Discovery of reversible monoacylglycerol lipase inhibitors

Jiang, M.

Chapter 3

Development of α-aryl ketones as monoacylglycerol lipase inhibitors

M. Jiang, A. Amedi, M. C. W. Huizenga, C. A. A. van Boeckel, R. J. B. H. N.van den Berg, M. van der Stelt*; *manuscript in preparation.*

3.1 Introduction

Monoacylglycerol lipase (MAGL) is a serine hydrolase and plays an important role in regulating endocannabinoid signaling and lipid metabolism.[1, 2] MAGL inhibitors are thought to be useful for the treatment of various diseases, including (neuro)inflammation, cancer, pain and anxiety. [3-13] In the past two decades a number of drug discovery programs have, therefore, been initiated to discover potent and selective MAGL inhibitors. Several chemotypes have been reported as MAGL inhibitors, such as carbamates[5, 9, 11], ureas[14], amides[4] and esters[15]. The first-in-class MAGL inhibitor ABX-1431, which has an activated carbamate warhead, is now in clinical phase 1b for the treatment of post-traumatic stress disorder.

During the Structure-Activity Relationship (SAR) study of β-sulfinyl esters in chapter 2, compound ± **1** (Figure 1A) was discovered as a highly potent and selective MAGL inhibitor. This compound contains an ester functionality, which is a metabolic

liability and may act as an electrophile for the incoming catalytic serine (See Chapter 2, Figure 3). To test this latter hypothesis, we envisioned that replacing the ester group with bioisosteres that covalently, albeit reversibly, bind to the nucleophilic serine may yield novel, potent MAGL inhibitors.

Previously, α-ketoheterocycle derivatives, such as OL-135 (**2**, Figure 1B) and LEI-105 (**3**, Figure 1B), have been reported as inhibitors of the serine hydrolases fatty acid amide hydrolase (FAAH) and diacylglycerol lipase (DAGL), which catalyze the hydrolysis of an amide and ester bond in anandamide and diacylglycerol, respectively.[16-20] Crystallography studies revealed the mechanism of action of α-ketoheterocycle inhibitors. For example, OL-135 interacted with FAAH through hemiketal formation with the catalytic serine (Figure 1C). Inspired by those studies, it is envisioned that replacement of the ester of compound **± 1** with activated ketones may also yield potent MAGL inhibitors (Figure 1A). In this chapter, a novel series of α-aryl ketones as MAGL inhibitors with the compound **± 1**-scaffold was generated and evaluated. Optimization of the α-aryl ketones as novel "warhead" of MAGL lead to the discovery of compound **± 24** as a covalent, reversible MAGL inhibitor with nanomolar potency.

3.2 Results and discussion

To test the feasibility of α-aryl ketones as MAGL inhibitors, compounds **± 4** to **± 24** were synthesized according to general synthesis scheme 1. First, an aromatic nucleophilic substitution was performed with commercially available building block **25** with sodium methylsulfide to obtain the sulfide **26**, which was oxidized by oxone to sulfoxide compound **27**. The *tert*-butyl protecting group was removed with TFA and benzoic acid was coupled with amine **± 29** through an EDCI/HOBt-mediated peptide coupling which furnished compound **± 30**. Finally, commercially available esters were reacted with compound **± 30** to yield the final compounds (**± 4 - ± 24**). MAGL inhibitory activities of synthesized compounds were determined using the natural substrate assay reported in Chapter 2.

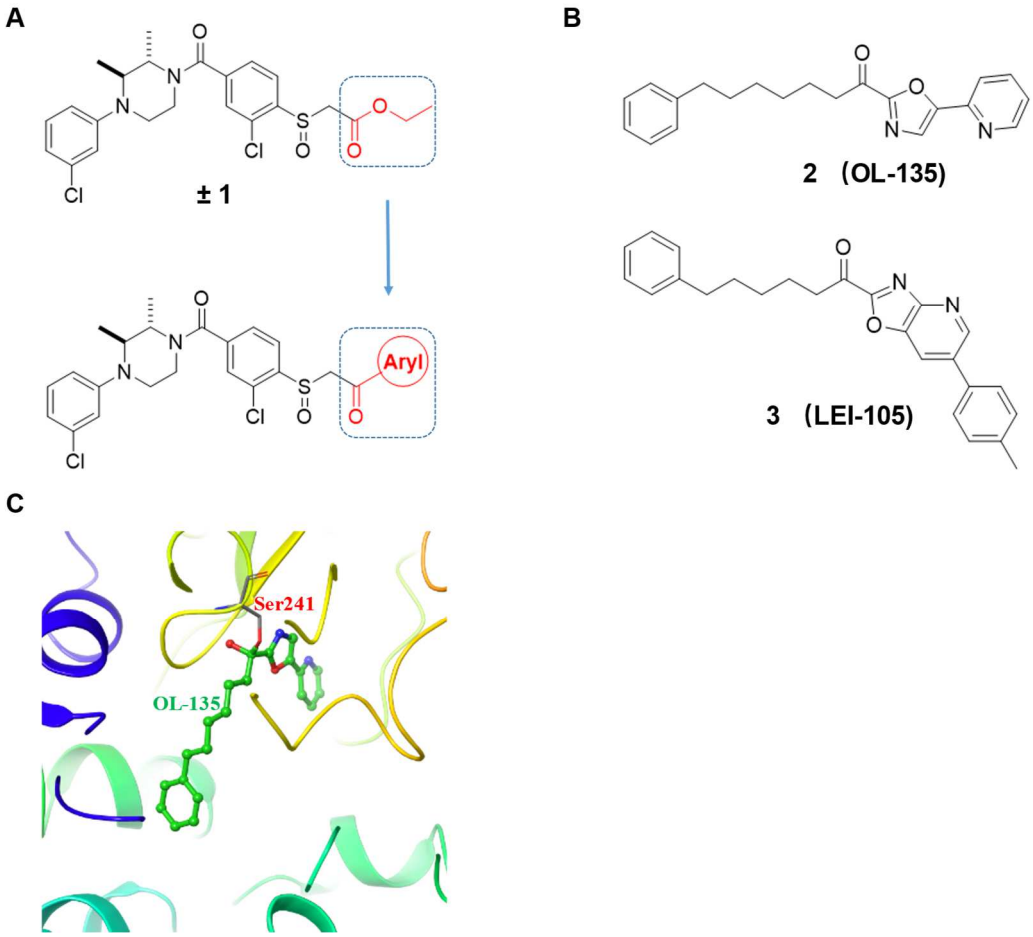
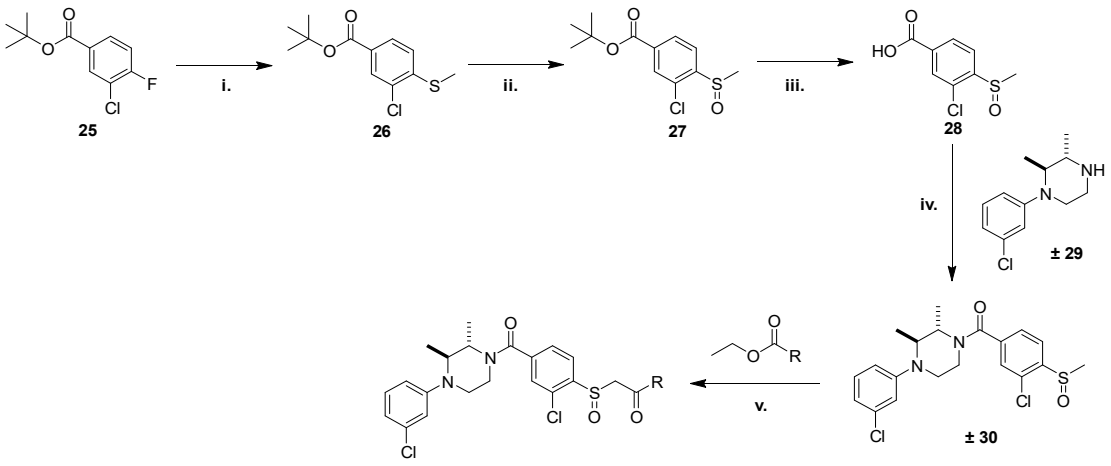


Figure 1. **A**) Design strategy of aryl ketones as MAGL inhibitors. **B**) Chemical structures of OL-135 and LEI-105. **C**) View of OL-135 in the binding pocket of FAAH (PDB ID: 3PR0). OL-135 binds to the catalytic Ser241 covalently and the deprotonated hemiketal mimics the enzymatic tetrahedral intermediate.

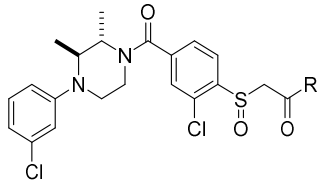


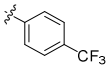
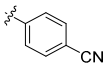
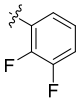
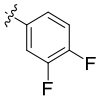
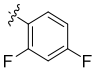
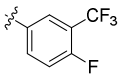
Scheme 1. General synthesis route of designed α-aryl ketones. i) CH_3SNa, DMF, -10 ºC – RT, 16h, 50%; ii) Oxone, MeOH / H_2O, 0 ºC – RT, 2h, 81%; iii) TFA, DCM, RT, 16h, 86%; iv) EDCI, HOBt, DiPEA, DCM, 16h, 50%; v) LDA, THF, -78 ºC.

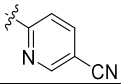
Replacing the ester moiety with phenyl ketone (± **4**) resulted in an active MAGL inhibitor, which was therefore used as the starting point for further optimization. To analyze the effect of the substitution pattern on the phenyl ring, compounds ± **5** – ± **15** were examined. Fluorine as an electron withdrawing substituent on the *ortho*- (± **5**) or *para*-position (± **9**), but not *meta*-position (± **8**), was allowed, albeit that there is hardly an increase in potency. Interestingly, the polar electron withdrawing para nitril substituent (± **7**) significantly increased the potency. Difluoro substitution (± **11 -** ± **14**) improved the potency, but trifluoromethyl substitution on *meta*-position (± **15)** abolished the MAGL inhibitory activity. Replacement of the phenyl ring to 3-pyridinyl ring (± **10**) decreased the potency. The Hammett constants (σ) of the substituents was plotted against the activity of the compounds, but no correlation (r^2 = 0.16, Figure S1) was found, suggesting that the electron-withdrawing effect is not the main contributor to the potency.

Since polar substitution is favored and reduces the lipophilicity, the phenyl ring was replaced with five or six-membered heterocycles (± **16** - ± **24**). These compounds displayed an increased MAGL inhibitory activity and lipophilic efficiency (LipE). Compounds with oxazol-2-yl (± **16**), 5-methyloxazol-2-yl (± **17**) and thiazol-2-yl (± **18**) groups showed around 10-fold increase in potency and 100-fold increase in LipE. For compounds with a six-membered heterocycle, hetero atoms at the *2*- and/or *4*-positions (± **21 -** ± **22)** were more favored than at the *3*-position (± **19,** ± **20** and ± **23**). Of these, compound ± **22** showed a higher LipE than compound ± **1**. Finally, 5-cyanopyridin-2-yl ketone (± **24**) was designed and evaluated. Compound ± **24** showed a pIC_{50} of 8.00 ± 0.10, which is 250-fold higher than the starting compound ± **4** and similar in magnitude as compound ± **1** (pIC_{50} = 8.50 ± 0.10).

Table 1. pIC_{50} values of α-aryl ketones (**±2** - **±24**).



Entry	R	pIC_{50} ± SD	MW	cLogP	tPSA	LipE
± 1		8.50 ± 0.10	497.63	4.93	67	3.57
± 4		5.64 ± 0.14	529.48	5.68	58	-0.04
± 5		5.72 ± 0.04	547.47	5.90	58	-0.18
± 6		5.53 ± 0.10	597.47	6.70	58	-1.17
± 7		7.04 ± 0.06	554.49	5.29	81	1.75
± 8		<5	547.47	5.90	58	N.A.
± 9		5.79 ± 0.22	547.47	5.45	58	-0.11
± 10		5.01 ± 0.05	530.46	4.58	70	0.43
± 11		5.68 ± 0.23	565.46	6.07	58	-0.39
± 12		6.24 ± 0.20	565.46	5.55	58	0.17
± 13		6.12 ± 0.21	565.46	6.00	58	0.05
± 14		6.63 ± 0.07	565.46	6.07	58	0.56
± 15		<5	615.46	6.87	58	N.A.
± 16		6.69 ± 0.15	520.43	4.16	79	2.53
± 17		6.42 ± 0.07	534.45	4.42	79	2.00
± 18		6.63 ± 0.10	536.49	4.81	70	1.82
± 19		6.60 ± 0.07	531.45	3.59	82	3.01

Entry	R	pIC_{50} ± SD	MW	cLogP	tPSA	LipE
± **20**		6.15 ± 0.05	531.45	3.59	82	2.56
± **21**		7.06 ± 0.16	531.45	4.02	82	3.47
± **22**		7.55 ± 0.14	531.45	4.02	82	3.96
± **23**		5.96 ± 0.12	531.45	4.02	82	2.37
± **24**		8.00 ± 0.10	555.47	4.53	94	3.47

3.3 Conclusion

In conclusion, a series of α-aryl ketones as MAGL inhibitors is reported in this chapter. SAR investigation supported the original hypothesis that the ester group of compound ± **1** may serve as an electrophilic site for a nucleophilic attack by the catalytic serine of MAGL. Replacing the ester with aryl ketones resulted in the discovery of ± **22** and ± **24** as potent MAGL inhibitors. Since these compounds contain a similar "warhead" as the FAAH inhibitor OL-135, they are expected to inhibit MAGL in a similar fashion through a covalent, reversible mechanism. To our knowledge, these α-aryl ketones are the first MAGL inhibitors with an activated ketone reported so far. The metabolic stability of this chemical series will be examined in Chapter 4.

3.4 Experimental procedures

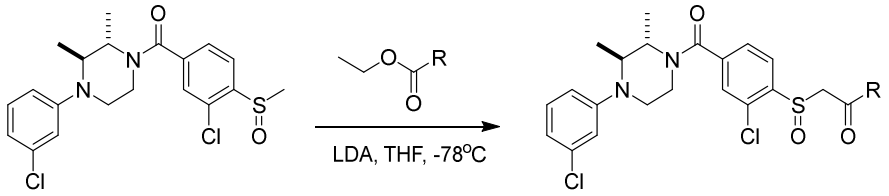
MAGL natural substrate assay

The natural substrate assay for MAGL was performed as previously reported in Chapter 2.[21]

Chemistry procedures

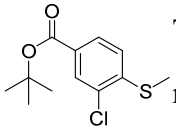
General remarks. All reactions were performed using oven or flame-dried glassware and dry solvents. Reagents were purchased from Sigma Aldrich, Acros and Merck and used without further purification unless noted otherwise. All moisture sensitive reactions were performed under an argon or nitrogen atmosphere. 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, quintet = 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 I



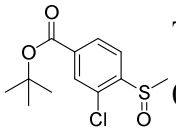
To a solution of (±) (3-chloro-4-(methylsulfinyl)phenyl)(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazin-1-yl)methanone (1 eq.) in anhydrous THF was added LDA (2 eq.) at -78 °C and the reaction mixture was stirred for 30 min before the appropriate ester (10 eq.) was added. The reaction progress was monitored by TLC. 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.

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



To a solution of *tert*-butyl 3-chloro-4-fluorobenzoate (**25**) (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 °C 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%). ^1H 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). ^{13C} 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.

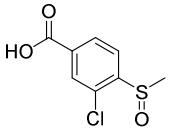
***tert*-Butyl 3-chloro-4-(methylsulfinyl)benzoate (27)**



To a solution of *tert*-butyl 3-chloro-4-(methylthio)benzoate (**26**) (0.24 g, 0.91 mmol, 1 eq.) in 10 mL MeOH was added Oxone (0.56 g, 0.91 mmol, 1 eq.) / H_2O (5 mL) solution at 0 °C and the mixture was stirred at RT for 1 h. The reaction progress was monitored by TLC. Once completed, the mixture was diluted with DCM, washed with water, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified using column chromatography (Et_2O

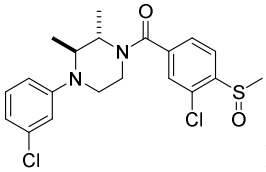
/ pentane, 25-40%) to yield the product (0.290 g, 1.17 mmol, quant.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.03 – 7.98 (m, 2H), 2.86 (s, 3H), 1.62 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.34, 147.97, 135.70, 130.48, 129.52, 128.73, 125.20, 82.24, 41.37, 27.94.

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



To a solution of *tert*-butyl 3-chloro-4-(methylsulfinyl)benzoate (**27**) (0.26 g, 0.94 mmol) in 8mL DCM was added 2 mL TFA and the mixture was stirred at RT for 6 h. The reaction progress was monitored by TLC. Once completed, the mixture was diluted with DCM, washed with saturated $NaHCO_3$ solution, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified using column chromatography (MeOH / DCM, 1-5%) to yield 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 (126 MHz, Methanol-*d*4) δ 167.19, 148.93, 136.49, 132.03, 131.20, 130.45, 126.47, 41.68.

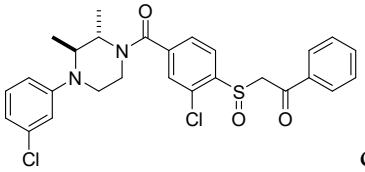
(±) (3-Chloro-4-(methylsulfinyl)phenyl)(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazin-1-yl)methanone (**30**)



To a stirred suspension of 3-chloro-4-((2-ethoxy-2-oxoethyl)sulfinyl)benzoic acid (**28**) (0.19 g, 0.87 mmol, 1 eq.) in DCM (10 ml) were added (±) trans-1-(3-chlorophenyl)-2,3-dimethylpiperazine (**30**) (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 EDCI (0.25 mg, 1.30 mmol, 1.5 eq.). The mixture was stirred at RT overnight. The reaction progress was monitored by TLC. Once completed, the mixture was washed with water and brine, dried ($MgSO_4$), 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,

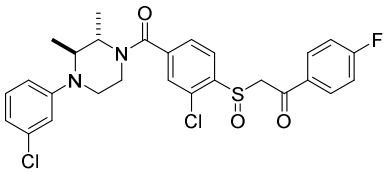
116.13, 114.19, 56.08, 49.57, 42.29, 41.64, 36.46, 17.76, 12.52.

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



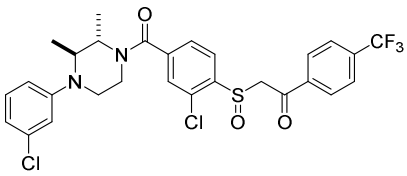
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl benzoate (177 mg, 1.175 mmol, 10 eq.) according to General Procedure I. This yielded the product (38.5 mg, 0.073 mmol, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 7.2 Hz, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.52 (d, J = 10.6 Hz, 2H), 7.49 (d, J = 7.5 Hz, 2H), 7.19 (t, J = 8.1 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 6.82 (d, J = 2.1 Hz, 1H), 6.73 (d, J = 10.1 Hz, 1H), 4.66 (dd, J = 14.7, 3.6 Hz, 1H), 4.42 (dd, J = 14.7, 2.7 Hz, 1H), 3.96 – 3.07 (br, 6H), 1.51 (d, J = 6.5 Hz, 3H), 1.06 (br, 3H). HRMS: calculated for $[C_{27}H_{26}Cl_2N_2O_3S+ H]^+$= 529.1114, found: 529.1112.

(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(4-fluorophenyl)ethan-1-one (5)



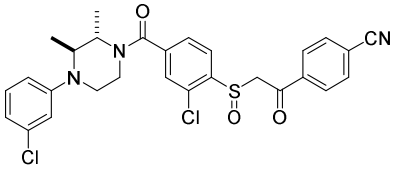
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl 4-fluorobenzoate (198 mg, 1.18 mmol, 10.0 eq.) according to general procedure I. This yielded the product (17 mg, 0.030? mmol, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, J = 5.0, 1.8 Hz, 1H), 7.97 (s, 1H), 7.95 (d, J = 3.0 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.21 – 7.15 (m, 3H), 6.85 – 6.80 (m, 2H), 6.75 – 6.70 (dd, 1H), 4.64 – 4.60 (m, 1H), 4.35 (dd, J = 14.3, 1.9 Hz, 1H), 4.09 – 2.97 (m, 6H), 1.51 (d, J = 7.2 Hz, 3H), 1.07 (m, 3H). HRMS: calculated for $[C_{27}H_{25}Cl_2FN_2O_3S+ H]^+$= 547.1020, found: 547.1018.

(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(4-(trifluoromethyl)phenyl)ethan-1-one (6)



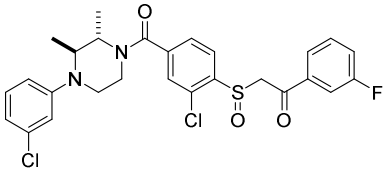
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl 4-(trifluoromethyl)benzoate (256 mg, 1.178 mmol, 10.0 eq.) according to general procedure I. This yielded the product (16.2 mg, 0.027 mmol, 23%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 8.6 Hz, 2H), 7.96 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.6 Hz, 2H), 7.53 (dd, J = 8.0, 1.4 Hz, 1H), 7.51 (d, J = 1.3 Hz, 1H), 7.18 (t, J = 8.1 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 6.81 (t, J = 2.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 4.70 (dd, J = 14.4, 3.8 Hz, 1H), 4.40 (dd, J = 14.4, 3.3 Hz, 1H), 3.89 – 3.15 (br, 6H), 1.52 (d, J = 6.6 Hz, 3H), 1.05 (br, 3H). HRMS: calculated for $[C_{25}H_{24}Cl_2N_4O_3S+ H]^+$= 597.0988, found: 597.0984.

(±) 4-(2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethyl-piperazine-1-carbonyl)phenyl)sulfinyl)acetyl)benzonitrile (**7**)



The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl 4-cyanobenzoate (206 mg, 1.18 mmol, 10 eq.) according to General Procedure I. This yielded the product (12 mg, 0.022 mmol, 18%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 8.0 Hz, 2H), 7.92 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.20 (t, J = 8.1 Hz, 1H), 6.85 (d, J = 8.3 Hz, 2H), 6.76 (d, J = 8.5 Hz, 1H), 4.69 (dd, J = 14.0, 3.4 Hz, 1H), 4.36 (dd, J = 14.1, 2.9 Hz, 1H), 3.83 – 3.17 (br, 6H), 1.53 (d, J = 6.7 Hz, 3H), 1.09 (br, 3H). HRMS: calculated for $[C_{27}H_{24}Cl_2F_2N_2O_3S+ H]^+$ = 554.1066, found: 554.1066.

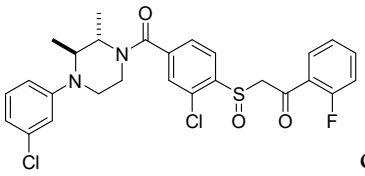
(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(3-fluorophenyl)ethan-1-one (**8**)



The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl 3-fluorobenzoate (198 mg, 1.18 mmol, 10.00 eq.) according to general procedure I. This yielded the product (8.0 mg, 0.002 mmol,

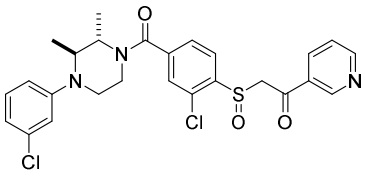
12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 9.1 Hz, 1H), 7.54 – 7.46 (m, 3H), 7.34 (t, J = 8.2 Hz, 1H), 7.19 (t, J = 7.8 Hz, 1H), 6.82 (d, J = 7.5 Hz, 2H), 6.72 (d, J = 8.1 Hz, 1H), 4.67 – 4.57 (m, 1H), 4.33 (d, J = 14.3 Hz, 1H), 3.92 – 3.12 (br, 6H), 1.54 – 1.45 (m, 3H), 1.16 – 1.00 (m, 3H). HRMS: calculated for $[C_{27}H_{25}Cl_2FN_2O_3S+ H]^+$ = 547.1020, found: 547.1019.

(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(2-fluorophenyl)ethan-1-one (9)



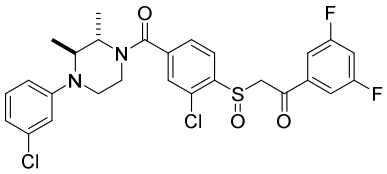
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl 2-fluorobenzoate (198 mg, 1.178 mmol, 10.0 eq.) according to general procedure I. This yielded the product (5.5 mg, 0.001 mmol, 9%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, J = 7.9 Hz, 1H), 7.96 (t, J = 8.5 Hz, 1H), 7.61 (d, J = 6.2 Hz, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 7.4 Hz, 1H), 7.21 – 7.11 (m, 2H), 6.98 (d, J = 10.9 Hz, 1H), 6.84 (d, J = 7.4 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 4.68 (d, J = 22.3 Hz, 1H), 4.37 (dt, J = 14.7, 2.8 Hz, 1H), 3.91 – 3.17 (br, 6H), 1.51 (d, J = 6.8 Hz, 3H), 1.08 (br, 3H). HRMS: calculated for $[C_{27}H_{25}Cl_2FN_2O_3S + H]^+$= 547.1020, found: 547.1024.

(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(pyridin-3-yl)ethan-1-one (10)



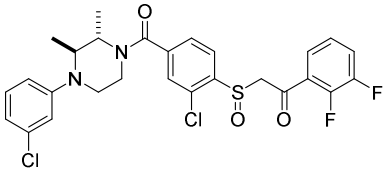
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl nicotinate (178 mg, 1.18 mmol, 10 eq.) according to general procedure I. This yielded the product (5 mg, 0.01 mmol, 8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.99 (d, J = 5.0 Hz, 1H), 8.80 (m, 1H), 7.98 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.19 (t, J = 8.3 Hz, 1H), 6.85 (d, J = 6.5 Hz, 2H), 6.76 (d, J = 8.4 Hz, 1H), 4.92 (d, J = 13.0 Hz, 1H), 4.47 (d, J = 13.2 Hz, 1H), 3.88 – 3.13 (br, 6H), 1.52 (d, J = 6.5 Hz, 3H), 1.09 (br, 3H). HRMS: calculated for $[C_{26}H_{25}Cl_2N_3O_3S + H]^+$= 530.1066, found: 530.1069.

(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(3,5-difluorophenyl)ethan-1-one (11)



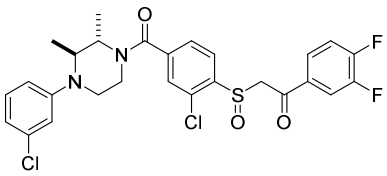
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl 3,5-difluorobenzoate (219 mg, 1.175 mmol, 10 eq.) according to general procedure I. This yielded the product (21 mg, 0.037 mmol, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, J = 8.0, 1.2 Hz, 1H), 7.46 (dd, J = 7.5, 2.1 Hz, 2H), 7.18 (t, J = 8.2 Hz, 1H), 7.12 (dt, J = 8.3, 2.3 Hz, 2H), 7.09 (t, J = 2.3 Hz, 1H), 6.85 – 6.79 (m, 2H), 6.73 (d, J = 9.2 Hz, 1H), 4.60 (dd, J = 14.1, 2.8 Hz, 1H), 4.30 (dd, J = 14.1, 2.8 Hz, 1H), 3.82 – 2.53 (br, 6H), 1.50 (d, J = 6.5 Hz, 3H), 1.09 (d, J = 34.8 Hz, 3H). HRMS: calculated for $[C_{27}H_{24}Cl_2F_2N_2O_3S+H]^+$ = 565.0926, found: 565.0926.

(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(2,3-difluorophenyl)ethan-1-one (12)



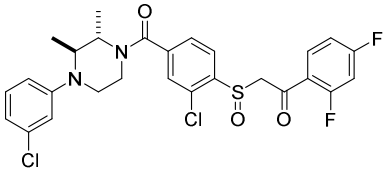
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl 2,3-difluorobenzoate (278 mg, 1.18 mmol, 10 eq.) according to general procedure I. This yielded the product (26 mg, 0.046 mmol, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 8.0, 2.2 Hz, 1H), 7.72 – 7.66 (t, 1H), 7.54 (dd, J = 8.0, 1.4 Hz, 1H), 7.50 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.26 – 7.22 (dd, 1H), 7.19 (t, J = 8.3 Hz, 1H), 6.84 (d, J = 6.6 Hz, 2H), 6.74 (d, J = 9.2 Hz, 1H), 4.70 (dt, J = 15.3, 2.7 Hz, 1H), 4.39 (dt, J = 15.3, 2.7 Hz, 1H), 4.06 – 2.73 (br, 6H), 1.51 (d, J = 6.7 Hz, 3H), 1.08 (br, 3H). HRMS: calculated for $[C_{27}H_{24}Cl_2F_2N_2O_3S+ H]^+$= 565.0926, found: 565.0926.

(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(3,4-difluorophenyl)ethan-1-one (13)



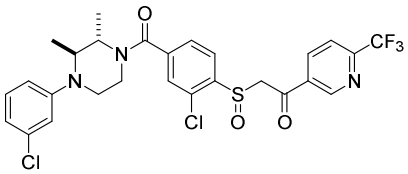
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl 3,4-difluorobenzoate (278 mg, 1.18 mmol, 10 eq.) according to general procedure I. This yielded the product (18.0 mg, 0.032 mmol, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.9 Hz, 1H), 7.81 (t, J = 8.0 Hz, 1H), 7.76 (d, J = 6.3 Hz, 1H), 7.54 (d, J = 11.3 Hz, 2H), 7.36 – 7.30 (br, 1H), 7.21 (t, J = 8.1 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 6.76 (d, J = 8.8 Hz, 1H), 4.63 (dd, J = 14.2, 2.5 Hz, 1H), 4.34 (dd, J = 14.2, 2.2 Hz, 1H), 4.00 – 2.99 (br, 6H), 1.54 (d, J = 6.7 Hz, 3H), 1.10 (br, 3H). HRMS: calculated for $[C_{27}H_{24}Cl_2F_2N_2O_3S + H]^+$= 565.0926, found: 565.0925.

(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(2,4-difluorophenyl)ethan-1-one (**14**)



The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl 2,4-difluorobenzoate (218 mg, 1.17 mmol, 10 eq.) according to general procedure I. This yielded the product (29.7 mg, 0.053 mmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.03 (m, 1H), 8.04 – 8.00 (m, 1H), 7.57 (dd, J = 8.0, 1.5 Hz, 1H), 7.52 (d, J = 1.4 Hz, 1H), 7.21 (t, J = 8.1 Hz, 1H), 7.08 – 7.02 (ddd, 1H), 6.92 (ddd, J = 11.1, 8.5, 2.3 Hz, 1H), 6.86 (d, J = 8.0 Hz, 2H), 6.76 (d, J = 9.1 Hz, 1H), 4.69 (dt, J = 15.5, 2.7 Hz, 1H), 4.38 (dt, J = 15.5, 2.5 Hz, 1H), 4.17 – 2.55 (br, 6H), 1.54 (d, J = 6.7 Hz, 3H), 1.11 (br, 3H). HRMS: calculated for $[C_{27}H_{24}Cl_2F_2N_2O_3S+ H]^+$= 565.0926, found: 565.0923.

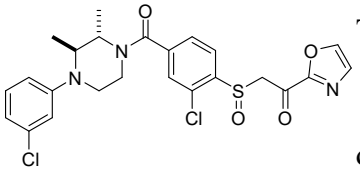
(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(6-(trifluoromethyl)pyridin-3-yl)ethan-1-one (**15**)



The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl 6-(trifluoromethyl)nicotinate (258 mg, 1.18 mmol, 10 eq.) according to general procedure I. This yielded the product (4.7 mg,

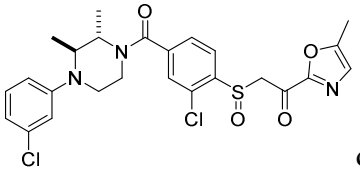
0.0078 mmol, 7%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.45 (d, J = 8.1 Hz, 1H), 7.86 (t, J = 8.3 Hz, 2H), 7.53 (d, J = 7.6 Hz, 2H), 7.20 (t, J = 8.3 Hz, 1H), 6.85 (s, 2H), 6.77 (d, J = 8.2 Hz, 1H), 4.74 (dd, J = 13.7, 4.0 Hz, 1H), 4.36 (dd, J = 13.7, 4.6 Hz, 1H), 3.83 – 3.16 (br, 6H), 1.52 (d, J = 6.7 Hz, 3H), 1.09 (br, 3H). HRMS: calculated for $[C_{27}H_{24}Cl_2F_3N_3O_3S + H]^+$= 598.0940, found: 598.0942.

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



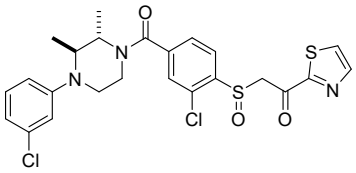
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (65 mg, 0.15 mmol, 1 eq.) and ethyl oxazole-2-carboxylate (216 mg, 1.53 mmol, 10 eq.) according to procedure I. This yielded the product (3.2 mg, 0.15 mmol, 3%). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.05, 168.68, 168.22, 151.35, 142.95, 142.25, 140.76, 135.28, 131.01, 130.37, 129.97, 128.58, 126.92, 126.05, 119.49, 116.25, 114.25, 61.04, 60.50, 49.66, 42.35, 36.53, 14.29, 12.58. HRMS: Calculated for $[C_{24}H_{23}Cl_2N_3O_4S + H]+$ = 520.0859, found = 520.0857.

(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(5-methyloxazol-2-yl)ethan-1-one (17)



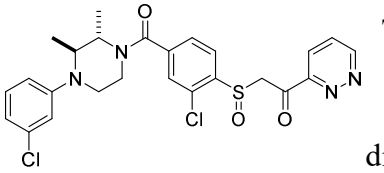
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (60 mg, 0.14 mmol, 1 eq.) and ethyl 5-methyloxazole-2-carboxylate (44 mg, 0.28 mmol, 2.00 eq.) according to general procedure I. This yielded the product (15 mg, 0.03 mmol, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.0 Hz, 1H), 7.54 – 7.44 (m, 2H), 7.18 (t, J = 7.7 Hz, 1H), 7.01 – 6.98 (m, 1H), 6.84 – 6.80 (m, 2H), 6.72 (d, J = 8.4 Hz, 1H), 4.87 – 3.05 (m, 8H), 2.44 (s, 3H), 1.53 – 1.46 (m, 3H), 1.08 (dd, J = 44.8, 6.6 Hz, 3H). HRMS: calculated for $[C_{25}H_{25}Cl_2N_3O_4S + H]^+$ = 534.1016, found: 534.1017.

(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(thiazol-2-yl)ethan-1-one (18)



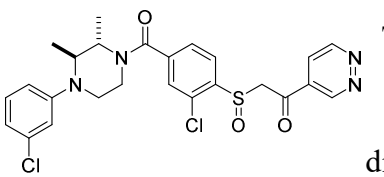
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (40 mg, 0.09 mmol, 1 eq.) and ethyl thiazole-2-carboxylate (148 mg, 0.94 mmol, 10 eq.) according to procedure I. This yielded the product (32 mg, 0.06 mmol, 63%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 – 7.95 (m, 2H), 7.76 (dd, J = 3.0, 1.4 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.18 (t, J = 8.1 Hz, 1H), 6.84 – 6.79 (m, 2H), 6.73 (d, 1H), 4.83 – 4.68 (m, 2H), 3.95 – 3.11 (m, 6H), 1.50 (d, J = 6.8 Hz, 3H), 1.16 – 0.97 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.64, 166.56, 152.19, 146.31, 143.48, 141.28, 136.27, 132.04, 132.00, 131.32, 128.93, 127.99, 127.03, 125.25, 120.60, 117.30, 115.26, 61.84, 61.79, 57.22, 56.24, 30.72, 13.80, 1.02. HRMS: Calculated for $[C_{24}H_{23}Cl_2N_3O_3S_2 + H]^+$ = 538.0600, found = 538.0600.

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



The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl pyridazine-3-carboxylate (179 mg, 1.18 mmol, 10 eq.) according to general procedure I. This yielded the product (13 mg, 0.024 mmol, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (d, J = 4.9 Hz, 1H), 8.21 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.75 (dd, J = 8.5, 5.0 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.46 (s, 1H), 7.21 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 6.2 Hz, 2H), 6.77 (d, J = 6.3 Hz, 1H), 5.07 – 4.96 (m, 2H), 3.83 – 3.15 (br, 6H), 1.52 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 6.2 Hz, 3H). HRMS: calculated for $[C_{25}H_{24}Cl_2N_4O_3S + H]^+$= 531.1019, found: 531.1020.

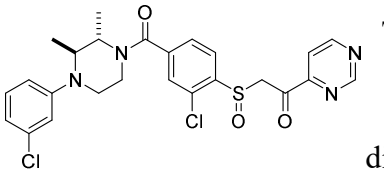
(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(pyridazin-4-yl)ethan-1-one (**20**)



The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and methyl pyridazine-4-carboxylate (162 mg, 1.175 mmol, 10 eq.)

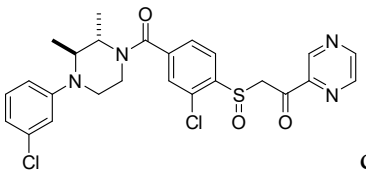
according to general procedure I. This yielded the product (42 mg, 0.079 mmol, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (d, J = 4.2 Hz, 2H), 7.97 (dt, J = 5.2, 2.3 Hz, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.19 (t, J = 8.3 Hz, 1H), 6.84 (d, J = 7.4 Hz, 2H), 6.75 (d, J = 9.2 Hz, 1H), 4.74 (dd, J = 13.5, 2.3 Hz, 1H), 4.42 (dd, J = 13.5, 3.4 Hz, 1H), 3.97 – 3.00 (br, 6H), 1.51 (d, J = 6.7 Hz, 3H), 1.08 (br, 3H). HRMS: calculated for $[C_{25}H_{24}Cl_2N_4O_3S + H]^+$= 531.1019, found: 531.1019.

(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(pyrimidin-4-yl)ethan-1-one (**21**)



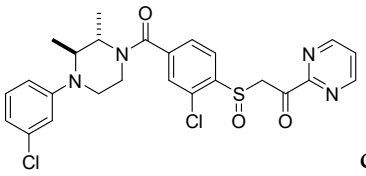
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl pyrimidine-4-carboxylate (179 mg, 1.175 mmol, 10 eq.) according to general procedure I. This yielded the product (3 mg, 0.0056 mmol, 5%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (s, 1H), 9.04 (d, J = 6.8 Hz, 1H), 7.99 – 7.93 (m, 2H), 7.54 – 7.48 (m, 2H), 7.22 (t, J = 8.4 Hz, 1H), 6.88 (d, J = 7.0 Hz, 2H), 6.80 (d, J = 7.9 Hz, 1H), 4.91 (dd, J = 13.8, 3.5 Hz, 1H), 4.77 (d, J = 13.8 Hz, 1H), 3.85 – 3.15 (br, 6H), 1.53 (dd, J = 6.8, 3.3 Hz, 3H), 1.10 (br, 3H). HRMS: calculated for $[C_{25}H_{24}Cl_2N_4O_3S+ H]^+$= 531.1019, found: 531.1018.

(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(pyrazin-2-yl)ethan-1-one (**22**)



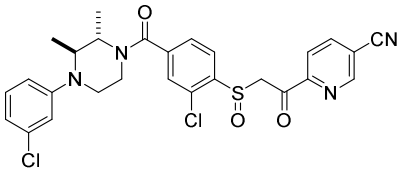
The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl pyrazine-2-carboxylate (179 mg, 1.18 mmol, 10.0 eq.) according to general procedure I. This yielded the product (27 mg, 0.051 mmol, 43%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.81 (s, 1H), 8.66 (s, 1H), 7.96 (d, J = 7.5 Hz, 1H), 7.50 (d, J = 9.7 Hz, 2H), 7.19 (t, J = 8.1 Hz, 1H), 6.87 – 6.81 (m, 2H), 6.74 (d, J = 8.2 Hz, 1H), 4.92 (d, J = 14.0 Hz, 1H), 4.77 (d, J = 14.0 Hz, 1H), 3.94 – 3.05 (br, 6H), 1.52 (d, J = 6.7 Hz, 3H), 1.08 (br, 3H). HRMS: calculated for $[C_{25}H_{24}Cl_2N_4O_3S+ H]^+$ = 531.1019, found: 531.1019.

(±) 2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)-1-(pyrimidin-2-yl)ethan-1-one (**23**)



The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and ethyl pyrimidine-2-carboxylate (179 mg, 1.18 mmol, 10 eq.) according to general procedure I. This yielded the product (30 mg, 0.056 mmol, 47 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (d, J = 4.9 Hz, 2H), 7.96 (d, J = 7.9 Hz, 1H), 7.55 (t, J = 4.9 Hz, 1H), 7.52 – 7.45 (t, 2H), 7.18 (t, J = 8.1 Hz, 1H), 6.83 (d, J = 12.3 Hz, 2H), 6.73 (d, J = 10.1 Hz, 1H), 5.01 (d, J = 13.9 Hz, 1H), 4.79 (d, J = 13.9 Hz, 1H), 4.03 – 3.07 (br, 6H), 1.51 (d, J = 6.6 Hz, 3H), 1.06 (br, 3H). HRMS: calculated for $[C_{25}H_{24}Cl_2N_4O_3S+ H]^+$= 531.1019, found: 531.1017.

(±) 6-(2-((2-Chloro-4-(4-(3-chlorophenyl)-trans-2,3-dimethylpiperazine-1-carbonyl)phenyl)sulfinyl)acetyl)nicotinonitrile (**24**)



The title compound was synthesized using (±) (3-chloro-4-(methylsulfinyl)phenyl)(trans-4-(3-chlorophenyl)-2,3-dimethylpiperazin-1-yl)methanone (**30**) (50 mg, 0.12 mmol, 1 eq.) and methyl 5-cyanopicolinate (191 mg, 1.18 mmol, 10 eq.) according to general procedure I. This yielded the product (31 mg, 0.057 mmol, 48%). 1HNMR (600 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.17 (s, 2H), 7.96 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 7.2 Hz, 1H), 7.46 (d, J = 21.8 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 6.82 (d, J = 8.2 Hz, 2H), 6.72 (s, 1H), 4.93 (s, 1H), 4.73 (s, 1H), 3.92 – 3.08 (br, 6H), 1.50 (d, J = 11.6 Hz, 3H), 1.08 (br, 3H). HRMS: calculated for $[C_{27}H_{24}Cl_2N_4O_3S+ H]^+$= 555.1019, found: 555.1022.

References

1. Nomura, D. K.; Lombardi, D. P.; Chang, J. W.; Niessen, S.; Ward, A. M.; Long, J. Z.; Hoover, H. H.; Cravatt, B. F. Monoacylglycerol lipase exerts dual control over endocannabinoid and fatty acid pathways to support prostate cancer. *Chemistry & biology* **2011,** 18, 846-56.
2. Nomura, D. K.; Long, J. Z.; Niessen, S.; Hoover, H. S.; Ng, S. W.; Cravatt, B. F. Monoacylglycerol lipase regulates a fatty acid network that promotes cancer pathogenesis. *Cell* **2010,** 140, 49-61.
3. Aghazadeh Tabrizi, M.; Baraldi, P. G.; Baraldi, S.; Ruggiero, E.; De Stefano, L.; Rizzolio, F.; Di Cesare Mannelli, L.; Ghelardini, C.; Chicca, A.; Lapillo, M.; Gertsch, J.; Manera, C.; Macchia, M.; Martinelli, A.; Granchi, C.; Minutolo, F.; Tuccinardi, T. Discovery of 1,5-Diphenylpyrazole-3-Carboxamide Derivatives as Potent, Reversible, and Selective Monoacylglycerol Lipase (MAGL) Inhibitors. *J Med Chem* **2018,** 61, 1340-1354.
4. Aida, J.; Fushimi, M.; Kusumoto, T.; Sugiyama, H.; Arimura, N.; Ikeda, S.; Sasaki, M.; Sogabe, S.; Aoyama, K.; Koike, T. Design, Synthesis, and Evaluation of Piperazinyl Pyrrolidin-2-ones as a Novel Series of Reversible Monoacylglycerol Lipase Inhibitors. *J Med Chem* **2018,** 61, 9205-9217.
5. Cisar, J. S.; Weber, O. D.; Clapper, J. R.; Blankman, J. L.; Henry, C. L.; Simon, G. M.; Alexander, J. P.; Jones, T. K.; Ezekowitz, R. A. B.; O'Neill, G. P.; Grice, C. A. Identification of ABX-1431, a Selective Inhibitor of Monoacylglycerol Lipase and Clinical Candidate for Treatment of Neurological Disorders. *J Med Chem* **2018,** 61, 9062-9084.
6. Cisneros, J. A.; Bjorklund, E.; Gonzalez-Gil, I.; Hu, Y.; Canales, A.; Medrano, F. J.; Romero, A.; Ortega-Gutierrez, S.; Fowler, C. J.; Lopez-Rodriguez, M. L. Structure-activity relationship of a new series of reversible dual monoacylglycerol lipase/fatty acid amide hydrolase inhibitors. *J Med Chem* **2012,** 55, 824-36.
7. Granchi, C.; Rizzolio, F.; Palazzolo, S.; Carmignani, S.; Macchia, M.; Saccomanni, G.; Manera, C.; Martinelli, A.; Minutolo, F.; Tuccinardi, T. Structural Optimization of 4-Chlorobenzoylpiperidine Derivatives for the Development of Potent, Reversible, and Selective Monoacylglycerol Lipase (MAGL) Inhibitors. *Journal of medicinal chemistry* **2016,** 59, 10299-10314.
8. Kapanda, C. N.; Masquelier, J.; Labar, G.; Muccioli, G. G.; Poupaert, J. H.; Lambert, D. M. Synthesis and pharmacological evaluation of 2,4-dinitroaryldithiocarbamate derivatives as novel monoacylglycerol lipase inhibitors. *Journal of medicinal chemistry* **2012,** 55, 5774-83.
9. Long, J. Z.; Li, W.; Booker, L.; Burston, J. J.; Kinsey, S. G.; Schlosburg, J. E.; Pavon, F. J.; Serrano, A. M.; Selley, D. E.; Parsons, L. H.; Lichtman, A. H.; Cravatt, B. F. Selective blockade of 2-arachidonoylglycerol hydrolysis produces cannabinoid behavioral effects. *Nature chemical biology* **2009,** 5, 37-44.
10. Matuszak, N.; Muccioli, G. G.; Labar, G.; Lambert, D. M. Synthesis and in vitro evaluation of N-substituted maleimide derivatives as selective monoglyceride lipase inhibitors. *Journal of medicinal chemistry* **2009,** 52, 7410-20.
11. McAllister, L. A.; Butler, C. R.; Mente, S.; O'Neil, S. V.; Fonseca, K. R.; Piro, J. R.; Cianfrogna, J. A.; Foley, T. L.; Gilbert, A. M.; Harris, A. R.; Helal, C. J.; Johnson, D. S.; Montgomery, J. I.; Nason, D. M.; Noell, S.; Pandit, J.; Rogers, B. N.; Samad, T. A.; Shaffer, C. L.; da Silva, R. G.; Uccello, D. P.; Webb, D.; Brodney, M. A. Discovery of Trifluoromethyl

Glycol Carbamates as Potent and Selective Covalent Monoacylglycerol Lipase (MAGL) Inhibitors for Treatment of Neuroinflammation. *J Med Chem* **2018,** 61, 3008-3026.
12. Muccioli, G. G.; Labar, G.; Lambert, D. M. CAY10499, a novel monoglyceride lipase inhibitor evidenced by an expeditious MGL assay. *ChemBioChem* **2008,** 9, 2704-2710.
13. Zvonok, N.; Pandarinathan, L.; Williams, J.; Johnston, M.; Karageorgos, I.; Janero, D. R.; Krishnan, S. C.; Makriyannis, A. Covalent inhibitors of human monoacylglycerol lipase: ligand-assisted characterization of the catalytic site by mass spectrometry and mutational analysis. *Chemistry & biology* **2008,** 15, 854-62.
14. Aaltonen, N.; Savinainen, J. R.; Ribas, C. R.; Rönkkö, J.; Kuusisto, A.; Korhonen, J.; Navia-Paldanius, D.; Häyrinen, J.; Takabe, P.; Käsnänen, H. Piperazine and piperidine triazole ureas as ultrapotent and highly selective inhibitors of monoacylglycerol lipase. *Chemistry & biology* **2013,** 20, 379-390.
15. Hernandez-Torres, G.; Cipriano, M.; Heden, E.; Bjorklund, E.; Canales, A.; Zian, D.; Feliu, A.; Mecha, M.; Guaza, C.; Fowler, C. J.; Ortega-Gutierrez, S.; Lopez-Rodriguez, M. L. A reversible and selective inhibitor of monoacylglycerol lipase ameliorates multiple sclerosis. *Angew Chem Int Ed Engl* **2014,** 53, 13765-70.
16. Ezzili, C.; Mileni, M.; McGlinchey, N.; Long, J. Z.; Kinsey, S. G.; Hochstatter, D. G.; Stevens, R. C.; Lichtman, A. H.; Cravatt, B. F.; Bilsky, E. J.; Boger, D. L. Reversible competitive α-ketoheterocycle inhibitors of fatty acid amide hydrolase containing additional conformational constraints in the acyl side chain: orally active, long-acting analgesics. *J Med Chem* **2011,** 54, 2805-22.
17. Mileni, M.; Garfunkle, J.; Ezzili, C.; Cravatt, B. F.; Stevens, R. C.; Boger, D. L. Fluoride-mediated capture of a noncovalent bound state of a reversible covalent enzyme inhibitor: X-ray crystallographic analysis of an exceptionally potent α-ketoheterocycle inhibitor of fatty acid amide hydrolase. *J Am Chem Soc* **2011,** 133, 4092-100.
18. Janssen, F. J.; Baggelaar, M. P.; Hummel, J. J.; Overkleeft, H. S.; Cravatt, B. F.; Boger, D. L.; van der Stelt, M. Comprehensive Analysis of Structure-Activity Relationships of α-Ketoheterocycles as sn-1-Diacylglycerol Lipase α Inhibitors. *J Med Chem* **2015,** 58, 9742-53.
19. Baggelaar, M. P.; Chameau, P. J.; Kantae, V.; Hummel, J.; Hsu, K. L.; Janssen, F.; van der Wel, T.; Soethoudt, M.; Deng, H.; den Dulk, H.; Allarà, M.; Florea, B. I.; Di Marzo, V.; Wadman, W. J.; Kruse, C. G.; Overkleeft, H. S.; Hankemeier, T.; Werkman, T. R.; Cravatt, B. F.; van der Stelt, M. Highly Selective, Reversible Inhibitor Identified by Comparative Chemoproteomics Modulates Diacylglycerol Lipase Activity in Neurons. *J Am Chem Soc* **2015,** 137, 8851-7.
20. Baggelaar, M. P.; Janssen, F. J.; van Esbroeck, A. C.; den Dulk, H.; Allarà, M.; Hoogendoorn, S.; McGuire, R.; Florea, B. I.; Meeuwenoord, N.; van den Elst, H.; van der Marel, G. A.; Brouwer, J.; Di Marzo, V.; Overkleeft, H. S.; van der Stelt, M. Development of an activity-based probe and in silico design reveal highly selective inhibitors for diacylglycerol lipase-α in brain. *Angew Chem Int Ed Engl* **2013,** 52, 12081-5.
21. van der Wel, T.; Janssen, F. J.; Baggelaar, M. P.; Deng, H.; den Dulk, H.; Overkleeft, H. S.; van der Stelt, M. A natural substrate-based fluorescence assay for inhibitor screening on diacylglycerol lipase α. *Journal of Lipid Research* **2015,** 56, 927-935.

Supplementary Information

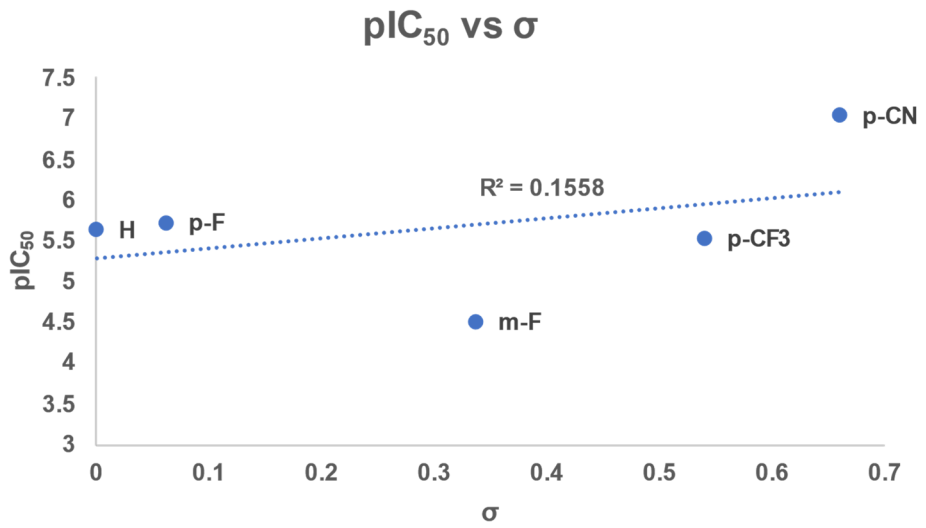


Figure S1. Plot of pIC_{50}-values of the aryl ketone series versus the corresponding substituent σ-values.