96 (dd, *J* = 9.4, 8.0 Hz, 3H), 5.08 (s, 5H), 2.66 (s, 9H)
^{13}C NMR (101 MHz, DMSO)	δ 172.85, 159.16, 149.05, 145.96 (d, *J* = 11.2 Hz), 144.99 (d, *J* = 10.8 Hz), 132.81 – 132.59 (m), 120.58 (dd, *J* = 13.1, 3.7 Hz), 113.23 (d, *J* = 5.5 Hz),111.37, 103.65 (t, *J* = 24.3 Hz), 12.06

N-(5-amino-2,4-difluorophenyl)-5-methyl-3-phenylisoxazole-4-carboxamide (190)

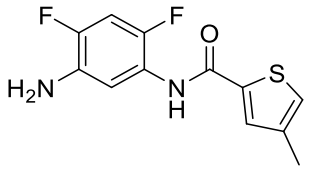


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 220 mg of N-(2,4-difluoro-5-nitrophenyl)-5-methyl-3-phenylisoxazole-4-carboxamide was used to obtain 179 mg of the product as brown solid.

$C_{17}H_{13}F_2N_3O_2$ (Mr = 329.31)

Yield	89%
HPLC	99% (t_r = 5.799 min)
ESI-MS	m/z 330.5 $[M+H]^+$
^{1}H NMR (400 MHz, DMSO)	δ 9.97 (s, 1H), 7.74 – 7.67 (m, 2H), 7.54 – 7.48 (m, 3H), 7.18 – 7.07 (m, *J* = 10.8 Hz, 2H), 5.10 (s, 2H), 2.59 (s, 3H)
^{13}C NMR (101 MHz, DMSO)	δ 170.19, 160.19, 148.09 (d, *J* = 10.1 Hz), 146.73 (d, *J* = 10.7 Hz), 145.72 (d, *J* = 10.9 Hz), 144.37 (d, *J* = 11.4 Hz), 132.74 (dd), 130.09, 128.78, 128.05, 127.79, 120.87 (d, *J* = 15.9 Hz), 112.73, 112.07 (d, *J* = 4.4 Hz), 103.66 (t, *J* = 24.1 Hz), 11.89

N-(5-amino-2,4-difluorophenyl)-4-methylthiophene-2-carboxamide (191)

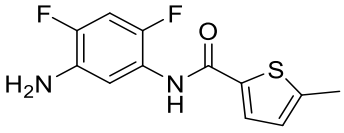


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 220 mg of N-(2,4-difluoro-5-nitrophenyl)-4-methylthiophene-2-carboxamide was used to obtain 180 mg of the product as dark solid.

$C_{12}H_{10}F_2N_2OS$ (Mr = 268.28)

Yield	89%
HPLC	88% (t_r = 5.274 min)
ESI-MS	m/z 269.2 $[M+H]^+$
^{1}H NMR (400 MHz, DMSO)	δ 9.83 (s, 1H), 7.77 (s, 1H), 7.43 (s, 1H), 7.11 (t, *J* = 10.7 Hz, 1H), 6.90 (dd, 1H), 5.07 (s, 2H), 2.25 (s, 3H)

N-(5-amino-2,4-difluorophenyl)-5-methylthiophene-2-carboxamide (192)



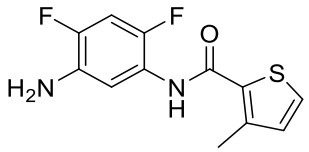
The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 240 mg of N-(2,4-difluoro-5-nitrophenyl)-5-methylthiophene-2-carboxamide was used to obtain 209 mg of the product as purple solid.

$C_{12}H_{10}F_2N_2OS$ (Mr = 268.28)

Yield	87%
HPLC	96% (t_r = 4.352 min)
ESI-MS	m/z 269.4 $[M+H]^+$
^{1}H NMR (400 MHz, MeOD)	δ 9.79 (s, 1H), 7.76 (d, *J* = 3.7 Hz, 1H), 7.11 (t, 1H), 6.93 – 6.87 (m, 2H), 5.06 (s, 2H), 2.49 (d, 3H)

^{13}C NMR (101 MHz, MeOD)	δ 159.85, 148.37 (d, *J* = 11.2 Hz), 147.66 (d, *J* = 11.6 Hz), 145.75, 136.65, 132.63 (dd), 126.66, 121.01, 120.93 (dd, *J* = 12.9, 3.2 Hz), 113.66 (d, *J* = 5.8 Hz), 103.66 (t, *J* = 24.3 Hz), 15.28

N-(5-amino-2,4-difluorophenyl)-3-methylthiophene-2-carboxamide (193)

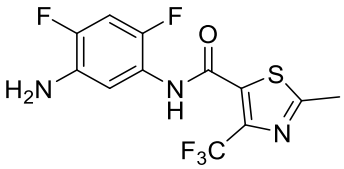


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 589 mg of N-(2,4-difluoro-5-nitrophenyl)-3-methylthiophene-2-carboxamide was used to obtain 386 mg of the product as yellow solid.

$C_{12}H_{10}F_2N_2OS$ (Mr = 268.28)

Yield	73%
HPLC	97% (t_r = 4.611 min)
ESI-MS	m/z 269.4 $[M+H]^+$
^{1}H NMR (400 MHz, DMSOO)	δ 9.45 (s, 1H), 7.65 (d, *J* = 5.0 Hz, 1H), 7.10 (t, 1H), 7.02 – 6.96 (m, 2H), 5.06 (s, 2H), 2.45 (s, 3H)
^{13}C NMR (101 MHz, DMSO)	δ 161.24, 147.85 (dd, *J* = 77.9, 10.8 Hz), 145.49 (dd, *J* = 76.6, 10.9 Hz), 140.92, 132.62 (dd, *J* = 14.0 Hz), 131.54, 121.35 (dd, *J* = 12.8, 3.3 Hz), 113.14 (d, *J* = 5.5 Hz), 103.59 (t, *J* = 24.4 Hz), 15.32

N-(5-amino-2,4-difluorophenyl)-2-methyl-4-(trifluoromethyl)thiazole-5-carboxamide (194)

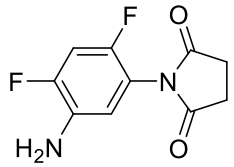


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 300 mg of N-(2,4-difluoro-5-nitrophenyl)-2-methyl-4-(trifluoromethyl)thiazole-5-carboxamide was used to obtain 153 mg of the product as brown solid.

$C_{12}H_8F_5N_3OS$ (Mr = 337.27)

Yield	55%
HPLC	87% (t_r = 3,798 min)
ESI-MS	m/z 360.4 $[M+Na]^+$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.03 (bs, 1H), 8.00 – 7.88 (m, 1H), 6.88 (t, *J* = 10.2 Hz, 1H), 2.76 (s, 3H)

1-(5-amino-2,4-difluorophenyl)pyrrolidine-2,5-dione (195)

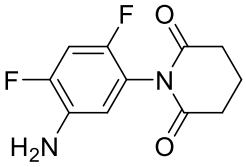


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 150 mg of 1-(2,4-difluoro-5-nitrophenyl)pyrrolidine-2,5-dione was used to obtain 89 mg of the product as colourless solid.

$C_{10}H_8F_2N_2O_2$ (Mr = 226.18)

Yield	67%
HPLC	90% (t_r = 2.306 min)
ESI-MS	m/z 225.3 $[M-H]^-$
^{1}H NMR (400 MHz, DMSO)	δ 7.23 (dd, *J* = 11.1, 10.0 Hz, 1H), 6.67 (dd, *J* = 9.3, 7.5 Hz, 1H), 5.24 (s, 2H), 2.82 (d, *J* = 5.5 Hz, 4H)

1-(5-amino-2,4-difluorophenyl)piperidine-2,6-dione (196)

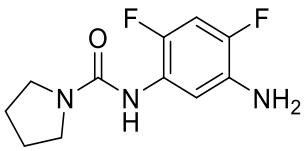


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 170 mg of 1-(2,4-difluoro-5-nitrophenyl)piperidine-2,6-dione was used to obtain 114 mg of the product as colourless solid.

$C_{11}H_{10}F_2N_2O_2$ (Mr = 240.21)

Yield	76%
HPLC	% (t_r = min)
ESI-MS	m/z 263.3 $[M+Na]^+$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 6.90 (dd, 1H), 6.58 (t, *J* = 8.0 Hz, 1H), 3.32 (s, 2H), 2.81 (h, *J* = 4.1 Hz, 4H), 2.13 – 2.04 (m, 2H)
^{13}C NMR (101 MHz, $CDCl_3$)	δ 172.00, 152.56 (d, *J* = 10.9 Hz), 150.13 (d, *J* = 10.8 Hz), 130.25 (dd, *J* = 15.0, 3.4 Hz), 118.60 (dd, *J* = 14.9, 4.2 Hz), 118.10 (d, *J* = 5.2 Hz), 104.81 (t), 56, 32.95, 17.30

N-(5-amino-2,4-difluorophenyl)pyrrolidine-1-carboxamide (197)

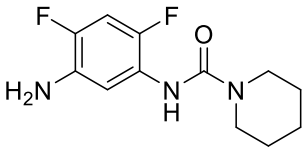


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 100 mg of N-(2,4-difluoro-5-nitrophenyl)pyrrolidine-1-carboxamide was used to obtain 68 mg of the product as brown solid.

$C_{11}H_{13}F_2N_3O$ (Mr =241.24)

Yield	76%
HPLC	78% (t_r = 4.044 min)
ESI-MS	m/z 241.8 $[M+H]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 7.63 (t, J = 8.8 Hz, 1H), 6.71 (t, J = 14.5, 6.6 Hz, 1H), 6.23 (s, 1H), 3.61 (s, 2H), 3.59 – 3.35 (m, J = 6.5 Hz, 4H), 2.19 – 1.84 (m, 4H)

N-(5-amino-2,4-difluorophenyl)piperidine-1-carboxamide (198)

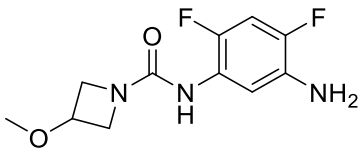


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 210 mg of N-(2,4-difluoro-5-nitrophenyl)piperidine-1-carboxamide was used to obtain 148 mg of the product as yellow solid.

$C_{12}H_{15}F_2N_3O$ (Mr =255.27)

Yield	79%
HPLC	100% (t_r = 3.315 min)
ESI-MS	m/z 278.3 $[M+Na]^+$
^{1}H NMR (400 MHz, DMSO)	δ 7.93 (s, 1H), 6.96 (t, *J* = 10.7 Hz, 1H), 6.78 (t, *J* = 8.8 Hz, 1H), 4.89 (bs, 2H), 3.37 – 3.34 (m, 4H), 1.59 – 1.53 (m, *J* = 4.4 Hz, 2H), 1.49 – 1.43 (m, 4H)
^{13}C NMR (101 MHz, DMSO)	δ 155.23, 147.54 (dd, *J* = 18.9, 10.9 Hz), 145.19 (dd, *J* = 20.0, 10.9 Hz), 132.12 (dd, *J* = 13.5, 2.6 Hz), 132.12 (dd, *J* = 13.5, 2.6 Hz), 123.49 (dd, *J* = 12.5, 3.4 Hz), 113.65 (dd, *J* = 5.3, 1.3 Hz), 103.18 (dd, *J* = 24.8, 23.9 Hz), 47.38, 44.77, 25.46, 25.37, 24.11

N-(5-amino-2,4-difluorophenyl)-3-methoxyazetidine-1-carboxamide (199)

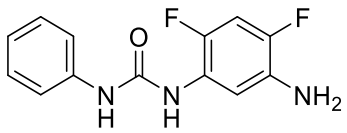


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 300 mg of N-(2,4-difluoro-5-nitrophenyl)-3-methoxyazetidine-1-carboxamide was used to obtain 246 mg of the product as brown solid.

$C_{11}H_{13}F_2N_3O_2$ (Mr =257.24)

Yield	100%
HPLC	79% (t_r = 2.309 min)
ESI-MS	m/z 255.8 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 7.58 (t, J = 8.8 Hz, 1H), 6.74 (t, J = 10.5 Hz, 1H), 6.05 (s, 1H), 4.26 – 4.09 (m, 3H), 3.92 (d, J = 5.4 Hz, 2H), 3.59 (s, 2H), 3.29 (s, 3H)

1-(5-amino-2,4-difluorophenyl)-3-phenylurea (200)

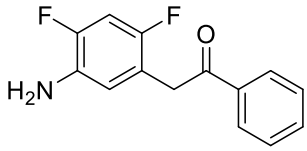


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 100 mg of 1-(2,4-difluoro-5-nitrophenyl)-3-phenylurea was used to obtain 70 mg of the product as brown solid.

$C_{13}H_{11}F_2N_3O$ (Mr =263.1)

Yield	90%
HPLC	95% (t_r = 5.177 min)
ESI-MS	m/z 264.1 $[M+H]^+$
^{1}H NMR (400 MHz, MeOD)	δ 7.75 – 7.66 (m, 1H), 7.39 – 7.32 (m, *J* = 8.0 Hz, 2H), 7.26 (t, *J* = 7.8 Hz, 2H), 7.01 (t, *J* = 7.3 Hz, 1H), 6.77 (t, *J* = 10.4 Hz, 1H)

2-(5-amino-2,4-difluorophenyl)-1-phenylethan-1-one (201)

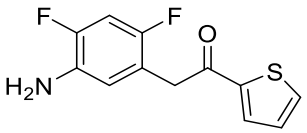


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 1.2 g of 2-(2,4-difluoro-5-nitrophenyl)-1-phenylethan-1-one was used to obtain 1.1 g of the product as brown solid.

$C_{13}H_8F_4N2O$ (Mr =284.21)

Yield	96%
HPLC	100% (t_r = 6.388 min)
ESI-MS	m/z 246.2 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.05 – 7.97 (m, 2H), 7.63 – 7.42 (m, 3H), 6.79 (dd, J = 10.6, 9.4 Hz, 1H), 6.64 (dd, J = 9.6, 7.4 Hz, 1H), 4.19 (s, 2H), 3.38 (s, 2H)

2-(5-amino-2,4-difluorophenyl)-1-(thiophen-2-yl)ethan-1-one (202)

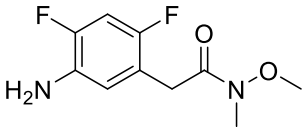


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 83 mg of 2-(2,4-difluoro-5-nitrophenyl)-1-(thiophen-2-yl)ethan-1-one was used to obtain 59 mg of the product as yellow oil.

$C_{12}H_9F_2NOS$ (Mr =253.27)

Yield	81%
HPLC	77% (t_r = 5.313 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 7.79 (d, J = 3.3 Hz, 1H), 7.65 (d, J = 4.8 Hz, 1H), 7.13 (t, 1H), 6.85 – 6.62 (m, 2H), 4.11 (s, 2H), 3.58 (bs, 2H)

2-(5-amino-2,4-difluorophenyl)-N-methoxy-N-methylacetamide (203)

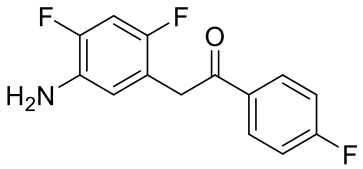


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 230 mg of 2-(2,4-difluoro-5-nitrophenyl)-N-methoxy-N-methylacetamide was used to obtain 183 mg of the product as yellow solid.

$C_{10}H_{12}F_2N_2O_2$ (Mr =230.21)

Yield	92%
HPLC	77% (t_r = 5.313 min)
^{1}H-NMR (200 MHz, DMSO-*d6*)	δ 7.05 – 6.88 (m, J = 10.5 Hz, 1H), 6.74 – 6.59 (m, 1H), 4.93 (s, 2H), 3.67 (s, 3H), 3.61 (s, 2H), 3.10 (s, 3H)

2-(5-amino-2,4-difluorophenyl)-1-(4-fluorophenyl)ethan-1-one (204)



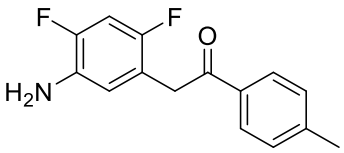
The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 300 mg of 2-(2,4-difluoro-5-nitrophenyl)- 1-(4-fluorophenyl)ethan-1-one was used to obtain 225 mg of the product as yellow solid.

$C_{14}H_{10}F_3NO$ (Mr =265.24)

Yield	76%
HPLC	96% (t_r = 6.792 min)

^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.09 – 7.98 (m, 2H), 7.19 – 7.09 (m, J = 8.6 Hz, 2H), 6.79 (dd, 1H), 6.63 (dd, J = 9.6, 7.4 Hz, 1H), 4.16 (s, 2H), 3.56 (s, 2H)
^{13}C NMR (50 MHz, $CDCl_3$)	δ 195.05, 168.59, 152.79 (d, J = 249.7 Hz), 150.63 (d, J = 250.7 Hz), 132.81 (d, J = 3.0 Hz), 131.24 (d, J = 9.2 Hz), 130.87 (d, J = 3.1 Hz), 118.41 (t, J = 4.6 Hz), 117.25 (dd, J = 17.0, 4.1 Hz), 115.97 (d, J = 21.9 Hz), 103.92 (dd, J = 27.3, 23.0 Hz), 38.02 (d, J = 1.7 Hz)

2-(5-amino-2,4-difluorophenyl)-1-(p-tolyl)ethan-1-one (205)

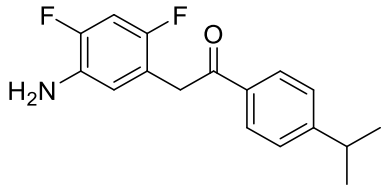


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 170 mg of 2-(2,4-difluoro-5-nitrophenyl)-1-(p-tolyl)ethan-1-one was used to obtain 153 mg of the product as yellow solid.

$C_{15}H_{13}F_2NO$ (Mr =261.27)

Yield	91%
HPLC	99% (t_r = 7.439 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 7.91 (d, J = 8.1 Hz, 6H), 7.27 (d, J = 8.0 Hz, 6H), 6.79 (t, J = 10.2 Hz, 3H), 6.64 (dd, J = 9.5, 7.5 Hz, 3H), 4.17 (s, 6H), 3.54 (s, 5H), 2.41 (s, 9H)

2-(5-amino-2,4-difluorophenyl)-1-(4-isopropylphenyl)ethan-1-one (206)

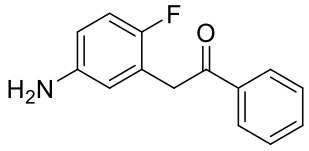


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 120 mg of 2-(2,4-difluoro-5-nitrophenyl)-1-(4-isopropylphenyl)ethan-1-one was used to obtain 101 mg of the product as colourless solid.

$C_{17}H_{17}F_2NO$ (Mr =289.33)

Yield	92%
HPLC	100% (t_r = 8.882 min)
ESI-MS	m/z 290.5 $[M+H]^+$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 6.79 (t, 1H), 6.65 (dd, *J* = 9.3, 7.6 Hz, 1H), 4.17 (s, 2H), 3.29 (bs, 2H), 3.02 – 2.91 (m, 1H), 1.28 (s, 3H), 1.26 (s, 3H)

2-(5-amino-2-fluorophenyl)-1-phenylethan-1-one (207)

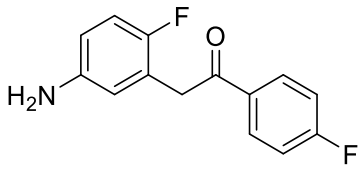


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 360 mg of 2-(2-fluoro-5-nitrophenyl)-1-phenylethan-1-one was used to obtain 227 mg of the product as orange crystals.

$C_{14}H_{12}FNO$ (Mr =229.25)

Yield	71%
HPLC	92% (t_r = 4.381 min)
ESI-MS	m/z 230.0 $[M+H]^+$
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 8.05 – 7.99 (m, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 6.87 (t, J = 12.7, 5.7 Hz, 1H), 6.62 – 6.52 (m, 2H), 4.22 (s, 2H), 3.48 (bs, 2H)

2-(5-amino-2-fluorophenyl)-1-(4-fluorophenyl)ethan-1-one (208)

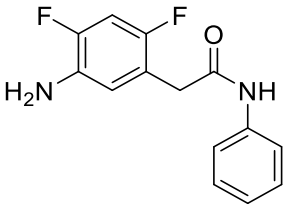


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 340 mg of 2-(2-fluoro-5-nitrophenyl)- 1-(4-fluorophenyl)ethan-1-one was used to obtain 223 mg of the product as orange crystals.

$C_{14}H_{11}F_2NO$ (Mr =247.08)

Yield	75%
HPLC	94% (t_r = 4.321 min)
^{1}H NMR (400 MHz, $CDCl_3$)	δ 8.07 – 8.02 (m, 2H), 7.16 – 7.10 (m, 2H), 6.90 – 6.84 (m, 1H), 6.59 – 6.53 (m, 2H), 4.18 (s, 2H), 3.44 (bs, 2H)

2-(5-amino-2,4-difluorophenyl)-N-phenylacetamide (209)

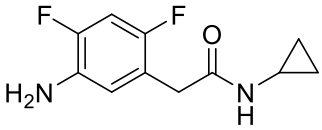


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 160 mg of 2-(2,4-difluoro-5-nitrophenyl)-1-(p-tolyl)ethan-1-one was used to obtain 48 mg of the product as yellow solid.

$C_{14}H_{12}F_2N_2O_2$ (Mr =261.27)

Yield	34%
HPLC	97% (t_r = 4.755 min)
ESI-MS	m/z 285.1 $[M+H]^+$
^{1}H-NMR (400 MHz, $CDCl_3$)	δ 7.46 (s, 1H), 7.45 (s, 1H), 7.30 (t, J = 7.9 Hz, 2H), 7.22 (bs, 1H), 7.10 (t, J = 7.4 Hz, 1H), 6.83 (t, 1H), 6.77 (dd, J = 9.3, 7.6 Hz, 1H), 3.88 – 3.40 (m, 4H)

2-(5-amino-2,4-difluorophenyl)-N-cyclopropylacetamide (210)

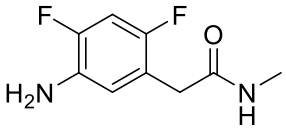


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 230 mg of N-cyclopropyl-2-(2,4-difluoro-5-nitrophenyl)acetamide was used to obtain 147 mg of the product as orange crystals.

$C_{11}H_{12}F_2N_2O$ (Mr =226.2)

Yield	34%
HPLC	97% (t_r = 3.244 min)
ESI-MS	m/z 227.1 $[M+H]^+$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 6.77 (dd, 1H), 6.71 (dd, *J* = 9.6, 7.5 Hz, 1H), 5.63 (bs, 1H), 3.41 (s, 2H), 3.23 (bs, *J* = 9.3 Hz, 2H), 2.66 (ddt, *J* = 10.8, 7.1, 3.7 Hz, 1H), 0.78 – 0.70 (m, 2H), 0.48 – 0.41 (m, 2H)

2-(5-amino-2,4-difluorophenyl)-N-methylacetamide (211)

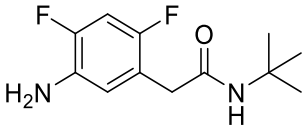


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 180 mg of 2-(2,4-difluoro-5-nitrophenyl)-N-methylacetamide was used to obtain 103 mg of the product as solid.

$C_9H_{10}F_2N_2O$ (Mr =200.19)

Yield	66%
HPLC	95% (t_r = 1.661 min)
ESI-MS	m/z 223.1 $[M+Na]^+$
^{1}H NMR (400 MHz, MeOD)	δ 6.75 (dd, *J* = 10.6, 9.4 Hz, 1H), 6.68 (dd, *J* = 9.6, 7.5 Hz, 1H), 3.40 (s, 2H), 2.73 (s, 3H)

2-(5-amino-2,4-difluorophenyl)-N-(tert-butyl)acetamide (212)

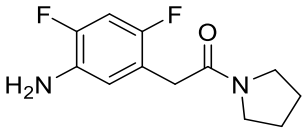


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 150 mg of N-(tert-butyl)-2-(2,4-difluoro-5-nitrophenyl)acetamide was used to obtain 133 mg of the product as orange solid.

$C_{12}H_{16}F_2N_2O$ (Mr =242.27)

Yield	100%
HPLC	86% (t_r = 5.474 min)
ESI-MS	m/z 243.1 $[M+H]^+$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 6.78 (dd, *J* = 10.6, 9.4 Hz, 1H), 6.70 (dd, *J* = 9.6, 7.4 Hz, 1H), 5.31 (bs, *J* = 13.0 Hz, 1H), 3.59 (bs, 2H), 3.35 (s, 2H), 1.30 (s, 9H)

2-(5-amino-2,4-difluorophenyl)-1-(pyrrolidin-1-yl)ethan-1-one (213)

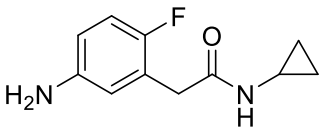


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 110 mg of 2-(2,4-difluoro-5-nitrophenyl)-1-(pyrrolidin-1-yl)ethan-1-one was used to obtain 72 mg of the product as brown solid.

$C_{12}H_{14}F_2N_2O$ (Mr =240.25)

Yield	74%
HPLC	96% (t_r = 4.668 min)
ESI-MS	m/z 263.1 $[M+Na]^+$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 6.82 (t, *J* = 8.3 Hz, 1H), 6.75 (dd, *J* = 14.6, 5.4 Hz, 1H), 3.54 (s, 2H), 3.50 – 3.44 (m, *J* = 14.3, 7.3 Hz, 4H), 3.29 (s, 2H), 1.99 – 1.91 (m, 2H), 1.89 – 1.83 (m, *J* = 13.3, 6.6 Hz, 2H)

2-(5-amino-2-fluorophenyl)-N-cyclopropylacetamide (214)

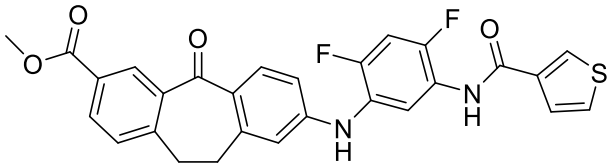


The title compound was synthesized according to the general procedure **6** reduction of the nitro-group. For the reaction, 500 mg of N-cyclopropyl-2-(2-fluoro-5-nitrophenyl)acetamide was used to obtain 356 mg of the product as beige solid.

$C_{11}H_{132}N_2O$ (Mr =208.22)

Yield	78%
HPLC	100% (t_r = 1.440 min)
ESI-MS	m/z 231.1 $[M+Na]^+$
^{1}H NMR (400 MHz, $CDCl_3$)	δ 6.77 (dd, 1H), 6.71 (dd, *J* = 9.6, 7.5 Hz, 1H), 5.63 (bs, 1H), 3.41 (s, 2H), 3.23 (bs, *J* = 9.3 Hz, 2H), 2.66 (ddt, *J* = 10.8, 7.1, 3.7 Hz, 1H), 0.78 – 0.70 (m, 2H), 0.48 – 0.41 (m, 2H)

Methyl 8-((2,4-difluoro-5-(thiophene-3-carboxamido)phenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate (215)

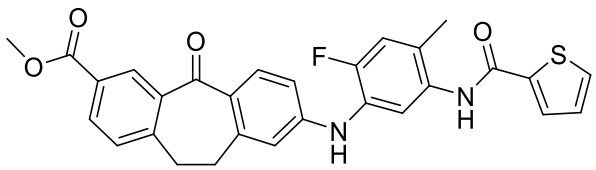


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 70 mg dibenzosuberone and 59 mg of N-(5-amino-2,4-difluorophenyl)thiophene-3-carboxamide were used to obtain 130 mg of the product as yellow solid.

$C_{28}H_{20}F_2N_2O_4S$ (Mr =518.53)

Yield	92%
HPLC	92% (t_r = 8.263 min)
ESI-MS	m/z 541.4 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.62 (d, J = 1.6 Hz, 1H), 8.29 (t, J = 8.3 Hz, 1H), 8.21 – 7.95 (m, 4H), 7.56 – 7.47 (m, J = 5.0 Hz, 1H), 7.41 – 7.32 (m, 1H), 7.24 (d, J = 7.9 Hz, 1H), 6.90 (dd, J = 20.0, 9.8 Hz, 2H), 6.74 (s, 1H), 6.44 (s, 1H), 3.90 (s, 3H), 3.25 – 3.00 (m, J = 10.1 Hz, 4H)

Methyl 8-((2-fluoro-4-methyl-5-(thiophene-2-carboxamido)phenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-2-carboxylate (216)



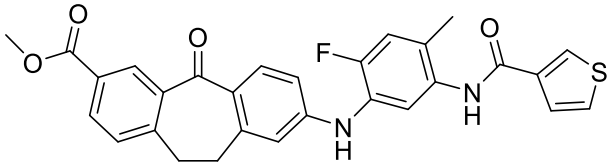
The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 70 mg dibenzosuberone and 59 mg of N-(5-amino-2-fluoro-4-methylphenyl)thiophene-2-carboxamide were used to obtain 36 mg of the product as yellow solid.

$C_{29}H_{23}FN_2O_4S$ (Mr =514.57)

Yield	31%
HPLC	83% (t_r = 8.207 min)
ESI-MS	m/z 537.6 $[M+Na]^+$

^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.62 (s, 1H), 8.19 – 7.95 (m, J = 16.7, 7.7 Hz, 2H), 7.85 – 7.74 (m, 1H), 7.67 (s, 1H), 7.52 (d, J = 4.4 Hz, 1H), 7.24 (d, J = 7.4 Hz, 1H), 7.05 (s, 1H), 7.01 – 6.69 (m, 3H), 6.15 (s, 1H), 3.90 (s, 3H), 3.77 – 3.55 (m, 1H), 3.27 – 2.96 (m, J = 11.4 Hz, 4H), 2.26 (s, 2H)

Methyl 8-((2-fluoro-4-methyl-5-(thiophene-3-carboxamido)phenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate (217)

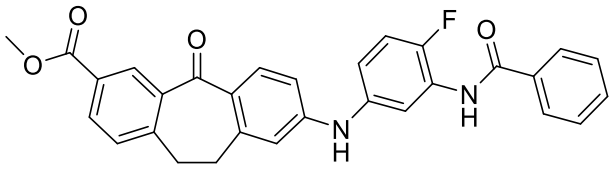


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 70 mg dibenzosuberone and 59 mg of N-(5-amino-2-fluoro-4-methylphenyl)thiophene-3-carboxamide were used to obtain 51 mg of the product as yellow solid.

$C_{29}H_{23}FN_2O_4S$ (Mr =514.57)

Yield	43%
HPLC	93% (t_r = 8.319 min)
ESI-MS	m/z 537.6 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.63 (d, J = 1.5 Hz, 1H), 8.06 (t, J = 8.7 Hz, 4H), 7.70 (d, J = 7.9 Hz, 1H), 7.54 (d, J = 4.6 Hz, 1H), 7.38 (s, 1H), 7.32 – 7.20 (m, 1H), 6.94 (d, J = 11.2 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.75 (s, 1H), 3.92 (s, 3H), 3.21 – 2.95 (m, 4H), 2.26 (s, 3H)

Methyl 8-((3-benzamido-4-fluorophenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate (218)

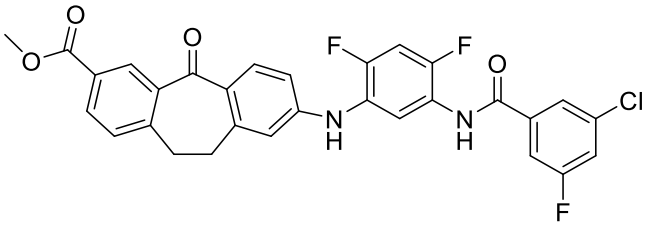


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 100 mg dibenzosuberone and 77 mg of N-(5-amino-2-fluorophenyl)benzamide were used to obtain 94 mg of the product as yellow solid.

$C_{30}H_{23}FN_2O_4$ (Mr =494.19)

Yield	56%
HPLC	90% (t_r = 8.743 min)
ESI-MS	m/z 517.6 $[M+Na]^+$
^{1}H-NMR (200 MHz, DMSO-d6)	δ 8.89 (s, 1H), 8.51 (m, 1H), 8.32 (d, 1H), 7.92 (m, 4H), 7.62 (m 4H), 7.23 (m, 4H), 6.86 (s, 1H), 3.21 (s, 3H)

Methyl 8-((5-(3-chloro-5-fluorobenzamido)-2,4-difluorophenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate (219)

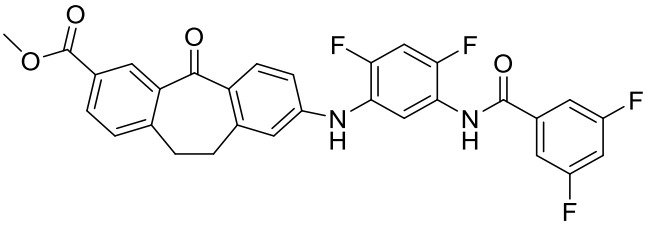


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 100 mg dibenzosuberone and 100 mg of N-(5-amino-2,4-difluorophenyl)-3-chloro-5-fluorobenzamide were used to obtain 60 mg of the product as brown oil.

$C_{30}H_{20}ClF_3N_2O_4$ (Mr =564.11)

Yield	70%
HPLC	89% (t_r = 9.436 min)
ESI-MS	m/z 587.2 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.69 – 8.60 (m, 1H), 8.47 (t, J = 8.4 Hz, 1H), 8.19 (d, J = 8.7 Hz, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.86 (s, 1H), 7.64 (s, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.29 (d, J = 9.3 Hz, 2H), 7.03 (t, J = 10.0 Hz, 1H), 6.88 (d, J = 10.2 Hz, 2H), 5.98 (s, 1H), 3.92 (s, 3H), 3.20 (s, 4H)

Methyl 8-((5-(3,5-difluorobenzamido)-2,4-difluorophenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate (220)

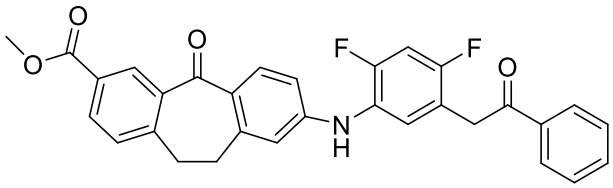


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 200 mg dibenzosuberone and 205 mg of N-(5-amino-2,4-difluorophenyl)-3,5-difluorobenzamide were used to obtain 187 mg of the product as brown solid.

$C_{30}H_{20}F_4N_2O_4$ (Mr =548.49)

Yield	57%
HPLC	94% (t_r = 9.386 min)
ESI-MS	m/z 547.4 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.69 – 8.60 (m, 1H), 8.47 (t, J = 8.4 Hz, 1H), 8.19 (d, J = 8.7 Hz, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.86 (s, 1H), 7.64 (s, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.29 (d, J = 9.3 Hz, 2H), 7.03 (t, J = 10.0 Hz, 1H), 6.88 (d, J = 10.2 Hz, 2H), 5.98 (s, 1H), 3.92 (s, 3H), 3.20 (s, 4H)

Methyl 8-((2,4-difluoro-5-(2-oxo-2-phenylethyl)phenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate (221)

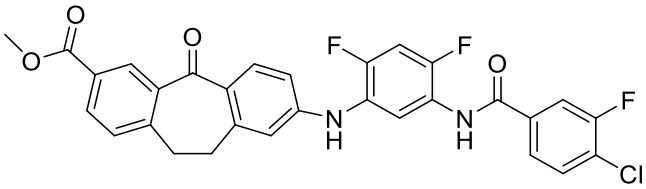


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 132 mg dibenzosuberone and 130 mg of 2-(5-amino-2,4-difluorophenyl)-1-phenylethan-1-one were used to obtain 185 mg of the product as yellow solid.

$C_{31}H_{23}F_2NO_4$ (Mr =511.52)

Yield	82%
HPLC	100% (t_r = 9.439 min)
ESI-MS	m/z 534.3 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.65 (d, J = 1.8 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 8.08 – 7.98 (m, J = 8.4, 4.1, 1.7 Hz, 3H), 7.65 – 7.55 (m, J = 6.2, 3.6, 1.4 Hz, 1H), 7.54 – 7.44 (m, 2H), 7.31 – 7.22 (m, J = 8.6, 4.3 Hz, 2H), 6.93 (dd, J = 10.2, 9.3 Hz, 1H), 6.81 (dd, J = 8.7, 2.3 Hz, 1H), 6.66 (d, J = 2.3 Hz, 1H), 4.29 (s, 2H), 3.91 (s, 3H), 3.12 (q, J = 9.2 Hz, 4H)

Methyl 8-((5-(4-chloro-3-fluorobenzamido)-2,4-difluorophenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate (222)

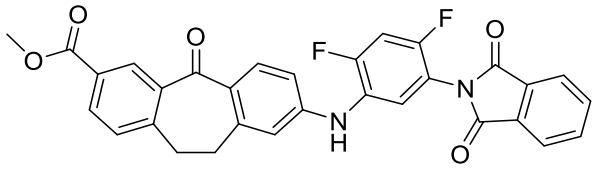


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 165 mg dibenzosuberone and 200 mg of N-(5-amino-2,4-difluorophenyl)-4-chloro-3-fluorobenzamide were used to obtain 81 mg of the product as yellow solid.

$C_{30}H_{20}ClF_3N_2O_4$ (Mr =564.11)

Yield	26%
HPLC	75% (t_r = 9.507 min)
ESI-MS	m/z 587.3 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.67 – 8.64 (m, J = 1.7 Hz, 1H), 8.42 (t, J = 8.4 Hz, 1H), 8.18 (d, J = 8.7 Hz, 1H), 8.12 – 8.03 (m, J = 7.9, 1.8 Hz, 2H), 7.73 (dd, J = 9.3, 1.8 Hz, 1H), 7.68 – 7.60 (m, 1H), 7.59 – 7.49 (m, 1H), 7.38 – 7.33 (m, J = 8.3 Hz, 1H), 7.03 (t, J = 10.1 Hz, 1H), 6.96 – 6.90 (m, 1H), 6.87 – 6.81 (m, 1H), 6.13 (s, 1H), 3.95 (s, 3H), 3.22 – 3.13 (m, 4H)

Methyl 8-((5-(1,3-dioxoisoindolin-2-yl)-2,4-difluorophenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate (223)

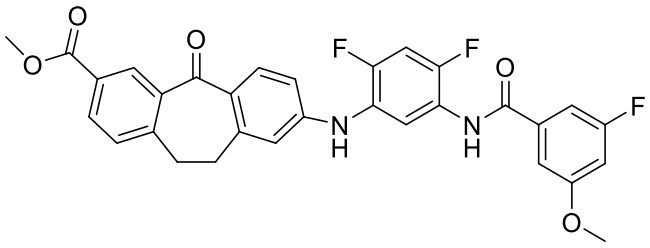


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 200 mg dibenzosuberone and 197 mg of 2-(5-amino-2,4-difluorophenyl)isoindoline-1,3-dione were used to obtain 147 mg of the product as yellow solid.

$C_{31}H_{20}F_2N_2O_5$ (Mr =538.51)

Yield	47%
HPLC	83% (t_r = 9.224 min)
ESI-MS	m/z 561.4 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.61 (d, J = 1.7 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 8.02 (dd, J = 7.9, 1.7 Hz, 1H), 7.96 – 7.75 (m, 4H), 7.39 (t, J = 7.9 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.06 (t, J = 9.7 Hz, 1H), 6.93 (dd, J = 8.7, 2.3 Hz, 1H), 6.80 (d, J = 1.9 Hz, 1H), 6.33 (s, 1H), 3.89 (s, 3H), 3.24 – 3.02 (m, 4H)

Methyl 8-((2,4-difluoro-5-(3-fluoro-5-methoxybenzamido)phenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate (224)

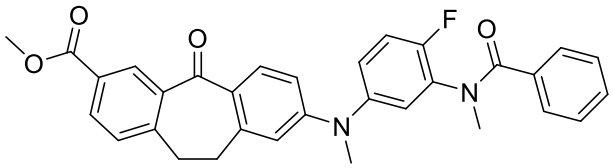


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 140 mg dibenzosuberone and 150 mg of N-(5-amino-2,4-difluorophenyl)-3-fluoro-5-methoxybenzamide were used to obtain 155 mg of the product as yellow solid.

$C_{31}H_{23}F_3N_2O_5$ (Mr =560.53)

Yield	66%
HPLC	94% (t_r = 9.194 min)
ESI-MS	m/z 583.0 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.64 (s, 1H), 8.46 (t, J = 8.1 Hz, 1H), 8.17 (d, J = 8.7 Hz, 1H), 8.05 (d, J = 7.7 Hz, 1H), 7.96 (s, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.20 (s, 1H), 7.12 (d, J = 8.2 Hz, 1H), 7.00 (t, 1H), 6.89 (d, 1H), 6.80 (d, J = 8.5 Hz, 2H), 6.06 (s, 1H), 3.89 (d, J = 9.4 Hz, 3H), 3.86 (s, 3H), 3.17 (s, 4H)

Methyl 8-((4-fluoro-3-(N-methylbenzamido)phenyl)(methyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate (225)



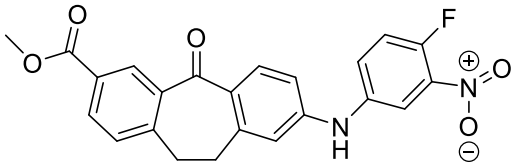
Methyl 8-((3-benzamido-4-fluorophenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate (85 mg, 1eq.) was dissolved in dry THF (1 ml), NaH (21 mg, 3 eq.) was added and it was stirred for 10 min. Methyl iodide was added dropwise and the reaction mixture was stirred at ambient temperature.

Work up: The reaction mixture was put on Celite and purified via flash chromatography on silica with DCM/MeOH (0-5%) as solvent, to obtain 28 mg product.

$C_{32}H_{27}FN_2O_4$ (Mr =522.58)

Yield	33%
HPLC	91% (t_r = 10.078 min)
ESI-MS	m/z 545.5 $[M+Na]^+$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.51 (m, 1H), 8.32 (d, 1H), 7.92 (m, 4H), 7.62 (m 4H), 7.23 (m, 4H), 3.21 (s, 3H), 3.91 (d, 6H)

Methyl 8-((4-fluoro-3-nitrophenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylate (226)

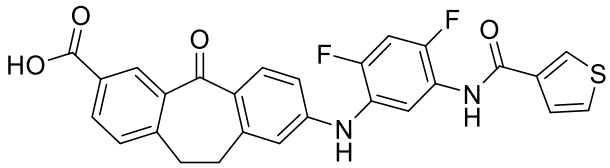


The title compound was synthesized according to the general procedure **1** for Buchwald-Hartwig amination. For the reaction, 400 mg dibenzosuberone and 225 mg of 4-fluoro-3-nitroaniline were used to obtain 282 mg of the product as yellow solid.

$C_{23}H_{17}FN_2O_5$ (Mr =420.11)

Yield	56%
HPLC	98% (t_r = 9.210 min)
ESI-MS	m/z 419.1 $[M-H]^-$

8-((2,4-difluoro-5-(thiophene-3-carboxamido)phenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylic acid (227)

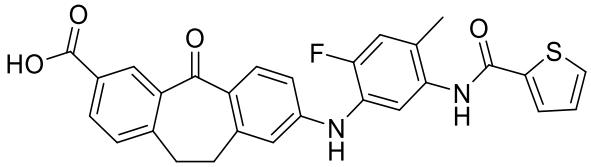


The title compound was synthesized according to the general procedure **4** for saponification. For the reaction, 100 mg of starting material was used to obtain 85 mg of the product as yellow solid.

$C_{27}H_{18}F_2N_2O_4S$ (Mr =504.51)

Yield	89%
HPLC	92% (t_r = 7.564 min)
ESI-MS	m/z 503.5 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.54 (s, 1H), 8.12 – 7.93 (m, J = 11.0 Hz, 4H), 7.50 – 7.39 (m, J = 5.4 Hz, 1H), 7.38 – 7.28 (m, 1H), 7.21 (d, J = 8.3 Hz, 1H), 6.92 (t, J = 10.7 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.68 (s, 1H), 3.19 – 2.95 (m, 4H)

8-((2-fluoro-4-methyl-5-(thiophene-2-carboxamido)phenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-2-carboxylic acid (228)

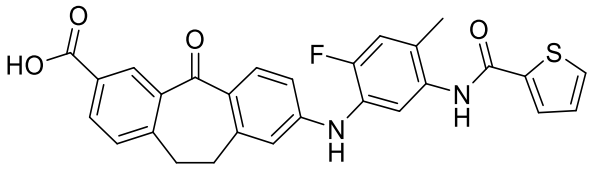


The title compound was synthesized according to the general procedure **4** for saponification. For the reaction, 30 mg of starting material was used to obtain 27 mg of the product as yellow solid.

$C_{28}H_{21}FN_2O_4S$ (Mr = 500.54)

Yield	93%
HPLC	85% (t_r = 7.313 min)
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.70 (s, 2H), 8.21 – 8.04 (m, J = 15.0, 7.3 Hz, 4H), 7.90 (d, J = 8.2 Hz, 1H), 7.72 – 7.60 (m, 2H), 7.55 (d, J = 4.7 Hz, 1H), 7.30 (dd, J = 8.1, 5.4 Hz, 2H), 7.14 (t, J = 4.0 Hz, 1H), 7.05 – 6.81 (m, 4H), 6.74 (d, 1H), 3.19 (s, 7H), 2.30 (s, 3H)

8-((2-fluoro-4-methyl-5-(thiophene-2-carboxamido)phenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylic acid (229)

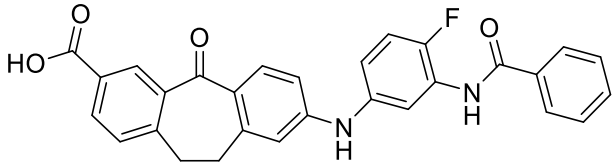


The title compound was synthesized according to the general procedure **4** for saponification. For the reaction, 50 mg of starting material was used to obtain 48 mg of the product as yellow solid.

$C_{28}H_{21}FN_2O_4S$ (Mr = 500.54)

Yield	100%
HPLC	100% (t_r = 7.472 min)
ESI-MS	m/z 499.4 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.59 (s, 1H), 8.03 (t, J = 8.6 Hz, 3H), 7.62 (s, 1H), 7.48 (d, 1H), 7.35 (s, 1H), 7.22 (d, J = 7.8 Hz, 1H), 6.94 (d, J = 11.0 Hz, 1H), 6.83 (d, J = 9.0 Hz, 1H), 6.72 (s, 1H), 3.18 – 2.95 (m, 4H), 2.23 (s, 3H)

8-((3-benzamido-4-fluorophenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylic acid (230)

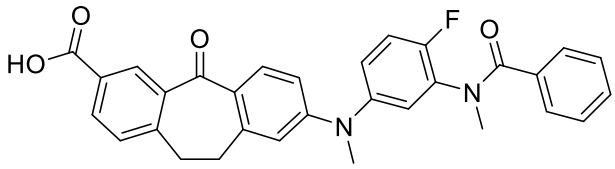


The title compound was synthesized according to the general procedure **4** for saponification. For the reaction, 150 mg of starting material was used to obtain 141 mg of the product as yellow solid.

$C_{29}H_{21}FN_2O_4$ (Mr = 480.15)

Yield	88%
HPLC	84% (t_r = 7.755 min)
ESI-MS	m/z 479.3 $[M-H]^-$
^{1}H-NMR (400 MHz, Aceton-*d*)	δ 8.92 (s, 1H), 8.44 (s, 1H), 8.05-7.95 (m, 4H), 7.65-7.58(m, 1H), 7.56-7.50 (m, 3H), 7.43 (m, 1H), 7.30-7.24 (m, 1H), 7.10-7.05 (m, 1H), 7.02-6.95 (m, 1H), 6.87 (s, 1H), 3.17-6.06 (m, 4H)

8-((4-fluoro-3-(N-methylbenzamido)phenyl)(methyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylic acid (231)

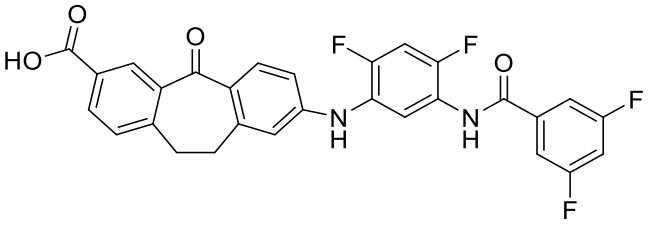


The title compound was synthesized according to the general procedure **4** for saponification. For the reaction, 28 mg of starting material was used to obtain 26 mg of the product as yellow solid. The compound was used for the next step without NMR spectroscopy due to solubility issues.

$C_{31}H_{25}FN_2O_4$ (Mr = 508.18)

Yield	93%
ESI-MS	m/z 507.3 $[M-H]^-$

8-((5-(3,5-difluorobenzamido)-2,4-difluorophenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylic acid (232)

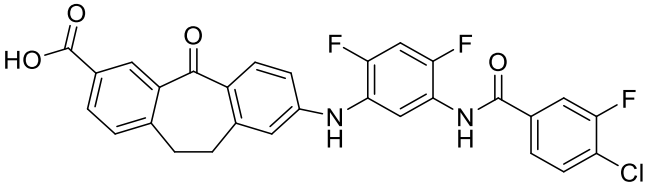


The title compound was synthesized according to the general procedure **4** for saponification. For the reaction, 150 mg of starting material was used to obtain 138 mg of the product as yellow solid.

$C_{29}H_{18}F_4N_2O_4$ (Mr = 534.12)

Yield	92%
HPLC	100% (t_r = 7.472 min)
ESI-MS	m/z 533.3 $[M-H]^-$
^{1}H-NMR (200 MHz, $CDCl_3$)	δ 8.64 – 8.54 (m, 1H), 8.13 – 7.96 (m, 2H), 7.50 (dd, J = 5.9 Hz, 1H), 7.44 – 7.07 (m, 2H), 7.07 – 6.54 (m, 4H), 3.19 – 2.99 (m, J = 12.8 Hz, 4H)

8-((5-(4-chloro-3-fluorobenzamido)-2,4-difluorophenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylic acid (234)

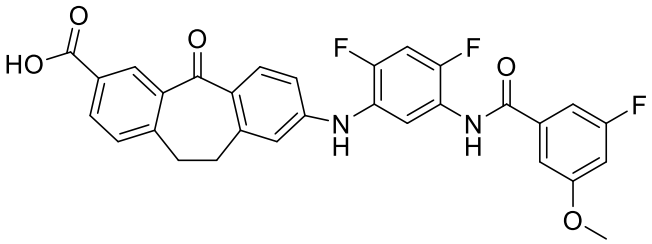


The title compound was synthesized according to the general procedure **4** for saponification. For the reaction, 60 mg of starting material was used to obtain 58 mg of the product as yellow solid. The compound was used for the next step without NMR spectroscopy due to solubility issues.

$C_{29}H_{18}F_4N_2O_4$ (Mr = 534.12)

Yield	93%
HPLC	65% (t_r = 8.916 min)
ESI-MS	m/z 549.3 $[M-H]^-$

8-((2,4-difluoro-5-(3-fluoro-5-methoxybenzamido)phenyl)amino)-5-oxo-10,11-dihydro-5H-dibenzo[a,d][7]annulene-3-carboxylic acid (235)



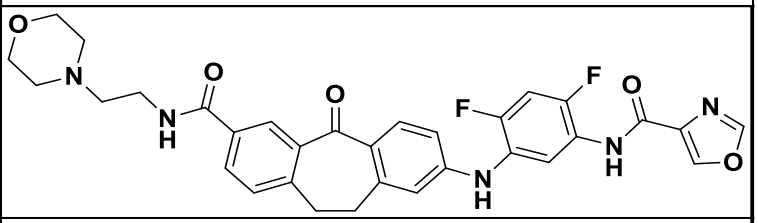
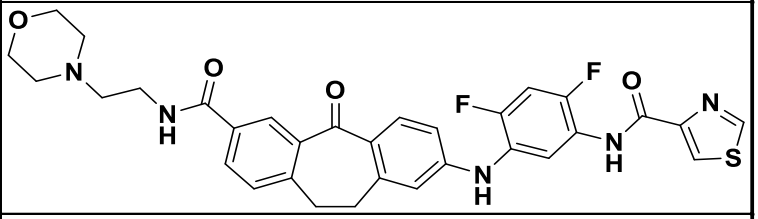
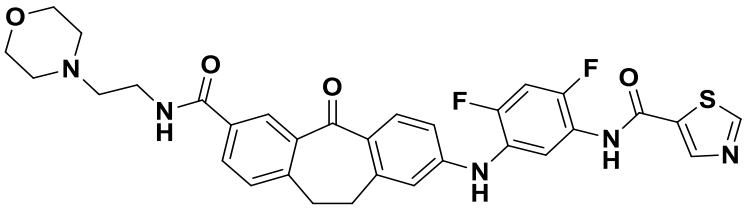
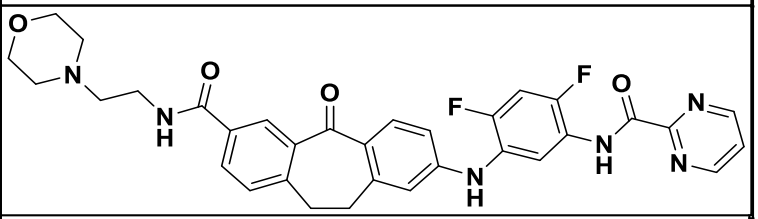
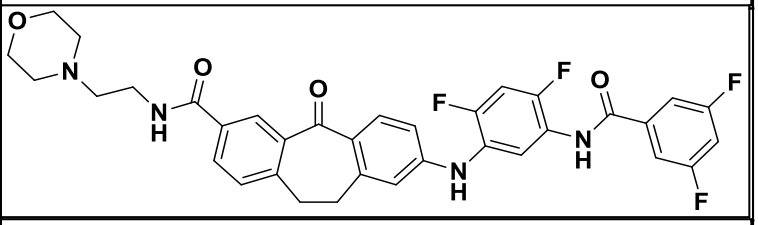
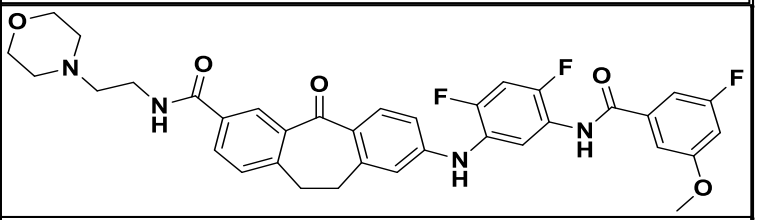
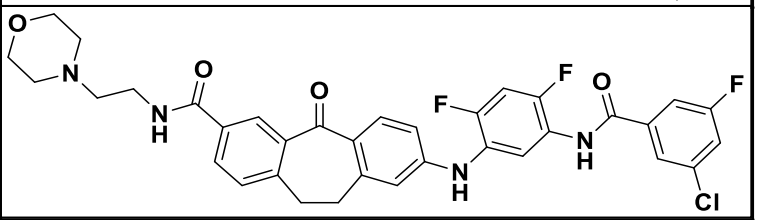
The title compound was synthesized according to the general procedure **4** for saponification. For the reaction, 155 mg of starting material was used to obtain 146 mg of the product as yellow solid. The compound was used for the next step without NMR spectroscopy due to solubility issues.

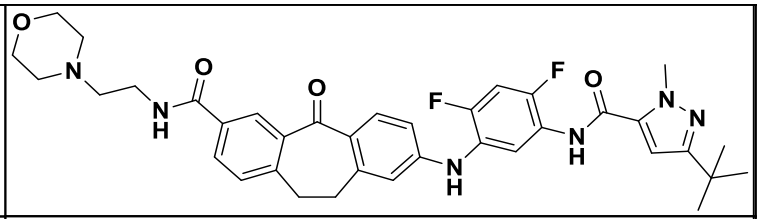
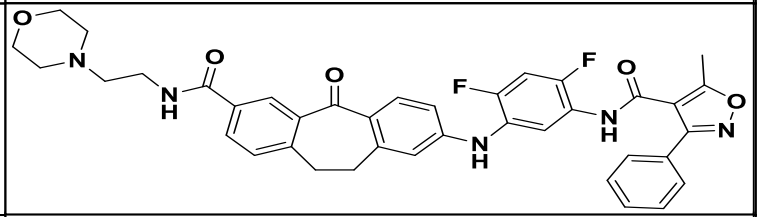
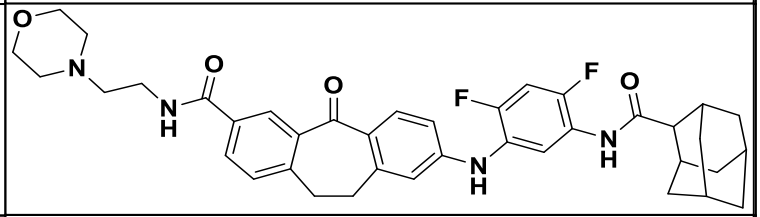
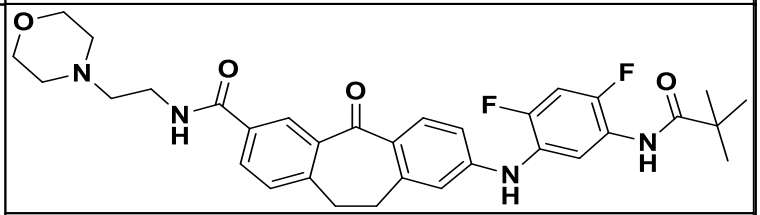
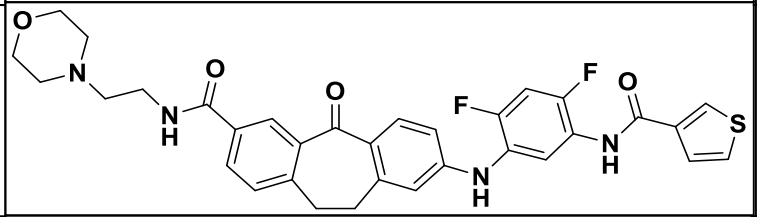
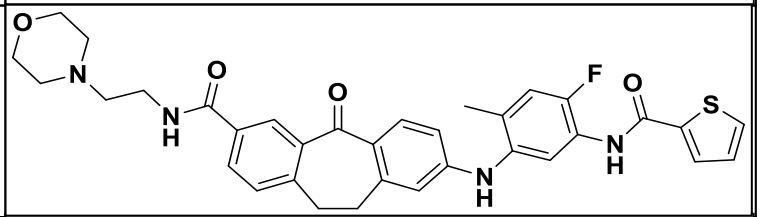
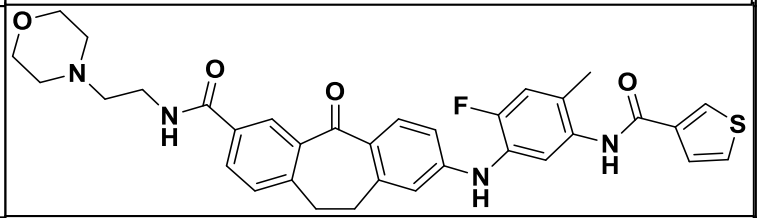
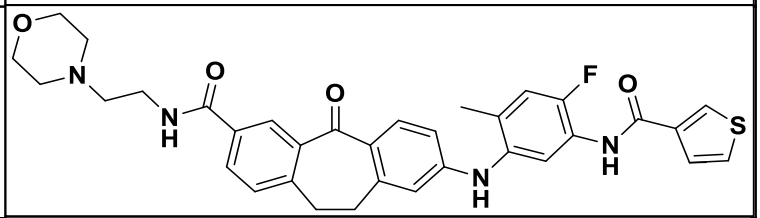
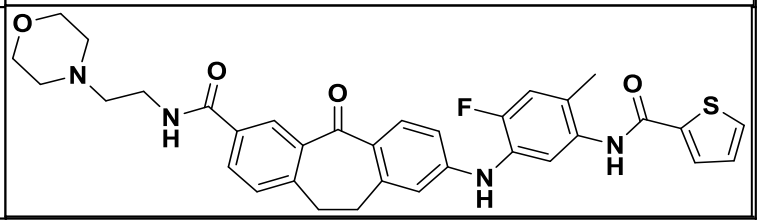
$C_{30}H_{21}F_3N_2O_5$ (Mr = 546.14)

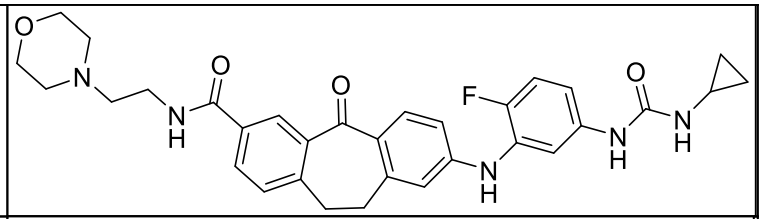
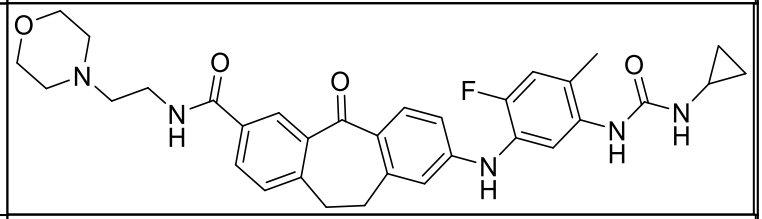
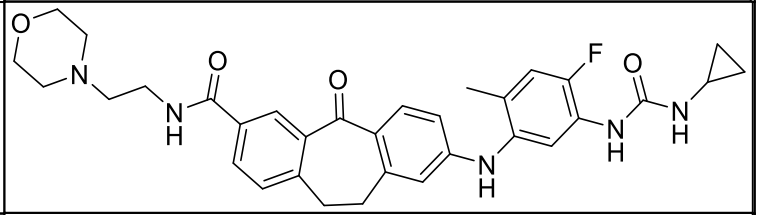
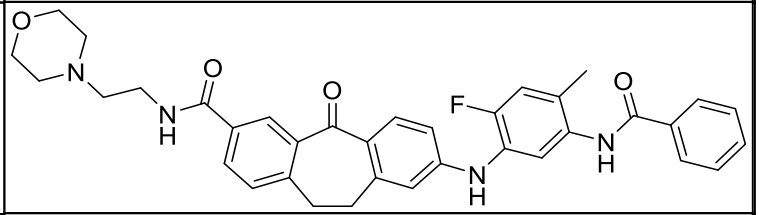
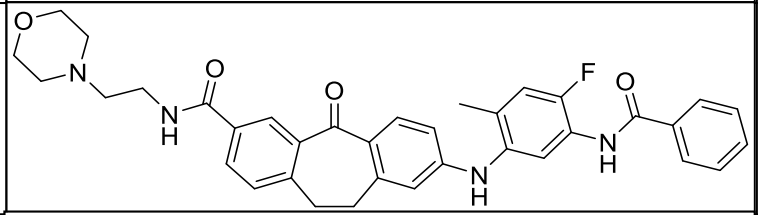
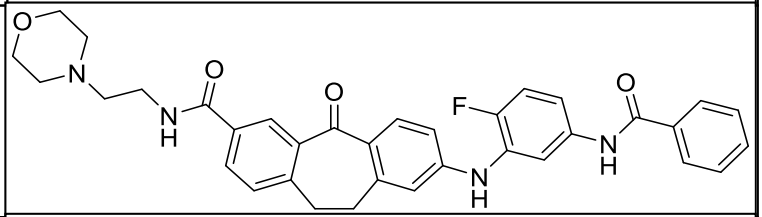
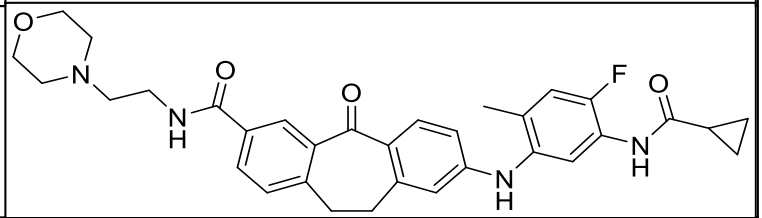
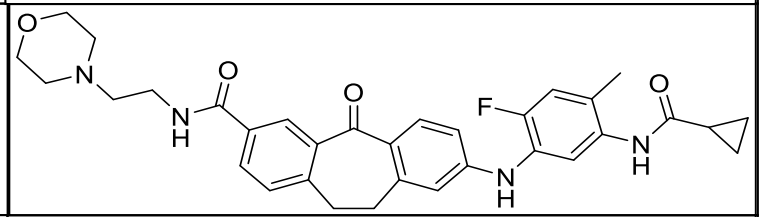
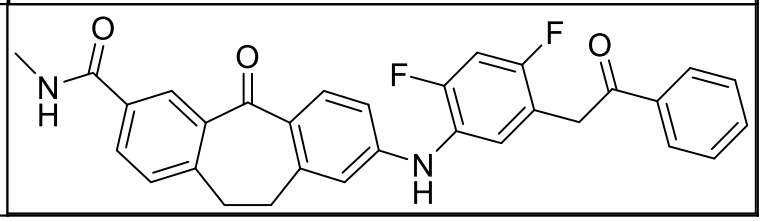
Yield	94%
HPLC	73% (t_r = 8.402 min)
ESI-MS	m/z 545.5 $[M-H]^-$

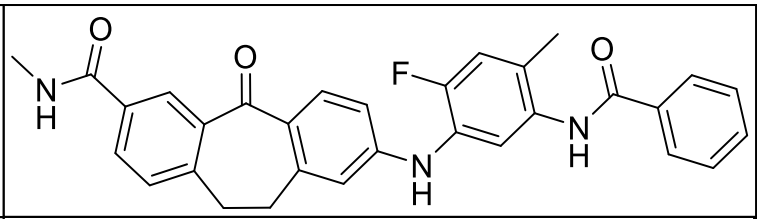
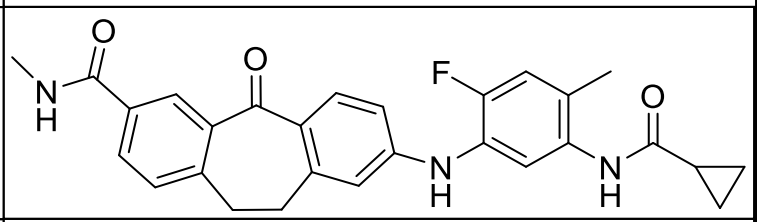
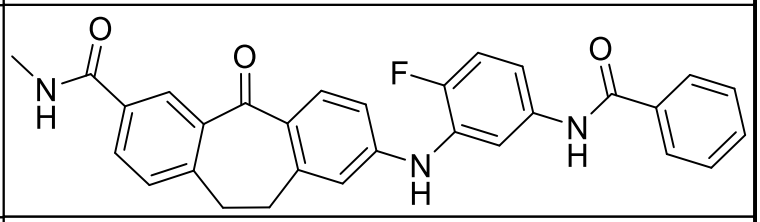
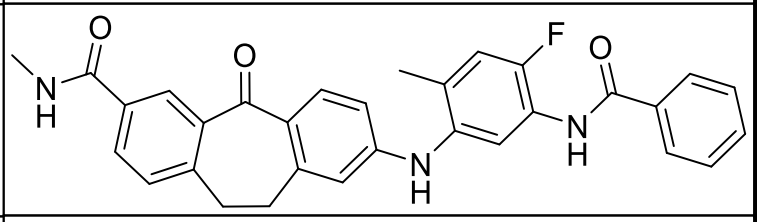
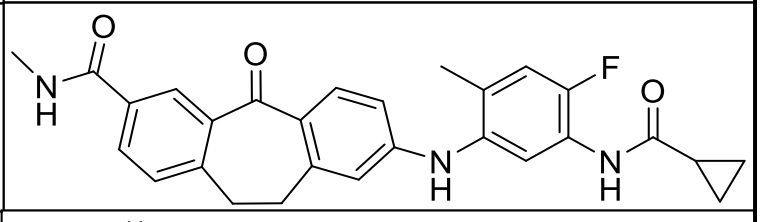
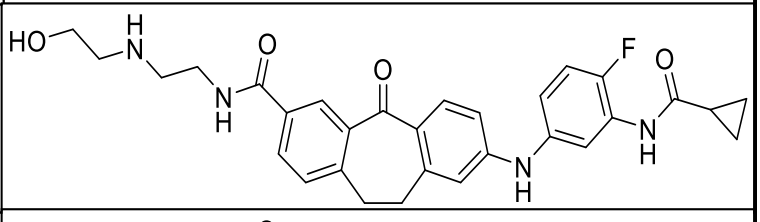
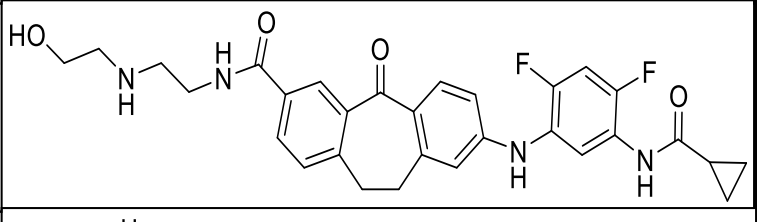
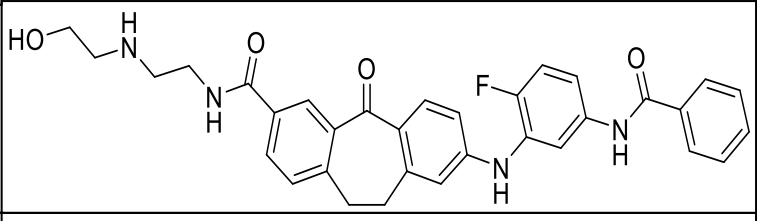
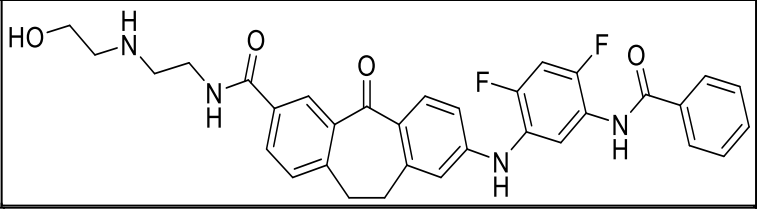
6. Appendix

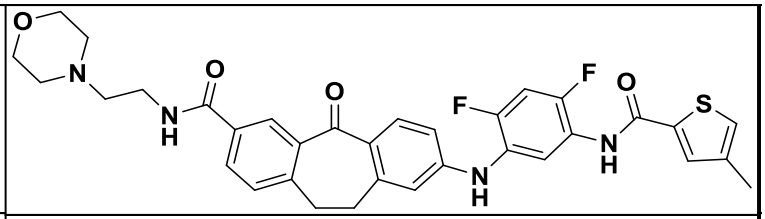
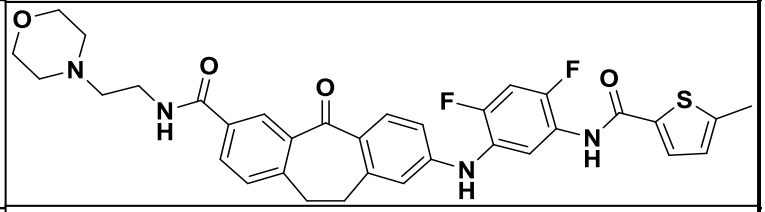
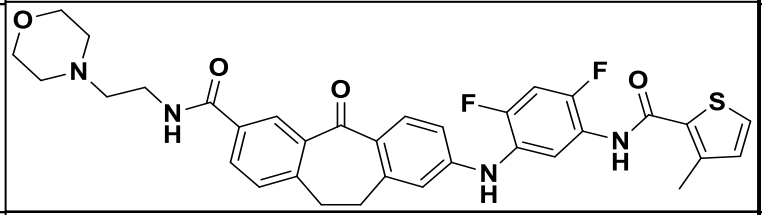
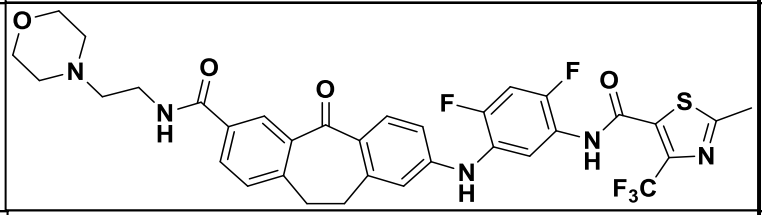
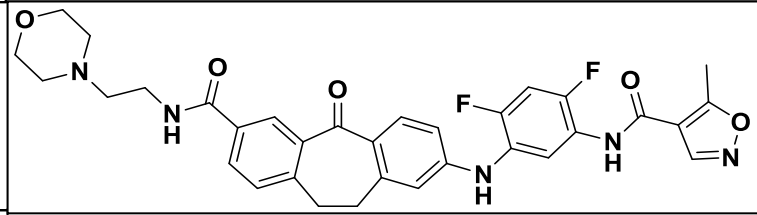
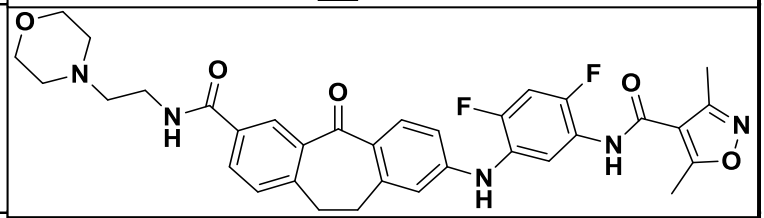
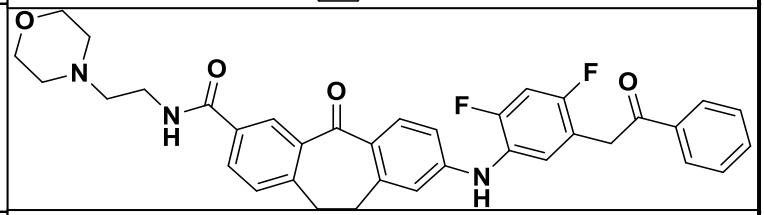
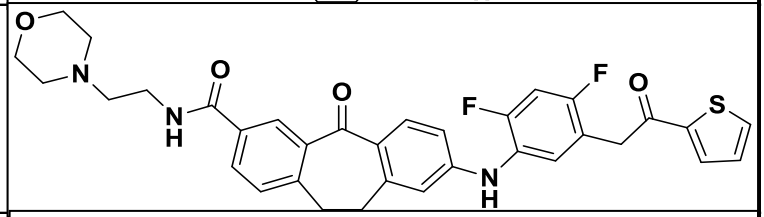
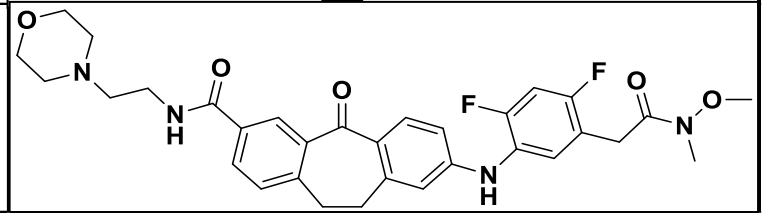
Overview of all synthesized final compounds

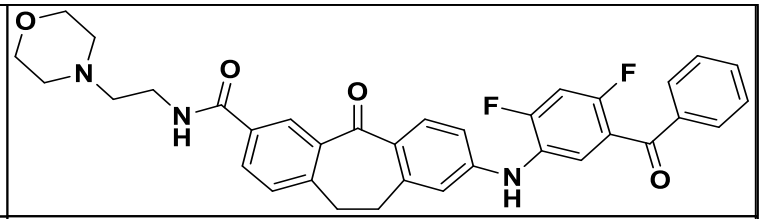
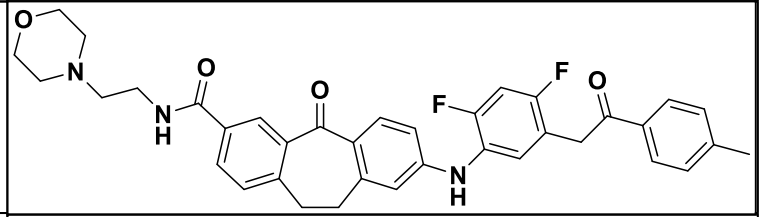
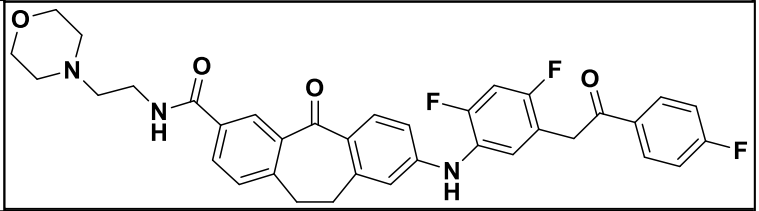
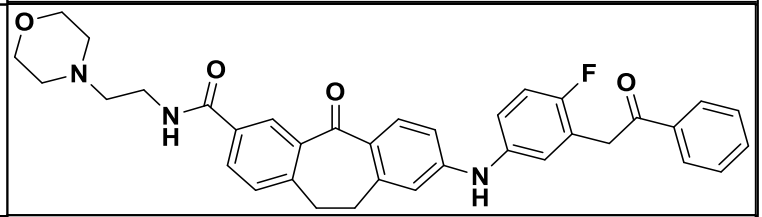
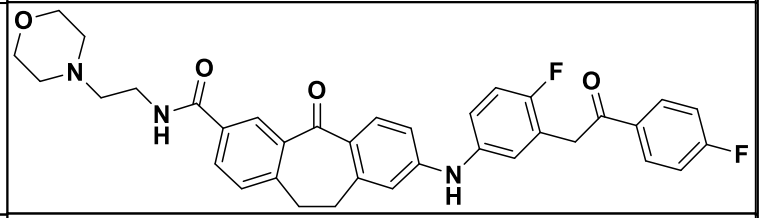
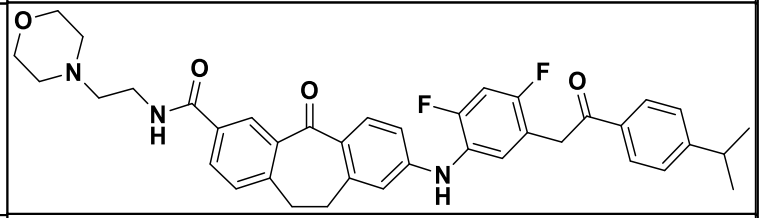
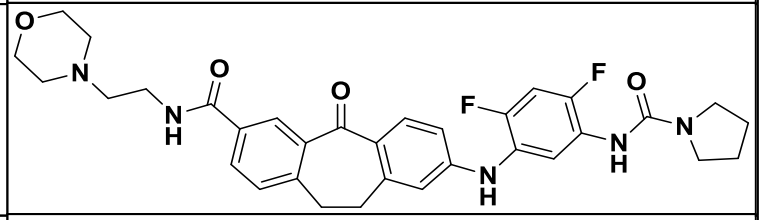
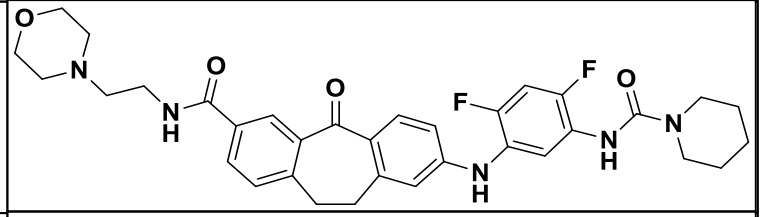
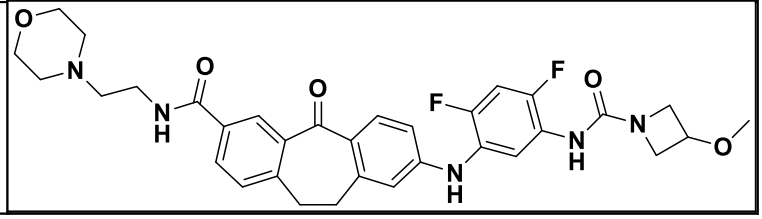
No.	Structure
89	
90	
91	
92	
93	
94	
95	

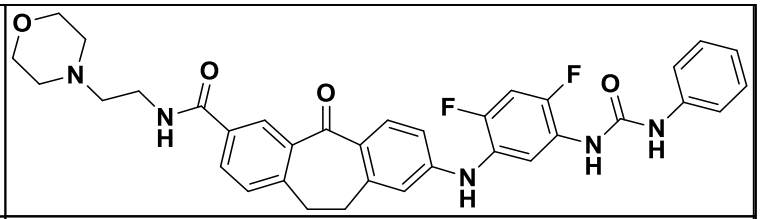
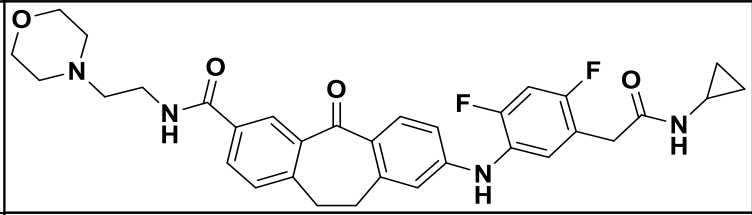
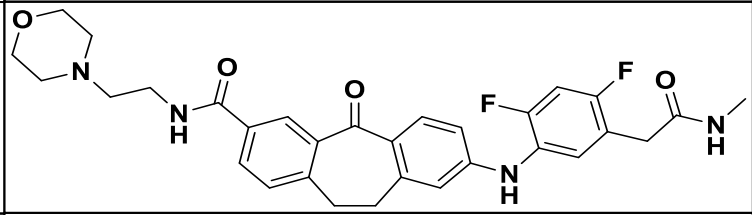
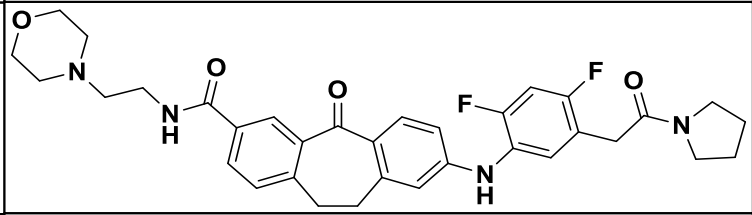
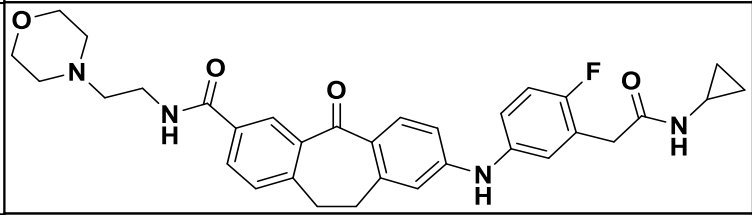
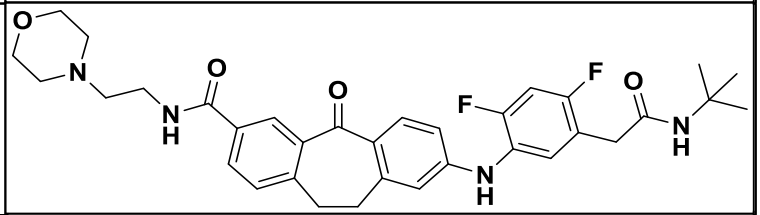
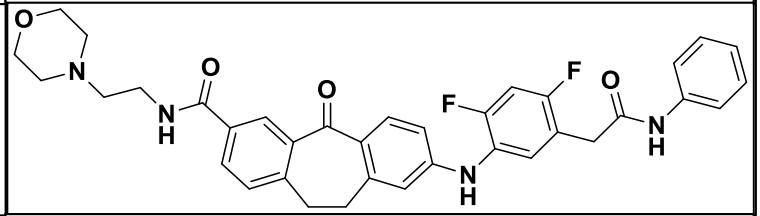
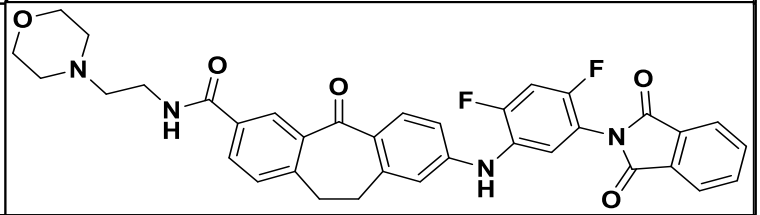
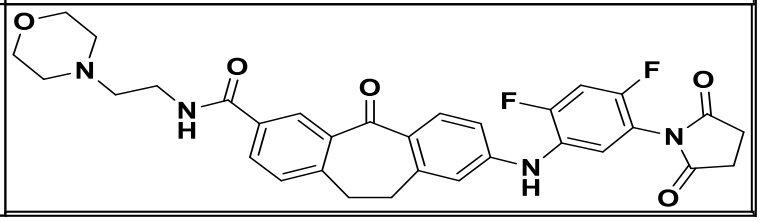
96	
97	
98	
99	
100	
101	
102	
103	
104	

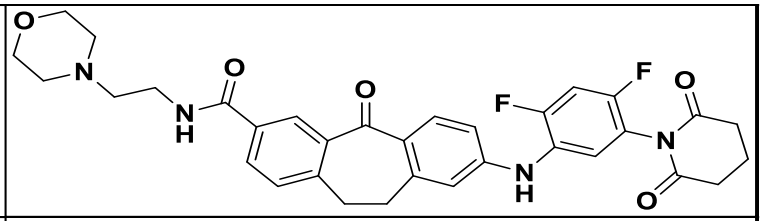
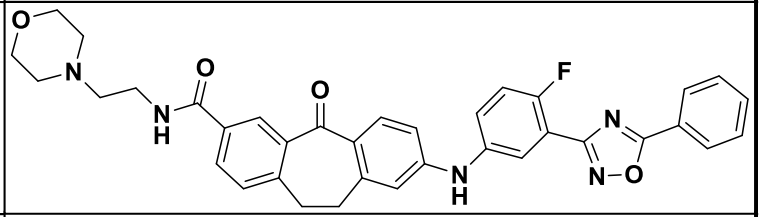
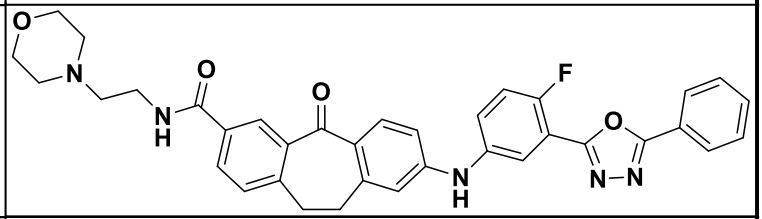
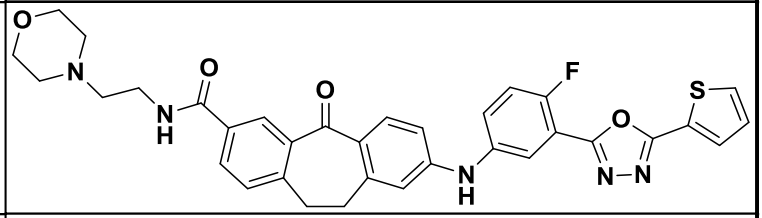
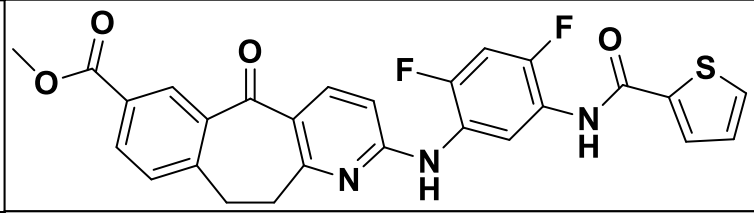
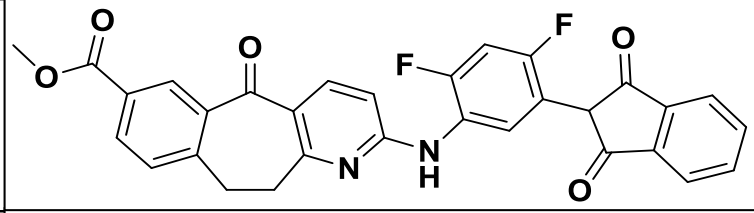
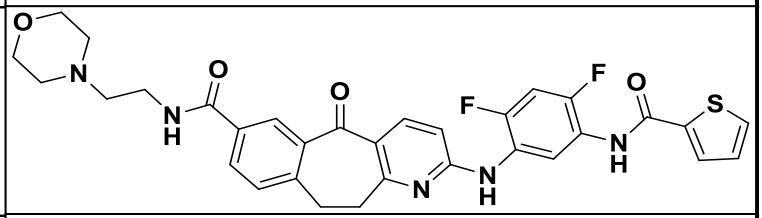
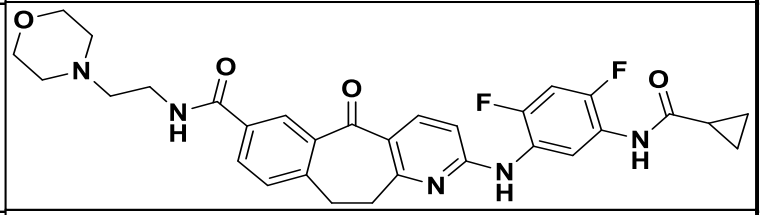
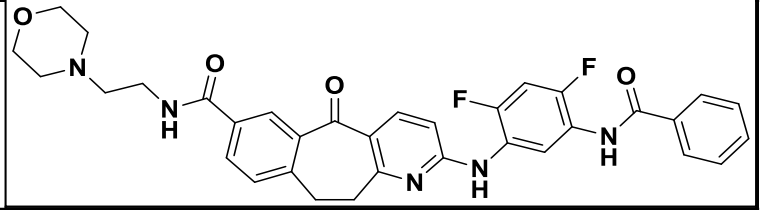
105	
106	
107	
108	
109	
110	
111	
112	
113	

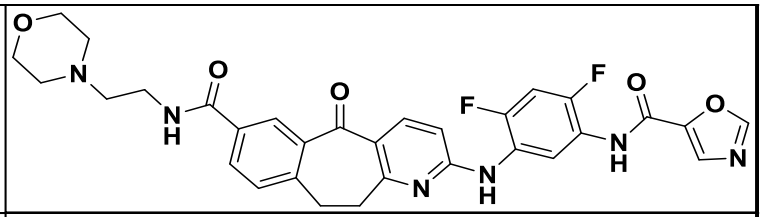
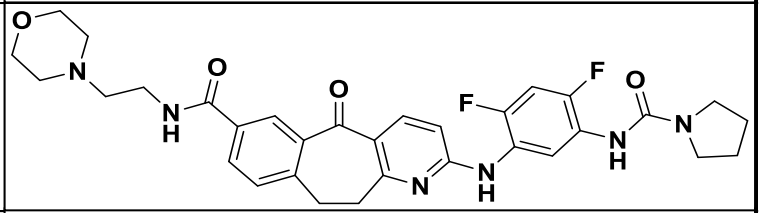
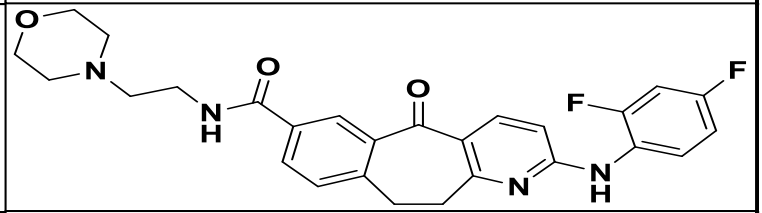
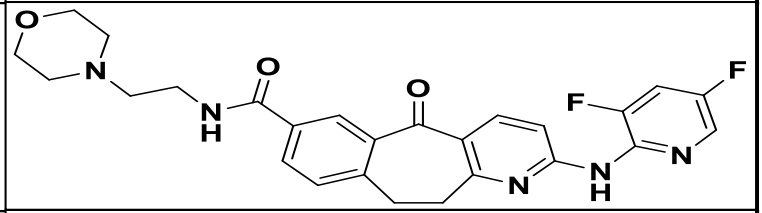
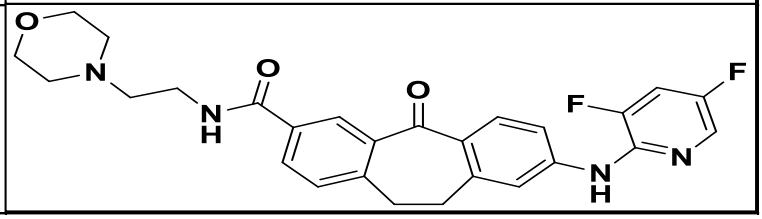
114	
115	
116	
117	
118	
119	
120	
121	
122	

123	
124	
125	
126	
127	
128	
129	
130	
131	

132	
133	
134	
135	
136	
137	
138	
139	
140	

141	
142	
143	
144	
145	
146	
147	
148	
149	

150	
151	
152	
153	
154	
155	
156	
157	
158	

159	
160	
161	
162	
163	

7. Literature

1. Hunter, T., [1] Protein kinase classification. In *Methods in Enzymology*, Academic Press: 1991; Vol. 200, pp 3-37.
2. Burnett, G.; Kennedy, E. P., The enzymatic phosphorylation of proteins. *Journal of Biological Chemistry* **1954,** *211* (2), 969-980.
3. Fabbro, D.; Cowan-Jacob, S. W.; Moebitz, H., Ten things you should know about protein kinases: IUPHAR Review 14. *British Journal of Pharmacology* **2015,** *172* (11), 2675-2700.
4. Fay, J. R.; Steele, V.; Crowell, J. A., Energy Homeostasis and Cancer Prevention: The AMP-Activated Protein Kinase. *Cancer Prevention Research* **2009,** *2* (4), 301.
5. Dar, A. C.; Shokat, K. M., The evolution of protein kinase inhibitors from antagonists to agonists of cellular signaling. *Annual review of biochemistry* **2011,** *80*, 769-795.
6. Haller, V.; Nahidino, P.; Forster, M.; Laufer, S. A., An updated patent review of p38 MAP kinase inhibitors (2014-2019). *Expert Opinion on Therapeutic Patents* **2020,** *30* (6), 453-466.
7. Manning, G.; Whyte, D. B.; Martinez, R.; Hunter, T.; Sudarsanam, S., The Protein Kinase Complement of the Human Genome. *Science* **2002,** *298* (5600), 1912.
8. Stamm, S.; Ben-Ari, S.; Rafalska, I.; Tang, Y.; Zhang, Z.; Toiber, D.; Thanaraj, T. A.; Soreq, H., Function of alternative splicing. *Gene* **2005,** *344*, 1-20.
9. Hunter, T., A thousand and one protein kinases. *Cell* **1987,** *50* (6), 823-829.
10. Endicott, J. A.; Noble, M. E. M.; Johnson, L. N., The Structural Basis for Control of Eukaryotic Protein Kinases. *Annual Review of Biochemistry* **2012,** *81* (1), 587-613.
11. Hanks, S. K., Genomic analysis of the eukaryotic protein kinase superfamily: a perspective. *Genome Biology* **2003,** *4* (5), 111.
12. Rufino, S. D.; Blundell, T. L., Structure-based identification and clustering of protein families and superfamilies. *Journal of Computer-Aided Molecular Design* **1994,** *8* (1), 5-27.
13. Robinson, M. J.; Cobb, M. H., Mitogen-activated protein kinase pathways. *Curr Opin Cell Biol* **1997,** *9* (2), 180-6.
14. Pearson, G.; Robinson, F.; Beers Gibson, T.; Xu, B. E.; Karandikar, M.; Berman, K.; Cobb, M. H., Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions. *Endocr Rev* **2001,** *22* (2), 153-183.
15. Cobb, M. H.; Goldsmith, E. J., How MAP kinases are regulated. *Journal of Biological Chemistry* **1995,** *270* (25), 14843-14846.
16. Martín-Blanco, E., p38 MAPK signalling cascades: ancient roles and new functions. *Bioessays* **2000,** *22* (7), 637-645.
17. Zarubin, T.; Han, J., Activation and signaling of the p38 MAP kinase pathway. *Cell Research* **2005,** *15* (1), 11-18.
18. Gerits, N.; Kostenko, S.; Moens, U., In vivo functions of mitogen-activated protein kinases: conclusions from knock-in and knock-out mice. *Transgenic Res* **2007,** *16* (3), 281-314.
19. Corre, I.; Paris, F.; Huot, J., The p38 pathway, a major pleiotropic cascade that transduces stress and metastatic signals in endothelial cells. *Oncotarget* **2017,** *8* (33), 55684-55714.
20. Goedert, M.; Cuenda, A.; Craxton, M.; Jakes, R.; Cohen, P., Activation of the novel stress-activated protein kinase SAPK4 by cytokines and cellular stresses is mediated by SKK3 (MKK6); comparison of its substrate specificity with that of other SAP kinases. *EMBO J* **1997,** *16* (12), 3563-3571.
21. Cuadrado, A.; Nebreda, Angel R., Mechanisms and functions of p38 MAPK signalling. *Biochemical Journal* **2010,** *429* (3), 403-417.
22. Raingeaud, J.; Gupta, S.; Rogers, J. S.; Dickens, M.; Han, J.; Ulevitch, R. J.; Davis, R. J., Pro-inflammatory cytokines and environmental stress cause p38 mitogen-activated protein kinase activation by dual phosphorylation on tyrosine and threonine. *J Biol Chem* **1995,** *270* (13), 7420-6.
23. Cuenda, A.; Rousseau, S., p38 MAP-kinases pathway regulation, function and role in human diseases. *Biochim Biophys Acta* **2007,** *1773* (8), 1358-75.

24. Raingeaud, J.; Gupta, S.; Rogers, J. S.; Dickens, M.; Han, J.; Ulevitch, R. J.; Davis, R. J., Pro-inflammatory cytokines and environmental stress cause p38 mitogen-activated protein kinase activation by dual phosphorylation on tyrosine and threonine. *Journal of Biological Chemistry* **1995,** *270* (13), 7420-7426.
25. Cuenda, A.; Cohen, P.; Buée-Scherrer, V.; Goedert, M., Activation of stress-activated protein kinase-3 (SAPK3) by cytokines and cellular stresses is mediated via SAPKK3 (MKK6); comparison of the specificities of SAPK3 and SAPK2 (RK/p38). *EMBO J* **1997,** *16* (2), 295-305.
26. Kaminska, B., MAPK signalling pathways as molecular targets for anti-inflammatory therapy—from molecular mechanisms to therapeutic benefits. *Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics* **2005,** *1754* (1), 253-262.
27. Hanahan, D.; Weinberg, R. A., Hallmarks of cancer: the next generation. *Cell* **2011,** *144* (5), 646-74.
28. Steelman, L. S.; Fitzgerald, T.; Lertpiriyapong, K.; Cocco, L.; Follo, M. Y.; Martelli, A. M.; Neri, L. M.; Marmiroli, S.; Libra, M.; Candido, S.; Nicoletti, F.; Scalisi, A.; Fenga, C.; Drobot, L.; Rakus, D.; Gizak, A.; Laidler, P.; Dulinska-Litewka, J.; Basecke, J.; Mijatovic, S.; Maksimovic-Ivanic, D.; Montalto, G.; Cervello, M.; Milella, M.; Tafuri, A.; Demidenko, Z.; Abrams, S. L.; McCubrey, J. A., Critical Roles of EGFR Family Members in Breast Cancer and Breast Cancer Stem Cells: Targets for Therapy. *Curr Pharm Des* **2016,** *22* (16), 2358-88.
29. Raftery, L.; Sanoff, H. K.; Goldberg, R., Colon cancer in older adults. *Semin Oncol* **2008,** *35* (6), 561-8.
30. Van Cutsem, E.; Cervantes, A.; Adam, R.; Sobrero, A.; Van Krieken, J. H.; Aderka, D.; Aranda Aguilar, E.; Bardelli, A.; Benson, A.; Bodoky, G.; Ciardiello, F.; D'Hoore, A.; Diaz-Rubio, E.; Douillard, J. Y.; Ducreux, M.; Falcone, A.; Grothey, A.; Gruenberger, T.; Haustermans, K.; Heinemann, V.; Hoff, P.; Köhne, C. H.; Labianca, R.; Laurent-Puig, P.; Ma, B.; Maughan, T.; Muro, K.; Normanno, N.; Österlund, P.; Oyen, W. J.; Papamichael, D.; Pentheroudakis, G.; Pfeiffer, P.; Price, T. J.; Punt, C.; Ricke, J.; Roth, A.; Salazar, R.; Scheithauer, W.; Schmoll, H. J.; Tabernero, J.; Taïeb, J.; Tejpar, S.; Wasan, H.; Yoshino, T.; Zaanan, A.; Arnold, D., ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* **2016,** *27* (8), 1386-422.
31. Joachim, C.; Macni, J.; Drame, M.; Pomier, A.; Escarmant, P.; Veronique-Baudin, J.; Vinh-Hung, V., Overall survival of colorectal cancer by stage at diagnosis: Data from the Martinique Cancer Registry. *Medicine* **2019,** *98* (35).
32. Gross, S.; Rahal, R.; Stransky, N.; Lengauer, C.; Hoeflich, K. P., Targeting cancer with kinase inhibitors. *The Journal of clinical investigation* **2015,** *125* (5), 1780-1789.
33. Bukhtiyarova, M.; Karpusas, M.; Northrop, K.; Namboodiri, H. V. M.; Springman, E. B., Mutagenesis of p38α MAP Kinase Establishes Key Roles of Phe169 in Function and Structural Dynamics and Reveals a Novel DFG-OUT State. *Biochemistry* **2007,** *46* (19), 5687-5696.
34. Phong, M. S.; Van Horn, R. D.; Li, S.; Tucker-Kellogg, G.; Surana, U.; Ye, X. S., p38 mitogen-activated protein kinase promotes cell survival in response to DNA damage but is not required for the G(2) DNA damage checkpoint in human cancer cells. *Mol Cell Biol* **2010,** *30* (15), 3816-3826.
35. Lavoie, J. N.; L'Allemain, G.; Brunet, A.; Müller, R.; Pouysségur, J., Cyclin D1 expression is regulated positively by the p42/p44MAPK and negatively by the p38/HOGMAPK pathway. *J Biol Chem* **1996,** *271* (34), 20608-16.
36. Chiacchiera, F.; Matrone, A.; Ferrari, E.; Ingravallo, G.; Lo Sasso, G.; Murzilli, S.; Petruzzelli, M.; Salvatore, L.; Moschetta, A.; Simone, C., p38α blockade inhibits colorectal cancer growth in vivo by inducing a switch from HIF1α- to FoxO-dependent transcription. *Cell Death & Differentiation* **2009,** *16* (9), 1203-1214.
37. McIntyre, R. E.; Buczacki, S. J. A.; Arends, M. J.; Adams, D. J., Mouse models of colorectal cancer as preclinical models. *Bioessays* **2015,** *37* (8), 909-920.
38. Gupta, J.; del Barco Barrantes, I.; Igea, A.; Sakellariou, S.; Pateras, Ioannis S.; Gorgoulis, Vassilis G.; Nebreda, Angel R., Dual Function of p38α MAPK in Colon Cancer: Suppression of Colitis-Associated Tumor Initiation but Requirement for Cancer Cell Survival. *Cancer Cell* **2014,** *25* (4), 484-500.

39. Murphy, L. O.; Blenis, J., MAPK signal specificity: the right place at the right time. *Trends in biochemical sciences* **2006,** *31* (5), 268-275.
40. Taylor, S. S.; Radzio-Andzelm, E., Three protein kinase structures define a common motif. *Structure* **1994,** *2* (5), 345-355.
41. Nolen, B.; Taylor, S.; Ghosh, G., Regulation of protein kinases; controlling activity through activation segment conformation. *Mol Cell* **2004,** *15* (5), 661-75.
42. Wilson, K. P.; Fitzgibbon, M. J.; Caron, P. R.; Griffith, J. P.; Chen, W.; McCaffrey, P. G.; Chambers, S. P.; Su, M. S. S., Crystal Structure of p38 Mitogen-activated Protein Kinase*. *Journal of Biological Chemistry* **1996,** *271* (44), 27696-27700.
43. Traxler, P., Tyrosine kinase inhibitors in cancer treatment (Part II). *Expert Opinion on Therapeutic Patents* **1998,** *8* (12), 1599-1625.
44. Fitzgerald, C. E.; Patel, S. B.; Becker, J. W.; Cameron, P. M.; Zaller, D.; Pikounis, V. B.; O'Keefe, S. J.; Scapin, G., Structural basis for p38α MAP kinase quinazolinone and pyridol-pyrimidine inhibitor specificity. *Nature Structural & Molecular Biology* **2003,** *10* (9), 764-769.
45. Martz, K. E.; Dorn, A.; Baur, B.; Schattel, V.; Goettert, M. I.; Mayer-Wrangowski, S. C.; Rauh, D.; Laufer, S. A., Targeting the hinge glycine flip and the activation loop: novel approach to potent p38α inhibitors. *J Med Chem* **2012,** *55* (17), 7862-74.
46. Martz, K. E.; Dorn, A.; Baur, B.; Schattel, V.; Goettert, M. I.; Mayer-Wrangowski, S. C.; Rauh, D.; Laufer, S. A., Targeting the Hinge Glycine Flip and the Activation Loop: Novel Approach to Potent p38α Inhibitors. *Journal of Medicinal Chemistry* **2012,** *55* (17), 7862-7874.
47. Zuccotto, F.; Ardini, E.; Casale, E.; Angiolini, M., Through the "Gatekeeper Door": Exploiting the Active Kinase Conformation. *Journal of Medicinal Chemistry* **2010,** *53* (7), 2681-2694.
48. Eyers, P. A.; Craxton, M.; Morricel, N.; Cohen, P.; Goedert, M., Conversion of SB 203580-insensitive MAP kinase family members to drug-sensitive forms by a single amino-acid substitution. *Chemistry & biology* **1998,** *5* (6), 321-328.
49. Kondoh, Y.; Honda, K.; Hiranuma, S.; Hayashi, T.; Shimizu, T.; Watanabe, N.; Osada, H., Comparative chemical array screening for p38γ/δ MAPK inhibitors using a single gatekeeper residue difference between p38α/β and p38γ/δ. *Scientific Reports* **2016,** *6* (1), 29881.
50. Johnson, L. N.; Lowe, E. D.; Noble, M. E. M.; Owen, D. J., The structural basis for substrate recognition and control by protein kinases1The previous Datta Lectures were given by: F. Melchers (1st, 1986), N. Sharon (2nd, FEBS Letters 217 (1987) 145–157); B.G. Malmström (3rd, FEBS Letters 250 (1989) 9–21; J.C. Skou (4th, FEBS Letters 268 (1990) 314–324); B.A. Lynch and D.E. Koshland, Jr. (5th, FEBS Letters 307 (1992) 3–9); A.R. Fersht (6th, FEBS Letters 325 (1993) 5–16); E. Sackmann (7th, FEBS Letters 346 (1994) 3–16); P. De Camilli (8th, FEBS Letters 369 (1995) 3–12); C. Weissmann (9th, FEBS Letters 389 (1996) 3–11); Ph. Cohen et al. (10th, FEBS Letters 410 (1997) 3–10).1. *FEBS Letters* **1998,** *430* (1), 1-11.
51. Wilson, K. P.; Fitzgibbon, M. J.; Caron, P. R.; Griffith, J. P.; Chen, W.; McCaffrey, P. G.; Chambers, S. P.; Su, M. S.-S., Crystal structure of p38 mitogen-activated protein kinase. *Journal of Biological Chemistry* **1996,** *271* (44), 27696-27700.
52. Nagar, B.; Bornmann, W. G.; Pellicena, P.; Schindler, T.; Veach, D. R.; Miller, W. T.; Clarkson, B.; Kuriyan, J., Crystal structures of the kinase domain of c-Abl in complex with the small molecule inhibitors PD173955 and imatinib (STI-571). *Cancer Res* **2002,** *62* (15), 4236-43.
53. Bishop, A. C.; Ubersax, J. A.; Petsch, D. T.; Matheos, D. P.; Gray, N. S.; Blethrow, J.; Shimizu, E.; Tsien, J. Z.; Schultz, P. G.; Rose, M. D.; Wood, J. L.; Morgan, D. O.; Shokat, K. M., A chemical switch for inhibitor-sensitive alleles of any protein kinase. *Nature* **2000,** *407* (6802), 395-401.
54. Treiber, Daniel K.; Shah, Neil P., Ins and Outs of Kinase DFG Motifs. *Chemistry & Biology* **2013,** *20* (6), 745-746.
55. Vijayan, R. S. K.; He, P.; Modi, V.; Duong-Ly, K. C.; Ma, H.; Peterson, J. R.; Dunbrack, R. L., Jr.; Levy, R. M., Conformational analysis of the DFG-out kinase motif and biochemical profiling of structurally validated type II inhibitors. *Journal of medicinal chemistry* **2015,** *58* (1), 466-479.

56. Taylor, S. S.; Kornev, A. P., Protein kinases: evolution of dynamic regulatory proteins. *Trends Biochem Sci* **2011,** *36* (2), 65-77.
57. McClendon, C. L.; Kornev, A. P.; Gilson, M. K.; Taylor, S. S., Dynamic architecture of a protein kinase. *Proceedings of the National Academy of Sciences* **2014,** *111* (43), E4623.
58. Hu, J.; Ahuja, L. G.; Meharena, H. S.; Kannan, N.; Kornev, A. P.; Taylor, S. S.; Shaw, A. S., Kinase regulation by hydrophobic spine assembly in cancer. *Mol Cell Biol* **2015,** *35* (1), 264-276.
59. Yurtsever, Z.; Scheaffer, S. M.; Romero, A. G.; Holtzman, M. J.; Brett, T. J., The crystal structure of phosphorylated MAPK13 reveals common structural features and differences in p38 MAPK family activation. *Acta Crystallogr D Biol Crystallogr* **2015,** *71* (Pt 4), 790-799.
60. Robinson, R., Confirming the importance of the R-spine: new insights into protein kinase regulation. *PLoS Biol* **2013,** *11* (10), e1001681-e1001681.
61. Zhang, J.; Adrián, F. J.; Jahnke, W.; Cowan-Jacob, S. W.; Li, A. G.; Iacob, R. E.; Sim, T.; Powers, J.; Dierks, C.; Sun, F.; Guo, G. R.; Ding, Q.; Okram, B.; Choi, Y.; Wojciechowski, A.; Deng, X.; Liu, G.; Fendrich, G.; Strauss, A.; Vajpai, N.; Grzesiek, S.; Tuntland, T.; Liu, Y.; Bursulaya, B.; Azam, M.; Manley, P. W.; Engen, J. R.; Daley, G. Q.; Warmuth, M.; Gray, N. S., Targeting Bcr-Abl by combining allosteric with ATP-binding-site inhibitors. *Nature* **2010,** *463* (7280), 501-6.
62. Wilson, K. P.; McCaffrey, P. G.; Hsiao, K.; Pazhanisamy, S.; Galullo, V.; Bemis, G. W.; Fitzgibbon, M. J.; Caron, P. R.; Murcko, M. A.; Su, M. S., The structural basis for the specificity of pyridinylimidazole inhibitors of p38 MAP kinase. *Chemistry & biology* **1997,** *4* (6), 423-431.
63. Schiebel, J.; Gaspari, R.; Wulsdorf, T.; Ngo, K.; Sohn, C.; Schrader, T. E.; Cavalli, A.; Ostermann, A.; Heine, A.; Klebe, G., Intriguing role of water in protein-ligand binding studied by neutron crystallography on trypsin complexes. *Nature Communications* **2018,** *9* (1), 3559.
64. Koeberle, S. C.; Romir, J.; Fischer, S.; Koeberle, A.; Schattel, V.; Albrecht, W.; Grütter, C.; Werz, O.; Rauh, D.; Stehle, T.; Laufer, S. A., Skepinone-L is a selective p38 mitogen-activated protein kinase inhibitor. *Nature Chemical Biology* **2012,** *8* (2), 141-143.
65. Kufareva, I.; Abagyan, R., Type-II Kinase Inhibitor Docking, Screening, and Profiling Using Modified Structures of Active Kinase States. *Journal of Medicinal Chemistry* **2008,** *51* (24), 7921-7932.
66. Goldstein, D. M.; Gray, N. S.; Zarrinkar, P. P., High-throughput kinase profiling as a platform for drug discovery. *Nature Reviews Drug Discovery* **2008,** *7* (5), 391-397.
67. Regan, J.; Pargellis, C. A.; Cirillo, P. F.; Gilmore, T.; Hickey, E. R.; Peet, G. W.; Proto, A.; Swinamer, A.; Moss, N., The kinetics of binding to p38MAP kinase by analogues of BIRB 796. *Bioorg Med Chem Lett* **2003,** *13* (18), 3101-4.
68. Fabbro, D., 25 Years of Small Molecular Weight Kinase Inhibitors: Potentials and Limitations. *Molecular Pharmacology* **2015,** *87* (5), 766.
69. Roskoski, R., Classification of small molecule protein kinase inhibitors based upon the structures of their drug-enzyme complexes. *Pharmacological Research* **2016,** *103*, 26-48.
70. Walter, N. M.; Wentsch, H. K.; Bührmann, M.; Bauer, S. M.; Döring, E.; Mayer-Wrangowski, S.; Sievers-Engler, A.; Willemsen-Seegers, N.; Zaman, G.; Buijsman, R.; Lämmerhofer, M.; Rauh, D.; Laufer, S. A., Design, Synthesis, and Biological Evaluation of Novel Type I1/2 p38α MAP Kinase Inhibitors with Excellent Selectivity, High Potency, and Prolonged Target Residence Time by Interfering with the R-Spine. *Journal of Medicinal Chemistry* **2017,** *60* (19), 8027-8054.
71. TopiVert Pharma Ltd, RespiVert Ltd. Diaryl urea derivatives as p38 kinase inhibitors. WO2016051187A1. 2016.
72. Capaldi, C.; Armani, E.; Hurley, C.; Avitabile-Woo, B. G.; Lanaro, R.; Jennings, N. S. Prepn. of 4-(([1,2,4]triazolo[4,3-a]pyridine-6-yl) oxy)-1,2,3,4-tetrahydronaphthalen-1-yl)ureido derivs. as p38 MAP kinase inhibitors for the treatment of inflammatory diseases of respiratory tract. WO2018224423A1, 2018.
73. Cacace, A. M.; Rojas Soto, L. G. A.; Thompson, L. A., III; Wallace, O. B. Use of p38 inhibitors to reduce expression of DUX4. WO2019071144A1, 2019.
74. Wang, C.; Hockerman, S.; Jacobsen, E. J.; Alippe, Y.; Selness, S. R.; Hope, H. R.; Hirsch, J. L.; Mnich, S. J.; Saabye, M. J.; Hood, W. F.; Bonar, S. L.; Abu-Amer, Y.; Haimovich, A.; Hoffman, H. M.; Monahan, J. B.; Mbalaviele, G., Selective inhibition of the p38α MAPK–MK2 axis inhibits

inflammatory cues including inflammasome priming signals. *The Journal of Experimental Medicine* **2018,** *215* (5), 1315-1325.
75. Gomez, P.; Carrasco, E.; Campos, P.; Deleyto, P.; Vega, M.; Gomez-Reino, J. J.; Conde, C.; Gualillo, O.; Perez, J. J.; Messeguer, A. p38 MAPK inhibitors for the treatment of inflammatory diseases. WO2014094816A1, 2014.
76. Ottosen, E. R.; Sørensen, M. D.; Björkling, F.; Skak-Nielsen, T.; Fjording, M. S.; Aaes, H.; Binderup, L., Synthesis and structure-activity relationship of aminobenzophenones. A novel class of p38 MAP kinase inhibitors with high antiinflammatory activity. *J Med Chem* **2003,** *46* (26), 5651-62.
77. Koeberle, S. C.; Fischer, S.; Schollmeyer, D.; Schattel, V.; Grütter, C.; Rauh, D.; Laufer, S. A., Design, Synthesis, and Biological Evaluation of Novel Disubstituted Dibenzosuberones as Highly Potent and Selective Inhibitors of p38 Mitogen Activated Protein Kinase. *Journal of Medicinal Chemistry* **2012,** *55* (12), 5868-5877.
78. Rudalska, R.; Dauch, D.; Longerich, T.; McJunkin, K.; Wuestefeld, T.; Kang, T.-W.; Hohmeyer, A.; Pesic, M.; Leibold, J.; Thun, A.; Schirmacher, P.; Zuber, J.; Weiss, K.; Powers, S.; Malek, N.; Eilers, M.; Sipos, B.; Lowe, S.; Geffers, R.; Zender, L., In vivo RNAi screening identifies a mechanism of sorafenib resistance in liver cancer. *Nature medicine* **2014,** *20*.
79. Wentsch-Teltschik, H. K., Design hochselektiver Typ I½ p38α MAP Kinase Inhibitoren durch Optimierung der Wechselwirkungen mit der R-Spine. *Eberhard Karls Universität Tübingen* **2017**.
80. Fischer, S.; Wentsch, H. K.; Mayer-Wrangowski, S. C.; Zimmermann, M.; Bauer, S. M.; Storch, K.; Niess, R.; Koeberle, S. C.; Grütter, C.; Boeckler, F. M.; Rauh, D.; Laufer, S. A., Dibenzosuberones as p38 Mitogen-Activated Protein Kinase Inhibitors with Low ATP Competitiveness and Outstanding Whole Blood Activity. *Journal of Medicinal Chemistry* **2013,** *56* (1), 241-253.
81. Wentsch, H. K.; Walter, N. M.; Bührmann, M.; Mayer-Wrangowski, S.; Rauh, D.; Zaman, G. J. R.; Willemsen-Seegers, N.; Buijsman, R. C.; Henning, M.; Dauch, D.; Zender, L.; Laufer, S., Optimized Target Residence Time: Type I Inhibitors for p38α MAP Kinase with Improved Binding Kinetics through Direct Interaction with the R-Spine. *Angewandte Chemie International Edition* **2017,** *56* (19), 5363-5367.
82. Shnidman, L.; Sunier, A. A., The Solubility of Urea in Water. *The Journal of Physical Chemistry* **1932,** *36* (4), 1232-1240.
83. Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B., B-Alkyl Suzuki−Miyaura Cross-Coupling Reactions with Air-Stable Potassium Alkyltrifluoroborates. *The Journal of Organic Chemistry* **2003,** *68* (14), 5534-5539.
84. Zhang, P.; Le, C. C.; MacMillan, D. W. C., Silyl Radical Activation of Alkyl Halides in Metallaphotoredox Catalysis: A Unique Pathway for Cross-Electrophile Coupling. *Journal of the American Chemical Society* **2016,** *138* (26), 8084-8087.
85. Goldstein, D. M.; Soth, M.; Gabriel, T.; Dewdney, N.; Kuglstatter, A.; Arzeno, H.; Chen, J.; Bingenheimer, W.; Dalrymple, S. A.; Dunn, J.; Farrell, R.; Frauchiger, S.; La Fargue, J.; Ghate, M.; Graves, B.; Hill, R. J.; Li, F.; Litman, R.; Loe, B.; McIntosh, J.; McWeeney, D.; Papp, E.; Park, J.; Reese, H. F.; Roberts, R. T.; Rotstein, D.; San Pablo, B.; Sarma, K.; Stahl, M.; Sung, M. L.; Suttman, R. T.; Sjogren, E. B.; Tan, Y.; Trejo, A.; Welch, M.; Weller, P.; Wong, B. R.; Zecic, H., Discovery of 6-(2,4-difluorophenoxy)-2-[3-hydroxy-1-(2-hydroxyethyl)propylamino]-8-methyl-8H-pyrido[2,3-d]pyrimidin-7-one (pamapimod) and 6-(2,4-difluorophenoxy)-8-methyl-2-(tetrahydro-2H-pyran-4-ylamino)pyrido[2,3-d]pyrimidin-7(8H)-one (R1487) as orally bioavailable and highly selective inhibitors of p38α mitogen-activated protein kinase. *J Med Chem* **2011,** *54* (7), 2255-65.
86. Walter, N., Dissertation: Entwicklung, Synthese und biologische Evaluation verschiedener neuartiger Konzepte zur Inhibition der peripheren und zentralen p38α MAP Kinase. *Eberhard-Karls-Universität Tübingen* **2017**.
87. Cerfontain, H., Nitration. Methods and Mechanisms. G. A. Olah, R. Malhotra and S. C. Narang. VCH Publishers, Weinheim, 1989. XII + 330 pp., DM 145.00/£52.00. ISBN 0-89573-144-4. *Recueil des Travaux Chimiques des Pays-Bas* **1990,** *109* (12), 594-594.
88. Baumann, E., Ueber eine einfache Methode der Darstellung von Benzoësäureäthern. *Berichte der deutschen chemischen Gesellschaft* **1886,** *19* (2), 3218-3222.

89. Smith, P. A. S., The Curtius Reaction. In *Organic Reactions*, pp 337-449.
90. Washbume, S. S.; Peterson, W. R., Curtius Degradation Utilizing Trimethylsilyl Azide. A facile isocyanate synthesis. *Synthetic Communications* **1972,** *2* (4), 227-230.
91. Bigi, F.; Maggi, R.; Sartori, G., Selected syntheses of ureas through phosgene substitutes. *Green Chemistry - GREEN CHEM* **2000,** *2*, 140-148.
92. Wang, G. T.; Chen, Y.; Wang, S.; Sciotti, R.; Sowin, T., Solid phase synthesis of ureas of secondary amines via carbamoyl chloride. *Tetrahedron letters* **1997,** *38* (11), 1895-1898.
93. Friedel, C., Charles Friedel. *Educación Química 20*, 447-455.
94. Jin, S.; Xue, G., Interaction between Thiophene and Solvated Lewis Acids and the Low-Potential Electrochemical Deposition of a Highly Anisotropic Conducting Polythiophene Film. *Macromolecules* **1997,** *30* (19), 5753-5757.
95. Gilman, H.; Ess, P. R. v., The Preparation of Ketones by the Carbonation of Organolithium Compounds. *Journal of the American Chemical Society* **1933,** *55* (3), 1258-1261.
96. Cason, J.; Kraus, K. W., Ketone Synthesis by the Grignard Reaction with Acid Chlorides in Presence of Ferric Chloride. *The Journal of Organic Chemistry* **1961,** *26* (6), 1768-1772.
97. E. E. Blaise, C. R., *Hebd. Acad. Sci.* **1901,** (133), 1217-1218.
98. Swain, C. G., The Mechanism of Addition of Grignard Reagents to Nitriles. *Journal of the American Chemical Society* **1947,** *69* (10), 2306-2309.
99. Pearson-Long, M. S. M.; Boeda, F.; Bertus, P., Double Addition of Organometallics to Nitriles: Toward an Access to Tertiary Carbinamines. *Advanced Synthesis & Catalysis* **2017,** *359* (2), 179-201.
100. Wang, X.-j.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H., Addition of Grignard Reagents to Aryl Acid Chlorides: An Efficient Synthesis of Aryl Ketones. *Organic Letters* **2005,** *7* (25), 5593-5595.
101. Zhang, F.; Zhang, S.; Duan, X.-F., Substitution of the Nitro Group with Grignard Reagents: Facile Arylation and Alkenylation of Pyridine N-Oxides. *Organic Letters* **2012,** *14* (21), 5618-5620.
102. Nahm, S.; Weinreb, S. M., N-methoxy-n-methylamides as effective acylating agents. *Tetrahedron Letters* **1981,** *22* (39), 3815-3818.
103. Bellamy, F. D.; Ou, K., Selective reduction of aromatic nitro compounds with stannous chloride in non acidic and non aqueous medium. *Tetrahedron Letters* **1984,** *25* (8), 839-842.
104. Bruno, N. C.; Tudge, M. T.; Buchwald, S. L., Design and preparation of new palladium precatalysts for C–C and C–N cross-coupling reactions. *Chemical Science* **2013,** *4* (3), 916-920.
105. Li, J. J.; Wang, Z.; Mitchell, L. H., A Practical Buchwald−Hartwig Amination of 2-Bromopyridines with Volatile Amines. *The Journal of Organic Chemistry* **2007,** *72* (9), 3606-3607.
106. Reaction biology p38a assay: https://www.reactionbiology.com/datasheet/p38a_mapk14_kin_malvern.
107. Drexler, C., HTRF® KinEASETM: a new solution for screening serine-threonine kinases. *Nature Methods* **2006,** *3* (6), I-II.
108. Linsenmaier, S. Entwicklung und Optimierung von in vitro Testverfahren zur Evaluierung von Hemmstoffen der p38α MAP kinase und JNK3. Ph.D. Thesis, Universität Tübingen, 2006.
109. Dahl, G.; Akerud, T., Pharmacokinetics and the drug-target residence time concept. *Drug Discov Today* **2013,** *18* (15-16), 697-707.
110. Susa ST, Preuss CV. Drug Metabolism. [Updated 2020 Nov 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK442023/.
111. Knights, K. M.; Stresser, D. M.; Miners, J. O.; Crespi, C. L., In Vitro Drug Metabolism Using Liver Microsomes. *Curr Protoc Pharmacol* **2016,** *74*, 7.8.1-7.8.24.
112. Szultka-Mlynska, M.; Buszewski, B., Study of in-vitro metabolism of selected antibiotic drugs in human liver microsomes by liquid chromatography coupled with tandem mass spectrometry. *Analytical and Bioanalytical Chemistry* **2016,** *408* (29), 8273-8287.
113. Lin, Y.; Fan, H.; Li, Y.; Zhan, X., Thiazole-Based Organic Semiconductors for Organic Electronics. *Advanced Materials* **2012,** *24* (23), 3087-3106.

114. Josse, P.; Chávez, P.; Dindault, C.; Dalinot, C.; McAfee, S.; Dabos-Seignon, S.; Tondelier, D.; Welch, G.; Blanchard, P.; Leclerc, N.; Cabanetos, C., Thiophene vs thiazole: Effect of the π-connector on the properties of phthalimide end-capped diketopyrrolopyrrole based molecular acceptors for organic photovoltaics. *Dyes and Pigments* **2016,** *137*.
115. Haake, P.; Miller, W. B., A Comparison of Thiazoles and Oxazoles. *Journal of the American Chemical Society* **1963,** *85* (24), 4044-4045.
116. Meanwell, N. A., Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *Journal of Medicinal Chemistry* **2018,** *61* (14), 5822-5880.
117. Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A., Applications of Fluorine in Medicinal Chemistry. *Journal of Medicinal Chemistry* **2015,** *58* (21), 8315-8359.
118. Meyers, J.; Carter, M.; Mok, N. Y.; Brown, N., On the origins of three-dimensionality in drug-like molecules. *Future Medicinal Chemistry* **2016,** *8* (14), 1753-1767.
119. Lovering, F.; Bikker, J.; Humblet, C., Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *Journal of Medicinal Chemistry* **2009,** *52* (21), 6752-6756.
120. Maanen, M. J. v.; Smeets, C. J. M.; Beijnen, J. H., Chemistry, pharmacology and pharmacokinetics of N,N′,N′′ -triethylenethiophosphoramide (ThioTEPA). *Cancer Treatment Reviews* **2000,** *26* (4), 257-268.
121. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J., Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced drug delivery reviews* **1997,** *23* (1-3), 3-25.
122. Tian, S.; Wang, J.; Li, Y.; Li, D.; Xu, L.; Hou, T., The application of in silico drug-likeness predictions in pharmaceutical research. *Advanced Drug Delivery Reviews* **2015,** *86*, 2-10.
123. Wei, W.; Cherukupalli, S.; Jing, L.; Liu, X.; Zhan, P., Fsp3: A new parameter for drug-likeness. *Drug Discovery Today* **2020,** *25* (10), 1839-1845.
124. Ursu, O.; Rayan, A.; Goldblum, A.; Oprea, T. I., Understanding drug-likeness. *WIREs Computational Molecular Science* **2011,** *1* (5), 760-781.
125. Hodge, C. N.; Aldrich, P. E.; Bacheler, L. T.; Chang, C. H.; Eyermann, C. J.; Garber, S.; Grubb, M.; Jackson, D. A.; Jadhav, P. K.; Korant, B.; Lam, P. Y.; Maurin, M. B.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Reid, C.; Sharpe, T. R.; Shum, L.; Winslow, D. L.; Erickson-Viitanen, S., Improved cyclic urea inhibitors of the HIV-1 protease: synthesis, potency, resistance profile, human pharmacokinetics and X-ray crystal structure of DMP 450. *Chem Biol* **1996,** *3* (4), 301-14.
126. Sweeney, J. B., Aziridines: epoxides' ugly cousins? *Chemical Society Reviews* **2002,** *31* (5), 247-258.
127. Okada-Junior, C. Y.; Monteiro, G. C.; Aguiar, A. C. C.; Batista, V. S.; de Souza, J. O.; Souza, G. E.; Bueno, R. V.; Oliva, G.; Nascimento-Júnior, N. M.; Guido, R. V. C.; Bolzani, V. S., Phthalimide Derivatives with Bioactivity against Plasmodium falciparum: Synthesis, Evaluation, and Computational Studies Involving bc1 Cytochrome Inhibition. *ACS Omega* **2018,** *3* (8), 9424-9430.
128. Mahlooji, I.; Shokri, M.; Manoochehri, R.; Mahboubi-Rabbani, M.; Rezaee, E.; Tabatabai, S. A., Discovery of phthalimide derivatives as novel inhibitors of a soluble epoxide hydrolase. *Archiv der Pharmazie* **2020,** *353* (8), 2000052.
129. Boström, J.; Hogner, A.; Llinàs, A.; Wellner, E.; Plowright, A. T., Oxadiazoles in Medicinal Chemistry. *Journal of Medicinal Chemistry* **2012,** *55* (5), 1817-1830.
130. Kumari, S.; Carmona, A. V.; Tiwari, A. K.; Trippier, P. C., Amide Bond Bioisosteres: Strategies, Synthesis, and Successes. *Journal of Medicinal Chemistry* **2020,** *63* (21), 12290-12358.
131. Reed, C. W.; Washecheck, J. P.; Quitlag, M. C.; Jenkins, M. T.; Rodriguez, A. L.; Engers, D. W.; Blobaum, A. L.; Conn, P. J.; Niswender, C. M.; Lindsley, C. W., Surveying heterocycles as amide bioisosteres within a series of mGlu7 NAMs: Discovery of VU6019278. *Bioorganic & medicinal chemistry letters* **2019,** *29* (10), 1211-1214.

8. Contributions

The following contributions have been made by others:

- The biological in-house testing (Fret-based IC_{50}-values, whole blood assay, metabolic stability) was done by Mark Kudolo, Jens Strohbach and Katharina Bauer.
- Compounds 105-122 were synthesized by Larissa Pünnel under my supervision.
- Dr. Tatu Pantsar contributed to this work by computer-aided compound design resulted inter alia in the idea for the azadibenzosuberones, the ketone and imide structures.
- The three oxadiazole-based type I ½ residuals utilized for compound 151-153 synthesis were kindly provided by Juliander Rainer.
- The idea for the successful azadibenzosuberone synthetic route was given by Dr. Michael Forster.