

2-PHENOXY-1-(4-(ALKYLSULFONYL)PIPERIDIN-1-YL)ETHAN-1-ONE AND 3-PHENYL-1-(4-(ALKYLSULFONYL)PIPERIDIN-1-YL)PROP-2-EN-1-ONE DERIVATIVES AS GPR183 ANTAGONISTS FOR THE TREATMENT OF CHRONIC PAIN

FIELD OF THE INVENTION

The present disclosure relates to novel pharmacologically active compounds as well as to pharmaceutical compositions comprising them and to their use as GPR183
5 antagonists.

BACKGROUND OF THE INVENTION

G protein-coupled receptor 183 (GPR183) also known as Epstein-Barr virus-induced G-protein coupled receptor 2 (EBI2) belongs to the G-protein coupled receptor (GPCR) superfamily of cellular integral membrane proteins involved in a broad
10 range of signaling pathways and physiological functions. GPCRs are important targets for pharmaceutical intervention as approximately 30 % of medicines in clinical use function as agonists, antagonists or modulators of the GPCRs. GPR183 is one of the most up-regulated genes (>200 fold) in Epstein-Barr virus-infected Burkitt lymphoma cells (Birkenbach et al.,1993). Following deorphanization of GPR183 by
15 identifying 7 α ,25-dihydroxycholesterol as a potent and selective endogenous agonist of the receptor (Hannedouche et al., 2011), the involvement of the receptor and ligand in cellular functions and physiological processes have been more extensively studied and revealed.

Intracellularly GPR183 has been shown to couple to G_i and inhibition of cyclic AMP
20 and activation of ERK (Benned-Jensen et al.,2011). Ligand-induced or constitutive GPR183 internalization is independent of β -arrestin whereas migration mediated by GPR183 is dependent on β -arrestin coupling (Kjær et al.,2023).

The cryo-EM structures of GPR183-G_i signalling complex with its endogenous agonist 7 α ,25-OHC and that of an inactive GPR183 receptor bound to the inverse
25 agonist GSK682753A have been revealed. Mutations within the oxysterol binding site and the G α_i interface attenuated G protein signalling and abolished oxysterol-

mediated cell migration indicating that G protein signalling is directly involved in the oxysterol GPR183 pathway (Chen et al., 2022).

GPR183 has been shown to be most abundantly expressed by immune cells and tissue, with highest expression in B-lymphocytes, followed by T lymphocytes, NK-
5 cells and lowest in monocytes. The lungs and the gastrointestinal tract also show comparably high expression levels (Rosenkilde et al. 2006). The expression pattern and the finding that $7\alpha,25$ -OHC and closely related oxysterols act as chemoattractants for immune cells expressing GPR183 by directing cell migration in vitro and in vivo (Hannedouche et al., 2011) implicates a possibility for targeting the
10 receptor for immunological indications and disorders.

Involvement of GPR183 in pain perception has been shown as acute intrathecal injection of the GPR183 ligand, $7\alpha,25$ -OHC in naive mice induced dose-dependent allodynia. GPR183 expression was upregulated in the dorsal spinal cord after chronic constriction injury (CCI) (Braden et al., 2020). Overexpression of the CH25H
15 enzyme, that metabolizes cholesterol to the GPR183 agonist $7\alpha,25$ -OHC, has been detected in the cartilage of human osteoarthritis patients (Choi et al., 2019). GPR183 expression in the central nervous system in human astrocytes (Rutowska et al., 2012) and microglia (Hsiao et al., 2019), as well as the upregulation of GPR183 receptor and induction of allodynia by the endogenous GPR183 agonist in rodents implicates
20 a potential for amelioration by GPR183 antagonists in pain indications.

Some compounds modulating the activity of GPR183 protein are known in the art. WO2023066190 describes some heterocyclic compounds as GPR183 inhibitors. GPR183 antagonists for the treatment of pain are disclosed in US20210122750. WO2015048567 describes some spirocyclic EBI2 modulators, and WO2015048570
25 describes amide derivatives as EBI2 modulators.

SUMMARY OF THE INVENTION

An object of the present disclosure is to provide novel pharmacologically active compounds that act as antagonist to GPR183 receptor. Accordingly, an object of the present disclosure is to provide further compounds to be used as GPR183 antagonist

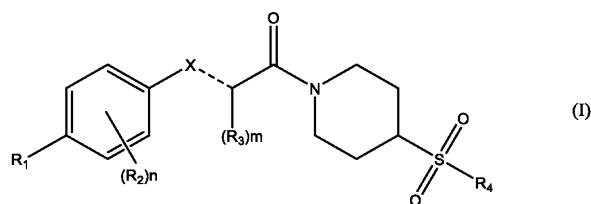
in the treatment of diseases and conditions such as, but not limited to, chronic pain e.g osteoarthritis, chronic low back pain, neuropathic pain and immune system diseases e.g inflammatory bowel diseases e.g. Colitis and Chron's diseases, multiple sclerosis, rheumatoid arthritis, inflammatory pulmonary diseases e.g. asthma and

5 psoriasis ameliorated by inhibition of GPR183 receptors. Furthermore, the pharmaceutical compositions comprising the presently disclosed compounds are also provided.

The novel GPR183 antagonists of the present disclosure have improved physicochemical properties and a more desirable pharmacokinetic profile.

10 DETAILED DESCRIPTION OF THE INVENTION

The present disclosure relates to novel compounds having the general formula I,



wherein;

the dotted line [- - -] represents a single or a double bond;

15 X is O, CH₂ or CH, provided that when X is O or CH₂ the dotted line is a single bond, and when X is CH the dotted line is a double bond;

R₁ is halogen, halo(C₁₋₃)alkyl or halo(C₁₋₃)alkoxy;

R₂ is halogen;

or R₁ and R₂ attached to adjacent carbon ring atoms form, together with the carbon

20 ring atoms a fused 2,2-difluoro-1,3-dioxolane ring;

R₃ is hydrogen;

R₄ is (C₂₋₆)alkyl, halo(C₁₋₃)alkyl, (C₁₋₃)alkoxy(C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, 6-membered heterocyclyl, heterocyclyl(C₁₋₃)alkyl, NHR₅ or NR₆R₇, wherein said (C₃₋₆)cycloalkyl or heterocyclyl is unsubstituted or substituted with one or more

25 substituents independently selected from hydroxy, (C₁₋₃)alkyl, and (C₁₋₃)alkoxy;

R₅ is hydrogen, (C₂₋₆)alkyl, (C₁₋₃)alkoxy(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl(C₁₋₃)alkyl, or heterocyclyl(C₁₋₃)alkyl, wherein said

- (C₃₋₆)cycloalkyl or heterocyclyl is unsubstituted or substituted with one or more substituents independently selected from hydroxy, (C₁₋₃)alkyl and phenyl(C₁₋₃)alkyl; R₆ and R₇ form, together with the nitrogen atom to which they are attached, a pyrrolidine ring wherein said pyrrolidine ring is substituted with 1 or 2 substituents
- 5 independently selected from (C₁₋₃)alkyl, hydroxy(C₁₋₆)alkyl and heterocyclyl; n is an integer selected from 0, 1 or 2; m is an integer selected from 1 or 2; or a pharmaceutically acceptable salt thereof; with the proviso that the compound is not
- 10 2-(4-chlorophenoxy)-1-(4-(ethylsulfonyl)piperidin-1-yl)ethan-1-one,
2-(4-fluorophenoxy)-1-(4-(isobutylsulfonyl)piperidin-1-yl)ethan-1-one,
2-(4-chlorophenoxy)-1-(4-(isobutylsulfonyl)piperidin-1-yl)ethan-1-one,
2-(2,4-dichlorophenoxy)-1-(4-(ethylsulfonyl)piperidin-1-yl)ethan-1-one,
2-(2,4-dichlorophenoxy)-1-(4-(isobutylsulfonyl)piperidin-1-yl)ethan-1-one,
- 15 2-(4-fluorophenoxy)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)ethan-1-one,
2-(4-chlorophenoxy)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)ethan-1-one,
2-(2,4-dichlorophenoxy)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)ethan-1-one,
3-(4-chlorophenyl)-1-(4-(ethylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
- 20 1-(4-(ethylsulfonyl)piperidin-1-yl)-3-(4-fluorophenyl)prop-2-en-1-one,
3-(4-chlorophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
3-(2,4-dichlorophenyl)-1-(4-(ethylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
3-(4-bromophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)propan-1-one,
3-(3,4-dichlorophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)propan-1-one,
- 25 3-(3-chloro-4-fluorophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)propan-1-one,
3-(4-chloro-3-fluorophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)propan-1-one,
3-(2,4-dichlorophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)propan-1-one,
3-(4-chlorophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
1-(4-(isobutylsulfonyl)piperidin-1-yl)-3-(4-(trifluoromethyl)phenyl)propan-1-one,
- 30 3-(4-bromophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)propan-1-one,
3-(3-chloro-4-fluorophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)propan-1-one,

- 3-(3,4-dichlorophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)propan-1-one,
- 3-(2,4-dichlorophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)propan-1-one,
- 5 3-(4-chloro-3-fluorophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)propan-1-one,
- 1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)-3-(4-(trifluoromethyl)phenyl)propan-1-one,
- 1-(4-(ethylsulfonyl)piperidin-1-yl)-3-(4-fluorophenyl)propan-1-one,
- 10 1-(3-(4-chlorophenyl)propanoyl)piperidine-4-sulfonamide, or
- 1-(3-(4-fluorophenyl)propanoyl)piperidine-4-sulfonamide.

In one embodiment the present disclosure relates to compounds of formula I, wherein the dotted line [- - -] represents a single or a double bond;

X is O, CH₂ or CH, provided that when X is O or CH₂ the dotted line is a single

- 15 bond, and when X is CH the dotted line is a double bond;

R₁ is halogen, halo(C₁₋₃)alkyl or halo(C₁₋₃)alkoxy;

R₂ is halogen;

R₃ is hydrogen;

R₄ is (C₂₋₆)alkyl, halo(C₁₋₃)alkyl, (C₁₋₃)alkoxy(C₁₋₆)alkyl, heterocyclyl(C₁₋₃)alkyl,

- 20 NHR₅ or NR₆R₇, wherein said heterocyclyl is unsubstituted or substituted with one or more substituents independently selected from hydroxy, and (C₁₋₃)alkyl;

R₅ is (C₂₋₆)alkyl, (C₁₋₃)alkoxy(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl(C₁₋₃)alkyl, or heterocyclyl(C₁₋₃)alkyl, wherein said (C₃₋₆)cycloalkyl or heterocyclyl is unsubstituted or substituted with one or more substituents

- 25 independently selected from hydroxy, and (C₁₋₃)alkyl;

R₆ and R₇ form, together with the nitrogen atom to which they are attached, a pyrrolidine ring wherein said pyrrolidine ring is substituted with 1 or 2 substituents independently selected from (C₁₋₃)alkyl, and heterocyclyl;

n is an integer selected from 0, 1 or 2;

- 30 m is an integer selected from 1 or 2;

or a pharmaceutically acceptable salt thereof,

- with the proviso that the compound is not
- 2-(4-chlorophenoxy)-1-(4-(ethylsulfonyl)piperidin-1-yl)ethan-1-one,
2-(4-fluorophenoxy)-1-(4-(isobutylsulfonyl)piperidin-1-yl)ethan-1-one,
2-(4-chlorophenoxy)-1-(4-(isobutylsulfonyl)piperidin-1-yl)ethan-1-one,
5 2-(2,4-dichlorophenoxy)-1-(4-(ethylsulfonyl)piperidin-1-yl)ethan-1-one,
2-(2,4-dichlorophenoxy)-1-(4-(isobutylsulfonyl)piperidin-1-yl)ethan-1-one,
2-(4-fluorophenoxy)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)ethan-1-one,
2-(4-chlorophenoxy)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)ethan-1-one,
2-(2,4-dichlorophenoxy)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)ethan-1-
10 one,
3-(4-chlorophenyl)-1-(4-(ethylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
1-(4-(ethylsulfonyl)piperidin-1-yl)-3-(4-fluorophenyl)prop-2-en-1-one,
3-(4-chlorophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
3-(2,4-dichlorophenyl)-1-(4-(ethylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
15 3-(4-bromophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)propan-1-one,
3-(3,4-dichlorophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)propan-1-one,
3-(3-chloro-4-fluorophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)propan-1-one,
3-(4-chloro-3-fluorophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)propan-1-one,
3-(2,4-dichlorophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)propan-1-one,
20 3-(4-chlorophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
1-(4-(isobutylsulfonyl)piperidin-1-yl)-3-(4-(trifluoromethyl)phenyl)propan-1-one,
3-(4-bromophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)propan-1-one,
3-(3-chloro-4-fluorophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)propan-
1-one,
25 3-(3,4-dichlorophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)propan-1-
one,
3-(2,4-dichlorophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)propan-1-
one,
3-(4-chloro-3-fluorophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)propan-
30 1-one,
1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)-3-(4-(trifluoromethyl)phenyl)-

propan-1-one, or

1-(4-(ethylsulfonyl)piperidin-1-yl)-3-(4-fluorophenyl)propan-1-one.

In one embodiment the present disclosure relates to compounds of formula I, wherein

X is O;

5 R₁ is halogen;

R₃ is hydrogen;

R₄ is (C₃₋₆)alkyl, (C₁₋₃)alkoxy(C₂₋₆)alkyl, heterocyclyl(C₁₋₃)alkyl, or NHR₅, wherein said heterocyclyl is unsubstituted;

R₅ is (C₁₋₃)alkoxy(C₂₋₆)alkyl, hydroxy(C₃₋₆)alkyl, (C₃₋₆)cycloalkyl(C₁₋₃)alkyl, or
10 heterocyclyl(C₁₋₃)alkyl, wherein said (C₃₋₆)cycloalkyl or heterocyclyl is unsubstituted or substituted with one substituent independently selected from hydroxy and (C₁₋₂)alkyl;

n is 0;

m is 2;

15 or a pharmaceutically acceptable salt thereof.

In one embodiment the present disclosure relates to compounds of formula I, wherein

X is CH;

R₁ is halogen;

R₃ is hydrogen;

20 R₄ is (C₃₋₆)alkyl, (C₁₋₃)alkoxy(C₂₋₆)alkyl, heterocyclyl(C₁₋₃)alkyl, or NHR₅, wherein said heterocyclyl is unsubstituted;

R₅ is (C₁₋₃)alkoxy(C₂₋₆)alkyl, hydroxy(C₃₋₆)alkyl, (C₃₋₆)cycloalkyl(C₁₋₃)alkyl, or heterocyclyl(C₁₋₃)alkyl, wherein said (C₃₋₆)cycloalkyl or heterocyclyl is unsubstituted or substituted with one substituent independently selected from hydroxy and
25 (C₁₋₂)alkyl;

n is 0;

m is 1;

or a pharmaceutically acceptable salt thereof.

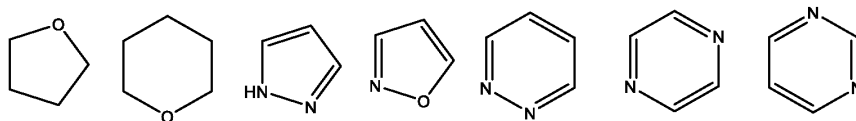
In one embodiment the present disclosure relates to compounds of formula I, wherein

30 X is O.

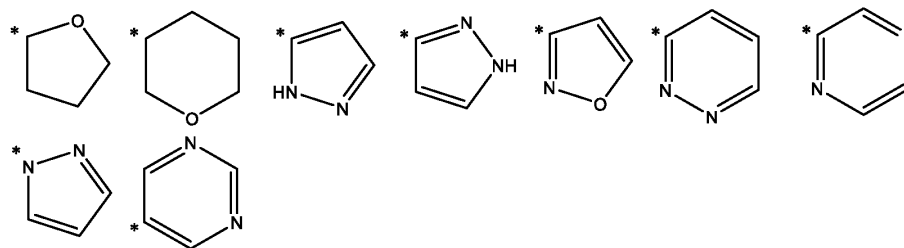
In one embodiment the present disclosure relates to compounds of formula I, wherein X is CH₂.

In one embodiment the present disclosure relates to compounds of formula I, wherein X is CH.

- 5 In one embodiment the present disclosure relates to compounds of formula I, wherein the heterocyclyl is any one of the following groups:



In one embodiment the present disclosure relates to compounds of formula I, wherein the heterocyclyl is any one of the following groups:



10

wherein atom marked with * is bonded to the parent molecular moiety.

In one embodiment the present disclosure relates to compounds of formula I, wherein the compound is;

- 2-(3,4-dichlorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one,
 15 2-(4-chlorophenoxy)-1-(4-(((tetrahydro-2H-pyran-3-yl)methyl)sulfonyl)piperidin-1-yl)ethan-1-one,
 2-(4-(difluoromethyl)phenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one,
 1-(4-((2-(1H-pyrazol-5-yl)ethyl)sulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one,
 20 1-(2-(4-chlorophenoxy)acetyl)-N-(2-ethoxyethyl)piperidine-4-sulfonamide,
 2-(4-chlorophenoxy)-1-(4-(pentan-3-ylsulfonyl)piperidin-1-yl)ethan-1-one,
 2-(3,4-difluorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one,
 2-(4-chlorophenoxy)-1-(4-((difluoromethyl)sulfonyl)piperidin-1-yl)ethan-1-one,

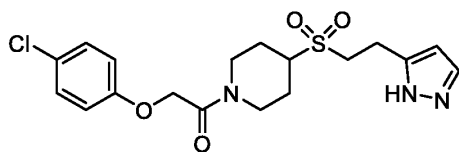
- 2-(4-chlorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one,
1-(4-(isopropylsulfonyl)piperidin-1-yl)-2-(4-(trifluoromethoxy)phenoxy)ethan-1-one,
2-(4-chloro-3-fluorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one,
1-(2-(4-chlorophenoxy)acetyl)-N-(2-methoxyethyl)piperidine-4-sulfonamide,
5 N-butyl-1-(2-(4-chlorophenoxy)acetyl)piperidine-4-sulfonamide,
1-(2-(4-chlorophenoxy)acetyl)-N-(4-hydroxy-4-methylpentyl)piperidine-4-sulfonamide,
1-(2-(4-chlorophenoxy)acetyl)-N-(3-hydroxy-3-methylbutyl)piperidine-4-sulfonamide,
10 2-(4-chlorophenoxy)-1-(4-((2,2-dimethylpyrrolidin-1-yl)sulfonyl)piperidin-1-yl)ethan-1-one,
1-(2-(4-chlorophenoxy)acetyl)-N-cyclopropylpiperidine-4-sulfonamide,
2-(4-chlorophenoxy)-1-(4-((3-methoxypropyl)sulfonyl)piperidin-1-yl)ethan-1-one,
1-(4-(sec-butylsulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one,
15 2-(4-chlorophenoxy)-1-(4-((2-(tetrahydrofuran-2-yl)ethyl)sulfonyl)piperidin-1-yl)ethan-1-one,
1-(2-(4-chlorophenoxy)acetyl)-N-(2-hydroxy-2-methylbutyl)piperidine-4-sulfonamide,
N-((1H-pyrazol-5-yl)methyl)-1-(2-(4-chlorophenoxy)acetyl)piperidine-4-sulfonamide,
20 1-(2-(4-chlorophenoxy)acetyl)-N-(isoxazol-3-ylmethyl)piperidine-4-sulfonamide,
(R)-1-(4-((3-(1H-pyrazol-5-yl)pyrrolidin-1-yl)sulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one,
1-(2-(4-chlorophenoxy)acetyl)-N-((1-hydroxycyclobutyl)methyl)piperidine-4-sulfonamide,
25 1-(2-(4-chlorophenoxy)acetyl)-N-((1-methyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide,
1-(2-(4-chlorophenoxy)acetyl)-N-((1-ethyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide,
30 1-(2-(4-chlorophenoxy)acetyl)-N-(pyridazin-3-ylmethyl)piperidine-4-sulfonamide,
1-(2-(4-chlorophenoxy)acetyl)-N-((1-hydroxycyclopentyl)methyl)piperidine-4-sulfonamide,

- 1-(2-(4-chlorophenoxy)acetyl)-N-(3-methoxypropyl)piperidine-4-sulfonamide,
1-(2-(4-chlorophenoxy)acetyl)-N-(pyrazin-2-ylmethyl)piperidine-4-sulfonamide,
2-(4-chlorophenoxy)-1-(4-(propylsulfonyl)piperidin-1-yl)ethan-1-one,
1-(4-(isopropylsulfonyl)piperidin-1-yl)-2-(4-(trifluoromethyl)phenoxy)ethan-1-one,
5 1-(2-(4-chlorophenoxy)acetyl)-N-(2-hydroxy-2-methylpropyl)piperidine-4-sulfonamide,
1-(3-(4-chlorophenyl)propanoyl)-N-(3-methoxypropyl)piperidine-4-sulfonamide,
(E)-3-(4-chlorophenyl)-1-(4-(isopropylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
(E)-1-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)acryloyl)-N-((1-ethyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide,
10 (E)-1-(3-(4-chlorophenyl)acryloyl)-N-((1-ethyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide,
(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(isopropylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
(E)-1-(3-(4-chlorophenyl)acryloyl)-N-(2-hydroxy-2-methylpropyl)piperidine-4-sulfonamide,
15 (E)-3-(4-bromophenyl)-1-(4-((3-methoxypropyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
(E)-1-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)acryloyl)-N-(3-hydroxy-3-methylbutyl)piperidine-4-sulfonamide,
20 (E)-1-(3-(4-chlorophenyl)acryloyl)-N-(3-hydroxy-3-methylbutyl)piperidine-4-sulfonamide,
(R,E)-1-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)acryloyl)-N-((tetrahydrofuran-2-yl)methyl)piperidine-4-sulfonamide,
25 (R,E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-((3-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
(E)-1-(3-(4-chlorophenyl)acryloyl)-N-(2-ethoxyethyl)piperidine-4-sulfonamide,
(E)-1-(4-((2-(1H-pyrazol-1-yl)ethyl)sulfonyl)piperidin-1-yl)-3-(4-chlorophenyl)prop-2-en-1-one,
30 (E)-N-(2-(1H-pyrazol-1-yl)ethyl)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide,
(R,E)-3-(4-chlorophenyl)-1-(4-((3-(2-hydroxypropan-2-yl)pyrrolidin-1-

- yl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
(R,E)-1-(3-(4-chlorophenyl)acryloyl)-N-((tetrahydrofuran-2-yl)methyl)piperidine-4-sulfonamide,
(E)-N-((1-benzyl-1H-pyrazol-3-yl)methyl)-1-(3-(4-chlorophenyl)acryloyl)piperidine-
5 4-sulfonamide,
(E)-N-(3-methoxypropyl)-1-(3-(4-(trifluoromethyl)phenyl)acryloyl)piperidine-4-sulfonamide,
(E)-1-(3-(4-chlorophenyl)acryloyl)-N-(3-methoxypropyl)piperidine-4-sulfonamide,
(E)-3-(4-chlorophenyl)-1-(4-(propylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
10 (E)-3-(4-chlorophenyl)-1-(4-((difluoromethyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
(E)-3-(4-chlorophenyl)-1-(4-(cyclobutylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
(E)-3-(4-chlorophenyl)-1-(4-((2-methoxypyrimidin-5-yl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
15 1-(4-((2-(1H-pyrazol-1-yl)ethyl)sulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one,
N-((1-benzyl-1H-pyrazol-3-yl)methyl)-1-(2-(4-chlorophenoxy)acetyl)piperidine-4-sulfonamide,
(E)-1-(3-(4-chlorophenyl)acryloyl)-N-(2-methoxyethyl)piperidine-4-sulfonamide,
20 (E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-((3-methoxypropyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
(E)-3-(4-chlorophenyl)-1-(4-((3-methoxypropyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
(E)-N-((1H-pyrazol-5-yl)methyl)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide, or
25 (E)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide,
or a pharmaceutically acceptable salt thereof

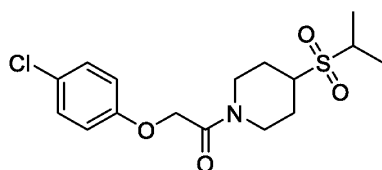
In one embodiment the present disclosure relates to compounds of formula I, wherein the compound is

12



or a pharmaceutically acceptable salt thereof.

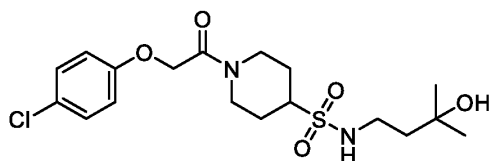
In one embodiment the present disclosure relates to compounds of formula I, wherein the compound is



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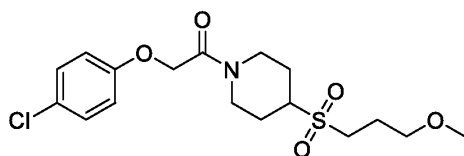
or a pharmaceutically acceptable salt thereof.

In one embodiment the present disclosure relates to compounds of formula I, wherein the compound is



10 or a pharmaceutically acceptable salt thereof.

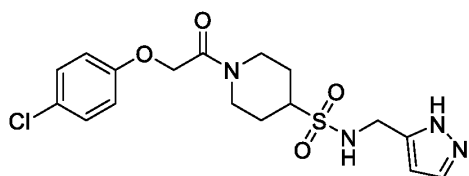
In one embodiment the present disclosure relates to compounds of formula I, wherein the compound is



or a pharmaceutically acceptable salt thereof.

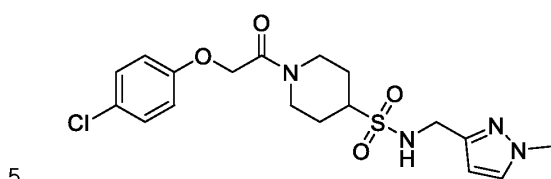
15 In one embodiment the present disclosure relates to compounds of formula I, wherein the compound is

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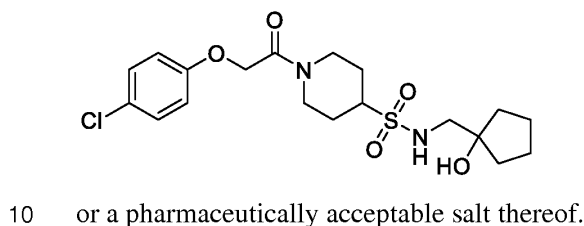
or a pharmaceutically acceptable salt thereof.

In one embodiment the present disclosure relates to compounds of formula I, wherein the compound is



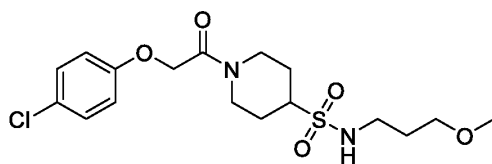
or a pharmaceutically acceptable salt thereof.

In one embodiment the present disclosure relates to compounds of formula I, wherein the compound is



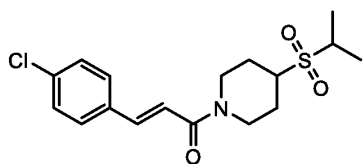
or a pharmaceutically acceptable salt thereof.

In one embodiment the present disclosure relates to compounds of formula I, wherein the compound is



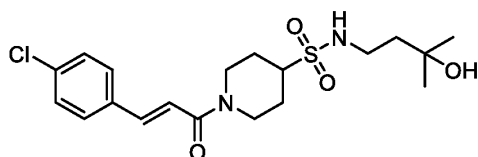
or a pharmaceutically acceptable salt thereof.

15 In one embodiment the present disclosure relates to compounds of formula I, wherein the compound is



or a pharmaceutically acceptable salt thereof.

In one embodiment the present disclosure relates to compounds of formula I, wherein the compound is



5

or a pharmaceutically acceptable salt thereof.

Unless otherwise specified, the terms employed herein have the meanings indicated below.

10 The term “at least one” employed in the meanings below refers to one or several. For example, the term “at least one fluorine” refers to one or several fluorines, for example three, two, or one fluorines.

The term “hydroxy”, as employed herein as such or as part of another group, refers to a –OH group.

15 The term “halo” or “halogen”, as employed herein as such or as part of another group, refers to fluorine, chlorine, bromine, or iodine.

The term “(C₁₋₂)alkyl”, as employed herein as such or as part of another group, refers to a saturated hydrocarbon group having a straight or branched moiety, containing 1 or 2 carbon atom(s). Representative examples of (C₁₋₂)alkyl include methyl and ethyl.

20 The term “(C₁₋₃)alkyl”, as employed herein as such or as part of another group, refers to a saturated hydrocarbon group having a straight or branched moiety, containing 1, 2, or 3 carbon atom(s). Representative examples of (C₁₋₃)alkyl include methyl, ethyl, n-propyl, and isopropyl.

The term “(C₁₋₆)alkyl”, as employed herein as such or as part of another group, refers to a saturated hydrocarbon group having a straight or branched moiety, containing 1, 2, 3, 4, 5 or 6 carbon atom(s). Representative examples of (C₁₋₆)alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, 5 tert-butyl, n-pentyl, iso-pentyl, pentan-3-yl, and n-hexyl.

The term “(C₂₋₆)alkyl”, as employed herein as such or as part of another group, refers to a saturated hydrocarbon group having a straight or branched moiety, containing 2, 3, 4, 5 or 6 carbon atom(s). Representative examples of (C₂₋₆)alkyl include, but are not limited to, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, 10 n-pentyl, iso-pentyl, pentan-3-yl, and n-hexyl.

The term “(C₃₋₆)alkyl”, as employed herein as such or as part of another group, refers to a saturated hydrocarbon group having a straight or branched moiety, containing 3, 4, 5 or 6 carbon atom(s). Representative examples of (C₃₋₆)alkyl include, but are not limited to, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, 15 iso-pentyl, pentan-3-yl, and n-hexyl.

The term “(C₁₋₃)alkoxy”, as employed herein as such or as part of another group, refers to an (C₁₋₃)alkyl group, as defined herein, bonded to an oxygen atom. Representative examples of (C₁₋₃)alkoxy include, but are not limited to, methoxy, ethoxy, and n-propoxy.

20 The term “(C₃₋₆)cycloalkyl”, as employed herein as such or as part of another group, refers to a saturated hydrocarbon group having cyclic moiety, containing 3, 4, 5, or 6 carbon atom(s). Representative examples of (C₃₋₆)cycloalkyl include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The term “heterocyclyl”, as employed herein as such or as part of another group, 25 refers to a 5 or 6 membered saturated, partially saturated, or aromatic monocyclig group containing 1 or 2 ring heteroatom(s) each independently selected from N and O. Said heterocyclyl can be optionally substituted or unsubstituted. Unless otherwise noted, the 5 or 6 membered heterocyclyl may be attached via any heteroatom or carbon atom of the ring, such that the result is a stable structure. Representative

examples of heterocyclyl include, but are not limited to, pyrrolidinyl, piperidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, tetrahydrofuranyl, tetrahydropyranyl, and isoxazolyl.

5 The term “halo(C₁₋₃)alkyl”, as employed herein as such or as part of another group, refers to at least one halogen bonded to a (C₁₋₃)alkyl group, as defined herein. When there are several halogens, the halogens can be attached to the same or different carbon atom and the halogens can be identical or different. Representative examples of halo(C₁₋₃)alkyl include, but are not limited to, fluoromethyl, chloromethyl, difluoromethyl, trifluoromethyl, 2-chloroethyl, 3-bromopropyl, and 2-chloropropyl.

10 The term “halo(C₁₋₃)alkoxy”, as employed herein as such or as part of another group, refers to at least one halogen bonded to a (C₁₋₃)alkoxy group, as defined herein. When there are several halogens, the halogens can be attached to the same or different carbon atom and the halogens can be identical or different. Representative examples of halo(C₁₋₃)alkoxy include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2,2,2 trifluoroethoxy, 15 3-fluoropropoxy, and 3,3,3-trifluoropropoxy.

The term “(C₁₋₃)alkoxy(C₁₋₆)alkyl” or “(C₁₋₃)alkoxy(C₂₋₆)alkyl”, as employed herein as such or as part of another group, refers to at least one (C₁₋₃)alkoxy group, as defined herein, bonded to an (C₁₋₆)alkyl or (C₂₋₆)alkyl group, as defined herein. When 20 there are several (C₁₋₃)alkoxy groups, the (C₁₋₃)alkoxy groups can be attached to the same or different carbon atom and the (C₁₋₃)alkoxy groups can be identical or different. Representative examples of (C₁₋₃)alkoxy(C₁₋₆)alkyl or (C₁₋₃)alkoxy(C₂₋₆)alkyl include, but are not limited to, methoxymethyl, ethoxymethyl, propoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, 2,2-dimethoxyethyl, 25 1-methyl-2-propoxyethyl, 1-methoxy-1-methylethyl, 3-methoxypropyl, and 4-methoxybutyl.

The term “hydroxy(C₁₋₆)alkyl” or “hydroxy(C₃₋₆)alkyl”, as employed herein as such or as part of another group, refers to at least one hydroxy group, as defined herein, bonded to an (C₁₋₆)alkyl or (C₃₋₆)alkyl group, as defined herein. When there are 30 several hydroxy groups, the hydroxy groups can be attached to the same or different

carbon atom. Representative examples of hydroxy(C₁₋₆)alkyl or hydroxy(C₃₋₆)alkyl include, but are not limited to, hydroxymethyl, 2,2-dihydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 1-hydroxypropyl, 1-methyl-1-hydroxyethyl, 1-methyl-1-hydroxypropyl, 2-hydroxy-2-methylpropyl, 3-hydroxy-3-methylbutyl, 4-hydroxy-4-methylpentyl, and 2-hydroxy-2-methylbutyl.

The term “(C₃₋₆)cycloalkyl(C₁₋₃)alkyl”, as employed herein refers to a (C₃₋₆)cycloalkyl group, as defined herein, bonded to an (C₁₋₃)alkyl group, as defined herein. Representative examples of (C₃₋₆)cycloalkyl(C₁₋₃)alkyl include, but are not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclobutylethyl, cyclobutylpropyl, cyclopentylmethyl, cyclopentylethyl, cyclopentylpropyl, cyclohexylmethyl, and cyclohexylethyl.

The term “heterocyclyl(C₁₋₃)alkyl”, as employed herein refers to a heterocyclyl group, as defined herein, bonded to an (C₁₋₃)alkyl group, as defined herein. Representative examples of heterocyclyl(C₁₋₃)alkyl include, but are not limited to, pyrazol-3-ylmethyl, pyrazin-2-ylmethyl, pyridazin-3-ylmethyl, pyrazol-5-ylethyl, pyrazol-1-ylethyl, tetrahydropyran-3-ylmethyl, tetrahydrofuran-2-ylmethyl, tetrahydrofuran-2-ylethyl, and isoxazol-3-ylmethyl.

The term “phenyl(C₁₋₃)alkyl”, as employed herein refers to a phenyl group bonded to an (C₁₋₃)alkyl group, as defined herein. Representative examples of phenyl(C₁₋₃)alkyl include, but are not limited to, benzyl, phenylethyl, and phenylpropyl.

The term “substituted”, as employed herein in connection with various residues refers to, if not otherwise defined, halogen, hydroxy, (C₁₋₂)alkyl, (C₁₋₃)alkyl, heterocyclyl, and phenyl(C₁₋₃)alkyl substituents. The substituted groups may contain 1 to 3, preferably 1 or 2, of the above substituents, if not otherwise defined. The substitution is meant to occur at any valency-allowed position on the compound, including the atom that is bonded to the parent molecular moiety, such that the result is a stable structure. The term “optionally substituted” means that the specific group is unsubstituted or substituted with one or more substituents.

The abbreviation “GPR183” refers to G protein-coupled receptor 183, also known as EBI2 (Epstein-Barr virus-induced G-protein coupled receptor 2).

The expression “compounds of the present disclosure” as employed herein refers to the compounds of formula I and the pharmaceutically acceptable salts thereof.

- 5 The “pharmaceutically acceptable salts” according to the present disclosure include therapeutically active, non-toxic, base and acid salt forms, which the compounds of formula I are able to form with both organic and inorganic bases and acids. Representative examples of pharmaceutically acceptable base addition salt forms, for example, metal or amine salts, include, but are not limited to, ammonium salts,
- 10 lithium, sodium, potassium, calcium, magnesium, aluminum and zinc salts, salts with organic bases, such as N-methyl-D-glucamine, hydrabamine salts and salts with amino acids, such as arginine, lysine, and the like. Representative examples of pharmaceutically acceptable acid addition salts include, but are not limited to, chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, methane sulfonates,
- 15 formates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates, acetates, oxalates, fumarates, and succinates.

The present disclosure includes all the possible geometric isomers, for example cis and trans isomers, of the compounds of formula I, as well as all the possible optical isomers, such as diastereomers and enantiomers, of the compound of formula I.

- 20 Furthermore, the present disclosure includes all the individual isomers and any mixtures thereof, such as racemic mixture. The individual isomers may be obtained using the corresponding isomeric forms of the starting materials or they may be separated after the preparation of the end compound according to conventional separation methods. For the separation of optical isomers, such as enantiomers, from
- 25 the mixture thereof, conventional resolution methods, for example fractional crystallization or preparative chiral chromatography, may be used.

The following general abbreviations are used: NaOH = sodium hydroxide, EtOH = ethanol, Boc = tert-butyloxycarbonyl protecting group, H₂O₂ = hydrogen peroxide, MeOH = methanol, MeCN = acetonitrile, EtOAc = ethyl acetate, HATU = (1-

30 [bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid

hexafluoro phosphate), DIPEA = N,N-disopropylethylamine, DMF = N,N-dimethylformamide, TEA = triethylamine, DCM = dichloromethane, HCl = hydrochloric acid, NaHSO₃ = sodium bisulfite, H₂O = water, DAST = diethylaminosulfur trifluoride, DMSO-d₆ = deuterated dimethyl sulfoxide, LiOH = lithium hydroxide, NaHCO₃ = sodium bicarbonate, CO₂ = carbon dioxide, NaCl = sodium chloride, KCl = potassium chloride, MgCl₂ = magnesium chloride, CaCl₂ = calcium chloride, THF = tetrahydrofuran, K₂CO₃ = potassium carbonate, CuI = copper(I) iodide, N₂ = dinitrogen, DMSO = dimethyl sulfoxide, KOtBu = potassium tert-butoxide, HEPES = 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid, RT = room temperature, h = hour, eq = equivalent, aq = aqueous, ¹H NMR = proton nuclear magnetic resonance, s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet, br d = broad doublet, LC-MS = liquid chromatography – mass spectrometry, H = proton, M = molarity, SM = starting material, Int = intermediate, MHz = mega hertz, mmol = millimole, g = gram, mg = milligram, ml = milliliter, and mM = millimolar.

The present disclosure will be explained in more detail by the following examples. The examples are meant for illustrating purposes only and do not limit the scope of the invention defined in the claims. Various modifications and embodiments can be made without departing from the spirit and scope thereof. It will be appreciated that where typical or preferred experimental conditions (i.e., reaction temperatures, time, moles of reagents, solvents etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the specific reactants or solvents used, but such conditions can be determined by the person skilled in the art, using routine optimization procedures. The synthetic routes described below are meant to illustrate the preparation of the compounds of formula I and the preparation is by no means limited thereto, that is, there are also other possible synthetic methods which are within the general knowledge of a person skilled in the art.

The compounds of formula I may be converted, if desired, into their pharmaceutically acceptable salt form using methods known in the art.

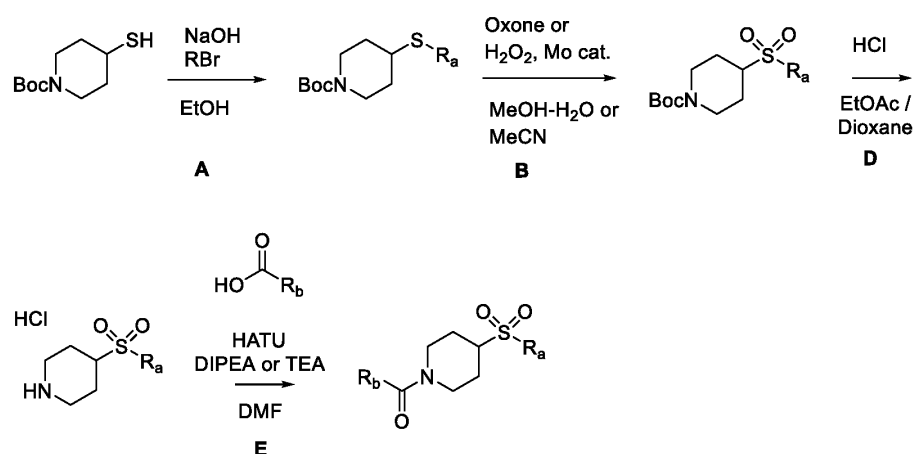
^1H NMR spectra of the products were measured by a Bruker Avance III HD 400 MHz or Bruker Avance NEO 600 MHz NMR instruments. LC-MS analyses were performed using a Waters Acquity UPLC/MS with a Q detector.

The starting materials used in the processes herein are either commercially available
5 or can be prepared via general synthetic routes.

The procedures for preparing the compounds of formula I are detailed below including the synthesis of various intermediates involved in process of preparing the compounds according to the present disclosure.

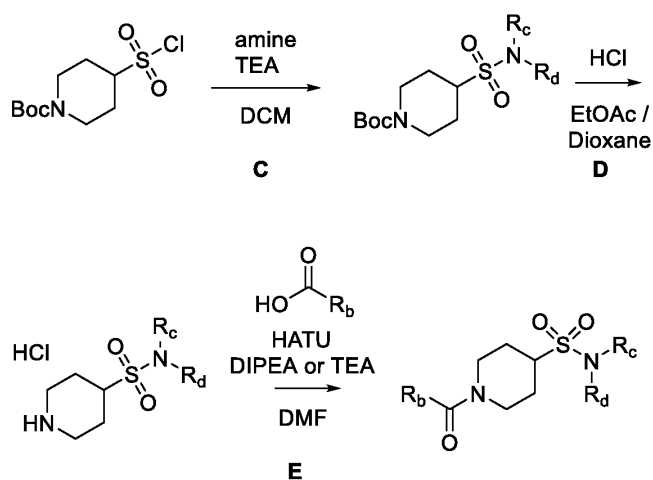
Preparation of the compounds of the present disclosure

10 General route 1:

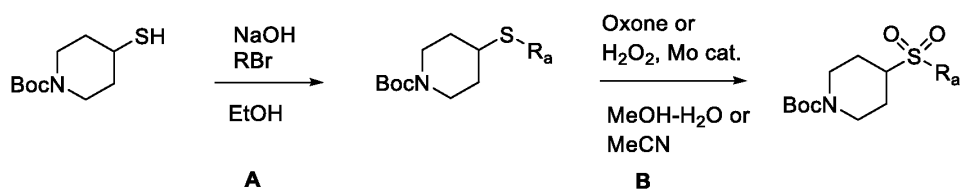


General route 2:

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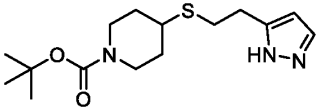
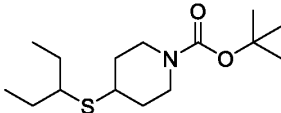
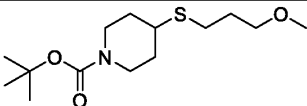
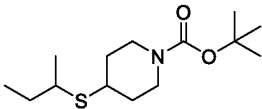
General procedures for sulfones:

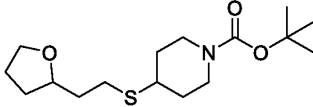
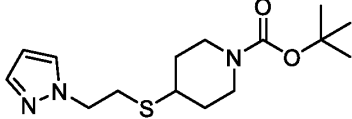
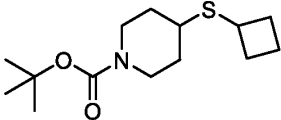


General procedure A:

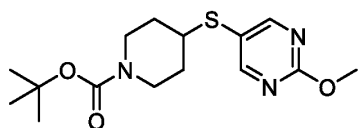
- 5 A mixture of tert-butyl 4-mercaptopiperidine-1-carboxylate (1 eq), alkyl halide (1-1.3 eq), and 2 M NaOH (aq., 1-1.3 eq) in EtOH (0.2-0.5 M) was stirred (RT - 60°C) until the starting material was consumed. The product sulfide was obtained by aqueous work-up. Optionally the crude product was purified by column chromatography.
- 10 Following compounds were synthesized using General procedure A:

No	Structure and starting materials	¹ H NMR / LC-MS
Int-1		MS: m/z 216.2 [M-Boc+H] ⁺

	tert-butyl 4-(((tetrahydro-2H-pyran-3-yl)methyl)thio)piperidine-1-carboxylate SM: 3-(bromomethyl)tetrahydro-2H-pyran	
Int-2	 tert-butyl 4-((2-(1H-pyrazol-5-yl)ethyl)thio)piperidine-1-carboxylate SM: 5-(2-chloroethyl)-1H-pyrazole	¹H NMR (400MHz, DMSO-d₆) δ: 12.50 (br s, 1H), 7.49 (br s, 1H), 6.09 (d, 1H), 3.85-3.75 (m, 2H), 2.93-2.74 (m, 6H), 1.91-1.82 (m, 2H), 1.39 (s, 9H), 1.36-1.21 (m, 2H), one proton under water signal. MS: m/z 312.5 [M+H]⁺
Int-3	 tert-butyl 4-(pentan-3-ylthio)piperidine-1-carboxylate SM: 3-pentylbromide	¹H NMR (400MHz, DMSO-d₆) δ: 3.78 (br d, 2H), 3.00-2.77 (m, 3H), 2.65-2.56 (m, 1H), 1.93-1.79 (m, 2H), 1.62-1.41 (m, 4H), 1.41-1.21 (m, 11H), 0.92 (t, 6H). MS: m/z 232.2 [M-t-butyl+H]⁺
Int-4	 tert-butyl 4-((3-methoxypropyl)thio)piperidine-1-carboxylate SM: 1-bromo-3-methoxypropane	¹H NMR (400MHz, DMSO-d₆) δ: 3.80 (br d, 2H), 3.37 (t, 2H), 3.22 (s, 3H), 2.96-2.78 (m, 3H), 2.55 (t, 2H), 1.90-1.81 (m, 2H), 1.78-1.68 (m, 2H), 1.39 (s, 9H), 1.34-1.22 (m, 2H). MS: m/z 334.2 [M-tBu+H]⁺
Int-5		¹H NMR (400MHz, DMSO-d₆) δ: 3.86-3.69 (m, 2H), 3.02-2.73 (m, 4H), 1.92-1.77 (m,

	tert-butyl 4-(sec-butylthio)piperidine-1-carboxylate SM: 2-bromobutane	2H), 1.58-1.40 (m, 2H), 1.39 (s, 9H), 1.35-1.22 (m, 2H), 1.20 (d, 3H), 0.92 (t, 3H). MS: m/z 218.2 [M-tBu+H] ⁺
Int-6	 tert-butyl 4-((2-(tetrahydrofuran-2-yl)ethyl)thio)piperidine-1-carboxylate SM: 2-(oxolan-2-yl)ethyl methanesulfonate	MS: m/z 260.2 [M-tBu+H] ⁺
Int-7	 tert-butyl 4-((2-(1H-pyrazol-1-yl)ethyl)thio)piperidine-1-carboxylate SM: 1-(2-chloroethyl)pyrazole	MS: m/z 312.5 [M+H] ⁺
Int-8	 tert-butyl 4-(cyclobutylthio)piperidine-1-carboxylate SM: Bromocyclobutane	MS: m/z 216.1 [M-tBu+H] ⁺

Procedure for **Int-9**:

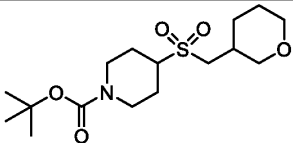


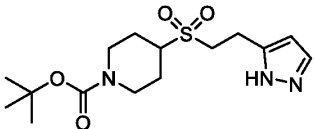
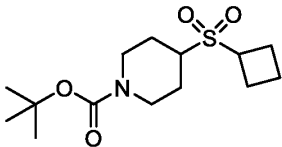
A microwave reactor vial was charged with 5-iodo-2-methoxypyrimidine (195 mg, 0.79 mmol, 1.2 eq), tert-butyl 4-mercaptopiperidine-1-carboxylate (0.15 g, 0.66 mmol, 1.0 eq), K₂CO₃ (181 mg, 1.31 mmol, 2 eq), 1,4-diazabicyclo[2.2.2]octane (7.4 mg, 0.066 mmol, 0.1 eq), CuI (6.3 mg, 0.033 mmol, 0.05 eq), and dry MeCN (3.5 ml). The resulting mixture was sparged with N₂ for 5 min and the vial was closed. The vial was heated in the microwave reactor at 120°C for 12 h. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic phase was dried and evaporated. The crude product was purified using column chromatography giving 107 mg of tert-butyl 4-((2-methoxypyrimidin-5-yl)thio)piperidine-1-carboxylate. ¹H NMR (400MHz, DMSO-d₆) δ: 8.67 (s, 2H), 3.93 (s, 3H), 3.86-3.78 (m, 2H), 3.25-3.16 (m, 1H), 2.93-2.73 (m, 2H), 1.85-1.77 (m, 2H), 1.37 (s, 9H), 1.33-1.21 (m, 2H). MS: m/z 270.1 [M-t-Bu+H]⁺.

General procedure B1:

Sulfide (1 eq) was dissolved in MeOH- H₂O (2:1 – 1:1, 50-200 mM) and the solution was cooled in an ice bath. Oxone® (2.2 eq) was added. The resulting mixture was stirred (0°C – RT) until the starting material was consumed. The product sulfone was obtained by aqueous work-up. Optionally the crude product was purified by column chromatography.

Following compounds were synthesized using General procedure B1:

No	Structure and starting materials	¹ H NMR / LC-MS
Int-10	 tert-butyl 4-(((tetrahydro-2H-pyran-3-yl)methyl)sulfonyl)piperidine-1-carboxylate SM: Int-1: tert-butyl 4-(((tetrahydro-2H-pyran-3-yl)methyl)thio)piperidine-1-carboxylate	¹ H NMR (400MHz, DMSO-d ₆) δ: 4.12-3.99 (m, 2H), 3.89-3.82 (m, 1H), 3.74-3.67 (m, 1H), 3.39-3.26 (m, 2H, partially under water signal), 3.20 (dd, 1H), 3.06-2.94 (m, 2H), 2.78 (br s, 2H), 2.21-2.10 (m, 1H), 2.05-1.89 (m, 3H), 1.63-1.34 (m, 14H).

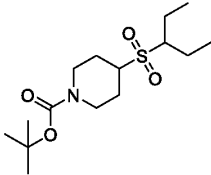
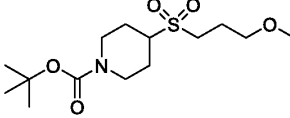
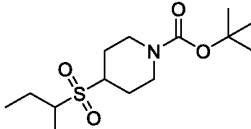
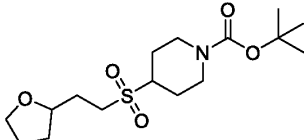
		MS: m/z 248.2 [M-Boc+H] ⁺
Int-11	 tert-butyl 4-((2-(1H-pyrazol-5-yl)ethyl)sulfonyl)piperidine-1-carboxylate SM: Int-2: tert-butyl 4-((2-(1H-pyrazol-5-yl)ethyl)thio)piperidine-1-carboxylate	¹H NMR (400MHz, DMSO-d₆) δ: 12.59 (br s, 1H), 7.57 (br s, 1H), 6.19 (d, 1H), 4.11-3.98 (m, 2H), 3.43-3.23 (m, 3H), 3.04-2.97 (m, 2H), 2.74 (br s, 2H), 2.03-1.94 (m, 2H), 1.50-1.37 (m, 11H). MS: m/z 342.2 [M-H]⁻
Int-12	 tert-butyl 4-(cyclobutylsulfonyl)piperidine-1-carboxylate SM: Int-8: tert-butyl 4-(cyclobutylthio)piperidine-1-carboxylate	MS: m/z 248.1 [M-tBu+H] ⁺

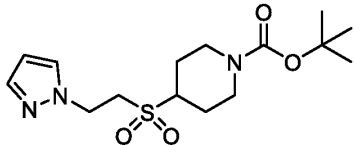
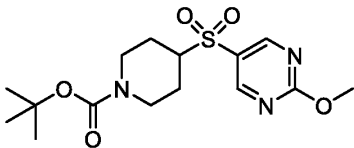
General procedure B2:

- Sulfide (1 eq) and ammonium heptamolybdate tetrahydrate (0.03 eq) were dissolved in MeCN (100-400 mM) and the solution was cooled in an ice bath. H₂O₂ (30-50 % aq., 6 eq) was added drop wise. The resulting mixture was stirred (0°C) until the starting material was consumed. The product sulfone was obtained by aqueous work-up (incl. NaHSO₃ wash). Optionally the crude product was purified by column chromatography.

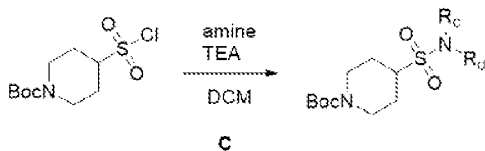
Following compounds were synthesized using General procedure B2:

No	Structure and starting materials	¹ H NMR / LC-MS
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Int-13	 tert-butyl 4-(pentan-3-ylsulfonyl)-piperidine-1-carboxylate SM: Int-3: tert-butyl 4-(pentan-3-ylthio)piperidine-1-carboxylate	¹ H NMR (400MHz, DMSO-d ₆) δ : 4.10-3.95 (m, 2H, overlapping EtOAc signal), 3.48-3.40 (m, 1H, overlapping water signal), 3.06-2.97 (m, 1H), 2.81 (br s, 2H), 1.94 (br d, 2H), 1.89-1.77 (m, 2H), 1.74-1.60 (m, 2H), 1.48-1.34 (m, 11H), 0.98 (t, 6H). MS: m/z 264.3 [M-t-butyl+H] ⁺
Int-14	 tert-butyl 4-((3-methoxypropyl)sulfonyl)piperidine-1-carboxylate SM: Int-4: tert-butyl 4-((3-methoxypropyl)thio)piperidine-1-carboxylate	¹ H NMR (400MHz, DMSO-d ₆) δ : 4.14-3.97 (m, 2H), 3.42 (t, 2H), 3.39-3.30 (m, 1H), 3.24 (s, 3H), 3.13-3.03 (m, 2H), 2.94-2.62 (m, 2H), 2.03-1.95 (m, 2H), 1.95-1.87 (m, 2H), 1.40 (s, 11H). MS: m/z 266.1 [M-tBu+H] ⁺
Int-15	 tert-butyl 4-(sec-butylsulfonyl)-piperidine-1-carboxylate SM: Int-5: tert-butyl 4-(sec-butylthio)piperidine-1-carboxylate	¹ H NMR (400MHz, DMSO-d ₆) δ : 4.14-3.89 (m, 2H), 3.55-3.41 (m, 1H), 3.19-3.07 (m, 1H), 2.97-2.70 (m, 2H), 1.98-1.82 (m, 3H), 1.51-1.32 (m, 12H), 1.23 (d, 3H), 0.97 (t, 3H). MS: m/z 250.1 [M-tBu+H] ⁺
Int-16	 tert-butyl 4-((2-(tetrahydrofuran-2-yl)ethyl)sulfonyl)piperidine-1-	¹ H NMR (400MHz, DMSO-d ₆) δ : 4.14-3.95 (m, 2H), 3.89-3.80 (m, 1H), 3.79-3.70 (m, 1H), 3.64-3.56 (m, 1H), 3.40-3.31 (m, 1H), 3.10 (t, 2H), 2.89-2.68

	carboxylate SM: Int-6: tert-butyl 4-((2-(tetrahydrofuran-2-yl)ethyl)thio)-piperidine-1-carboxylate	(m, 2H), 2.03-1.72 (m, 7H), 1.53-1.34 (m, 12H). MS: m/z 292.2 [M-tBu+H] ⁺
Int-17	 tert-butyl 4-((2-(1H-pyrazol-1-yl)ethyl)sulfonyl)piperidine-1-carboxylate SM: Int-7: tert-butyl 4-((2-(1H-pyrazol-1-yl)ethyl)thio)piperidine-1-carboxylate	MS: m/z 288.4 [M-tBu+H] ⁺
Int-18	 tert-butyl 4-((2-methoxypyrimidin-5-yl)sulfonyl)piperidine-1-carboxylate SM: Int-9: tert-butyl 4-((2-methoxypyrimidin-5-yl)thio)-piperidine-1-carboxylate	¹ H NMR (400MHz, DMSO-d ₆) δ : 8.97 (s, 2H), 4.04 (s, 3H), 4.01 (br s, 2H), 3.62-3.52 (m, 1H), 2.70 (br s, 2H), 1.94-1.85 (m, 2H), 1.45-1.31 (m, 11H) MS: m/z 356.2 [M-H] ⁻

General procedure for sulfonamides

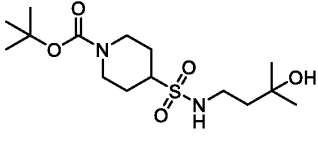
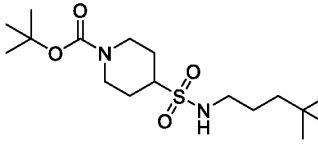
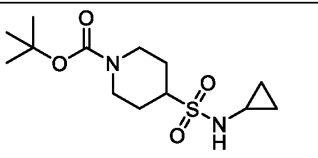


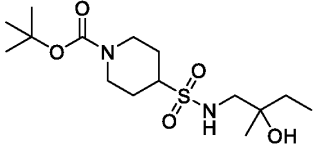
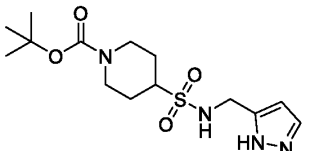
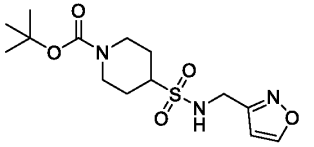
General Procedure C:

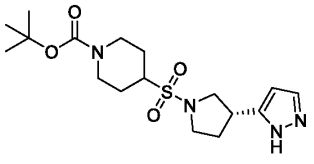
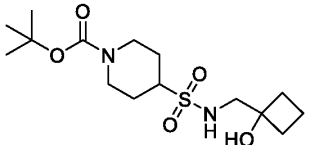
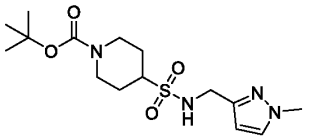
- 5 A flask was charged with amine (or its salt) (1-1.1 eq.), TEA (2-3 eq.) or DIPEA (3eq.) and DCM or DMF (0.5-0.8 M). Then 1-Boc-4-piperidinesulfonyl chloride (1

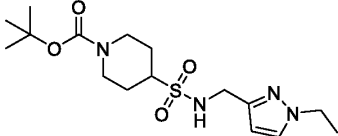
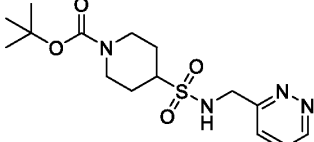
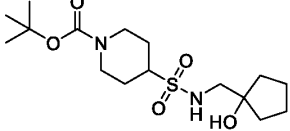
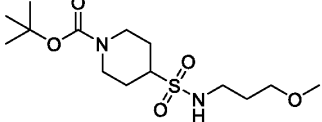
eq.) was added. Reaction was stirred at rt until completion. Mixture was diluted with DCM, washed with 1 M HCl, sat. NaHCO₃. Organic phase was evaporated to dryness. Product was used as such or optionally purified by column chromatography.

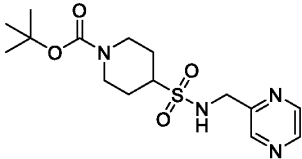
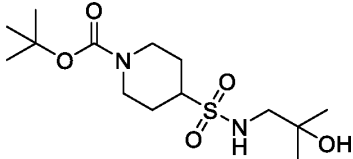
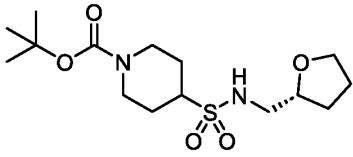
Following compounds were synthesized using General procedure C:

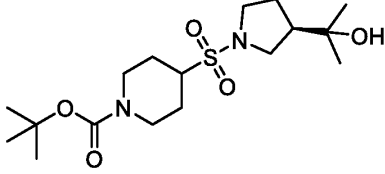
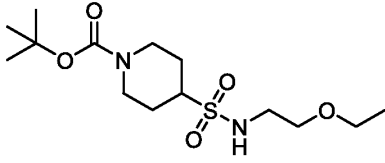
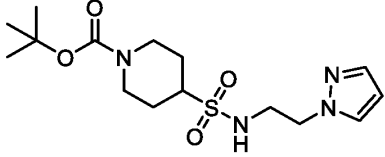
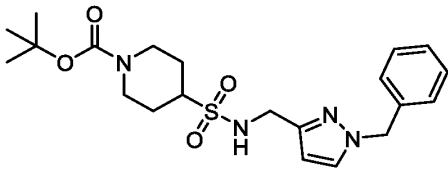
No	Structure and starting materials	¹ H NMR / LC-MS
Int-19	 tert-butyl 4-(N-(3-hydroxy-3-methylbutyl)sulfamoyl)piperidine-1-carboxylate SM: 4-amino-2-methylbutan-2-ol	¹ H NMR (400MHz, DMSO-d ₆) δ: 6.95 (t, 1H), 4.32 (s, 1H), 4.02-3.98 (m, 2H), 3.22-3.13 (m, 1H), 3.06-2.98 (m, 2H), 2.89-2.66 (m, 2H), 1.97-1.91 (m, 2H), 1.60-1.53 (m, 2H), 1.40 (s, 11H), 1.08 (s, 6H). MS: m/z 349.2[M-H] ⁻
Int-20	 tert-butyl 4-(N-(4-hydroxy-4-methylpentyl)sulfamoyl)piperidine-1-carboxylate SM: 5-amino-2-methylpentan-2-ol	¹ H NMR (400MHz, DMSO-d ₆) δ: 7.07 (t, 1H), 4.01 (br d, 2H), 3.19-3.10 (m, 1H), 2.91 (q, 2H), 2.83-2.70 (m, 2H), 1.99-1.90 (m, 2H), 1.50-1.31 (m, 15H), 1.06 (s, 6H). MS: m/z 363.3 [M-H] ⁻
Int-21	 tert-butyl 4-(N-cyclopropylsulfamoyl)piperidine-1-carboxylate SM: cyclopropylamine	¹ H NMR (400MHz, DMSO-d ₆) δ: 7.49 (d, 1H), 4.09-3.94 (m, 2H), 3.31-3.24 (m, 1H), 2.91-2.70 (m, 2H), 2.49-2.42 (m, 1H), 1.99-1.92 (m, 2H), 1.40 (s, 10H), 0.67-0.48 (m, 4H).

		MS: m/z 303.1 [M-H] ⁻
Int-22	 tert-butyl 4-(N-(2-hydroxy-2-methylbutyl)sulfamoyl)piperidine-1-carboxylate SM: 1-amino-2-methylbutan-2-ol hydrochloride	¹H NMR (400MHz, DMSO-d₆) δ: 6.89 (t, 1H), 4.24 (s, 1H), 4.12-3.91 (m, 2H), 3.27-3.14 (m, 1H), 2.86 (d, 2H), 2.83-2.63 (m, 2H), 1.95 (br d, 2H), 1.50-1.32 (m, 13H), 1.02 (s, 3H), 0.81 (t, 3H). MS: m/z 349.4 [M-H]⁻
Int-23	 tert-butyl 4-(N-((1H-pyrazol-5-yl)methyl)sulfamoyl)piperidine-1-carboxylate SM: 1H-pyrazol-3-ylmethanamine dihydrochloride	¹H NMR (400MHz, DMSO-d₆) δ: 12.82-12.50 (m, 1H), 7.77-7.32 (m, 2H), 6.22 (s, 1H), 4.27-4.07 (m, 2H), 4.06-3.86 (m, 2H), 3.14-2.96 (m, 1H), 2.88-2.54 (m, 2H), 1.97-1.81 (m, 2H), 1.49-1.26 (m, 11H). MS: m/z 343.3 [M-H]⁻
Int-24	 tert-butyl 4-(N-(isoxazol-3-ylmethyl)sulfamoyl)piperidine-1-carboxylate SM: 1,2-oxazol-3-ylmethanamine hydrochloride	¹H NMR (400MHz, DMSO-d₆) δ: 8.87 (d, 1H), 7.85 (t, 1H), 6.56 (d, 1H), 4.27 (d, 2H), 4.12-3.88 (m, 2H), 3.24-3.12 (m, 1H), 2.88-2.61 (m, 2H), 2.04-1.86 (m, 2H), 1.53-1.30 (m, 11H). MS: m/z 344.4 [M-H]⁻

Int-25	 tert-butyl (R)-4-((3-(1H-pyrazol-5-yl)pyrrolidin-1-yl)sulfonyl)piperidine-1-carboxylate SM: (R)-5-(pyrrolidin-3-yl)-1H-pyrazole dihydrochloride	¹ H NMR (400MHz, DMSO-d ₆) δ: 12.79-12.38 (m, 1H), 7.71-7.39 (m, 1H), 6.18 (d, 1H), 4.00 (br d, 2H), 3.75-3.61 (m, 1H), 3.52-3.33 (m, 5H), 2.88-2.64 (m, 2H), 2.31-2.19 (m, 1H), 2.13-1.99 (m, 1H), 1.96-1.82 (m, 2H), 1.52-1.33 (m, 11H). MS: m/z 385.3 [M+H] ⁺
Int-26	 tert-butyl 4-(N-((1-hydroxycyclobutyl)methyl)sulfamoyl)piperidine-1-carboxylate SM: 1-(Aminomethyl)cyclobutanol	¹ H NMR (400MHz, DMSO-d ₆) δ: 7.01 (t, 1H), 5.08 (s, 1H), 4.01 (br d, 2H), 3.29-3.17 (m, 1H), 3.01 (d, 2H), 2.88-2.61 (m, 2H), 2.13-1.81 (m, 6H), 1.69-1.53 (m, 1H), 1.51-1.31 (m, 13H). MS: m/z 347.4 [M-H] ⁻
Int-27	 tert-butyl 4-(N-((1-methyl-1H-pyrazol-3-yl)methyl)sulfamoyl)piperidine-1-carboxylate SM: 1-(1-Methyl-1H-pyrazol-3-yl)methanamine	¹ H NMR (400MHz, DMSO-d ₆) δ: 7.62-7.59 (m, 1H), 7.59-7.54 (m, 1H), 6.18 (d, 1H), 5.76 (s, 2H), 4.09 (d, 2H), 4.05-3.92 (m, 2H), 3.79 (s, 3H), 3.13-3.00 (m, 1H), 2.81-2.54 (m, 2H), 1.98-1.84 (m, 2H), 1.40 (s, 11H). MS: m/z 357.5 [M-H] ⁻

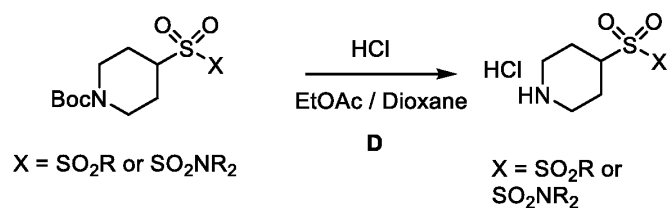
Int-28	 tert-butyl 4-(N-((1-ethyl-1H-pyrazol-3-yl)methyl)sulfamoyl)piperidine-1-carboxylate SM: (1-ethylpyrazol-3-yl)methanamine	¹H NMR (400MHz, DMSO-d₆) δ: 7.68-7.63 (m, 1H), 7.57 (t, 1H), 6.18 (d, 1H), 5.75 (s, 2H), 4.13-4.04 (m, 4H), 4.03-3.90 (m, 2H), 3.08-2.97 (m, 1H), 2.76-2.53 (m, 2H), 1.89 (br d, 2H), 1.44-1.28 (m, 14H). MS: m/z 373.2 [M+H]⁺
Int-29	 tert-butyl 4-(N-(pyridazin-3-ylmethyl)sulfamoyl)piperidine-1-carboxylate SM: (pyridazin-3-ylmethyl)amine	¹H NMR (400MHz, DMSO-d₆) δ: 9.18-9.14 (m, 1H), 7.95 (t, 1H), 7.80-7.66 (m, 2H), 4.49 (d, 2H), 4.15-3.90 (m, 2H), 3.31-3.21 (m, 1H), 2.91-2.63 (m, 2H), 2.05-1.90 (m, 2H), 1.40 (s, 11H). MS: m/z 375.2 [M+H]⁺
Int-30	 tert-butyl 4-(N-((1-hydroxycyclopentyl)methyl)sulfamoyl)piperidine-1-carboxylate SM: 1-aminomethyl cyclopentanol	¹H NMR (400MHz, DMSO-d₆) δ: 6.97 (t, 1H), 4.33 (s, 1H), 4.11-3.91 (m, 2H), 3.28-3.17 (m, 1H), 2.98 (d, 2H), 2.88-2.62 (m, 2H), 2.01-1.89 (m, 2H), 1.78-1.32 (m, 19H). MS: m/z 361.1 [M-H]⁻
Int-31		¹H NMR (400MHz, DMSO-d₆) δ: 7.08 (t, 1H), 4.02 (br d, 2H), 3.35 (s, 2H), 3.38-3.31 (m, 5H), 3.21-3.12 (m,

	tert-butyl 4-(N-(3-methoxypropyl)-sulfamoyl)piperidine-1-carboxylate SM: 3-methoxypropan-1-amine	¹ H), 3.03-2.95 (m, 2H), 2.89-2.63 (m, 2H), 2.00-1.89 (m, 2H), 1.72-1.62 (m, 2H), 1.47-1.33 (m, 11H). MS: m/z 335.2 [M-H] ⁻
Int-32	 tert-butyl 4-(N-(pyrazin-2-ylmethyl)-sulfamoyl)piperidine-1-carboxylate SM: 2-Pyrazinylmethylamine hydrochloride	¹ H NMR (400MHz, DMSO-d ₆) δ: 8.71-8.67 (m, 1H), 8.63-8.59 (m, 1H), 8.59-8.56 (m, 1H), 7.92-7.83 (m, 1H), 4.35 (d, 2H), 4.12-3.93 (m, 2H), 3.31-3.22 (m, 1H), 2.85-2.61 (m, 2H), 2.03-1.91 (m, 2H), 1.40 (s, 11H). MS: m/z 355.4 [M-H] ⁻
Int-33	 tert-butyl 4-(N-(2-hydroxy-2-methylpropyl)sulfamoyl)piperidine-1-carboxylate SM: 1-amino-2-methyl-2-propanol	¹ H NMR (400MHz, DMSO-d ₆) δ: 6.97 (t, 1H), 4.39 (s, 1H), 4.07-3.94 (m, 2H), 3.25-3.16 (m, 1H), 2.85 (d, 2H), 2.74 (br s, 2H), 1.99-1.91 (m, 2H), 1.47-1.34 (m, 11H), 1.08 (s, 6H). MS: m/z 335.2 [M-H] ⁻
Int-34	 tert-butyl (R)-4-(N-((tetrahydrofuran-2-yl)methyl)sulfamoyl)piperidine-1-carboxylate	MS: m/z 347.5 [M-H] ⁻

	SM: (R)-(tetrahydrofuran-2-yl)methanamine	
Int-35	 tert-butyl (R)-4-((3-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)sulfonyl)piperidine-1-carboxylate SM: (R)-2-(pyrrolidin-3-yl)propan-2-ol hydrochloride	¹H NMR (400MHz, DMSO-d₆) δ: 4.40 (s, 1H), 4.08-3.95 (m, 2H), 3.47-3.11 (m, 5H), 2.76 (br s, 2H), 2.28-2.17 (m, 1H), 1.98-1.73 (m, 4H), 1.52-1.34 (m, 11H), 1.09 (d, 6H) MS: m/z 375.2 [M-H]⁻
Int-36	 tert-butyl 4-(N-(2-ethoxyethyl)sulfamoyl)piperidine-1-carboxylate SM: 2-Ethoxyethylamine	MS: m/z 335.4 [M-H] ⁻
Int-37	 tert-butyl 4-(N-(2-(1H-pyrazol-1-yl)ethyl)sulfamoyl)piperidine-1-carboxylate SM: 2-(1H-pyrazol-1-yl)ethan-1-amine	MS: m/z 357.5 [M-H] ⁻
Int-38		MS: m/z 435.4 [M+H] ⁺

	tert-butyl 4-(N-((1-benzyl-1H-pyrazol-3-yl)methyl)sulfamoyl)piperidine-1-carboxylate SM: (1-benzylpyrazol-3-yl)methanamine	
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Deprotection

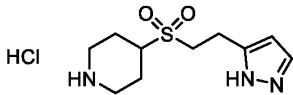
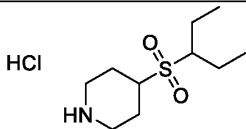
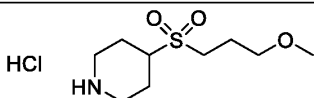


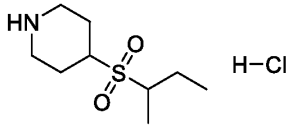
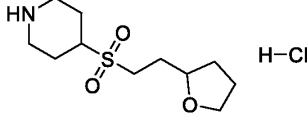
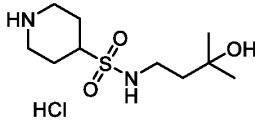
General procedure D:

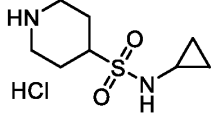
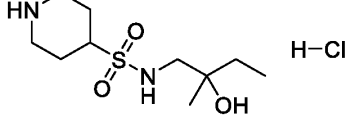
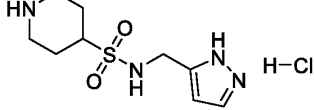
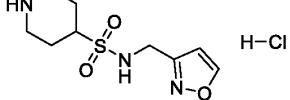
- 5 The boc protected amine (1 eq) was dissolved in EtOAc (0.3-0.6 M). 3.7-4.3 M HCl in dioxane (8-10 eq) was added to the solution and the mixture was stirred in room temperature until the starting material was consumed. The product HCl salt was filtered and washed with EtOAc or diethyl ether.

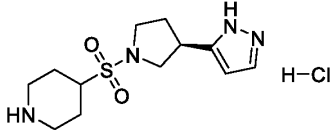
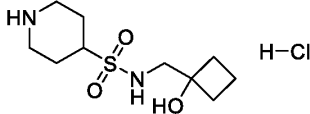
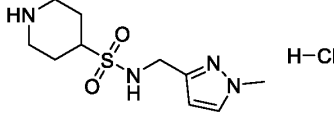
Following compounds were synthesized using General procedure D:

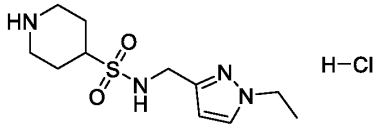
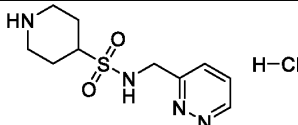
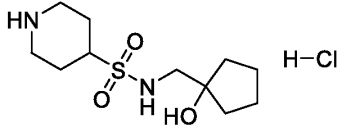
No	Structure and starting materials	¹ H NMR / LC-MS
Int-39	HCl 4-(((tetrahydro-2H-pyran-3-yl)methyl)sulfonyl)piperidine hydrochloride SM: Int-10: tert-butyl 4-(((tetrahydro-2H-pyran-3-yl)methyl)sulfonyl)piperidine-1-carboxylate	¹ H NMR (400MHz, DMSO-d ₆) δ: 9.38 (br s, 1H), 8.94 (br s, 1H), 3.90-3.82 (m, 1H), 3.75-3.66 (m, 1H), 3.52-3.29 (m, 4H, partially under water signal), 3.21 (dd, 1H), 3.12-2.99 (m, 2H), 2.98-2.84 (m, 2H), 2.22-2.10 (m, 3H), 1.98-1.78 (m, 3H), 1.63-1.34 (m, 3H).

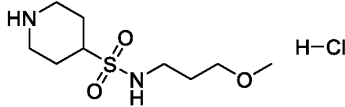
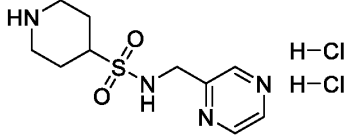
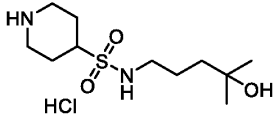
		MS: m/z 248.2 [M+H] ⁺
Int-40	HCl  4-((2-(1H-pyrazol-5-yl)ethyl)sulfonyl)-piperidine hydrochloride SM: Int-11: tert-butyl 4-((2-(1H-pyrazol-5-yl)ethyl)sulfonyl)piperidine-1-carboxylate	¹H NMR (400MHz, DMSO-d₆) δ: 9.57 (br d, 1H), 9.18 (br q, 1H), 7.96 (d, 1H), 6.51 (d, 1H), 3.62-3.51 (m, 3H), 3.42-3.33 (m, 2H), 3.19-3.11 (m, 2H), 2.98-2.85 (m, 2H), 2.25-2.15 (m, 2H), 1.97-1.83 (m, 2H). MS: m/z 244.2 [M+H]⁺
Int-41	HCl  4-(pentan-3-ylsulfonyl)piperidine hydrochloride SM: Int-13: tert-butyl 4-(pentan-3-ylsulfonyl)piperidine-1-carboxylate	¹H NMR (400MHz, DMSO-d₆) δ: 9.37 (br s, 1H), 8.90 (br s, 1H), 3.65-3.57 (m, 1H, overlapping 1,4-dioxane signal), 3.35 (br d, 2H), 3.11-3.02 (m, 1H), 2.94 (q, 2H), 2.11 (br d, 2H), 1.91-1.76 (m, 4H), 1.76-1.60 (m, 2H), 0.99 (t, 6H). MS: m/z 220.1 [M+H]⁺
Int-42	HCl  4-((3-methoxypropyl)sulfonyl)-piperidine SM: Int-14: tert-butyl 4-((3-methoxypropyl)sulfonyl)piperidine-1-carboxylate	¹H NMR (400MHz, DMSO-d₆) δ: 9.45-8.67 (m, 2H), 3.54-3.36 (m, 5H), 3.25 (s, 3H), 3.19-3.08 (m, 2H), 3.00-2.83 (m, 2H), 2.23-2.10 (m, 2H), 2.00-1.74 (m, 4H). MS: m/z 222.2 [M+H]⁺

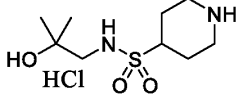
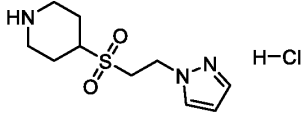
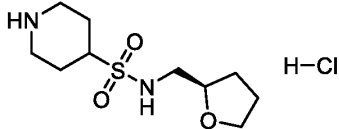
Int-43	 4-(sec-butylsulfonyl)piperidine, HCl SM: Int-15: tert-butyl 4-(sec-butylsulfonyl)piperidine-1-carboxylate	¹ H NMR (400MHz, DMSO-d ₆) δ: 9.67-8.52 (m, 2H), 3.66-3.55 (m, 5H), 3.40-3.33 (m, 2H), 3.25-3.13 (m, 1H), 3.03-2.85 (m, 2H), 2.18-2.05 (m, 2H), 1.98-1.76 (m, 3H), 1.51-1.35 (m, 1H), 1.24 (d, 3H), 0.98 (t, 3H). MS: m/z 206.3 [M+H] ⁺
Int-44	 4-((2-(tetrahydrofuran-2-yl)ethyl)sulfonyl)piperidine, HCl SM: Int-16: tert-butyl 4-((2-(tetrahydrofuran-2-yl)ethyl)sulfonyl)piperidine-1-carboxylate	¹ H NMR (400MHz, DMSO-d ₆) δ: 9.48-8.52 (m, 2H), 3.92-3.80 (m, 1H), 3.80-3.70 (m, 1H), 3.67-3.55 (m, 1H), 3.54-3.43 (m, 1H), 3.42-3.35 (m, 2H), 3.14 (br t, 2H), 2.90 (br t, 2H), 2.15 (br d, 2H), 2.04-1.72 (m, 7H), 1.56-1.42 (m, 1H). MS: m/z 248.2 [M+H] ⁺
Int-45	 N-(3-hydroxy-3-methylbutyl)piperidine-4-sulfonamide hydrochloride SM: Int-19: tert-butyl 4-(N-(3-hydroxy-3-methylbutyl)sulfamoyl)piperidine-1-carboxylate Solvent: MTBE/DCM	MS: m/z 251.2 [M+H] ⁺

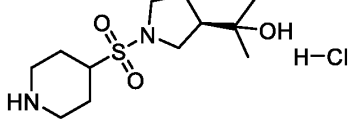
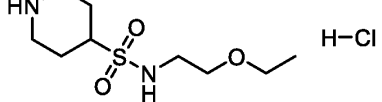
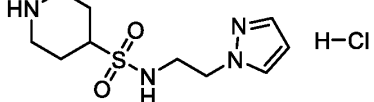
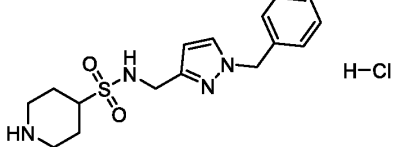
Int-46	 N-cyclopropylpiperidine-4-sulfonamide hydrochloride SM: Int-21: tert-butyl 4-(N-cyclopropylsulfamoyl)piperidine-1-carboxylate	¹ H NMR (400MHz, D ₂ O) δ: 3.68-3.56 (m, 3H), 3.09 (td, 2H), 2.57-2.51 (m, 1H), 2.38-2.31 (m, 2H), 2.04-1.92 (m, 2H), 0.74-0.61 (m, 4H). MS: m/z 205.1 [M+H] ⁺
Int-47	 N-(2-hydroxy-2-methylbutyl)piperidine-4-sulfonamide, HCl SM: Int-22: tert-butyl 4-(N-(2-hydroxy-2-methylbutyl)sulfamoyl)piperidine-1-carboxylate	¹ H NMR (400MHz, DMSO-d ₆) δ: 9.30 (br s, 1H), 8.88 (br d, 1H), 7.13 (t, 1H), 4.53-4.09 (m, 1H), 3.47-3.18 (m, 5H), 2.97-2.79 (m, 4H), 2.17-2.06 (m, 2H), 1.89-1.78 (m, 2H), 1.38 (q, 2H), 1.03 (s, 3H), 0.82 (t, 3H). MS: m/z 251.2 [M+H] ⁺
Int-48	 N-((1H-pyrazol-5-yl)methyl)piperidine-4-sulfonamide, 2HCl SM: Int-23: tert-butyl 4-(N-((1H-pyrazol-5-yl)methyl)sulfamoyl)piperidine-1-carboxylate	¹ H NMR (400MHz, DMSO-d ₆) δ: 9.45-9.25 (m, 1H), 9.05-8.75 (m, 1H), 7.81 (t, 1H), 7.70 (d, 1H), 6.29 (d, 1H), 4.18 (d, 2H), 3.33 (br d, 2H), 3.29-3.22 (m, 1H), 2.88-2.77 (m, 2H), 2.13-2.03 (m, 2H), 1.87-1.75 (m, 2H). MS: m/z 245.2 [M+H] ⁺
Int-49		MS: m/z 246.2 [M+H] ⁺

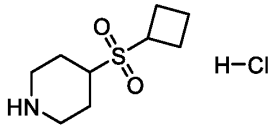
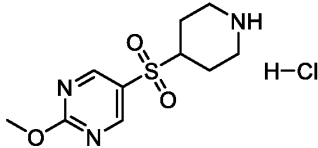
	N-(isoxazol-3-ylmethyl)piperidine-4-sulfonamide, HCl SM: Int-24: tert-butyl 4-(N-(isoxazol-3-ylmethyl)sulfamoyl)piperidine-1-carboxylate	
Int-50	 (R)-4-((3-(1H-pyrazol-5-yl)pyrrolidin-1-yl)sulfonyl)piperidine, HCl SM: Int-25: tert-butyl (R)-4-((3-(1H-pyrazol-5-yl)pyrrolidin-1-yl)sulfonyl)piperidine-1-carboxylate	¹H NMR (400MHz, DMSO-d₆) δ: 9.49-9.20 (m, 1H), 9.12-8.71 (m, 1H), 7.72 (s, 1H), 6.30 (s, 1H), 3.71 (br t, 1H), 3.66-3.21 (m, 7H), 3.00-2.78 (m, 2H), 2.37-2.21 (m, 1H), 2.19-1.99 (m, 3H), 1.98-1.79 (m, 2H). MS: m/z 285.2 [M+H]⁺
Int-51	 N-((1-hydroxycyclobutyl)methyl)piperidine-4-sulfonamide, HCl SM: Int-26: tert-butyl 4-(N-((1-hydroxycyclobutyl)methyl)sulfamoyl)piperidine-1-carboxylate	¹H NMR (400MHz, DMSO-d₆) δ: 9.31-9.06 (m, 1H), 8.93-8.63 (m, 1H), 7.24 (t, 1H), 5.50-4.73 (m, 1H), 3.46-3.4 (m, 3H, under water signal), 3.01 (d, 2H), 2.95-2.81 (m, 2H), 2.12 (br d, 2H), 2.07-1.96 (m, 2H), 1.95-1.76 (m, 4H), 1.68-1.54 (m, 1H), 1.49-1.31 (m, 1H). MS: m/z 249.2 [M+H]⁺
Int-52	 N-((1-methyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide, HCl	¹H NMR (400MHz, DMSO-d₆) δ: 9.53-9.28 (m, 1H), 9.14-8.82 (m, 1H), 7.84-7.70 (m, 1H), 7.63 (d, 1H), 6.20 (d, 1H), 4.09 (br d, 2H), 3.79

	SM: Int-27: tert-butyl 4-(N-((1-methyl-1H-pyrazol-3-yl)methyl)sulfamoyl)-piperidine-1-carboxylate	(s, 3H), 3.42-3.17 (m, 3H), 2.94-2.74 (m, 2H), 2.08 (br d, 2H), 1.94-1.72 (m, 2H). MS: m/z 259.2 [M+H]⁺
Int-53	 N-((1-ethyl-1H-pyrazol-3-yl)-methyl)-piperidine-4-sulfonamide, HCl SM: Int-28: tert-butyl 4-(N-((1-ethyl-1H-pyrazol-3-yl)methyl)sulfamoyl)-piperidine-1-carboxylate	¹H NMR (400MHz, DMSO-d₆) δ: 9.54-9.32 (m, 1H), 9.11-8.85 (m, 1H), 7.76 (br t, 1H), 7.68 (d, 1H), 6.21 (d, 1H), 4.15-4.04 (m, 4H), 3.38-3.28 (m, 2H), 3.27-3.18 (m, 1H), 2.88-2.73 (m, 2H), 2.14-2.02 (m, 2H), 1.90-1.75 (m, 2H), 1.35 (t, 3H). MS: m/z 273.2 [M+H]⁺
Int-54	 N-(pyridazin-3-ylmethyl)piperidine-4-sulfonamide, HCl SM: Int-29: tert-butyl 4-(N-(pyridazin-3-ylmethyl)sulfamoyl)piperidine-1-carboxylate	¹H NMR (400MHz, DMSO-d₆) δ: 9.38-9.28 (m, 1H), 9.25 (t, 1H), 9.06-8.82 (m, 1H), 8.23 (t, 1H), 7.88 (d, 2H), 4.54 (d, 2H), 3.51-3.40 (m, 1H), 3.36 (br d, 2H), 2.96-2.84 (m, 2H), 2.16 (br d, 2H), 1.95-1.81 (m, 2H). MS: m/z 257.2 [M+H]⁺
Int-55	 N-((1-hydroxycyclopentyl)methyl)-piperidine-4-sulfonamide, HCl SM: Int-30: tert-butyl 4-(N-((1-	¹H NMR (400MHz, DMSO-d₆) δ: 9.17-8.97 (m, 1H), 8.79-8.53 (m, 1H), 7.20 (t, 1H), 4.68-4.10 (m, 1H), 3.45-3.25 (m, 3H, under water signal), 2.99 (d, 2H), 2.95-

	hydroxycyclopentyl)methyl)sulfamoyl) piperidine-1-carboxylate	2.82 (m, 2H), 2.18-2.07 (m, 2H), 1.89-1.74 (m, 2H), 1.74-1.63 (m, 2H), 1.63-1.42 (m, 6H). MS: m/z 263.2 [M+H] ⁺
Int-56	 N-(3-methoxypropyl)piperidine-4-sulfonamide, HCl SM: Int-31: tert-butyl 4-(N-(3-methoxypropyl)sulfamoyl)piperidine-1-carboxylate	MS: m/z 237.2 [M+H] ⁺
Int-57	 N-(pyrazin-2-ylmethyl)piperidine-4-sulfonamide, 2HCl SM: Int-32: tert-butyl 4-(N-(pyrazin-2-ylmethyl)sulfamoyl)piperidine-1-carboxylate	¹ H NMR (400MHz, DMSO-d ₆) δ: 9.53-9.32 (m, 1H), 9.12-8.86 (m, 1H), 8.71 (s, 1H), 8.64-8.61 (m, 1H), 8.60-8.57 (m, 1H), 8.10 (t, 1H), 4.36 (d, 2H), 3.51-3.39 (m, 1H), 3.39-3.30 (m, 2H), 2.96-2.82 (m, 2H), 2.20-2.09 (m, 2H), 1.95-1.81 (m, 2H). MS: m/z 257.4 [M+H] ⁺
Int-58	 N-(4-hydroxy-4-methylpentyl)piperidine-4-sulfonamide hydrochloride SM: Int-20: tert-butyl 4-(N-(4-hydroxy-4-methylpentyl)sulfamoyl)piperidine-1-	MS: m/z 265.2 [M+H] ⁺

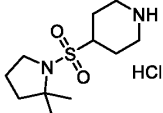
	carboxylate Solvent: DCM	
Int-59	 N-(2-hydroxy-2-methylpropyl)-piperidine-4-sulfonamide hydrochloride SM: Int-33: tert-butyl 4-(N-(2-hydroxy-2-methylpropyl)sulfamoyl)piperidine-1-carboxylate	¹H NMR (400MHz, DMSO-d₆) δ: 9.45 (br d, 1H), 9.04 (br q, 1H), 7.21 (t, 1H), 4.12 (br s, 2H), 3.40-3.30 (m, 2H), 2.96-2.81 (m, 4H), 2.16-2.06 (m, 2H), 1.92-1.79 (m, 2H), 1.09 (s, 6H). MS: m/z 237.2 [M+H]⁺
Int-60	 4-((2-(1H-pyrazol-1-yl)ethyl)sulfonyl)piperidine hydrochloride SM: Int-17: tert-butyl 4-((2-(1H-pyrazol-1-yl)ethyl)sulfonyl)piperidine-1-carboxylate	¹H NMR (400MHz, DMSO-d₆) δ: 9.47 (br s, 1H), 9.18-8.97 (m, 1H), 7.84 (d, 1H), 7.51 (d, 1H), 6.27 (t, 1H), 4.56 (t, 2H), 3.70 (t, 2H), 3.40-3.29 (m, 2H), 3.29-3.19 (m, 1H), 2.87-2.72 (m, 2H), 2.14-2.03 (m, 2H), 1.92-1.77 (m, 2H). MS: m/z 244.2 [M+H]⁺
Int-61	 (R)-N-((tetrahydrofuran-2-yl)methyl)-piperidine-4-sulfonamide hydrochloride SM: Int-34: tert-butyl (R)-4-(N-((tetrahydrofuran-2-yl)methyl)sulfamoyl)piperidine-1-carboxylate	MS: m/z 249.3 [M+H]⁺

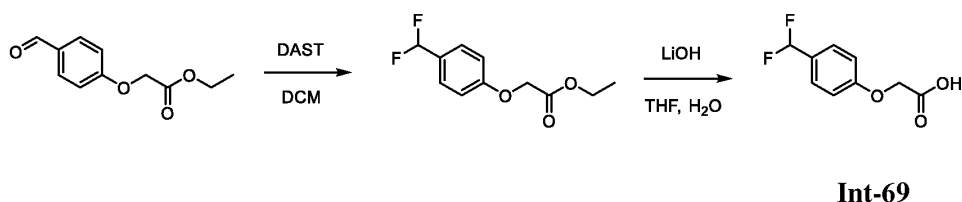
Int-62	 (R)-2-(1-(piperidin-4-ylsulfonyl)-pyrrolidin-3-yl)propan-2-ol hydrochloride SM: Int-35: tert-butyl (R)-4-((3-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)sulfonyl)piperidine-1-carboxylate	¹ H NMR (400MHz, DMSO-d ₆) δ: 9.42 (br d, 1H), 9.04 (br q, 1H), 3.62-3.51 (m, 2H), 3.45-3.14 (m, 6H), 2.96-2.82 (m, 2H), 2.29-2.18 (m, 1H), 2.13-2.01 (m, 2H), 1.97-1.75 (m, 4H), 1.09 (d, 6H). MS: m/z 277.2 [M+H] ⁺
Int-63	 N-(2-ethoxyethyl)piperidine-4-sulfonamide hydrochloride SM: Int-36: tert-butyl 4-(N-(2-ethoxyethyl)sulfamoyl)piperidine-1-carboxylate	MS: m/z 237.2 [M+H] ⁺
Int-64	 N-(2-(1H-pyrazol-1-yl)ethyl)piperidine-4-sulfonamide hydrochloride SM: Int-37: tert-butyl 4-(N-(2-(1H-pyrazol-1-yl)ethyl)sulfamoyl)piperidine-1-carboxylate	MS: m/z 259.3 [M+H] ⁺
Int-65	 N-((1-benzyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide hydrochloride	MS: m/z 335.3 [M+H] ⁺

	SM: Int-38: tert-butyl 4-(N-((1-benzyl-1H-pyrazol-3-yl)methyl)sulfamoyl)-piperidine-1-carboxylate	
Int-66	 4-(cyclobutylsulfonyl)piperidine hydrochloride SM: Int-12: tert-butyl 4-(cyclobutylsulfonyl)piperidine-1-carboxylate	MS: m/z 204.3 [M+H] ⁺
Int-67	 2-methoxy-5-(piperidin-4-ylsulfonyl)pyrimidine hydrochloride SM: Int-18: tert-butyl 4-((2-methoxypyrimidin-5-yl)sulfonyl)-piperidine-1-carboxylate	¹H NMR (400MHz, DMSO-d₆) δ: 9.37 (br s, 1H), 8.99 (s, 2H), 8.93 (br s, 1H), 4.05 (s, 3H), 3.74-3.64 (m, 1H), 3.34-3.29 (m, 1H), 2.90-2.76 (m, 2H), 2.12-2.03 (m, 2H), 1.87-1.74 (m, 2H). MS: m/z 258.3 [M+H]⁺

Procedure for **Int-68**:

Tert-butyl 4-(N-(4-hydroxy-4-methylpentyl)sulfamoyl)piperidine-1-carboxylate (Int-20) (1.59 g, 1 eq) was dissolved in 10 ml dichloromethane. Trifluoroacetic acid (10
5 eq) was added dropwise. The mixture was stirred in room temperature until starting material was consumed (2-3 hours). Volatiles were evaporated to yield a viscous oil. 20 ml of water and 2 M HCl (2 eq) was added to the crude and the solution was lyophilised to give oily solid. This material was recrystallised from MeOH/methyl tert-butyl ether to give a white solid of 4-((2,2-dimethylpyrrolidin-1-yl)sulfonyl)-
10 piperidine, HCl (0.91 g, 80% pure), which was used in the following step.

No	Structure and starting materials	LC-MS
Int-68	 tert-butyl-4-(N-(4-hydroxy-4-methylphenyl)-sulfamoyl)piperidine-1-carboxylate	MS: m/z 247.4 [M-H] ⁻

Procedure for **Int-69**:

5 Ethyl 2-(4-(difluoromethyl)phenoxy)acetate

Ethyl 2-(4-formylphenoxy)acetate (253 mg, 1.22 mmol) was dissolved in DCM (10 ml). DAST (0.48 ml, 3.65 mmol) was added at 0°C. The resulting mixture was stirred at 0°C for 15 min and at RT overnight. DAST (0.48 ml, 3.65 mmol) addition and stirring was repeated twice. After aqueous work-up 217 mg of ethyl 2-(4-(difluoromethyl)phenoxy)acetate was obtained. ¹H NMR (400MHz, DMSO-d₆) δ: 7.54-7.48 (m, 2H), 7.08-7.03 (m, 2H), 6.96 (t, 1H), 4.85 (s, 2H), 4.18 (q, 2H), 1.22 (t, 3H).

Int-69: 2-(4-(Difluoromethyl)phenoxy)acetic acid

Ethyl 2-(4-(difluoromethyl)phenoxy)acetate (215 mg, 0.93 mmol) was dissolved in THF (1.5 ml). LiOH·H₂O (58.8 mg, 1.40 mmol) and H₂O (0.5 ml) were added and the mixture was stirred at RT overnight. The mixture was acidified with 1 M HCl and extracted with EtOAc yielding 207 mg of 2-(4-(difluoromethyl)phenoxy)acetic acid. ¹H NMR (400MHz, DMSO-d₆) δ: 12.72 (br s, 1H), 7.53-7.48 (m, 1H), 7.06-7.00 (m, 2H), 6.96 (t, 1H), 4.75 (s, 2H). MS: m/z 201.2 [M-H]⁻.

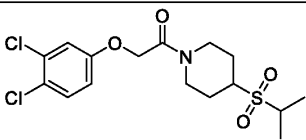
General procedure E:

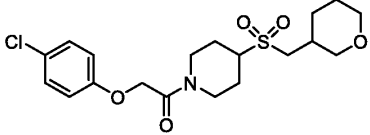
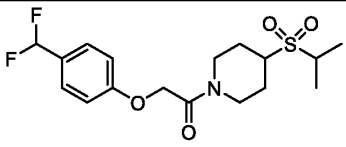
- A flask was charged with acid (1.0 eq.), amine salt (1.0-1.2 eq), HATU (1.2-1.5 eq.), DMF (0.2-0.3 M). Then DIPEA (5 eq.) was added and mixture was stirred at rt until completion. Reaction was diluted with EtOAc and water or sat. NaHCO₃. Phases
 5 were separated and organic phase was evaporated. Residue was purified with column chromatography to give amide coupling product.

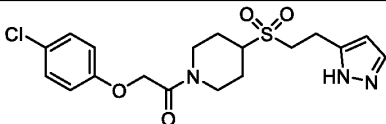
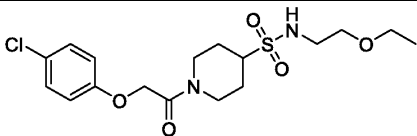
General procedure for compounds **10** and **11**:

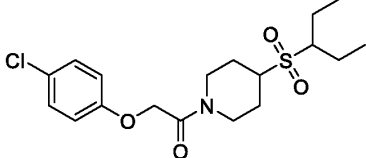
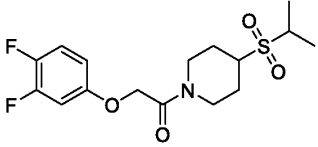
- 4-(isopropylsulfonyl)piperidine, HCl (1 eq), the carboxylic acid (1 eq) and triethylamine (5 eq) was weighed to a vial and dry DMF (0.2-0.3 M) was added. The
 10 mixture was flushed with nitrogen. 1-Propanephosphonic acid cyclic anhydride 50% in DMF (1.5-3 eq) was added dropwise. The mixture was stirred at room temperature until the starting material was consumed. The product was obtained by aqueous work-up.

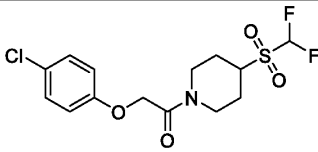
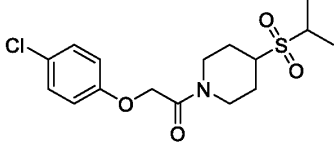
Following compounds were synthesized using General procedure E:

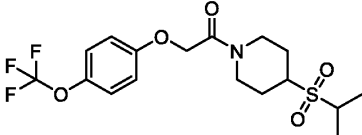
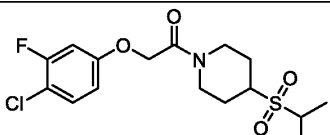
No.	Structure and starting materials	¹ H NMR / LC-MS
1	 2-(3,4-dichlorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one SM: 4-(isopropylsulfonyl)piperidine hydrochloride, (3,4-dichloro-phenoxy)-acetic acid	¹ H NMR (600MHz, DMSO-d ₆) δ: 7.51 (d, 1H), 7.24 (d, 1H), 6.95 (dd, 1H), 5.03-4.86 (m, 2H), 4.47-4.35 (m, 1H), 3.96-3.85 (m, 1H), 3.61-3.51 (m, 1H), 3.41-3.33 (m, 1H, partially under water signal), 3.19-3.08 (m, 1H), 2.76-2.65 (m, 1H), 2.04-1.96 (m, 2H), 1.74-1.62 (m, 1H),

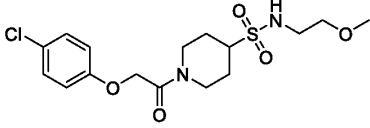
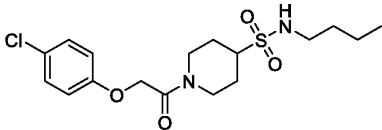
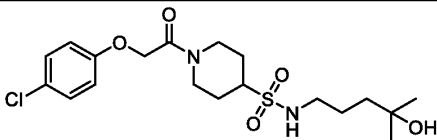
		1.48-1.37 (m, 1H), 1.25 (d, 6H). MS: m/z 394.1 [M+H] ⁺
2	 2-(4-chlorophenoxy)-1-(4-(((tetrahydro-2H-pyran-3-yl)methyl)sulfonyl)piperidin-1-yl)ethan-1-one SM: Int-39: 4-(((tetrahydro-2H-pyran-3-yl)methyl)sulfonyl)piperidine hydrochloride and 2-(4-chlorophenoxy)acetic acid	¹ H NMR (400MHz, DMSO-d ₆) δ: 7.33-7.30 (m, 2H), 6.96-6.92 (m, 2H), 4.92-4.80 (m, 2H), 4.47-4.39 (m, 1H), 3.97-3.90 (m, 1H), 3.88-3.83 (m, 1H), 3.73-3.68 (m, 1H), 3.44-3.37 (m, 1H), 3.36-3.31 (m, 1H, partially under water signal), 3.20 (dd, 1H), 3.12-2.95 (m, 3H), 2.68-2.61 (m, 1H), 2.20-2.12 (m, 1H), 2.07-2.00 (m, 2H), 1.96-1.90 (m, 1H), 1.69-1.61 (m, 1H), 1.61-1.47 (m, 2H), 1.46-1.35 (m, 2H). MS: m/z 416.2 [M+H] ⁺
3	 2-(4-(difluoromethyl)phenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one SM: 4-(isopropylsulfonyl)piperidine hydrochloride	¹ H NMR (400MHz, DMSO-d ₆) δ: 7.51-7.47 (m, 2H), 7.05-7.01 (m, 2H), 6.95 (t, 1H), 5.00-4.87 (m, 2H), 4.45-4.39 (m, 1H), 3.97-3.90 (m, 1H), 3.59-3.53 (m, 1H),

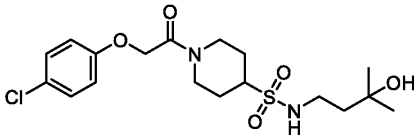
	and Int-69: 2-(4-(difluoromethyl)phenoxy)acetic acid	3.40-3.30 (m, 1H, partially under water signal), 3.18-3.10 (m, 1H), 2.74-2.67 (m, 1H), 2.03-1.97 (m, 2H), 1.72-1.62 (m, 1H), 1.47-1.37 (m, 1H), 1.24 (d, 6H). MS: m/z 376.2 [M+H] ⁺
4	 1-(4-((2-(1H-pyrazol-5-yl)ethyl)sulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one SM: Int-40: 4-((2-(1H-pyrazol-5-yl)ethyl)sulfonyl)piperidine hydrochloride and 2-(4-chlorophenoxy)acetic acid	¹ H NMR (400MHz, DMSO-d ₆) δ: 12.61 (br s, 1H), 7.57 (br s, 1H), 7.35-7.28 (m, 2H), 6.98-6.91 (m, 2H), 6.20 (d, 1H), 4.95-4.79 (m, 2H), 4.49-4.38 (m, 1H), 3.99-3.88 (m, 1H), 3.45-3.32 (m, 3H, partially under water signal), 3.11-2.96 (m, 3H), 2.69-2.55 (m, 1H), 2.09-1.99 (m, 2H), 1.75-1.60 (m, 1H), 1.51-1.36 (m, 1H). MS: m/z 412.2 [M+H] ⁺
5	 1-(2-(4-chlorophenoxy)acetyl)-N-(2-ethoxyethyl)piperidine-4-sulfonamide	¹ H NMR (400MHz, DMSO-d ₆) δ: 7.34-7.29 (m, 2H), 7.23 (t, 1H), 6.96-6.92 (m, 2H), 4.93-4.79 (m, 2H), 4.40

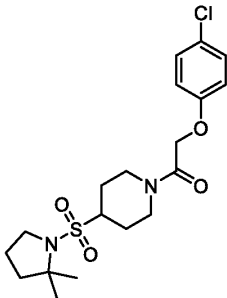
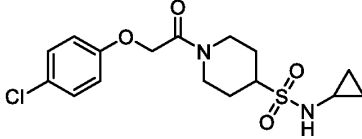
	SM: N-(2-ethoxyethyl)piperidine-4-sulfonamide and 2-(4-chlorophenoxy)acetic acid	(br d, 1H), 3.92 (br d, 1H), 3.47-3.38 (m, 4H), 3.30-3.25 (m, 1H, overlapping water signal), 3.10 (q, 2H), 3.05 (br d, 1H), 2.63 (br t, 1H), 2.01 (br d, 2H), 1.68-1.55 (m, 1H), 1.46-1.32 (m, 1H), 1.11 (t, 3H). MS: m/z 405.3 [M+H]⁺
6	 2-(4-chlorophenoxy)-1-(4-(pentan-3-ylsulfonyl)piperidin-1-yl)ethan-1-one SM: Int-41: 4-(pentan-3-ylsulfonyl)piperidine hydrochloride and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.34-7.29 (m, 2H), 6.97-6.92 (m, 2H), 4.94-4.80 (m, 2H), 4.41 (br d, 1H), 3.92 (br d, 1H), 3.58-3.49 (m, 1H), 3.18-3.07 (m, 1H), 3.07-3.00 (m, 1H), 2.69 (br t, 1H), 1.99 (br d, 2H), 1.89-1.78 (m, 2H), 1.74-1.59 (m, 3H), 1.47-1.33 (m, 1H), 0.99 (t, 6H). MS: m/z 388.3 [M+H]⁺
7	 2-(3,4-difluorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one	¹H NMR (400MHz, DMSO-d₆) δ: 7.34 (q, 1H), 7.10-7.05 (m, 1H), 6.78-6.74 (m, 1H), 4.95-4.82 (m, 2H), 4.42 (br d, 1H), 3.90 (br d,

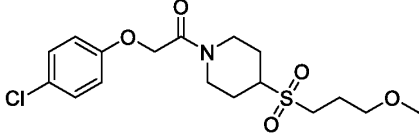
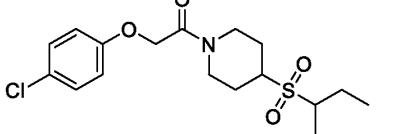
	SM: 4-(isopropylsulfonyl)piperidine hydrochloride and 2-(3,4-difluorophenoxy)acetic acid	¹ H), 3.59-3.52 (m, 1H), 3.40-3.33 (m, 1H), 3.13 (br t, 1H), 2.70 (br t, 1H), 2.00 (br d, 2H), 1.73-1.61 (m, 1H), 1.46-1.37 (m, 1H), 1.25 (d, 6H). MS: m/z 362.2 [M+H] ⁺
8	 2-(4-chlorophenoxy)-1-(4-((difluoromethyl)sulfonyl)piperidin-1-yl)ethan-1-one SM: 4-((difluoromethyl)sulfonyl)piperidine and 2-(4-chlorophenoxy)acetic acid	¹ H NMR (400MHz, DMSO-d ₆) δ: 7.32 (d, 2H), 7.25 (t, 1H), 6.95 (d, 2H), 4.95-4.80 (m, 2H), 4.43 (br d, 1H), 4.00-3.84 (m, 2H), 3.21-3.07 (m, 1H), 2.73 (br t, 1H), 2.06 (br d, 2H), 1.87-1.68 (m, 1H), 1.61-1.44 (m, 1H). MS: m/z 368.1 [M+H] ⁺
9	 2-(4-chlorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one SM: 4-(isopropylsulfonyl)piperidine hydrochloride and 2-(4-chlorophenoxy)acetic acid	¹ H NMR (400MHz, DMSO-d ₆) δ: 7.34-7.29 (m, 2H), 6.97-6.91 (m, 2H), 4.94-4.81 (m, 2H), 4.42 (br d, 1H), 3.93 (br d, 1H), 3.60-3.51 (m, 1H), 3.40-3.30 (m, 1H), 3.13 (br t, 1H), 2.70 (br t, 1H), 2.00 (br d, 2H), 1.72-1.60 (m,

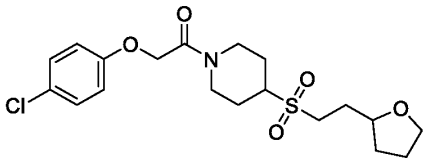
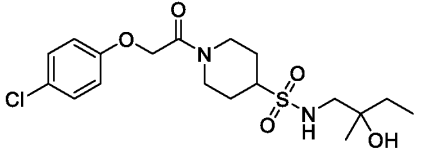
		1H), 1.47-1.35 (m, 1H), 1.24 (d, 6H). MS: m/z 360.2 [M+H] ⁺
10	 1-(4-(isopropylsulfonyl)piperidin-1-yl)-2-(4-(trifluoromethoxy)phenoxy)ethan-1-one SM: 4-(isopropylsulfonyl)piperidine, HCl and 2-(4-(trifluoromethoxy)phenoxy)acetic acid	¹ H NMR (400MHz, DMSO-d ₆) δ: 7.28 (d, 2H), 7.01 (d, 2H), 4.98-4.83 (m, 2H), 4.50-4.35 (m, 1H), 3.98-3.87 (m, 1H), 3.62-3.51 (m, 1H), 3.48-3.36 (m, 1H), 3.21-3.08 (m, 1H), 2.77-2.65 (m, 1H), 2.08-1.94 (m, 2H), 1.75-1.60 (m, 1H), 1.48-1.37 (m, 1H), 1.25 (d, 6H). MS: m/z 410.2 [M+H] ⁺
11	 2-(4-chloro-3-fluorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one SM: 4-(isopropylsulfonyl)piperidine, HCl and 2-(4-chloro-3-fluorophenoxy)acetic acid	¹ H NMR (400MHz, DMSO-d ₆) δ: 7.46 (t, 1H), 7.12-7.02 (m, 1H), 6.88-6.75 (m, 1H), 5.01-4.82 (m, 2H), 4.47-4.37 (m, 1H), 3.96-3.82 (m, 1H), 3.62-3.49 (m, 1H), 3.42-3.35 (m, 1H), 3.19-3.07 (m, 1H), 2.75-2.66 (m, 1H), 1.78-1.55 (m, 2H), 1.50-1.33 (m, 2H), 1.30-1.21 (m, 6H).

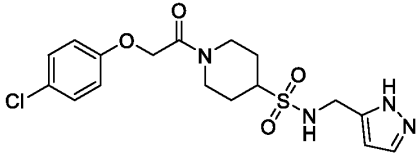
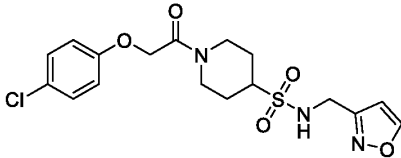
		MS: m/z 378.2 [M+H] ⁺
12	 1-(2-(4-chlorophenoxy)acetyl)-N-(2-methoxyethyl)piperidine-4-sulfonamide SM: N-(2-methoxyethyl)piperidine-4-sulfonamide and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.32 (d, 2H), 7.25 (br t, 1H), 6.94 (br d, 2H), 4.94-4.78 (m, 2H), 4.40 (br d, 1H), 3.91 (br d, 1H), 3.36 (t, 2H), 3.30-3.23 (m, 4H), 3.18-3.02 (m, 3H), 2.64 (br t, 1H), 2.00 (br d, 2H), 1.68-1.54 (m, 1H), 1.46-1.32 (m, 1H). MS: m/z 391.2 [M+H]⁺
13	 N-butyl-1-(2-(4-chlorophenoxy)acetyl)piperidine-4-sulfonamide SM: N-butylpiperidine-4-sulfonamide and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.34-7.29 (m, 2H), 7.10 (t, 1H), 6.97-6.91 (m, 2H), 4.93-4.78 (m, 2H), 4.40 (br d, 1H), 3.91 (br d, 1H), 3.31-3.21 (m, 1H), 3.08 (br t, 1H), 2.93 (q, 2H), 2.65 (br t, 1H), 1.98 (br d, 2H), 1.67-1.54 (m, 1H), 1.46-1.24 (m, 5H), 0.87 (t, 3H). MS: m/z 389.3 [M+H]⁺
14		¹H NMR (400MHz, DMSO-d₆) δ: 7.35-7.28 (m, 2H), 7.11 (t, 1H),

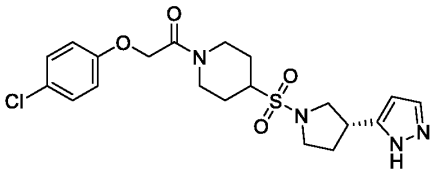
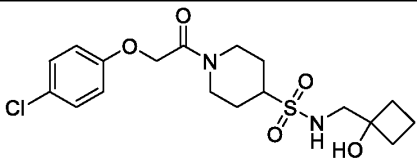
	1-(2-(4-chlorophenoxy)acetyl)-N-(4-hydroxy-4-methylpentyl)piperidine-4-sulfonamide SM: Int-58: N-(4-hydroxy-4-methylpentyl)-piperidine-4-sulfonamide, and 2-(4-chlorophenoxy)acetic acid	6.97-6.91 (m, 2H), 4.93-4.78 (m, 2H), 4.44-4.36 (m, 1H), 4.33-4.00 (m, 1H), 3.91 (br d, 1H), 3.34-3.19 (m, 1H), 3.08 (br t, 1H), 2.92 (q, 2H), 2.76- 2.55 (m, 1H), 1.99 (br d, 2H), 1.66-1.56 (m, 1H), 1.56-1.31 (m, 5H), 1.07 (s, 6H). MS: m/z 433.3 [M+H]⁺
15	 1-(2-(4-chlorophenoxy)acetyl)-N-(3-hydroxy-3-methylbutyl)piperidine-4-sulfonamide SM: Int-45: N-(3-hydroxy-3-methylbutyl)-piperidine-4-sulfonamide, HCl and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.32 (d, 2H), 7.01-6.92 (m, 3H), 4.94-4.79 (m, 2H), 4.41 (br d, 1H), 4.34 (s, 1H), 3.92 (br d, 1H), 3.34-3.23 (m, 1H), 3.15-2.98 (m, 3H), 2.67 (br t, 1H), 2.00 (br d, 2H), 1.68-1.53 (m, 3H), 1.48-1.33 (m, 1H), 1.10 (s, 6H). MS: m/z 419.2 [M+H]⁺

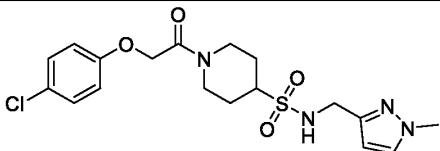
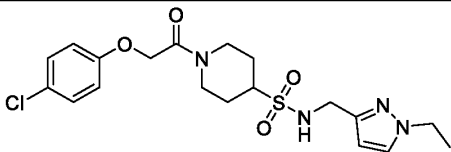
16	 2-(4-chlorophenoxy)-1-(4-((2,2-dimethylpyrrolidin-1-yl)sulfonyl)piperidin-1-yl)ethan-1-one SM: Int-68: N-(4-hydroxy-4-methylpentyl)piperidine-4-sulfonamide, HCl and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.33-7.30 (m, 2H), 6.95-6.93 (m, 2H), 4.93-4.78 (m, 2H), 4.41 (br d, 1H), 3.91 (br d, 1H), 3.40-3.30 (m, 3H partially under solvent), 3.08 (br t, 1H), 2.64 (br t, 1H), 1.98 (br d, 2H), 1.83-1.79 (m, 4H), 1.66 (br dd, 1H), 1.49-1.39 (m, 1H), 1.38 (s, 6H). MS: m/z 415.3 [M+H]⁺
17	 1-(2-(4-chlorophenoxy)acetyl)-N-cyclopropylpiperidine-4-sulfonamide SM: Int-46: N-cyclopropylpiperidine-4-sulfonamide hydrochloride and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.56-7.49 (m, 1H), 7.34-7.29 (m, 2H), 6.96-6.92 (m, 2H), 4.94-4.79 (m, 2H), 4.45-4.35 (m, 1H), 3.98-3.86 (m, 1H), 3.42-3.36 (m, 1H), 3.19-3.06 (m, 1H), 2.73-2.64 (m, 1H), 2.48-2.43 (m, 1H), 2.00 (br d, 2H), 1.72-1.56 (m, 1H), 1.48-1.35 (m, 1H), 0.62-0.51 (m, 4H). MS: m/z 373.2 [M+H]⁺

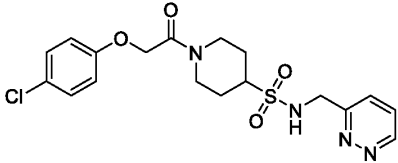
18	 2-(4-chlorophenoxy)-1-(4-((3-methoxypropyl)sulfonyl)piperidin-1-yl)ethan-1-one SM: Int-42: 4-((3-methoxypropyl)sulfonyl)piperidine and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.36-7.28 (m, 2H), 6.99-6.91 (m, 2H), 4.95-4.80 (m, 2H), 4.44 (br d, 1H), 3.95 (br d, 1H), 3.50-3.40 (m, 3H), 3.25 (s, 3H), 3.15-3.04 (m, 3H), 2.74-2.59 (m, 1H), 2.04 (br d, 2H), 1.96-1.88 (m, 2H), 1.76-1.59 (m, 1H), 1.50-1.35 (m, 1H). MS: m/z 390.2 [M+H]⁺
19	 1-(4-(sec-butylsulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one SM: Int-43: 4-(sec-butylsulfonyl)piperidine, HCl and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.35-7.29 (m, 2H), 6.97-6.91 (m, 2H), 4.95-4.79 (m, 2H), 4.49-4.35 (m, 1H), 4.00-3.86 (m, 1H), 3.62-3.51 (m, 1H), 3.22-3.06 (m, 2H), 2.77-2.64 (m, 1H), 2.06-1.85 (m, 3H), 1.75-1.56 (m, 1H), 1.52-1.33 (m, 2H), 1.24 (d, 3H), 0.98 (t, 3H). MS: m/z 374.2 [M+H]⁺

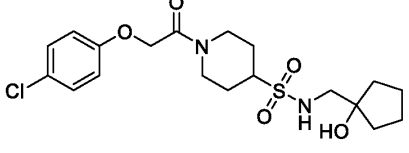
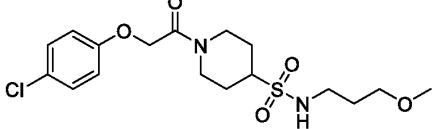
20	 2-(4-chlorophenoxy)-1-(4-((2-(tetrahydrofuran-2-yl)ethyl)-sulfonyl)piperidin-1-yl)ethan-1-one SM: Int-44: 4-((2-(tetrahydrofuran-2-yl)ethyl)sulfonyl)piperidine, HCl and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.36-7.25 (m, 2H), 6.98-6.90 (m, 2H), 4.96-4.78 (m, 2H), 4.49-4.37 (m, 1H), 4.00-3.89 (m, 1H), 3.89-3.81 (m, 1H), 3.80-3.72 (m, 1H), 3.66-3.56 (m, 1H), 3.50-3.39 (m, 1H), 3.18-.3.03 (m, 3H), 2.73-2.59 (m, 1H), 2.09-2.00 (m, 2H), 2.00-1.74 (m, 5H), 1.73-1.59 (m, 1H), 1.55-1.34 (m, 2H). MS: m/z 416.3 [M+H]⁺
21	 1-(2-(4-chlorophenoxy)acetyl)-N-(2-hydroxy-2-methylbutyl)piperidine-4-sulfonamide SM: Int-47: N-(2-hydroxy-2-methylbutyl)-piperidine-4-sulfonamide, HCl and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.37-7.27 (m, 2H), 7.00-6.90 (m, 3H), 4.96-4.76 (m, 2H), 4.40 (br d, 1H), 4.25 (s, 1H), 3.92 (br d, 1H), 3.31-3.26 (m, 1H, partially under water signal), 3.16-2.99 (m, 1H), 2.87 (d, 2H), 2.72-2.56 (m, 1H), 2.01 (br d, 2H), 1.71-1.53 (m,

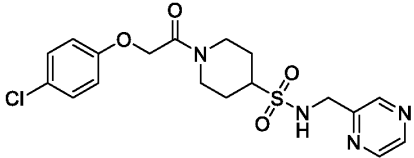
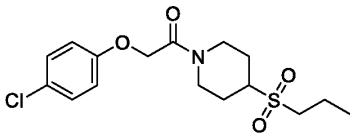
		1H), 1.39 (q, 3H), 1.03 (s, 3H), 0.82 (t, 3H). MS: m/z 419.2 [M+H]⁺
22	 N-((1H-pyrazol-5-yl)methyl)-1-(2-(4-chlorophenoxy)acetyl)piperidine-4-sulfonamide SM: Int-48: N-((1H-pyrazol-5-yl)methyl)-piperidine-4-sulfonamide, 2HCl and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.67-7.57 (m, 2H), 7.31 (d, 2H), 6.98-6.89 (m, 2H), 6.23 (d, 1H), 4.92-4.75 (m, 2H), 4.45-4.30 (m, 1H), 4.15 (d, 2H), 3.97-3.82 (m, 1H), 3.20-3.09 (m, 1H), 3.05-2.89 (m, 1H), 2.61-2.51 (m, 1H, partially under solvent signal), 2.00-1.89 (m, 2H), 1.69-1.47 (m, 1H), 1.46-1.28 (m, 1H). MS: m/z 419.2 [M+H]⁺
23	 1-(2-(4-chlorophenoxy)acetyl)-N-(isoxazol-3-ylmethyl)piperidine-4-sulfonamide SM: Int-49: N-(isoxazol-3-ylmethyl)piperidine-4-sulfonamide, HCl and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 8.88 (d, 1H), 7.90 (t, 1H), 7.35-7.27 (m, 2H), 6.98-6.90 (m, 2H), 6.56 (d, 1H), 4.95-4.76 (m, 2H), 4.46-4.34 (m, 1H), 4.27 (d, 2H), 3.97-3.86 (m, 1H), 3.32-3.23 (m, 1H, partially under water signal), 3.11-2.98 (m, 1H), 2.66-2.55 (m, 1H),

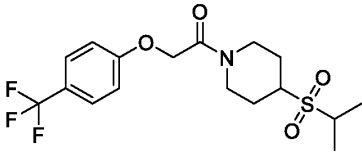
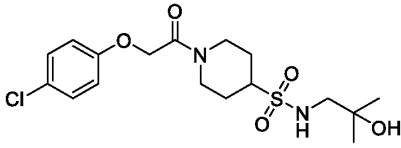
		2.05-1.95 (m, 2H), 1.73-1.52 (m, 1H), 1.51-1.31 (m, 1H). MS: m/z 414.2 [M+H]⁺
24	 (R)-1-(4-((3-(1H-pyrazol-5-yl)pyrrolidin-1-yl)sulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one SM: Int-50: (R)-4-((3-(1H-pyrazol-5-yl)pyrrolidin-1-yl)sulfonyl)piperidine, HCl and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 12.81-12.45 (m, 1H), 7.74-7.35 (m, 1H), 7.32 (d, 2H), 6.95 (d, 2H), 6.19 (br s, 1H), 5.00-4.74 (m, 2H), 4.50-4.32 (m, 1H), 4.00-3.81 (m, 1H), 3.79-3.62 (m, 1H), 3.61-3.36 (m, 5H), 3.16-2.99 (m, 1H), 2.73-2.56 (m, 1H), 2.34-2.20 (m, 1H), 2.16-2.01 (m, 1H), 2.01-1.87 (m, 2H), 1.77-1.57 (m, 1H), 1.53-1.32 (m, 1H). MS: m/z 453.2 [M+H]⁺
25	 1-(2-(4-chlorophenoxy)acetyl)-N-((1-hydroxycyclobutyl)methyl)piperidine-4-sulfonamide SM: Int-51: N-((1-hydroxycyclobutyl)-	¹H NMR (400MHz, DMSO-d₆) δ: 7.35-7.28 (m, 2H), 7.06 (t, 1H), 6.98-6.90 (m, 2H), 5.10 (br s, 1H), 4.95-4.77 (m, 2H), 4.46-4.34 (m, 1H), 3.98-3.84 (m, 1H), 3.41-3.34 (m, 1H),

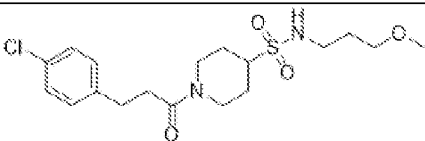
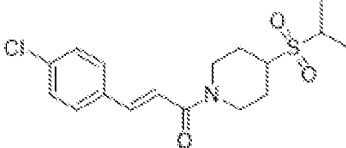
	methyl)piperidine-4-sulfonamide, HCl and 2-(4-chlorophenoxy)acetic acid	parially under water signal), 3.12-2.98 (m, 3H), 2.70-2.56 (m, 1H), 2.08-1.96 (m, 4H), 1.95-1.83 (m, 2H), 1.70-1.55 (m, 2H), 1.49-1.33 (m, 2H). MS: m/z 417.2 [M+H]⁺
26	 1-(2-(4-chlorophenoxy)acetyl)-N-((1-methyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide SM: Int-52: N-((1-methyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide, HCl and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.65-7.57 (m, 2H), 7.36-7.27 (m, 2H), 6.99-6.91 (m, 2H), 6.19 (d, 1H), 4.94-4.76 (m, 2H), 4.45-4.32 (m, 1H), 4.09 (d, 2H), 3.95-3.84 (m, 1H), 3.79 (s, 3H), 3.23-3.12 (m, 1H), 3.06-2.92 (m, 1H), 2.62-2.52 (m, 1H, partially under solvent signal), 2.01-1.90 (m, 2H), 1.70-1.48 (m, 1H), 1.47-1.30 (m, 1H). MS: m/z 427.2 [M+H]⁺
27	 1-(2-(4-chlorophenoxy)acetyl)-N-((1-ethyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide	¹H NMR (400MHz, DMSO-d₆) δ: 7.65 (d, 1H), 7.62 (t, 1H), 7.35-7.28 (m, 2H), 6.98-6.89 (m, 2H), 6.19 (d, 1H), 4.94-4.74 (m, 2H),

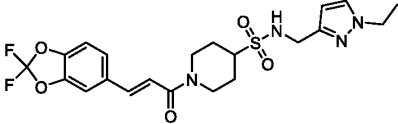
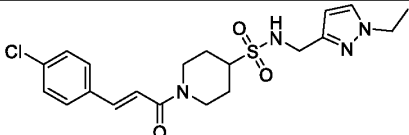
	SM: Int-53: N-((1-ethyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide, HCl and 2-(4-chlorophenoxy)acetic acid	4.44-4.31 (m, 1H), 4.15-4.03 (m, 4H), 3.96-3.82 (m, 1H), 3.20-3.09 (m, 1H), 3.04-2.91 (m, 1H), 2.59-2.50 (m, 1H, partially under solvent signal), 2.00-1.90 (m, 2H), 1.67-1.51 (m, 1H), 1.44-1.27 (m, 4H). MS: m/z 441.5 [M+H]⁺
28	 1-(2-(4-chlorophenoxy)acetyl)-N-(pyridazin-3-ylmethyl)piperidine-4-sulfonamide SM: Int-54: N-(pyridazin-3-ylmethyl)piperidine-4-sulfonamide, HCl and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 9.17 (dd, 1H), 7.99 (br s, 1H), 7.81-7.67 (m, 2H), 7.38-7.29 (m, 2H), 7.02-6.89 (m, 2H), 4.98-4.77 (m, 2H), 4.50 (br s, 2H), 4.46-4.34 (m, 1H), 4.00-3.84 (m, 1H), 3.46-3.37 (m, 1H, partially under water signal), 3.14-2.98 (m, 1H), 2.71-2.56 (m, 1H), 2.10-1.98 (m, 2H), 1.76-1.54 (m, 1H), 1.52-1.35 (m, 1H). MS: m/z 425.4 [M+H]⁺

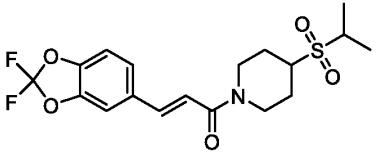
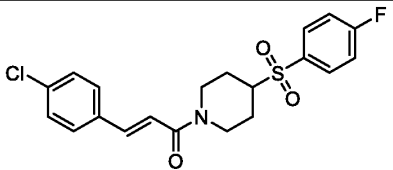
29	 1-(2-(4-chlorophenoxy)acetyl)-N-((1-hydroxycyclopentyl)methyl)piperidine-4-sulfonamide SM: Int-55: N-((1-hydroxycyclopentyl)-methyl)piperidine-4-sulfonamide, HCl and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.35-7.29 (m, 2H), 7.03 (t, 1H), 6.98-6.91 (m, 2H), 4.95-4.77 (m, 2H), 4.44-4.37 (m, 1H), 4.35 (s, 1H), 3.98-3.86 (m, 1H), 3.32-3.28 (m, 1H, partially under water signal), 3.13-3.02 (m, 1H), 3.00 (d, 2H), 2.71-2.58 (m, 1H), 2.06-1.97 (m, 2H), 1.76-1.33 (m, 10H). MS: m/z 431.5 [M+H]⁺
30	 1-(2-(4-chlorophenoxy)acetyl)-N-(3-methoxypropyl)piperidine-4-sulfonamide SM: Int-56: N-(3-methoxypropyl)piperidine-4-sulfonamide, HCl and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.35-7.28 (m, 2H), 7.12 (t, 1H), 6.97-6.90 (m, 2H), 4.95-4.77 (m, 2H), 4.46-4.35 (m, 1H), 3.98-3.84 (m, 1H), 3.35 (t, 2H), 3.31-3.23 (m, 1H, partially under water signal), 3.22 (s, 3H), 3.14-3.03 (m, 1H), 3.03-2.95 (m, 2H), 2.71-2.59 (m, 1H), 2.03-1.93 (m, 2H),

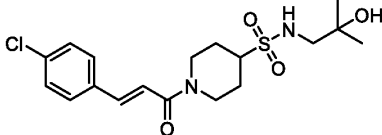
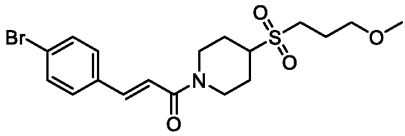
		1.72-1.53 (m, 3H), 1.47-1.31 (m, 1H). MS: m/z 405.3 [M+H]⁺
31	 1-(2-(4-chlorophenoxy)acetyl)-N-(pyrazin-2-ylmethyl)piperidine-4-sulfonamide SM: Int-57: N-(pyrazin-2-ylmethyl)piperidine-4-sulfonamide, 2HCl and 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 8.70 (d, 1H), 8.61 (dd, 1H), 8.58 (d, 1H), 7.92 (br s, 1H), 7.35-7.29 (m, 2H), 6.98-6.92 (m, 2H), 4.95-4.77 (m, 2H), 4.47-4.38 (m, 1H), 4.36 (s, 2H), 4.00-3.87 (m, 1H), 3.43-3.37 (m, 1H, partially under water signal), 3.13-3.01 (m, 1H), 2.71-2.58 (m, 1H), 2.07-1.97 (m, 2H), 1.74-1.58 (m, 1H), 1.52-1.35 (m, 1H). MS: m/z 425.5 [M+H]⁺
32	 2-(4-chlorophenoxy)-1-(4-(propylsulfonyl)piperidin-1-yl)ethan-1-one SM: 4-(propylsulfonyl)piperidine hydrochloride, 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.36-7.27 (m, 2H), 6.98-6.90 (m, 2H), 4.96-4.78 (m, 2H), 4.49-4.36 (m, 1H), 4.01-3.86 (m, 1H), 3.45-3.34 (m, 1H, partially under water signal), 3.17-2.99 (m, 3H), 2.74-2.58 (m, 1H),

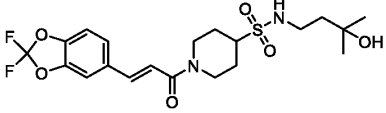
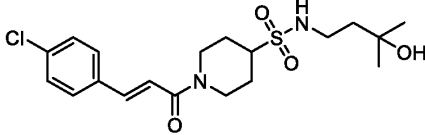
		2.09-1.97 (m, 2H), 1.78-1.53 (m, 3H), 1.51-1.33 (m, 1H), 1.01 (t, 3H). MS: m/z 360.2 [M+H]⁺
33	 1-(4-(isopropylsulfonyl)piperidin-1-yl)-2-(4-(trifluoromethyl)phenoxy)ethan-1-one SM: 4-(isopropylsulfonyl)piperidine hydrochloride, 2-(4-(trifluoromethyl)-phenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.69-7.60 (m, 2H), 7.14-7.05 (m, 2H), 5.10-4.90 (m, 2H), 4.49-4.36 (m, 1H), 4.00-3.86 (m, 1H), 3.64-3.51 (m, 1H), 3.43-3.33 (m, 1H, partially under water signal), 3.20-3.06 (m, 1H), 2.78-2.63 (m, 1H), 2.05-1.95 (m, 2H), 1.77-1.60 (m, 1H), 1.52-1.33 (m, 1H), 1.25 (d, 6H). MS: m/z 394.3 [M+H]⁺
34	 1-(2-(4-chlorophenoxy)acetyl)-N-(2-hydroxy-2-methylpropyl)piperidine-4-sulfonamide SM: Int-59: N-(2-hydroxy-2-methylpropyl)-piperidine-4-sulfonamide hydrochloride, 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.36-7.28 (m, 2H), 7.02 (t, 1H), 6.97-6.90 (m, 2H), 4.96-4.77 (m, 2H), 4.48-4.33 (m, 2H), 4.00-3.84 (m, 1H), 3.31-3.25 (m, 1H, partially under water

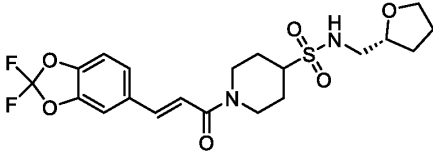
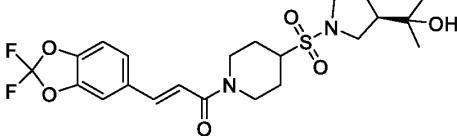
		signal), 3.14-3.00 (m, 1H), 2.86 (d, 2H), 2.70-2.57 (m, 1H), 2.06-1.95 (m, 2H), 1.70-1.54 (m, 1H), 1.50-1.32 (m, 1H), 1.08 (s, 6H). MS: m/z 405.2 [M+H]⁺
35	 1-(3-(4-chlorophenyl)propanoyl)-N-(3-methoxypropyl)piperidine-4-sulfonamide SM: Int-56: N-(3-methoxypropyl)piperidine-4-sulfonamide hydrochloride, 3-(4-chlorophenyl)propanoic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.35-7.24 (m, 4H), 7.10 (t, 1H), 4.47 (br d, 1H), 3.97 (br d, 1H), 3.37-3.32 (m, 2H, partially under water signal), 3.29-3.18 (m, 4H), 3.07-2.93 (m, 3H), 2.85-2.74 (m, 2H), 2.73-2.52 (m, 3H), 2.01-1.88 (m, 2H), 1.73-1.61 (m, 2H), 1.55-1.27 (m, 2H). MS: m/z 403.6 [M+H]⁺
36	 (E)-3-(4-chlorophenyl)-1-(4-(isopropylsulfonyl)piperidin-1-yl)prop-2-en-1-one SM: 4-(isopropylsulfonyl)piperidine hydrochloride, 4-chlorocinnamic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.77 (d, 2H), 7.53-7.43 (m, 3H), 7.32 (d, 1H), 4.68-4.33 (m, 2H), 3.66-3.54 (m, 1H), 3.45-3.33 (m, 1H), 3.26-3.11 (m, 1H), 2.88-2.70 (m, 1H), 2.04

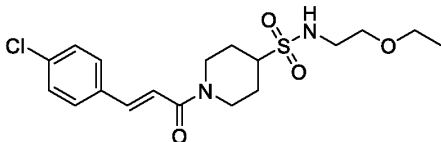
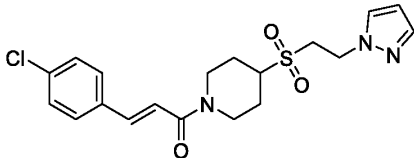
		(br d, 2H), 1.66-1.38 (m, 2H), 1.26 (d, 6H). MS: m/z 356.2 [M+H] ⁺
37	 (E)-1-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)acryloyl)-N-((1-ethyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide SM: Int-53: N-((1-ethyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide, HCl, (E)-3-(2,2-difluoro-1,3-benzodioxol-5-yl)prop-2-enoic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.94 (d, 1H), 7.65 (d, 1H), 7.62 (t, 1H), 7.54 (dd, 1H), 7.48 (d, 1H), 7.43 (d, 1H), 7.28 (d, 1H), 6.18 (d, 1H), 4.57-4.47 (m, 1H), 4.43-4.33 (m, 1H), 4.13-4.03 (m, 4H), 3.22-3.12 (m, 1H), 3.07-2.95 (m, 1H), 2.65-2.53 (m, 1H), 2.03-1.93 (m, 2H), 1.55-1.36 (m, 2H), 1.33 (t, 3H). MS: m/z 483.8 [M+H]⁺
38	 (E)-1-(3-(4-chlorophenyl)acryloyl)-N-((1-ethyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide SM: Int-53: N-((1-ethyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide, HCl, (E)-3-(4-chlorophenyl)acrylic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.79-7.74 (m, 2H), 7.65 (d, 1H), 7.61 (t, 1H), 7.49-7.43 (m, 3H), 7.29 (d, 1H), 6.19 (d, 1H), 4.57-4.47 (m, 1H), 4.42-4.32 (m, 1H), 4.13-4.03 (m, 4H), 3.22-3.12 (m, 1H), 3.07-2.95 (m, 1H), 2.65-2.53 (m, 1H),

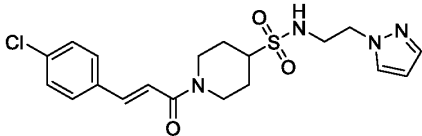
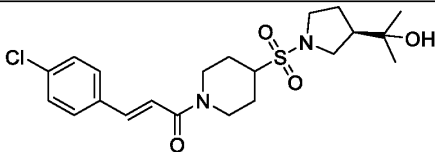
		2.02-1.93 (m, 2H), 1.55-1.37 (m, 2H), 1.33 (t, 3H). MS: m/z 437.3 [M+H] ⁺
39	 (E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(isopropylsulfonyl)piperidin-1-yl)prop-2-en-1-one SM: 4-(isopropylsulfonyl)piperidine hydrochloride, (E)-3-(2,2-difluoro-1,3-benzodioxol-5-yl)prop-2-enoic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.94 (d, 1H), 7.55 (dd, 1H), 7.50 (d, 1H), 7.44 (d, 1H), 7.30 (d, 1H), 4.62-4.52 (m, 1H), 4.47-4.37 (m, 1H), 3.65-3.55 (m, 1H), 3.43-3.31 (m, 1H, overlapping with water signal), 3.25-3.12 (m, 1H), 2.83-2.70 (m, 1H), 2.08-1.99 (m, 2H), 1.61-1.38 (m, 2H), 1.25 (d, 6H). MS: m/z 402.6 [M+H]⁺
40	 (E)-3-(4-chlorophenyl)-1-(4-((4-fluorophenyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one SM: 4-((4-fluorophenyl)sulfonyl)piperidine, (E)-3-(4-chlorophenyl)acrylic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.96-7.89 (m, 2H), 7.77-7.71 (m, 2H), 7.57-7.49 (m, 2H), 7.48-7.41 (m, 3H), 7.26 (d, 1H), 4.60-4.50 (m, 1H), 4.43-4.33 (m, 1H), 3.69-3.58 (m, 1H), 3.14-3.01 (m, 1H), 2.72-2.58 (m, 1H),

		1.94-1.86 (m, 2H), 1.52-1.28 (m, 2H). MS: m/z 408.4 [M+H] ⁺
41	 (E)-1-(3-(4-chlorophenyl)acryloyl)-N-(2-hydroxy-2-methylpropyl)piperidine-4-sulfonamide SM: Int-59: N-(2-hydroxy-2-methylpropyl)-piperidine-4-sulfonamide hydrochloride, (E)-3-(4-chlorophenyl)acrylic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.79-7.74 (m, 2H), 7.50-7.44 (m, 3H), 7.31 (d, 1H), 7.02 (br s, 1H), 4.60-4.50 (m, 1H), 4.45-4.34 (m, 2H), 3.39-3.29 (m, 1H, overlapping with water signal), 3.18-3.05 (m, 1H), 2.87 (s, 2H), 2.75-2.65 (m, 1H), 2.09-2.00 (m, 2H), 1.59-1.38 (m, 2H), 1.08 (s, 6H). MS: m/z 401.4 [M+H]⁺
42	 (E)-3-(4-bromophenyl)-1-(4-((3-methoxypropyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one SM: Int-42: 4-((3-methoxypropyl)sulfonyl)-piperidine, HCl, (E)-3-(4-bromophenyl)acrylic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.72-7.67 (m, 2H), 7.62-7.58 (m, 2H), 7.46 (d, 1H), 7.32 (d, 1H), 4.64-4.54 (m, 1H), 4.47-4.37 (m, 1H), 3.52-3.40 (m, 3H), 3.24 (s, 3H), 3.19-3.07 (m, 3H), 2.78-2.65 (m, 1H), 2.10-2.02 (m, 2H), 1.96-1.87 (m, 2H), 1.63-1.38 (m, 2H).

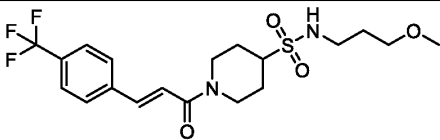
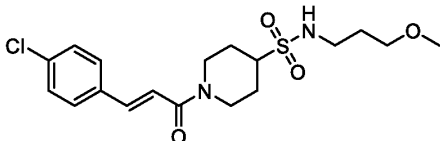
		MS: m/z 432.3 [M+H] ⁺
43	 (E)-1-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)acryloyl)-N-(3-hydroxy-3-methylbutyl)-piperidine-4-sulfonamide SM: Int-45: N-(3-hydroxy-3-methylbutyl)-piperidine-4-sulfonamide, HCl, (E)-3-(2,2-difluoro-1,3-benzodioxol-5-yl)prop-2-enoic acid	¹H NMR (600MHz, DMSO-d₆) δ: 7.95 (d, 1H), 7.55 (dd, 1H), 7.49 (d, 1H), 7.44 (d, 1H), 7.30 (d, 1H), 7.03-6.98 (m, 1H), 4.59-4.51 (m, 1H), 4.44-4.37 (m, 1H), 4.33 (s, 1H), 3.34-3.29 (m, 1H, overlapping with water signal), 3.15 (t, 1H), 3.06-3.00 (m, 2H), 2.73 (t, 1H), 2.06-1.99 (m, 2H), 1.60-1.38 (m, 4H), 1.09 (s, 6H). MS: m/z 461.5 [M+H]⁺
44	 (E)-1-(3-(4-chlorophenyl)acryloyl)-N-(3-hydroxy-3-methylbutyl)piperidine-4-sulfonamide SM: Int-45: N-(3-hydroxy-3-methylbutyl)-piperidine-4-sulfonamide, HCl, (E)-3-(4-chlorophenyl)acrylic acid	¹H NMR (600MHz, DMSO-d₆) δ: 7.78-7.75 (m, 2H), 7.49-7.45 (m, 3H), 7.31 (d, 1H), 7.00 (br s, 1H), 4.59-4.52 (m, 1H), 4.43-4.36 (m, 1H), 4.33 (s, 1H), 3.35-3.28 (m, 1H, overlapping with water signal), 3.15 (t, 1H), 3.06-3.00 (m, 2H), 2.73 (t, 1H), 2.05-1.99 (m,

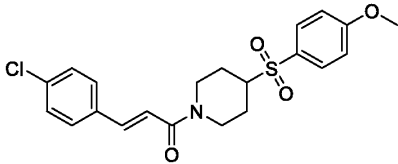
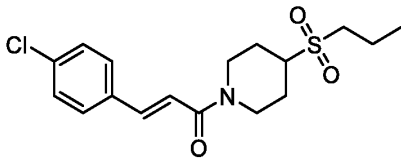
		2H), 1.60-1.38 (m, 4H), 1.08 (s, 6H). MS: m/z 415.3 [M+H] ⁺
45	 (R,E)-1-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)acryloyl)-N-((tetrahydrofuran-2-yl)methyl)-piperidine-4-sulfonamide SM: Int-61: (R)-N-((tetrahydrofuran-2-yl)methyl)-piperidine-4-sulfonamide hydrochloride, (E)-3-(2,2-difluoro-1,3-benzodioxol-5-yl)prop-2-enoic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.95 (d, 1H), 7.55 (dd, 1H), 7.49 (d, 1H), 7.44 (d, 1H), 7.34-7.23 (m, 2H), 4.60-4.50 (m, 1H), 4.45-4.35 (m, 1H), 3.88-3.80 (m, 1H), 3.78-3.71 (m, 1H), 3.65-3.58 (m, 1H), 3.38-3.28 (m, 1H, overlapping with water signal), 3.19-3.06 (m, 1H), 3.00 (d, 2H), 2.75-2.64 (m, 1H), 2.09-1.98 (m, 2H), 1.93-1.74 (m, 3H), 1.62-1.36 (m, 3H) MS: m/z 459.6 [M+H]⁺
46	 (R,E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-((3-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)sulfonyl)piperidin-1-yl)prop-2-en-1-one SM: Int-62: (R)-2-(1-(piperidin-4-ylsulfonyl)-pyrrolidin-3-yl)propan-2-ol hydrochloride, (E)-3-	¹H NMR (400MHz, DMSO-d₆) δ: 7.94 (d, 1H), 7.55 (dd, 1H), 7.49 (d, 1H), 7.44 (d, 1H), 7.29 (d, 1H), 4.61-4.51 (m, 1H), 4.45-4.34 (m, 2H), 3.61-3.51 (m, 1H), 3.45-3.32 (m, 2H,

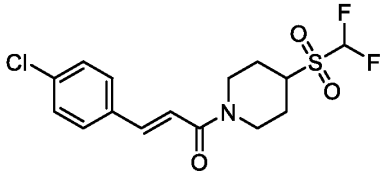
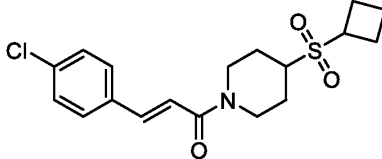
	(2,2-difluoro-1,3-benzodioxol-5-yl)prop-2-enoic acid	overlapping with water signal), 3.30-3.21 (m, 1H), 3.20-3.07 (m, 2H), 2.77-2.64 (m, 1H), 2.29-2.17 (m, 1H), 2.07-1.94 (m, 2H), 1.89-1.72 (m, 2H), 1.64-1.41 (m, 2H), 1.09 (d, 6H). MS: m/z 487.6 [M+H] ⁺
47	 (E)-1-(3-(4-chlorophenyl)acryloyl)-N-(2-ethoxyethyl)piperidine-4-sulfonamide SM: Int-63; N-(2-ethoxyethyl)piperidine-4-sulfonamide hydrochloride, (E)-3-(4-chlorophenyl)acrylic acid	¹ H NMR (400MHz, DMSO-d ₆) δ: 7.79-7.74 (m, 2H), 7.50-7.44 (m, 3H), 7.31 (d, 1H), 7.23 (t, 1H), 4.61-4.51 (m, 1H), 4.45-4.35 (m, 1H), 3.47-3.37 (m, 4H), 3.37-3.27 (m, 1H), overlapping with water signal), 3.18-3.04 (m, 3H), 2.75-2.63 (m, 1H), 2.08-2.00 (m, 2H), 1.59-1.36 (m, 2H), 1.11 (t, 3H). MS: m/z 401.3 [M+H] ⁺
48		¹ H NMR (400MHz, DMSO-d ₆) δ: 7.83 (dd, 1H), 7.79-7.73 (m, 2H), 7.52-7.43 (m, 4H), 7.29 (d, 1H), 6.29-6.26 (m,

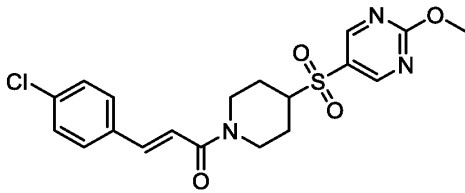
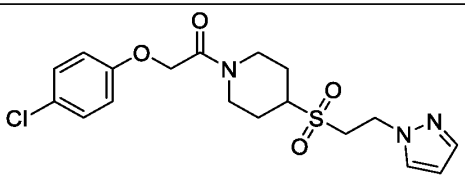
	(E)-1-(4-((2-(1H-pyrazol-1-yl)ethyl)sulfonyl)-piperidin-1-yl)-3-(4-chlorophenyl)prop-2-en-1-one SM: Int-60: 4-((2-(1H-pyrazol-1-yl)ethyl)sulfonyl)piperidine hydrochloride, (E)-3-(4-chlorophenyl)acrylic acid	1H), 4.62-4.51 (m, 3H), 4.46-4.35 (m, 1H), 3.68 (t, 2H), 3.16-2.94 (m, 2H), 2.66-2.54 (m, 1H), 2.03-1.94 (m, 2H), 1.59-1.34 (m, 2H). MS: m/z 408.5 [M+H]⁺
49	 (E)-N-(2-(1H-pyrazol-1-yl)ethyl)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide SM: Int -64: N-(2-(1H-pyrazol-1-yl)ethyl)-piperidine-4-sulfonamide hydrochloride, (E)-3-(4-chlorophenyl)acrylic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.79-7.71 (m, 3H), 7.50-7.43 (m, 4H), 7.37 (br s, 1H), 7.29 (d, 1H), 6.25-6.22 (m, 1H), 4.57-4.47 (m, 1H), 4.40-4.30 (m, 1H), 4.18 (t, 2H), 3.39 (t, 2H), 3.16-2.98 (m, 2H), 2.69-2.56 (m, 1H), 1.94-1.85 (m, 2H), 1.46-1.25 (m, 2H). MS: m/z 423.3 [M+H]⁺
50	 (R,E)-3-(4-chlorophenyl)-1-(4-((3-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)sulfonyl)-piperidin-1-yl)prop-2-en-1-one SM: Int-62: (R)-2-(1-(piperidin-4-ylsulfonyl)-pyrrolidin-3-yl)propan-2-ol hydrochloride, (E)-3-(4-chlorophenyl)acrylic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.79-7.73 (m, 2H), 7.50-7.43 (m, 3H), 7.30 (d, 1H), 4.61-4.51 (m, 1H), 4.44-4.34 (m, 2H), 3.60-3.50 (m, 1H), 3.45-3.33 (m, 2H), 3.30-3.20 (m, 1H), 3.20-3.07 (m, 2H), 2.77-2.64 (m, 1H),

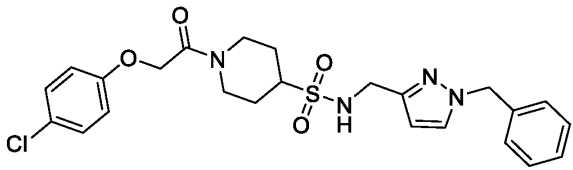
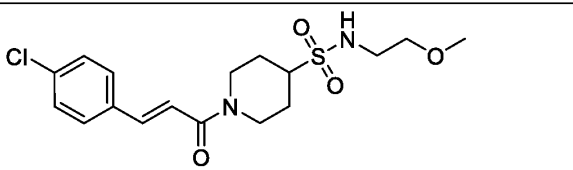
		2.29-2.17 (m, 1H), 2.06-1.93 (m, 2H), 1.89-1.72 (m, 2H), 1.65-1.40 (m, 2H), 1.08 (d, 6H). MS: m/z 441.3 [M+H]⁺
51	 (R,E)-1-(3-(4-chlorophenyl)acryloyl)-N- ((tetrahydrofuran-2-yl)methyl)piperidine-4- sulfonamide SM: Int-61: (R)-N-((tetrahydrofuran-2-yl)methyl)- piperidine-4-sulfonamide hydrochloride, (E)-3-(4- chlorophenyl)acrylic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.79-7.73 (m, 2H), 7.50-7.43 (m, 3H), 7.31 (d, 1H), 7.26 (br s, 1H), 4.60-4.50 (m, 1H), 4.44-4.34 (m, 1H), 3.88-3.79 (m, 1H), 3.78-3.71 (m, 1H), 3.65-3.58 (m, 1H), 3.37-3.27 (m, 1H, overlapping with water signal), 3.18-3.05 (m, 1H), 3.00 (d, 2H), 2.76- 2.63 (m, 1H), 2.08-1.98 (m, 2H), 1.93-1.73 (m, 3H), 1.62-1.36 (m, 3H). MS: m/z 413.4 [M+H]⁺
52	 (E)-N-((1-benzyl-1H-pyrazol-3-yl)methyl)-1-(3- (4-chlorophenyl)acryloyl)piperidine-4- sulfonamide	¹H NMR (600MHz, DMSO-d₆) δ: 7.79 (d, 1H), 7.78-7.74 (m, 2H), 7.66 (br s, 1H), 7.48- 7.44 (m, 3H), 7.34-7.30 (m, 2H), 7.29-7.22 (m, 4H), 6.25 (d, 1H), 5.27

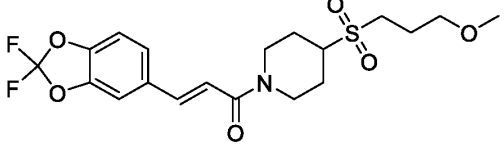
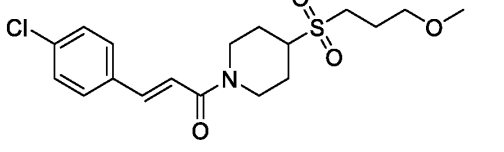
	SM: Int-65: N-((1-benzyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide hydrochloride, (E)-3-(4-chlorophenyl)acrylic acid	(s, 2H), 4.49-4.42 (m, 1H), 4.32-4.25 (m, 1H), 4.11 (s, 2H), 3.12-3.05 (m, 1H), 2.85 (t, 1H), 2.46 (t, 1H), 1.95-1.86 (m, 2H), 1.49-1.31 (m, 2H). MS: m/z 499.4 [M+H]⁺
53	 (E)-N-(3-methoxypropyl)-1-(3-(4-(trifluoromethyl)phenyl)acryloyl)piperidine-4-sulfonamide SM: Int-56: N-(3-methoxypropyl)piperidine-4-sulfonamide, HCl, (E)-3-(4-(trifluoromethyl)phenyl)acrylic acid	¹H NMR (600MHz, DMSO-d₆) δ: 7.97-7.93 (m, 2H), 7.77-7.74 (m, 2H), 7.54 (d, 1H), 7.44 (d, 1H), 7.14 (t, 1H), 4.60-4.53 (m, 1H), 4.45-4.37 (m, 1H), 3.37-3.28 (m, 3H), 3.21 (s, 3H), 3.16 (t, 1H), 3.03-2.98 (m, 2H), 2.74 (t, 1H), 2.06-1.99 (m, 2H), 1.70-1.64 (m, 2H), 1.58-1.38 (m, 2H). MS: m/z 435.2 [M+H]⁺
54	 (E)-1-(3-(4-chlorophenyl)acryloyl)-N-(3-methoxypropyl)piperidine-4-sulfonamide SM: Int-56: N-(3-methoxypropyl)piperidine-4-sulfonamide, HCl, (E)-3-(4-chlorophenyl)acrylic acid	¹H NMR (600MHz, DMSO-d₆) δ: 7.78-7.75 (m, 2H), 7.49-7.45 (m, 3H), 7.31 (d, 1H), 7.13 (br s, 1H), 4.59-4.51 (m, 1H), 4.43-4.35 (m, 1H), 3.41-3.25 (m, 6H), 3.13 (t, 1H), 3.00 (t,

		2H), 2.72 (t, 1H), 2.05-1.98 (m, 2H), 1.70-1.64 (m, 2H), 1.56-1.37 (m, 2H). MS: m/z 401.2 [M+H]⁺
55	 (E)-3-(4-chlorophenyl)-1-(4-((4-methoxyphenyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one SM: 4-((4-methoxyphenyl)sulfonyl)piperidine, (E)-3-(4-chlorophenyl)acrylic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.79-7.71 (m, 4H), 7.48-7.41 (m, 3H), 7.26 (d, 1H), 7.21-7.16 (m, 2H), 4.59-4.49 (m, 1H), 4.42-4.32 (m, 1H), 3.86 (s, 3H), 3.57-3.47 (m, 1H), 3.07 (t, 1H), 2.64 (t, 1H), 1.95-1.86 (m, 2H), 1.48-1.24 (m, 2H). MS: m/z 420.1 [M+H]⁺
56	 (E)-3-(4-chlorophenyl)-1-(4-(propylsulfonyl)piperidin-1-yl)prop-2-en-1-one SM: 4-(propylsulfonyl)piperidine hydrochloride, (E)-3-(4-chlorophenyl)acrylic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.79-7.74 (m, 2H), 7.51-7.44 (m, 3H), 7.31 (d, 1H), 4.58 (br d, 1H), 4.42 (br d, 1H), 3.46-3.36 (m, 1H), 3.21-3.10 (m, 1H), 3.10-3.03 (m, 2H), 2.79-2.65 (m, 1H), 2.11-2.02 (m, 2H), 1.77-1.66 (m, 2H),

		1.62-1.39 (m, 2H), 1.01 (t, 3H). MS: m/z 356.2 [M+H] ⁺
57	 (E)-3-(4-chlorophenyl)-1-(4-((difluoromethyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one SM: 4-difluoromethanesulfonylpiperidine hydrochloride, (E)-3-(4-chlorophenyl)acrylic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.79-7.73 (m, 2H), 7.52-7.44 (m, 3H), 7.31 (d, 1H), 7.26 (t, 1H), 4.58 (br d, 1H), 4.43 (br d, 1H), 3.98-3.88 (m, 1H), 3.28-3.14 (m, 1H), 2.87-2.73 (m, 1H), 2.14-2.05 (m, 2H), 1.74-1.49 (m, 2H). MS: m/z 364.1 [M+H]⁺
58	 (E)-3-(4-chlorophenyl)-1-(4-(cyclobutylsulfonyl)piperidin-1-yl)prop-2-en-1-one SM: Int-66: 4-(cyclobutylsulfonyl)piperidine hydrochloride, (E)-3-(4-chlorophenyl)acrylic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.79-7.74 (m, 2H), 7.50-7.44 (m, 3H), 7.30 (d, 1H), 4.62-4.51 (m, 1H), 4.46-4.35 (m, 1H), 4.15-4.05 (m, 1H), 3.38-3.28 (m, 1H, overlapping with water signal), 3.19-3.05 (m, 1H), 2.77-2.64 (m, 1H), 2.41-2.29 (m, 2H), 2.26-2.15 (m, 2H), 2.07-1.82 (m, 4H), 1.59-1.35 (m, 2H). MS: m/z 368.2 [M+H]⁺

59	 (E)-3-(4-chlorophenyl)-1-(4-((2-methoxypyrimidin-5-yl)sulfonyl)piperidin-1-yl)prop-2-en-1-one SM: Int-67: 2-methoxy-5-(piperidin-4-ylsulfonyl)-pyrimidine hydrochloride, (E)-3-(4-chlorophenyl)acrylic acid	¹H NMR (400MHz, DMSO-d₆) δ: 8.97 (s, 2H), 7.77-7.71 (m, 2H), 7.49-7.42 (m, 3H), 7.27 (d, 1H), 4.64-4.52 (m, 1H), 4.47-4.35 (m, 1H), 4.04 (s, 3H), 3.75-3.64 (m, 1H), 3.15-3.00 (m, 1H), 2.71-2.58 (m, 1H), 2.03-1.94 (m, 2H), 1.59-1.34 (m, 2H). MS: m/z 422.1 [M+H]⁺
60	 1-(4-((2-(1H-pyrazol-1-yl)ethyl)sulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one SM: Int-60: 4-((2-(1H-pyrazol-1-yl)ethyl)sulfonyl)piperidine hydrochloride, 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.83 (d, 1H), 7.51 (d, 1H), 7.31 (d, 2H), 6.97-6.91 (m, 2H), 6.28 (t, 1H), 4.85 (q, 2H), 4.56 (t, 2H), 4.47-4.35 (m, 1H), 3.98-3.86 (m, 1H), 3.68 (t, 2H), 3.12-3.02 (m, 1H), 3.01-2.91 (m, 1H), 2.53-2.51 (m, 1H), 2.01-1.90 (m, 2H), 1.72-1.54 (m, 1H), 1.48-1.30 (m, 1H). MS: m/z 412.3 [M+H]⁺

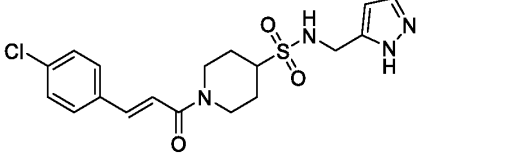
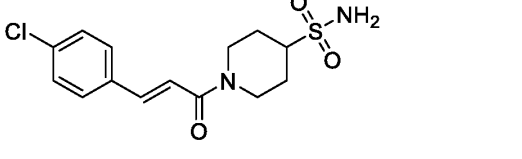
61	 N-((1-benzyl-1H-pyrazol-3-yl)methyl)-1-(2-(4-chlorophenoxy)acetyl)piperidine-4-sulfonamide SM: Int-65: N-((1-benzyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide hydrochloride, 2-(4-chlorophenoxy)acetic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.79 (d, 1H), 7.65 (t, 1H), 7.37-7.29 (m, 4H), 7.29-7.21 (m, 3H), 6.97-6.40 (m, 2H), 6.25 (d, 1H), 5.28 (s, 2H), 4.82 (q, 2H), 4.37-4.25 (m, 1H), 4.11 (d, 2H), 3.88-3.76 (m, 1H), 3.06 (tt, 1H), 2.80 (t, 1H), 2.38 (t, 1H), 1.94-1.82 (m, 2H), 1.63-1.46 (m, 1H), 1.40-1.25 (m, 1H). MS: m/z 503.4 [M+H]⁺
62	 (E)-1-(3-(4-chlorophenyl)acryloyl)-N-(2-methoxyethyl)piperidine-4-sulfonamide SM: N-(2-methoxyethyl)piperidine-4-sulfonamide, (E)-3-(4-chlorophenyl)acrylic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.80-7.72 (m, 2H), 7.51-7.44 (m, 3H), 7.32 (d, 1H), 7.25 (t, 1H), 4.63-4.48 (m, 1H), 4.48-4.33 (m, 1H), 3.37 (t, 2H), 3.33-3.27 (m, 1H), 3.26 (t, 3H), 3.19-3.05 (m, 3H), 2.78-2.64 (m, 1H), 2.08-1.98 (m, 2H), 1.60-1.36 (m, 2H). MS: m/z 387.2 [M+H]⁺

63	 (E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-((3-methoxypropyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one SM: Int-42: 4-((3-methoxypropyl)sulfonyl)-piperidine, (E)-3-(2,2-difluoro-1,3-benzodioxol-5-yl)prop-2-enoic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.95 (d, 1H), 7.56 (dd, 1H), 7.49 (d, 1H), 7.46 (d, 1H), 7.30 (d, 1H), 4.68-4.52 (m, 1H), 4.51-4.37 (m, 1H), 3.54-3.41 (mt, 3H), 3.25 (s, 3H), 3.22-3.08 (m, 3H), 2.80-2.66 (m, 1H), 2.13-2.02 (m, 2H), 1.98-1.87 (m, 2H), 1.64-1.38 (m, 2H). MS: m/z 432.3 [M+H]⁺
64	 (E)-3-(4-chlorophenyl)-1-(4-((3-methoxypropyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one SM: Int-42: 4-((3-methoxypropyl)sulfonyl)-piperidine, (E)-3-(4-chlorophenyl)acrylic acid	¹H NMR (400MHz, DMSO-d₆) δ: 7.73-7.67 (m, 2H), 7.45-7.37 (m, 3H), 7.25 (d, 1H), 4.61-4.45 (m, 1H), 4.45-4.27 (m, 1H), 3.47-3.32 (t, 3H), 3.18 (s, 3H), 3.14-3.01 (m, 3H), 2.75-2.58 (m, 1H), 2.06-1.94 (m, 2H), 1.91-1.79 (m, 2H), 1.58-1.30 (m, 2H). MS: m/z 386.2 [M+H]⁺

Procedure for compound 65 and 66:

(E)-N-((1-benzyl-1H-pyrazol-3-yl)methyl)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide (52) (21 mg, 1 eq) was dissolved in 0.3 ml DMSO and cooled in ice

- bath. KOtBu (1 M in THF, 0.295 ml, 7 eq) was added. Dioxygen was bubbled through the solution for 10 min. The reaction was quenched with 10 % citric acid (aq) and extrated with EtOAc. Volatiles were evaporated to yield a solid. The crude product was purified by column chromatography to give (E)-N-((1H-pyrazol-5-yl)methyl)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide (65) or (E)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide (66).

65	 (E)-N-((1H-pyrazol-5-yl)methyl)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide SM: (E)-N-((1-benzyl-1H-pyrazol-3-yl)methyl)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide	¹H NMR (600MHz, DMSO-d₆) δ: 12.66 (br s, 1H), 7.78-7.74 (m, 2H), 7.67 (br s, 1H), 7.61 (br s, 1H), 7.49-7.44 (m, 3H), 7.30 (d, 1H), 6.23 (br s, 1H), 4.57-4.49 (m, 1H), 4.41-4.33 (m, 1H), 4.15 (br s, 2H), 3.23-3.14 (m, 1H), 3.07-2.96 (m, 1H), 2.66-2.55 (m, 1H), 2.01-1.93 (m, 2H), 1.53-1.35 (m, 2H). MS: m/z 409.5 [M+H]⁺
66	 (E)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide SM: 52: (E)-N-((1-benzyl-1H-pyrazol-3-yl)methyl)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide	¹H NMR (600MHz, DMSO-d₆) δ: 7.79-7.75 (m, 2H), 7.50-7.45 (m, 3H), 7.32 (d, 1H), 6.80 (br s, 2H), 4.60-4.52 (m, 1H), 4.46-4.38 (m, 1H), 3.19-3.10 (m, 2H), 2.71 (t, 1H), 2.09-2.01 (m, 2H), 1.56-1.40 (m, 2H). MS: m/z 329.3 [M+H]⁺

As already mentioned hereinbefore, the compounds of formula I show interesting pharmacological properties, namely they exhibit antagonistic activity for GPR183 receptor. Said properties are demonstrated with the pharmacological test presented below.

5 EXPERIMENT 1: In vitro pharmacology

- Human THP-1 monocyte-like cell line (ATCC) endogenously expressing human GPR183 receptors were used to study GPR183 pharmacology in vitro. Cells were maintained at 37°C in a 5 % CO₂ 95 % air atmosphere in RPMI-1640 medium (ATCC) supplemented with 10 % foetal bovine serum and 0.05 mM 2-mercaptoethanol.
- Cells in suspension plated at a density of 22500 cells/ well in 384-well plates were incubated with Calcium 6 Assay reagent (Molecular Devices, CA, USA) and compounds in the concentration range 0.04 nM – 1 µM diluted in Ringer buffer for 90 minutes at 37°C in the dark. Ringer buffer consisted of (in mM): 143 NaCl, 4 KCl, 1.2 MgCl₂, 1 CaCl₂, 5 glucose, 10 HEPES and (pH 7.4 adjusted with 1.0 M NaOH). 1µM 7α25-dihydroxysterol was used as agonist and changes in intracellular calcium were monitored using FLIPRtetra (Molecular Devices, CA, USA) and displayed using Screen Works software. The samples were excited at 470-495 nm and emission was detected at 515-575 nm. All experiments were performed at 37°C.
- Baseline fluorescence minimum was subtracted from maximum for the calculation of in vitro antagonism pharmacology. The IC₅₀ values were determined using a four-parameter logistic fit model (ActivityBase XE). The results are shown in Table 1.

Compound no.	Name	IC ₅₀ human
1	2-(3,4-dichlorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one	52 nM
2	2-(4-chlorophenoxy)-1-(4-(((tetrahydro-2H-pyran-3-yl)methyl)sulfonyl)piperidin-1-yl)ethan-1-one	133 nM

3	2-(4-(difluoromethyl)phenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one	39 nM
4	1-(4-((2-(1H-pyrazol-5-yl)ethyl)sulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one	2 nM
5	1-(2-(4-chlorophenoxy)acetyl)-N-(2-ethoxyethyl)-piperidine-4-sulfonamide	2 nM
6	2-(4-chlorophenoxy)-1-(4-(pentan-3-ylsulfonyl)piperidin-1-yl)ethan-1-one	13 nM
7	2-(3,4-difluorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one	286 nM
8	2-(4-chlorophenoxy)-1-(4-((difluoromethyl)sulfonyl)piperidin-1-yl)ethan-1-one	36 nM
9	2-(4-chlorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one	8 nM
10	1-(4-(isopropylsulfonyl)piperidin-1-yl)-2-(4-(trifluoromethoxy)phenoxy)ethan-1-one	84 nM
11	2-(4-chloro-3-fluorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one	36 nM
12	1-(2-(4-chlorophenoxy)acetyl)-N-(2-methoxyethyl)-piperidine-4-sulfonamide	9 nM
13	N-butyl-1-(2-(4-chlorophenoxy)acetyl)piperidine-4-sulfonamide	2 nM
14	1-(2-(4-chlorophenoxy)acetyl)-N-(4-hydroxy-4-methylpentyl)piperidine-4-sulfonamide	64 nM
15	1-(2-(4-chlorophenoxy)acetyl)-N-(3-hydroxy-3-methylbutyl)piperidine-4-sulfonamide	2 nM
16	2-(4-chlorophenoxy)-1-(4-((2,2-dimethylpyrrolidin-1-yl)sulfonyl)piperidin-1-yl)ethan-1-one	20 nM
17	1-(2-(4-chlorophenoxy)acetyl)-N-cyclopropylpiperidine-4-sulfonamide	10 nM

18	2-(4-chlorophenoxy)-1-(4-((3-methoxypropyl)sulfonyl)piperidin-1-yl)ethan-1-one	10 nM
19	1-(4-(sec-butylsulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one	6 nM
20	2-(4-chlorophenoxy)-1-(4-((2-(tetrahydrofuran-2-yl)ethyl)sulfonyl)piperidin-1-yl)ethan-1-one	15 nM
21	1-(2-(4-chlorophenoxy)acetyl)-N-(2-hydroxy-2-methylbutyl)piperidine-4-sulfonamide	36 nM
22	N-((1H-pyrazol-5-yl)methyl)-1-(2-(4-chlorophenoxy)acetyl)piperidine-4-sulfonamide	0.23 nM
23	1-(2-(4-chlorophenoxy)acetyl)-N-(isoxazol-3-ylmethyl)piperidine-4-sulfonamide	33 nM
24	(R)-1-(4-((3-(1H-pyrazol-5-yl)pyrrolidin-1-yl)sulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one	11 nM
25	1-(2-(4-chlorophenoxy)acetyl)-N-((1-hydroxycyclobutyl)methyl)piperidine-4-sulfonamide	9 nM
26	1-(2-(4-chlorophenoxy)acetyl)-N-((1-methyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide	2 nM
27	1-(2-(4-chlorophenoxy)acetyl)-N-((1-ethyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide	1 nM
28	1-(2-(4-chlorophenoxy)acetyl)-N-(pyridazin-3-ylmethyl)piperidine-4-sulfonamide	18 nM
29	1-(2-(4-chlorophenoxy)acetyl)-N-((1-hydroxycyclopentyl)methyl)piperidine-4-sulfonamide	4 nM
30	1-(2-(4-chlorophenoxy)acetyl)-N-(3-methoxypropyl)piperidine-4-sulfonamide	3 nM
31	1-(2-(4-chlorophenoxy)acetyl)-N-(pyrazin-2-ylmethyl)piperidine-4-sulfonamide	432 nM

32	2-(4-chlorophenoxy)-1-(4-(propylsulfonyl)-piperidin-1-yl)ethan-1-one	107 nM
33	1-(4-(isopropylsulfonyl)piperidin-1-yl)-2-(4-(trifluoromethyl)phenoxy)ethan-1-one	31 nM
34	1-(2-(4-chlorophenoxy)acetyl)-N-(2-hydroxy-2-methylpropyl)piperidine-4-sulfonamide	18 nM
35	1-(3-(4-chlorophenyl)propanoyl)-N-(3-methoxypropyl)piperidine-4-sulfonamide	3 nM
36	(E)-3-(4-chlorophenyl)-1-(4-(isopropylsulfonyl)-piperidin-1-yl)prop-2-en-1-one	0.6 nM
37	(E)-1-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)acryloyl)-N-((1-ethyl-1H-pyrazol-3-yl)methyl)-piperidine-4-sulfonamide	0.5 nM
38	(E)-1-(3-(4-chlorophenyl)acryloyl)-N-((1-ethyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide	0.5 nM
39	(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(isopropylsulfonyl)piperidin-1-yl)prop-2-en-1-one	1.5 nM
40	(E)-3-(4-chlorophenyl)-1-(4-((4-fluorophenyl)-sulfonyl)piperidin-1-yl)prop-2-en-1-one	0.5 nM
41	(E)-1-(3-(4-chlorophenyl)acryloyl)-N-(2-hydroxy-2-methylpropyl)piperidine-4-sulfonamide	2 nM
42	(E)-3-(4-bromophenyl)-1-(4-((3-methoxypropyl)-sulfonyl)piperidin-1-yl)prop-2-en-1-one	0.7 nM
43	(E)-1-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)acryloyl)-N-(3-hydroxy-3-methylbutyl)-piperidine-4-sulfonamide	2 nM
44	(E)-1-(3-(4-chlorophenyl)acryloyl)-N-(3-hydroxy-3-methylbutyl)piperidine-4-sulfonamide	0.8 nM
45	(R,E)-1-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)acryloyl)-N-((tetrahydrofuran-2-yl)methyl)-piperidine-4-sulfonamide	1 nM

46	(R,E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-((3-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)sulfonyl)piperidin-1-yl)prop-2-en-1-one	0.3 nM
47	(E)-1-(3-(4-chlorophenyl)acryloyl)-N-(2-ethoxyethyl)piperidine-4-sulfonamide	0.6 nM
48	(E)-1-(4-((2-(1H-pyrazol-1-yl)ethyl)sulfonyl)piperidin-1-yl)-3-(4-chlorophenyl)prop-2-en-1-one	1 nM
49	(E)-N-(2-(1H-pyrazol-1-yl)ethyl)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide	1 nM
50	(R,E)-3-(4-chlorophenyl)-1-(4-((3-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)sulfonyl)piperidin-1-yl)prop-2-en-1-one	0.2 nM
51	(R,E)-1-(3-(4-chlorophenyl)acryloyl)-N-((tetrahydrofuran-2-yl)methyl)piperidine-4-sulfonamide	0.1 nM
52	(E)-N-((1-benzyl-1H-pyrazol-3-yl)methyl)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide	0.3 nM
53	(E)-N-(3-methoxypropyl)-1-(3-(4-(trifluoromethyl)phenyl)acryloyl)piperidine-4-sulfonamide	2 nM
54	(E)-1-(3-(4-chlorophenyl)acryloyl)-N-(3-methoxypropyl)piperidine-4-sulfonamide	0.3 nM
55	(E)-3-(4-chlorophenyl)-1-(4-((4-methoxyphenyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one	0.1 nM
56	(E)-3-(4-chlorophenyl)-1-(4-(propylsulfonyl)piperidin-1-yl)prop-2-en-1-one	0.6 nM
57	(E)-3-(4-chlorophenyl)-1-(4-((difluoromethyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one	0.3 nM
58	(E)-3-(4-chlorophenyl)-1-(4-(cyclobutylsulfonyl)piperidin-1-yl)prop-2-en-1-one	1 nM
59	(E)-3-(4-chlorophenyl)-1-(4-((2-methoxypyrimidin-5-yl)sulfonyl)piperidin-1-yl)prop-2-en-1-one	0.4 nM

60	1-(4-((2-(1H-pyrazol-1-yl)ethyl)sulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one	28 nM
61	N-((1-benzyl-1H-pyrazol-3-yl)methyl)-1-(2-(4-chlorophenoxy)acetyl)piperidine-4-sulfonamide	20 nM
62	(E)-1-(3-(4-chlorophenyl)acryloyl)-N-(2-methoxyethyl)piperidine-4-sulfonamide	1 nM
63	(E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-((3-methoxypropyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one	0.6 nM
64	(E)-3-(4-chlorophenyl)-1-(4-((3-methoxypropyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one	0.4 nM
65	(E)-N-((1H-pyrazol-5-yl)methyl)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide	0.3 nM
66	(E)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide	9 nM

Table 1. GPR183 antagonistic activity in vitro.

EXPERIMENT 2: In vivo efficacy

The efficacy of GPR183 antagonist compounds can be studied in a preclinical in vivo mono-iodoacetate (MIA) model of osteoarthritis pain in rats according to the method
5 described by Combe et al., in Neuroscience Letters, 370 (2004).

The compounds of formula I exhibit GPR183 antagonistic activity. The present disclosure thus provides compounds for use as a medicament. Compounds for use in the treatment of disorder, condition, or disease where a GPR183 antagonist is indicated to be useful are also provided. Furthermore, a method for the treatment of
10 disorder, condition, or disease where a GPR183 antagonist is indicated to be useful is provided. In said method an effective amount of at least one compound of formula I is administered to a mammal, such as human, in need of such treatment. The use of the compounds of formula I for the manufacture of a medicament for the treatment of disorder, condition, or disease where a GPR183 antagonist is indicated to be useful is
15 also provided.

In one embodiment the aforementioned disorder, condition or disease where a GPR183 antagonist is indicated to be useful is chronic pain e.g osteoarthritis, chronic low back pain, neuropathic pain and immune system diseases e.g. inflammatory bowel diseases e.g. Colitis and Chron's diseases, multiple sclerosis, rheumatoid arthritis, or inflammatory pulmonary diseases e.g. asthma and psoriasis ameliorated by inhibition of GPR183 receptors.

The compounds of the present disclosure can be administered, for example, enterally, topically, or parenterally by means of any pharmaceutical formulation useful for said administration and comprising at least one active compound of formula I in pharmaceutically acceptable and effective amounts together with pharmaceutically acceptable diluents, carriers and/or excipients known in the art. The manufacture of such pharmaceutical formulations is known in the art.

The therapeutic dose to be given to a subject in need of the treatment will vary depending on the compound being administered, the species, the age and the sex of the subject being treated, the particular condition being treated, as well as the route and method of administration, and is easily determined by a person skilled in the art. Accordingly, the typical dosage for oral administration is from 10 ng/kg to 100 mg/kg per day and for parenteral administration from 1 ng/kg to 10 mg/kg for an adult mammal.

The compounds of the present disclosure are given to the subject as such or in combination with one or more other active ingredients, each in its own composition or some or all of the active ingredients combined in a single composition, and/or suitable pharmaceutical excipients. Suitable pharmaceutical excipients include conventionally used excipients and formulation aids, such as fillers, binders, disintegrating agents, lubricants, solvents, gel forming agents, emulsifiers, stabilizers, colorants, and/or preservatives.

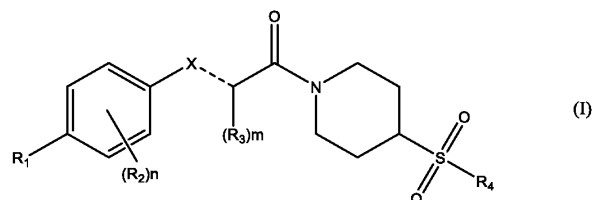
The compounds of the present disclosure are formulated into dosage forms using commonly known pharmaceutical manufacturing methods. The dosage forms can be, for example, tablets, capsules, granules, suppositories, emulsions, suspensions, or solutions. Depending on the route of administration and the galenic form, the amount

of the active ingredient in a formulation can typically vary between 0.01 % and 100 % by weight.

- A person skilled in the art will appreciate that the embodiments described herein can be modified without departing from the inventive concept. A person skilled in the art
- 5 also understands that the present disclosure is not limited to the particular embodiments disclosed but is intended to also cover modifications of the embodiments that are within the scope of the present disclosure.

CLAIMS

1. A compound of formula I,



5 wherein;

the dotted line [- - -] represents a single or a double bond;

X is O, CH₂ or CH, provided that when X is O or CH₂ the dotted line is a single bond, and when X is CH the dotted line is a double bond;

R₁ is halogen, halo(C₁₋₃)alkyl or halo(C₁₋₃)alkoxy;

10 R₂ is halogen;

or R₁ and R₂ attached to adjacent carbon ring atoms form, together with the carbon ring atoms a fused 2,2-difluoro-1,3-dioxolane ring;

R₃ is hydrogen;

R₄ is (C₂₋₆)alkyl, halo(C₁₋₃)alkyl, (C₁₋₃)alkoxy(C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, 6-

15 membered heterocyclyl, heterocyclyl(C₁₋₃)alkyl, NHR₅ or NR₆R₇, wherein said (C₃₋₆)cycloalkyl or heterocyclyl is unsubstituted or substituted with one or more substituents independently selected from hydroxy, (C₁₋₃)alkyl and (C₁₋₃)alkoxy;

R₅ is hydrogen, (C₂₋₆)alkyl, (C₁₋₃)alkoxy(C₁₋₆)alkyl, hydroxy(C₁₋₆)alkyl, (C₃₋₆)cycloalkyl, (C₃₋₆)cycloalkyl(C₁₋₃)alkyl, or heterocyclyl(C₁₋₃)alkyl, wherein said (C₃₋

20 6)cycloalkyl or heterocyclyl is unsubstituted or substituted with one or more substituents independently selected from hydroxy, (C₁₋₃)alkyl and phenyl(C₁₋₃)alkyl;

R₆ and R₇ form, together with the nitrogen atom to which they are attached, a pyrrolidine ring wherein said pyrrolidine ring is substituted with 1 or 2 substituents independently selected from (C₁₋₃)alkyl, hydroxy(C₁₋₆)alkyl and heterocyclyl;

25 n is an integer selected from 0, 1 or 2;

m is an integer selected from 1 or 2;

or a pharmaceutically acceptable salt thereof;

with the proviso that the compound is not

2-(4-chlorophenoxy)-1-(4-(ethylsulfonyl)piperidin-1-yl)ethan-1-one,

- 2-(4-fluorophenoxy)-1-(4-(isobutylsulfonyl)piperidin-1-yl)ethan-1-one,
2-(4-chlorophenoxy)-1-(4-(isobutylsulfonyl)piperidin-1-yl)ethan-1-one,
2-(2,4-dichlorophenoxy)-1-(4-(ethylsulfonyl)piperidin-1-yl)ethan-1-one,
2-(2,4-dichlorophenoxy)-1-(4-(isobutylsulfonyl)piperidin-1-yl)ethan-1-one,
5 2-(4-fluorophenoxy)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)ethan-1-one,
2-(4-chlorophenoxy)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)ethan-1-one,
2-(2,4-dichlorophenoxy)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)ethan-1-one,
3-(4-chlorophenyl)-1-(4-(ethylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
10 1-(4-(ethylsulfonyl)piperidin-1-yl)-3-(4-fluorophenyl)prop-2-en-1-one,
3-(4-chlorophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
3-(2,4-dichlorophenyl)-1-(4-(ethylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
3-(4-bromophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)propan-1-one,
3-(3,4-dichlorophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)propan-1-one,
15 3-(3-chloro-4-fluorophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)propan-1-one,
3-(4-chloro-3-fluorophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)propan-1-one,
3-(2,4-dichlorophenyl)-1-(4-(isobutylsulfonyl)piperidin-1-yl)propan-1-one,
3-(4-chlorophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
1-(4-(isobutylsulfonyl)piperidin-1-yl)-3-(4-(trifluoromethyl)phenyl)propan-1-one,
20 3-(4-bromophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)propan-1-one,
3-(3-chloro-4-fluorophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)propan-1-one,
3-(3,4-dichlorophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)propan-1-one,
25 3-(2,4-dichlorophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)propan-1-one,
3-(4-chloro-3-fluorophenyl)-1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)propan-1-one,
1-(4-((furan-2-ylmethyl)sulfonyl)piperidin-1-yl)-3-(4-(trifluoromethyl)phenyl)-
30 propan-1-one,
1-(4-(ethylsulfonyl)piperidin-1-yl)-3-(4-fluorophenyl)propan-1-one,

1-(3-(4-chlorophenyl)propanoyl)piperidine-4-sulfonamide, or
1-(3-(4-fluorophenyl)propanoyl)piperidine-4-sulfonamide.

2. The compound according to claim 1, wherein

X is O;

5 R₁ is halogen;

R₃ is hydrogen;

R₄ is (C₃₋₆)alkyl, (C₁₋₃)alkoxy(C₂₋₆)alkyl, heterocyclyl(C₁₋₃)alkyl, or NHR₅, wherein
said heterocyclyl is unsubstituted;

R₅ is (C₁₋₃)alkoxy(C₂₋₆)alkyl, hydroxy(C₃₋₆)alkyl, (C₃₋₆)cycloalkyl(C₁₋₃)alkyl, or
10 heterocyclyl(C₁₋₃)alkyl, wherein said (C₃₋₆)cycloalkyl or heterocyclyl is unsubstituted
or substituted with one substituent independently selected from hydroxy and
(C₁₋₂)alkyl;

n is 0;

m is 2;

15 or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1, wherein

X is CH;

R₁ is halogen;

R₃ is hydrogen;

20 R₄ is (C₃₋₆)alkyl, (C₁₋₃)alkoxy(C₂₋₆)alkyl, heterocyclyl(C₁₋₃)alkyl, or NHR₅, wherein
said heterocyclyl is unsubstituted;

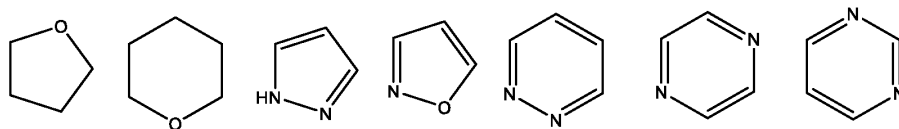
R₅ is (C₁₋₃)alkoxy(C₂₋₆)alkyl, hydroxy(C₃₋₆)alkyl, (C₃₋₆)cycloalkyl(C₁₋₃)alkyl, or
heterocyclyl(C₁₋₃)alkyl, wherein said (C₃₋₆)cycloalkyl or heterocyclyl is unsubstituted
or substituted with one substituent independently selected from hydroxy and
25 (C₁₋₂)alkyl;

n is 0;

m is 1;

or a pharmaceutically acceptable salt thereof.

4. The compound according to any one of claims 1 to 3, wherein the heterocyclyl is any one of the following groups:



5. The compound according to claim 1, wherein the compound is;

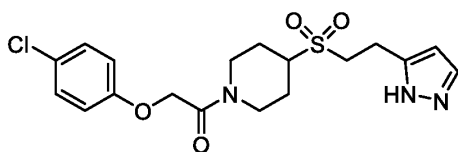
- 5 2-(3,4-dichlorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one,
2-(4-chlorophenoxy)-1-(4-(((tetrahydro-2H-pyran-3-yl)methyl)sulfonyl)piperidin-1-yl)ethan-1-one,
2-(4-(difluoromethyl)phenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one,
1-(4-((2-(1H-pyrazol-5-yl)ethyl)sulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-
10 1-one,
1-(2-(4-chlorophenoxy)acetyl)-N-(2-ethoxyethyl)piperidine-4-sulfonamide,
2-(4-chlorophenoxy)-1-(4-(pentan-3-ylsulfonyl)piperidin-1-yl)ethan-1-one,
2-(3,4-difluorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one,
2-(4-chlorophenoxy)-1-(4-((difluoromethyl)sulfonyl)piperidin-1-yl)ethan-1-one,
15 2-(4-chlorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one,
1-(4-(isopropylsulfonyl)piperidin-1-yl)-2-(4-(trifluoromethoxy)phenoxy)ethan-1-one,
2-(4-chloro-3-fluorophenoxy)-1-(4-(isopropylsulfonyl)piperidin-1-yl)ethan-1-one,
1-(2-(4-chlorophenoxy)acetyl)-N-(2-methoxyethyl)piperidine-4-sulfonamide,
N-butyl-1-(2-(4-chlorophenoxy)acetyl)piperidine-4-sulfonamide,
20 1-(2-(4-chlorophenoxy)acetyl)-N-(4-hydroxy-4-methylpentyl)piperidine-4-sulfonamide,
1-(2-(4-chlorophenoxy)acetyl)-N-(3-hydroxy-3-methylbutyl)piperidine-4-sulfonamide,
2-(4-chlorophenoxy)-1-(4-((2,2-dimethylpyrrolidin-1-yl)sulfonyl)piperidin-1-yl)ethan-1-one,
25 1-(2-(4-chlorophenoxy)acetyl)-N-cyclopropylpiperidine-4-sulfonamide,
2-(4-chlorophenoxy)-1-(4-((3-methoxypropyl)sulfonyl)piperidin-1-yl)ethan-1-one,
1-(4-(sec-butylsulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one,
2-(4-chlorophenoxy)-1-(4-((2-(tetrahydrofuran-2-yl)ethyl)sulfonyl)piperidin-1-

- yl)ethan-1-one,
1-(2-(4-chlorophenoxy)acetyl)-N-(2-hydroxy-2-methylbutyl)piperidine-4-sulfonamide,
N-((1H-pyrazol-5-yl)methyl)-1-(2-(4-chlorophenoxy)acetyl)piperidine-4-sulfonamide,
5 1-(2-(4-chlorophenoxy)acetyl)-N-(isoxazol-3-ylmethyl)piperidine-4-sulfonamide,
(R)-1-(4-((3-(1H-pyrazol-5-yl)pyrrolidin-1-yl)sulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-1-one,
1-(2-(4-chlorophenoxy)acetyl)-N-((1-hydroxycyclobutyl)methyl)piperidine-4-sulfonamide,
10 1-(2-(4-chlorophenoxy)acetyl)-N-((1-methyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide,
1-(2-(4-chlorophenoxy)acetyl)-N-((1-ethyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide,
15 1-(2-(4-chlorophenoxy)acetyl)-N-(pyridazin-3-ylmethyl)piperidine-4-sulfonamide,
1-(2-(4-chlorophenoxy)acetyl)-N-((1-hydroxycyclopentyl)methyl)piperidine-4-sulfonamide,
1-(2-(4-chlorophenoxy)acetyl)-N-(3-methoxypropyl)piperidine-4-sulfonamide,
1-(2-(4-chlorophenoxy)acetyl)-N-(pyrazin-2-ylmethyl)piperidine-4-sulfonamide,
20 2-(4-chlorophenoxy)-1-(4-(propylsulfonyl)piperidin-1-yl)ethan-1-one,
1-(4-(isopropylsulfonyl)piperidin-1-yl)-2-(4-(trifluoromethyl)phenoxy)ethan-1-one,
1-(2-(4-chlorophenoxy)acetyl)-N-(2-hydroxy-2-methylpropyl)piperidine-4-sulfonamide,
1-(3-(4-chlorophenyl)propanoyl)-N-(3-methoxypropyl)piperidine-4-sulfonamide,
25 (E)-3-(4-chlorophenyl)-1-(4-(isopropylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
(E)-1-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)acryloyl)-N-((1-ethyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide,
(E)-1-(3-(4-chlorophenyl)acryloyl)-N-((1-ethyl-1H-pyrazol-3-yl)methyl)piperidine-4-sulfonamide,
30 (E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-(isopropylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
(E)-1-(3-(4-chlorophenyl)acryloyl)-N-(2-hydroxy-2-methylpropyl)piperidine-4-

- sulfonamide,
(E)-3-(4-bromophenyl)-1-(4-((3-methoxypropyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
(E)-1-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)acryloyl)-N-(3-hydroxy-3-methylbutyl)piperidine-4-sulfonamide,
5 (E)-1-(3-(4-chlorophenyl)acryloyl)-N-(3-hydroxy-3-methylbutyl)piperidine-4-sulfonamide,
(R,E)-1-(3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)acryloyl)-N-((tetrahydrofuran-2-yl)methyl)piperidine-4-sulfonamide,
10 (R,E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-((3-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
(E)-1-(3-(4-chlorophenyl)acryloyl)-N-(2-ethoxyethyl)piperidine-4-sulfonamide,
(E)-1-(4-((2-(1H-pyrazol-1-yl)ethyl)sulfonyl)piperidin-1-yl)-3-(4-chlorophenyl)prop-2-en-1-one,
15 (E)-N-(2-(1H-pyrazol-1-yl)ethyl)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide,
(R,E)-3-(4-chlorophenyl)-1-(4-((3-(2-hydroxypropan-2-yl)pyrrolidin-1-yl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
(R,E)-1-(3-(4-chlorophenyl)acryloyl)-N-((tetrahydrofuran-2-yl)methyl)piperidine-4-sulfonamide,
20 (E)-N-((1-benzyl-1H-pyrazol-3-yl)methyl)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide,
(E)-N-(3-methoxypropyl)-1-(3-(4-(trifluoromethyl)phenyl)acryloyl)piperidine-4-sulfonamide,
25 (E)-1-(3-(4-chlorophenyl)acryloyl)-N-(3-methoxypropyl)piperidine-4-sulfonamide,
(E)-3-(4-chlorophenyl)-1-(4-(propylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
(E)-3-(4-chlorophenyl)-1-(4-((difluoromethyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
(E)-3-(4-chlorophenyl)-1-(4-(cyclobutylsulfonyl)piperidin-1-yl)prop-2-en-1-one,
30 (E)-3-(4-chlorophenyl)-1-(4-((2-methoxypyrimidin-5-yl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
1-(4-((2-(1H-pyrazol-1-yl)ethyl)sulfonyl)piperidin-1-yl)-2-(4-chlorophenoxy)ethan-

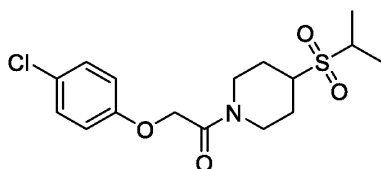
- 1-one,
 N-((1-benzyl-1H-pyrazol-3-yl)methyl)-1-(2-(4-chlorophenoxy)acetyl)piperidine-4-sulfonamide,
 (E)-1-(3-(4-chlorophenyl)acryloyl)-N-(2-methoxyethyl)piperidine-4-sulfonamide,
 5 (E)-3-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-1-(4-((3-methoxypropyl)sulfonyl)-piperidin-1-yl)prop-2-en-1-one,
 (E)-3-(4-chlorophenyl)-1-(4-((3-methoxypropyl)sulfonyl)piperidin-1-yl)prop-2-en-1-one,
 (E)-N-((1H-pyrazol-5-yl)methyl)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide, or
 10 (E)-1-(3-(4-chlorophenyl)acryloyl)piperidine-4-sulfonamide,
 or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 1, wherein the compound is



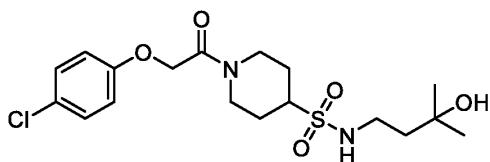
- 15 or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 1, wherein the compound is



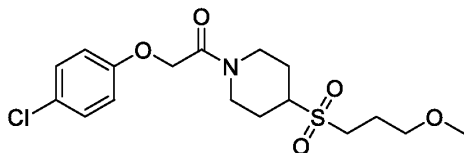
- or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 1, wherein the compound is



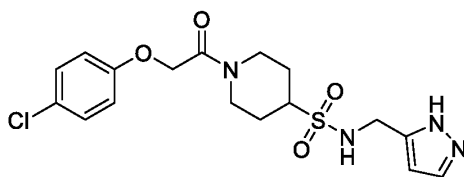
- 20 or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

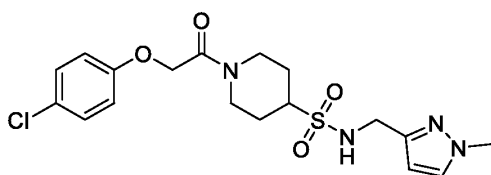
10. The compound according to claim 1, wherein the compound is



5

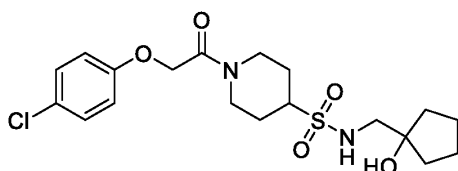
or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 1, wherein the compound is



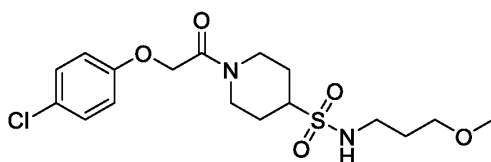
or a pharmaceutically acceptable salt thereof.

- 10 12. The compound according to claim 1, wherein the compound is



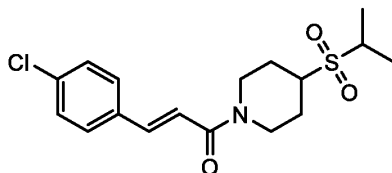
or a pharmaceutically acceptable salt thereof.

13. The compound according to claim 1, wherein the compound is



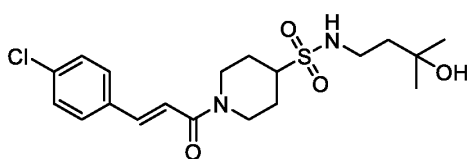
- 15 or a pharmaceutically acceptable salt thereof.

14. The compound according to claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

15. The compound according to claim 1, wherein the compound is



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or a pharmaceutically acceptable salt thereof.

16. The compound according to any one of claims 1 to 15 for use as a medicament.

17. The compound according to any one of claims 1 to 16 for use in the treatment
10 of a disorder, condition, or disease where a GPR183 antagonist is indicated to be useful.

18. The compound according to claim 17, wherein the disorder, condition, or
disease is chronic pain e.g osteoarthritis, chronic low back pain, neuropathic pain and
immune system diseases e.g inflammatory bowel diseases e.g. Colitis and Chron's
15 diseases, multiple sclerosis, rheumatoid arthritis, inflammatory pulmonary diseases
e.g. asthma and psoriasis ameliorated by inhibition of GPR183 receptors.

19. A method for the treatment of a disorder, condition, or disease where a
GPR183 antagonist is indicated to be useful, which method comprises administering
to a mammal in need of such treatment an effective amount of at least one compound
20 according to claim 1.

20. The method according to claim 19, wherein the disorder, condition, or disease
is chronic pain e.g osteoarthritis, chronic low back pain, neuropathic pain and
immune system diseases e.g inflammatory bowel diseases e.g. Colitis and Chron's

diseases, multiple sclerosis, rheumatoid arthritis, inflammatory pulmonary diseases e.g. asthma and psoriasis ameliorated by inhibition of GPR183 receptors.

21. A pharmaceutical composition comprising at least one compound according to any one of claims 1 to 15 and a pharmaceutically acceptable carrier, diluent and/or
5 excipient.

22. The pharmaceutical composition according to claim 21 wherein the composition comprises further at least one other active ingredient.