Discovery of reversible monoacylglycerol lipase inhibitors

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Chapter 2

Hit Optimization of *β*-Sulfinyl Esters as Highly Potent and Selective MAGL Inhibitors

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2.1 Introduction

2-Arachidonoylglycerol (2-AG) is an endogenous agonist of the cannabinoid CB_1 and CB_2 receptors and serves as a precursor for a pool of arachidonic acid (AA) which may form pro-inflammatory prostaglandins in the brain, lung and liver.[1] The central role of monoacylglycerol lipase (MAGL) in the metabolism of 2-AG makes it, therefore, an attractive therapeutic target for a variety of disorders, including inflammation-induced tissue injury and pain, multiple sclerosis and cancer.[2, 3] MAGL is a membrane-associated serine hydrolase and employs a serine-histidine-aspartate catalytic triad to hydrolyze the ester moiety of monoacylglycerols.[4] Currently, the covalent, irreversible MAGL inhibitor ABX-1431 is in clinical phase 1b studies for the treatment of post-traumatic stress disorder as well as for other indications, such as neuromyelitis optica and multiple sclerosis.[5] Irreversible inhibitors may have several advantages to act as

therapeutics, like increased potency, long residence time and a less stringent pharmacokinetic profile.[6] However, the irreversible mode of action may also have some drawbacks, such as reduced selectivity and the formation of covalent-protein adducts might result in idiosyncratic drug-related toxicity.[7] In case of MAGL inhibition, chronic exposure to the covalent inhibitor JZL184 resulted in pharmacological tolerance, development of physical dependence, impaired synaptic plasticity and receptor desensitization in the nervous system.[8, 9] Reversible inhibitors may avoid these unfavorable side-effects.[10]

To harness the therapeutic potential of MAGL, a high-throughput screen (HTS) was previously performed within the Cancer Drug Discovery Initiative (CDDI)[11] to identify novel reversible MAGL inhibitors. A natural substrate assay was employed that utilizes an enzymatic cascade to convert glycerol, a metabolite produced by MAGL, into a fluorescent signal.[12] A compound library containing 233.820 unique structures was screened. After hit triaging and hit confirmation using activity-based protein profiling (ABPP) seven hits were identified[13], which could serve as a starting point for a drug discovery project. In this chapter the medicinal chemistry efforts to optimize hit **1** (ethyl 2-((4-(3-methyl-4-(*m*-tolyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl) acetate) are described (Figure 1).

Compound **1** showed a half maximal inhibitory concentration (IC_{50}) of 630 nM in the HTS and was selective over fatty acid amide hydrolase (FAAH), an enzyme that inactivates anandamide, another endocannabinoid. It has a Molecular Weight (MW) of 473.54 Da and a calculated lipophilicity (cLogP) of 3.2, which resulted in a Lipophilic Efficiency (LipE)[14] of 3.0. Compound **1** has a topological polar surface area (tPSA) of 119 A^2, which reduces cell penetration[15]. Furthermore, it contains an aromatic nitro group, which is associated with genotoxicity[16] and an ester functionality that poses a metabolic liability[17]. The aim of the hit optimization program was, therefore a) to improve the potency, b) to reduce the polar surface area, c) to replace the aromatic nitro; and d) to improve its metabolic stability, while maintaining its selectivity.

Here, in this chapter a ligand-based drug design (LBDD) approach is used to develop a structure-activity relationship (SAR) of hit **1** and to improve its potency,

while reducing the polar surface area and genotoxicity liability by replacing the aromatic nitro group. The optimization of the metabolic stability will be described in Chapter 4.

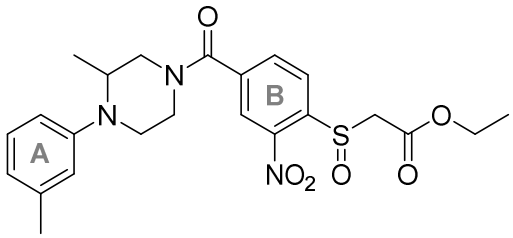
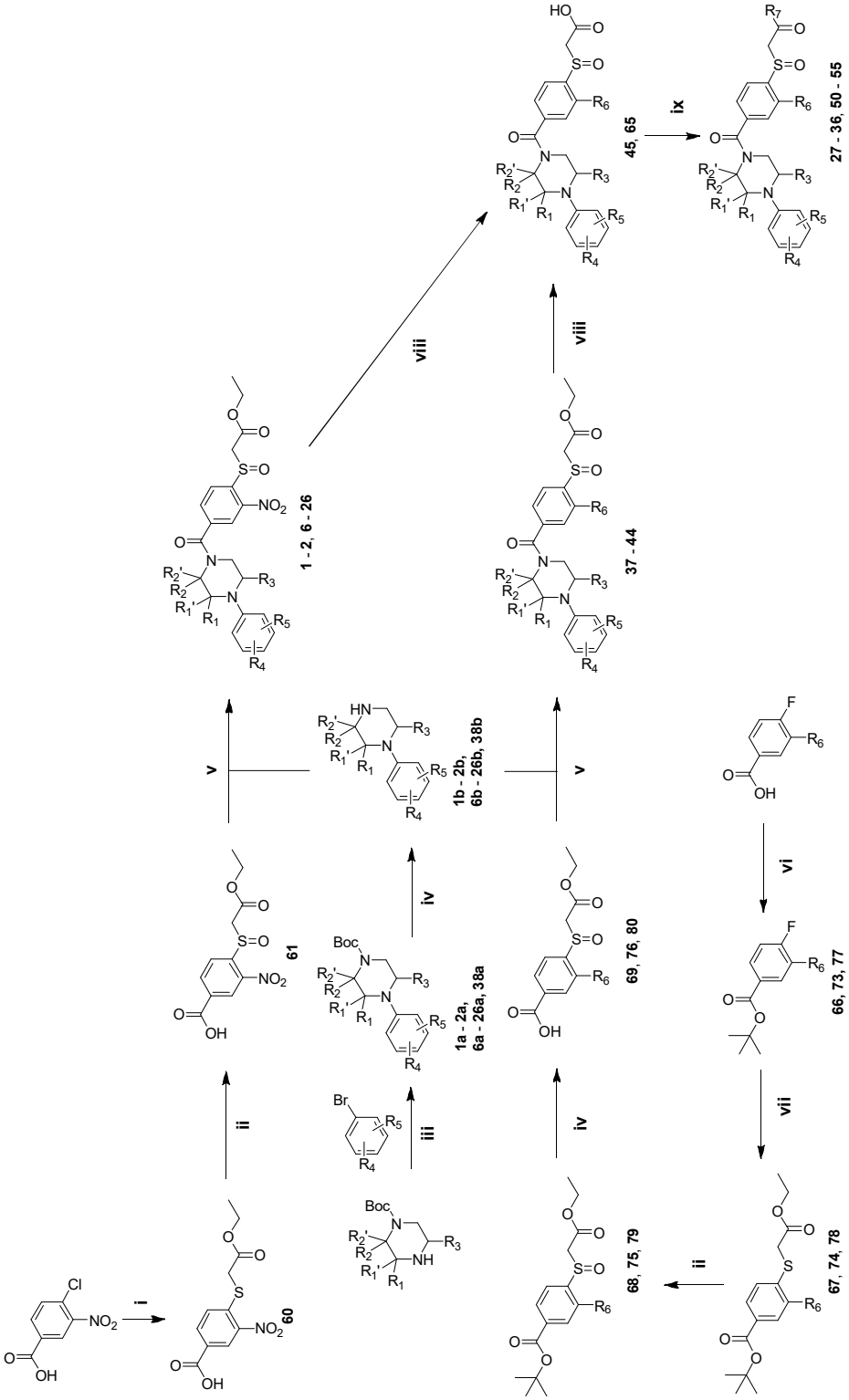


Figure 1. Chemical structure of HTS hit **1.**

2.2 Results and discussion

To study the SAR of compound **1**, various synthetic routes were employed that allowed the systematic investigation of the substitution pattern of piperazine moiety, phenyl A and B, and variations of the *β*-sulfinyl ester (Scheme 1 and S1). This led to the synthesis of compounds **1**-**55.** The synthesis started with palladium catalyzed Buchwald-Hartwig cross coupling of the appropriate Boc-piperazine and bromobenzene to obtain tertiary amine. Subsequent TFA mediated Boc-cleavage resulted in amine building block. Concurrently, nucleophilic aromatic substitution of ethyl 2-mercaptoacetate with chloro nitrobenzoic acid or appropriate *tert*-butyl 4-fluorobenzoate obtained sulfide, which was oxidized by oxone to yield sulfinylbenzoic acid building block. Peptide coupling of the amine building block with benzoic acid afforded the ethyl ester compounds. To make different ester or amide variations, the ethyl ester was hydrolyzed by using triethylamine and the obtained carboxylic acid was coupled with different alcohols or amines.

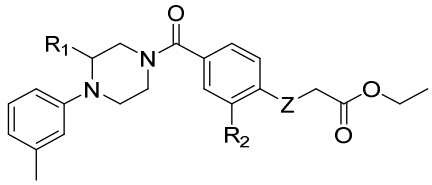
Compound **1** is a racemic mixture. To investigate which enantiomer is the most active compound, both the (***S***)-**1** and (***R***)-**1** enantiomers were synthesized and tested. Both compounds showed similar inhibitory potencies as the initial hit (Table 1), indicating that the chirality of the methyl substituent at the 3-position of piperazine did not impact the inhibition of MAGL. On the other hand, removal of the methyl group (**2**) led to a 10-fold drop in activity. The oxidation state of the sulfur atom in compound **1** was important, because reducing the sulfoxide to a sulfur (**3**) or oxidizing it to a sulfonyl



Scheme 1. General synthesis route for hit optimization of compound **1**. Reagents and conditions: i) ethyl 2-mercaptoacetate, pyridine, 115 ºC, 85 %. ii) Oxone, MeOH / H_2O, 70 %. iii) sodium *tert*-butoxide, BINAP, $Pd(OAc)_2$, 1,4-dioxane, 85 ºC. iv) TFA, DCM. v) HATU, DiPEA, DCM. vi) Boc_2O, DMAP, *tert*-BuOH, 65 ºC. vii) ethyl 2-mercaptoacetate, K_2CO_3, ACN. viii) TEA, MeOH, H_2O. ix) appropriate alcohol or amine, oxalyl chloride, DiPEA, DCM.

(**4**) abolished the activity. Removal of the nitro-group (**5**) also led to a significant reduction in activity.

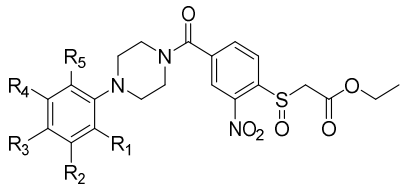
Table 1. pIC_{50} values of resynthesized hit **1** and designed derivatives **2** - **5**.



Entry	R_1	R_2	Z	pIC_{50} ± SD
(***S***)-**1**		NO_2	SO	6.57±0.13
(***R***)-**1**		NO_2	SO	6.71±0.05
2		NO_2	SO	5.65±0.05
3		NO_2	S	<5
4		NO_2	SO_2	<5
5		H	SO	5.25±0.05

To analyze the effect of the substitution pattern on phenyl A, compounds **6**-**22** were evaluated (Table 2) using the scaffold of compound **2** (for the ease of synthesis). Electron donating substituents on the meta- (methyl (**2**), methoxy (**15**)) or para-position (methoxy (**16**)) reduced the potency compared to compound **6**. In contrast, electron withdrawing groups (EWG) were preferred on the meta-position (F (**7**), Cl (**8**), Br (**11**), CF_3 (**13**), but not nitro (**17**)). The electron withdrawing effect was absent or less pronounced on the para-position (Cl (**9**), Br (**12**) or CF_3 (**14**)). Of interest, a phenyl substitution (**18**) was tolerated at the meta-position, suggesting the presence of a hydrophobic pocket. Dichloro substitution did not improve the potency (**19**-**22**).

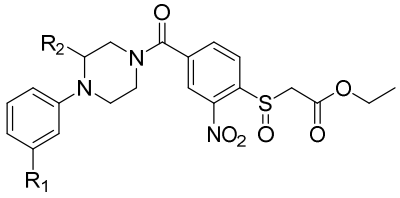
Table 2. pIC_{50} values of designed analogues **6** – **22**.



Entry	R_1	R_2	R_3	R_4	R5	pIC_{50} ± SD
2	H	CH_3	H	H	H	5.65 ± 0.05
6	H	H	H	H	H	5.91 ± 0.11
7	H	F	H	H	H	6.20 ± 0.18
8	H	Cl	H	H	H	6.33 ± 0.08
9	H	H	Cl	H	H	6.00 ± 0.08
10	Cl	H	H	H	H	5.37 ± 0.07
11	H	Br	H	H	H	6.44 ± 0.06
12	H	H	Br	H	H	5.95 ± 0.08
13	H	CF_3	H	H	H	6.42 ± 0.09
14	H	H	CF_3	H	H	6.23 ± 0.13
15	H	OCH_3	H	H	H	5.18 ± 0.07
16	H	H	OCH_3	H	H	5.31 ± 0.04
17	H	NO_2	H	H	H	5.59 ± 0.06
18	H	Phenyl	H	H	H	5.87±0.08
19	H	Cl	H	Cl	H	6.31 ± 0.04
20	H	Cl	Cl	H	H	5.59±0.11
21	Cl	H	Cl	H	H	5.71± 0.13
22	Cl	H	H	H	Cl	5.74 ± 0.13

Next, an EWG at the meta-position of phenyl A was combined with the chiral substituted piperazines (**23-26**) (Table 3). Substitution of the *m*-methyl of the toluyl group with a halogen on the chiral pure scaffold of compound **1** increased the inhibitory potency on both enantiomers equally well. The *m*-chloro-substituted (***R***)-**24** and (***S***)-**24** were the most active compounds with a pIC_{50} around 7.4.

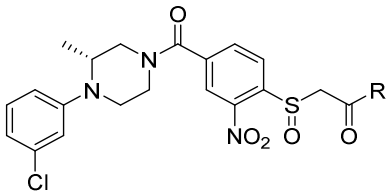
Table 3. pIC_{50} values of designed analogues **23** - **26**.

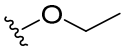
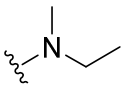
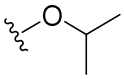
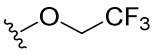
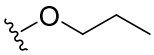
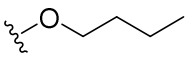
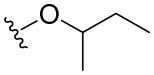
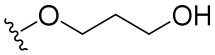


Entry	R_1	R_2	pIC_{50} ± SD
(***S***)-**1**	H		6.57±0.13
(***R***)-**1**	H		6.71±0.05
23	F		6.81±0.03
(***R***)-**24**	Cl		7.40±0.11
(***S***)-**24**	Cl		7.36±0.08
(***R***)-**25**	Br		7.06±0.07
(***S***)-**25**	Br		7.09±0.06
(***R***)-**26**	CF_3		6.94±0.04
(***S***)-**26**	CF_3		6.70±0.08

Employing the scaffold of (***R***)-**24**, which was the most active compound identified thus far, the SAR of the ester moiety was studied. To this end, compounds **27** - **35** were evaluated (Table 4). Replacement of the ethyl ester with methyl (**27**), or trifluoroethyl (**30**) esters resulted in decreased MAGL activity, while elongating the alkyl chain to a propyl (**31**) or butyl (**31**) increased the potency compared to the ethyl (**24**). Of note, branching of the alkyl chain (isopropyl (**29**), sec-butyl (**33**) and *tert*-pentyl (**34**) reduced the activity. Introduction of a polar group was tolerated, as witnessed by hydroxypropyl ester (**35**), which had a similar activity as (***R***)-**24**. However, changing the ester to a secondary amide (**28**) resulted in inactive compound.

Table 4. pIC_{50} values of different ester and amide analogues **27** - **35**.

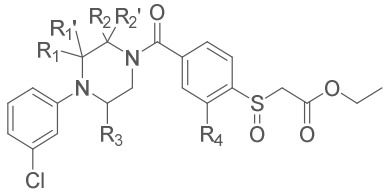


Entry	R	pIC_{50} ± SD
(*R*)-24		7.40±0.11
27		7.11±0.10
28		<5
29		6.96±0.06
30		7.13±0.09
31		7.54±0.09
32		7.58±0.09
33		7.41±0.10
34		6.22±0.12
35		7.46±0.11

Next, the SAR of the piperazine and the 2-nitrophenyl ring was revisited. Various methyl substituted piperazines and the nitro-group bio-isosteres (compounds **36** – **44)** were analyzed. An additional methyl group at the 5-position (**36**) decreased the MAGL inhibitory activity. Replacing the nitro group with a fluorine (**37**) in the scaffold maintained the activity, and, importantly, reduced the liability for potential genotoxicity and significantly reduced the polar surface area of the compound. 2-Methyl-piperazine (**38**) had similar MAGL inhibitory activity as compound **37**. 2,2-Dimethyl (**42**) or 3,3-dimethyl (**41**) substitution resulted in decreased potency as compared to 3-methyl substituted piperazines. Interestingly, trans-2,3-dimethyl substitution (± **40**) significantly elevated the potency, while cis-2,3-dimethyl substitution (± **39**) slightly

decreased the MAGL activity compared to compound **37**. Furthermore, changing the fluoro to chloro (± **43**) and bromo (± **44**) further increased the potency. Compound ± **43** was the most potent compound identified with a pIC_{50} of 8.50 ± 0.10.

Table 5. pIC_{50} values of designed analogues **36** - **44**.

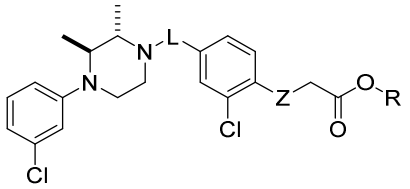


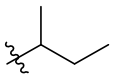
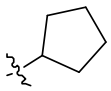
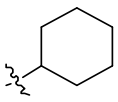
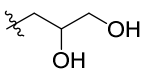
Entry	R_1	R_1'	R_2	R_2'	R_3	R_4	pIC_{50} ± SD
(*R*)-24	(*R*)CH_3	H	H	H	H	NO_2	7.40±0.11
36	CH_3	H	H	H	CH_3	NO_2	6.68±0.07
37	(*R*)CH_3	H	H	H	H	F	7.56±0.04
38	H	H	CH_3	H	H	F	7.56±0.10
± 39	cis-CH_3	H	cis-CH_3	H	H	F	7.29±0.07
± 40	trans-CH_3	H	trans-CH_3	H	H	F	8.13±0.07
41	CH_3	CH_3	H	H	H	F	7.33±0.07
42	H	H	CH_3	CH_3	H	F	7.24±0.07
± 43	trans-CH_3	H	trans-CH_3	H	H	Cl	8.50±0.10
± 44	trans-CH_3	H	trans-CH_3	H	H	Br	8.24±0.17

Finally, on the basis of the potency of compound ± **43**, several analogues (± **45** - ± **55**) were evaluated (Table 6). Hydrolysis of the ethyl ester to carboxylic acid (± **45**) resulted in >500-fold loss of MAGL inhibitory activity, while replacing the linker amide to amine (± **48**) was allowed. Changing the sulfinyl group to sulfur (± **46**) abolished the inhibitory activity and replacing it with a sulfonyl (± **47**) or carbonyl (± **49**) resulted in a 1000-fold reduced inhibitory activity. Compounds in which the ethyl ester was replaced with an isopropyl (± **50**), *sec*-butyl (± **51**), cyclobutyl (± **52**), cyclopentanyl (± **53**) or cyclohexanyl (± **54**) esters displayed similar MAGL inhibitory activity, but decreased lipophilic efficiency (LipE) compared to compound ± **43**. The polar 1-glycerol ester (± **55**) showed similar potency compared to the other esters. Altogether, this SAR study revealed that compounds ± **43** and ± **48** showed the most promising

combination of activity and physical-chemical properties (Table 6).

Table 6. pIC_{50} values of designed analogues 45 - 55.



Entry	L	Z	R	pIC_{50} ± SD	cLogP	tPSA	LipE
± 43	CO	SO		8.50±0.10	4.93	67	3.57
± 45	CO	SO	H	6.18±0.06	4.22	78	1.96
± 46	CO	S		<5	6.23	50	-
± 47	CO	SO_2		6.47±0.07	4.87	84	1.60
± 48	CH_2	SO		8.21 ± 0.11	5.70	50	2.51
± 49	CO	CO		5.94±0.08	5.19	67	0.75
± 50	CO	SO		8.57±0.12	5.23	67	3.34
± 51	CO	SO		8.41±0.08	5.76	67	2.65
± 52	CO	SO		8.38 ± 0.09	5.31	67	3.07
± 53	CO	SO		8.41 ± 0.08	5.89	67	2.52
± 54	CO	SO		8.53 ± 0.08	6.43	67	2.10
± 55	CO	SO		8.18 ± 0.09	2.92	107	5.26

Compounds **± 43** and **± 48** were selected for further profiling. To determine the selectivity of compounds **± 43** and **± 48** over other serine hydrolases, gel-based and mass spectrometry (MS)-based activity-based protein profiling (ABPP) was employed on mouse brain proteome. ABPP is a versatile chemical proteomic method to assess target engagement and proteome-wide selectivity for small-molecule inhibitors. It

makes use of activity-based probes (ABPs) to assess the functional state of entire enzyme classes directly in native biological systems. ABPs with fluorescent reporter groups enable visualization of enzyme activities in complex proteomes by SDS–polyacrylamide gel electrophoresis (SDS-PAGE) using in-gel fluorescence scanning, while ABPs with a biotin reporter group enable affinity enrichment and identification of enzyme activities by mass spectrometry (MS)-based proteomics.[18] For gel-based ABPP, two broad-spectrum probes MB064 and TAMRA-FP were used as reported before.[19-21] Compound ± **43** displayed high selectivity over the other endocannabinoid hydrolases (*e.g.* DAGL-α, FAAH, ABHD6 and ABHD12) (Figure 2A). Compound ± **48** reduced MAGL activity with a pIC_{50} of 7.4 ± 0.1 and was able to inhibit FAAH in a dose-manner with a pIC_{50} of 6.8 ± 0.2 (Figure 2B, C). This indicates that compound ± **43** is a selective MAGL inhibitor, while compound ± **48** is a dual MAGL/FAAH inhibitor. It has been reported that inactivation of both MAGL and FAAH could cause catalepsy and THC-like drug discrimination responses, which limited its therapeutic applications.[22] Based on these data, chemical proteomics using MB108 and FP-biotin was carried out to further investigate the selectivity of ± **43**, but not ± **48**, over a broader range of specified proteins. Compound ± **43** did not reduce labeling of the detected proteins by more than 50%, except for MAGL and nitrilase family member 2 (Nit2) (Figure 2B, C). Together, these data indicate that compound ± **43** is a highly selective MAGL inhibitor.

To study the interactions of compound ± **43** with the amino acids in the active site of MAGL, docking studies were performed using the reported MAGL crystal structure.[23] As shown in figure 3, the carbonyl of the ester group forms two H-bonds with Ala51 and Met123, respectively, which are also frequently observed in other co-crystal structures of MAGL.[24-27] The carbonyl of the ester group serves as an electrophile which could be attacked by the catalytic serine (Ser122), since the distance between them is around 3 Å. The ethyl moiety inserts into the hydrophilic cytoplasmic access (CA) channel, while the rest of the compound occupies the large hydrophobic tunnel. The chloro-group on phenyl ring B occupies a hydrophobic subpocket of MAGL, which

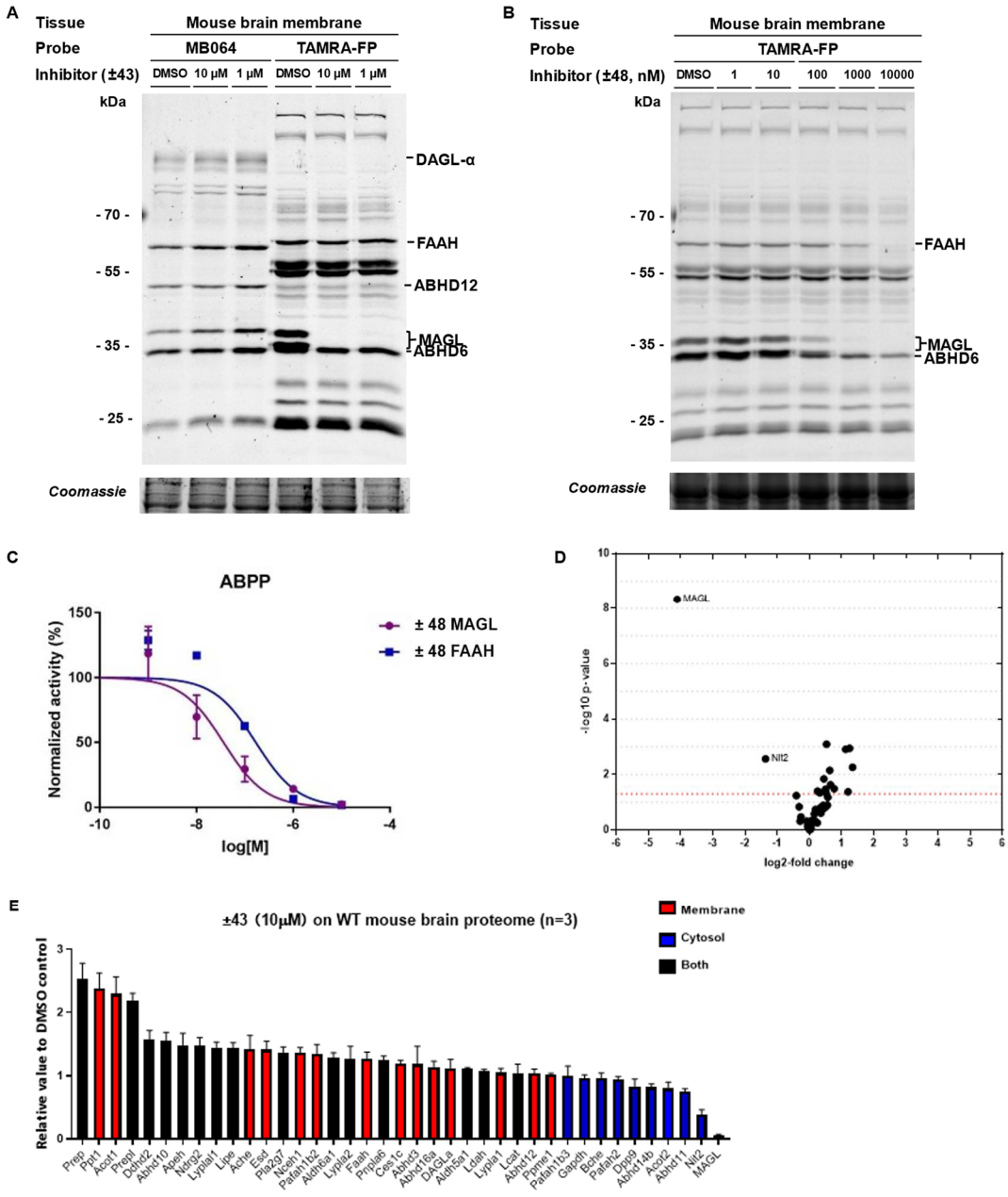


Figure 2. (A) Selectivity profiles of compound ± **43** on mouse brain membrane proteome using broad-spectrum probe MB064 (250 nM, 10 min) or TAMRA-FP (100 nM, 10 min) for gel-based ABPP. (B, C) Selectivity profiles of compound ± **48** on mouse brain proteome using broad-spectrum probe TAMRA-FP (100 nM, 10 min) for gel-based ABPP. (D, E) Selectivity profiles of compound ± **43** on mouse brain proteome (MBP) using broad-spectrum probe MB108 and FP-biotin (10 μM, 60 min) for chemical proteomics.

match the SAR data. The two methyl groups on the piperazine ring are orientated to different directions in the hydrophobic pocket, which enhance the hydrophobic interaction. No specific interaction is observed between the amide moiety of ± **43** and MAGL, suggesting that the amide acts as a linker which is in line with compound ± **48**

being active. This proposed binding mode is thus consistent with the observed SAR reported in this chapter.

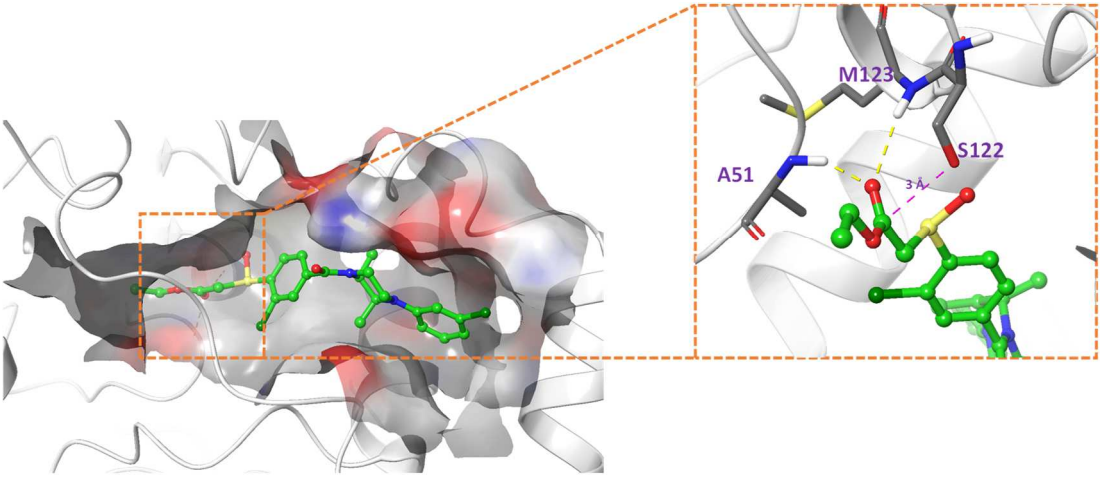


Figure 3. Docking pose of compound **± 43** with MAGL (PDB code: 3HJU). Two H-bounds (yellow dotted line) with Ala51 and Met123 were observed in this docking model.

2.3 Conclusion

In conclusion, a ligand-based optimization of β-sulfinyl esters as MAGL inhibitors is described in this chapter, which leads to the discovery of a highly potent and selective MAGL inhibitor (compound ± **43**). A summary of the SAR is presented in Figure 4. Compared with the original hit **1**, the MAGL inhibitory activity of ± **43** increased around 100-fold. Importantly, by replacing the nitro group with chloro, the potential genotoxicity liability was removed. By using ABPP and chemical proteomics, the selectivity of ± **43** was profiled and it showed high selectivity against other serine hydrolases in the ECS. Notwithstanding the important role of the ester group in the binding activity, its metabolic stability should be investigated to assess the *in vivo* stability of the compound.

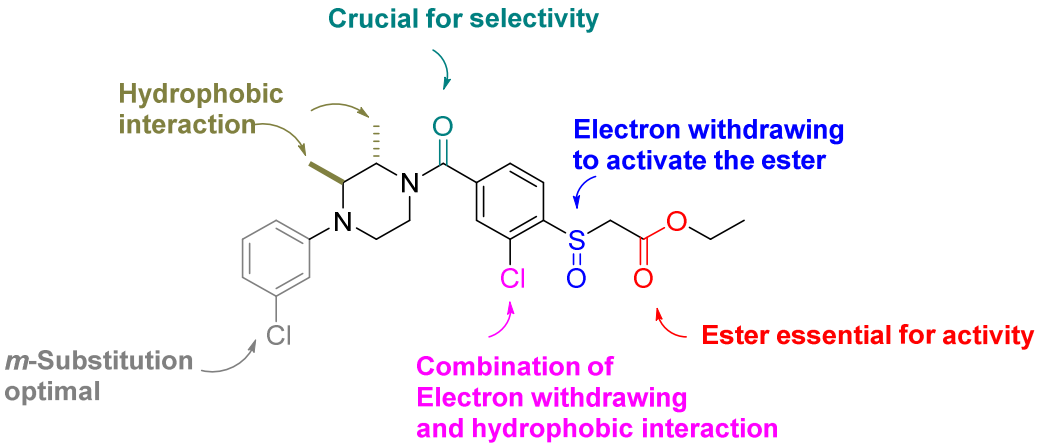


Figure 4. An overview of the structure-activity relationship for the β-sulfinyl esters MAGL inhibitor library.

2.4 Experimental procedures

Biological Procedures

MAGL natural substrate assay. The MAGL activity assay is based on the production of glycerol from 2-arachidonoylglycerol (2-AG) hydrolysis by MAGL-overexpressing membrane preparations from transiently transfected HEK293T cells, as previously reported. The produced glycerol is coupled to the oxidation of commercially available Amplifu™Red via a multi-enzyme cascade, resulting in a fluorescent signal from the dye resorufin. Standard assays were performed in HEMNB buffer (50 mM HEPES pH 7.4, 1 mM EDTA, 5 mM $MgCl_2$, 100 mM NaCl, 0.5% (w/v) BSA) in black, flat bottom 96-wells plates. Final protein concentration of membrane preparations from overexpressing hMAGL HEK293T cells was 1.5 μg/mL (0.3 μg per well). Inhibitors were added from 40x concentrated DMSO stocks. After 20 min. incubation, 100 μL assay mix containing glycerol kinase (GK), glycerol-3-phosphate oxidase (GPO), horse radish peroxidase (HRP), adenosine triphosphate (ATP), Amplifu™Red and 2-arachidonoylglycerol (2-AG) was added and fluorescence was measured in 5 min. intervals for 60 min. on a plate reader. Final assay concentrations: 0.2 U/mL GK, GPO and HRP, 0.125 mM ATP, 10 μM Amplifu™Red, 25 μM 2-AG, 5% DMSO, 0.5% ACN in a total volume of 200 μL. All measurements were performed in N = 2, n = 2 or N = 2, n = 4 for controls, with Z' ≥ 0.6. For IC_{50} determination, the MAGL-overexpressing membranes were incubated with different inhibitor concentrations. Slopes of corrected fluorescence in time were determined in the linear interval of t = 10 to t = 35 min and then scaled to the corrected positive control of hMAGL-overexpressing membranes treated with vehicle (DMSO) as a 100% activity reference point. The data was exported to GraphPad Prism 5.0 and analyzed in a non-linear dose-response analysis with variable slope.

Preparation of mouse brain membrane proteome. Mouse brains were isolated according to guidelines approved by the ethical committee of Leiden University (DEC#10095). Isolated brains were thawed on ice, dounce homogenized in lysis buffer A (20 mM Hepes, 2 mM DTT, 1 mM $MgCl_2$, 25 u/ml Benzonase, pH 7.2) and

incubated for 15 min on ice. Then debris was removed by low-speed spin (2500 g, 1 min, 4 ºC) and the supernatant was subjected to ultracentrifugation (100.000 g, 45 min, 4 ºC, Beckman Coulter, Type Ti70 rotor) to yielded the membrane fraction as a pellet. The pellet was resuspended in lysis buffer B (20 mM Hepes, 2 Mm DTT). The total protein concentration was determined with Quick Start Bradford assay. The obtained membranes were stored in small aliquots at -80 ºC until use.

Activity based protein profiling. The competitive ABPP assay on mouse brain proteome was performed as previously reported.[20] In brief, to 19 µl mouse brain proteome (2mg/ml) was added 0.5 µl of the inhibitor or pure DMSO, vortexed gently and incubated for 30 min at RT. Subsequently, 0.5 µl probe was added to the proteome sample, vortexed gently and incubated for 10 min. The reaction was quenched by adding 10 µl of 4*Laemmli-buffer and 10 µl of quenched reaction mixture was resolved on 10 % acrylamide SDS-PAGE (180V, 75 min). Fluorescence was measured using a Biorad ChemiDoc MP system. Gels were then stained using Coomassie staining and imaged for protein loading control.

Chemical proteomics. Mouse brain proteome (245 µL, 2.0 mg/mL) membrane or soluble fraction was incubated with vehicle (DMSO) or inhibitor (1 µM) in DMSO for 30 minutes at 37 ºC. The proteome was labeled with a probe cocktail (2.5 µM MB108 and 5 µM FP-Biotin, 30 minutes, 37 ºC). Subsequently the labeling reaction was quenched and excess probe was removed by chloroform methanol precipitation. Precipitated proteome was suspended in 250 µL 6M Urea/25 mM ammonium bicarbonate and allowed to incubate overnight. 2.5 µL (1 M DTT) was added and the mixture was heated to 65 ºC for 15 minutes. The sample was allowed to cool to rt before 20 µL (0.5 M) iodoacetamide was added and the sample was alkylated for 30 minutes in the dark. 70 µL 10% (wt/vol) SDS was added and the proteome was heated for 5 minutes at 65 ºC. The sample was diluted with 6 mL PBS. 100 µL of 50% slurry of Avidin−Agarose from egg white (Sigma-Aldrich) was washed with PBS and added to the proteome sample. The beads were incubated with the proteome > 3h. The beads were isolated by centrifugation and washed with 0.5% (wt/vol) SDS and PBS (3x). The proteins were digested overnight with sequencing grade trypsin (Promega) in 250 µL

OB-Dig buffer (100 mM Tris, 100 mM NaCl, 1 mM $CaCl_2$, 2 % ACN and 500 ng trypin) at 37 °C with vigorous shaking. The pH was adjusted with formic acid to pH 3 and the beads were removed from filtration. The peptides were washed and eluted with stage tips according to the procedure below.

Step	Solution	Centrifugation speed
Conditioning 1	50 µL MeOH	2 min 300g
Conditioning 2	50 µL Stage tip solution B	2 min 300g
Conditioning 3	50 µL Stage tip solution A	2 min 300g
Loading		2 min 600g
Washing	100 µL Stage tip solution A	2 min 600g
Elution	100 µL Stage tip solution B	2 min 600g

Stage tip solution A: 0.5% (vol/vol) FA in H_2O. (Freshly prepared solution)
Stage tip solution B: 0.5% (vol/vol) FA in 80% (vol/vol) ACN/H_2O. (Freshly prepared solution).

After the final elution step, the obtained peptides were concentrated on a speedvac to remove the ACN. The residue was reconstituted in 95:3:0.1 H2O/ACN/FA (vol/vol) before LC/MS analysis.

For LC-MS analysis, each sample in duplicate was loaded onto the ultra-performance liquid chromatography-ion mobility spectrometry-mass spectrometry system a NanoACQUITY UPLC System coupled to SYNAPT G2-Si high definition mass spectrometer[28]. A trap-elute protocol was followed, where 1 µL of the digest was loaded on a trap column (C18 100 Å, 5 µM, 180 µMx20 mm; Waters), followed by elution and separation on an analytical column (HSS-T3 C18 1.8µM, 75 µMx250 mm; Waters). The sample was loaded onto this column at a flow rate of 10 µL/min with 99.5% solvent A for 2 minutes before switching to the analytical column. Peptide separation was achieved by using a multistep concave gradient based on gradients previously described[29]. The column was re-equilibrated to initial conditions after washing with 90% solvent B as previously described[29]. The rear seals of the pump were flushed every 30 minutes with 10% (v/v) acetonitrile. [Glu1] fibrinopeptide B was used as a lock mass compound. The auxiliary pump of the LC system was used to deliver this peptide to the

reference sprayer (0.2 µL/min). An ultradefinition MSE method was set up as previously described[29]. Briefly, the mass range was set at 50-2,000 Da, with a scan time of 0.6 seconds in positive resolution mode. The collision energy was set to 4 V in the trap cell for low-energy MS mode. For the elevated energy scan, the transfer cell collision energy was ramped using drift-time specific collision energies. The lock mass was sampled every 30 seconds.

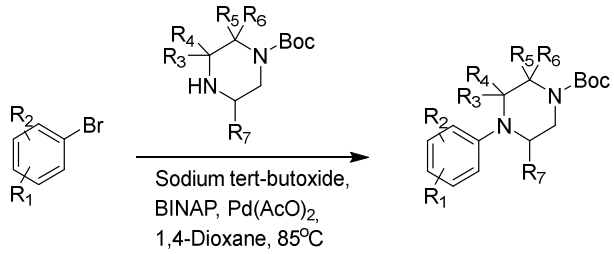
Docking studies. All docking studies were performed in the Schrödinger suite (Schrödinger Release 2017-4: Maestro, Schrödinger, LLC, New York, NY, 2017). The crystal structure of MAGL (PDB code: 3HJU) was prepared using the protein preparation wizard and ligands were prepared using LigPrep. Docking was done using induced fit docking with SP precision and poses with the best docking scores were manually examined. One pose per ligand was selected.

Chemistry procedures

General remarks. All reactions were performed using oven or flame-dried glassware and dry solvents. Reagents were purchased from Sigma Aldrich, Acros and Merck and used without further purification unless noted otherwise. All moisture sensitive reactions were performed under an argon or nitrogen atmosphere. Traces of water were removed from starting compounds by co-evaporation with toluene. Reactions were followed by thin layer chromatography and was performed using TLC Silica gel 60 F_{245} on aluminums sheets. Compounds were visualized using a $KMnO_4$ stain (K_2CO_3 (40 g), $KMnO_4$ (6 g), H_2O (600 mL) and 10% NaOH (5 mL)). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AV-400, 500, 600 or 850 using $CDCl_3$ or CD_3OD as solvent, unless stated otherwise. Chemical shift values are reported in ppm with tetramethylsilane or solvent resonance as the internal standard ($CDCl_3$: δ 7.26 for ^{1}H, δ 77.16 for ^{13}C, CD_3OD: δ 3.31 for ^{1}H, δ 49.00 for ^{13}C). Data are reported as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, dd = double doublet, td = triple doublet, t = triplet, q = quartet, quinted = quint, br = broad, m = multiplet), coupling constants *J* (Hz), and integration. LC-MS measurements were performed on a Thermo Finnigan LCQ Advantage Max ion-trap mass spectrometer (ESI^+) coupled to a

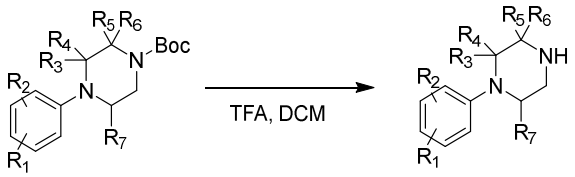
Surveyor HPLC system (Thermo Finnigan) equipped with a standard C18 (Gemini, 4.6 mmD × 50 mmL, 5 µm particle size, Phenomenex) analytical column and buffers A: H_2O, B: ACN, C: 0.1% aq. TFA. Preparative HPLC purification was performed on a Waters Acquity Ultra Performance LC with a C18 column (Gemini, 150 × 21.2 mm, Phenomenex). Diode detection was done between 210 and 600 nm. Gradient: ACN in (H_2O + 0.2% TFA). High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific LTQ Orbitrap XL.

General procedure A



A mixture of the appropriate bromobenzene (1 eq.), mono Boc-protected piperazine (1 eq.), palladium diacetate (0.04 eq.), BINAP (0.06 eq.) and sodium *tert*-butoxide (1.5 eq.) in degassed 1,4-dioxane was heated to 85 °C under nitrogen atmosphere overnight. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was diluted with DCM, washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (pentane/diethyl ether) to give the product.

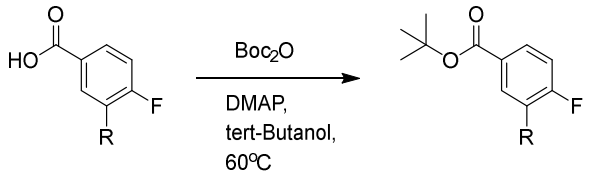
General procedure B



To a solution of the appropriate *tert*-butyl phenylpiperazine-1-carboxylate in DCM was added TFA (final TFA concentration, 20% *v/v*) and the mixture was stirred at room temperature for 2h. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was diluted with DCM and washed with saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered and

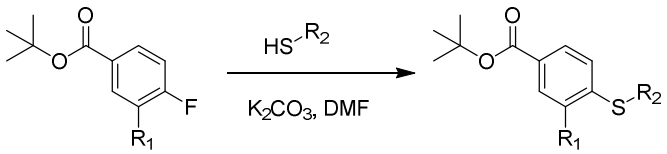
concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/MeOH) to give the product.

General procedure C



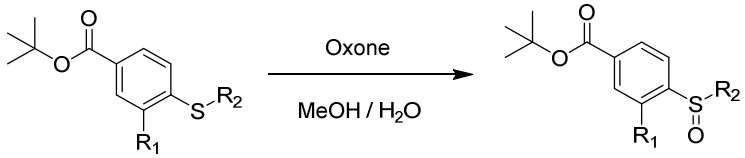
A mixture of the appropriate benzoic acid (1 eq.), di-*tert*-butyl dicarbonate (3 eq.) and DMAP (0.3 eq.) in *tert*-butanol was heated to 60 ºC and stirred overnight. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting meterials, the solvent was evaporated and the residue was purified by silica gel column chromatography (pentane/diethyl ether) to give the product.

General procedure D



To a solution of the appropriate *tert*-butyl 4-fluorobenzoate (1.2 eq.) in ACN were added K_2CO_3 (3 eq.) and the appropriate thiol (1 eq.). The reaction mixture was stirred at RT overnight. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was diluted with Et_2O and washed with water, dried ($MgSO_4$). After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (pentane/diethyl ether).

General procedure E



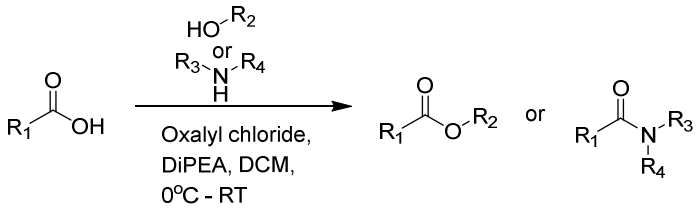
To a cooled (0 ºC) solution of the appropriate sulfure (1 eq.) in MeOH was dropwise added an oxone / water solution and the mixture was stirred at RT for 2h. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials,

the mixture was diluted with EtOAc and washed with water. The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica column chromatography (pentane/EtOAc).

General procedure F

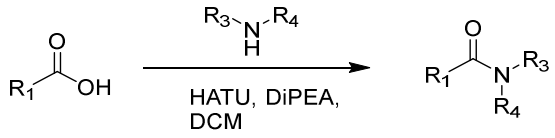
To a solution of the appropriate *tert*-butyl protected carboxylic acid in DCM was added TFA (final TFA concentration, 20% *v/v*) and the mixture was stirred at RT for 6 h. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the solvent was removed under reduced pressure and the residue was purified silica gel column chromatography (DCM/MeOH).

General procedure G



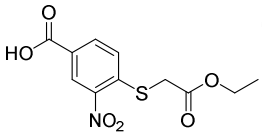
To a cooled solution of the appropriate carboxylic acid (1 eq.) in dried DCM was subsequently added 2 drops of DMF and oxalyl chloride (1.2 eq.). Then the mixture was allowed to warm to room temperature and continuously stirred for 2h. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was dropwise added to a cooled (0 °C) solution of the appropriate alcohol (3eq.) or amine (3eq.) and DiPEA (3 eq.) in DCM. Then the reaction mixture was stirred at room temperature overnight. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was diluted with DCM and washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by HPLC-MS.

General procedure H



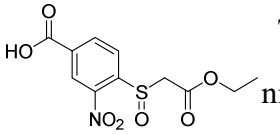
To a suspension or solution of the appropriate benzoic acid (1 eq.) in DCM was added HATU (1.5 eq.) and DiPEA (3 eq.) and then the mixture was stirred at room temperature for 1h. The appropriate phenylpiperazine (1eq.) was added and the mixture was stirred overnight. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting meterials, the mixture was diluted with DCM and washed with water, dried ($MgSO_4$), filtered and concentrated under reduce pressure. The residue was purified by silica gel column chromatography (pentane/EtOAc) or HPLC-MS.

4-((2-Ethoxy-2-oxoethyl)thio)-3-nitrobenzoic acid (**60**)



To a solution of 4-chloro-3-nitrobenzoic acid (1.26 mg, 6.24 mmol, 1.50 eq.) in pyridine (5 mL) was added ethyl mercaptoacetate (0.5 g, 4.16 mmol, 1.00 eq.) and the mixture was heated to 115 °C overnight in an oil bath. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting meterials, the mixture was allowed to cool to rt and the pH was adjusted to 1 with 1M HCl solution. The precipitate was filtered and the solid were washed with water to provide the product (1.01 g, 3.54 mmol, 85%). ^{1}H NMR (400 MHz, Methanol-*d*4) δ 8.73 (d, *J* = 1.9 Hz, 1H), 8.16 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.00 (s, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-*d*4) δ 170.38, 167.34, 143.24, 135.02, 129.44, 128.46, 128.08, 63.20, 35.65, 14.53.

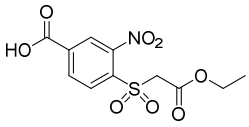
4-((2-Ethoxy-2-oxoethyl)sulfinyl)-3-nitrobenzoic acid (**61**)



To a cooled solution of 4-((2-ethoxy-2-oxoethyl)thio)-3-nitrobenzoic acid (285 mg, 1.00 mmol, 1.00 eq.) in methanol (13mL) was dropwise added a solution of oxone (62 mg, 1.00 mmol, 1.00 eq.) in water (4 mL) and the reaction mixture was stirred at rt for 2.5 h. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was diluted with water and extracted with DCM. The combined

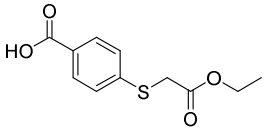
organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/DCM, 1%→2%) to afford the product (210 mg, 0.70 mmol, 70%). ^{1}H NMR (400 MHz, Methanol-*d*4) δ 8.88 (d, *J* = 1.6 Hz, 1H), 8.61 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.34 (d, *J* = 8.2 Hz, 1H), 4.36 (d, *J* = 14.4 Hz, 1H), 4.29 – 4.13 (m, 2H), 3.82 (d, *J* = 14.5 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-*d*4) δ 166.82, 166.60, 147.30, 136.89, 136.55, 128.43, 127.26, 63.37, 61.32, 14.54.

4-((2-Ethoxy-2-oxoethyl)sulfonyl)-3-nitrobenzoic acid (**62**)



To a solution of 4-((2-ethoxy-2-oxoethyl)thio)-3-nitrobenzoic acid (1.10 g, 3.86 mmol, 1.00 eq.) in AcOH (20mL) was added H_2O_2 (35%, 5mL), *tert*-butylammonium hydrogen sulfate (65 mg, 0.19 mmol, 0.05 eq.) and sodium tungstate dihydrate (127 mg, 0.39 mmol, 0.1 eq.) and the reaction mixture was refluxed for 3h. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was cooled down to rt and diluted with water, extracted with EtOAc and dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/DCM, 1%→2%) to afford the product (0.62g, 1.95 mmol, 51%). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.51 (d, *J* = 1.6 Hz, 1H), 8.43 (dd, *J* = 8.2, 1.7 Hz, 1H), 8.26 (d, *J* = 8.2 Hz, 1H), 4.93 (s, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 1.10 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (101 MHz, DMSO-*d*6) δ 164.46, 162.06, 148.41, 137.81, 134.35, 133.34, 133.28, 125.63, 62.09, 60.66, 13.71.

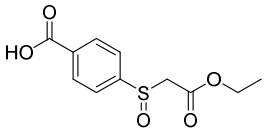
4-((2-Ethoxy-2-oxoethyl)thio)benzoic acid (**63**)



To a suspension of 4-mercaptobenzoic acid (0.46 g, 2.99 mmol, 1.00 eq.) in water (5mL) was added NaOH (0.18 g, 4.49 mmol, 1.50 eq.) and the resulting solution was stirred for 30min at room temperature. Then ethyl 2-bromoacetate (0.50 g, 2.99 mmol, 1.00 eq.) was slowly added to the solution and the reaction mixture was stirred for another 2h at rt. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was acidified with 1M HCl and the obtained precipitate was filtered, washed with water and dried to give the product (252 mg, 1.05 mmol, 35 %). ^{1}H NMR

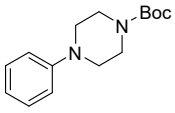
($CDCl_3$, 400 MHz) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.26 (d, *J* = 8.3 Hz, 2H), 4.10 (q, *J* = 7.3 Hz, 2H), 3.79 (s, 2H), 1.15 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (MeOD, 101 MHz) δ 170.94, 169.28, 143.74, 131.16, 129.19, 127.98, 62.72, 35.35, 14.37.

4-((2-Ethoxy-2-oxoethyl)sulfinyl)benzoic acid (**64**)



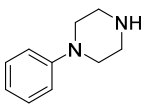
To a cooled solution of 4-((2-ethoxy-2-oxoethyl)thio)benzoic acid (100 mg, 0.42 mmol, 1.00 eq.) in methanol (5mL) was dropwise added a solution of oxone (26 mg, 1.00 mmol, 1.00 eq.) in water (5 mL) and the reaction mixture was stirred at rt for 2.5 h. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/DCM, 1%→2%) to afford the product (83mg, 0.33 mmol, 78%). ^{1}H NMR (400 MHz, Methanol-*d*4) δ 8.22 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.06 (d, *J* = 14.4 Hz, 1H), 3.94 (d, *J* = 14.3 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-*d*4) δ 168.37, 166.14, 148.49, 135.28, 131.64, 125.61, 63.07, 61.45, 14.33.

***tert*-Butyl 4-phenylpiperazine-1-carboxylate** (**6a**)



The title compound was synthesized using bromobenzene (160 mg, 1.00 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (190 mg, 1.00 mmol, 1 eq.), sodium *tert*-butoxide (240 mg, 2.50 mmol, 2.5 eq.), *rac*-BINAP (60 mg, 0.10 mmol, 0.10 eq.) and palladium diacetate (3 mg, 0.015 mmol, 0.015 eq.) according to general procedure A in a yield of 252mg (0.10 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 6.97 – 6.91 (m, 2H), 6.91 – 6.86 (m, 1H), 3.58 (t, *J* = 5.2 Hz, 4H), 3.13 (t, *J* = 5.2 Hz, 4H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.82, 151.37, 129.28, 120.37, 116.72, 79.95, 49.51, 28.53.

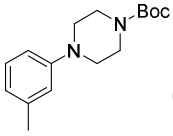
1-Phenylpiperazine (**6b**)



The title compound was synthesized using *tert*-butyl 4-phenylpiperazine-1-carboxylate (100 mg, 0.38 mmol, 1 eq.) according to general procedure B in a yield of 54 mg (0.34 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.21 (m, 2H), 6.96 – 6.88 (m, 2H), 6.90 – 6.81 (m, 1H), 3.13 (t, *J* = 5.2 Hz, 4H), 3.02 (t, *J* = 5.2 Hz,

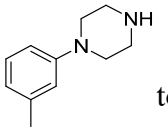
4H), 2.37 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.57, 129.20, 120.46, 116.63, 83.53.

***tert*-Butyl 4-(*m*-tolyl)piperazine-1-carboxylate (2a)**



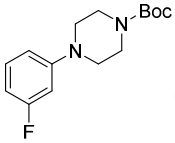
The title compound was synthesized using 1-bromo-3-methylbenzene (0.50 g, 2.92 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (0.82 g, 4.39 mmol, 1.5 eq.), cesium carbonate (1.43 g, 4.39 mmol, 1.5 eq.), rac-BINAP (116 mg, 0.18 mmol, 0.06 eq.) and palladium diacetate (26.3 mg, 0.12 mmol, 0.04 eq.) according to general procedure A in a yield of 0.75 g (2.70 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J* = 7.8 Hz, 1H), 6.75 – 6.64 (m, 3H), 3.54 (t, *J* = 5.2 Hz, 4H), 3.06 (t, *J* = 5.2 Hz, 4H), 2.30 (s, 3H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.51, 151.22, 138.59, 128.86, 121.01, 117.33, 113.63, 79.57, 49.34, 28.32, 21.63.

1-(*m*-Tolyl)piperazine (2b)



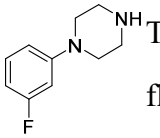
The title compound was synthesized using *tert*-butyl 4-(m-tolyl)piperazine-1-carboxylate (0.75 g, 2.70 mmol, 1 eq.) according to general procedure B in a yield of 450 mg (2.55 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 8.2, 7.2 Hz, 1H), 6.85 – 6.68 (m, 3H), 5.93 (s, 1H), 3.37 – 3.27 (m, 4H), 3.26 – 3.19 (m, 4H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.88, 138.88, 129.02, 121.48, 117.42, 113.72, 48.52, 44.66, 21.70.

***tert*-Butyl 4-(3-fluorophenyl)piperazine-1-carboxylate (7a)**



The title compound was synthesized using 1-bromo-3-fluorobenzene (100 mg, 0.57 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (128 mg, 0.69 mmol, 1.2 eq.), sodium *tert*-butoxide (82 mg, 0.86 mmol, 1.5 eq.), rac-BINAP (21 mg, 0.034 mmol, 0.06 eq.) and palladium diacetate (5 mg, 0.023 mmol, 0.04 eq.) according to general procedure A in a yield of 145 mg (0.52 mmol, 91%).

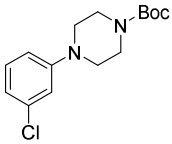
1-(3-Fluorophenyl)piperazine (7b)



The title compound was synthesized using *tert*-butyl 4-(3-fluorophenyl)piperazine-1-carboxylate (100 mg, 0.36 mmol, 1 eq.) according to general procedure B in a yield of 62 mg (0.34 mmol, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (td, *J* = 8.2, 7.0 Hz, 1H), 6.67 (ddd, *J* = 8.4, 2.4, 0.8 Hz, 1H), 6.62 – 6.46 (m, 2H),3.37 (br, 1H), 3.25 – 3.12 (m, 4H), 3.08 – 2.95 (m, 4H).

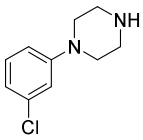
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.89 (d, *J* = 243.2 Hz), 153.32 (d, *J* = 9.7 Hz), 130.19 (d, *J* = 10.0 Hz), 111.30, 106.05 (d, *J* = 21.5 Hz), 102.80 (d, *J* = 25.0 Hz), 49.54, 45.76.

***tert*-Butyl 4-(3-chlorophenyl)piperazine-1-carboxylate (8a)**



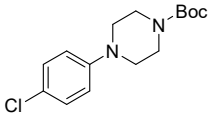
The title compound was synthesized using 1-bromo-3-chlorobenzene (191 mg, 1.00 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (186 mg, 1.00 mmol, 1.00 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (9 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 190 mg (0.64 mmol, 64 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, J = 8.1 Hz, 1H), 6.87 (t, J = 2.2 Hz, 1H), 6.82 (ddd, J = 7.9, 2.0, 0.9 Hz, 1H), 6.77 (ddd, J = 8.4, 2.4, 0.9 Hz, 1H), 3.97 – 3.35 (m, 4H), 3.12 (t, J = 5.2 Hz, 4H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.67, 152.31, 134.99, 130.15, 119.83, 116.30, 114.44, 80.01, 48.89, 28.45.

1-(3-Chlorophenyl)piperazine (8b)



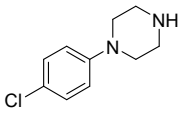
The title compound was synthesized using *tert*-butyl 4-(3-chlorophenyl)piperazine-1-carboxylate (100 mg, 0.34 mmol, 1 eq.) according to general procedure B in a yield of 62 mg (0.31 mmol, 93 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 8.0 Hz, 1H), 6.94 – 6.67 (m, 3H), 6.47 (br, 1H), 3.24 (t, *J* = 5.1 Hz, 4H), 3.14 (t, *J* = 5.2 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.09, 135.03, 130.23, 120.18, 116.31, 114.43, 48.41, 44.78.

***tert*-Butyl 4-(4-chlorophenyl)piperazine-1-carboxylate (9a)**

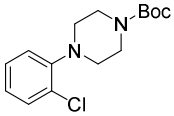


The title compound was synthesized using 1-bromo-4-chlorobenzene (191 mg, 1.00 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (186 mg, 1 mmol, 1.00 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (9 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 264 mg (0.89 mmol, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.16 (m, 2H), 6.86 – 6.76 (m, 2H), 3.62 – 3.49 (m, 4H), 3.08 (t, *J* = 5.2 Hz, 4H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.73, 149.97, 129.11, 125.18, 117.89, 80.05, 49.48, 28.50.

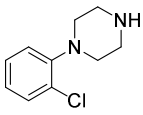
1-(4-Chlorophenyl)piperazine (9b)


The title compound was synthesized using *tert*-butyl 4-(4-chlorophenyl)piperazine-1-carboxylate (100 mg, 0.34 mmol, 1 eq.) according to general procedure B in a yield of 66 mg (0.33 mmol, 99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.17 (m, 2H), 6.86 – 6.79 (m, 2H), 3.12 (dt, *J* = 6.1, 3.7 Hz, 4H), 3.05 (dd, *J* = 6.4, 3.3 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.32, 129.06, 124.84, 117.50, 50.10, 45.81.

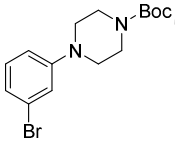
***tert*-Butyl 4-(2-chlorophenyl)piperazine-1-carboxylate (10a)**


The title compound was synthesized using 1-bromo-2-chlorobenzene (191 mg, 1.00 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (186 mg, 1 mmol, 1.00 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (9 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 241 mg (0.81 mmol, 81 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dt, *J* = 7.9, 1.6 Hz, 1H), 7.28 – 7.11 (m, 1H), 7.05 – 6.89 (m, 2H), 3.68 – 3.49 (m, 4H), 3.09 – 2.83 (m, 4H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.74, 149.05, 130.62, 128.87, 127.58, 123.95, 120.45, 79.66, 51.18, 44.08, 28.42.

1-(2-Chlorophenyl)piperazine (10b)

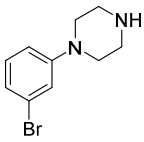

The title compound was synthesized using *tert*-butyl 4-(2-chlorophenyl)piperazine-1-carboxylate (100 mg, 0.34 mmol, 1 eq.) according to general procedure B in a yield of 63 mg (0.32 mmol, 95 %.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.08 – 6.90 (m, 2H), 4.27 (br, 1H), 3.21 – 2.86 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.21, 131.61, 130.64, 127.65, 123.94, 120.50, 51.62, 45.63.

***tert*-Butyl 4-(3-bromophenyl)piperazine-1-carboxylate (11a)**


The title compound was synthesized using 1,3-dibromobenzene (236 mg, 1.00 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (186 mg, 1 mmol, 1.00 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (9 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 259 mg (0.76 mmol, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (t, *J* = 8.1 Hz, 1H), 7.02 (t, *J* = 2.1 Hz, 1H), 6.97 (ddd, *J* = 7.9, 1.8, 0.9 Hz, 1H), 6.81 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 3.62 – 3.46 (m, 4H), 3.11 (t,

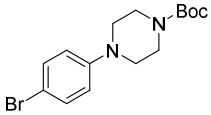
J = 5.1 Hz, 4H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.66, 152.45, 130.44, 123.26, 122.79, 119.24, 114.94, 80.02, 48.91, 43.69, 28.46.

1-(3-Bromophenyl)piperazine (11b)



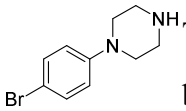
The title compound was synthesized using *tert*-butyl 4-(3-bromophenyl)piperazine-1-carboxylate (100 mg, 0.29 mmol, 1 eq.) according to general procedure B in a yield of 66 mg (0.28 mmol, 94 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.05 (m, 1H), 7.02 (t, *J* = 2.1 Hz, 1H), 6.98 – 6.89 (m, 1H), 6.82 (ddd, *J* = 8.4, 2.5, 0.9 Hz, 1H), 3.12 (m, 4H), 3.03 – 2.94 (m, 4H), 1.84 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.02, 130.35, 123.27, 122.23, 118.71, 114.44, 49.89, 46.02.

***tert*-Butyl 4-(4-bromophenyl)piperazine-1-carboxylate (12a)**



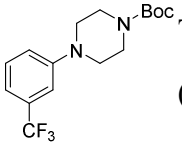
The title compound was synthesized using 1,4-dibromobenzene (236 mg, 1.00 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (186 mg, 1 mmol, 1.00 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (9 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 256 mg (0.75 mmol, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H), 6.82 – 6.73 (m, 2H), 3.68 – 3.41 (m, 4H), 3.09 (t, *J* = 5.2 Hz, 4H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.71, 150.33, 132.02, 118.25, 112.49, 80.06, 49.29, 43.74, 28.50.

1-(4-Bromophenyl)piperazine (12b)



The title compound was synthesized using *tert*-butyl 4-(4-bromophenyl)piperazine-1-carboxylate (100 mg, 0.29 mmol, 1 eq.) according to general procedure B in a yield of 66 mg (0.28 mmol, 93 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 6.82 – 6.75 (m, 2H), 3.16 – 3.09 (m, 4H), 3.07 – 2.97 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.80, 131.98, 117.85, 112.07, 50.07, 45.91.

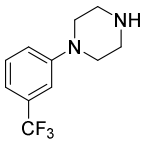
***tert*-Butyl 4-(3-(trifluoromethyl)phenyl)piperazine-1-carboxylate (13a)**



The title compound was synthesized using 1-bromo-3-(trifluoromethyl)benzene (225 mg, 1.00 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (186 mg, 1 mmol, 1.00 eq.), sodium *tert*-

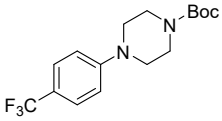
butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (9 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 289 mg (0.88 mmol, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (ddt, *J* = 8.2, 7.2, 0.9 Hz, 1H), 8.14 – 8.05 (m, 3H), 4.65 – 4.55 (m, 4H), 4.19 (t, *J* = 5.2 Hz, 4H), 2.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.78, 151.41, 131.65 (q, *J* = 31.7 Hz), 129.79, 124.35 (q, *J* = 272.70 Hz), 119.51, 116.65 (q, *J* = 3.6 Hz), 112.89 (q, *J* = 3.8 Hz), 80.22, 49.10, 28.54.

1-(3-(Trifluoromethyl)phenyl)piperazine (13b)



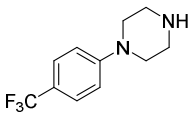
The title compound was synthesized using *tert*-butyl 4-(3-(trifluoromethyl)phenyl)piperazine-1-carboxylate (100 mg, 0.30 mmol, 1 eq.) according to general procedure B in a yield of 68 mg (0.29 mmol, 97 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.9 Hz, 1H), 7.17 – 6.99 (m, 3H), 3.87 (s, 1H), 3.27 – 3.19 (m, 4H), 3.14 – 3.01 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.62, 131.43 (q, *J* = 31.7 Hz), 129.65, 124.35 (q, *J* = 272.4 Hz), 119.03, 116.19 (q, *J* = 3.8 Hz), 112.39 (q, *J* = 3.9 Hz), 49.24, 45.50.

***tert*-Butyl 4-(4-(trifluoromethyl)phenyl)piperazine-1-carboxylate (14a)**



The title compound was synthesized using 1-bromo-4-(trifluoromethyl)benzene (225 mg, 1.00 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (186 mg, 1 mmol, 1.00 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (9 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 218 mg (0.66 mmol, 66 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.44 (m, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 3.65 – 3.53 (m, 4H), 3.25 (t, *J* = 5.2 Hz, 4H). 1.49 (s, 9 H).

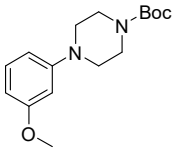
1-(4-(Trifluoromethyl)phenyl)piperazine (14b)



The title compound was synthesized using *tert*-butyl 4-(4-(trifluoromethyl)phenyl)piperazine-1-carboxylate (100 mg, 0.30 mmol, 1 eq.) according to general procedure B in a yield of 60 mg (0.26 mmol, 86 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 4.26 (br, 1H), 3.36 – 3.24 (m, 4H), 3.13 – 3.04 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.48,

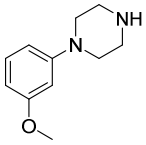
126.47 (q, *J* = 3.7 Hz), 124.75 (q, *J* = 271.69 Hz), 120.86 (q, *J* = 32.6 Hz), 114.82, 48.49, 45.36.

***tert*-Butyl 4-(3-methoxyphenyl)piperazine-1-carboxylate (15a)**



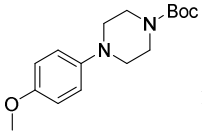
The title compound was synthesized using 1-bromo-3-methoxybenzene (374 mg, 2.00 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (373 mg, 2 mmol, 1.00 eq.), sodium *tert*-butoxide (288 mg, 3.00 mmol, 1.5 eq.), rac-BINAP (75 mg, 0.12 mmol, 0.06 eq.) and palladium diacetate (18 mg, 0.08 mmol, 0.04 eq.) according to general procedure A in a yield of 433 mg (1.48 mmol, 74 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 8.1 Hz, 1H), 6.52 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.47 – 6.41 (m, 2H), 3.77 (s, 3H), 3.56 (t, *J* = 5.0 Hz, 4H), 3.21 – 2.99 (m, 4H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.57, 154.63, 152.61, 129.81, 109.25, 104.93, 102.95, 79.77, 55.10, 49.25, 28.41.

1-(3-Methoxyphenyl)piperazine (15b)



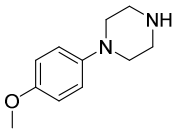
The title compound was synthesized using *tert*-butyl 4-(4-(trifluoromethyl)phenyl)piperazine-1-carboxylate (200 mg, 0.68 mmol, 1 eq.) according to general procedure B in a yield of 130 mg (0.68 mmol, 99 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (br, 1H), 7.21 (t, *J* = 8.2 Hz, 1H), 6.55 – 6.49 (m, 2H), 6.45 (t, *J* = 2.3 Hz, 1H), 3.79 (s, 3H), 3.41 (m, 4H), 3.33 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.81, 151.45, 130.32, 109.86, 106.53, 103.90, 55.39, 46.99, 43.47.

***tert*-Butyl 4-(4-methoxyphenyl)piperazine-1-carboxylate (16a)**



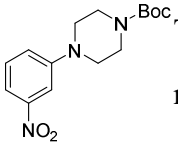
The title compound was synthesized using 1-bromo-4-methoxybenzene (500 mg, 2.67 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (597 mg, 3.21 mmol, 1.2 eq.), cesium carbonate (1307 mg, 4.01 mmol, 1.5 eq.), rac-BINAP (106 mg, 0.16 mmol, 0.06 eq.) and palladium diacetate (24 mg, 0.11 mmol, 0.04 eq.) according to general procedure A in a yield of 438 mg (1.50 mmol, 56 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 – 6.72 (m, 4H), 3.70 (s, 3H), 3.60 – 3.46 (m, 4H), 3.01 – 2.87 (m, 4H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.52, 154.07, 145.48, 118.68, 114.30, 79.57, 55.31, 50.76, 28.32.

1-(4-Methoxyphenyl)piperazine (16b)



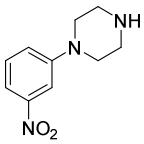
The title compound was synthesized using *tert*-butyl 4-(4-methoxyphenyl)piperazine-1-carboxylate (438 mg, 1.50 mmol, 1 eq.) according to general procedure B in a yield of 260 mg (1.35 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 – 6.77 (m, 4H), 3.70 (s, 3H), 2.96 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.66, 146.20, 118.07, 114.30, 55.38, 51.76, 46.20.

***tert*-Butyl 4-(3-nitrophenyl)piperazine-1-carboxylate (17a)**



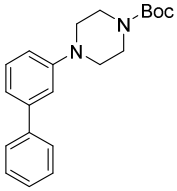
The title compound was synthesized using 1-bromo-3-nitrobenzene (202 mg, 1.00 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (186 mg, 1 mmol, 1.00 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (9 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 150 mg (0.49 mmol, 49 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.55 (m, 2H), 7.39 (t, *J* = 8.2 Hz, 1H), 7.20 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.03 – 3.44 (t, *J* = 5.2 Hz, 4H), 3.25 (t, *J* = 5.2 Hz, 4H), 1.50 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.57, 151.71, 149.17, 129.79, 121.61, 114.61, 110.02, 80.13, 48.44, 28.38.

1-(3-Nitrophenyl)piperazine (17b)



The title compound was synthesized using *tert*-butyl 4-(3-nitrophenyl)piperazine-1-carboxylate (100 mg, 0.33 mmol, 1 eq.) according to general procedure B in a yield of 66 mg (0.32 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.1 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 8.3, 2.5 Hz, 1H), 3.40 – 3.16 (m, 4H), 3.13 – 2.95 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.31, 149.32, 129.76, 121.27, 113.80, 109.74, 49.48, 45.88.

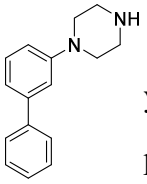
***tert*-Butyl 4-([1,1'-biphenyl]-3-yl)piperazine-1-carboxylate (18a)**



To a mixture of phenylboronic acid (107 mg, 0.88 mmol, 1.5 eq.) and *tert*-butyl 4-(3-bromophenyl)piperazine-1-carboxylate (200 mg, 0.59 mmol, 1 eq.) in 1.4-dioxane (5mL) was added cesium carbonate (573 mg, 1.76 mmol, 3 eq.) and tetrakis(triphenylphosphine)palladium (14 mg, 0.012 mmol, 0.02 eq.). Then the reaction mixture was degassed with N_2 for 30 min. The mixture was heated to 80 ºC for 5h. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was diluted with

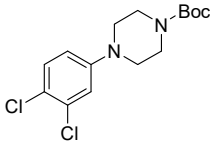
DCM and washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Et_2O / pentane, 0 – 10 %) to yielded the product (181 mg, 0.53 mmol, 91 %). 1H NMR (400 MHz, $CDCl_3$) δ 7.55 (dt, *J* = 6.3, 1.2 Hz, 2H), 7.39 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.30 (td, *J* = 7.6, 2.6 Hz, 2H), 7.14 – 7.05 (m, 2H), 6.88 (dd, *J* = 8.1, 2.5 Hz, 1H), 3.57 (t, *J* = 5.2 Hz, 4H), 3.15 (t, *J* = 5.1 Hz, 4H), 1.48 (s, 9H). 13C NMR (101 MHz, $CDCl_3$) δ 154.66, 151.64, 142.31, 141.56, 129.51, 128.67, 127.26, 127.19, 119.31, 115.59, 115.54, 79.81, 49.44, 28.42.

1-([1,1'-Biphenyl]-3-yl)piperazine (18b)



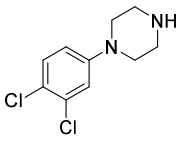
The title compound was synthesized using *tert*-butyl 4-([1,1'-biphenyl]-3-yl)piperazine-1-carboxylate (100 mg, 0.30mmol, 1 eq.) according to general procedure B. The obtained crude product was used directly without any purification.

***tert*-Butyl 4-(3,4-dichlorophenyl)piperazine-1-carboxylate (20a)**



The title compound was synthesized using 4-bromo-1,2-dichlorobenzene (226 mg, 1.00 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (186 mg, 1.00 mmol, 1 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (8.96 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 209 mg (0.63 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 2.4 Hz, 1H), 7.19 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 3.65 – 3.54 (m, 4H), 2.95 (t, *J* = 4.9 Hz, 4H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.86, 147.93, 130.45, 129.71, 128.67, 127.76, 121.35, 79.97, 51.29, 28.52.

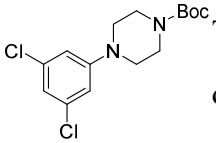
1-(3,4-Dichlorophenyl)piperazine (20b)



The title compound was synthesized using *tert*-butyl 4-(3,4-dichlorophenyl)piperazine-1-carboxylate (100 mg, 0.30 mmol, 1 eq.) according to general procedure B in a yield of 63 mg (0.27 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 2.4 Hz, 1H), 7.22 – 7.18 (m, 1H), 6.96 (d, *J*

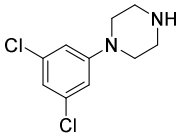
= 8.6 Hz, 1H), 3.58 (br, 1H), 3.12 (m, 4H), 3.05 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.07, 130.45, 129.69, 128.64, 127.80, 121.39, 51.69, 45.71.

***tert*-Butyl 4-(3,5-dichlorophenyl)piperazine-1-carboxylate (19a)**



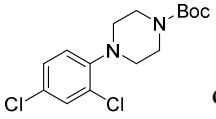
The title compound was synthesized using 1-bromo-3,5-dichlorobenzene (226 mg, 1.00 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (186 mg, 1.00 mmol, 1 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (8.96 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 192 mg (0.58 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (t, J = 1.7 Hz, 1H), 6.74 (d, J = 1.7 Hz, 2H), 3.62 – 3.48 (m, 4H), 3.15 (t, J = 5.2 Hz, 4H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.71, 152.65, 135.61, 119.44, 114.35, 80.28, 48.48, 28.52.

1-(3,5-Dichlorophenyl)piperazine (19b)



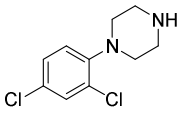
The title compound was synthesized using *tert*-butyl 4-(3,5-dichlorophenyl)piperazine-1-carboxylate (130 mg, 0.39 mmol, 1 eq.) according to general procedure B in a yield of 90 mg (0.39 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (t, J = 1.7 Hz, 1H), 6.74 (d, J = 1.8 Hz, 2H), 3.17 – 3.11 (m, 4H), 3.04 – 2.96 (m, 4H), 1.42 (br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.05, 135.47, 118.90, 113.87, 49.25, 45.74.

***tert*-Butyl 4-(2,4-dichlorophenyl)piperazine-1-carboxylate (21a)**



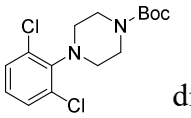
The title compound was synthesized using 1-bromo-2,4-dichlorobenzene (226 mg, 1.00 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (186 mg, 1.00 mmol, 1 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (8.96 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 200 mg (0.60 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 2.5 Hz, 1H), 7.19 (dd, J = 8.6, 2.4 Hz, 1H), 6.93 (d, J = 8.6 Hz, 1H), 3.59 (t, 4H), 2.95 (t, 4H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.87, 147.96, 130.46, 129.72, 128.66, 127.76, 121.35, 79.97, 51.30, 28.53.

1-(2,4-Dichlorophenyl)piperazine (21b)



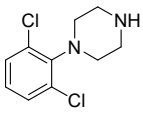
The title compound was synthesized using *tert*-Butyl 4-(2,4-dichlorophenyl)piperazine-1-carboxylate (100 mg, 0.30 mmol, 1.00 eq.) according to general procedure B in a yield of 66 mg (0.28 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.18 (d, *J* = 8.6 Hz, 1H), 6.95 (d, *J* = 8.6, 2.0 Hz, 1H), 3.06 – 3.02 (m, 4H), 3.01 – 2.90 (m, 4H), 2.14 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.48, 130.33, 129.55, 128.17, 127.66, 121.24, 52.56, 46.19.

tert-Butyl 4-(2,6-dichlorophenyl)piperazine-1-carboxylate (22a)



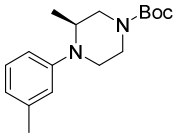
The title compound was synthesized using 2-bromo-1,3-dichlorobenzene (226 mg, 1.00 mmol, 1 eq.), *tert*-butyl piperazine-1-carboxylate (186 mg, 1.00 mmol, 1 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (8.96 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 35 mg (0.11 mmol, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.0 Hz, 2H), 6.99 (t, *J* = 8.3 Hz, 1H), 3.58 – 3.54 (m, 4H), 3.19 – 3.15 (m, 4H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.08, 135.18, 129.25, 126.32, 79.76, 49.56, 28.59.

1-(2,6-Dichlorophenyl)piperazine (22b)



The title compound was synthesized using *tert*-Butyl 4-(2,6-dichlorophenyl)piperazine-1-carboxylate (35 mg, 0.11 mmol, 1.00 eq.) according to general procedure B in a yield of 22 mg (0.10 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.1 Hz, 2H), 6.97 (t, 1H), 3.21 – 3.17 (m, 4H), 3.03 – 2.99 (m, 4H), 2.19 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.41, 135.29, 129.22, 126.03, 50.81, 46.81.

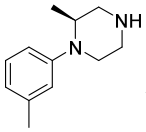
tert-Butyl (_S_)-3-methyl-4-(_m_-tolyl)piperazine-1-carboxylate ((_S_)-1a)



The title compound was synthesized using 1-bromo-3-methylbenzene (100 mg, 0.59 mmol, 1 eq.), *tert*-butyl (*S*)-3-methylpiperazine-1-carboxylate (176 mg, 0.88 mmol, 1.5 eq.), Cs_2CO_3 (286 mg, 0.88 mmol, 1.5 eq.), rac-BINAP (23.25 mg, 0.04 mmol, 0.06 eq.) and palladium diacetate (5.25 mg, 0.02 mmol, 0.04 eq.) according to general procedure A in a yield of 130 mg (0.45 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, *J* = 7.7 Hz, 1H), 6.71 – 6.67 (m, 3H), 4.04 – 3.66 (m, 3H), 3.44 – 2.99 (m, 4H), 2.30 (s, 3H), 1.48 (s, 9H), 0.98 (d, *J* = 6.5 Hz, 3H).

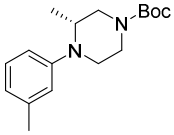
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.13, 150.22, 138.86, 129.07, 120.93, 118.05, 114.33, 79.70, 51.65, 49.45, 48.25, 44.30, 28.50, 21.85, 12.25.

(S)-2-Methyl-1-(*m*-tolyl)piperazine ((*S*)-1b)



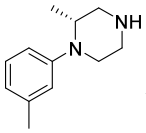
The title compound was synthesized using *tert*-butyl (*S*)-3-methyl-4-(*m*-tolyl)piperazine-1-carboxylate (150 mg, 0.52 mmol, 1.00 eq.) according to general procedure B in a yield of 90 mg (0.47 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, *J* = 7.5 Hz, 1H), 6.78 – 6.62 (m, 3H), 3.73 (qq, *J* = 6.7, 3.7, 3.3 Hz, 1H), 3.15 – 2.78 (m, 6H), 2.31 (s, 3H), 1.03 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.78, 138.76, 128.94, 120.80, 118.44, 114.69, 51.85, 51.40, 46.46, 45.97, 21.83, 12.64.

***tert*-Butyl (*R*)-3-methyl-4-(*m*-tolyl)piperazine-1-carboxylate ((*R*)-1a)**



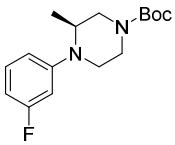
The title compound was synthesized using 1-bromo-3-methylbenzene (1 g, 5.85 mmol, 1 eq.), *tert*-butyl (*R*)-3-methylpiperazine-1-carboxylate (1.17 g, 5.85 mmol, 1 eq.), Cs_2CO_3 (2.86 g, 8.77 mmol, 1.5 eq.), rac-BINAP (233 mg, 0.35 mmol, 0.06 eq.) and palladium diacetate (52.53 mg, 0.23 mmol, 0.04 eq.) according to general procedure A in a yield of 1.05 g (3.62 mmol, 62%).

(*R*)-2-Methyl-1-(*m*-tolyl)piperazine ((*R*)-1b)



The title compound was synthesized using *tert*-butyl (*R*)-3-methyl-4-(*m*-tolyl)piperazine-1-carboxylate (0.75 g, 2.58 mmol, 1.00 eq.) according to general procedure B in a yield of 405 mg (2.13 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.08 (m, 1H), 6.80 – 6.68 (m, 3H), 3.72 (m, 1H), 3.67 – 3.50 (br, 1H), 3.19 – 2.82 (m, 6H), 2.31 (s, 3H), 1.03 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.56, 138.84, 128.98, 121.47, 119.16, 115.41, 51.38, 51.30, 46.09, 45.93, 21.78, 13.00.

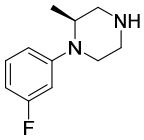
***tert*-Butyl (*S*)-4-(3-fluorophenyl)-3-methylpiperazine-1-carboxylate (23a)**



The title compound was synthesized using 1-bromo-3-fluorobenzene (175 mg, 1.00 mmol, 1 eq.), *tert*-butyl (*S*)-3-methylpiperazine-1-carboxylate (200 mg, 1.00 mmol, 1 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (8.96 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 177 mg (0.60 mmol,

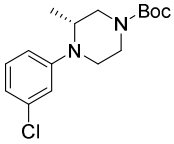
60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (td, *J* = 8.2, 7.0 Hz, 1H), 6.62 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.58 – 6.44 (m, 2H), 4.36 – 3.70 (m, 3H), 3.40 – 2.96 (m, 4H), 1.49 (s, 9H), 1.02 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.00 (d, *J* = 243.2 Hz), 155.09, 151.72 (d, *J* = 9.8 Hz), 130.26 (d, *J* = 10.0 Hz), 111.50, 105.71 (d, *J* = 21.4 Hz), 103.05 (d, *J* = 25.3 Hz), 79.86, 51.12, 48.96, 47.69, 42.36, 28.43, 12.05.

(*S*)-1-(3-Fluorophenyl)-2-methylpiperazine (**23b**)



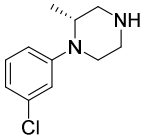
The title compound was synthesized using *tert*-butyl (*S*)-4-(3-fluorophenyl)-3-methylpiperazine-1-carboxylate (100 mg, 0.34 mmol, 1.00 eq.) according to general procedure B. The obtained crude product was used directly without any purification.

***tert*-Butyl (*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carboxylate** (**(*R*)-24a**)



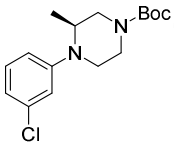
The title compound was synthesized using 1-bromo-3-chlorobenzene (191 mg, 1.00 mmol, 1 eq.), *tert*-butyl (*R*)-3-methylpiperazine-1-carboxylate (200 mg, 1.00 mmol, 1 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (8.96 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 233 mg (0.75 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, *J* = 8.1 Hz, 1H), 6.95 – 6.63 (m, 3H), 4.27 – 3.70 (m, 3H), 3.40 – 2.89 (m, 4H), 1.48 (s, 9H), 1.01 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.07, 151.17, 135.09, 130.19, 119.25, 116.31, 114.40, 79.87, 51.22, 49.11, 47.81, 42.84, 28.46, 12.16.

(*R*)-1-(3-Chlorophenyl)-2-methylpiperazine (**(*R*)-24b**)



The title compound was synthesized using *tert*-butyl (*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carboxylate (100 mg, 0.34 mmol, 1.00 eq.) according to general procedure B. The obtained crude product was used directly without any purification.

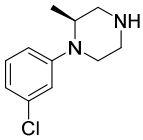
***tert*-Butyl (*S*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carboxylate** (**(*S*)-24a**)



The title compound was synthesized using 1-bromo-3-chlorobenzene (191 mg, 1.00 mmol, 1 eq.), *tert*-butyl (*S*)-3-methylpiperazine-1-carboxylate (200 mg, 1.00 mmol, 1 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate

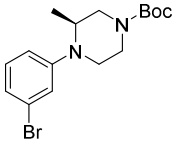
(8.96 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 117 mg (0.38 mmol, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 8.1 Hz, 1H), 6.93 – 6.44 (m, 3H), 4.23 – 3.71 (m, 3H), 3.41 – 2.92 (m, 4H), 1.48 (s, 9H), 1.02 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.12, 151.18, 135.12, 130.20, 119.31, 116.38, 114.51, 79.93, 51.25, 49.15, 42.92, 28.48, 12.19.

(*S*)-1-(3-Chlorophenyl)-2-methylpiperazine ((*S*)-24b)



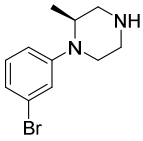
The title compound was synthesized using *tert*-butyl (*S*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carboxylate (100 mg, 0.34 mmol, 1.00 eq.) according to general procedure B in a yield of 56 mg (0.26 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, *J* = 8.1 Hz, 1H), 6.92 – 6.67 (m, 3H), 3.82 (tt, *J* = 6.7, 3.2 Hz, 1H), 3.59 (br, 1H), 3.29 – 2.78 (m, 6H), 1.08 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.54, 135.04, 130.15, 119.50, 116.88, 114.99, 50.97, 50.72, 45.84, 44.22, 12.47.

***tert*-Butyl (*S*)-4-(3-bromophenyl)-3-methylpiperazine-1-carboxylate ((*S*)-25a)**



The title compound was synthesized using 1,3-dibromobenzene (236 mg, 1.00 mmol, 1 eq.), *tert*-butyl (*S*)-3-methylpiperazine-1-carboxylate (200 mg, 1.00 mmol, 1 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (8.96 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 154 mg (0.43 mmol, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (t, *J* = 8.1 Hz, 1H), 7.02 – 6.89 (m, 2H), 6.78 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.03 – 3.72 (m, 2H), 3.36 – 2.99 (m, 5H), 1.48 (s, 9H), 1.01 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.05, 151.31, 130.46, 123.37, 122.19, 119.26, 114.87, 79.87, 51.23, 49.12, 47.69, 42.78, 28.44, 12.18.

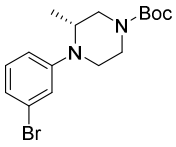
(*S*)-1-(3-Bromophenyl)-2-methylpiperazine ((*S*)-25b)



The title compound was synthesized using *tert*-Butyl (S)-4-(3-bromophenyl)-3-methylpiperazine-1-carboxylate (100 mg, 0.28 mmol, 1.00 eq.) according to general procedure B in a yield of 72 mg (0.28 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (t, *J* = 8.1 Hz, 1H), 7.01 (t, *J* = 2.1 Hz, 1H), 6.95 (ddd, *J* = 7.9, 1.9, 0.9 Hz, 1H), 6.81 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H), 3.81 (m, 1H), 3.77 (br, 1H), 3.19 – 2.86 (m, 6H), 1.07 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ

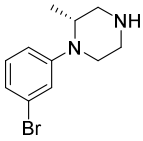
151.66, 130.41, 123.30, 122.36, 119.73, 115.42, 50.92, 50.68, 45.79, 44.17, 12.44.

tert-Butyl (_R_)-4-(3-bromophenyl)-3-methylpiperazine-1-carboxylate ((_R_)-25a)



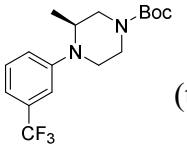
The title compound was synthesized using 1,3-dibromobenzene (236 mg, 1.00 mmol, 1 eq.), *tert*-butyl (*R*)-3-methylpiperazine-1-carboxylate (200 mg, 1.00 mmol, 1 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (8.96 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 257 mg (0.72 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (t, *J* = 8.1 Hz, 1H), 7.03 – 6.90 (m, 2H), 6.78 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.26 – 3.70 (m, 3H), 3.44 – 2.93 (m, 4H), 1.48 (s, 9H), 1.01 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.10, 151.35, 130.50, 123.41, 122.25, 119.30, 114.92, 79.93, 51.28, 49.20, 47.76, 42.95, 28.48, 12.22.

(_R_)-1-(3-Bromophenyl)-2-methylpiperazine ((_R_)-25b)



The title compound was synthesized using *tert*-Butyl (*R*)-4-(3-bromophenyl)-3-methylpiperazine-1-carboxylate (100 mg, 0.28 mmol, 1.00 eq.) according to general procedure B in a yield of 68 mg (0.27 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (t, *J* = 8.1 Hz, 1H), 7.06 – 6.97 (m, 2H), 6.83 (ddd, *J* = 8.3, 2.4, 0.9 Hz, 1H), 4.17 (s, 1H), 3.82 (qt, *J* = 6.7, 3.7 Hz, 1H), 3.24 – 2.90 (m, 6H), 1.09 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.56, 130.49, 123.33, 123.00, 120.42, 116.07, 50.75, 50.61, 45.50, 44.31, 12.79.

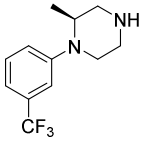
tert-Butyl (_S_)-3-methyl-4-(3-(trifluoromethyl)phenyl)piperazine-1-carboxylate ((_S_)-26a)



The title compound was synthesized using 1-bromo-3-(trifluoromethyl)benzene (225 mg, 1.00 mmol, 1 eq.), *tert*-butyl (*S*)-3-methylpiperazine-1-carboxylate (200 mg, 1.00 mmol, 1 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (8.96 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 176 mg (0.51 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.8 Hz, 1H), 7.15 – 6.90 (m, 3H), 4.03 – 3.77 (m, 3H), 3.41 – 2.98 (m, 4H), 1.49 (s, 9H), 1.03 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.06, 150.22, 131.55 (q, *J* =

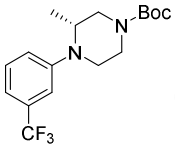
31.7 Hz), 129.70, 124.36 (q, *J* = 272.4 Hz), 119.27, 115.75, 112.67, 79.90, 51.21, 49.09, 47.81, 42.81, 28.38, 12.09.

(*S*)-2-Methyl-1-(3-(trifluoromethyl)phenyl)piperazine ((*S*)-26b)



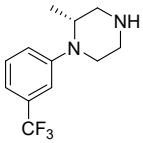
The title compound was synthesized using *tert*-butyl (S)-3-methyl-4-(3-(trifluoromethyl)phenyl)piperazine-1-carboxylate (100 mg, 0.29 mmol, 1.00 eq.) according to general procedure B in a yield of 62 mg (0.26 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.24 (m, 1H), 7.19 – 6.94 (m, 3H), 3.87 (qt, *J* = 6.6, 3.3 Hz, 1H), 3.32 – 2.80 (m, 6H), 2.50 (s, 1H), 1.08 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.63, 131.39 (q, *J* = 31.5 Hz), 129.57, 124.42 (q, *J* = 272.5 Hz), 119.28, 115.46 (q, *J* = 3.8 Hz), 112.66 (q, *J* = 3.9 Hz), 51.18, 50.60, 46.02, 44.09, 12.06.

***tert*-Butyl (*R*)-3-methyl-4-(3-(trifluoromethyl)phenyl)piperazine-1-carboxylate ((*R*)-26a)**



The title compound was synthesized using 1-bromo-3-(trifluoromethyl)benzene (225 mg, 1.00 mmol, 1 eq.), *tert*-butyl (*R*)-3-methylpiperazine-1-carboxylate (200 mg, 1.00 mmol, 1 eq.), sodium *tert*-butoxide (144 mg, 1.50 mmol, 1.5 eq.), rac-BINAP (37.4 mg, 0.06 mmol, 0.06 eq.) and palladium diacetate (8.96 mg, 0.04 mmol, 0.04 eq.) according to general procedure A in a yield of 176 mg (0.51 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 1H), 7.18 – 6.91 (m, 3H), 4.28 – 3.70 (m, 3H), 3.47 – 3.00 (m, 4H), 1.49 (s, 9H), 1.03 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.10, 150.24, 131.58 (q, *J* = 31.6 Hz), 129.73, 124.38 (q, *J* = 272.4 Hz), 119.26, 115.79, 112.70, 79.94, 51.23, 49.14, 47.83, 42.84, 28.42, 12.15.

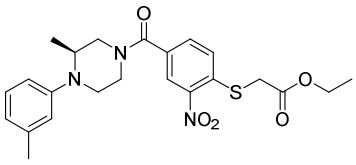
(*R*)-2-Methyl-1-(3-(trifluoromethyl)phenyl)piperazine ((*R*)-26b)



The title compound was synthesized using *tert*-Butyl (R)-3-methyl-4-(3-(trifluoromethyl)phenyl)piperazine-1-carboxylate (100 mg, 0.29 mmol, 1.00 eq.) according to general procedure B in a yield of 70 mg (0.29 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 8.0 Hz, 1H), 7.13 – 7.00 (m, 3H), 3.88 (qt, *J* = 6.7, 3.4 Hz, 1H), 3.25 – 2.89 (m, 6H), 1.08 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.64, 131.50 (q, *J* = 31.6 Hz), 129.66, 124.43 (q, *J* = 272.4 Hz),

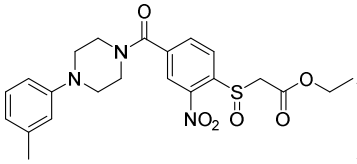
119.68, 115.87 (q, *J* = 3.8 Hz), 113.11 (q, *J* = 3.9 Hz), 51.07, 50.70, 45.90, 44.29, 12.32.

Ethyl (*S*)-2-((4-(3-methyl-4-(m-tolyl)piperazine-1-carbonyl)-2-nitrophenyl)thio)acetate (3)



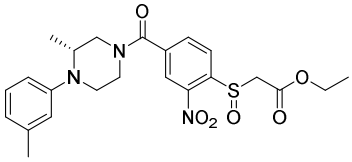
The title compound was synthesized using (*R*)-2-methyl-1-(*m*-tolyl)piperazine (60.6 mg, 0.32 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)thio)-3-nitrobenzoic acid (100 mg, 0.35 mmol, 1.1 eq.), HATU (147 mg, 0.48 mmol, 1.5 eq.) and DiPEA (124 mg, 0.96 mmol, 3 eq.) according to general procedure H. This yielded the product (108 mg, 0.24 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 1.9 Hz, 1H), 7.70 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.17 (t, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 5.8 Hz, 3H), 4.49-3.01 (m, 7H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 2H), 2.32 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.01 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.26, 167.70, 149.38, 144.90, 138.78, 138.48, 132.42, 132.36, 128.85, 126.69, 124.90, 121.48, 118.91, 115.14, 61.98, 52.72, 51.87, 47.65, 45.06, 34.72, 21.49, 13.86, 12.47. HRMS: Calculated for $[C_{23}H_{27}N_3O_5S + H]^+$ = 458.1744, found = 458.1743.

Ethyl 2-((2-nitro-4-(4-(*m*-tolyl)piperazine-1-carbonyl)phenyl)sulfinyl)acetate (2)



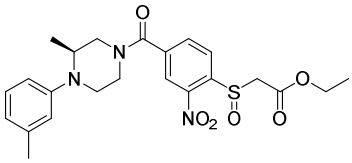
The title compound was synthesized using 1-(*m*-tolyl)piperazine (29.3 mg, 0.17 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)-3-nitrobenzoic acid (50 mg, 0.17 mmol, 1 eq.), HATU (95 mg, 0.25 mmol, 1.5 eq.) and DiPEA (64.4 mg, 0.50 mmol, 3 eq.) according to general procedure H in a yield of 53.4 mg (0.12 mmol, 70%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 8.44 (d, *J* = 1.7 Hz, 1H), 8.37 (d, *J* = 8.1 Hz, 1H), 8.07 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.24 – 7.17 (m, 2H), 7.15 (dd, *J* = 7.5, 1.5 Hz, 1H), 4.32 – 4.08 (m, 5H), 3.90 (m, 2H), 3.77 (d, *J* = 14.2 Hz, 1H), 3.54 (m, 4H), 2.39 (s, 3H), 1.26 (t, *J* = 7.7Hz, 3H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 166.90, 164.84, 144.96, 144.18, 143.94, 140.85, 138.59, 133.88, 130.21, 128.65, 128.02, 124.49, 120.28, 116.68, 62.62, 59.96, 53.48, 53.30, 45.78, 40.63, 21.56, 14.08.

Ethyl 2-((4-((*R*)-3-methyl-4-(*m*-tolyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate ((*R*)-1)



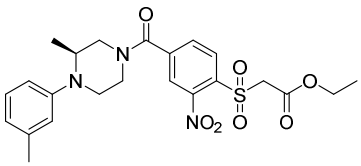
The title compound was synthesized using (*R*)-2-methyl-1-(*m*-tolyl)piperazine (57.4 mg, 0.30 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)-3-nitrobenzoic acid (100 mg, 0.33 mmol, 1.1 eq.), HATU (140 mg, 0.45 mmol, 1.5 eq.) and DiPEA (117 mg, 0.91 mmol, 3 eq.) according to general procedure H in a yield of 98 mg (0.21 mmol, 69%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 8.47 – 8.34 (m, 2H), 8.07 – 7.97 (m, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.83 – 6.68 (m, 3H), 4.47 – 4.08 (m, 4H), 3.78 (d, *J* = 13.8 Hz, 2H), 3.72 – 3.06 (m, 5H), 2.33 (s, 3H), 1.28 (td, *J* = 7.1, 1.7 Hz, 3H), 1.12 – 0.92 (m, 3H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 166.88, 164.60, 149.51, 144.89, 143.86, 139.88, 139.17, 133.69, 129.20, 127.89, 124.24, 121.93, 119.36, 115.60, 62.44, 60.04, 52.25, 47.72, 45.62, 42.59, 21.79, 14.18, 12.71.

Ethyl 2-((4-((*S*)-3-methyl-4-(*m*-tolyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate ((*S*)-1)



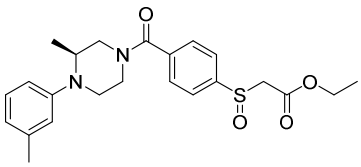
The title compound was synthesized using (*S*)-2-methyl-1-(*m*-tolyl)piperazine (57.4 mg, 0.30 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)-3-nitrobenzoic acid (100 mg, 0.33 mmol, 1.1 eq.), HATU (140 mg, 0.45 mmol, 1.5 eq.) and DiPEA (117 mg, 0.91 mmol, 3 eq.) according to general procedure H in a yield of 140 mg (0.30 mmol, 98%).

Ethyl (*S*)-2-((4-(3-methyl-4-(*m*-tolyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfonyl)acetate (4)



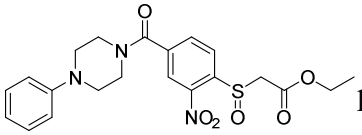
The title compound was synthesized using (*S*)-2-methyl-1-(*m*-tolyl)piperazine (12 mg, 0.06 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfonyl)-3-nitrobenzoic acid (20 mg, 0.06 mmol, 1 eq.), HATU (36 mg, 0.10 mmol, 1.5 eq.) and DiPEA (24 mg, 0.19 mmol, 3 eq.) according to general procedure H in a yield of 2 mg (0.004 mmol, 6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 3.9 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.76 (s, 3H), 4.68 (s, 2H), 4.45-3.05 (m, 7H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 1.27 (t, *J* = 7.0 Hz, 4H), 1.02 (m, 3H).

Ethyl 2-((4-((*S*)-3-methyl-4-(*m*-tolyl)piperazine-1-carbonyl)phenyl)sulfinyl)acetate (5)



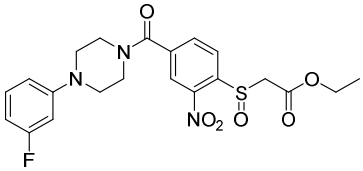
The title compound was synthesized using (*S*)-2-methyl-1-(*m*-tolyl)piperazine (22 mg, 0.12 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (30 mg, 0.12 mmol, 1 eq.), oxalyl chloride (16.34 mg, 0.13 mmol, 1.1 eq.) and DiPEA (45 mg, 0.35 mmol, 3 eq.) according to general procedure G in a yield of 21 mg (0.05 mmol, 42%).

Ethyl 2-((2-nitro-4-(4-phenylpiperazine-1-carbonyl)phenyl)sulfinyl)acetate (**6**)



The title compound was synthesized using 1-phenylpiperazine (25 mg, 0.16 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (70 mg, 0.23 mmol, 1.5 eq.), HATU (140 mg, 0.37 mmol, 2.3 eq.) and DiPEA (65 µl, 0.37 mmol, 2.3 eq.) according to general procedure H in a yield of 64 mg (0.14 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 – 8.37 (m, 2H), 8.01 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.34 – 7.25 (m, 2H), 6.98 – 6.91 (m, 3H), 4.28 – 4.17 (m, 2H), 4.14 (d, *J* = 13.7 Hz, 1H), 3.98 (s, 2H), 3.77 (d, *J* = 13.7 Hz, 1H), 3.59 (s, 2H), 3.31 (s, 2H), 3.18 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.54, 164.58, 150.65, 144.91, 143.98, 139.79, 133.72, 129.41, 127.93, 124.22, 121.13, 117.00, 62.44, 60.08, 50.12, 49.62, 47.82, 42.51, 38.68, 14.18. HRMS: calculated for $[C_{21}H_{23}N_3O_6S+H]^+$ = 446.1380, found = 446.1379.

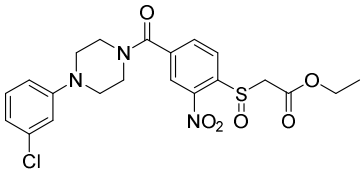
Ethyl 2-((4-(4-(3-fluorophenyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (**7**)



The title compound was synthesized using 1-(3-fluorophenyl)piperazine (18 mg, 0.10 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (30 mg, 0.12 mmol, 1 eq.), oxalyl chloride (13.90 mg, 0.11 mmol, 1.1 eq.) and DiPEA (39 mg, 0.30 mmol, 3 eq.) according to general procedure G in a yield of 30 mg (0.07 mmol, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 4.8, 3.2 Hz, 2H), 8.02 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.23 (ddd, *J* = 8.3, 6.6, 1.4 Hz, 1H), 6.77 – 6.66 (m, 1H), 6.65 – 6.56 (m, 2H), 4.26 – 4.18 (m, 2H), 4.14 (d, *J* = 13.7 Hz, 1H), 3.98 (s, 2H), 3.78 (d, *J* = 13.6 Hz, 1H), 3.59 (s, 2H), 3.32 – 3.20 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.63, 165.09, 163.63 (d, *J* = 196.4 Hz), 152.26 (d, *J* = 9.6 Hz), 144.98, 144.18, 139.69, 133.76, 130.58 (d, *J* = 9.8 Hz), 128.06, 124.28, 112.09 (d, *J* = 2.4 Hz), 107.46 (d, *J* =

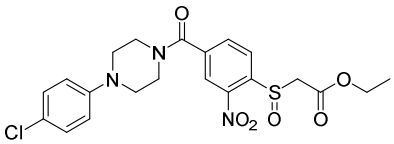
21.3 Hz), 103.81 (d, *J* = 24.9 Hz), 62.53, 60.12, 49.55, 42.32, 14.24.

Ethyl 2-((4-(4-(3-chlorophenyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (8)



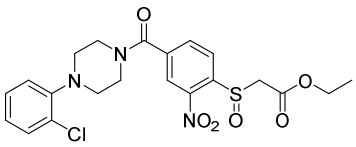
The title compound was synthesized using 1-(3-chlorophenyl)piperazine (20 mg, 0.10 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (30 mg, 0.12 mmol, 1 eq.), oxalyl chloride (13.90 mg, 0.11 mmol, 1.1 eq.) and DiPEA (39 mg, 0.30 mmol, 3 eq.) according to general procedure G in a yield of 28 mg (0.06 mmol, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 – 8.31 (m, 2H), 8.01 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.21 (t, *J* = 8.4 Hz, 1H), 6.92 – 6.86 (m, 2H), 6.80 (ddd, *J* = 8.3, 2.3, 1.0 Hz, 1H), 4.30 – 4.16 (m, 2H), 4.13 (d, *J* = 13.7 Hz, 1H), 3.97 (s, 2H), 3.78 (d, *J* = 13.7Hz, 1H), 3.59 (s, 2H), 3.31 – 3.19 (m, 4H), 1.33 – 1.19 (t, *J* = 7.2, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.62, 164.58, 151.75, 144.98, 144.18, 139.69, 135.24, 133.74, 130.40, 128.04, 124.25, 120.83, 116.86, 114.87, 62.51, 60.13, 49.58, 49.18, 47.62, 42.38, 14.24.

Ethyl 2-((4-(4-(4-chlorophenyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (9)



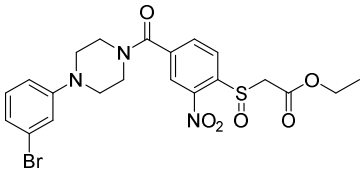
The title compound was synthesized using 1-(4-chlorophenyl)piperazine (19mg, 0.10 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (30 mg, 0.12 mmol, 1 eq.), oxalyl chloride (13.90 mg, 0.11 mmol, 1.1 eq.) and DiPEA (39 mg, 0.30 mmol, 3 eq.) according to general procedure G in a yield of 8 mg (0.02 mmol, 18%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 8.47 – 8.36 (m, 2H), 8.02 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.30 – 7.27 (m, 2H), 6.97 (m, 2H), 4.26 – 4.18 (m, 2H), 4.14 (d, *J* = 13.8 Hz, 1H), 4.04 (m, 2H), 3.79 (d, *J* = 13.8 Hz, 1H), 3.65 (m, 2H), 3.38 – 3.11 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 166.66, 164.61, 148.42, 145.00, 144.25, 139.55, 133.78, 129.55, 128.12, 127.21, 124.30, 118.79, 62.57, 60.09, 50.68, 50.15, 47.41, 42.17, 14.26.

Ethyl 2-((4-(4-(2-chlorophenyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (10)



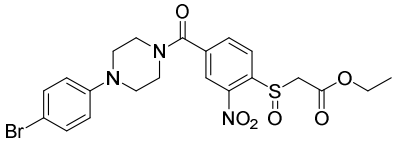
The title compound was synthesized using 1-(2-chlorophenyl)piperazine (26mg, 0.13 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (40 mg, 0.13 mmol, 1 eq.), oxalyl chloride (19 mg, 0.15 mmol, 1.1 eq.) and DiPEA (52 mg, 0.40 mmol, 3 eq.) according to general procedure G in a yield of 41 mg (0.09 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 – 8.26 (m, 2H), 8.03 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.11 – 6.94 (m, 2H), 4.22 (qd, *J* = 7.2, 3.9 Hz, 2H), 4.14 (d, *J* = 13.7 Hz, 1H), 4.02 (s, 2H), 3.78 (d, *J* = 13.7 Hz, 1H), 3.62 (s, 2H), 3.17 – 3.05 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.68, 164.61, 148.28, 144.93, 143.95, 139.99, 133.76, 130.91, 129.08, 127.97, 127.90, 124.77, 124.24, 120.73, 62.49, 60.12, 51.74, 50.99, 48.22, 42.87, 14.22. HRMS: Calculated for $[C_{21}H_{22}ClN_3O_6S + H]^+$ = 480.0991, found = 480.0991.

Ethyl 2-((4-(4-(3-bromophenyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (11)



The title compound was synthesized using 1-(3-bromophenyl)piperazine (23mg, 0.10 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (30 mg, 0.10 mmol, 1 eq.), oxalyl chloride (13.90 mg, 0.11 mmol, 1.1 eq.) and DiPEA (39 mg, 0.30 mmol, 3 eq.) according to general procedure G in a yield of 26 mg (0.05 mmol, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 – 8.34 (m, 2H), 8.01 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.15 (dd, *J* = 8.6, 7.4 Hz, 1H), 7.05 (dd, *J* = 8.0, 1.2 Hz, 2H), 6.90 – 6.78 (m, 1H), 4.28 – 4.18 (m, 2H), 4.14 (d, *J* = 13.7 Hz, 1H), 3.97 (s, 2H), 3.79 (d, *J* = 13.7 Hz, 1H), 3.70 – 3.02 (m, 6H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.66, 164.60, 151.93, 145.01, 144.21, 139.70, 133.76, 130.71, 128.09, 124.28, 123.85, 123.47, 119.85, 115.43, 62.55, 60.13, 49.65, 49.20, 47.65, 42.42, 14.27.

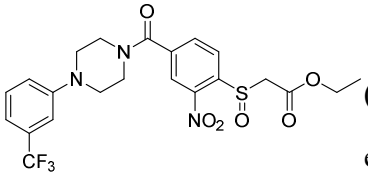
Ethyl 2-((4-(4-(4-bromophenyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (12)



The title compound was synthesized using 1-(4-bromophenyl)piperazine (23mg, 0.10 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (30 mg,

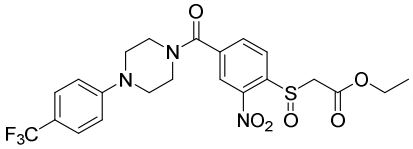
0.10 mmol, 1 eq.), oxalyl chloride (13.90 mg, 0.11 mmol, 1.1 eq.) and DiPEA (39 mg, 0.30 mmol, 3 eq.) according to general procedure G in a yield of 31 mg (0.06 mmol, 61%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 4.8, 3.1 Hz, 2H), 8.02 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.41 – 7.39 (m, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.27 – 4.17 (m, 2H), 4.14 (d, *J* = 13.7 Hz, 1H), 4.00 (m, 2H), 3.79 (d, *J* = 13.8 Hz, 1H), 3.61 (m, 2H), 3.34 – 3.09 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 166.65, 164.61, 149.31, 145.00, 144.22, 139.63, 133.78, 132.40, 128.11, 124.30, 118.91, 62.57, 60.10, 50.31, 49.75, 47.57, 42.25, 14.26.

Ethyl 2-((2-nitro-4-(4-(3-(trifluoromethyl)phenyl)piperazine-1-carbonyl)phenyl)sulfinyl)acetate (13)



The title compound was synthesized using 1-(3-(trifluoromethyl)phenyl)piperazine (31mg, 0.13 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (40 mg, 0.13 mmol, 1 eq.), oxalyl chloride (19 mg, 0.15 mmol, 1.1 eq.) and DiPEA (52 mg, 0.40 mmol, 3 eq.) according to general procedure G in a yield of 42 mg (0.08 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 – 8.29 (m, 2H), 8.02 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.21 – 7.07 (m, 3H), 4.26 – 4.18 (m, 2H), 4.14 (d, *J* = 13.7 Hz, 1H), 4.00 (br, 2H), 3.79 (d, *J* = 13.7 Hz, 1H), 3.62 (br, 2H), 3.30 (br, 4H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.67, 164.60, 150.87, 145.00, 144.23, 139.65, 133.76, 131.81 (q, *J* = 32.3 Hz), 129.99, 128.09, 124.28, 122.85(q, *J* = 273.71 Hz) 119.87, 117.48 (q, *J* = 4.04 Hz), 113.28(q, *J* = 3.03 Hz), 62.54, 60.11, 49.57, 47.57, 14.25. HRMS: Calculated for $[C_{22}H_{22}F_3N_3O_6S + H]^+$ = 514.1254, found = 514.1252.

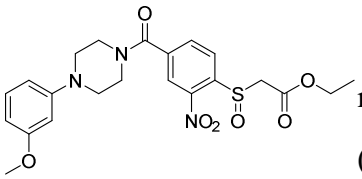
Ethyl 2-((2-nitro-4-(4-(4-(trifluoromethyl)phenyl)piperazine-1-carbonyl)phenyl)sulfinyl)acetate (14)



The title compound was synthesized using 1-(4-(trifluoromethyl)phenyl)piperazine (31mg, 0.13 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (40 mg, 0.13 mmol, 1 eq.), oxalyl chloride (19 mg, 0.15 mmol, 1.1 eq.) and DiPEA (52 mg, 0.40 mmol, 3 eq.) according to general procedure G in a yield of 39 mg (0.08 mmol,

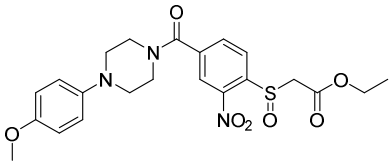
57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 – 8.29 (m, 2H), 8.02 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.62 – 7.45 (m, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 4.22 (m, 2H), 4.14 (d, *J* = 13.7 Hz, 1H), 3.99 (br, 2H), 3.78 (d, *J* = 13.7 Hz, 1H), 3.62 (br, 2H), 3.35 (br, 4H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.57, 164.52, 152.66, 144.88, 144.14, 139.49, 133.67, 127.97, 126.62 (q, *J* = 3.75), 124.48(q, *J* = 271.94 Hz) , 122.32 (q, *J* = 32.32 Hz) 124.19, 115.49, 62.44, 60.01, 48.84, 48.31, 47.51, 42.15, 14.14. HRMS: Calculated for $[C_{22}H_{22}F_3N_3O_6S + H]^+$ = 514.1254, found = 514.1253.

Ethyl 2-((4-(4-(3-methoxyphenyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (15)



The title compound was synthesized using 1-(3-methoxyphenyl)piperazine (19mg, 0.10 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (30 mg, 0.10 mmol, 1 eq.), oxalyl chloride (14 mg, 0.11 mmol, 1.1 eq.) and DiPEA (39 mg, 0.30 mmol, 3 eq.) according to general procedure G in a yield of 29 mg (0.06 mmol, 55%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 8.43 – 8.39 (m, 2H), 8.02 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.23 (t, *J* = 8.2 Hz, 1H), 6.68 – 6.45 (m, 3H), 4.26 – 4.17 (m, 2H), 4.14 (d, *J* = 13.8 Hz, 1H), 4.01 (m, 2H), 3.81 (s, 3H), 3.78 (d, *J* = 13.8 Hz, 1H), 3.60 (m, 2H), 3.39 – 3.15 (m, 4H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 166.51, 164.53, 160.67, 151.51, 144.87, 143.99, 139.62, 133.69, 130.19, 127.94, 124.21, 109.75, 106.14, 103.75, 62.44, 60.01, 55.32, 50.26, 49.76, 47.49, 42.20, 14.14.

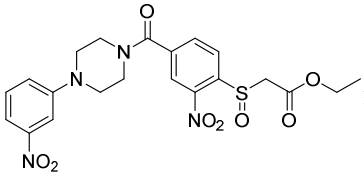
Ethyl 2-((4-(4-(4-methoxyphenyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (16)



The title compound was synthesized using 1-(4-methoxyphenyl)piperazine (32 mg, 0.17 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfonyl)-3-nitrobenzoic acid (50 mg, 0.17 mmol, 1 eq.), HATU (95 mg, 0.25 mmol, 1.5 eq.) and DiPEA (64 mg, 0.50 mmol, 3 eq.) according to general procedure H in a yield of 71 mg (0.15 mmol, 90%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 8.41 (d, *J* = 1.6 Hz, 1H), 8.40 (d, *J* = 8.1 Hz, 1H), 8.02 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.89 – 6.82 (m, 2H), 4.26 – 4.16 (m, 2H), 4.14 (d, *J* = 13.9 Hz, 1H), 3.99 (m, 2H), 3.81 – 3.74 (m, 4H), 3.59 (m, 2H), 3.23 –

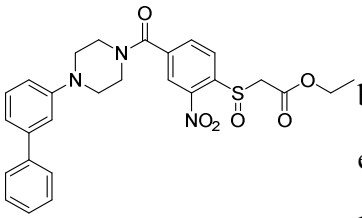
2.98 (m, 4H), 1.28 (t, *J* = 7.6Hz, 3H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 166.50, 164.61, 154.84, 144.87, 144.65, 143.88, 139.82, 133.73, 127.89, 124.22, 119.31, 114.63, 62.45, 60.06, 55.60, 51.59, 51.04, 47.89, 42.56, 14.17.

Ethyl 2-((2-nitro-4-(4-(3-nitrophenyl)piperazine-1-carbonyl)phenyl)sulfinyl)acetate (17)



The title compound was synthesized using 1-(3-nitrophenyl)piperazine (21mg, 0.10 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (30 mg, 0.10 mmol, 1 eq.), oxalyl chloride (14 mg, 0.11 mmol, 1.1 eq.) and DiPEA (39 mg, 0.30 mmol, 3 eq.) according to general procedure G in a yield of 29 mg (0.05 mmol, 45%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 8.44 – 8.40 (m, 2H), 8.04 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.76 – 7.73 (m, 2H), 7.46 – 7.42 (m, 1H), 7.24 (ddd, *J* = 8.3, 2.5, 1.0 Hz, 1H), 4.26 – 4.18 (m, 2H), 4.15 (d, *J* = 13.8 Hz, 1H), 4.02 (M, 2H), 3.79 (d, *J* = 13.8 Hz, 1H), 3.71 – 3.60 (m, 2H), 3.50 – 3.25 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 166.69, 164.63, 151.23, 149.29, 144.95, 144.20, 139.47, 133.76, 130.15, 128.05, 124.28, 122.14, 115.19, 110.69, 62.52, 60.08, 49.17, 48.70, 47.39, 42.20, 14.21.

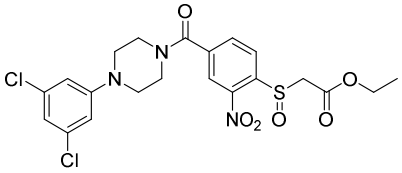
Ethyl 2-((4-(4-([1,1'-biphenyl]-3-yl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (18)



The title compound was synthesized using 1-([1,1'-biphenyl]-3-yl)piperazine (32mg, 0.13 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (40 mg, 0.13 mmol, 1 eq.), oxalyl chloride (19 mg, 0.15 mmol, 1.1 eq.) and DiPEA (52 mg, 0.4 mmol, 3 eq.) according to general procedure G in a yield of 40 mg (0.08 mmol, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 – 8.26 (m, 2H), 8.02 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.48 – 7.41 (m, 2H), 7.40 – 7.33 (m, 2H), 7.21 – 7.13 (m, 2H), 7.01 – 6.86 (m, 1H), 4.22 (qq, J = 7.4, 3.6 Hz, 2H), 4.14 (d, J = 13.7 Hz, 1H), 4.01 (br, 2H), 3.78 (d, *J* = 13.7 Hz, 1H), 3.62 (br, 2H), 3.31 (br, 4H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.62, 164.61, 151.12, 144.98, 144.09,

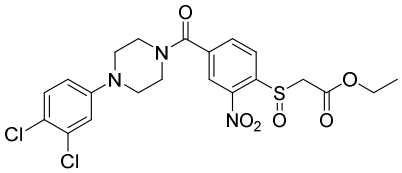
142.73, 141.42, 139.83, 133.77, 129.84, 128.88, 128.03, 127.60, 127.33, 124.29, 120.38, 116.16, 116.03, 62.52, 60.13, 50.26, 49.85, 47.82, 42.54, 14.25. HRMS: Calculated for $[C_{27}H_{27}N_3O_6S + H]^+$ = 522.1693, found = 522.1690.

Ethyl 2-((4-(4-(3,5-dichlorophenyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (19)



The title compound was synthesized using 1-(3,5-dichlorophenyl)piperazine (23mg, 0.10 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (30 mg, 0.10 mmol, 1 eq.), oxalyl chloride (14 mg, 0.11 mmol, 1.1 eq.) and DiPEA (39 mg, 0.3 mmol, 3 eq.) according to general procedure G in a yield of 12 mg (0.02 mmol, 23%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 8.43 – 8.40 (m, 2H), 8.02 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.90 (t, *J* = 1.7 Hz, 1H), 6.79 (d, *J* = 1.7 Hz, 2H), 4.26 – 4.18 (m, 2H), 4.14 (d, *J* = 13.8 Hz, 1H), 3.97 (m, 2H), 3.79 (d, *J* = 13.8 Hz, 1H), 3.60 (m, 2H), 3.27 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 166.67, 164.61, 151.92, 144.97, 144.23, 139.47, 135.80, 133.75, 128.08, 124.28, 120.56, 114.91, 62.54, 60.08, 49.16, 48.70, 47.34, 42.16, 14.23.

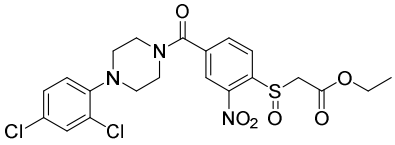
Ethyl 2-((4-(4-(3,4-dichlorophenyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (20)



The title compound was synthesized using 1-(3,4-dichlorophenyl)piperazine (23mg, 0.10 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (30 mg, 0.10 mmol, 1 eq.), oxalyl chloride (14 mg, 0.11 mmol, 1.1 eq.) and DiPEA (39 mg, 0.3 mmol, 3 eq.) according to general procedure G in a yield of 36 mg (0.07 mmol, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 – 8.33 (m, 2H), 8.02 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.23 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 1H), 4.28 – 4.16 (m, 2H), 4.14 (d, *J* = 13.6 Hz, 1H), 4.01 (s, 2H), 3.78 (d, *J* = 13.7 Hz, 1H), 3.61 (s, 2H), 3.08 (br, 4H), 1.28 (t, *J* = 7.1 Hz, 3H). 13C NMR (126 MHz, $CDCl_3$) δ 166.70, 164.56, 147.05, 144.95, 144.06, 139.86, 133.73, 130.63, 129.85, 129.45, 128.03, 127.95, 124.21, 121.49, 62.50, 60.09, 51.70, 50.99, 48.13, 42.74, 14.21.

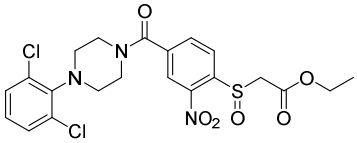
Ethyl 2-((4-(4-(2,4-dichlorophenyl)piperazine-1-carbonyl)-2-

nitrophenyl)sulfinyl)acetate (21)



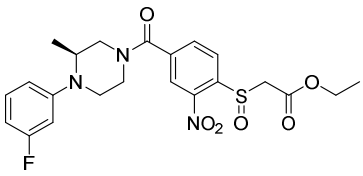
The title compound was synthesized using 1-(2,4-dichlorophenyl)piperazine (23 mg, 0.10 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfonyl)-3-nitrobenzoic acid (30 mg, 0.10 mmol, 1 eq.), HATU (57 mg, 0.15 mmol, 1.5 eq.) and DiPEA (39 mg, 0.30 mmol, 3 eq.) according to general procedure H in a yield of 41 mg (0.08 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 – 8.37 (m, 2H), 8.02 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.23 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 4.28 – 4.15 (m, 2H), 4.14 (d, *J* = 13.7 Hz, 1H), 4.00 (s, 2H), 3.78 (d, *J* = 13.7 Hz, 1H), 3.61 (s, 2H), 3.15 (s, 2H), 3.01 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.66, 164.58, 147.05, 144.91, 143.99, 139.83, 133.72, 130.57, 129.79, 129.35, 127.96, 127.92, 124.20, 121.50, 62.45, 60.08, 50.93, 48.10, 14.19. HRMS: Calculated for $[C_{21}H_{21}Cl_2N_3O_6S + H]^+$ = 514.0601, found = 514.0602.

Ethyl 2-((4-(4-(2,6-dichlorophenyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (22)



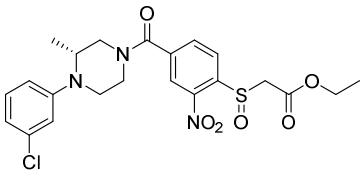
The title compound was synthesized using 1-(2,6-dichlorophenyl)piperazine (20 mg, 0.09 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfonyl)-3-nitrobenzoic acid (39 mg, 0.14 mmol, 1.5 eq.), HATU (53 mg, 0.14 mmol, 1.5 eq.) and DiPEA (38 mg, 0.30 mmol, 3 eq.) according to general procedure H in a yield of 63 mg (0.08 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 – 8.37 (m, 2H), 8.01 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.98 – 6.91 (m, 3H), 4.28 – 4.17 (m, 2H), 4.14 (d, *J* = 13.7 Hz, 1H), 3.98 (s, 2H), 3.77 (d, *J* = 13.7 Hz, 1H), 3.59 (s, 2H), 3.31 (s, 2H), 3.18 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). 13C NMR (101 MHz, $CDCl_3$) δ 166.54, 164.58, 150.65, 144.91, 143.98, 139.79, 133.72, 129.41, 127.93, 124.22, 121.13, 117.00, 62.44, 60.08, 50.12, 49.62, 47.82, 42.51, 38.68, 14.18. HRMS: Calculated for $[C_{21}H_{21}Cl_2N_3O_6S + H]^+$ = 514.0601, found = 514.0600.

Ethyl 2-((4-((*S*)-4-(3-fluorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (23)



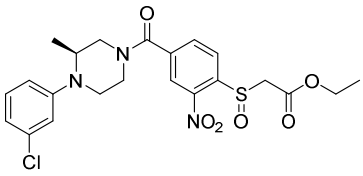
The title compound was synthesized using (*S*)-1-(3-fluorophenyl)-2-methylpiperazine (26mg, 0.13 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (40 mg, 0.13 mmol, 1 eq.), oxalyl chloride (19 mg, 0.15 mmol, 1.1 eq.) and DiPEA (52 mg, 0.40 mmol, 3 eq.) according to general procedure G in a yield of 38 mg (0.08 mmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 – 8.27 (m, 2H), 8.06 – 7.91 (m, 1H), 7.22 (td, *J* = 8.4, 6.8 Hz, 1H), 6.76 – 6.46 (m, 3H), 4.47 (m, 1H), 4.21 (m, 2H), 4.14 (d, *J* = 13.7 Hz, 1H), 3.94 (m, 1H), 3.78 (d, *J* = 13.7 Hz, 1H), 3.74 – 2.99 (m, 5H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.08 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.37, 163.97 (d, *J* = 244.1 Hz), 164.59, 151.16 (d, *J* = 9.5 Hz), 144.96, 144.05, 139.73, 133.74, 130.55 (d, *J* = 9.9 Hz), 128.02, 124.22, 112.38 (d, *J* = 2.4 Hz), 106.99(d, *J* = 21.3 Hz), 104.00(d, *J* = 24.9 Hz), 62.50, 60.09, 52.53, 51.68, 47.39, 42.43, 14.23, 12.52. HRMS: Calculated for $[C_{22}H_{24}FN_3O_6S + H]^+$ = 478.1443, found = 478.1440.

Ethyl 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate ((*R*)-24)



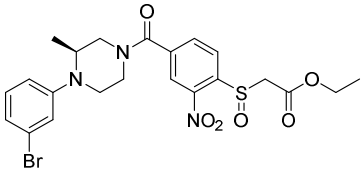
The title compound was synthesized using (*R*)-1-(3-fluorophenyl)-2-methylpiperazine (28mg, 0.13 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (40 mg, 0.13 mmol, 1 eq.), oxalyl chloride (19 mg, 0.15 mmol, 1.1 eq.) and DiPEA (52 mg, 0.40 mmol, 3 eq.) according to general procedure G in a yield of 22 mg (0.05 mmol, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 – 8.38 (m, 2H), 8.11 – 7.94 (m, 1H), 7.20 (t, *J* = 8.3 Hz, 1H), 6.90 – 6.74 (m, 3H), 4.63 – 4.27 (m, 1H), 4.22 (m, 2H), 4.14 (d, *J* = 13.7 Hz, 1H), 3.92 (m, 1H), 3.78 (d, *J* = 13.7 Hz, 1H), 3.74 – 3.00 (m, 5H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.06 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.35, 164.59, 150.62, 144.95, 144.04, 139.71, 135.24, 133.73, 130.40, 128.01, 124.23, 120.43, 117.19, 115.18, 62.50, 60.10, 52.61, 51.81, 47.61, 42.41, 14.23, 12.63. HRMS: Calculated for $[C_{22}H_{24}ClN_3O_6S + H]^+$ = 494.1147, found = 494.1142.

Ethyl 2-((4-((*S*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate ((*S*)-24)



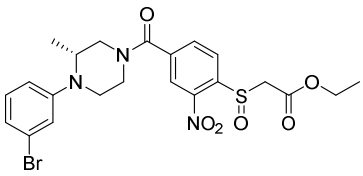
The title compound was synthesized using (*S*)-1-(3-fluorophenyl)-2-methylpiperazine (28mg, 0.13 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (40 mg, 0.13 mmol, 1 eq.), oxalyl chloride (19 mg, 0.15 mmol, 1.1 eq.) and DiPEA (52 mg, 0.40 mmol, 3 eq.) according to general procedure G in a yield of 50 mg (0.10 mmol, 76%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 – 8.33 (m, 2H), 8.04 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 6.95 (m, 3H), 4.57 – 4.09 (m, 4H), 4.05 – 3.08 (m, 7H), 1.28 (d, *J* = 7.2Hz, 3H), 1.09 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.39, 164.59, 149.17, 144.98, 143.92, 139.42, 135.45, 133.77, 130.63, 128.09, 124.29, 121.66, 117.78, 115.87, 62.56, 60.02, 52.87, 52.41, 47.21, 42.19, 14.19, 12.81. HRMS: Calculated for $[C_{22}H_{24}ClN_3O_6S + H]^+$ = 494.1147, found = 494.1143.

Ethyl 2-((4-((R)-4-(3-bromophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate ((*S*)-25)



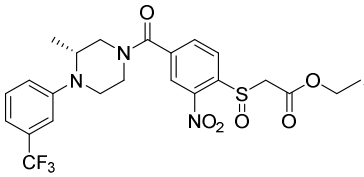
The title compound was synthesized using (*S*)-1-(3-bromophenyl)-2-methylpiperazine (34mg, 0.13 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (40 mg, 0.13 mmol, 1 eq.), oxalyl chloride (19 mg, 0.15 mmol, 1.1 eq.) and DiPEA (52 mg, 0.40 mmol, 3 eq.) according to general procedure G in a yield of 40mg (0.07 mmol, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 – 8.34 (m, 2H), 8.14 – 7.89 (m, 1H), 7.14 (m, 1H), 7.02 (m, 2H), 6.83 (d, *J* = 8.3 Hz, 1H), 4.42 (m, 1H), 4.22 (m, 2H), 4.14 (d, *J* = 13.7 Hz, 1H), 4.01 (m, 1H), 3.78 (d, *J* = 13.6 Hz, 1H), 3.72 – 3.02 (m, 5H), 1.28 (d, *J* = 7.1 Hz, 3H), 1.07 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.36, 164.58, 150.78, 144.94, 144.06, 139.70, 133.73, 130.69, 128.00, 124.23, 123.47, 123.40, 120.06, 115.66, 62.49, 60.08, 52.62, 51.84, 47.38, 42.40, 14.23, 12.66. HRMS: Calculated for $[C_{22}H_{24}BrN_3O_6S + H]^+$ = 538.0642, found = 538.0638.

Ethyl 2-((4-((*R*)-4-(3-bromophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate ((*R*)-25)



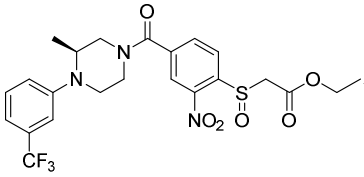
The title compound was synthesized using (*R*)-1-(3-bromophenyl)-2-methylpiperazine (34mg, 0.13 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (40 mg, 0.13 mmol, 1 eq.), oxalyl chloride (19 mg, 0.15 mmol, 1.1 eq.) and DiPEA (52 mg, 0.40 mmol, 3 eq.) according to general procedure G in a yield of 50mg (0.09 mmol, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 – 8.35 (m, 2H), 8.03 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.23 – 7.09 (m, 3H), 6.96 (m, 1H), 4.50 – 4.04 (m, 4H), 3.99 – 3.13 (m, 7H), 1.27 (t, *J* = 7.1Hz, 3H), 1.16 – 0.92 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.42, 164.59, 149.38, 144.99, 143.89, 139.36, 133.78, 130.94, 128.10, 124.86, 124.31, 121.41, 117.19, 62.58, 60.01, 53.10, 52.37, 47.17, 42.14, 14.19, 12.89. HRMS: Calculated for $[C_{22}H_{24}BrN_3O_6S + H]^+$ = 538.0642, found = 538.0639.

Ethyl 2-((4-((R)-3-methyl-4-(3-(trifluoromethyl)phenyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (*(R)*-26)



The title compound was synthesized using (*R*)-1-(3-bromophenyl)-2-methylpiperazine (32mg, 0.13 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (40 mg, 0.13 mmol, 1 eq.), oxalyl chloride (19 mg, 0.15 mmol, 1.1 eq.) and DiPEA (52 mg, 0.40 mmol, 3 eq.) according to general procedure G in a yield of 60mg (0.11 mmol, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 – 8.33 (m, 2H), 8.05 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.44 (m, 1H), 7.20 (m, 3H), 4.61 – 4.13 (m, 4H), 4.11 – 3.16 (m, 7H), 1.28 (t, *J* = 7.2Hz, 3H), 1.19 – 1.01 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.47, 164.60, 148.82, 145.00, 143.79, 139.39, 133.78, 131.97 (q, *J* = 32.0 Hz), 130.18, 128.10, 124.09 (q, *J* = 271.8Hz), 124.31, 120.76, 118.53, 114.60, 62.59, 59.99, 52.98, 52.47, 47.33, 42.28, 14.17, 12.81. HRMS: Calculated for $[C_{23}H_{24}F_3N_3O_6S + H]^+$ = 528.1411, found = 528.1409.

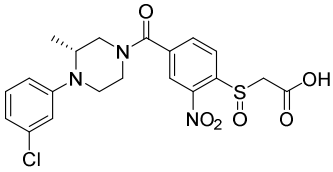
Ethyl 2-((4-((*S*)-3-methyl-4-(3-(trifluoromethyl)phenyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (*(S)*-26)



The title compound was synthesized using (*S*)-1-(3-bromophenyl)-2-methylpiperazine (32mg, 0.13 mmol, 1 eq.), 4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (40

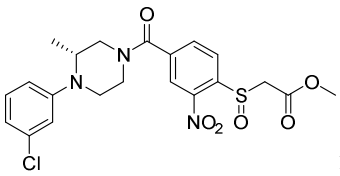
mg, 0.13 mmol, 1 eq.), oxalyl chloride (19 mg, 0.15 mmol, 1.1 eq.) and DiPEA (52 mg, 0.40 mmol, 3 eq.) according to general procedure G in a yield of 57mg (0.11 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 – 8.36 (m, 2H), 8.03 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.20 – 6.98 (m, 3H), 4.62 – 4.29 (m, 1H), 4.26 – 4.18 (m, 2H), 4.14 (d, *J* = 13.7 Hz, 1H), 4.11 – 3.83 (m, 1H), 3.79 (d, *J* = 13.7 Hz, 1H), 3.74 – 3.06 (m, 5H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.20 – 0.93 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.43, 164.61, 149.71, 144.96, 144.08, 139.68, 133.74, 131.78 (q, *J* = 31.8 Hz), 129.98, 128.02, 124.24, 124.22 (q, *J* = 273.71 Hz), 120.16, 117.04, 113.59, 62.49, 60.08, 52.61, 51.80, 47.38, 42.38, 14.21, 12.66. HRMS: Calculated for $[C_{23}H_{24}F_3N_3O_6S + H]^+$ = 528.1411, found = 528.1411.

2-((4-((*R*)-3-Methyl-4-(m-tolyl)piperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetic acid (**65**)



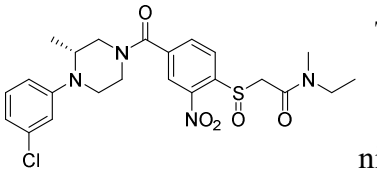
To a solution of ethyl 2-((4-((R)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (38 mg, 0.08 mmol, 1 eq.) in MeOH (2mL) were added TEA (2mL) and water (1mL). Then the reaction mixture was stirred overnight at room temperature. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the pH of resulted mixture was adjusted to 1 with 1M HCl solution. Then the mixture was diluted with EtOAc and the organic layer was washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/DCM, 1%→2%) to afford the product (31 mg, 0.07 mmol, 86 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.31 (s, 1H), 8.51 – 8.30 (m, 2H), 8.07 – 7.96 (m, 1H), 7.20 (t, *J* = 8.3 Hz, 1H), 6.84 (m, 3H), 4.59 – 3.19 (m, 9H), 1.18 – 0.95 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.39, 166.68, 150.52, 145.00, 143.44, 139.44, 135.30, 133.92, 130.46, 128.16, 124.32, 120.58, 117.27, 115.26, 59.62, 52.63, 51.95, 47.52, 42.50, 12.83.

Methyl 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (**27**)



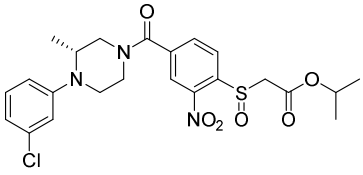
The title compound was synthesized using 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetic acid (40 mg, 0.09 mmol, 1 eq.), MeOH (55 mg, 1.72 mmol, 20 eq.), oxalyl chloride (12 mg, 0.94 mmol, 1.1 eq.) and DiPEA (33 mg, 0.26 mmol, 3 eq.) according to general procedure G in a yield of 28mg (0.061 mmol, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 – 8.30 (m, 2H), 8.04 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.24 (t, *J* = 8.2 Hz, 1H), 7.05 – 6.79 (m, 3H), 4.57 – 3.61 (m, 8H), 3.60 – 3.12 (m, 4H), 1.09 (d, *J* = 78.9 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.42, 165.03, 149.47, 145.03, 143.88, 139.53, 135.46, 133.81, 130.62, 128.05, 124.33, 122.12, 118.30, 116.40, 59.90, 53.18, 52.71, 52.44, 46.22, 42.24, 12.80. HRMS: Calculated for $[C_{21}H_{22}ClN_3O_6S + H]^+$ = 480.0991, found = 480.0989.

2-((4-((*R*)-4-(3-Chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)-*N*-ethyl-N-methylacetamide (**28**)



The title compound was synthesized using 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetic acid (40 mg, 0.09 mmol, 1 eq.), *N*-methylethanamine (102 mg, 1.72 mmol, 20 eq.), oxalyl chloride (12 mg, 0.94 mmol, 1.1 eq.) and DiPEA (33 mg, 0.26 mmol, 3 eq.) according to general procedure G in a yield of 18mg (0.036 mmol, 41%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (m, 2H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 6.88 (m, 3H), 4.36 – 3.91 (m, 2H), 3.76 (m, 3H), 3.58 – 3.32 (m, 4H), 3.32 – 3.12 (m, 2H), 3.09 – 2.95 (m, 3H), 1.27 – 0.91 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.22, 163.56, 150.06, 145.10, 144.32, 139.36, 135.37, 133.70, 130.52, 128.10, 124.16, 121.00, 117.45, 115.51, 59.51, 52.40, 47.45, 45.51, 43.43, 42.30, 33.36, 13.72, 12.88. HRMS: Calculated for $[C_{23}H_{27}ClN_4O_5S + H]^+$ = 507.1463, found = 507.1463.

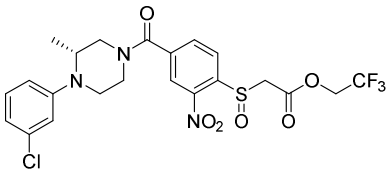
Isopropyl 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (**29**)



The title compound was synthesized using 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetic acid (40 mg, 0.09 mmol, 1 eq.),

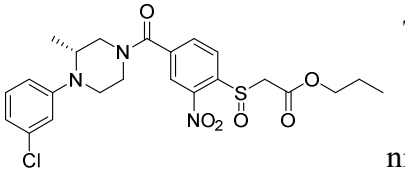
propan-2-ol (103 mg, 1.72 mmol, 20 eq.), oxalyl chloride (12 mg, 0.94 mmol, 1.1 eq.) and DiPEA (33 mg, 0.26 mmol, 3 eq.) according to general procedure G in a yield of 16mg (0.03 mmol, 37%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 – 8.33 (m, 2H), 8.03 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.22 (t, *J* = 8.1 Hz, 1H), 6.88 (m, 3H), 5.07 (m, 1H), 4.52 – 4.38 (m, 1H), 4.13 (d, *J* = 13.8 Hz, 1H), 3.90 (m, 1H), 3.76 (d, *J* = 13.8 Hz, 1H), 3.74 – 3.10 (m, 5H), 1.31 – 1.22 (m, 6H), 1.14 – 1.02 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.13, 164.17, 150.12, 145.00, 144.12, 139.55, 135.39, 133.76, 130.54, 128.19, 124.28, 121.53, 117.52, 115.53, 70.72, 60.24, 52.36, 47.38, 45.08, 42.35, 21.83, 12.75. HRMS: Calculated for $[C_{23}H_{26}ClN_3O_6S + H]^+$ = 508.1304, found = 508.1305.

2,2,2-Trifluoroethyl 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (30)



The title compound was synthesized using 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetic acid (40 mg, 0.09 mmol, 1 eq.), 2,2,2-trifluoroethan-1-ol (172 mg, 1.72 mmol, 20 eq.), oxalyl chloride (12 mg, 0.94 mmol, 1.1 eq.) and DiPEA (33 mg, 0.26 mmol, 3 eq.) according to general procedure G in a yield of 8mg (0.015 mmol, 17%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 – 8.33 (m, 2H), 8.10 – 7.95 (m, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 6.95 – 6.75 (m, 3H), 4.52 (qd, *J* = 8.2, 1.8 Hz, 2H), 4.35 – 3.05 (m, 9H), 1.07 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.35, 163.16, 150.41, 145.00, 143.45, 140.02, 135.38, 133.95, 130.51, 128.18, 124.42, 122.56 (q, *J* = 277.4 Hz), 120.88, 117.47, 115.46, 61.54 (q, *J* = 37.3 Hz), 59.13, 52.62, 52.19, 47.49, 42.44, 12.72. HRMS: Calculated for $[C_{22}H_{21}ClF_3N_3O_6S + H]^+$ = 548.0864, found = 548.0864.

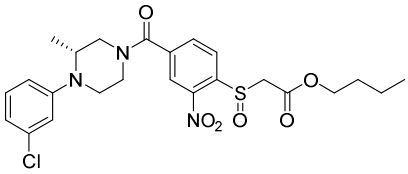
Propyl 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (31)



The title compound was synthesized using 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetic acid (40 mg, 0.09 mmol, 1 eq.), propan-1-ol (103 mg, 1.72 mmol, 20 eq.), oxalyl chloride (12 mg, 0.94 mmol, 1.1 eq.) and DiPEA (33 mg, 0.26 mmol, 3 eq.) according to general procedure G in a yield

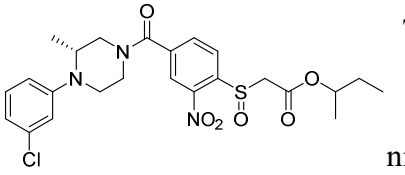
of 26mg (0.051 mmol, 60%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 8.42 (d, *J* = 7.9 Hz, 2H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.24 (s, 1H), 7.05 – 6.85 (m, 3H), 4.50 – 3.14 (m, 11H), 1.69 (p, *J* = 7.0 Hz, 2H), 1.20 – 0.98 (m, 3H), 0.96 (td, *J* = 7.4, 1.1 Hz, 3H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 167.08, 164.70, 149.57, 145.00, 144.09, 139.47, 135.46, 133.78, 130.63, 128.10, 124.32, 121.58, 118.31, 116.32, 68.10, 60.15, 52.73, 52.45, 47.17, 42.22, 21.94, 12.77, 10.41. HRMS: Calculated for $[C_{23}H_{26}ClN_3O_6S + H]^+$ = 508.13036, found = 508.13022.

Butyl 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (32)



The title compound was synthesized using 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetic acid (40 mg, 0.09 mmol, 1 eq.), butan-1-ol (127 mg, 1.72 mmol, 20 eq.), oxalyl chloride (12 mg, 0.94 mmol, 1.1 eq.) and DiPEA (33 mg, 0.26 mmol, 3 eq.) according to general procedure G in a yield of 22mg (0.042 mmol, 49%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 8.45 – 8.36 (m, 2H), 8.03 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.21 (t, *J* = 8.1 Hz, 1H), 6.94 – 6.86 (m, 2H), 6.84 – 6.78 (m, 1H), 4.41 - 3.11 (m, 11H), 1.67 – 1.61 (m, 2H), 1.39 (m, 2H), 1.17 – 0.98 (m, 3H), 0.94 (td, *J* = 7.4, 1.6 Hz, 3H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 167.08, 164.74, 150.24, 144.97, 143.99, 139.60, 135.34, 133.77, 130.50, 128.05, 124.29, 120.80, 117.87, 115.94, 66.42, 60.17, 52.14, 47.37, 44.79, 42.36, 30.52, 19.11, 13.77, 12.64. HRMS: Calculated for $[C_{24}H_{28}ClN_3O_6S + H]^+$ = 522.14601, found = 522.14572.

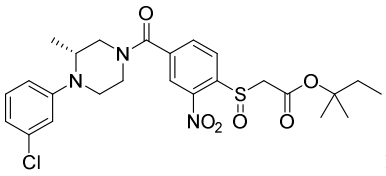
***sec*-Butyl 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (33)**



The title compound was synthesized using 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetic acid (40 mg, 0.09 mmol, 1 eq.), butan-2-ol (127 mg, 1.72 mmol, 20 eq.), oxalyl chloride (12 mg, 0.94 mmol, 1.1 eq.) and DiPEA (33 mg, 0.26 mmol, 3 eq.) according to general procedure G in a yield of 12mg (0.023 mmol, 27%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 8.48 – 8.35 (m, 2H), 8.08 – 8.01 (m, 1H), 7.28 (m, 1H), 7.11 – 6.91 (m, 3H), 4.93 (m, 1H), 4.47-3.20 (m, 9H),

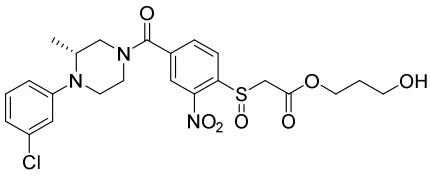
1.65 (m, 1H), 1.62 – 1.53 (m, 1H), 1.25 (m, 3H), 1.18 – 1.04 (m, 3H), 0.95 – 0.90 (m, 3H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 167.18, 164.32, 147.91, 145.00, 144.07, 139.13, 135.67, 133.83, 130.84, 128.24, 124.38, 123.57, 118.95, 117.16, 75.40, 60.20, 54.46, 52.24, 46.99, 41.97, 28.78, 19.44, 13.27, 9.70. HRMS: Calculated for $[C_{24}H_{28}ClN_3O_6S + H]^+$ = 522.14601, found = 522.14612.

***tert*-Pentyl 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (34)**



The title compound was synthesized using 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetic acid (40 mg, 0.09 mmol, 1 eq.), 2-methylbutan-2-ol (151 mg, 1.72 mmol, 20 eq.), oxalyl chloride (12 mg, 0.94 mmol, 1.1 eq.) and DiPEA (33 mg, 0.26 mmol, 3 eq.) according to general procedure G. This yielded the product (12 mg, 0.022 mmol, 26%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 8.49 – 8.38 (m, 2H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.28 (s, 1H), 7.05 (s, 3H), 4.51 – 3.19 (m, 9H), 1.80 (tt, *J* = 14.1, 6.8 Hz, 2H), 1.47 (d, *J* = 13.0 Hz, 6H), 1.19 – 1.05 (m, 3H), 0.93 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 167.13, 163.73, 145.01, 144.43, 139.13, 135.68, 133.80, 130.84, 128.26, 124.36, 86.81, 61.28, 53.78, 52.28, 46.94, 41.87, 33.64, 25.56, 13.34, 8.34. HRMS: Calculated for $[C_{25}H_{30}ClN_3O_6S + H]^+$ = 536.1617, found = 536.1617.

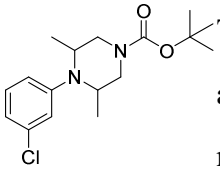
3-Hydroxypropyl 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (35)



The title compound was synthesized using 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetic acid (40 mg, 0.09 mmol, 1 eq.), propane-1,3-diol (131 mg, 1.72 mmol, 20 eq.), oxalyl chloride (12 mg, 0.94 mmol, 1.1 eq.) and DiPEA (33 mg, 0.26 mmol, 3 eq.) according to general procedure G in a yield of 12 mg (0.040 mmol, 47%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 8.50 – 8.34 (m, 2H), 8.05 (s, 1H), 7.25 (s, 1H), 6.97 (m, 3H), 4.59 – 3.12 (m, 13H), 3.01 (s, 1H), 1.93 – 1.75 (m, 2H), 1.21 – 0.97 (m, 3H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 167.21, 164.38, 149.95, 145.04, 143.65, 139.57, 135.51, 133.86, 130.67, 128.26, 124.29, 121.56, 118.46,

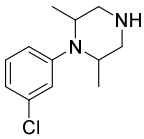
116.56, 64.61, 63.54, 59.10, 58.95, 52.47, 47.20, 42.19, 31.18, 13.06.

***tert*-Butyl 4-(3-chlorophenyl)-3,5-dimethylpiperazine-1-carboxylate (36a)**



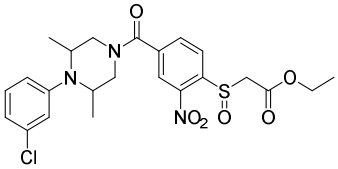
To a solution of 1-bromo-3-chlorobenzene (191 mg, 1 mmol, 1 eq.) and *tert*-butyl 3,5-dimethylpiperazine-1-carboxylate (257 mg, 1.2 mmol, 1.2 eq.) in dry 1,4-dioxane (2mL) was added KHMDS (239 mg, 1,2 mmol, 1.2 eq.) and the reaction mixture was heated to 100°C and stirred overnight. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was cool to room temperature, diluted with EtOAc, washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (diethyl ether/pentane, 5%→20%) to afford the product (70mg, 0.22 mmol, 22%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (td, *J* = 8.2, 1.4 Hz, 1H), 7.06 (dt, *J* = 8.1, 1.3 Hz, 2H), 6.94 (dq, *J* = 8.0, 1.4 Hz, 1H), 3.80 (br, 2H), 3.38 – 2.81 (m, 4H), 1.50 (s, 9H), 0.84 (dd, *J* = 6.3, 1.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.75, 150.43, 134.70, 129.99, 124.18, 124.06, 122.50, 54.31, 28.54, 18.12.

1-(3-Chlorophenyl)-2,6-dimethylpiperazine (36b)



The title compound was synthesized using *tert*-butyl 4-(3-chlorophenyl)-3,5-dimethylpiperazine-1-carboxylate (70 mg, 0.22 mmol, 1 eq.) according to general procedure B in a yield of 42 mg (0.19 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 2H), 7.25 (t, *J* = 1.9 Hz, 1H), 7.16 (dt, *J* = 7.7, 1.6 Hz, 1H), 3.52 (d, *J* = 11.0 Hz, 2H), 3.44 – 3.36 (m, 2H), 2.99 (t, *J* = 11.8 Hz, 2H), 0.84 (d, *J* = 6.3 Hz, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 134.97, 130.45, 127.74, 54.18, 49.39, 17.80.

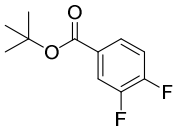
Ethyl 2-((4-(4-(3-chlorophenyl)-3,5-dimethylpiperazine-1-carbonyl)-2-nitrophenyl)sulfinyl)acetate (36)



The title compound was synthesized using 4-((2-ethoxy-2-oxoethyl)sulfinyl)-3-nitrobenzoic acid (40 mg, 0.13 mmol, 1 eq.), 1-(3-chlorophenyl)-2,6-dimethylpiperazine (30 mg, 0.13 mmol, 1 eq.), oxalyl chloride (19 mg, 0.15 mmol, 1.1 eq.) and DiPEA (52 mg, 0.40 mmol, 3 eq.) according to general procedure G in a yield of 36 mg (0.07 mmol,

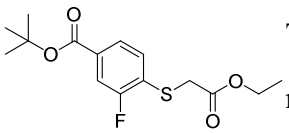
53%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.42 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.39 (m, 4H), 4.76 (s, 1H), 4.25 – 4.12 (m, 3H), 3.92 (s, 1H), 3.80 (d, *J* = 13.9 Hz, 1H), 3.75 – 3.33 (m, 4H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.06 (m, 6H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 166.57, 164.68, 145.16, 144.39, 142.76, 138.73, 136.19, 133.88, 131.35, 129.33, 128.14, 124.78, 123.92, 123.03, 62.61, 60.63, 60.03, 51.89, 46.59, 16.21, 14.21. HRMS: Calculated for $[C_{23}H_{26}ClN_3O_6S + H]^+$ = 508.1304, found = 508.1303.

***tert*-Butyl 3,4-difluorobenzoate (66)**



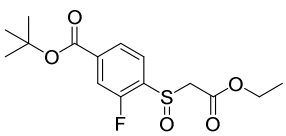
The title compound was synthesized using 3,4-difluorobenzoic acid (200 mg, 1.27 mmol, 1 eq.) according to procedure general procedure G in a yield of 198 mg (0.92 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.67 (m, 2H), 7.18 (q, *J* = 9.5, 8.8 Hz, 1H), 1.60 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.74, 153.31 (dd, *J* = 254.9, 12.8 Hz), 150.00 (dd, *J* = 249.3, 13.0 Hz), 129.14 (dd, *J* = 5.3, 3.6 Hz), 126.31 (dd, *J* = 7.3, 3.6 Hz), 118.75 (d, *J* = 18.6 Hz), 117.06 (d, *J* = 17.8 Hz), 81.83, 28.07.

***tert*-Butyl 4-((2-ethoxy-2-oxoethyl)thio)-3-fluorobenzoate (67)**



The title compound was synthesized using ethyl 2-mercaptoacetate (101 mg, 0.84 mmol, 1 eq.) and *tert*-butyl 3,4-difluorobenzoate (198 mg, 0.92 mmol, 1.1eq.) according to general procedure D in a yield of 188 mg (0.60 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.64 (dd, *J* = 10.4, 1.7 Hz, 1H), 7.42 (dd, *J* = 8.2, 7.3 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 2H), 1.59 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.86, 164.20, 160.22 (d, *J* = 246.1 Hz), 132.42 (d, *J* = 7.1 Hz), 130.11 (d, *J* = 1.9 Hz), 127.99 (d, *J* = 17.4 Hz), 125.48 (d, *J* = 3.4 Hz), 116.27 (d, *J* = 23.7 Hz), 81.72, 61.83, 34.70, 28.14, 14.10.

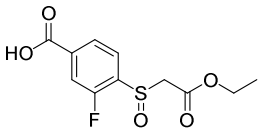
***tert*-Butyl 4-((2-ethoxy-2-oxoethyl)sulfinyl)-3-fluorobenzoate (68)**



The title compound was synthesized using *tert*-butyl 4-((2-ethoxy-2-oxoethyl)thio)-3-fluorobenzoate (40 mg, 0.13 mmol, 1.00 eq.) according to general procedure E in a yield of 38 mg (0.12 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.91

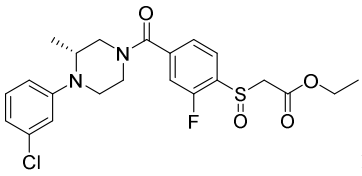
(dd, *J* = 8.1, 6.6 Hz, 1H), 7.74 (dd, *J* = 10.1, 1.4 Hz, 1H), 4.20 (qd, *J* = 7.2, 1.2 Hz, 2H), 3.97 (d, *J* = 13.7 Hz, 1H), 3.78 (d, *J* = 13.7 Hz, 1H), 1.61 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.23, 163.55, 157.35 (d, *J* = 247.8 Hz), 137.41 (d, *J* = 6.9 Hz), 134.60 (d, *J* = 17.2 Hz), 126.37, 126.32 (d, *J* = 4.1 Hz), 116.73 (d, *J* = 22.0 Hz), 82.65, 62.44, 58.64, 28.18, 14.17.

4-((2-Ethoxy-2-oxoethyl)sulfinyl)-3-fluorobenzoic acid (**69**)



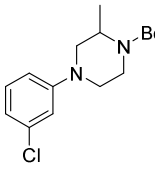
The title compound was synthesized using *tert*-butyl 4-((2-ethoxy-2-oxoethyl)sulfinyl)-3-fluorobenzoate (30mg, 0.09 mmol, 1 eq.) according to general procedure F in a yield of 18 mg (0.7 mmol, 72%). ^{1}H NMR (400 MHz, Methanol-*d*4) δ 8.10 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.95 – 7.80 (m, 2H), 4.27 – 4.05 (m, 3H), 3.95 (d, *J* = 14.2 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-*d*4) δ 167.20, 165.75, 159.03 (d, *J* = 247.7 Hz), 137.86 (d, *J* = 7.1 Hz), 135.69 (d, *J* = 16.9 Hz), 127.66 (d, *J* = 3.3 Hz), 127.53 (d, *J* = 2.1 Hz), 117.91 (d, *J* = 22.2 Hz), 63.17, 59.38, 14.31.

Ethyl 2-((4-((*R*)-4-(3-chlorophenyl)-3-methylpiperazine-1-carbonyl)-2-fluorophenyl)sulfinyl)acetate (**37**)



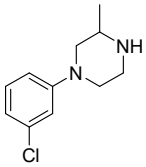
The title compound was synthesized using 4-((2-ethoxy-2-oxoethyl)sulfinyl)-3-fluorobenzoic acid (40 mg, 0.15 mmol, 1 eq.), (*R*)-1-(3-chlorophenyl)-2-methylpiperazine (31 mg, 0.15 mmol, 1 eq.), oxalyl chloride (20 mg, 0.16 mmol, 1.1 eq.) and DiPEA (57 mg, 0.44 mmol, 3 eq.) according to general procedure G in a yield of 36 mg (0.07 mmol, 53%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 7.95 (t, *J* = 7.2 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.31 (t, *J* = 11.5 Hz, 2H), 7.24 – 6.98 (m, 3H), 4.35 – 3.17 (m, 11H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.22 – 0.94 (m, 3H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 168.20, 164.20, 157.65 (d, *J* = 246.3 Hz), 146.52, 140.01 (d, *J* = 29.3 Hz), 135.80, 132.01, 131.01, 127.15, 124.17, 124.01, 118.82, 117.08, 115.23 (d, *J* = 22.0 Hz), 62.61, 58.57, 55.09, 51.80, 46.42, 41.44, 14.10, 13.39. HRMS: Calculated for $[C_{22}H_{24}ClFN_2O_4S + H]^+$ = 467.1202, found = 467.1202.

***tert*-Butyl 4-(3-chlorophenyl)-2-methylpiperazine-1-carboxylate** (**38a**)



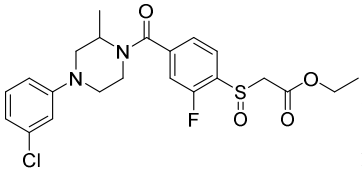
The title compound was synthesized using 1-bromo-3-chlorobenzene (96 mg, 0.50 mmol, 1 eq.), *tert*-butyl 2-methylpiperazine-1-carboxylate (100 mg, 0.50 mmol, 1 eq.), sodium *tert*-butoxide (72 mg, 0.75 mmol, 1.5 eq.), rac-BINAP (19 mg, 0.03 mmol, 0.06 eq.) and palladium diacetate (4.45 mg, 0.02 mmol, 0.04 eq.) according to general procedure A in a yield of 121 mg (0.39 mmol, 78%).

1-(3-Chlorophenyl)-3-methylpiperazine (38b)



The title compound was synthesized using *tert*-Butyl 4-(3-chlorophenyl)-2-methylpiperazine-1-carboxylate (104mg, 0.34 mmol, 1 eq.) according to general procedure B in a yield of 66 mg (0.31 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, *J* = 8.1 Hz, 1H), 6.87 (t, *J* = 2.2 Hz, 1H), 6.79 (ddt, *J* = 9.6, 7.5, 1.2 Hz, 2H), 3.50 (dq, *J* = 11.5, 1.5 Hz, 2H), 3.13 (ddd, *J* = 12.0, 3.3, 2.3 Hz, 1H), 3.07 – 2.92 (m, 2H), 2.85 – 2.69 (m, 2H), 2.41 (dd, *J* = 11.9, 10.2 Hz, 1H), 1.16 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.47, 134.96, 130.08, 119.33, 115.89, 114.07, 56.18, 50.59, 48.75, 45.60, 19.58.

Ethyl 2-((4-(4-(3-chlorophenyl)-2-methylpiperazine-1-carbonyl)-2-fluorophenyl)sulfinyl)acetate (38)



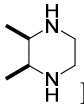
The title compound was synthesized using 4-((2-ethoxy-2-oxoethyl)sulfinyl)-3-fluorobenzoic acid (18 mg, 0.07 mmol, 1 eq.), 1-(3-chlorophenyl)-3-methylpiperazine (14 mg, 0.07 mmol, 1 eq.), oxalyl chloride (9 mg, 0.07 mmol, 1.1 eq.) and DiPEA (25 mg, 0.20 mmol, 3 eq.) according to general procedure G in a yield of 15 mg (0.03 mmol, 49%). ^{1}H NMR (850 MHz, $CDCl_3$) δ 8.09 – 7.88 (m, 1H), 7.56 – 7.38 (m, 1H), 7.22 (m, 2H), 7.02 – 6.75 (m, 3H), 4.79 (m, 1H), 4.36 – 4.18 (m, 2H), 3.97 (d, *J* = 13.8 Hz, 1H), 3.81 (d, *J* = 13.9 Hz, 1H), 3.51 (m, 3H), 3.13 – 2.67 (m, 3H), 1.45 (m, 3H), 1.27 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (214 MHz, $CDCl_3$) δ 167.75, 164.30, 157.69 (d, *J* = 250.3 Hz), 152.28, 141.31, 135.19, 131.92 (d, *J* = 16.9 Hz), 130.38, 127.07, 123.74, 120.68, 116.95, 114.98, 114.77, 62.54, 58.99, 54.51, 49.37, 42.94, 37.36, 16.45, 14.19.

5,6-Dimethyl-2,3-dihydropyrazine (70)

To a cooled (0°C) solution of ethylenediamine (6.6 mL, 100 mmol) in Et_2O (250 mL) was dropwise added a solution of 2,3-butanedione (8.8 mL, 100 mmol) in

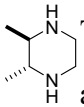
Et_2O (250 mL) and the suspension was allowed to stir for 16h. The resulting clear liquid was dried using potassium hydroxide for 30 min. After filtration, the mixture was concentrated and the residue was purified by short-neck distillation which yielded the product (9.36 g; 85 mmol; 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 (s, 4H), 2.15 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 44.9, 23.4.

***cis*-2,3-Dimethylpiperazine (71)**



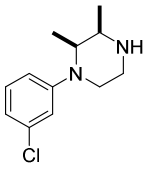
A solution of 5,6-dimethyl-2,3-dihydropyrazine (3.49 g, 31.7 mmol, 1 eq.) in EtOH (100mL) was degassed for 30 min by bubbling argon through the solution. Palladium loaded on carbon (10%, 3.2 g, 30.1 mmol) was added under constant bubbling. The solution was flushed three times with hydrogen after which the pressure was increased to 40 bar. The reaction mixture was stirred for 72h on 40 bar. The suspension was filtered over celite and rinsed three times with EtOH (3x 50 mL). After evaporating the volatiles, the residue was purified by column chromatography (Et_2O:MeOH:NH_4OH, 10:4:1) to obtain the product (197 mg, 1.73 mmol, 5%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (s, 2H), 3.29-3.21 (m, 2H), 3.09-2.94 (m, 4H), 1.18 (d, J = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.5, 40.9, 13.7.

(±) *trans*-2,3-Dimethylpiperazine (72)



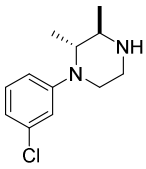
To a solution of 5,6-dimethyl-2,3-dihydropyrazine (9.36 g, 85 mmol, 1 eq.) in absolute ethanol (300mL) was portion wise added sodium metal (23 g, 1 mol, 11.8 eq.) over six hours, after which the solution was refluxed for an additional 16h. The slurry was neutralized by addition of acetic acid (50 mL) at 0°C. The suspension was diluted with DCM, after stirring for 30 mins the precipitated sodium acetate was filtered off. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (Et_2O : MeOH : NH_4OH, 10:4:1) to afford the product (3.71 g, 32.5 mmol, 38%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 1H), 2.98 (m, 4H), 2.53 (m, 2H), 1.12-1.09 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 57.2, 45.8, 18.5.

(±) *cis*-1-(3-Chlorophenyl)-2,3-dimethylpiperazine (±39b)



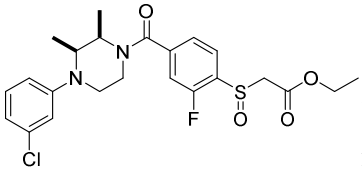
To a solution of 1-bromo-3-chlorobenzene (335 mg, 1.75 mmol, 1 eq.) in 2ml 1,4-dioxane was added cis-2,3-dimethylpiperazine (200 mg, 1.75 mmol, 1eq.) and KHMDS (524mg, 2.63mmol, 1.5eq.). Then the reaction mixture was stirred for 2h at room temperature. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was diluted with DCM, washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/DCM, 1%→5%) to afford the product (43 mg, 0.12 mmol, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, *J* = 8.1 Hz, 1H), 6.81 (t, *J* = 2.2 Hz, 1H), 6.74 (tdd, *J* = 8.0, 2.2, 1.0 Hz, 2H), 3.76 (m, 1H), 3.26 – 2.59 (m, 5H), 1.11 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.40, 135.15, 130.16, 118.36, 115.43, 113.54, 54.95, 54.04, 46.07, 41.26, 19.03, 6.51.

(±) *trans*-1-(3-Chlorophenyl)-2,3-dimethylpiperazine (±40b)



To a solution of (±) *trans*-2,3-dimethylpiperazine (0.70 g, 6.1 mmol, 1 eq.) in anhydrous dioxane (17 ml) were added 1-bromo-2-chlorobenzene (0.60 ml, 6.1 mmol, 1 eq.) and KHMDS solution (1M in THF, 6.1 ml, 6.1 mmol, 1 eq.). The reaction mixture was stirred at RT for 2h. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was diluted with DCM, washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified using column chromatography (1% -> 10% MeOH in DCM with 1% TEA) to yielded the product (0.51 mg, 2.0 mmol, 32%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (t, *J* = 8.1 Hz, 1H), 6.97 (t, *J* = 2.2 Hz, 1H), 6.89 (dddd, *J* = 18.0, 8.3, 2.1, 0.9 Hz, 2H), 3.24 – 2.82 (m, 6H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ153.01, 134.81, 130.07, 121.22, 120.23, 118.30, 57.84, 54.59, 48.88, 42.59, 19.04, 14.91.

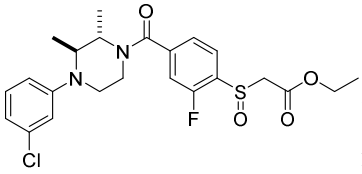
(±) Ethyl 2-((4-(4-(3-chlorophenyl)-*cis*-2,3-dimethylpiperazine-1-carbonyl)-2-fluorophenyl)sulfinyl)acetate (±39)



The title compound was synthesized using 4-((2-ethoxy-2-oxoethyl)sulfinyl)-3-fluorobenzoic acid (30 mg, 0.11 mmol, 1 eq.), *cis*-1-(3-chlorophenyl)-2,3-

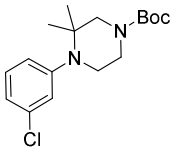
dimethylpiperazine (25 mg, 0.11 mmol, 1 eq.), oxalyl chloride (15 mg, 0.12 mmol, 1.1 eq.) and DiPEA (42 mg, 0.33 mmol, 3 eq.) according to general procedure G in a yield of 12 mg (0.03 mmol, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (t, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.32 – 7.14 (m, 4H), 7.10 (d, *J* = 7.9 Hz, 1H), 4.50 – 2.90 (m, 10H), 1.40 (dd, *J* = 6.6, 1.5 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 6.3 Hz, 3H). HRMS: Calculated for $[C_{22}H_{24}ClFN_2O_4S + H]^+$ = 481.1359, found = 481.1357.

(±)Ethyl 2-((4-(4-(3-chlorophenyl)-*trans*-2,3-dimethylpiperazine-1-carbonyl)-2-fluorophenyl)sulfinyl)acetate (±40)



The title compound was synthesized using 4-((2-ethoxy-2-oxoethyl)sulfinyl)-3-fluorobenzoic acid (30 mg, 0.11 mmol, 1 eq.), (±) *trans*-1-(3-chlorophenyl)-2,3-dimethylpiperazine (25 mg, 0.11 mmol, 1 eq.), oxalyl chloride (15 mg, 0.12 mmol, 1.1 eq.) and DiPEA (42 mg, 0.33 mmol, 3 eq.) according to general procedure G in a yield of 18 mg (0.04 mmol, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.90 (m, 1H), 7.44 (q, *J* = 7.5 Hz, 1H), 7.26 – 7.12 (m, 2H), 6.90 – 6.61 (m, 3H), 4.88 – 4.55 (m, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.97 (d, *J* = 13.8 Hz, 1H), 3.81 (d, *J* = 13.9 Hz, 1H), 3.71 – 3.45 (m, 2H), 3.38 – 3.05 (m, 3H), 1.56 – 1.41 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.17 – 0.96 (m, 3H). HRMS: Calculated for $[C_{22}H_{24}ClFN_2O_4S + H]^+$ = 481.1359, found = 481.1358.

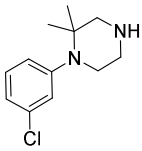
***tert*-Butyl 4-(3-chlorophenyl)-3,3-dimethylpiperazine-1-carboxylate (41a)**



To a solution of *tert*-butyl 3,3-dimethylpiperazine-1-carboxylate (0.20 g, 0.93 mmol, 1 eq.) in anhydrous dioxane (3mL) were added 1-bromo-2-chlorobenzene (179 mg, 0.93 mmol, 1 eq.) and KHMDS solution (1M in THF, 1.1 ml, 1.1 mmol, 1.2 eq.). The reaction mixture was stirred at RT for 2h. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was diluted with DCM, washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified using column chromatography (Diethyl ether/Pentane, 5%-15%) to yielded the product (86 mg, 0.27 mmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 8.1 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 1H), 3.55 (t, *J* = 7.0 Hz, 2H), 3.32 (s, 2H), 3.05 (t, *J* = 5.2 Hz, 2H), 1.48 (s, 9H), 1.03 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.88,

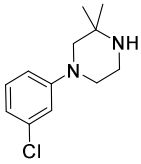
150.41, 133.71, 129.06, 127.58, 125.80, 124.78, 79.69, 56.45, 55.07, 46.91, 43.94, 28.49, 21.75.

1-(3-Chlorophenyl)-2,2-dimethylpiperazine (**41b**)



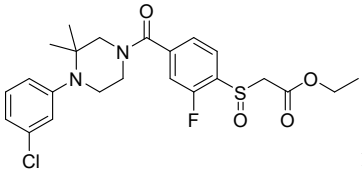
The title compound was synthesized using *tert*-butyl 4-(3-chlorophenyl)-3,3-dimethylpiperazine-1-carboxylate (86 mg, 0.27 mmol, 1 eq.) according to procedure B in a yield of 57 mg (0.25 mmol, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 7.09 (dd, *J* = 7.2, 1.3 Hz, 2H), 7.02 – 6.95 (m, 1H), 3.99 (s, 1H), 3.19 – 2.96 (m, 4H), 2.81 (s, 2H), 1.07 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.68, 133.70, 129.04, 127.54, 125.91, 124.71, 58.40, 54.59, 47.59, 46.72, 22.22.

1-(3-Chlorophenyl)-3,3-dimethylpiperazine (**42b**)



To a mixture of 1-bromo-3-chlorobenzene (335 mg, 1.75 mmol, 1 eq.) and 2,2-dimethylpiperazine (200 mg, 1.75 mmol, 1 eq.) in anhydrous dioxane (3mL) was added KHMDS solution (1M in THF, 2.1 ml, 2.1 mmol, 1.2 eq.). Then the reaction mixture was stirred at room temperature for 2h. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was diluted with DCM, washed with water, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified using column chromatography (MeOH/DCM, 1%-10%) to yielded the product (96 mg, 0.27 mmol, 28%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 – 7.10 (m, 1H), 6.84 (t, *J* = 2.2 Hz, 1H), 6.80 – 6.74 (m, 2H), 3.11 – 2.95 (m, 4H), 2.89 (s, 2H), 1.22 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.20, 134.98, 130.09, 119.12, 116.04, 114.21, 60.82, 49.41, 48.19, 41.20, 26.29.

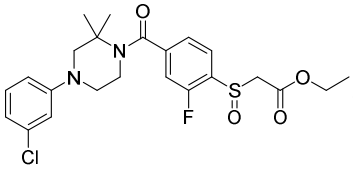
Ethyl 2-((4-(4-(3-chlorophenyl)-3,3-dimethylpiperazine-1-carbonyl)-2-fluorophenyl)sulfinyl)acetate (**41**)



The title compound was synthesized using 4-((2-ethoxy-2-oxoethyl)sulfinyl)-3-fluorobenzoic acid (30 mg, 0.11 mmol, 1 eq.), 1-(3-chlorophenyl)-2,2-dimethylpiperazine (25 mg, 0.11 mmol, 1 eq.), oxalyl chloride (15 mg, 0.12 mmol, 1.1 eq.) and DiPEA (42 mg, 0.33 mmol, 3 eq.) according to general procedure G in a yield of 26 mg (0.05 mmol,

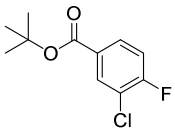
49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (t, *J* = 7.2 Hz, 1H), 7.50 (s, 1H), 7.36 (d, *J* = 6.5 Hz, 2H), 7.29 (m, 3H), 4.27 – 3.30 (m, 10H), 1.27 (m, 6H), 1.12 (s, 3H). HRMS: Calculated for $[C_{22}H_{24}ClFN_2O_4S + H]^+$ = 481.1359, found = 481.1358.

Ethyl 2-((4-(4-(3-chlorophenyl)-2,2-dimethylpiperazine-1-carbonyl)-2-fluorophenyl)sulfinyl)acetate (42)



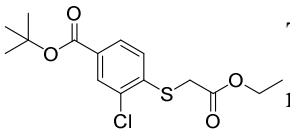
The title compound was synthesized using 4-((2-ethoxy-2-oxoethyl)sulfinyl)-3-fluorobenzoic acid (30 mg, 0.11 mmol, 1 eq.), 1-(3-chlorophenyl)-3,3-dimethylpiperazine (25 mg, 0.11 mmol, 1 eq.), oxalyl chloride (15 mg, 0.12 mmol, 1.1 eq.) and DiPEA (42 mg, 0.33 mmol, 3 eq.) according to general procedure G in a yield of 28 mg (0.06 mmol, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (t, *J* = 7.0 Hz, 1H), 7.47 (s, 1H), 7.32 – 7.05 (m, 5H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.07 – 3.15 (m, 8H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.21 (s, 3H), 1.03 (s, 3H). HRMS: Calculated for $[C_{22}H_{24}ClFN_2O_4S + H]^+$ = 481.1359, found = 481.1358.

***tert*-Butyl 3-chloro-4-fluorobenzoate (73)**



The title compound was synthesized using 4-fluoro-3-chlorobenzoic acid (1 g, 5.73 mmol, 1 eq.), Boc_2O (3.13 g, 14.3 mmol, 2.5 eq.) and DMAP (210 mg, 1.72 mmol, 0.30 eq.) according to general procedure C in a yield of 1.16 g (5.04 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.2, 2.2 Hz, 1H), 7.88 (ddd, *J* = 8.6, 4.7, 2.2 Hz, 1H), 7.17 (t, *J* = 8.6 Hz, 1H), 1.59 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.9, 160.9 (d, *J* = 255.2 Hz), 132.3, 129.9 (d, *J* = 8.4 Hz), 129.3 (d, *J* = 3.6 Hz), 121.3 (d, *J* = 18.2 Hz), 116.5 (d, *J* = 21.6 Hz), 82.1, 28.3.

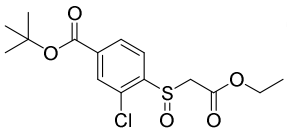
***tert*-Butyl 3-chloro-4-((2-ethoxy-2-oxoethyl)thio)benzoate (74)**



The title compound was synthesized using ethyl 2-mercaptoacetate (1.21 g, 10.1 mmol, 2 eq.) and *tert*-butyl 3-chloro-4-fluorobenzoate (1.16 g, 5.04 mmol, 1eq.) according to general procedure D in a yield of 1.62 g (4.60 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.8 Hz, 1H), 7.83 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 2H), 1.58 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 164.4, 140.6, 132.2, 130.6, 130.5, 128.2, 126.6, 81.8, 62.2, 34.5,

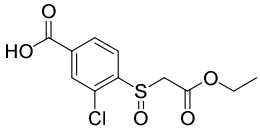
28.3, 14.2.

***tert*-Butyl 3-chloro-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoate (75)**



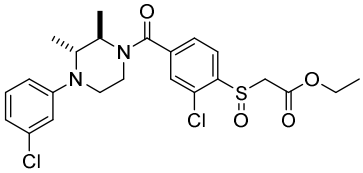
The title compound was synthesized using *tert*-butyl 3-chloro-4-((2-ethoxy-2-oxoethyl)thio)benzoate (140 mg, 0.42 mmol, 1.00 eq.) according to general procedure E in a yield of 147 mg (0.42 mmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.1 Hz, 1H), 8.06 – 7.92 (m, 2H), 4.29 – 4.18 (m, 2H), 4.03 (d, *J* = 13.1 Hz, 1H), 3.69 (d, *J* = 13.8 Hz, 1H), 1.61 (s, 9H), 1.26 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.5, 163.6, 145.2, 136.5, 130.8, 130.1, 128.8, 126.5, 82.7, 62.4, 58.1, 28.2, 14.2.

3-Chloro-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (76)



The title compound was synthesized using *tert*-butyl 3-chloro-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoate (1.39 g, 4.00 mmol, 1 eq.) according to general procedure F in a yield of 1.04 g (3.59 mmol, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.07 (d, *J* = 1.5, 1H), 7.99 (d, *J* = 8.1, 1H), 4.26 – 4.14 (m, 2H), 4.04 (d, *J* = 14.0 Hz, 1H), 3.72 (d, *J* = 14.0 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 164.5, 145.4, 135.0, 131.2, 130.2, 129.3, 126.7, 62.5, 58.0, 14.1.

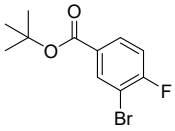
(±) Ethyl 2-((2-chloro-4-(4-(3-chlorophenyl)-*trans*-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)acetate (±43)



The title compound was synthesized using (±) *trans*-1-(3-chlorophenyl)-2,3-dimethylpiperazine (23.2 mg, 0.10 µmol, 1 eq.), 3-chloro-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (30 mg, 0.10 mmol, 1 eq.), HATU (39.2 mg, 0.10 mmol, 1.00 eq.) and DiPEA (31 mg, 0.30 mmol, 3 eq.) according to general procedure H in a yield of 38.3 mg (77.3 µmol, 75 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.54 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.51 – 7.42 (m, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.83 – 6.78 (m, 2H), 6.70 (d, *J* = 8.4 Hz, 1H), 4.80 (t, *J* = 6.7 Hz, 1H), 4.62 (s, 1H), 4.29 – 4.17 (m, 2H), 4.04 (dd, *J* = 14.1, 1.7 Hz, 1H), 3.87 (d, *J* = 7.0 Hz, 1H), 3.69 (dd, *J* = 14.0, 1.2 Hz, 1H), 3.67 – 3.60 (m, 1H), 3.57 – 3.49 (m, 1H), 3.37 – 3.06 (m, 3H), 1.52 – 1.44 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.16 – 097 (m, 3H). ^{13}C NMR (126 MHz,

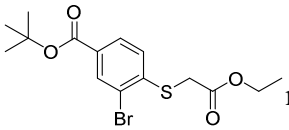
$CDCl_3$) δ 168.8, 168.3, 164.5, 151.3, 142.4, 140.5, 135.3, 130.8, 130.4, 128.4, 127.7, 127.1, 126.3, 125.8, 119.5, 116.3, 114.3, 62.5, 58.4, 56.2, 55.6, 49.8, 42.4, 41.3, 40.5, 36.6, 17.8, 16.8, 14.2, 12.8, 12.6. HRMS: Calculated for $[C_{23}H_{27}Cl_2N_2O_4S + H]^+$ = 497.1063, found = 497.1065.

***tert*-Butyl 3-bromo-4-fluorobenzoate (77)**



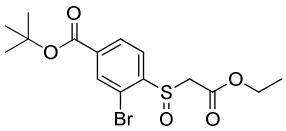
The title compound was synthesized using 3-bromo-4-fluorobenzoic acid (212 mg, 1 mmol, 1 eq.) according to general procedure C in a yield of 228 mg (0.83 mmol, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 6.7, 2.0 Hz, 1H), 8.04 – 7.81 (m, 1H), 7.13 (t, *J* = 8.4 Hz, 1H), 1.58 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.10, 161.38 (d, *J* = 247.8 Hz), 134.84, 130.37 (d, *J* = 8.4 Hz), 129.38 (d, *J* = 3.4 Hz), 115.93 (d, *J* = 22.8 Hz), 108.70 (d, *J* = 21.6 Hz), 81.43, 27.86.

***tert*-Butyl 3-bromo-4-((2-ethoxy-2-oxoethyl)thio)benzoate (78)**



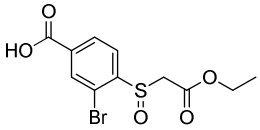
The title compound was synthesized using ethyl 2-mercaptoacetate (36 mg, 0.30 mmol, 1.1 eq.) and *tert*-butyl 3-bromo-4-fluorobenzoate (100 mg, 0.27 mmol, 1eq.) according to procedure D in a yield of 34 mg (0.09 mmol, 34%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, *J* = 1.8 Hz, 1H), 7.90 (dt, *J* = 8.3, 4.3 Hz, 1H), 7.37 – 7.20 (m, 1H), 4.31 – 4.10 (m, 2H), 3.76 (s, 2H), 1.61 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.58, 164.09, 142.52, 133.63, 130.40, 128.67, 126.12, 121.48, 81.58, 62.02, 34.90, 28.14, 13.99.

***tert*-Butyl 3-bromo-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoate (79)**



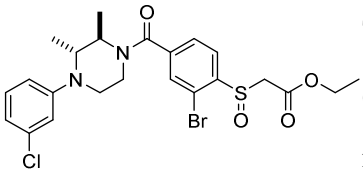
The title compound was synthesized *tert*-butyl 3-bromo-4-((2-ethoxy-2-oxoethyl)thio)benzoate (110 mg, 0.29 mmol, 1.00 eq.) according to general procedure E in a yield of 92 mg (0.23 mmol, 81%.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 7.4, 1.2 Hz, 2H), 7.98 (d, *J* = 8.6 Hz, 1H), 4.22 (m, 2H), 4.07 (d, *J* = 13.8 Hz, 1H), 3.69 (d, *J* = 13.8 Hz, 1H), 1.61 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.45, 163.31, 146.81, 136.39, 133.80, 129.24, 126.75, 118.32, 82.58, 62.32, 58.24, 28.07, 14.11.

3-Bromo-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (80)



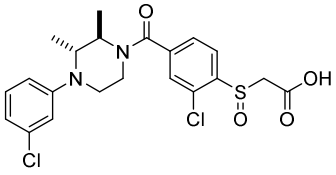
The title compound was synthesized using *tert*-butyl 3-bromo-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoate (167 mg, 0.43 mmol, 1 eq.) according to general procedure F in a yield of 60 mg (0.18 mmol, 43 %). ^{1}H NMR (300 MHz, Methanol-*d*4) δ 8.32 – 8.12 (m, 2H), 7.96 (d, *J* = 8.5 Hz, 1H), 4.22 – 4.18(m, 3H), 3.86 (d, *J* = 14.3 Hz, 1H), 1.31 – 1.10 (m, 3H). ^{13}C NMR (75 MHz, Methanol-*d*4) δ 165.64, 164.61, 146.54, 135.50, 133.81, 129.35, 126.54, 118.38, 61.85, 57.72, 12.98.

(±) Ethyl 2-((2-bromo-4-(4-(3-chlorophenyl)-*trans*-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)acetate (±44)



The title compound was synthesized using 3-bromo-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (50.0 mg, 0.150 mmol, 1eq.), (±)-1-(3-chlorophenyl)-trans-2,3-dimethylpiperazine (33.6 mg, 0.150 mmol, 1 eq.), HATU (85.0 mg, 0.23 mmol, 1.5 eq.) and DiPEA (58.0 mg, 0.450 mmol) according to general procedure H in a yield of 68.4 mg (0.126 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 1.2 Hz, 1H), 7.62 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.19 (t, *J* = 8.2 Hz, 1H), 6.83 (dd, *J* = 8.1, 1.2 Hz, 2H), 6.73 (d, *J* = 9.0 Hz, 1H), 4.93 – 4.53 (m, 1H), 4.26 (qd, *J* = 7.1, 1.4 Hz, 2H), 4.10 (dd, *J* = 14.1, 0.8 Hz, 1H), 3.97 – 3.02 (m, 6H), 1.51 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.18 – 0.99 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.43, 158.30, 151.18, 143.91, 140.39, 135.19, 131.26, 130.29, 127.30, 126.73, 119.48, 119.26, 116.19, 114.20, 62.50, 58.46, 56.08, 49.83, 40.37, 36.62, 17.73, 14.10, 12.47.

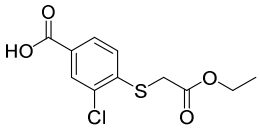
(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)acetic acid (±45)



To a solution of (±) ethyl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)acetate (180 mg, 0.36 mmol, 1 eq.) in MeOH (2mL) were added TEA (2mL) and water (2mL). The reaction mixture was stirred at room temperature overnight. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the mixture was acidified with 3M HCl solution to pH 2, extracted with EtOAc, dried ($MgSO_4$), filtered and

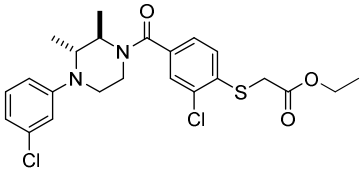
concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/DCM, 1-5%) to afford the product (0.16 g, 0.35 mmol, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 1H), 7.63 – 7.43 (m, 2H), 7.17 (t, *J* = 8.3 Hz, 1H), 6.85 – 6.77 (m, 2H), 6.73 – 6.69 (m, 1H), 4.85 – 4.59 (m, 2H), 4.08 (dd, *J* = 14.2, 3.0 Hz, 1H), 3.92 – 3.49 (m, 4H), 3.36 – 3.11 (m, 2H), 1.54 – 1.44 (m, 3H), 1.15 – 0.98 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.17, 169.06, 151.35, 141.69, 140.54, 135.28, 130.87, 130.30, 128.51, 127.15, 126.01, 119.52, 116.25, 114.25, 57.76, 56.16, 49.88, 40.47, 36.69, 17.81, 12.84. HRMS: Calculated for $[C_{21}H_{22}Cl_2N_2O_4S + H]^+$ = 496.0750, found = 496.0746.

3-Chloro-4-((2-ethoxy-2-oxoethyl)thio)benzoate (**81**)



The title compound was synthesized using *tert*-butyl 3-chloro-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoate (62 mg, 0.19 mmol, 1 eq.) according to general procedure F in a yield of 51 mg (0.19 mmol, 92 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.95 (d, *J* = 8.3 Hz, 1H) , 7.37 (d, *J* = 8.2 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.34, 168.37, 142.67, 130.76, 128.58, 127.15, 125.87, 61.98, 34.03, 13.91.

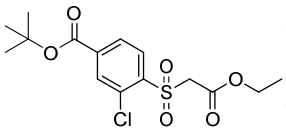
(±) Ethyl 2-((2-chloro-4-(4-(3-chlorophenyl)-*trans*-2,3-dimethylpiperazine-1-carbonyl)phenyl)thio)acetate (**±46**)



The title compound was synthesized using 3-chloro-4-((2-ethoxy-2-oxoethyl)thio)benzoic acid (33 mg, 0.12 mmol, 1 eq.), (±)1-(3-chlorophenyl)-trans-2,3-dimethylpiperazine (27 mg, 0.12 mmol, 1 eq.), HATU (68 mg, 0.18 mmol, 1.5 eq.) and DiPEA (46 mg, 0.36 mmol, 3 eq.) according to general procedure H in a yield of 11 mg (0.02 mmol, 19 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.36 (m, 2H), 7.34 – 7.27 (m, 1H), 7.17 (t, *J* = 8.3 Hz, 1H), 6.80 (d, *J* = 6.1 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 1H), 4.84 – 4.53 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 2H), 3.69 – 3.01 (m, 5H), 1.51 – 1.41 (m, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.06 (dd, *J* = 46.6, 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.52, 168.85, 151.39, 137.10, 135.16, 134.77, 133.25,130.25, 128.12, 128.87, 125.47, 119.18, 116.02, 114.05, 61.99, 56.06, 49.45, 40.43, 36.42, 34.69, 17.69, 14.13, 12.49. HRMS:

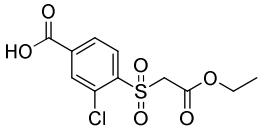
Calculated for $[C_{23}H_{26}Cl_2N_2O_3S + H]^+$ = 483.1084, found = 483.1079.

***tert*-Butyl 3-chloro-4-((2-ethoxy-2-oxoethyl)sulfonyl)benzoate (82)**



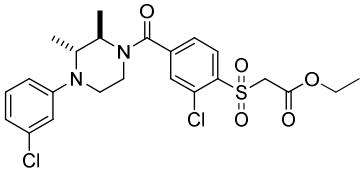
To a cooled (0ºC) solution of *tert*-butyl-3-chloro-4-((2-ethyoxy-2oxoethyl)sulfinyl)benzoate (70 mg, 0.21 mmol, 1 eq.) in MeOH (7mL) was added a solution of Oxone (390 mg, 0.64 mmol, 3 eq.) in H_2O (3.5mL). The reaction mixture was stirred at RT overnight. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the reaction mixture was extracted with DCM, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/pentane, 0-15%) to yield the product (65 mg, 0.18 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.2 Hz, 1H), 8.14 (d, *J* = 1.5 Hz, 1H), 8.05 (dd, *J* = 8.3, 1.6 Hz, 1H), 4.47 (s, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 1.61 (s, 9H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.97, 162.11, 139.35, 138.42, 132.84, 132.72, 132.25, 128.11, 83.23, 62.70, 58.74, 28.17, 13.96.

***tert*-Butyl 3-chloro-4-((2-ethoxy-2-oxoethyl)sulfonyl)benzoate (83)**



The title compound was synthesized using *tert*-butyl 3-chloro-4-((2-ethoxy-2-oxoethyl)sulfonyl)benzoate (65 mg, 0.18 mmol, 1 eq.) according to general procedure F in a yield of 50.2 mg (0.16 mmol, 91%). ^{1}H NMR (400 MHz, MeOD) δ 8.28 – 8.05 (m, 3H), 4.61 (s, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 1.08 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 165.24, 162.16, 139.79, 137.42, 132.58, 132.39, 131.98, 128.13, 61.91, 58.48, 12.67.

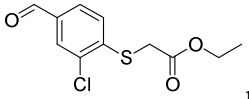
(±) Ethyl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfonyl)acetate (± 47)



The title compound was synthesized using *tert*-butyl 3-chloro-4-((2-ethoxy-2-oxoethyl)sulfonyl)benzoate (27 mg, 0.09 mmol, 1 eq.), (±)1-(3-chlorophenyl)-trans-2,3-dimethylpiperazine (20 mg, 0.09 mmol, 1 eq.), HATU (51 mg, 0.13 mmol, 1.5 eq.) and DiPEA (35 mg, 0.27 mmol, 3 eq.) according to general procedure H in a yield of 8 mg (0.02 mmol, 18 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.1 Hz, 1H), 7.67 – 7.42 (m, 2H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.86 – 6.78 (m, 2H), 6.72 (d, *J* = 8.5 Hz, 1H), 4.47 (s,

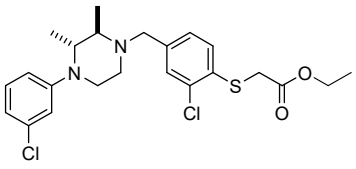
2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.95 – 3.00 (m, 6H), 1.49 (dd, *J* = 16.0, 6.7 Hz, 3H), 1.19 (td, *J* = 7.2, 3.0 Hz, 3H), 1.13 (d, *J* = 6.6 Hz, 2H), 1.02 (d, *J* = 6.5 Hz, 1H).

Ethyl 2-((2-chloro-4-formylphenyl)thio)acetate (84)



To a solution of 3-chloro-4-fluorobenzaldehyde (300 mg, 1.89 mmol, 1eq.) in DMF (5mL) were added K_2CO_3 (523 mg, 3.78 mmol, 2 eq.) and ethyl 2-mercaptoacetate (227 mg, 1.89 mmol, 2 eq.) and stirred at rt overnight. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the reaction mixture was extracted with DCM, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Et_2O /pentane, 20-35%) to yield the product (446 mg, 1.72 mmol, 91%,). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.84 (d, *J* = 1.8 Hz, 1H), 7.72 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.1, 168.5, 143.9, 134.6, 132.6, 130.1, 128.4, 126.3, 62.3, 34.2, 14.2.

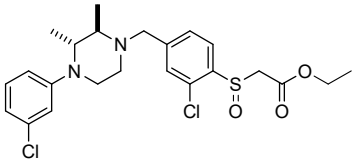
(±) **Ethyl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazin-1-yl)methyl)phenyl)thio)acetate (±85)**



To a solution of ethyl-2-((2-chloro-4-formylphenyl)thio)acetate (31.8 mg, 0.12 mmol, 1.2 eq.) in 1,2-dichloroethane (1.0 mL) was added (±)1-(3-chlorophenyl)- trans-2,3-dimethylpiperazine (23.0 mg, 0.10 mmol, 1 eq.) and the reaction mixture was stirred at rt for 30min. Then sodium triacetoxyborohydride (65.1 mg, 0.31 mmol, 3 eq.) was added and the reaction mixture was stirred at rt overnight. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the reaction mixture was extracted with DCM, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/pentane, 20%) to yield the product (19 mg, 0.04 mmol, 40 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 6.84 – 6.79 (m, 1H), 6.73 (t, *J* = 8.0 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.75 – 3.67 (m, 3H), 3.57 (q, *J* = 13.9 Hz, 2H), 3.27 – 3.09 (m, 2H), 2.91 – 2.81 (m, 1H), 2.75 (td, *J* = 11.4 Hz, 1H), 2.52 (d, *J* = 11.5 Hz, 1H), 1.27 (d, *J* =

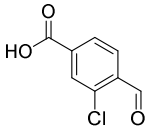
7.2 Hz, 3H), 1.24 – 1.19 (m, 3H), 1.15 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 152.1, 140.2, 135.1, 134.6, 132.3, 130.5, 130.1, 129.9, 127.6, 118.0, 115.5, 113.6, 61.8, 58.0, 56.7, 56.6, 44.9, 42.0, 35.6, 14.2, 13.0, 9.5.

(±) Ethyl 2-((2-chloro-4-((4-(3-chlorophenyl)-trans-2,3-dimethylpiperazin-1-yl)methyl)phenyl)sulfinyl)acetate (±48)



The title compound was synthesized using (±) ethyl 2-((2-chloro-4-((4-(3-chlorophenyl)-*trans*-2,3-dimethylpiperazin-1-yl)methyl)phenyl)thio)acetate (19 mg, 0.04 mmol, 1 eq.) according to general procedure E in a yield of 6.3 mg (0.01 mmol, 32 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.55 (ddd, *J* = 8.0, 3.0, 1.5 Hz, 1H), 7.49 (dd, *J* = 3.9, 1.5 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.80 (t, *J* = 2.2 Hz, 1H), 6.76 – 6.68 m, 2H), 4.26 – 4.18 (m, 2H), 4.02 (dd, *J* = 13.7, 2.8 Hz, 1H), 3.75 – 3.66 (m, 2H), 3.61 (d, *J* = 14.3 Hz, 1H), 3.24 – 3.19 (m, 1H), 3.15 (dd, *J* = 4.0, 1.5 Hz, 1H), 2.85 (q, *J* = 6.4 Hz, 1H), 2.78 (td, *J* = 11.5, 4.2 Hz, 1H), 2.51 (dt, *J* = 11.5, 1.8 Hz, 1H), 1.27 (td, *J* = 7.2, 1.0 Hz, 3H), 1.22 (dd, *J* = 6.6, 1.4 Hz, 3H), 1.17 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 152.1, 145.6, 139.3, 135.2, 130.2, 130.2, 129.8, 128.2, 126.4, 118.2, 115.6, 113.7, 62.3, 58.7, 58.2, 57.0, 56.8, 45.0, 42.0, 14.3, 13.0, 9.6. HRMS: Calculated for $[C_{23}H_{28}Cl_2N_2O_3S + H]^+$ = 483.1270, found = 483.1273.

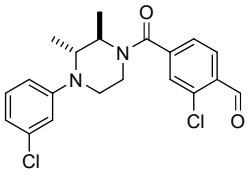
3-Chloro-4-formylbenzoic acid (86)



To a cooled (-78 °C) solution of 4-bromo-3-chlorobenzoic acid (300 mg, 1.27 mmol, 1.00 eq.) in abs. THF (5.0 mL) was added Turbo-GRIGNARD (1.3 M in THF, 2.94 ml, 3.82 mmol, 3.00 eq.). The temperature was raised to 0 °C after 10 min and the reaction mixture was stirred at 0 °C for 1 h. Subsequently DMF (6.37 ml, 0.49 mmol, 5.00 eq.) was added, the reaction mixture warmed up to room temperature and stirred further for 1.5 h. The reaction was quenched by addition of sat. aq. NH_4Cl, followed by washing with EtOAc. Then the pH of the aqueous layer was adjusted with aq. 1 N HCl and extracted with EtOAc. The combined organic layers were neutralized with sat. aq. $NaHCO_3$, washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The title compound was obtained without any further purification (165 mg, 0.89 mmol, 70%). ^{1}H NMR (500 MHz, DMSO-*d*6) δ

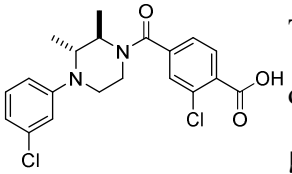
10.38 (s, 1H), 8.07 – 8.00 (m, 2H), 8.01 – 7.95 (m, 1H). ^{13}C NMR (126 MHz, DMSO-*d*6) δ 189.6, 165.4, 136.8, 136.1, 134.8, 131.1, 130.1, 128.3.

(±) 2-Chloro-4-(4-(3-chlorophenyl)-*trans*-2,3-dimethylpiperazine-1-carbonyl)benzaldehyde (±87)



The title compound was synthesized using 3-chloro-4-formylbenzoic acid (65.0 mg, 35.0 mmol, 1.00 eq.), (±) 1-(3-chlorophenyl)-trans-2,3-dimethylpiperazine (79.0 mg, 0.35 mmol, 1.00 eq.), DiPEA (137 mg, 1.06 mmol, 3.00 eq.) and HATU (161 mg, 0.42 mmol, 1.20 eq.) according to procedure H in a yield of 69.0 mg (0.18 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 – 10.45 (m, 1H), 7.97 (d, *J* = 7.9 Hz, 1H), 7.49 (dd, *J* = 11.0, 1.5 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.18 – 7.12 (m, 1H), 6.82 – 6.76 (m, 3H), 4.48 – 4.78 (m, 1H), 4.04 – 3.74 (m, 1H), 3.72 – 3.01 (m, 4H), 1.48 (d, *J* = 6.8 Hz, 1H), 1.45 (d, *J* = 6.8 Hz, 2H), 1.11 (d, *J* = 6.6 Hz, 1H), 1.00 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.9, 168.6, 168.2, 151.3, 142.7, 142.6, 138.4, 135.2, 132.9, 130.3, 129.9, 129.8, 129.1, 128.7, 125.6, 125.2, 119.4, 116.2, 114.2, 114.1, 60.4, 56.1, 55.4, 49.5, 42.2, 41.2, 40.4, 36.4, 17.7, 16.7, 14.2, 12.8, 12.5.

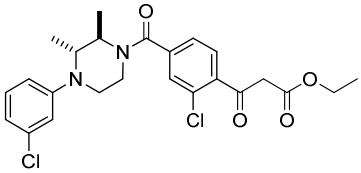
(±) 2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)benzoic acid (±88)



To a solution of (±) 2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)benzaldehyde (69.0 mg, 176 µmol, 1.00 eq.) in DMF (1.0 ml) was added oxone (108 mg, 176 µmol, 1.00 eq.) and the mixture was stirred at rt overnight. The reaction progress was monitored by TLC analysis. Upon full conversion of the starting materials, the reaction mixture was extracted with DCM, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/DCM, 2% - 5%) to yield the product (68.0 mg, 0.15 mmol, 50%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H, OH), 7.74 (dd, *J* = 8.0, 3.4 Hz, 1H), 7.39 (dd, *J* = 10.4, 1.5 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.17 – 7.10 (m, 1H), 6.80 – 6.74 (m, 2H), 6.71 – 6.65 (m, 1H), 4.75 (q, *J* = 6.9 Hz, 1H), 4.61 – 4.53 (m, 1H), 3.87 – 3.79 (m, 1H), 3.55 – 2.99 (m, 3H), 1.44 (d, *J* = 6.8 Hz, 1H), 1.44 (m, 2H), 1.08 (d, *J* = 6.7 Hz, 1H), 0.95 (d, *J* =

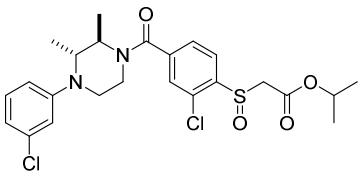
6.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 169.6, 169.1, 151.4, 138.6, 135.7, 132.7, 130.9, 130.3, 128.8, 128.4, 125.2, 124.5, 119.3, 116.1, 114.2, 69.7, 56.1, 55.4, 49.6, 42.3 , 41.3, 40.5, 36.5, 17.7, 16.7, 14.2, 12.8, 12.5.

(±) Ethyl 3-(2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)-3-oxopropanoate (±49)



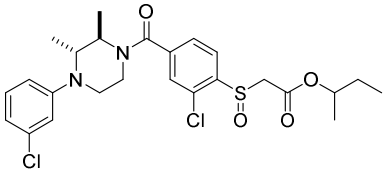
To a solution of (±) 2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)benzoic acid (12.0 mg, 29.0 µmol, 1.00 eq.) in dry THF (250 µL), carbonyldiimidazole (5.30 mg, 32.0 mmol, 1.10 eq.) was added and the reaction mixture was stirred at rt for 2 h. Then a mixture of ethyl potassium malonate (5.00 mg, 29.0 µmol, 1.00 eq.) [which had been prepared from ethyl hydrogen malonate (1 g) and KOH (0.4 g) in abs. ethyl alcohol 4 ml], anhydr. $MgCl_2$ (5.61 mg, 59.0 µmol, 2.00 eq.) and TEA (9.86 µl, 7.16 mg, 71.0 µmol, 2.40 eq.) were added. The reaction mixture was stirred further at rt for 24 h. After concentration under reduced pressure the obtained residue was resuspended in 2 M aq. HCl and extracted with DCM. The combined organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography (pentane/EtOAc, 3:1) resulted in the title compound as a colorless oil (0.82 mg, 1.72 µmol, 6%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 10.0, 7.9 Hz, 1H), 7.48 (d, *J* = 4.5 Hz, 1H), 7.35 (dd, *J* = 13.4, 7.9 Hz, 1H), 7.20 – 7.14 (m, 1H), 6.84 – 6.79 (m, 2H), 6.71 (dd, *J* = 9.1, 2.1 Hz, 1H), 5.59 – 4.71 (m, 1H), 4.29 (q, *J* = 7.1 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 1H), 4.04 (s, 2H), 3.92 – 3.09 (m, 5H), 1.47 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 2H), 1.07 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 169.4, 166.8, 151.4, 139.0, 138.8, 135.4, 132.9, 132.2, 130.5, 130.4, 119.6, 119.5, 116.3, 114.3, 94.0, 61.8, 60.9, 56.3, 49.2, 14.4, 14.2. HRMS: Calculated for $[C_{24}H_{28}Cl_2N_2O_4S + H]^+$ = 477.1342, found = 477.1346.

(±) Isopropyl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)acetate (±50)



The title compound was synthesized using (±) 2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)benzoic acid (30.0 mg, 64.0 µmol, 1.00 eq.), oxalyl chloride (2 M in DCM, 35.0 µl, 70.0 µmol, 1.10 eq.), 2-propanol (19.2 mg, 320 µmol, 5.00 eq.) and DiPEA (9.09 mg, 70.0 µmol, 1.10 eq.) according to general procedure G in a yield of 14.0 mg (27.5 µmol, 43 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.9 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.51 – 7.43 (m, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.84 – 6.79 (m, 2H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.08 – 5.14 (m, 1H), 4.86 – 4.58 (m, 1H), 4.04 (d, *J* = 14.1 Hz, 1H), 3.92 – 3.07 (m, 6H), 1.53 – 1.44 (m, 3H), 1.32 – 1.24 (m, 6H), 1.16 – 0.99 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 164.2, 151.4, 142.7, 140.6, 135.4, 130.4, 126.2, 119.6, 116.3, 114.3, 70.6, 58.8, 56.3, 55.5, 49.7, 42.4, 41.4, 40.6, 36.6, 21.9, 17.9, 16.8, 12.9, 12.6. HRMS: Calculated for $[C_{24}H_{28}Cl_2N_2O_4S + H]^+$ = 511.1220, found = 511.1227.

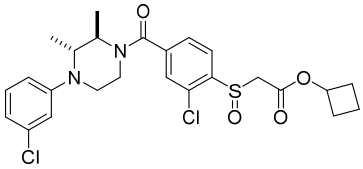
(±) *sec*-Butyl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)acetate (±51)



The title compound was synthesized using (±) 2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)benzoic acid (50.0 mg, 107 µmol, 1.00 eq.), oxalyl chloride (2 M in DCM, 80.0 µl, 160 µmol, 1.50 eq.), butan-2-ol (49.0 µl, 39.5 mg, 533 µmol, 5.00 eq.) and DiPEA (28.0 µl, 20.7 mg, 160 µmol, 1.50 eq.) according to general procedure G in a yield of 14.1 mg (26.8 µmol, 25 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.59 – 7.51 (m, 1H), 7.50 – 7.42 (m, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.85 – 6.77 (m, 2H), 6.70 (dd, *J* = 7.9, 3.2 Hz, 1H), 5.00 – 4.90 (m, 1H), 4.85 – 4.57 (m, 1H), 4.04 (d, *J* = 14.0 Hz, 1H), 3.92 – 3.07 (m, 5H), 1.70 – 1.53 (m, 3H), 1.53 – 1.43 (m, 3H), 1.30 – 1.21 (m, 3H), 1.16 – 0.99 (m, 2H), 0.97 – 0.88 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4, 164.3, 151.4, 142.8, 140.7, 135.3, 130.8, 130.4, 128.6, 127.9, 127.0, 126.4, 126.2, 125.9, 119.6, 116.3, 114.3, 75.2, 59.0, 58.8, 56.2, 55.5, 49.7, 42.4, 41.4, 40.5, 36.6, 28.8, 19.5, 17.9, 16.8, 12.9, 12.6, 9.7. HRMS: Calculated for $[C_{25}H_{30}Cl_2N_2O_4S + H]^+$ = 525.1376, found = 525.1385.

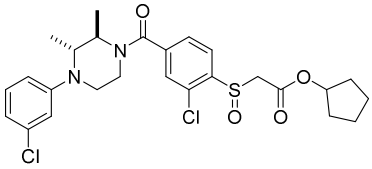
(±) Cyclobutyl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-

carbonyl)phenyl)sulfinyl)acetate (±52)



The title compound was synthesized using (±) 2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)benzoic acid (50.0 mg, 107 µmol, 1.00 eq.), oxalyl chloride (2 M in DCM, 80.0 µl, 160 µmol, 1.50 eq.), cyclobutanol (77 mg, 1.07 mmol, 10 eq.) and DiPEA (28.0 µl, 20.7 mg, 160 µmol, 1.50 eq.) according to general procedure G in a yield of 8mg (0.015 mmol, 14%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.40 (m, 2H), 7.18 (t, *J* = 8.1 Hz, 1H), 6.89 – 6.76 (m, 2H), 6.72 (d, *J* = 8.4 Hz, 1H), 5.06 (tt, *J* = 7.9, 7.1 Hz, 1H), 4.88 – 3.00 (m, 8H), 2.45 – 2.27 (m, 2H), 2.19 – 2.00 (m, 2H), 1.89 – 1.57 (m, 2H), 1.49 (d, *J* = 10.0 Hz, 3H), 1.20 – 0.86 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.03, 163.85, 151.33, 142.36, 140.47, 135.36, 130.95, 130.43, 128.36, 127.16, 125.85, 119.66, 116.37, 114.34, 70.27, 58.23, 56.27, 49.92, 40.54, 36.71, 30.37, 30.32, 18.42, 14.12, 12.61. HRMS: Calculated for $[C_{25}H_{28}Cl_2N_2O_4S + H]^+$ = 523.1220, found = 523.1218.

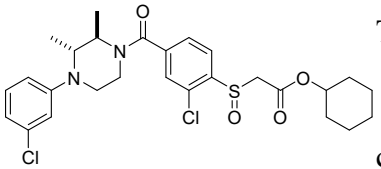
(±) Cyclopentyl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)acetate (±53)



The title compound was synthesized using (±) 2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)benzoic acid (50.0 mg, 107 µmol, 1.00 eq.), oxalyl chloride (2 M in DCM, 80.0 µl, 160 µmol, 1.50 eq.), cyclopentanol (92 mg, 1.07 mmol, 10 eq.) and DiPEA (28.0 µl, 20.7 mg, 160 µmol, 1.50 eq.) according to general procedure G in a yield of 12 mg (0.022 mmol, 21%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.41 (m, 2H), 7.18 (t, *J* = 8.1 Hz, 1H), 6.87 – 6.76 (m, 2H), 6.72 (d, *J* = 8.7 Hz, 1H), 5.29 – 5.19 (m, 1H), 5.12 – 3.05 (m, 8H), 1.87 (q, *J* = 6.9 Hz, 2H), 1.79 – 1.40 (m, 9H), 1.22 – 0.88 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.01, 164.34, 151.32, 140.35, 135.36, 130.95, 130.43, 128.58, 127.17, 126.39, 119.68, 116.38, 114.35, 79.90, 58.42, 56.28, 49.97, 40.53, 36.75, 32.84, 32.72, 23.81, 23.78, 17.89, 12.60. HRMS: Calculated for $[C_{26}H_{30}Cl_2N_2O_4S + H]^+$ = 537.1376, found = 537.1376.

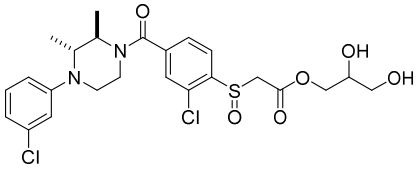
(±) Cyclohexyl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-

1-carbonyl)phenyl)sulfinyl)acetate (±54)



The title compound was synthesized using (±) 2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)benzoic acid (50.0 mg, 107 µmol, 1.00 eq.), oxalyl chloride (2 M in DCM, 80.0 µl, 160 µmol, 1.50 eq.), cyclohexanol (107 mg, 1.07 mmol, 10 eq.) and DiPEA (28.0 µl, 20.7 mg, 160 µmol, 1.50 eq.) according to general procedure G in a yield of 3 mg (0.005mmol, 5%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.62 – 7.43 (m, 2H), 7.18 (t, *J* = 8.1 Hz, 1H), 6.87 – 6.77 (m, 2H), 6.71 (d, *J* = 8.3 Hz, 1H), 4.88 (tt, *J* = 8.9, 3.9 Hz, 1H), 4.84 – 2.94 (m, 8H), 1.70 – 1.20 (m, 13H), 1.20 – 0.96 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.06, 163.57, 151.37, 142.76, 140.55, 134.94, 130.90, 130.40, 128.34, 127.08, 126.37, 119.62, 116.35, 114.32, 75.45, 58.72, 56.27, 49.78, 40.54, 36.65, 31.58, 25.34, 23.73, 17.89, 12.62. HRMS: Calculated for $[C_{27}H_{32}Cl_2N_2O_4S + H]^+$ = 551.1533, found = 551.1533.

(±) 2,3-Dihydroxypropyl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)acetate (±55)



The title compound was synthesized using (±) 2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)benzoic acid (50.0 mg, 107 µmol, 1.00 eq.), oxalyl chloride (2 M in DCM, 80.0 µl, 160 µmol, 1.50 eq.), glycerol (98 mg, 1.07 mmol, 10 eq.) and DiPEA (28.0 µl, 20.7 mg, 160 µmol, 1.50 eq.) according to general procedure G. This yielded the product(3mg, 0.006mmol, 5%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.87 (m, 1H), 7.60 – 7.42 (m, 2H), 7.18 (t, *J* = 8.1 Hz, 1H), 6.85 – 6.77 (m, 2H), 6.71 (d, *J* = 7.5 Hz, 1H), 4.87 – 3.05 (m, 13H), 1.95 (br, 2H), 1.50 (dd, *J* = 15.0, 6.7 Hz, 3H), 1.08 (m, 3H). HRMS: Calculated for $[C_{24}H_{28}Cl_2N_2O_6S + H]^+$ = 543.1118, found = 543.1117.

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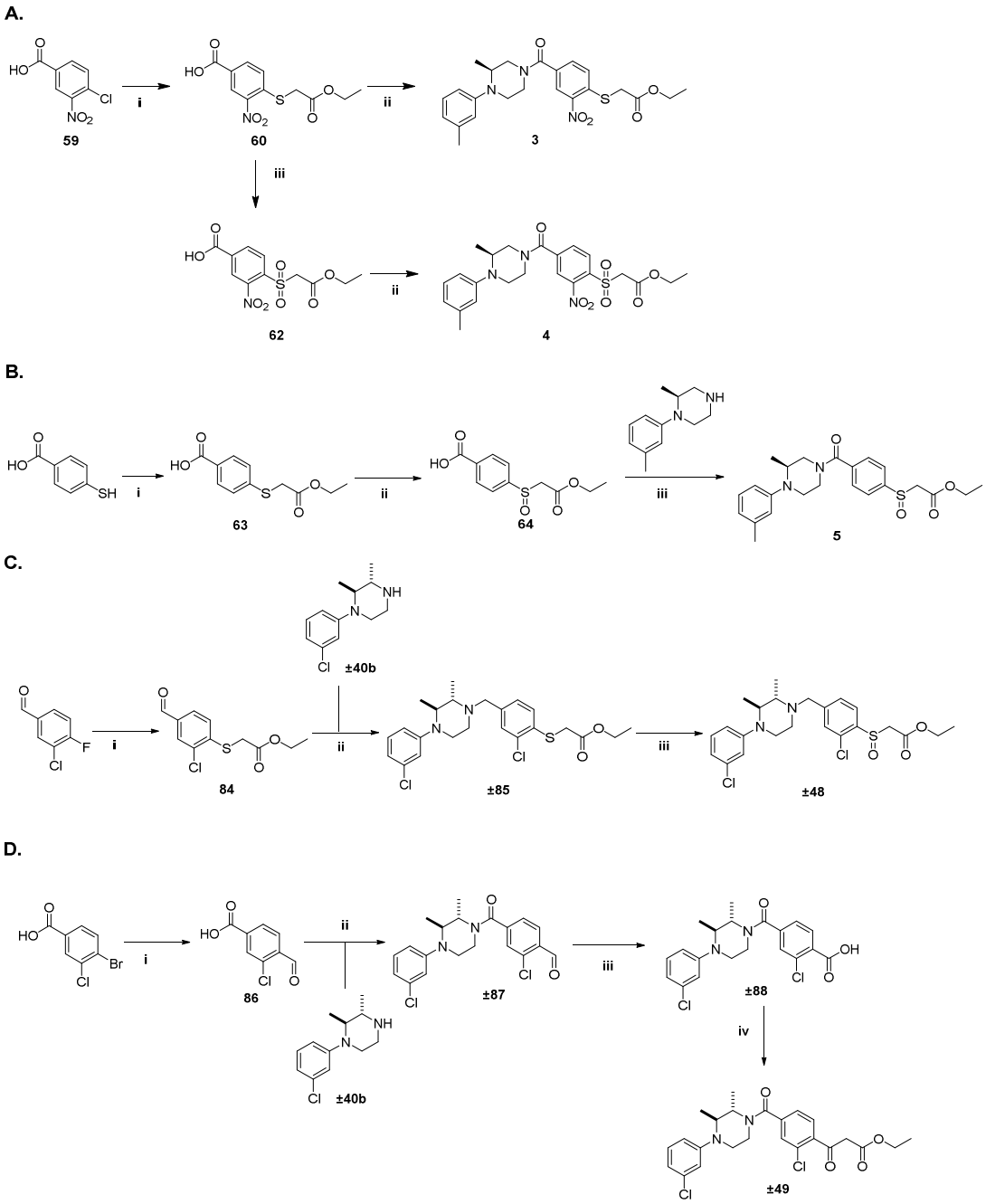
Supplementary Information



Scheme S1. (A) Synthesis route for compounds **3** and **4**. Reagents and conditions: i) 1-chloro-3-methylbenzene, sodium *tert*-butoxide, BINAP, $Pd(OAc)_2$, 1,4-dioxane, 85 °C. ii) TFA, DCM, iii) ethyl 2-mercaptoacetate, pyridine, 115 °C. iv) Oxone (1 eq), MeOH / H_2O. v) HATU, DiPEA, DCM. vi) Oxone (10 eq), MeOH / H_2O. (B) Synthesis route for compound **5**. Reagents and conditions: i) ethyl 2-bromoacetate, NaOH, H_2O. ii) Oxone (1 eq), MeOH / H_2O. iii) HATU, DiPEA, DCM. (C) Synthesis routes for compound **±48.** Reagents and conditions: i) ethyl 2-mercaptoacetate, K_2CO_3, ACN. ii) HATU, DiPEA, DCM. iii) oxone, MeOH / H_2O. (D) Synthesis routes for compound **±49**. iv) Turbo-Grignard, DMF, THF, -78 °C - RT. v) oxone, DMF. vi) carbonyldiimidazole, ethyl potassium malonate, $MgCl_2$, TEA, THF.