Discovery of reversible monoacylglycerol lipase inhibitors

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Chapter 4

Discovery of LEI-515 as a novel ultrapotent, reversible MAGL inhibitor with improved metabolic stability

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4.1 Introduction

A primary concern for medicinal chemists is to design molecules that not only show desired activity and selectivity, but also display suitable pharmacokinetic (PK) properties to have an appropriate duration of action. The primary PK properties are Volume of distribution (V_d (L/kg)) and Clearance (Cl (mL/min/kg)), which determine the *in vivo* half-life ($t_{1/2} = 0.7 \times V_d / Cl$ (h)) of a compound.[1] The V_d is not a real volume, but is a theoretical amount of fluid required to dissolve the compound to obtain the measured plasma concentration at the time of administration. It is an assessment of the compound's ability to distribute through the body. The V_d is an intrinsic property of the compound and determined to a large extent by the lipophilicity and acidity of a compound. Basic compounds have a high V_d, whereas acidic compounds have a low

V_d. Increasing the V_d will increase the half life of a compound. Clearance indicates the volume of blood that is cleared from the compound per unit of time. It is a first order process and not dependent on plasma concentration of the compound. It is an intrinsic property of the drug. Clearance is defined as the extraction ratio times the blood flow. Hepatic clearance is performed by metabolic enzymes in the liver and its maximum equals the liver blood flow. Increasing the metabolic stability of a compound reduces the hepatic clearance and increases its half life.

In the early phases of drug discovery, it is impossible for new chemical entities to be administered to humans, therefore, human PK predictions are made from *in vivo* and *in vitro* systems.[2] Since hepatic clearance is considered a major determinant for overall clearance for many compounds, metabolic stability studies using *in vitro* test systems are employed to assess and optimize the clearance of compounds. Metabolic stability is defined as the percentage of parent compound lost over time in the presence of a metabolically active test system.[3] Several types of systems are currently available, including recombinant enzymes, liver microsomes, liver S9 fractions and hepatocytes, to test the metabolic stability. A liver S9 fraction is usually the preferred test system. It consists of the 9000g supernatant of a liver homogenate preparation (Figure 1) and contains both Phase I and Phase II metabolic enzymes[4, 5]. Compared to hepatocytes the S9 fraction does not have an extra layer of complexity (*i.e.*, permeability across the hepatocyte cell membrane to gain access to the metabolizing enzymes). A metabolic stability assay using the S9 fraction provides the same quality of data in a more efficient, high throughput and cost-effective manner compared to intact hepatocytes assays.[6] The liver S9 system is therefore widely used as a primary *in vitro* screen to guide the optimization of the metabolic stability of compounds.[7] In Chapter 2, compound ± **1** has been described as highly potent and selective MAGL inhibitor. Here, the metabolic stability of compound ± **1** was evaluated and optimized.

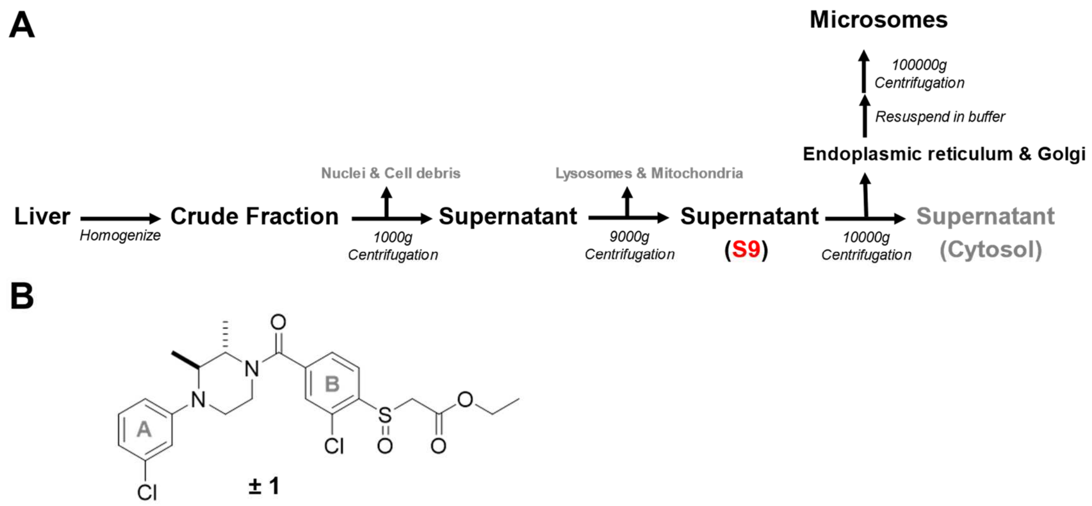
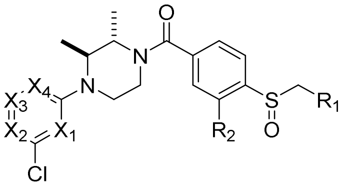


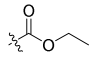
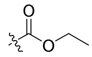
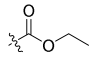
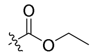
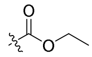
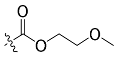
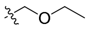
Figure 1. (**A**) Preparation of liver subcellular fractions. (**B**) Chemical structure of compound ± **1**.

4.2 Results and Discussion

The metabolic stability of compound ± **1** was evaluated by using a liver S9 stability assay. The compound was incubated with liver S9 fraction and the amount of remaining compound was determined with liquid chromatography–mass spectrometry/mass spectrometry (LC-MS/MS) in time-dependent manner. The results are presented as intrinsic clearance (Cl_{int}), which is calculated as V × 0.693 / $t_{1/2}$ (μL/min/mg) in which V is the volume of incubation in μL per mg protein and $t_{1/2}$ is the measured half life in min. Compound ± **1** showed a high Cl_{int} (> 346 μL/min/mg, Table 1), revealing that compound ± **1** is rapidly metabolized by the enzymes from the liver. This is not surprising, because compound has a high lipophilicity (calculated octanol-water partition coefficient (cLogP) of 4.9) and contains a potential metabolically labile ester functionality. Since it is well known that reducing lipophilicity may increase metabolic stability, several analogues (compound ± **2** - ± **6**) were synthesized in which phenyl ring A was replaced with different pyridyls (compound ± **2** - ± **5**) or in which the ethyl ester was substituted with a more polar group (compound ± **6**) (Synthetic scheme in SI). Of note, compounds (± **2** - ± **6**) showed high MAGL inhibitory activities (Table 1), while the cLogP was ten-fold lower compared to compound ± **1**. The metabolic stability of these compounds was, however, not improved (Table 1). This indicated that Cl_{int} of compound ± **1** cannot be improved by only reducing the lipophilicity and suggested that the ester was the main metabolic hot spot. To test this hypothesis, compound ± **7** was synthesized in which the ester moiety was replaced by a metabolically stable ether. Indeed, the intrinsic clearance dropped significantly from > 346 (μL/min/mg) to < 4 (μL/min/mg), indicating that the ester group was the primary site of metabolism. Of note, as expected compound ± **7** displayed no MAGL inhibitory activity anymore.

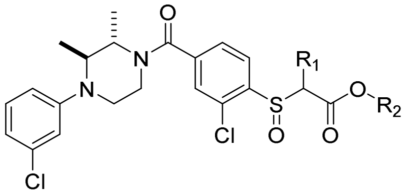
Table 1. pIC_{50} values, intrinsic clearance rate and physical-chemical parameters of compound ± **1** derivatives.

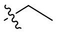
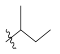
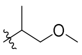
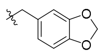


Entry	X1	X2	X3	X4	R1	R2	pIC_{50} ± SD	Cl_{int} (μL/min/mg)	cLogP	LipE
± 1	CH	CH	CH	CH		Cl	8.50 ± 0.10	> 346	4.93	3.57
± 2	CH	CH	N	CH		Cl	7.68 ± 0.14	-	3.89	3.79
± 3	CH	N	CH	CH		Cl	7.06 ± 0.13	-	3.89	3.17
± 4	N	CH	CH	CH		Cl	8.04 ± 0.11	> 346	3.89	4.15
± 5	CH	CH	CH	N		Cl	8.06 ± 0.12	-	3.89	4.17
± 6	CH	CH	CH	CH		Cl	8.04 ± 0.10	> 346	4.34	3.70
± 7	CH	CH	CH	CH		F	<5	3.6	4.40	-

Introducing steric hindrance has been previously successfully applied as a strategy to stabilize ester functionalities by preventing the attack of a catalytic serine of carboxylesterases on the carbonyl[8]. Here, this strategy was employed by introducing a methyl group on the alpha-carbon (compounds ± **8** and ± **9**) or next to the oxygen (compound ± **10**) (Table 2). While compounds (± **8** and ± **10)** showed slightly decreased MAGL inhibitory activity, they were still rapidly metabolized with a Cl_{int} > 346 (μL/min/mg). Introducing more bulky group, such as 3,4-methylenedioxybenzyl group in compound (± **11)**, which was previously used in an in vivo active MAGL inhibitor[9], also did not improve the metabolic stability (Table 2).

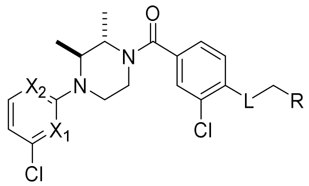
Table 2. pIC_{50} values, intrinsic clearance rate and physical-chemical parameters of compound ± **1** derivatives.

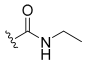
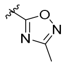
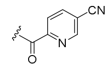
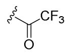
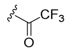
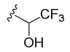
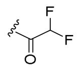


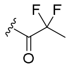
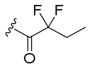
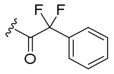
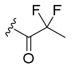
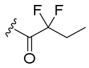
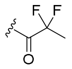
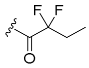
Entry	R_1	R_2	pIC_{50} ± SD	Cl_{int} (µL/min/mg)	cLogP	LipE
± **8**	CH_3		7.86 ± 0.12	> 346	5.23	2.63
± **9**	CH_3		8.35 ± 0.08	-	6.07	2.28
± **10**	H		7.95 ± 0.13	> 346	4.87	3.08
± **11**	H		8.21 ± 0.11	> 346	5.71	2.50

Since introducing steric hinderance did not improve metabolic stability, it was decided to replace the ester group with a bioisostere, such as an amide (± **12)**, an oxadiazole (± **13**) or an alpha-ketoheterocycle (see Chaper 3). See SI for their synthesis. Unfortunately, compounds ± **12** and ± **13** are not MAGL inhibitors and therefore not tested in the metabolic stability assay (Table 3). Previously, compound ± **14** was found to be a potent MAGL inhibitor. Gratifyingly, it showed an improved stability with a Cl_{int} of 169 (µL/min/mg). Thus, compound ± **14** provided the first indication that it was possible to increase the metabolic stability, while maintaining MAGL inhibitory activity at the same time. Encouraged by this result, other activated ketones were explored, such as trifluoromethyl (±**15** and ±**16**), difluoromethyl (± **18**) and difluoro alkyl groups (± **19** - ± **21**) (See SI for synthesis). Compound ± **16** with a trifluoromethylketone showed high MAGL inhibitory activity (pIC_{50} = 8.2) (Table 4) and was the most stable compound with a Cl_{int} of 19 µL/min/mg. Of note, if the carbonyl was reduced to the corresponding hydroxyl (± **17**), the compound was inactive ($pIC_{50} < 5$). This is in line with the hypothesis that the carbonyl acts as an electrophilic warhead for the nucleophilic serine of MAGL. Moreover, the sulfinyl group was not essential for the MAGL inhibitory activity, as compound ± **15** still showed reasonable inhibitory activity with a pIC_{50} = 7.8. Replacing the trifluoromethyl group to difluoromethyl (± **18)** increased the MAGL inhibitory activity by 3-fold, but slightly decreased the metabolic stability (Cl_{int} = 35 µL/min/mg). Substituting a fluorine with a phenyl group resulted in compound ± **21**, which decreased the potency 50-fold. Changing the trifluoromethyl group to difluoroethyl (± **19**) or difluoropropyl (± **20**), however, significantly improved the potency. Compound ± **20 (LEI-515)** is the most potent compound identified in this study with subnanomolar potency (pIC_{50} = 9.3). Importantly, both compounds displayed good metabolic stability (Cl_{int} = 27 and 30 µL/min/mg, respectively). Finally, compounds ± **22** to ± **25,** in which phenyl ring A was replaced with a pyridyl to reduce the lipophilicity, were synthesized. All four compounds showed high MAGL inhibitory activity and enhanced lipophilic efficiency, however, their metabolic stability was significantly decreased. This might be possibly attributed to the potential reactivity of the chloropyridine moieties.[10, 11]

Table 3. pIC_{50} values, intrinsic clearance rate and physical-chemical parameters of compound ± **1** derivatives.



Entry	**X1**	**X2**	**L**	**R**	**pIC_{50} ± SD**	**Cl_{int} (µL/min/mg)**	**cLogP**	**LipE**	**tPSA**
± 12	CH	CH	SO		<5	-	4.07	-	70
± 13	CH	CH	SO		<5	-	3.68	-	75
± 14	CH	CH	SO		8.00 ± 0.10	169	4.53	3.47	94
± 15	CH	CH	S		7.68 ± 0.13	33	5.87	1.81	41
± 16	CH	CH	SO		8.13 ± 0.08	19	4.69	3.44	58
± 17	CH	CH	SO		<5	-	4.74	-	61
± 18	CH	CH	SO		8.63 ± 0.06	35	4.43	4.20	58

± 19	CH	CH	SO		8.83 ± 0.05	27	4.96	3.87	58
± 20 (LEI-515)	CH	CH	SO		9.30 ± 0.04	30	5.49	3.81	58
± 21	CH	CH	SO		7.06 ± 0.21	-	6.44	0.62	58
± 22	CH	N	SO		9.07 ± 0.07	108	3.92	5.63	70
± 23	CH	N	SO		9.19 ± 0.06	126	4.45	4.74	70
± 24	N	CH	SO		8.47 ± 0.10	100	3.92	4.55	70
± 25	N	CH	SO		8.55 ± 0.09	95	4.45	4.10	70

4.3 Conclusion

In this chapter the optimization of the metabolic stability of *β*-sulfinyl esters as MAGL inhibitors is described. Three different strategies were employed to improve the metabolic stability. 1) reducing the lipophilicity; 2) applying steric hindrance and 3) replacing the ester group with bioisosteres. This led to the discovery of compound ± **20** (named LEI-515), in which the ethyl ester group of compound ± **1** was replaced by a difluoropropyl. LEI-515 is the most active, reversible MAGL inhibitor reported to date, showing subnanomolar potency (pIC_{50} = 9.3). Importantly, LEI-515 has improved metabolic stability (Cl_{int} = 30 μL/min/mg) compared to compound ± **1** (Cl_{int} > 346 μL/min/mg). Further biological and ADME profiling of LEI-515 will be described in Chapter 5.

4.4 Experimental 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 $Z' \geq 0.6$. 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 analysed in a non-linear dose-response analysis with variable slope.

Liver S9 stability assay. The rate of metabolism was assessed by incubation at 37 °C, pH 7.4 with mouse liver S9 fraction (1 mg protein/ mL) supplemented with 5 mM NADP, 25 mM G6P and 25 U/ml G6PD. The concentration of the initial substrate is 1 µM. Substrate depletion over a time course was measured by LC-MS/MS following protein precipitation. Amitryptilin (2.5 µM in ACN) was used as internal standard. The ln peak area ratio (compound peak area/internal standard peak area) is plotted against time and the gradient of the line determined.

Elimination rate constant (k) = (- gradient)

Half life ($t_{1/2}$, min) = 0.693 / k

V (µL / mg) = volume of incubation (µL) / protein in the incubation (mg)

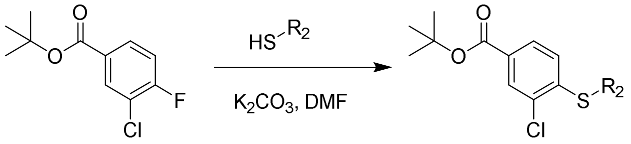
Intrinsic Clearance (CL_{int}, µL/min/mg) = V × 0.693 / $t_{1/2}$

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)). ^1H- 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 ^1H, δ 77.16 for ^{13}C, CD_3OD: δ 3.31 for ^1H, 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

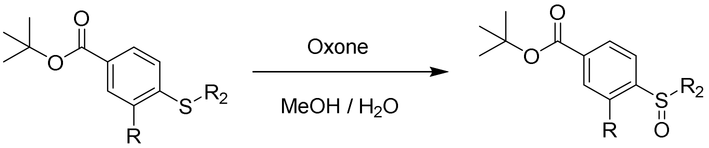
Scientific LTQ Orbitrap XL.

General procedure A



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

General procedure B

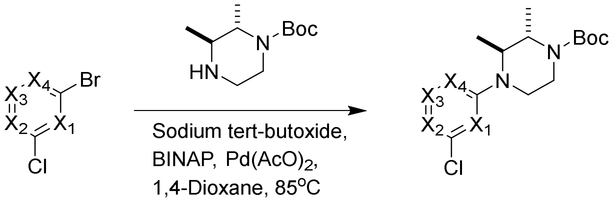


To a solution of appropriate sulfur (1 eq.) in MeOH was added oxone / water solution dropwise at 0 °C and the mixture was stirred at RT for 2h. The reaction progress was monitored by TLC analysis. Once completed, the mixture was diluted with EtOAc and washed with water. The organic layer was dried over anhydrous $MgSO_4$ and after filtration, the filtrated was concentrated under reduced pressure. The residue was purified by silica column chromatography.

General procedure C

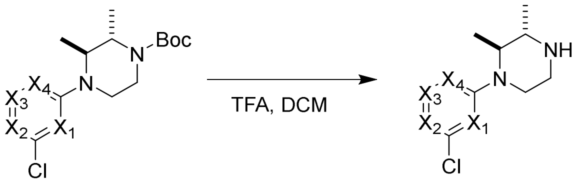
To a solution of appropriate *tert* butyl protected carboxylic acid in DCM was added TFA (20%) and the mixture was stirred at RT for 6 h. The reaction progress was monitored by TLC analysis. Once completed, the solvent was removed under reduced pressure and the residue was purified silica gel column chromatography.

General procedure D



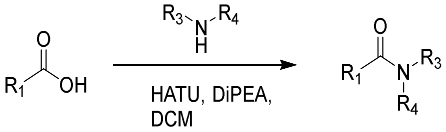
A mixture of appropriate bromobenzene (1eq.) and appropriate mono boc-protected piperazine (1eq.) in the presence of palladium diacetate (0.04eq.), BINAP (0.06eq.) and sodium tert-butoxide (1.5eq.) in degassed 1,4-dioxane was heated to 85 °C under nitrogen atmosphere overnight. The reaction progress was monitored by TLC analysis. Once completed, the reaction mixture was diluted with DCM, washed with water, dried over anhydrous $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the product.

General procedure E



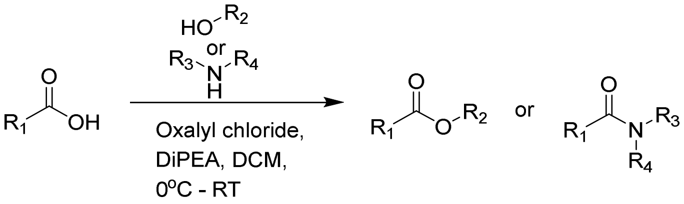
To a solution of appropriate tert-butyl phenylpiperazine-1-carboxylate in DCM was added TFA (20%, v/v) and the mixture was stirred at RT for 2h. The reaction progress was monitored by TLC. Once completed, then the mixture was diluted with DCM and washed with saturated aqueous $NaHCO_3$. The organic layers were collected and dried over anhydrous $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified silica gel column chromatography to give the product.

General procedure F



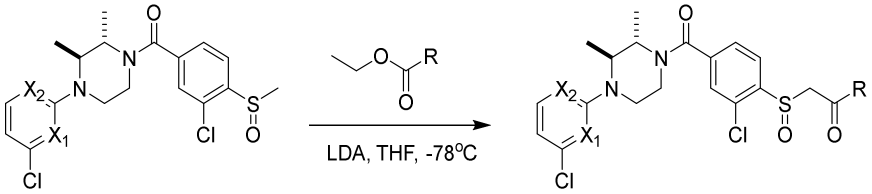
To a suspension or solution of appropriate benzoic acid (1eq.) in DCM was added HATU (1.5eq.) and DiPEA (3eq.) and the mixture was stirred for 1h. The appropriate phenylpiperazine(1eq.) was added and the mixture was stirred overnight. The reaction progress was monitored by TLC analysis. Once completed, the mixture was diluted with DCM, washed with water (1x), dried over anhydrous $MgSO_4$, filterated and concentrated under reduce pressure. The residue was purified by silica gel column chromatography or prep-HPLC to give the product.

General procedure G



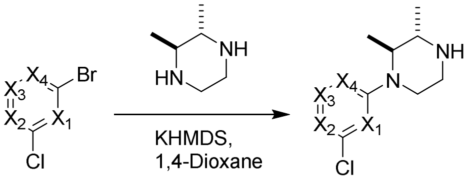
To a solution of appropriate carboxylic acid (1eq.) in anhydrous DCM was cooled down to 0 °C with an ice bath. Then, two drops of DMF and oxalyl chloride (1.2 eq.) were added and the mixture was allowed to warm to room temperature and continuously stirred for 2h. The reaction progress was monitored by TLC analysis. Once completed, the mixture was added to a solution of appropriate alcohol or amine (3eq.) and DiPEA (3eq.) in a dropwise manner at 0 °C. Then, the reaction mixture was stirred at room temperature overnight and diluted with DCM, washed with water (1x), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by HPLC-MS to give the product.

General procedure H



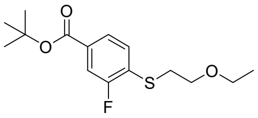
To a solution of appropriate methyl sulfoxide (1 eq.) in anhydrous THF was added LDA (2 eq.) at -78 °C and the reaction mixture was stirred for 30 min before the appropriate ester (10 eq.) was added. The reaction progress was monitored by TLC analysis. Once completed, the mixture was quenched with NH_4Cl solution, extracted with DCM and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography or prep-HPLC.

General procedure I



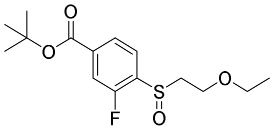
To a solution of appropriate piperazine (1 eq.) and bromochloropyridine (1 eq.) in anhydrous 1,4-dioxane was added KHMDS (1.5 eq.) and the mixture was stirred overnight at 100 °C or RT. The reaction progress was monitored by TLC analysis. Once completed, the reaction mixture was diluted with DCM, washed with water and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography.

***tert*-Butyl 4-((2-ethoxyethyl)thio)-3-fluorobenzoate (7a)**



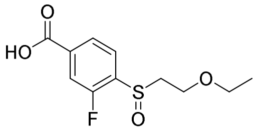
To a solution of tert-butyl 3,4-difluorobenzoate (191mg, 0.89mmol, 1eq.) in 5ml DMF was added NaHS (50mg, 0.89mmol, 1eq.), K_2CO_3 (370mg, 0.89mmol, 1eq.) and 1-chloro-2-ethoxyethane(97mg, 0.89mmol, 1eq.) and the mixture was stirred at 65 °C overnight under nitrogen. The reaction progress was monitored with TLC analysis. Once completed, the reaction mixture was diluted with diethyl ether, washed with water and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Diethyl ether/pentane, 5-25%) to give the product (130mg, 0.43mmol, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 8.1, 1.8 Hz, 1H), 7.61 (dd, J = 10.5, 1.7 Hz, 1H), 7.39 – 7.34 (m, 1H), 3.65 (t, J = 6.7 Hz, 2H), 3.51 (q, J = 7.0 Hz, 2H), 3.17 (t, J = 6.7 Hz, 2H), 1.59 (s, 9H), 1.19 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ164.33, 159.91 (d, J = 245.1 Hz), 131.22 (d, J = 7.0 Hz), 129.76 (d, J = 17.4 Hz), 128.75, 125.37 (d, J = 3.3 Hz), 116.05 (d, J = 23.7 Hz), 81.52, 68.78, 66.55, 31.76, 28.13, 15.12.

***tert*-Butyl 4-((2-ethoxyethyl)sulfinyl)-3-fluorobenzoate** (**7b**)



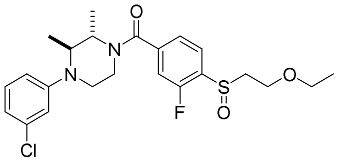
The title compound was synthesized using tert-butyl 4-((2-ethoxyethyl)thio)-3-fluorobenzoate (130mg, 0.43mmol, 1eq.) according to procedure B. This yielded the product (**7a**) (97mg, 0.31mmol, 71%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.99 (dd, J = 8.1, 1.5 Hz, 1H), 7.90 (dd, J = 8.1, 6.6 Hz, 1H), 7.71 (dd, J = 10.1, 1.4 Hz, 1H), 3.92 (dddd, J = 10.7, 8.6, 4.2, 0.8 Hz, 1H), 3.79 (dt, J = 10.4, 5.0 Hz, 1H), 3.50 (qq, J = 9.3, 7.0 Hz, 2H), 3.35 – 3.23 (m, 1H), 3.03 (dt, J = 13.5, 4.6 Hz, 1H), 1.61 (s, 9H), 1.15 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 163.61, 158.42, 155.96, 136.55, 135.96, 125.83, 116.57, 82.31, 66.66, 62.18, 55.10, 28.07, 14.93.

4-((2-Ethoxyethyl)sulfinyl)-3-fluorobenzoic acid (**7c**)



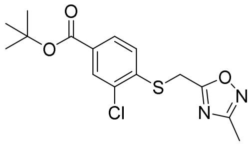
The title compound was synthesized using *tert*-butyl 4-((2-ethoxyethyl)sulfinyl)-3-fluorobenzoate (**7b**) (97mg, 0.31mmol, 1eq.) according to procedure C. This yielded the product (74mg, 0.28mmol, 93%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 10.96 (br, 1H), 8.12 (dd, J = 8.1, 1.4 Hz, 1H), 7.99 (dd, J = 8.1, 6.6 Hz, 1H), 7.83 (dd, J = 9.8, 1.5 Hz, 1H), 4.15 – 3.74 (m, 2H), 3.66 – 3.33 (m, 3H), 3.19 (ddd, J = 13.5, 4.9, 3.8 Hz, 1H), 1.13 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 168.19, 157.39 (d, J = 248.4 Hz), 136.16, 134.75, 126.86 (d, J = 3.2 Hz), 126.40 (d, J = 2.2 Hz), 117.18 (d, J = 22.2 Hz), 66.83, 62.12, 54.80, 14.92.

(±) (4-(3-Chlorophenyl)-trans-2,3-dimethylpiperazin-1-yl)(4-((2-ethoxyethyl)sulfinyl)-3-fluorophenyl)methanone (7)



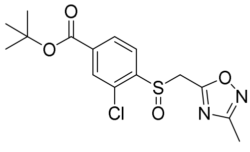
The title compound was synthesized using 4-((2-ethoxyethyl)sulfinyl)-3-fluorobenzoic acid (**7c**) (30mg, 0.115mmol, 1eq.) according to procedure F. This yielded the product (10mg, 0.021mmol, 19%).

***tert*-Butyl 3-chloro-4-(((3-methyl-1,2,4-oxadiazol-5-yl)methyl)sulfinyl)benzoate** (**13a**)



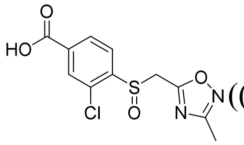
To a solution of *tert*-butyl 3-chloro-4-fluorobenzoate (200 mg, 0.867 mmol, 1eq.), NaHS (97 mg, 1.73 mmol, 2eq.) and 5-(chloromethyl)-3-methyl-1,2,4-oxadiazole (115 mg, 0.867 mmol, 1eq.) were dissolved in DMF (2 ml). The mixture was allowed to stir for 17 h. Then reaction was monitored by TLC analysis. Once complete, the mixture was diluted with DCM and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was further purified by column chromatography (0-50% Et_2O in pentane). This yielded the product (65.5 mg, 0.192 mmol, 22%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.8 Hz, 1H), 7.86 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 4.34 (s, 2H), 2.39 (s, 3H), 1.60 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.18, 167.59, 164.03, 138.61, 133.12, 131.46, 130.56, 128.27 (d, *J* = 9.3 Hz), 127.88, 81.87, 28.13, 26.82, 11.59.

tert-Butyl 3-chloro-4-(((3-methyl-1,2,4-oxadiazol-5-yl)methyl)sulfinyl)benzoate (13b)



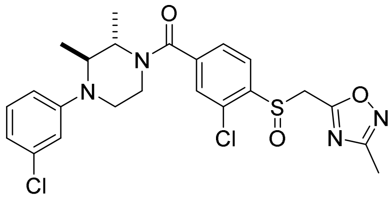
The title compound was synthesized using *tert*-butyl 3-chloro-4-(((3-methyl-1,2,4-oxadiazol-5-yl)methyl)sulfinyl) benzoate (**13a**) (65.0 mg, 0.191 mmol, 1eq.) according to procedure B. This yielded the product (71.1 mg, 0.199 mmol, quantitative). ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.01 (d, *J* = 1.3 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 4.47 (dd, *J* = 66.0, 13.8 Hz, 2H), 2.34 (s, 3H), 1.59 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.65, 167.81, 163.34, 144.02, 136.82, 130.89, 130.19, 128.82, 126.40, 82.78, 49.80, 28.15, 11.61.

3-Chloro-4-(((3-methyl-1,2,4-oxadiazol-5-yl)methyl)sulfinyl)benzoic acid (13c)



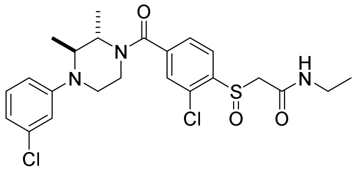
The title compound was synthesized using *tert*-butyl 3-chloro-4-(((3-methyl-1,2,4-oxadiazol-5-yl)methyl)sulfinyl) benzoate (**13b**) (68 mg, 0.191 mmol, 1eq.) according to procedure C. This yielded the product (47 mg, 0.156 mmol, 82%). ^1H NMR (400 MHz, Methanol-*d*4) δ 8.16 – 8.04 (dd, *J* = 10.2, 2.1 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 1H), 4.73 (dd, *J* = 69.2, 14.2 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, Methanol-*d*4) δ 171.62, 168.89, 167.08, 145.37, 137.13, 132.00, 131.67, 130.03, 127.52, 50.26, 11.19.

(±)- (3-Chloro-4-(((3-methyl-1,2,4-oxadiazol-5-yl)methyl)sulfinyl)phenyl)(-4-(3-chlorophenyl)-trans-2,3-dimethylpiperazin-1-yl)methanone (13)



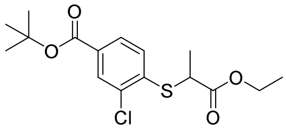
The title compound was synthesized using 3-chloro-4-(((3-methyl-1,2,4-oxadiazol-5-yl)methyl)sulfinyl)benzoic acid (**13c**) (45.0 mg, 0.150 mmol, 1eq.) according to procedure F. This yielded the product (61.8 mg, 0.122 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 6.8 Hz, 1H), 7.48 (d, *J* = 12.7 Hz, 2H), 7.17 (t, *J* = 8.1 Hz, 1H), 6.81 (d, *J* = 7.0 Hz, 2H), 6.71 (d, *J* = 9.2 Hz, 1H), 4.85 – 4.38 (m, 3H), 3.92 – 3.02 (m, 5H), 2.37 (d, *J* = 3.4 Hz, 3H), 1.48 (d, *J* = 4.7 Hz, 3H), 1.06 (d, *J* = 43.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.68, 168.76, 167.82, 151.28, 141.28, 140.85, 135.29, 131.02, 130.38, 128.31, 126.81, 125.87, 119.60, 116.31, 114.28, 56.19, 55.67, 49.72, 40.48, 36.66, 17.80, 12.47, 11.55. LC-MS, m/z: calculated for $C_{23}H_{24}Cl_2N_4O_3S$, 506.09; found 507.29 ([M + H$^+$])

(±) 2-((2-Chloro-4-(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-N-ethylacetamide (12)



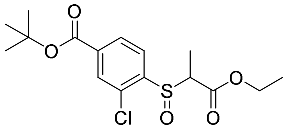
The title compound was synthesized using (±) 2-((2-chloro-4-(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)propanoic acid (0.16 g, 0.34 mmol, 1 eq.) according to procedure G. This yielded the product (1.5 mg, 3.0 µmol, 2%). HRMS: Calculated for $[C_{23}H_{27}Cl_2N_3O_3S + H]^+ = 496.1223$, found = 496.1220.

tert-Butyl 3-chloro-4-((1-ethoxy-1-oxopropan-2-yl)thio)benzoate (8a)



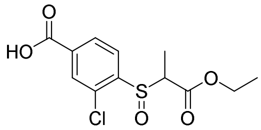
The title compound was synthesized using *tert*-butyl 3-chloro-4-fluorobenzoate (0.270 g, 1.18 mmol, 1.2 eq.) and ethyl 2-mercaptopropanoate (0.13 ml, 0.98 mmol, 1 eq.) according to procedure A. This yielded the product (0.27 g, 0.78 mmol, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 4.22 – 4.10 (m, 2H), 4.07 – 3.97 (m, 1H), 1.59 (m, 12H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.99, 164.21, 139.65, 133.70, 131.23, 130.49, 129.45, 127.94, 81.76, 61.69, 43.25, 28.17, 17.18, 14.11.

tert-Butyl 3-chloro-4-((1-ethoxy-1-oxopropan-2-yl)sulfinyl)benzoate (8b)



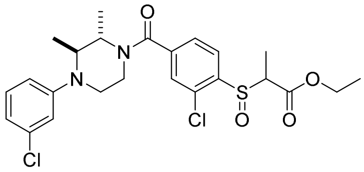
The title compound was synthesized using *tert*-butyl 3-chloro-4-((1-ethoxy-1-oxopropan-2-yl) thiol)benzoate (**8a**) (0.13 g, 0.38 mmol, 1 eq.) according to procedure B. This yielded the product (0.13 g, 0.35 mmol, 92%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.11 (dd, J = 8.2, 1.5 Hz, 1H), 8.00 (d, J = 1.6 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 4.31 (q, J = 8 Hz, 2H), 3.91 (q, J = 8 Hz, 1H), 1.61 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H), 1.25 (d, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 168.58, 163.61, 144.19, 136.33, 130.88, 130.32, 128.49, 127.58, 82.73, 77.48, 77.16, 76.85, 62.57, 60.49, 28.21, 14.26, 6.62.

3-Chloro-4-((1-ethoxy-1-oxopropan-2-yl)sulfinyl)benzoic acid (8c)



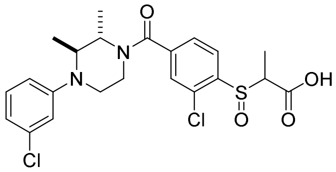
The title compound was synthesized using *tert*-butyl 3-chloro-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoate (**8b**) (0.14 g, 0.40 mmol, 1 eq.) according to procedure C. This yielded the product (0.12 g, 0.40 mmol, 100%). ^{1}H NMR (400 MHz, Methanol-$d4$): δ 8.22 (dd, J = 8.1, 1.5 Hz, 1H), 8.11 (d, J = 1.5 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 4.30 (qd, J = 7.1, 2.3 Hz, 2H), 4.13 (q, J = 7.1 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.21 (d, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Methanol-$d4$): δ 169.70, 144.80, 136.92, 132.16, 131.70, 129.93, 128.61, 63.50, 61.67, 48.58, 14.42, 6.78.

(±) Ethyl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)propanoate (8)



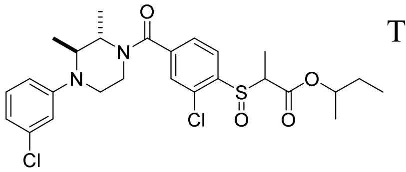
The title compound was synthesized using 3-chloro-4-((1-ethoxy-1-oxopropan-2-yl)sulfinyl)benzoic acid (0.10 g, 0.34 mmol, 1 eq.) according to procedure F. This yield the product (0.15 g, 0.29 mmol, 85%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 – 7.85 (m, 1H), 7.60 – 7.39 (m, 2H), 7.17 (t, J = 8.3 Hz, 1H), 6.86 – 6.78 (m, 2H), 6.78 – 6.66 (m, 1H), 4.91 – 4.53 (m, 1H), 4.32 (q, J = 7.2 Hz, 1H), 4.10 – 3.05 (m, 7H), 1.56 – 1.43 (m, 3H), 1.40 – 1.31 (m, 3H), 1.31 – 1.24 (m, 3H), 1.17 – 0.97 (m, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 168.56, 166.53, 151.31, 140.49, 135.26, 131.61, 131.03, 130.34, 128.61, 128.10, 125.35, 119.45, 116.21, 114.20, 62.50, 60.52, 56.14, 40.47, 38.68, 36.50, 17.81, 14.21, 12.57, 6.60. HRMS: Calculated for [$C_{24}H_{28}Cl_2N_2O_4S$ + Na]$^+$ = 535.1008, found = 535.1009.

(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)propanoic acid (9a)



To a solution of (±) ethyl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)propanoate (0.15 g, 0.29 mmol, 1 eq.) in 4ml MeOH was added 4ml TEA and 2ml water. Then, the mixture was stirred overnight. The reaction progress was monitored by TLC analysis. Once completed, the mixture was extracted with DCM and washed with water, dried over anhydrous Mg_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/DCM, 0-5%). This yielded the product (0.13 g, 0.28 mmol, quant.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.96 (dd, *J* = 23.2, 7.9 Hz, 1H), 7.58 – 7.42 (m, 2H), 7.18 (t, *J* = 8.1 Hz, 1H), 6.85 – 6.79 (m, 2H), 6.71 (d, *J* = 8.3 Hz, 1H), 4.95 – 4.58 (m, 1H), 3.96 (q, *J* = 7.1 Hz, 1H), 3.92 – 3.02 (m, 5H), 1.74 (d, *J* = 7.0 Hz, 1H), 1.54 – 1.45 (m, 3H), 1.30 (d, *J* = 7.2 Hz, 3H), 1.17 – 0.96 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.41, 169.00, 151.30, 140.59, 140.22, 135.34, 131.47, 130.42, 128.78, 128.21, 126.10, 119.64, 116.36, 114.33, 60.57, 56.25, 39.89, 36.77, 17.88, 16.84, 12.56, 7.02.

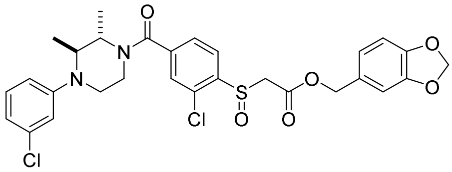
(±) sec-Butyl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)propanoate (9)



The title compound was synthesized using (±) 2-((2-chloro-4-(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)propanoic acid (**9a**) (60 mg, 0.12 mmol, 1 eq.), butan-2-ol (1 ml, 10.87 mmol, 88 eq.), 2M oxalyl chloride solution (0.07 ml, 0.14 mmol. 1.1 eq.) and DIPEA (0.1 ml, 0.57 mmol, 4.6 eq.) according to the G. This yielded the product (8.1 mg, 0.02 mmol, 12%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, 1H), 7.57 – 7.46 (m, 2H), 7.19 (t, *J* = 8.0 Hz, 1H), 6.86 – 6.81 (m, 2H), 6.74 (d, *J* = 8.4 Hz, 1H), 5.06 – 4.99 (m, 1H), 3.90 (qd, *J* = 7.2, 5.0 Hz, 1H), 3.84 – 3.11 (m, 6H), 1.77 – 1.60 (m, 2H), 1.51 (d, *J* = 6.7 Hz, 3H), 1.31 (dd, *J* = 6.3, 0.9 Hz, 3H), 1.27 (ddd, *J* = 7.3, 6.0, 1.5 Hz, 3H), 1.14 – 1.04 (m, 3H), 0.97 (dt, *J* = 11.0, 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ

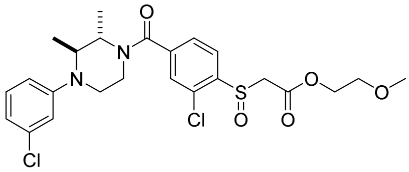
166.53, 165.29, 151.34, 141.97, 140.49, 135.38, 131.84, 130.42, 128.30, 127.91, 125.92, 119.66, 116.37, 114.35, 74.55, 74.38, 62.00, 61.35, 56.31, 28.74, 19.34, 12.46, 12.24, 9.61. HRMS: Calculated for [$C_{26}H_{32}Cl_2N_2O_4S$ + H]$^+$ = 541.1503, found = 541.1501.

(±) Benzo[d][1,3]dioxol-5-ylmethyl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)acetate (**11**)



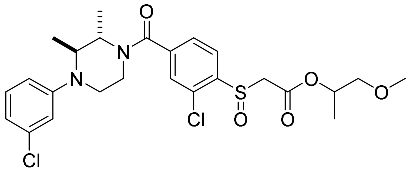
The title compound was synthesized using benzo[d][1,3]dioxol-5-ylmethanol (20 mg, 0.13 mmol, 3 eq.) according to general procedure G. This yielded the product (8 mg, 0.01 mmol, 31%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.39 (m, 2H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.88 – 6.76 (m, 5H), 6.71 (d, *J* = 8.4 Hz, 1H), 5.98 (s, 2H), 5.18 – 5.04 (m, 2H), 4.16 – 3.08 (m, 8H), 1.55 – 1.43 (m, 3H), 1.30 – 1.22 (m, 3H). HRMS: Calculated for [$C_{29}H_{28}Cl_2N_2O_6S$ + H]$^+$ = 603.1118, found = 603.1116.

(±) 2-Methoxyethyl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)acetate (**6**)



The title compound was synthesized using 2-methoxyethan-1-ol (1 ml, 12.68 mmol, 238 eq.) according to procedure G. This yielded the product (8 mg, 0.02 mmol, 29%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 9.5 Hz, 1H), 7.49 (d, *J* = 1.5 Hz, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 9.3 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 1H), 4.72 (d, *J* = 75.1 Hz, 1H), 4.40 – 4.27 (m, 2H), 4.11 (dd, *J* = 14.0, 1.1 Hz, 1H), 3.87 (s, 1H), 3.75 (d, *J* = 14.0 Hz, 1H), 3.61 (ddd, *J* = 5.8, 3.8, 2.2 Hz, 4H), 3.39 (s, 3H), 3.34 – 3.08 (m, 2H), 1.50 (d, *J* = 6.6 Hz, 3H), 1.31 – 0.94 (m, 3H). HRMS: Calculated for [$C_{24}H_{28}Cl_2N_2O_5S$ + H]$^+$ = 527.1169, found = 527.1163.

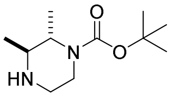
(±) 1-Methoxypropan-2-yl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)acetate (**10**)



The title compound was synthesized using 1-methoxypropan-2-ol (1 ml, 10.21 mmol, 192 eq.) according to procedure G. This yielded the product (5.3 mg, 9.8 μmol, 18%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.9 Hz, 1H), 7.64 –

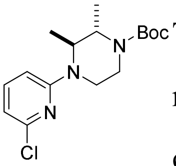
7.39 (m, 2H), 7.18 (t, J = 8.1 Hz, 1H), 6.87 – 6.77 (m, 2H), 6.72 (d, J = 8.5 Hz, 1H), 5.24 – 5.11 (m, 1H), 5.04 – 4.54 (m, 1H), 4.08 (d, J = 10.6 Hz, 1H), 3.87 (s, 1H), 3.70 (dd, J = 14.0, 3.7, 0.8 Hz, 1H), 3.52 – 3.40 (m, 3H), 3.38 (s, 3H), 3.19 (s, 3H), 1.49 (d, J = 6.7 Hz, 3H), 1.28 (dd, J = 19.0, 6.5 Hz, 3H), 1.18 – 0.96 (m, 3H). HRMS: Calculated for $[C_{25}H_{30}Cl_2N_2O_5S + H]^+$ = 541.1325, found = 541.1323.

(±) *tert* Butyl trans-2,3-dimethylpiperazine-1-carboxylate (4a)



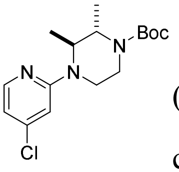
(±) trans-2,3-Dimethylpiperazine (262 mg, 2.29 mmol, 1 eq.) was dissolved in DCM (100 ml). Boc_2O (500 mg, 2.29 mmol, 1 eq.) dissolved in DCM (10 ml) was added slowly via a syringe pump over 45 h at rt. After adding, the reaction mixture was concentrated and the residue was purified by column chromatography (0-10% MeOH in DCM). This yielded the product as a yellow oil (282 mg, 1.31 mmol, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (br, 1H), 3.92 (dd, J = 5.5, 1.6 Hz, 1H), 3.80 (d, J = 10.5 Hz, 1H), 3.12 – 2.71 (m, 4H), 1.38 (s, 9H), 1.24 (d, J = 5.2 Hz, 3H), 1.23 (d, J = 5.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.12, 79.87, 51.40, 50.70, 38.46, 37.41, 28.39, 17.21, 16.19.

(±) *tert*-Butyl 4-(6-chloropyridin-2-yl)-trans-2,3-dimethylpiperazine-1-carboxylate (4b)



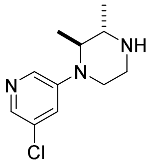
The title compound was synthesized using 2-bromo-6-chloropyridine (45 mg, 0.23 mmol, 1 eq.)and (±) *tert*-butyl trans-2,3-dimethylpiperazine-1-carboxylate (50 mg, 0.23 mmol, 1 eq.) according to procedure D. This yielded the product (35 mg, 0.11 mmol, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, J = 7.9 Hz, 1H), 6.56 (d, J = 7.4 Hz, 1H), 6.42 (dd, J = 8.4, 2.8 Hz, 1H), 4.25 – 3.81 (m, 4H), 3.25 – 3.05 (m, 2H), 1.47 (s, 9H), 1.21 (d, J = 6.8 Hz, 3H), 1.17 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.04, 155.48, 149.65, 139.84, 111.85, 104.33, 79.95, 51.9, 50.54, 38.69, 37.37, 28.55, 17.20, 15.08.

(±) *tert*-Butyl 4-(4-chloropyridin-2-yl)-trans-2,3-dimethylpiperazine-1-carboxylate (5b)



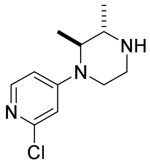
The title compound was synthesized using 2-bromo-4-chloropyridine (45 mg, 0.23 mmol, 1 eq.), (±) *tert*-butyl trans-2,3-dimethylpiperazine-1-carboxylate (50 mg, 0.23 mmol, 1 eq.) according to procedure D. This yielded the product (14.5 mg, 0.045 mmol, 19%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 5.3 Hz, 1H), 6.59 (dd, *J* = 5.4, 1.6 Hz, 1H), 6.55 (s, 1H), 4.65 – 3.63 (m, 4H), 3.31 – 2.88 (m, 2H), 1.48 (s, 9H), 1.23 (d, *J* = 6.8 Hz, 3H), 1.17 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.09, 149.01, 145.17, 128.48, 113.23, 106.50, 80.00, 52.03, 50.61, 38.93, 37.43, 28.59, 17.27, 15.20.

(±) 1-(5-Chloropyridin-3-yl)-trans-2,3-dimethylpiperazine (**2c**)



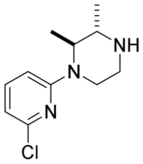
The title compound was synthesized using 3-bromo-5-chloropyridine (385 mg, 2 mmol, 2 eq.) and (±) trans-2,3-dimethylpiperazine (114 mg, 1 mmol, 1 eq.) according to procedure I. This yielded the product (9.3 mg, 0.041 mmol, 4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 2.5 Hz, 1H), 8.09 (d, *J* = 2.0 Hz, 1H), 7.19 (t, *J* = 2.3 Hz, 1H), 3.36 – 3.29 (m, 1H), 3.22 – 3.09 (m, 3H), 3.04 – 2.90 (m, 2H), 2.29 (br, 1H), 1.34 (d, *J* = 6.7 Hz, 3H), 1.11 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.95, 140.23, 139.53, 132.17, 125.13, 56.92, 53.98, 46.70, 41.54, 18.74, 14.70.

(±) 1-(2-Chloropyridin-4-yl)-trans-2,3-dimethylpiperazine (**3c**)



The title compound was synthesized using 4-bromo-2-chloropyridine (385 mg, 2 mmol, 2 eq.) and (±) trans-2,3-dimethylpiperazine (114 mg, 1 mmol, 1 eq.) according to procedure I. This yielded the product (11 mg, 0.049 mmol, 5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 6.1 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 6.52 (dd, *J* = 6.1, 2.4 Hz, 1H), 3.76 – 3.58 (m, 1H), 3.51 – 3.36 (m, 1H), 3.24 – 2.83 (m, 4H), 2.48 (br, 1H), 1.30 (d, *J* = 6.7 Hz, 3H), 1.25 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.95, 152.91, 149.67, 107.19, 107.07, 54.06, 51.98, 40.48, 39.12, 18.70, 14.37.

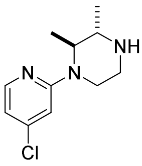
(±) 1-(6-Chloropyridin-2-yl)-trans-2,3-dimethylpiperazine (**4c**)



The title compound was synthesized using (±) *tert*-butyl-4-(6-chloropyridin-2-yl)-trans-2,3-dimethylpiperazine-1-carboxylate (35 mg, 0.11 mmol) according to procedure E. This yielded the product (19 mg, 0.083 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.3, 7.6 Hz, 1H), 6.58 (d, *J* = 7.5 Hz, 1H), 6.43 (d, *J* = 8.4 Hz, 1H), 4.34 (br, 1H), 3.54 (dq, *J* = 14.5, 7.3 Hz, 1H), 3.28 – 3.02 (m, 5H), 1.39 (d, *J* = 6.8 Hz, 3H), 1.33 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz,

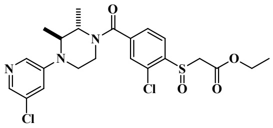
$CDCl_3$) δ 158.78, 149.66, 139.96, 112.23, 104.46, 52.06, 51.73, 38.68, 37.85, 17.39, 14.57.

(±) 1-(4-Chloropyridin-2-yl)-trans-2,3-dimethylpiperazine (**5c**)



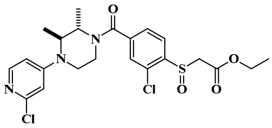
The title compound was synthesized using (±) *tert*-butyl-4-(4-chloropyridin-2-yl)-trans-2,3-dimethylpiperazine-1-carboxylate (14.5 mg, 0.045 mmol) according to procedure E. This yielded the product (7.2 mg, 0.032 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 5.3 Hz, 1H), 6.66 (dd, *J* = 5.4, 1.6 Hz, 1H), 6.58 (d, *J* = 1.6 Hz, 1H), 4.38 (q, *J* = 6.4 Hz, 1H), 4.27 – 4.17 (m, 1H), 3.56 (qd, *J* = 7.0, 1.7 Hz, 1H), 3.47 – 3.23 (m, 3H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.45 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.21, 149.07, 145.56, 114.45, 106.82, 52.27, 51.02, 37.92, 36.48, 15.88, 14.68.

(±) Ethyl 2-((2-chloro-4-(-4-(5-chloropyridin-3-yl)-trans-2,3-dimethylpiperazine-1-carbonyl) phenyl)sulfinyl)acetate (**2**)



The title compound was synthesized using 3-chloro-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (11.6 mg, 0.04 mmol, 1 eq.) and (±) 1-(5-chloropyridin-3-yl)-trans-2,3-dimethylpiperazine (9 mg, 0.04 mmol, 1 eq.) according to the procedure F. This yielded the product (12.4 mg, 0.025 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) 8.40 (s, 1H), 8.08 (s, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.62 – 7.54 (m, 1H), 7.47 (d, *J* = 13.7 Hz, 2H), 4.98 – 4.65 (m, 1H), 4.33 – 4.17 (m, 2H), 4.06 (dd, *J* = 14.0, 1.9 Hz, 1H), 4.00 – 3.19 (m, 6H), 1.52 – 1.17 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.99, 164.36, 148.19, 142.53, 139.55, 135.34, 131.00, 130.26, 128.53, 128.24, 127.90, 127.09, 126.08, 62.57, 58.06, 54.94, 49.27, 40.23, 35.82, 17.67, 14.07, 13.76.

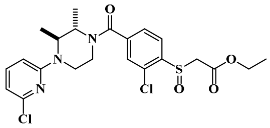
(±) Ethyl 2-((2-chloro-4-(-4-(2-chloropyridin-4-yl)-trans-2,3-dimethylpiperazine-1-carbonyl) phenyl)sulfinyl) acetate (**3**)



The title compound was synthesized using 3-chloro-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (14.5 mg, 0.05 mmol) and (±) 1-(2-chloropyridin-4-yl)-trans-2,3-dimethylpiperazine (11 mg, 0.05 mmol, 1eq.) according to the procedure F. This yielded the product (7.5 mg, 0.015 mmol, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 6.4 Hz, 1H), 8.04

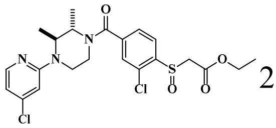
(d, *J* = 7.9 Hz, 1H), 7.60 – 7.42 (m, 2H), 6.77 (d, *J* = 7.5 Hz, 2H), 4.96 – 4.62 (m, 1H), 4.24 (qd, *J* = 7.1, 1.5 Hz, 2H), 4.10 – 3.27 (m, 7H), 1.47 – 1.20 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.88, 164.42, 158.23, 146.19, 143.54, 142.89, 139.39, 131.04, 128.60, 127.27, 126.28, 107.48, 106.82, 62.53, 58.17, 54.62, 49.33, 40.32, 35.84, 17.78, 15.38, 14.09.

(±) Ethyl 2-((2-chloro-4-(-4-(6-chloropyridin-2-yl)-trans-2,3-dimethylpiperazine-1-carbonyl) phenyl)sulfinyl)acetate (4)



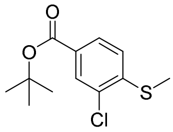
The title compound was synthesized using 3-chloro-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (24 mg, 0.082 mmol, 1 eq.) and (±) 1-(6-chloropyridin-2-yl)-trans-2,3-dimethylpiperazine (18.6 mg, 0.082 mmol) according to the procedure F. This yielded the product (32.6 mg, 0.065 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.0, 2.8 Hz, 1H), 7.61 – 7.41 (m, 3H), 6.66 (dd, *J* = 7.5, 2.9 Hz, 1H), 6.49 (dd, *J* = 12.1, 8.4 Hz, 1H), 4.91 – 4.56 (m, 1H), 4.38 – 4.05 (m, 5H), 3.77 – 3.06 (m, 4H), 1.45 – 1.14 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.96, 164.51, 158.63, 149.76, 142.42, 140.45, 140.15, 130.89, 128.59, 127.19, 126.41, 112.80, 104.55, 62.59, 58.36, 51.75, 49.08, 38.85, 36.52, 17.81, 16.81, 14.21.

(±) Ethyl 2-((2-chloro-4-(-4-(4-chloropyridin-2-yl)-trans-2,3-dimethylpiperazine-1-carbonyl) phenyl)sulfinyl)acetate (5)



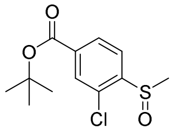
The title compound was synthesized using 3-chloro-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (9.3 mg, 0.032 mmol, 1 eq.) and (±) 1-(4-chloropyridin-2-yl)-trans-2,3-dimethylpiperazine (7.2 mg, 0.032 mmol, 1 eq.) according to the procedure F. This yielded the product (15.6 mg, 0.031 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (t, *J* = 3.8 Hz, 1H), 8.06 (d, *J* = 6.1 Hz, 1H), 7.63 – 7.46 (m, 2H), 6.93 – 6.87 (m, 2H), 4.96 – 4.63 (m, 1H), 4.41 – 3.96 (m, 5H), 3.83 – 3.28 (m, 4H), 1.48 – 1.24 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.89, 164.49, 155.08, 150.38, 143.34, 142.86, 139.46, 130.96, 128.56, 127.02, 126.32, 114.69, 109.82, 62.47, 58.29, 54.03, 49.17, 40.73, 35.82, 17.50, 15.63, 14.10.

***tert*-Butyl 3-chloro-4-(methylthio)benzoate (26)**



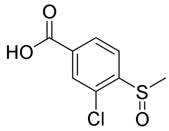
To a solution of *tert*-butyl 3-chloro-4-fluorobenzoate (0.510 g, 2.22 mmol, 1 eq.) in degassed DMF was added sodium methanethiolate (0.230 g, 3.32 mmol, 1.5 eq.) at -10 ºC and the mixture was stirred at RT overnight. The reaction progress was monitored by TLC. Once completed, the mixture was diluted with Et_2O, washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified using column chromatography (Et_2O / pentane, 0-10%) to yield the product (0.24 g, 0.91 mmol, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 1.8 Hz, 1H), 7.85 (dd, J = 8.3, 1.8 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 2.49 (s, 3H), 1.59 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.54, 143.80, 130.83, 129.94, 129.04, 128.05, 123.94, 81.49, 28.22, 14.92.

tert-Butyl 3-chloro-4-(methylsulfinyl)benzoate (27)



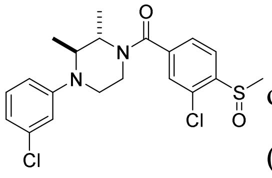
The title compound was synthesized using *tert*-butyl 3-chloro-4-(methylthio)benzoate (0.24 g, 0.91 mmol, 1 eq.) according to procedure B. This yielded the product (0.290 g, 1.17 mmol, quant.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (dd, J = 8.0, 1.6 Hz, 1H), 8.03 – 7.98 (m, 2H), 2.86 (s, 3H), 1.62 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 163.34, 147.97, 135.70, 130.48, 129.52, 128.73, 125.20, 82.24, 41.37, 27.94.

3-Chloro-4-(methylsulfinyl)benzoic acid (28)



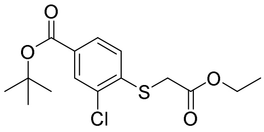
The title compound was synthesized using *tert*-butyl 3-chloro-4-(methylsulfinyl)benzoate (0.26 g, 0.94 mmol) according to procedure C. This yielded the product (0.19 g, 0.87 mmol, 92%). ^{1}H NMR (400 MHz, Methanol-*d*4) δ 8.22 (dd, J = 8.2, 1.6 Hz, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 2.90 (s, 3H). ^{13}C NMR (400 MHz, Methanol-*d*4) δ 167.19, 148.93, 136.49, 132.03, 131.20, 130.45, 126.47, 41.68.

(±) (3-Chloro-4-(methylsulfinyl)phenyl)(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazin-1-yl)methanone (29)



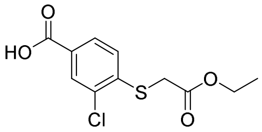
To a stirred suspension of 3-chloro-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (0.19 g, 0.87 mmol, 1 eq.) in DCM (10 ml) were added (±) trans-1-(3-chlorophenyl)-2,3-dimethylpiperazine (32, 0.230 g, 1.04 mmol, 1.2 eq.), DIPEA (0.34 mg, 2.59 mmol, 3 eq.), HOBt (0.18 mg, 1.30 mmol, 1.5 eq.) and EDCl (0.25 mg, 1.30 mmol, 1.5 eq.). The mixture was stirred overnight. The reaction progress was monitored by TLC analysis. Once completed, the mixture was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified using column chromatography (EtOAc / pentane, 0%-60%) to yield the product (0.27 mg, 0.64 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 2H), 7.56 – 7.38 (m, 2H), 7.14 (t, *J* = 8.2 Hz, 1H).6.60 (d, *J* = 2.4 Hz, 1H), 6.56 – 6.47 (m, 1H), 4.85 – 4.49 (m, 1H), 3.98 – 3.07 (m, 5H), 2.82 (s, 3H), 1.42 – 1.33 (m, 3H), 1.28 – 1.06 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.83, 151.33, 145.25, 140.18, 135.19, 130.47, 130.33, 128.43, 127.77, 125.85, 119.34, 116.13, 114.19, 56.08, 49.57, 42.29, 41.64, 36.46, 17.76, 12.52.

tert-Butyl 3-chloro-4-((2-ethoxy-2-oxoethyl)thio)benzoate (30)



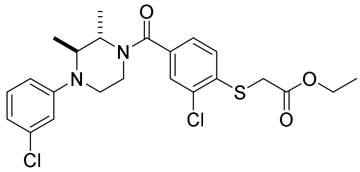
The title compound was synthesized using *tert*-butyl 3-chloro-4-fluorobenzoate (0.33 g, 1.45 mmol, 1.2 eq.) and ethyl 2-mercaptoacetate (0.13 ml, 1.21 mmol, 1 eq.) according to procedure A. This yielded the product (0.31 g, 0.95 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 1.8 Hz, 1H), 7.83 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 2H), 1.58 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.75, 164.35, 140.61, 132.17, 130.61, 130.44, 128.19, 126.62, 81.79, 62.12, 34.51, 28.25, 14.21.

3-Chloro-4-((2-ethoxy-2-oxoethyl)thio)benzoate (31)



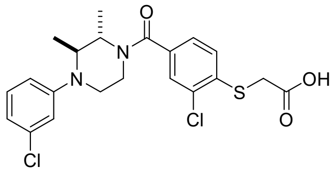
The title compound was synthesized using *tert*-butyl 3-chloro-4-((2-ethoxy-2-oxoethyl)thio)benzoate (61.5 mg, 0.19 mmol) according to procedure C. This yielded the product (51.1 mg, 0.19 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.95 (d, *J* = 8.3 Hz, 1H) , 7.37 (d, *J* = 8.2 Hz, 1H), 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 (32)



The title compound was synthesized using 3-chloro-4-((2-ethoxy-2-oxoethyl)thio)benzoic acid (27, 0.15 mg, 0.54 mmol, 1 eq.) according to procedure F. This yielded the product (0.25 g, 0.46 mmol, 85%). ^{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 (carbon spectrum shows a mixture of rotamers). HRMS: Calculated for [$C_{23}H_{26}Cl_2N_2O_3S$ + H]+ = 483.1084, found = 483.1079.

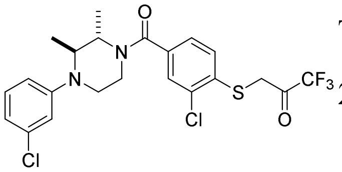
(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)thio)acetic acid (**33**)



To a solution of (±) ethyl 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)thio)acetate (0.36 mg, 0.75 mmol,1 eq.) in MeOH (10 ml) was added 2 M NaOH solution (0.75 ml, 1.25 mmol, 2 eq.) and the reaction mixture was stirred for 2h. The reaction progress was monitored by TLC analysis. Once completed, the solution was acidified to pH 3 using 3M HCl and extracted with DCM. The organic layer was dried over anhydrous MgSO$_4$, filterated and concentrated under reduced pressure. The residue was purified with column chromatography (EtOAc / pentane, 0 – 100 % with 1 % acetic acid) to yield the product (0.33 mg, 0.72 mmol, 96%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 – 7.36 (m, 2H), 7.29 (d, *J* = 6.0 Hz, 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), 4.80 – 4.50 (m, 1H), 4.04 – 3.95 (m, 1H), 3.90 (s, 2H), 3.86 – 3.38 (m, 2H), 3.32 – 3.06 (m, 2H), 1.52 – 1.45 (m, 3H), 1.04 (dd, *J* = 55.7, 6.5 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 172.24, 170.27, 151.35, 137.79, 135.25, 133.79, 132.72, 130.33, 129.11, 128.18, 125.37, 119.39, 116.17, 114.18, 56.16, 49.90, 40.48, 36.75, 34.50, 17.75, 12.49.

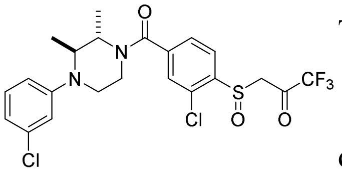
(±) 3-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-

carbonyl)phenyl)thio)-1,1,1-trifluoropropan-2-one (34)



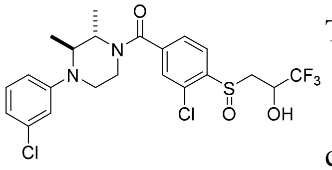
To a solution of trifluoroacetic anhydride (34 µl, 0.24 mmol, 2.2 eq.) in toluene (0.5 ml) was added (±) 2-((2-chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)thio)acetic acid (50 mg, 0.11 mmol, 1 eq.) and the mixture was cooled to 0 ºC. Then, pyridine (22µl, 0.28 mmol, 2.5 equiv.) in toluene (0.5 ml) was slowly added and the mixture was stirred at 65 ºC overnight. Afterwards it was cooled to 0 ºC and 1 ml water was added dropwise. Then the temperature was brought up to 45 ºC and maintained for 2h. After cooling, the aqueous phase of the mixture was separated and washed with ethyl acetate. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by prep HPLC to provide a white solid (9.4 mg, 0.11 mmol, 17%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.27 (m, 3H), 7.17 (t, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 7.2 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 1H), 4.69 (dd, *J* = 76.4, 10.1 Hz, 1H), 4.06 (s, 1H), 3.98 – 3.02 (m, 5H), 1.47 (dd, *J* = 9.7, 6.7 Hz, 3H), 1.06 (dd, *J* = 45.1, 6.7 Hz, 3H). HRMS: Calculated for $[C_{22}H_{21}Cl_2F_3N_2O_2S + H_2O + H]^+$ = 523.0831, found = 523.0828.

(±) 3-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1,1,1-trifluoropropan-2-one (16)



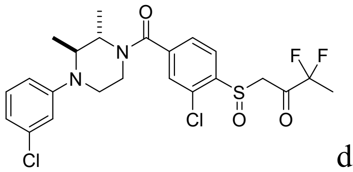
The title was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (50 mg, 0.12 mmol, 1 eq.) and ethyl 2,2,2-trifluoroacetate (167 mg, 1.18 mmol, 10 eq.) according to procedure H. This yielded the product (48 mg, 0.09 mmol, 79%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.66 – 7.47 (m, 2H), 7.19 (t, *J* = 8.1 Hz, 1H), 6.86 – 6.80 (m, 2H), 6.72 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.77 – 2.99 (m, 7H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.07 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.76, 168.28, 151.30, 141.82, 140.78, 135.27, 130.60, 130.38, 128.68, 126.78, 121.76 (q, *J* = 287.3 Hz), 119.53, 116.26, 114.26, 93.88 (q, *J* = 33.8 Hz), 56.18, 53.97, 49.80, 40.45, 36.64, 17.81, 12.25 (carbon spectrum shows a mixture of rotamers). HRMS: Calculated for $[C_{22}H_{21}Cl_2F_3N_2O_3S + H_2O + H]^+$ = 539.0780, found = 539.0779.

(±) (3-chloro-4-((3,3,3-trifluoro-2-hydroxypropyl)sulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**17**)



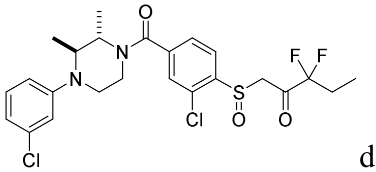
To a cooled (0°C) solution of (±) 3-((2-chloro-4-(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1,1,1-trifluoropropan-2-one 1,1,1-trifluoropropan-2-one (25 mg, 0.05 mmol, 1 eq.) in MeOH (1.7 mL) was added NaBH4 (1.5 mg, 0.04 mmol, 0.8 eq.). The resulting solution was stirred for 1h. The reaction was quenched with sat. aq. NH_4Cl, extracted with DCM (3x), dried (MgSO4), filtered and concentrated. The crude product, which was purified with prep HPLC to afford compound as a white solid (9.3 mg, 0.05 mmol, 37%). HRMS: Calculated for $[C_{22}H_{23}Cl_2F_3N_2O_3S + H]^+ = 523.0829$, found = 523.0831.

(±) 1-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-3,3-difluorobutan-2-one (**19**)



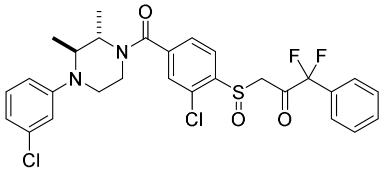
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (25 mg, 0.06 mmol, 1 eq.) and ethyl 2,2-difluoropropanoate (81 mg, 0.59 mmol, 10 eq.) according to procedure H. This yielded the product (4.9 mg, 0.06 mmol, 16%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 18.3, 8.0 Hz, 1H), 7.63 – 7.49 (m, 2H), 7.20 (t, *J* = 8.0 Hz, 1H), 6.88 – 6.82 (m, 2H), 6.76 (d, *J* = 8.4 Hz, 1H), 4.44 (dd, *J* = 15.1, 4.4 Hz, 1H), 4.07 (dd, *J* = 15.1, 3.4 Hz, 1H), 3.85 – 3.10 (m, 6H), 1.78 (t, *J* = 19.3 Hz, 3H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.67, 168.19, 151.36, 142.33, 140.83, 135.32, 130.67, 130.40, 128.68, 126.98, 126.52, 119.56, 117.31 (t, *J* = 249 Hz), 116.30, 114.28, 59.45, 56.22, 49.72, 40.52, 36.58, 18.73 (t, *J* = 24 Hz), 17.87, 12.60 (carbon spectrum shows a mixture of rotamers). HRMS: Calculated for $[C_{23}H_{24}Cl_2F_2N_2O_3S + H_2O + H]^+ = 535.1031$, found = 535.1027.

(±) 1-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-3,3-difluoropentan-2-one (**20**)



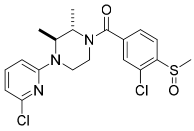
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (20 mg, 0.05 mmol, 1 eq.) and ethyl 2,2-difluorobutanoate (72 mg, 0.47 mmol, 10 eq.) according to procedure H. This yielded the product (2.5 mg, 0.05 mmol, 10%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.1, 4.5 Hz, 1H), 7.62 – 7.49 (m, 2H), 7.22 (t, *J* = 8.3 Hz, 1H), 6.89 (d, *J* = 7.2 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 1H), 4.41 (dd, *J* = 15.1, 4.3 Hz, 1H), 4.05 (dd, *J* = 15.2, 3.4 Hz, 1H), 3.85 – 3.13 (m, 8H), 2.17 – 2.02 (m, 3H), 1.54 (d, *J* = 6.8 Hz, 3H), 1.08 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.65, 168.17, 151.36, 142. 26, 140.93, 135.33, 130.65, 130.40, 128.67, 127.08, 126.51, 119.55, 118.14 (t, *J* = 253 Hz), 116.30, 114.28, 60.15, 56.22, 49.70, 40.52, 36.57, 25.52 (t, *J* = 23 Hz), 17.86, 12.60, 5.47 (t, *J* = 5 Hz). HRMS: Calculated for $[C_{24}H_{26}Cl_2F_2N_2O_3S + H_2O + H]^+$ = 549.1188, found = 549.1183.

(±) 3-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1,1-difluoro-1-phenylpropan-2-one (21)



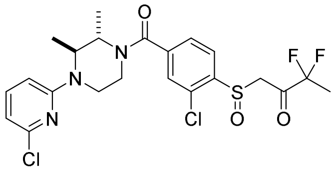
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (40 mg, 0.09 mmol, 1 eq.) and ethyl 2,2-difluoro-2-phenylacetate (188 mg, 0.94 mmol, 10 eq.) according to procedure LDA. This yielded the product (13.4 mg, 0.02 mmol, 25%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.9 Hz, 1H), 7.63 – 7.42 (m, 7H), 7.17 (t, *J* = 8.1, 2.4 Hz, 1H), 6.85 – 6.78 (m, 2H), 6.74 – 6.68 (m, 1H), 4.69 – 4.32 (m, 1H), 4.07 – 3.01 (m, 5H), 1.54 – 1.41 (m, 3H), 1.17 – 0.97 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 191.69, 191.44, 152.19, 143.10, 141.58, 136.27, 132.65 (t), 131.65, 131.31, 131.18, 130.07, 129.20, 128.43, 128.03, 126.86 (t), 120.59, 117.27, 116.39 (t), 115.24, 61.07, 61.04, 57.17, 56.53, 30.71, 13.74, 1.01. HRMS: Calculated for $[C_{28}H_{26}Cl_2F_2N_2O_3S + H_2O + H]^+$ = 597.1188, found = 597.1189.

(±) (3-Chloro-4-(methylsulfinyl)phenyl)(4-(6-chloropyridin-2-yl)-trans-2,3-dimethylpiperazin-1-yl)methanone (35)



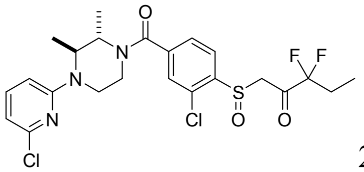
The title compound was synthesized using (±) 1-(6-chloropyridin-2-yl)-trans-2,3-dimethylpiperazine (70 mg, 0.31 mmol, 1.2 eq.) and 3-chloro-4-(methylsulfinyl)benzoic acid (57 mg, 0.26 mmol, 1 eq.) according to procedure F. This yielded the product (86 mg, 0.20 mmol, 78 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.0, 3.8 Hz, 1H), 7.66 – 7.37 (m, 3H), 6.63 (dd, *J* = 7.5, 3.7 Hz, 1H), 6.48 (dd, *J* = 15.7, 8.4 Hz, 1H), 4.84 – 3.15 (m, 6H), 2.86 (d, *J* = 1.9 Hz, 3H), 1.47 – 1.04 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.83, 158.60, 149.60, 145.35, 140.04, 130.46, 128.43, 127.74, 126.38, 125.85, 112.59, 104.46, 52.20, 42.10, 41.61, 36.28, 29.72, 17.74, 14.28

(±) 1-((2-chloro-4-(4-(6-chloropyridin-2-yl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-3,3-difluorobutan-2-one (**24**)



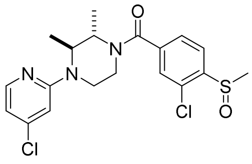
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(4-(6-chloropyridin-2-yl)-trans-2,3-dimethylpiperazin-1-yl)methanone (33 mg, 0.08 mmol, 1.0 eq.) and ethyl 2,2-difluoropropanoate (107 mg, 0.77 mmol, 10 eq.) according to general procedure I. This yielded the product (18 mg, 0.04 mmol, 45%). HRMS: Calculated for $[C_{22}H_{23}Cl_2F_2N_3O_3S + H_2O + H]^+ = 536.0984$, found = 536.0984.

(±) 1-((2-Chloro-4-(4-(6-chloropyridin-2-yl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-3,3-difluoropentan-2-one (**25**)



The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(4-(6-chloropyridin-2-yl)-trans-2,3-dimethylpiperazin-1-yl)methanone (33 mg, 0.08 mmol, 1.0 eq.) and ethyl 2,2-difluorobutanoate (118 mg, 0.77 mmol, 10 eq.) according to general procedure I. This yielded the product (18 mg, 0.02 mmol, 29%). HRMS: Calculated for $[C_{23}H_{25}Cl_2F_2N_3O_3S + H_2O + H]^+ = 550.1140$, found = 550.1141.

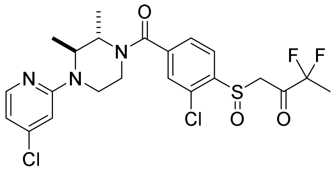
(±) (3-chloro-4-(methylsulfinyl)phenyl)(4-(4-chloropyridin-2-yl)-trans-2,3-dimethylpiperazin-1-yl)methanone (**36**)



The title compound was synthesized using (±) 1-(4-chloropyridin-2-yl)-trans-2,3-dimethylpiperazine (40 mg, 0.18 mmol, 1.2 eq.) and 3-chloro-4-(methylsulfinyl)benzoic acid (32 mg, 0.15 mmol, 1 eq.)

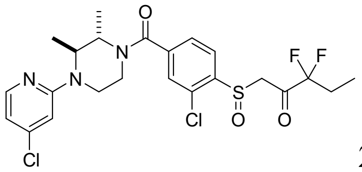
according to procedure F. This yielded the product (56 mg, 0.13 mmol, 89 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 – 7.81 (m, 2H), 7.70 – 7.33 (m, 2H), 6.94 – 6.57 (m, 2H), 5.11 – 3.06 (m, 6H), 2.89 (d, *J* = 4.4 Hz, 3H), 1.44 – 1.19 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.10, 156.72, 149.65, 145.50, 144.74, 139.58, 130.74, 128.58, 126.49, 126.11, 114.61, 109.18, 53.64, 49.32, 41.53, 39.62, 36.02, 17.63, 15.48.

(±) 1-((2-Chloro-4-(4-(4-chloropyridin-2-yl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-3,3-difluorobutan-2-one (**22**)



The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(4-(4-chloropyridin-2-yl)-trans-2,3-dimethylpiperazin-1-yl)methanone (55 mg, 0.13 mmol, 1.0 eq.) and ethyl 2,2-difluoropropanoate (89 mg, 0.65 mmol, 5 eq.) according to general procedure I. This yielded the product (26 mg, 0.05 mmol, 39 %). HRMS: Calculated for $[C_{22}H_{23}Cl_2F_2N_3O_3S + H_2O + H]^+$ = 536.0984, found = 536.0983.

(±) 1-((2-Chloro-4-(4-(4-chloropyridin-2-yl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-3,3-difluoropentan-2-one (**23**)



The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(4-(4-chloropyridin-2-yl)-trans-2,3-dimethylpiperazin-1-yl)methanone (55 mg, 0.13 mmol, 1.0 eq.) and ethyl 2,2-difluorobutanoate (98 mg, 0.65 mmol, 5 eq.) according to general procedure I. This yielded the product (29 mg, 0.05 mmol, 42 %).

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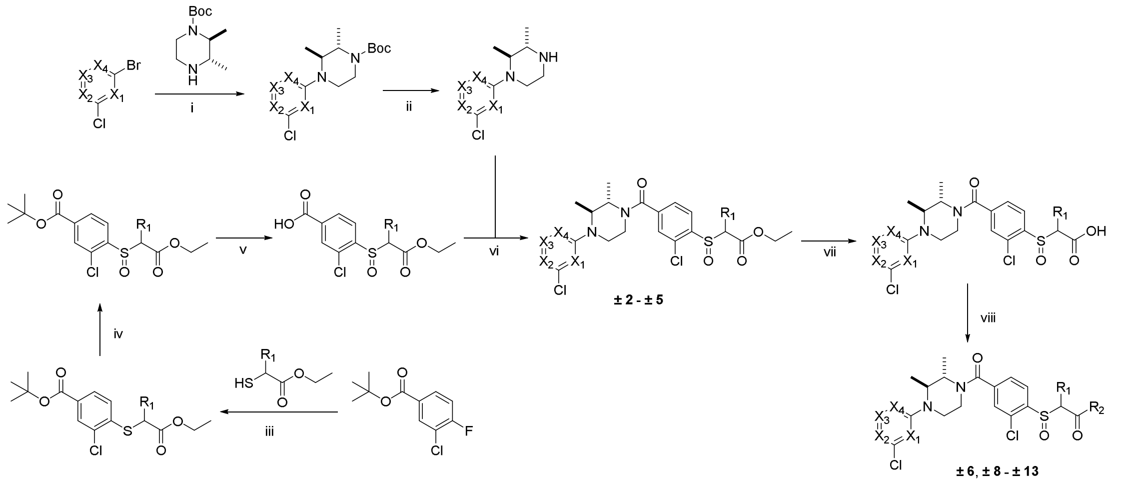
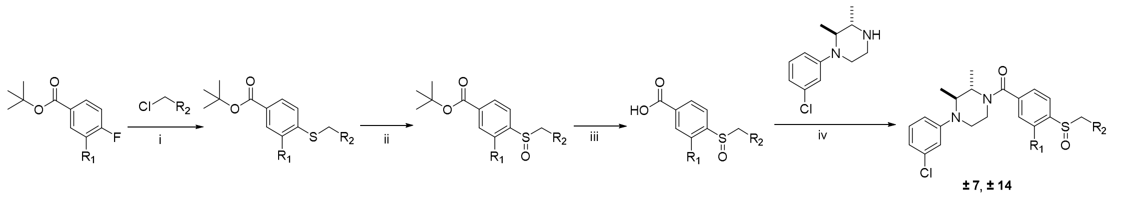
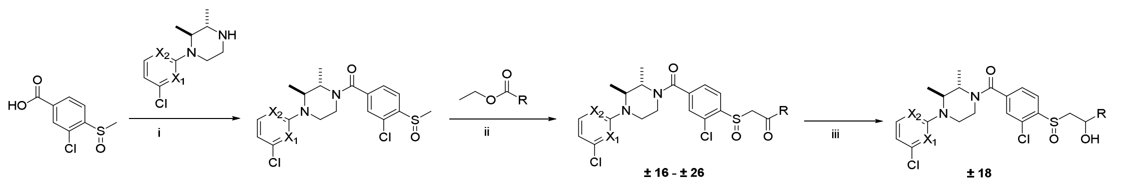
Supplementary information



Scheme S1. Synthesis route of compounds ± **2** - ± **6** and ± **8** - ± **13**. Reagents and conditions: i) sodium *tert*-butoxide, BINAP, $Pd(OAc)_2$, 1,4-dioxane, 85 ºC. ii) TFA, DCM. iii) K_2CO_3, ACN. iv) Oxone, MeOH / H_2O. v) TFA, DCM. vi) HATU, DiPEA, DCM. vii) TEA, MeOH, H_2O. viii) appropriate alcohol or amine, oxalyl chloride, DiPEA, DCM.



Scheme S2. Synthesis route of compounds ± **7** and ± **14**. Reagents and conditions: i) NaHS, K_2CO_3, DMF. ii) Oxone, MeOH / H_2O. iii) TFA, DCM. iv) HATU, DiPEA, DCM.



Scheme S3. Synthesis route of compounds ± **16** - ± **26**. Reagents and conditions: i) HATU, DiPEA, DCM. ii) LDA, THF, -78 °C. iii) $NaBH_4$, MeOH.