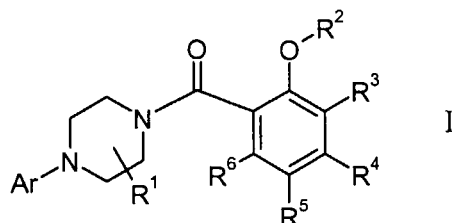


PIPERAZINE WITH OR-SUBSTITUTED PHENYL GROUP AND THEIR USE AS GLYT1 INHIBITORS

The present invention relates to compounds of the general formula I



wherein

- 5 Ar is unsubstituted or substituted aryl or 6-membered heteroaryl, containing one, two or three nitrogen atoms, and wherein the aryl and the heteroaryl groups may be substituted by one or more substituents selected from the group consisting of hydroxy, halogen, NO₂, CN, (C₁-C₆)-alkyl, (C₁-C₆)-alkyl substituted by halogen, (C₁-C₆)-alkyl substituted by hydroxy, (CH₂)_n-(C₁-C₆)-alkoxy, (C₁-C₆)-alkoxy substituted by halogen, NR⁷R⁸, C(O)R⁹, SO₂R¹⁰, -C(CH₃)=NOR⁷, or by a 5-
 10 membered aromatic heterocycle, containing 1 – 4 heteroatoms, selected from N and O, which is optionally substituted by (C₁-C₆)-alkyl;

R¹ is hydrogen or (C₁-C₆)-alkyl;

15

- R² is hydrogen, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₁-C₆)-alkyl substituted by halogen, (C₁-C₆)-alkyl substituted by hydroxy, (CH₂)_n-(C₃-C₇)-cycloalkyl optionally substituted by (C₁-C₆)-alkoxy or by halogen, or is CH(CH₃)-(C₃-C₇)-cycloalkyl, (CH₂)_{n+1}-C(O)-R⁹, (CH₂)_{n+1}-CN, bicyclo[2.2.1]heptyl, (CH₂)_{n+1}-O-(C₁-C₆)-alkyl,
 20 (CH₂)_n-heterocycloalkyl, (CH₂)_n-aryl or (CH₂)_n-5 or 6-membered heteroaryl containing one, two or three heteroatoms, selected from the group consisting of oxygen, sulphur or nitrogen wherein aryl, heterocycloalkyl and heteroaryl are unsubstituted or substituted by one or more substituents selected from the group consisting of hydroxy, halogen, (C₁-C₆)-alkyl or (C₁-C₆)-alkoxy;

R^3 , R^4 and R^6 independently from each other are hydrogen, hydroxy, halogen,
(C_1 - C_6)-alkyl, (C_1 - C_6)-alkoxy or O-(C_3 - C_6)-cycloalkyl;

R^5 is NO_2 , CN, $C(O)R^9$ or SO_2R^{10} ;

5

R^7 and R^8 independently from each other are hydrogen or (C_1 - C_6)-alkyl;

R^9 is hydrogen, (C_1 - C_6)-alkyl, (C_1 - C_6)-alkoxy or NR^7R^8 ;

10 R^{10} is (C_1 - C_6)-alkyl optionally substituted by halogen, $(CH_2)_n$ -(C_3 - C_6)-cycloalkyl,
 $(CH_2)_n$ -(C_3 - C_6)-alkoxy, $(CH_2)_n$ -heterocycloalkyl or NR^7R^8 ;

n is 0, 1, or 2;

15 and to pharmaceutically acceptable acid addition salts thereof,
with the proviso that

1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-(3-chlorophenyl)-piperazine,

1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-(4-fluorophenyl)-piperazine,

1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-[3-(trifluoromethyl)phenyl]-piperazine,

20 4-(3-amino-4-nitrophenyl)-1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-
methyl-piperazine,

1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-methyl-4-(4-nitrophenyl)-
piperazine,

4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-methyl-1-(4-nitrophenyl)-
25 piperazine,

1-(2-chloro-4-nitrophenyl)-4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-
piperazine,

1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-4-(2,4-dinitrophenyl)-2-methyl-
piperazine,

30 1-(4-chloro-2-nitrophenyl)-4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-
piperazine and

4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-1-(2,4-dinitrophenyl)-2-methyl-
piperazine

are excluded.

35 The compounds

1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-(3-chlorophenyl)-piperazine,

1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-(4-fluorophenyl)-piperazine and
1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-[3-(trifluoromethyl)phenyl]-piperazine
are specifically described in EP 0171636, possessing inhibiting activity towards carbonic
anhydrase which plays a determining role in many physiological and pathological

5 processes.

The other excluded compounds are commercially available products.

The present invention relates to compounds of general formula I, to
pharmaceutical composition containing them and their use in the treatment of
neurological and neuropsychiatric disorders. It has surprisingly been found that the
10 compounds of general formula I are good inhibitors of the glycine transporter 1
(GlyT-1), and that they have a good selectivity to glycine transporter 2 (GlyT-2)
inhibitors.

Schizophrenia is a progressive and devastating neurological disease characterized by
episodic positive symptoms such as delusions, hallucinations, thought disorders and
15 psychosis and persistent negative symptoms such as flattened affect, impaired attention
and social withdrawal, and cognitive impairments (Lewis DA and Lieberman JA, *Neuron*,
, 28:325-33, 2000). For decades research has focused on the "dopaminergic hyperactivity"
hypothesis which has led to therapeutic interventions involving blockade of the
dopaminergic system (Vandenberg RJ and Aubrey KR., *Exp. Opin. Ther. Targets*, 5(4):
20 507-518, 2001; Nakazato A and Okuyama S, et al., *Exp. Opin. Ther. Patents*, 10(1):
75-98, 2000). This pharmacological approach poorly address negative and cognitive
symptoms which are the best predictors of functional outcome (Sharma T., *Br.J.*
Psychiatry, 174(suppl. 28): 44-51, 1999).

A complementary model of schizophrenia was proposed in the mid-1960' based
25 upon the psychotomimetic action caused by the blockade of the glutamate system by
compounds like phencyclidine (PCP) and related agents (ketamine) which are non-
competitive NMDA receptor antagonists. Interestingly in healthy volunteers, PCP-
induced psychotomimetic action incorporates positive and negative symptoms as well as
cognitive dysfunction, thus closely resembling schizophrenia in patients (Javitt DC et al.,
30 *Biol. Psychiatry*, 45: 668-679, 1999). Furthermore transgenic mice expressing reduced
levels of the NMDAR1 subunit displays behavioral abnormalities similar to those
observed in pharmacologically induced models of schizophrenia, supporting a model in
which reduced NMDA receptor activity results in schizophrenia-like behavior (Mohn AR
et al., *Cell*, 98: 427-236, 1999).

35 Glutamate neurotransmission, in particular NMDA receptor activity, plays a
critical role in synaptic plasticity, learning and memory, such as the NMDA receptors
appears to serve as a graded switch for gating the threshold of synaptic plasticity and
memory formation (Wiley, NY; Bliss TV and Collingridge GL, *Nature*, 361: 31-39, 1993).

Transgenic mice overexpressing the NMDA NR2B subunit exhibit enhanced synaptic plasticity and superior ability in learning and memory (Tang JP et al., *Natur*, 401- 63-69, 1999).

Thus, if a glutamate deficit is implicate in the pathophysiology of schizophrenia,
5 enhancing glutamate transmission, in particular via NMDA receptor activation, would be predicted to produce both anti-psychotic and cognitive enhancing effects.

The amino acid glycine is known to have at least two important functions in the CNS. It acts as an inhibitory amino acid, binding to strychnine sensitive glycine receptors, and it also influences excitatory activity, acting as an essential co-agonist with
10 glutamate for N-methyl-D-aspartate (NMDA) receptor function. While glutamate is released in an activity-dependent manner from synaptic terminals, glycine is apparently present at a more constant level and seems to modulate/control the receptor for its response to glutamate.

One of the most effective ways to control synaptic concentrations of
15 neurotransmitter is to influence their re-uptake at the synapses. Neurotransmitter transporters by removing neurotransmitters from the extracellular space, can control their extracellular lifetime and thereby modulate the magnitude of the synaptic transmission (Gainetdinov RR et al, *Trends in Pharm. Sci.*, 23(8): 367-373, 2002).

Glycine transporters, which form part of the sodium and chloride family of
20 neurotransmitter transporters, play an important role in the termination of post-synaptic glycinergic actions and maintenance of low extracellular glycine concentration by re-uptake of glycine into presynaptic nerve terminals and surrounding fine glial processes.

Two distinct glycine transporter genes have been cloned (GlyT-1 and GlyT-2) from mammalian brain, which give rise to two transporters with ~50 % amino acid sequence
25 homology. GlyT-1 presents four isoforms arising from alternative splicing and alternative promoter usage (1a, 1b, 1c and 1d). Only two of these isoforms have been found in rodent brain (GlyT-1a and GlyT-1b). GlyT-2 also presents some degree of heterogeneity. Two GlyT-2 isoforms (2a and 2b) have been identified in rodent brains. GlyT-1 is known to be located in CNS and in peripheral tissues, whereas GlyT-2 is specific to the CNS.
30 GlyT-1 has a predominantly glial distribution and is found not only in areas corresponding to strychnine sensitive glycine receptors but also outside these areas, where it has been postulated to be involved in modulation of NMDA receptor function (Lopez-Corcuera B et al., *Mol. Mem. Biol.*, 18: 13-20, 2001). Thus, one strategy to enhance NMDA receptor activity is to elevate the glycine concentration in the local
35 microenvironment of synaptic NMDA receptors by inhibition of GlyT-1 transporter (Bergereon R. et al., *Proc. Natl. Acad. Sci. USA*, 95: 15730-15734, 1998; Chen L. et al., *J. Neurophysiol.*, 89(2): 691-703, 2003).

Glycine transporters inhibitors are suitable for the treatment of neurological and neuropsychiatric disorders. The majority of diseases states implicated are psychoses, schizophrenia (Armer RE and Miller DJ, *Exp. Opin. Ther. Patents*, 11 (4): 563-572, 2001), psychotic mood disorders such as severe major depressive disorder, mood disorders
5 associated with psychotic disorders such as acute mania or depression, associated with bipolar disorders and mood disorders, associated with schizophrenia, (Pralong ET et al., *Prog. Neurobiol.*, 67: 173-202, 2002), autistic disorders (Carlsson ML, *J. Neural Trans.*, 105: 525-535, 1998), cognitive disorders such as dementias, including age related dementia and senile dementia of the Alzheimer type, memory disorders in a mammal,
10 including a human, attention deficit disorders and pain (Armer RE and Miller DJ, *Exp. Opin. Ther. Patents*, 11 (4): 563-572, 2001).

Thus, increasing activation of NMDA receptors via GlyT-1 inhibition may lead to agents that treat psychosis, schizophrenia, dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's disease.

15 Objects of the present invention are the compounds of formula I per se, the use of compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases related to activation of NMDA receptors via Glyt-1 inhibition, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I in
20 the control or prevention of illnesses such as psychoses, disfunction in memory and learning, schizophrenia, dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's disease.

The preferred indications using the compounds of the present invention are schizophrenia, cognitive impairment and Alzheimer's disease.

25 Furthermore, the invention includes all racemic mixtures, all their corresponding enantiomers and/or optical isomers.

As used herein, the term "alkyl" denotes a saturated straight- or branched-chain group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred alkyl groups are groups
30 with 1 - 4 carbon atoms.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "aryl" denotes a monovalent cyclic aromatic hydrocarbon radical consisting of one or more fused rings in which at least one ring is aromatic in nature, for example phenyl, benzyl, naphthyl, biphenyl or indanyl.

The term "6-membered heteroaryl containing one, two or three nitrogen atoms" denotes a monovalent aromatic carbocyclic radical, for example pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl or 1,3,5-triazinyl.

The term "heterocycloalkyl" denotes a non aromatic hydrocarbon radical, for example oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or thiomorpholinyl.

The term "5-membered aromatic heterocycle, containing 1 – 4 heteroatoms, selected from N and O" denotes for example 1,2,4-oxadiazolyl, oxazolyl, 1,3,4-oxadiazolyl or tetrazolyl.

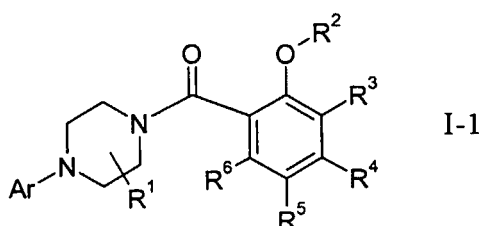
The term "5 or 6-membered heteroaryl containing one, two or three heteroatoms, selected from the group consisting of oxygen, sulphur or nitrogen" denotes a monovalent aromatic carbocyclic radical, for example pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiazolyl, thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl or isoxazolyl.

The term "alkyl, substituted by halogen" denotes for example the following groups: CF_3 , CHF_2 , CH_2F , CH_2CF_3 , CH_2CHF_2 , $\text{CH}_2\text{CH}_2\text{F}$, $\text{CH}_2\text{CH}_2\text{CF}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$, $\text{CH}_2\text{CH}_2\text{Cl}$, $\text{CH}_2\text{CF}_2\text{CF}_3$, $\text{CH}_2\text{CF}_2\text{CHF}_2$, CF_2CHF_2 , $\text{C}(\text{CH}_3)_2\text{CF}_3$, $\text{CH}(\text{CH}_3)\text{CF}_3$ or $\text{CH}(\text{CH}_2\text{F})\text{CH}_2\text{F}$.

The term "alkyl, substituted by hydroxy" denotes for example the following groups: $\text{CH}(\text{OH})\text{CH}_3$, $\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$, $(\text{CH}_2)_2\text{OH}$, $(\text{CH}_2)_3\text{OH}$ or $\text{CH}_2\text{C}[(\text{CH}_3)]_2\text{-CH}_2\text{OH}$.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

One embodiment of the invention are compounds of the general formula



wherein

- Ar is substituted aryl or unsubstituted or substituted 6-membered heteroaryl,
containing one, two or three nitrogen atoms, and wherein the aryl and the heteroaryl
5 groups are substituted by one or more substituents selected from the group
consisting of hydroxy, halogen, NO₂, CN, (C₁-C₆)-alkyl, (C₁-C₆)-alkyl substituted by
halogen,
(C₁-C₆)-alkoxy, (C₁-C₆)-alkoxy substituted by halogen, NR⁷R⁸, C(O)R⁹ or SO₂R¹⁰;
- 10 R¹ is hydrogen or (C₁-C₆)-alkyl;
- R² is (C₁-C₆)-alkyl, (C₁-C₆)-alkyl substituted by halogen, (C₃-C₆)-cycloalkyl,
heterocycloalkyl, (C₁-C₆)-alkyl-(C₃-C₆)-cycloalkyl, (C₁-C₆)-alkyl-heterocycloalkyl,
(C₁-C₆)-alkyl-C(O)-R⁹, (C₁-C₆)-alkyl-CN, (C₂-C₆)-alkyl-O-R¹³, (C₂-C₆)-alkyl-
15 NR⁷R⁸, aryl or 6-membered heteroaryl containing one, two or three nitrogen atoms,
(C₁-C₆)-alkyl-aryl or (C₁-C₆)-alkyl-5 or-6-membered heteroaryl containing one, two
or three heteroatoms, selected from the group consisting of oxygen, sulphur or
nitrogen wherein aryl, heterocycloalkyl and heteroaryl are unsubstituted or
substituted by one or more substituents selected from the group consisting of
20 hydroxy, halogen, (C₁-C₆)-alkyl or (C₁-C₆)-alkoxy;
- R³, R⁴ and R⁶ independently from each other are hydrogen, hydroxy, halogen, CN,
(C₁-C₆)-alkyl, (C₁-C₆)-alkoxy or NR⁷R⁸;
- R⁵ is NO₂, CN, C(O)R⁹, SO₂R¹⁰ or NR¹¹R¹²;
- 25 R⁷ and R⁸ independently from each other are hydrogen or (C₁-C₆)-alkyl;
- R⁹ is hydroxy, (C₁-C₆)-alkyl, (C₃-C₆)-cycloalkyl, (C₁-C₆)-alkoxy or NR⁷R⁸;
- 30 R¹⁰ is (C₁-C₆)-alkyl, (C₃-C₆)-cycloalkyl or NR⁷R⁸;
- R¹¹ and R¹² independently from each other are hydrogen, C(O)-(C₁-C₆)-alkyl,
SO₂-(C₁-C₆)-alkyl, or form together with the N-atom a 5-membered heteroaryl
group, optionally substituted by halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkyl substituted by
35 halogen or (C₃-C₆)-cycloalkyl;

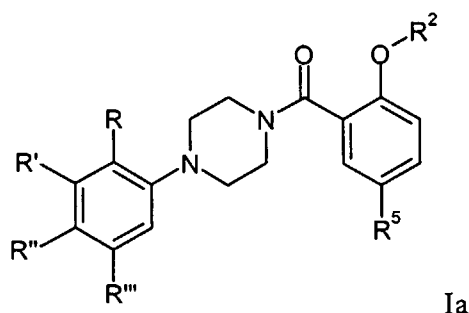
R^{13} is hydroxy, (C_1-C_6) -alkyl or (C_3-C_6) -cycloalkyl;

and pharmaceutically acceptable acid addition salts thereof,

with the proviso that

- 5 1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-(3-chlorophenyl)-piperazine,
 - 1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-(4-fluorophenyl)-piperazine,
 - 1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-[3-(trifluoromethyl)phenyl]-piperazine,
 - 4-(3-amino-4-nitrophenyl)-1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-methyl-piperazine,
 - 10 1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-methyl-4-(4-nitrophenyl)-piperazine,
 - 4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-methyl-1-(4-nitrophenyl)-piperazine,
 - 1-(2-chloro-4-nitrophenyl)-4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-piperazine,
 - 15 1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-4-(2,4-dinitrophenyl)-2-methyl-piperazine,
 - 1-(4-chloro-2-nitrophenyl)-4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-piperazine and
 - 20 4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-1-(2,4-dinitrophenyl)-2-methyl-piperazine
- are excluded.

Another embodiment of the present invention are compounds of formula Ia



wherein

R is hydrogen or halogen;

R' is hydrogen or halogen;

R'' is CN, $C(O)-(C_1-C_6)$ -alkyl, (C_1-C_6) -alkyl substituted by halogen or $S(O)_2-(C_1-C_6)$ -alkyl;

R''' is hydrogen;

R⁵ is S(O)₂-(C₁-C₆)-alkyl, S(O)₂NH₂ or NO₂; and

R² is (C₁-C₆)-alkyl, (C₃-C₆)-cycloalkyl, (C₁-C₆)-alkyl-(C₃-C₆)-cycloalkyl, (C₁-C₆)-alkyl substituted by halogen, -(CH₂)₂O-(C₁-C₆)-alkyl, benzyl or aryl, optionally

5 substituted by halogen;

and pharmaceutically acceptable acid addition salts thereof, with the exception of

1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-(3-chlorophenyl)-piperazine and

1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-[3-(trifluoromethyl)phenyl]-piperazine.

10 A further embodiment of the invention are those compounds of formula Ia, wherein

R is hydrogen or fluoro;

R' is hydrogen or fluoro;

R'' is CN, C(O)CH₃, CF₃ or S(O)₂-CH₃;

R''' is hydrogen;

15 R⁵ is S(O)₂-CH₃, S(O)₂NH₂ or NO₂; and

R² is (C₁-C₆)-alkyl, -CH₂-cyclopropyl, cyclopentyl, -CH₂-CF₃, or -(CH₂)₂-O-CH₃, benzyl or phenyl substituted by fluoro;

for example the following compounds:

2-Fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,

20 [4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,

1-{3-fluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,

4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,

25 3-fluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,

2-fluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,

(2-isobutoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,

[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-

30 methanesulfonyl-phenyl)-methanone or

[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone.

A further embodiment of the present invention are compounds, wherein R^5 is $S(O)_2-CH_3$ and R^2 is

CH_2 -cyclopropyl, for example the following compound:

4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-
5 benzonitrile.

Compounds of formula Ia are further those, wherein R^5 is $S(O)_2-CH_3$ and R^2 is CH_2CF_3 , for example the following compounds:

[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-tri-
fluoro-ethoxy)-phenyl]-methanone or
10 [4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-tri-
fluoro-ethoxy)-phenyl]-methanone.

Compounds of formula Ia are further those, wherein R^5 is $S(O)_2-CH_3$ and R^2 is cyclopentyl, for example the following compounds:

4-[4-(2-cyclopentylloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-
15 benzonitrile or
4-[4-(2-cyclopentylloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-
benzonitrile.

Preferred compounds of formula I of the present invention are those, wherein Ar is substituted phenyl, R^2 is (C_1-C_6) -alkyl and R^5 is $S(O)_2CH_3$ or $S(O)_2CH_2CH_3$.

20 The following specific compounds relate to this group:

1-{3-fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-
ethanone,
3-fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
2-Fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
25 [4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-
methanesulfonyl-phenyl)-methanone,
1-{3-fluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-
ethanone,
4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
30 3-fluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
2-fluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
(2-isobutoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-
methanone,

- [4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone,
 [4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone,
 5 [4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone,
 [4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
 2,3-difluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-
 10 benzonitrile,
 2,3-difluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
 2,5-difluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
 15 2,6-difluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
 3,5-difluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
 4-[4-(2-tert-butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,3-difluoro-
 20 benzonitrile,
 5-chloro-2-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
 4-[4-(2-tert-butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,5-difluoro-benzonitrile,
 4-[4-(2-tert-butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile,
 25 (2-tert-butoxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 (2-tert-butoxy-5-methanesulfonyl-phenyl)-[4-(2,5-difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone,
 1-(4-{4-[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-3-
 30 fluoro-phenyl)-ethanone,
 4-{4-[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile,
 4-{4-[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-3-fluoro-benzonitrile,
 35 4-{4-[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-2-fluoro-benzonitrile,
 [2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(4-trifluoromethyl-phenyl)-

- piperazin-1-yl]-methanone,
[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
5 [2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(2-fluoro-4-ethanesulfonyl-phenyl)-piperazin-1-yl]-methanone,
rac-1-{4-[4-(2-sec-butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,
10 rac-4-[4-(2-sec-butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile,
rac-4-[4-(2-sec-butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-benzonitrile,
rac-(2-sec-butoxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
15 rac-(2-sec-butoxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
(2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethanesulfonyl-phenyl)-piperazin-1-yl]-methanone,
20 (2-isobutoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethanesulfonyl-phenyl)-piperazin-1-yl]-methanone,
2-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile,
1-{2-fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,
25 [4-(3-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone,
1-{2-fluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,
30 2-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile,
(5-ethanesulfonyl-2-isopropoxy-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
[4-(4-difluoromethyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
35 [4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,

- 3-fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzaldehyde,
 [4-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone,
 rac-(2-sec-butoxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-
 5 piperazin-1-yl]-methanone,
 [4-(4-cyclobutanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
 [4-(4-cyclopentanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
 10 [4-(4-cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone and
 [4-(4-cyclopropanesulfonyl-2,5-difluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone.

A further preferred group of compounds of formula I are those, wherein Ar is
 15 substituted phenyl, R^2 is $(CH_2)_n$ -(C₃-C₇)-cycloalkyl and R^5 is $S(O)_2CH_3$, for example the following compounds

- 1-{4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,
 4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
 20 4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile,
 4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-benzonitrile,
 (2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-
 25 piperazin-1-yl]-methanone,
 (2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 (2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 30 1-{4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,
 4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
 4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile,
 35 4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-benzonitrile,

- (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
5 (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
Rac-[2-(1-cyclopropyl-ethoxy)-5-methanesulfonyl-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,3-difluoro-
10 benzonitrile,
4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,5-difluoro-benzonitrile,
4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-
15 benzonitrile,
4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile,
(2-cyclobutylmethoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
20 1-[4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl]-ethanone,
2-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile,
4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,3-difluoro-
25 benzonitrile,
4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,5-difluoro-benzonitrile,
4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3,5-difluoro-benzonitrile,
30 4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,6-difluoro-benzonitrile,
4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3,5-difluoro-benzonitrile,
4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3,5-difluoro-
35 benzonitrile,
4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,6-difluoro-benzonitrile,

- 4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,6-difluoro-benzonitrile,
5-chloro-2-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
- 5 4-[4-(2-cyclohexyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
4-[4-(2-cyclohexyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile,
4-[4-(2-cyclohexyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-benzonitrile,
- 10 (2-cyclohexyloxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
(2-cyclohexyloxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
(2-cyclohexyloxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone,
- 15 1-{4-[4-(2-cyclobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,
4-[4-(2-cyclobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile,
(2-cyclobutoxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
- 20 (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethanesulfonyl-phenyl)-piperazin-1-yl]-methanone,
1-{4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-phenyl}-ethanone,
- 25 2-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile,
(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone,
(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone,
- 30 (2-cyclohexyloxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone,
(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone,
- 35 (2-cyclohexyloxy-5-methanesulfonyl-phenyl)-[4-(4-cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone,

(2-cyclobutoxy-5-methanesulfonyl-phenyl)-[4-(4-cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone

Preferred are further compounds, wherein Ar is substituted phenyl, R² is (C₁-C₆)-alkyl substituted by halogen and R⁵ is S(O)₂CH₃. The following compounds
5 relate to this group:

- 1-(3-fluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,
3-fluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile,
10 [4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone,
[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone,
[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-
15 trifluoro-ethoxy)-phenyl]-methanone,
3-fluoro-4-{4-[5-methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-benzoyl]-piperazin-1-yl}-benzonitrile,
[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-phenyl]-methanone,
20 [4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-phenyl]-methanone,
1-(3-fluoro-4-{4-[5-methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,
2,5-difluoro-4-{4-(5-methanesulfonyl-2-trifluoromethoxy-benzoyl)-piperazin-1-yl}-
25 benzonitrile,
2,3-difluoro-4-{4-[2-(2-fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile,
2-fluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-benzoyl]-piperazin-1-yl}-benzonitrile,
30 [5-methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
2,3-difluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-benzoyl]-piperazin-1-yl}-benzonitrile,
3,5-difluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-benzoyl]-
35 piperazin-1-yl}-benzonitrile,

- 2-[4-[2-(2-fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl]-5-trifluoromethyl-benzonitrile,
rac-2,3-difluoro-4-[4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl]-benzonitrile,
5 2-Fluoro-4-[4-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoro-propoxy)-benzoyl]-piperazin-1-yl]-benzonitrile,
3-fluoro-4-[4-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoro-propoxy)-benzoyl]-piperazin-1-yl]-benzonitrile,
[5-methanesulfonyl-2-(2,2,3,3-tetrafluoro-propoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
10 [4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoro-propoxy)-phenyl]-methanone,
2,3-difluoro-4-[4-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoro-propoxy)-benzoyl]-piperazin-1-yl]-benzonitrile,
15 3,5-Difluoro-4-[4-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoro-propoxy)-benzoyl]-piperazin-1-yl]-benzonitrile,
[4-(3,4-dichloro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone,
rac-5-chloro-2-[4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl]-benzonitrile,
20 rac-3,5-difluoro-4-[4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl]-benzonitrile,
rac-2,5-difluoro-4-[4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl]-benzonitrile,
25 rac-2,6-difluoro-4-[4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl]-benzonitrile,
rac-4-[4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl]-benzonitrile,
rac-3-fluoro-4-[4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl]-benzonitrile,
30 rac-2-fluoro-4-[4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl]-benzonitrile,
rac-5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
35 rac-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone,
rac-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-

(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone,
 [4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-((S or R)-
 2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone,
 [5-methanesulfonyl-2-((S or R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-
 5 trifluoromethyl-phenyl)-piperazin-1-yl]-methanone and
 [5-methanesulfonyl-2-((R or S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-
 trifluoromethyl-phenyl)-piperazin-1-yl]-methanone.

Preferred compounds of formula I of the present invention are further those,
 wherein Ar is substituted phenyl, R² is (C₁-C₆)-alkyl, (C₁-C₆)-alkyl substituted by
 10 halogen, (CH₂)_n-(C₃-C₇)-cycloalkyl, bicycle[2.2.1]heptyl, (CH₂)_n-O-(C₁-C₆)-alkyl or
 (CH₂)_n-heterocycloalkyl and R⁵ is NO₂, for example the following compounds:

1-(3-fluoro-4-{4-[2-(2-methoxy-ethoxy)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-
 ethanone,
 (2-isopropoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-
 15 methanone,
 (2-cyclopropylmethoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-
 methanone,
 (2-cyclobutylmethoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-
 methanone,
 20 (2-butoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 [2-(2,2-dimethyl-propoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-
 yl]-methanone,
 (2-isobutoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-
 methanone,
 25 (2-cyclopentyloxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-
 methanone,
 (5-nitro-2-propoxy-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 (2-cyclobutoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-
 methanone,
 30 Rac-(2-sec-butoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-
 methanone,
 [5-nitro-2-(2,2,3,3-tetrafluoro-propoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-
 piperazin-1-yl]-methanone,
 [5-nitro-2-(2,2,2-trifluoro-ethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-
 35 yl]-methanone,

[2-(bicyclo[2.2.1]hept-2-yloxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,

[2-(2-chloro-ethoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone and

- 5 [5-nitro-2-(2,2,3,3,3-pentafluoro-propoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone.

Preferred are further compounds, wherein Ar is substituted phenyl, R² is (C₁-C₆)-alkyl, (C₁-C₆)-alkyl substituted by halogen or (CH₂)_n-(C₃-C₇)-cycloalkyl and R⁵ is S(O)₂NHCH₃.

- 10 3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-trifluoromethoxy-benzenesulfonamide,
 3-[4-(4-cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-isobutoxy-N-methyl-benzenesulfonamide,
 3-[4-(4-cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclopentyloxy-N-methyl-
 15 benzenesulfonamide,
 3-[4-(4-cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclobutoxy-N-methyl-benzenesulfonamide,
 3-[4-(4-cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclobutylmethoxy-N-methyl-benzenesulfonamide,
 20 3-[4-(4-cyano-phenyl)-piperazine-1-carbonyl]-4-isobutoxy-N-methyl-benzenesulfonamide,
 3-[4-(4-cyano-phenyl)-piperazine-1-carbonyl]-4-cyclopentyloxy-N-methyl-benzenesulfonamide,
 3-[4-(4-cyano-phenyl)-piperazine-1-carbonyl]-4-cyclobutylmethoxy-N-methyl-
 25 benzenesulfonamide,
 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-isobutoxy-N-methyl-benzenesulfonamide,
 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(2,2-dimethyl-propoxy)-N-methyl-benzenesulfonamide,
 30 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-N-methyl-benzenesulfonamide,
 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclopentyloxy-N-methyl-benzenesulfonamide,
 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclobutoxy-N-methyl-
 35 benzenesulfonamide,

- 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclopropylmethoxy-N-methyl-benzenesulfonamide,
- 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclobutylmethoxy-N-methyl-benzenesulfonamide,
- 5 3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-isobutoxy-N-methyl-benzenesulfonamide,
- 3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(2,2-dimethyl-propoxy)-N-methyl-benzenesulfonamide,
- 3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclopentyloxy-N-methyl-
- 10 benzenesulfonamide,
- 3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclobutoxy-N-methyl-benzenesulfonamide,
- 3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclopropylmethoxy-N-methyl-benzenesulfonamide,
- 15 4-isobutoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
- 4-(2,2-dimethyl-propoxy)-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
- 4-isopropoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-
- 20 benzenesulfonamide,
- 4-cyclopentyloxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
- 4-cyclobutoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
- 25 4-cyclopropylmethoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
- 4-cyclobutylmethoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
- N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-4-(3,3,3-trifluoro-
- 30 propoxy)-benzenesulfonamide,
- 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(2,2,2-trifluoroethoxy)-benzenesulfonamide,
- N-methyl-4-(2,2,2-trifluoro-ethoxy)-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
- 35 rac-N-methyl-4-(2,2,2-trifluoro-1-methyl-ethoxy)-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
- rac-3-[4-(4-cyano-2,5-difluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(2,2,2-

trifluoro-1-methyl-ethoxy)-benzenesulfonamide and
 rac-3-[4-(4-cyano-2,3-difluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(2,2,2-
 trifluoro-1-methyl-ethoxy)-benzenesulfonamide.

A further preferred group of compounds of formula I are those, wherein Ar is a
 5 substituted 6-membered heteroaryl group, containing one, two or three nitrogen atoms,
 R^2 is (C_1-C_6) -alkyl or $CH_2)_n-(C_3-C_7)$ -cycloalkyl, and R^5 is SO_2CH_3 , for example:

[4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-cyclopropylmethoxy-5-
 methanesulfonyl-phenyl)-methanone,
 6-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-nicotinonitrile,
 10 (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-pyridin-2-yl)-
 piperazin-1-yl]-methanone,
 [4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-cyclopentyloxy-5-
 methanesulfonyl-phenyl)-methanone,
 (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(6-trifluoromethyl-pyridin-3-yl)-
 15 piperazin-1-yl]-methanone,
 [4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-
 methanesulfonyl-phenyl)-methanone and
 (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-5-trifluoromethyl-pyridin-2-
 yl)-piperazin-1-yl]-methanone.

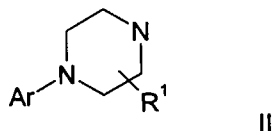
20 Further preferred are compounds of formula I, wherein Ar is a substituted 6-
 membered heteroaryl group, containing one, two or three nitrogen atoms, R^2 is
 (C_1-C_6) -alkyl substituted by halogen and R^5 is SO_2CH_3 , for example the following
 compounds:

rac-[4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-
 25 (2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone,
 rac-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-
 trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone,
 rac-[4-(5-bromo-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-
 methyl-ethoxy)-phenyl]-methanone,
 30 rac-[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-
 (2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone,
 rac-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(6-
 trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone,
 [5-methanesulfonyl-2-((S or R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-
 35 trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone,

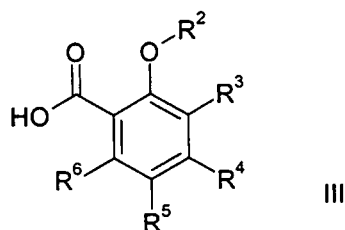
- [5-methanesulfonyl-2-((R or S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone,
 [4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone and
 5 [4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-phenyl]-methanone.

The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

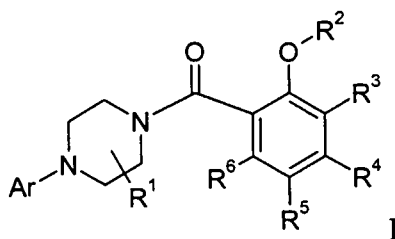
- 10 a) reacting a compound of formula



with a compound of formula

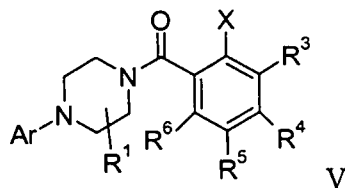


- in the presence of an activating agent such as TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate)
 15 to a compound of formula



wherein the substituents are as defined above, or

- b) reacting a compound of formula

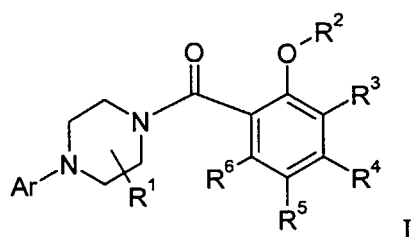


20

with a compound of formula

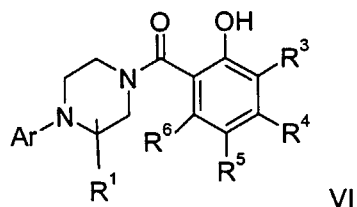


optionally in the presence of a catalyst, such as Cu(I)I and a base like potassium carbonate, cesium carbonate or sodium, to a compound of formula



5 wherein X is halogen and the other substituents are as defined above, or

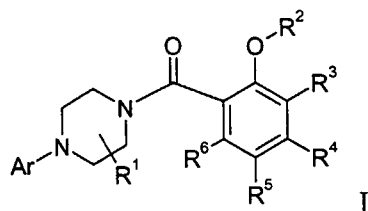
c) reacting a compound of formula



with a compound of formula

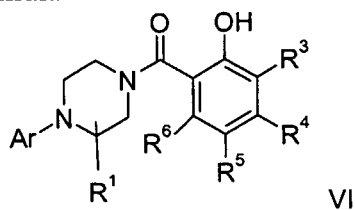


10 in the presence of a base and optionally in the presence of microwaves to a compound of formula



wherein X is halogen, mesylate or triflate and the other substituents are as defined above, or

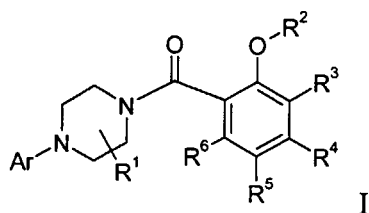
15 d) reacting a compound of formula



with a compound of formula

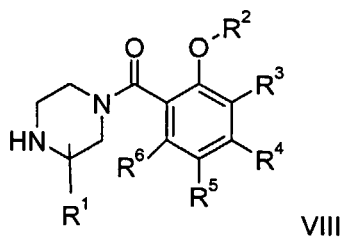


under Mitsunobu conditions in the present of a phosphine to a compound of formula



wherein the substituents are as defined above, or

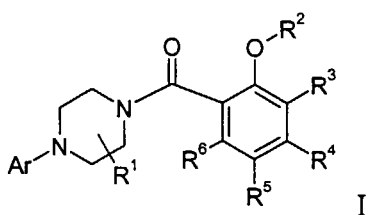
e) reacting a compound of formula



5 with a compound of formula

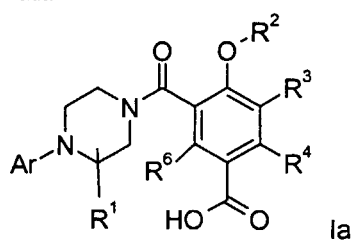


to a compound of formula

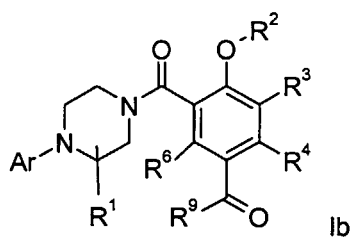


wherein X is halogen and the other substituents are as defined above, or

10 f) reacting a compound of formula



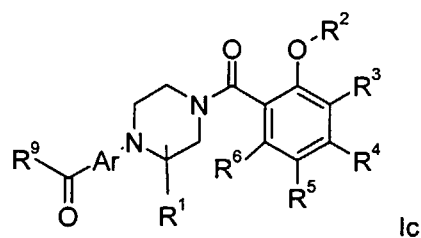
with a corresponding amine or alcohol in the presence of an activating agent
to a compound of formula



15 wherein R⁹ is (C₁-C₆)-alkyl, (C₃-C₆)-cycloalkyl, (C₁-C₆)-alkoxy or NR⁷R⁸;

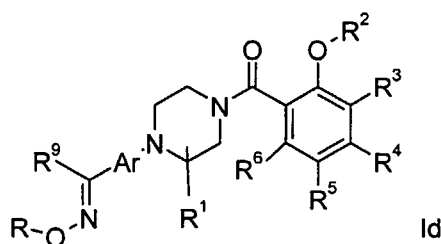
and the other substituents are as defined above, or

g) reacting a compound of formula



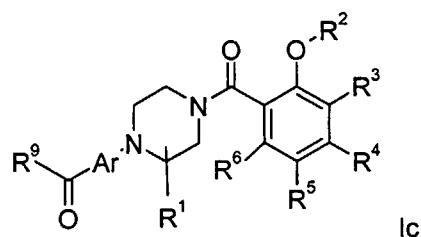
with a compound of formula RONH_2

5 to a compound of formula



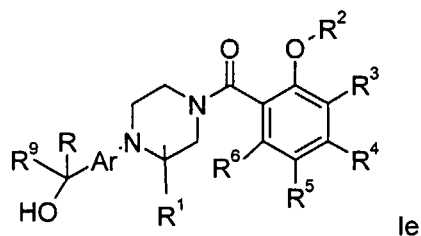
wherein R is H or alkyl and the other substituents are as defined above, or

h) reacting a compound of formula



10 with a reducing agent like sodium borohydride (when R is H) or an alkylating agent like alkyllithium (when R is alkyl)

to a compound of formula



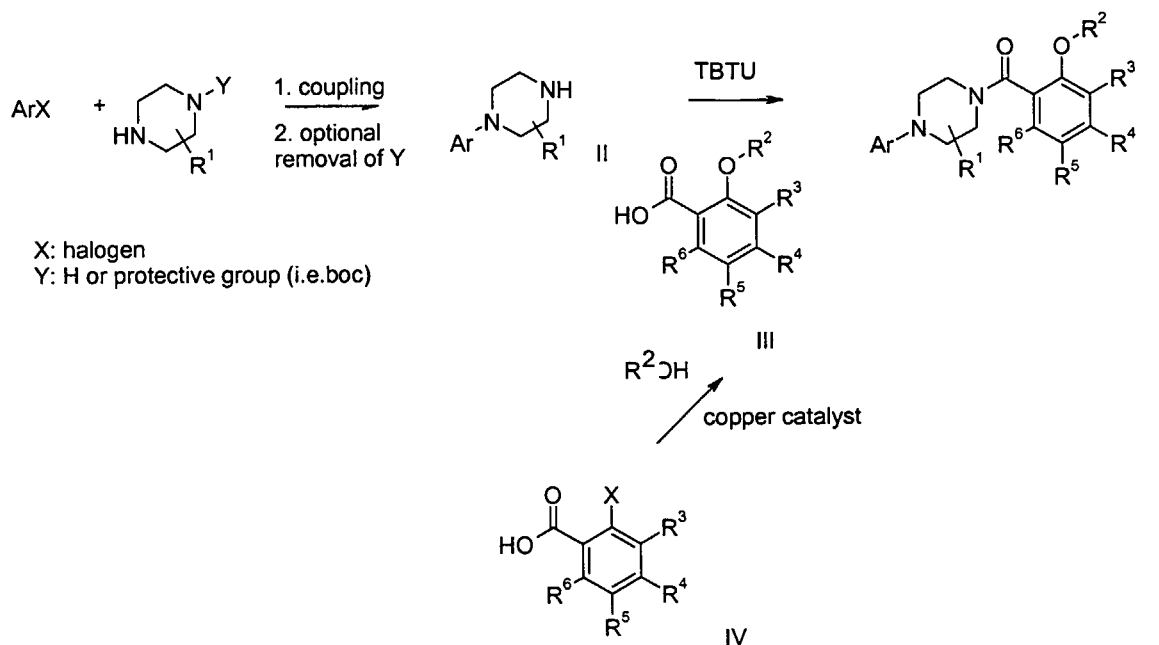
wherein R is H or alkyl and the other substituents are as defined above, and

15 if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

The compounds of formula I may be prepared in accordance with process variant a) to h) and with the following schemes 1 to 8. The starting material is commercially available or may be prepared in accordance with known methods.

5

Scheme 1



Compounds of general formula I can be prepared by reacting piperazine derivatives of formula II with a corresponding acid of formula III in the presence of an activating agent like TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate).

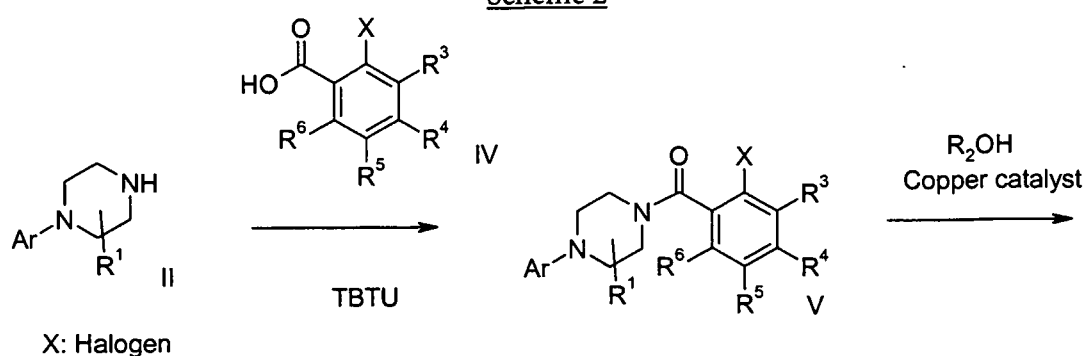
- 10 The acid of formula III can be prepared by reaction of an acid of formula IV with an alcohol of formula R^2OH , optionally in the presence of a copper salt like Cu(I)Br .

Piperazine derivatives of formula II can be prepared by heating of the corresponding piperazine with ArX or by reacting of a N-protected piperazine with ArX in the presence of palladium catalyst followed by cleavage of the protective group. The protective group

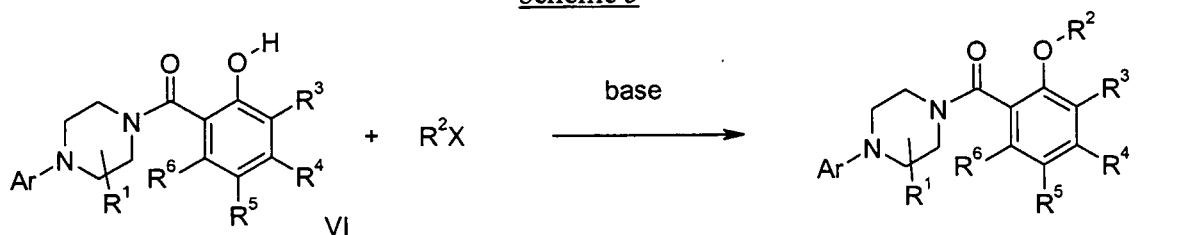
- 15 is typically tert-butoxycarbonyl (Boc).

20

25

Scheme 2

- 5 Alternatively, compounds of general formula I can be prepared by reaction of an acyl-
 piperazine of formula V and an alcohol of formula R²OH, optionally in the presence of a
 copper salt like Cu(I)I. Acylpiperazine derivatives of formula V can be prepared by
 reaction of an acid of formula IV with piperazine derivatives of formula II in the presence
 of an activating agent like TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-
 10 tetramethyluroniumtetrafluoroborate).

Scheme 3

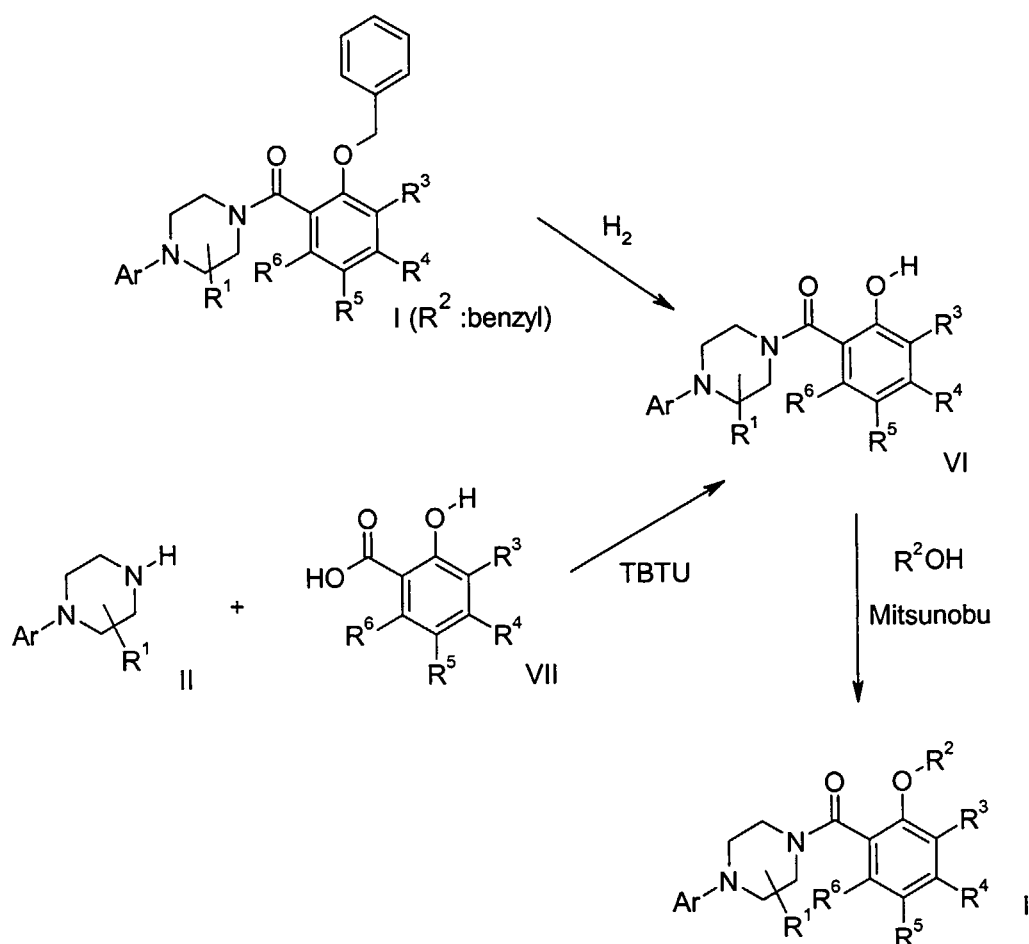
15

- Compounds of general formula I can be prepared by reacting a compound of formula VI
 with an electrophile of formula R²X in the presence of base like potassium carbonate and
 20 optionally in the presence of microwaves, wherein X is an halogen, mesylate or triflate.

25

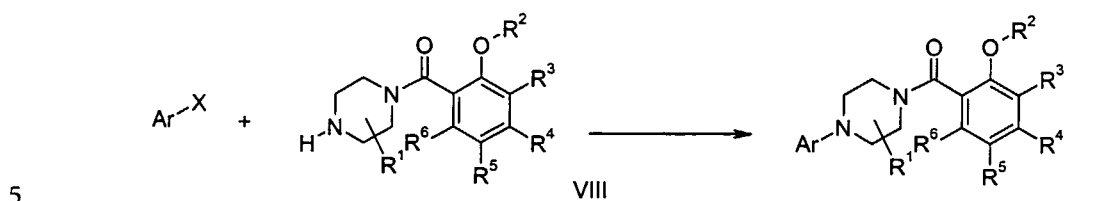
5

Scheme 4



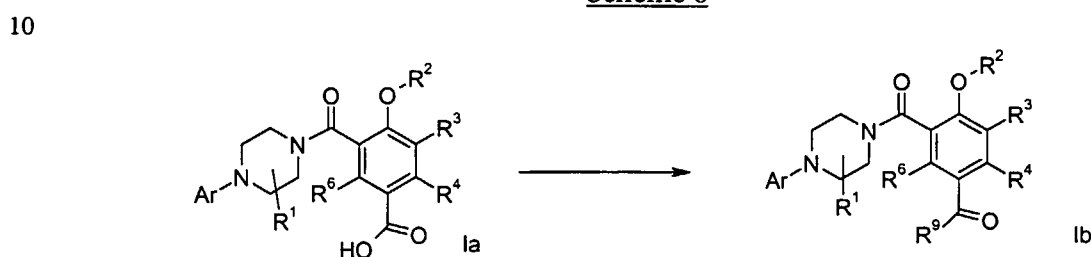
- Compounds of general formula I can be prepared by reacting phenol of formula VI with an alcohol of formula R^2OH under Mitsunobu condition, in the presence of a phosphine like triphenylphosphine or diphenyl-2-pyridylphosphine, and a dialkylazodicarboxylate like diethylazodicarboxylate or di-tert-butyl azodicarboxylate.
- The compound of formula VI can be prepared by deprotection (for example using hydrogen) of a phenol protected as a benzyl ether (I with R^2 : benzyl).
- Alternatively a compound of formula VI can be prepared by reacting piperazine derivatives of formula II with an acid of formula VII in the presence of an activating agent like TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate).

Scheme 5



Compounds of general formula I can be prepared by reacting a piperazine of formula VIII with ArX.

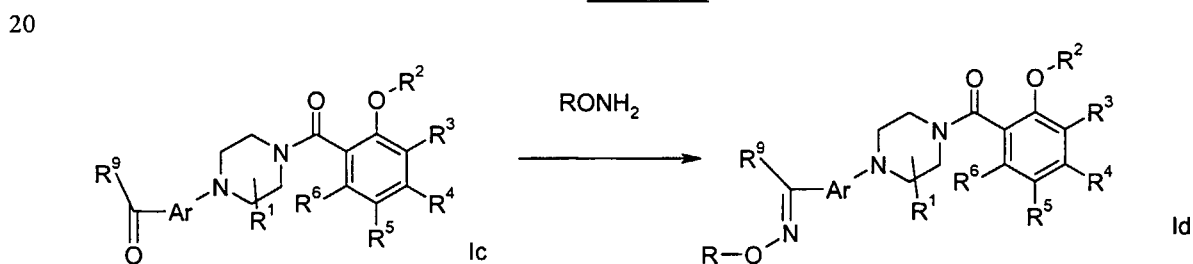
Scheme 6



wherein R^9 is (C_1-C_6) -alkoxy or NR^7R^8 ;

- 15 Compounds of general formula Ib wherein R^9 is as defined above can be prepared by reacting an acid of formula Ia with a corresponding amine or alcohol in the presence of an activating agent like carbonyldimidazole.

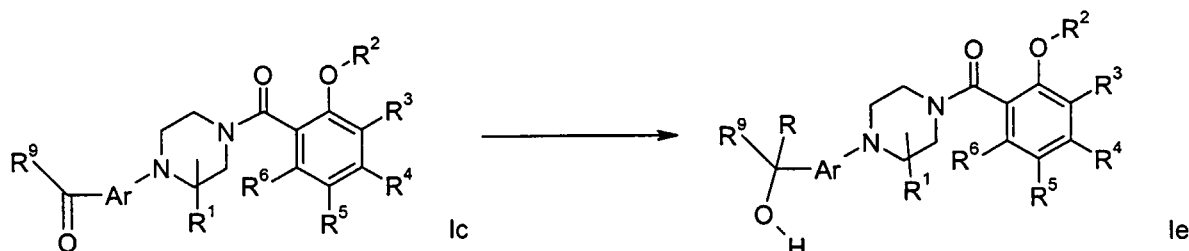
Scheme 7



- Compounds of general formula Id can be prepared in accordance with scheme 7 by reacting a compound of formula Ic bearing a carbonyl group, with a compound of formula $RONH_2$, wherein R is H or alkyl and R^9 is (C_1-C_6) -alkyl, (C_3-C_6) -cycloalkyl, (C_1-C_6) -alkoxy or NR^7R^8 .
- 25

Scheme 8

5



Compounds of general formula Ie wherein R is H or alkyl and R⁹ is

- 10 (C₁-C₆)-alkyl or (C₃-C₆)-cycloalkyl can be prepared by reacting a compound of formula Ic bearing a carbonyl group, with a reducing agent like sodium borohydride (when R is H) or an alkylating agent like alkyl lithium (when R is alkyl).

Racemic mixtures of chiral compounds of formula I can be separated using chiral HPLC.

- 15 The acid addition salts of the basic compounds of formula I may be converted to the corresponding free bases by treatment with at least a stoichiometric equivalent of a suitable base such as sodium or potassium hydroxide, potassium carbonate, sodium bicarbonate, ammonia, and the like.

The following 660 examples illustrate the present invention without limiting it. All
20 temperatures are given in degree Celsius.

The following abbreviations were used in the examples:

RT: room temperature;

n-Boc-piperazine: tert-Butyl 1-piperazinecarboxylate,

oxone®: (potassium peroxydisulfate) 2KHSO₅•KHSO₄•K₂SO₄,

- 25 EtOAc: ethyl acetate;

THF: tetrahydrofuran;

TBTU: 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate;

DIPEA: diisopropylethylamine,

DMF: N,N-dimethylformamide

30

Example 1.1

Preparation of 1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine

(a) 4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

A mixture of 20 mmol 1-bromo-2-fluoro-4-trifluoromethyl-benzene, 24.7 mmol n-Boc-piperazine, 0.1 mmol Tris(dibenzylideneacetone)dipalladium chloroform complex, 28.8 mmol sodium-t-butoxide and 0.4 mmol 2-(dicyclohexylphosphino)biphenyl in 50 ml toluene was heated for 16 h at 80 °C. After cooling to RT the mixture was treated with 15 g Isolute HM-N and all volatiles were removed under vacuum. The residue was purified on silica eluting with a gradient of heptane / EtOAc to yield after evaporation the title compound.

(b) 1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine

A mixture of 9 mmol 4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester in 20 ml dioxane was treated with 8.93 ml 4N HCl in dioxane for 2 h at 80°C. The mixture was concentrated and treated with 20 ml water, 20 ml 2M Na₂CO₃ and extracted with 50 ml EtOAc. The organic phase was washed with 30 ml saturated NaCl. All aqueous phases were combined and extracted with 50 ml EtOAc. The combined organic phases were dried with MgSO₄ and evaporated to yield the title compound 1.1.

¹H-NMR (300 MHz, CDCl₃) δ= 7.50 (d, J = 13.3 Hz, 1H, H-3), 7.45 (d, J = 8.8 Hz, 1H, H-5), 7.16 (dd, J₁ = 8.8 Hz, J₂ = 8.8 Hz, 1H, H-6), 3.5-3.2 (s, br, 1H, NH), 3.04 (m, 4H, piperazine), 2.87 (m, 4H, piperazine).

MS (m/e): 249.2 (MH⁺, 100%)

20

Example 1.2

Preparation of 2-isopropoxy-5-methanesulfonyl-benzoic acid

(a) 2-Chloro-5-methanesulfonyl-benzoic acid

To 99 mmol 2-chloro-5-(methylthio) benzoic acid in 400 ml methanol at 0 °C 296 mmol oxone® was added and the mixture was allowed to stir at RT for 3.5 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was extracted 3 x with 400 ml ethyl acetate and the combined organic phases washed 2 x with 300 ml 1N HCl and with 300 ml saturated aqueous NaCl solution and dried with MgSO₄. Evaporation under reduced pressure yielded the title compound.

(b) 2-Isopropoxy-5-methanesulfonyl-benzoic acid

A mixture of 2.13 mmol 2-chloro-5-methanesulfonyl-benzoic acid, 0.64 mmol Cu(I)Br in 5 ml NEt₃ and 25 ml isopropanol was heated to 120 °C for 16 h in a sealed tube. The

volatiles were removed under vacuum and the residue was taken up in 70 ml 1N HCl. Extraction with ethyl acetate drying of the combined organic fractions and evaporation yielded a residue which was purified by reversed phase preparative HPLC eluting with an acetonitrile / water gradient. Evaporation of the product fractions yielded the title

5 compound 1.2.

MS (m/e): 257.0 (MH⁺, 100%)

In analogy to Example 1.2(b) compounds 1.3 to 1.7 of the following table were prepared from 2-chloro-5-methanesulfonyl-benzoic acid and the appropriate alcohol:

	Compound name	Alcohol	MS (m/e)
1.3	2-isobutoxy-5-methanesulfonyl-benzoic acid	isobutanol	271.1 (MH ⁺ , 100 %)
1.4	2-cyclopropylmethoxy-5-methanesulfonyl-benzoic acid	cyclopropyl-methanol	269.1 (MH ⁺ , 100 %)
1.5	5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid	2,2,2-trifluoro-ethanol	297.0 (MH ⁺ , 100 %)
1.6	2-cyclopentyloxy-5-methanesulfonyl-benzoic acid	cyclopentanol	282.9 (MH ⁺ , 100 %)
1.7	2-(4-fluoro-phenoxy)-5-methanesulfonyl-benzoic acid	4-fluoro-phenol (in THF)	309.1 (MH ⁺ , 100 %)

10

Example 1.8

Preparation of 1-{3-fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone

A solution of 0.261 mmol 2-fluoro-5-nitro-benzoyl chloride [CAS: 7304-32-7; Feng and Burgess, Chem.Europ.J. EN, 5:3261-3272 (1999)] in 1 ml dioxane was treated with 0.522
 15 mmol triethylamine and then with a solution of 0.261 mmol 1-(3-fluoro-4-piperazin-1-yl-phenyl)-ethanone (CAS: 189763-57-3; WO 97/14,690) in 1 ml dioxane. The mixture was stirred at RT for 30 min. The solvent was removed in vacuo. The crude oil was taken up in water. The aqueous layer was extracted 3 times with CH₂Cl₂. The combined

extracts were dried over Na_2SO_4 , filtered and the solvent was removed in vacuo. The crude gum was purified on silicagel (eluent: heptane/ethylacetate 0%-20% (10 min) to provide the title compound 1.8.

MS (m/e): 390.2 (MH^+ , 100%)

5

Example 1.9

Preparation of (2-iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

(a) 2-Amino-5-methanesulfonyl-benzoic acid

A mixture of 4.26 mmol 2-chloro-5-methanesulfonyl-benzoic acid, 0.39 mmol Copper powder and 10 ml ammonium hydroxide 25% was heated at 125-130°C with stirring for 18 hours. Mixture was cooled to room temperature and filtered. The solid was washed with methanol. The filtrate was concentrated in vacuo. The residue was acidified with HCl 1N to pH=2. The obtained solid was washed with water and dried (HV, 50°C, 1 hour) to yield the title compound. MS (m/e): 214.1 (M-H, 100%)

15 (b) 2-Iodo-5-methanesulfonyl-benzoic acid

To a suspension of 3.0 mmol 2-amino-5-methanesulfonyl-benzoic acid in a mixture of 1.7 ml sulfuric acid and 1.7 ml water was added dropwise a solution of 3.92 mmol sodium nitrite in 1.7 ml water at such rate that the temperature did not exceed 3°C. The mixture was stirred at 0°C for 1 hour. A solution of 3.0 mmol KI in 1.7 ml water was added dropwise at 0°C. The brown suspension was allowed to warm to rt and stirred for 30 minutes. Excess iodine was destroyed by addition of a few drops of a sodium hydrogensulfite solution. The solid was filtered, washed with water and dried (HV, 50°C, 1 hour) to yield the title compound. MS (m/e): 325.0 (M-H, 100%)

25 (c) (2-iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]methanone

To a solution of 9.2 mmol 2-iodo-5-methanesulfonyl-benzoic acid in 20 ml dimethylformamide 11.5 mmol TBTU, 46.0 mmol N-ethyl-diisopropylamine and 11.0 mmol 1-(4-trifluoromethylphenyl)piperazine (ABCR F07741NB, [30459-17-7]) were successively added. The reaction was then stirred at RT for two hours, concentrated in vacuo and purified by column chromatography (SiO_2 , 50 g, $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3 = 100/0/0$ to 95/4.5/0.5), to give the title compound 1.9. MS (m/e): 539.1 ($\text{M}+\text{H}^+$)

Example 5

Preparation of [4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

A mixture of 0.05 mmol 2-isopropoxy-5-methanesulfonyl-benzoic acid (Compound 1.2),
 5 0.06 mmol 1-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine, 0.055 mmol TBTU and
 0.25 mmol DIPEA in 1 ml DMF was stirred at RT for 16 h. 0.5 ml MeOH / HCOOH 1/1
 was added and the mixture was subjected to reversed phase preparative HPLC separation
 eluting with an acetonitrile / water gradient yielding the title compound.

MS (m/e): 489.2 (MH⁺, 100%)

- 10 In analogy to Example 5 compounds 1 to 4, 6 to 46 and 52-54 of the following table were
 prepared from the acid derivatives and piperazine derivatives:

Expl.- No.	Systematic Name	Starting materials	MW found (MH ⁺)
1	1-{3-fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-(3-fluoro-4-piperazin-1-yl-phenyl)-ethanone and Compound 1.2	463.2
2	4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	4-piperazin-1-yl-benzonitrile and Compound 1.2	428.2
3	3-fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	3-fluoro-4-piperazin-1-yl-benzonitrile and Compound 1.2	446.2
4	2-Fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	2-fluoro-4-piperazin-1-yl-benzonitrile and Compound 1.2	446.2
5	[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine and Compound 1.2	489.2

6	[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(3-fluoro-4-trifluoromethyl-phenyl)-piperazine and Compound 1.2	489.2
7	1-{3-fluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-(3-fluoro-4-piperazin-1-yl-phenyl)-ethanone and Compound 1.3	477.2
8	4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	4-piperazin-1-yl-benzonitrile and Compound 1.3	442.2
9	3-fluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	3-fluoro-4-piperazin-1-yl-benzonitrile and Compound 1.3	460.3
10	2-fluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	2-fluoro-4-piperazin-1-yl-benzonitrile and Compound 1.3	460.3
11	(2-isobutoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-trifluoromethyl-phenyl)-piperazine and Compound 1.3	485.3
12	[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone	1-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine and Compound 1.3	503.2
13	[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone	1-(3-fluoro-4-trifluoromethyl-phenyl)-piperazine and Compound 1.3	503.1

14	[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone	1-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine and Compound 1.3	513.3
15	1-{4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-(3-fluoro-4-piperazin-1-yl-phenyl)-ethanone and Compound 1.4	475.2
16	4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	4-piperazin-1-yl-benzonitrile and Compound 1.4	440.3
17	4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile	3-fluoro-4-piperazin-1-yl-benzonitrile and Compound 1.4	458.3
18	4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-benzonitrile	2-fluoro-4-piperazin-1-yl-benzonitrile and Compound 1.4	458.3
19	(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-trifluoromethyl-phenyl)-piperazine and Compound 1.4	483.2
20	(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine and Compound 1.4	501.2

21	(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(3-fluoro-4-trifluoromethyl-phenyl)-piperazine and Compound 1.4	501.2
22	(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine and Compound 1.4	511.3
23	1-(3-fluoro-4-[4-[5-methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoyl]-piperazin-1-yl]-phenyl)-ethanone	1-(3-fluoro-4-piperazin-1-yl-phenyl)-ethanone and Compound 1.5	503.1
24	4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	4-piperazin-1-yl-benzonitrile and Compound 1.5	468.1
25	3-fluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	3-fluoro-4-piperazin-1-yl-benzonitrile and Compound 1.5	468.2
26	2-fluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2-fluoro-4-piperazin-1-yl-benzonitrile and Compound 1.5	486.2
27	[5-methanesulfonyl-2-(2,2,2-trifluoroethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-trifluoromethyl-phenyl)-piperazine and Compound 1.5	511.2

28	[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine and Compound 1.5	529.2
29	[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(3-fluoro-4-trifluoromethyl-phenyl)-piperazine and Compound 1.5	529.2
30	[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine and Compound 1.5	539.2
31	1-{4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone	1-(3-fluoro-4-piperazin-1-yl-phenyl)-ethanone and Compound 1.6	489.2
32	4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	4-piperazin-1-yl-benzonitrile and Compound 1.6	454.2
33	4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile	3-fluoro-4-piperazin-1-yl-benzonitrile and Compound 1.6	472.2
34	4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-benzonitrile	2-fluoro-4-piperazin-1-yl-benzonitrile and Compound 1.6	472.2
35	(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine and Compound 1.6	515.2

36	(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(3-fluoro-4-trifluoromethyl-phenyl)-piperazine and Compound 1.6	515.2
37	(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine and Compound 1.6	525.3
38	1-(3-fluoro-4-{4-[2-(4-fluorophenoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-(3-fluoro-4-piperazin-1-yl-phenyl)-ethanone and Compound 1.7	515.2
39	4-{4-[2-(4-fluorophenoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile	4-piperazin-1-yl-benzonitrile and Compound 1.7	480.2
40	3-fluoro-4-{4-[2-(4-fluorophenoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile	3-fluoro-4-piperazin-1-yl-benzonitrile and Compound 1.7	498.2
41	2-fluoro-4-{4-[2-(4-fluorophenoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile	2-fluoro-4-piperazin-1-yl-benzonitrile and Compound 1.7	498.2
42	[2-(4-fluorophenoxy)-5-methanesulfonyl-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-trifluoromethyl-phenyl)-piperazine and Compound 1.7	523.3

43	[2-(4-fluoro-phenoxy)-5-methanesulfonyl-phenyl]-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(2-fluoro-4-trifluoromethyl-phenyl)-piperazine and Compound 1.7	541.2
44	[2-(4-fluoro-phenoxy)-5-methanesulfonyl-phenyl]-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(3-fluoro-4-trifluoromethyl-phenyl)-piperazine and Compound 1.7	541.2
45	[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[2-(4-fluoro-phenoxy)-5-methanesulfonyl-phenyl]-methanone	1-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine and Compound 1.7	551.3
46	[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine and Compound 1.2	499.2
52	3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-methoxy-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone and 2-methoxy-5-sulfamoyl-benzoic acid	434.2
53	3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-ethoxy-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone and 2-Ethoxy-5-sulfamoyl-benzoic acid	448.2
54	1-(3-Fluoro-4-{4-[2-(2-methoxyethoxy)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone and 2-(2-Methoxyethoxy)-5-nitrobenzoic acid	446.1

Example 47**Preparation of 1-{3-fluoro-4-[4-(2-methoxy-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone**

To a solution of 0.257 mmol 1-{3-fluoro-4-[4-(2-fluoro-5-nitro-benzoyl)-piperazin-1-yl]-phenyl}-ethanone (Compound 1.8) in 1.5 ml dioxane 102 mg sodium methoxyde was added portionwise. The mixture was stirred at 100 °C for 4h. The reaction mixture was diluted with 10 ml water, neutralized with 1N HCl and then extracted with ethylacetate (3 x 10 ml). Combined organic phases were concentrated in vacuo. The residue was chromatographed on silica gel: eluent: heptane/ethylacetate 0%-30% (10 min) to provide compound 47.

MS (m/e): 402.2 (M+H⁺, 100%).

Example 48**Preparation of (2-benzyloxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone**

A mixture of 0.19 mmol (2-iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (Compound 1.9), 0.037 mmol CuI, 0.37 mmol Cs₂CO₃, 0.074 mmol 1,10-phenanthroline and 0.4 ml benzylic alcohol was heated at 110 °C for 16 hours. The mixture was cooled to RT, diluted with ethylacetate and filtered. The organic layer was washed twice with water, dried over Na₂SO₄, filtered and the solvent was removed in vacuo. The crude oil was purified on silica gel, eluent: heptane/ethylacetate 0 % -50 % (25 min) to provide compound 48.

MS (m/e): 519.2 (M+H⁺, 100%)

In analogy to Example 48 compounds 49 to 51 of the following table were prepared from (2-iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (Compound 1.9) and alcohols:

Expl.- No	Systematic Name	Starting materials	MW found (MH ⁺)
49	(2-ethoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	Compound 1.9 and ethanol	457.2
50	(2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	Compound 1.9 and isopropylalcohol	471.2
51	(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	Compound 1.9 and cyclopentanol	497.2

Example 1.10

Preparation of 5-Methanesulfonyl-2-(2-methoxy-ethoxy)-benzoic acid

(a) 2-Amino-5-methanesulfonyl-benzoic acid

A mixture of 4.26 mmol 2-chloro-5-methanesulfonyl-benzoic acid (compound 1.2a),
 5 0.39 mmol Copper powder and 10 ml ammonium hydroxide 25% was heated at 125-130°C with stirring for 18 hours. Mixture was cooled to room temperature and filtered. The solid was washed with methanol. The filtrate was concentrated in vacuo. The residue was acidified with HCl 1N to pH=2. The obtained solid was washed with water and dried (HV, 50°C, 1 hour) to yield the title compound. MS (m/e): 214.1 (M-H, 100%)

10 (b) 2-Iodo-5-methanesulfonyl-benzoic acid

To a suspension of 3.0 mmol 2-amino-5-methanesulfonyl-benzoic acid in a mixture of 1.7 ml sulfuric acid and 1.7 ml water was added dropwise a solution of 3.92 mmol sodium nitrite in 1.7 ml water at such rate that the temperature did not exceed 3°C. The mixture was stirred at 0°C for 1 hour. A solution of 3.0 mmol KI in 1.7 ml water was
 15 added dropwise at 0°C. The brown suspension was allowed to warm to rt and stirred for 30 minutes. Excess iodine was destroyed by addition of a few drops of a sodium hydrogensulfite solution. The solid was filtered, washed with water and dried (HV, 50°C, 1 hour) to yield the title compound. MS (m/e): 325.0 (M-H, 100%)

(c) 5-Methanesulfonyl-2-(2-methoxy-ethoxy)-benzoic acid

To a solution of 1.6 mmol 2-iodo-5-methanesulfonyl-benzoic acid in 30 ml 2-methoxyethanol and 6 ml triethylamine were added 79 mg copper (I)bomide and the reaction mixture heated to 120°C for 4 h. The solvent was distilled off and the residue
5 dissolved in 90 ml 1N HCl. The aqueous phase was extracted twice with ethyl acetate and the pooled organic extracts washed twice with water and once with brine. The organic layer was dried with Na₂SO₄, filtered and evaporated to yield the title compound 1.10. MS (m/e): 273.1 (MH⁺, 100%).

Example 1.11

10 **Preparation of 5-Cyano-2-(2-methoxy-ethoxy)-benzoic acid**

(a) 2-Bromo-5-cyano-benzoic acid

To a suspension of 7.1 mmol copper (II) bromide in acetonitrile (30 ml) was added dropwise 8.63 mmol tert-butylnitrite at 0°C within 2 minutes. 6.17 mmol 2-Amino-5-cyano-benzoic acid (CAS: 99767-45-0; WO9518097) was added portionwise within 10
15 minutes at 0°C. The mixture was stirred at 0°C for 2 hours and then at room temperature overnight. Half of the solvent was removed in vacuo. The residue was taken in HCl 1N (15 ml) and ethyl acetate (30 ml). The organic layer was extracted with NaOH 1N (3x10 ml). The aqueous layer was acidified with HCl 2N. The resulting solid was filtered, washed with water and dried (high vacuum, 50°C) to provide the title compound MS
20 (m/e): 227.1(M+H⁺, 100%)

(b) 5-Cyano-2-(2-methoxy-ethoxy)-benzoic acid

To a solution of 0.16 mmol 2-bromo-5-cyano-benzoic acid in 6 ml 2-methoxyethanol and 1.2 ml triethylamine were added 23 mg copper (I) bromide and the reaction mixture heated to 120°C for 4 h. The solvent was distilled off and the residue dissolved in 20 ml
25 1N HCl. The aqueous phase was extracted twice with ethyl acetate and the pooled organic extracts washed twice with water and once with brine. The organic layer was dried with Na₂SO₄, filtered and evaporated to yield the title compound 1.11. MS (m/e): 220.4 (MH⁺, 100%).

Example 1.12

30 **Preparation of 5-Cyano-2-(2,2,2-trifluoro-ethoxy)-benzoic acid**

A mixture of 11.3 mmol sodium in 66 mmol 2,2,2-trifluoroethanol was heated to 100°C until all sodium was dissolved (20 min.). Then a solution of 5.5 mmol 5-cyano-2-iodo-benzoic acid [CAS: 219841-92-6; WO9901455] in 2 ml N-methyl-2-pyrrolidone and 0.5 mmol copper (I) bromide were added and the reaction mixture heated to 120° C for 2 h.

- 5 The reaction mixture was poured onto water, acidified to pH 2 with conc. HCl and extracted 3x with ethyl acetate. The pooled organic extracts were washed with brine, dried over Na₂SO₄ and evaporated. Flash chromatography on silica gel with heptane/ethyl acetate provided the title compound 1.12. MS (EI) (m/e): 245.1 (M⁺, 94%), 146.0 ([M-CF₃CH₂O]⁺, 100%).
- 10 In analogy to Example 1.12 compounds 1.13 to 1.16 of the following table were prepared from 5-cyano-2-iodo-benzoic acid and the appropriate alcohol:

	Compound name	Alcohol	MS (m/e)
1.13	o-2-isopropoxy-benzoic acid	isopropanol	204.1 (M-H ⁻ , 100 %)
1.14	5-Cyano-2-cyclopropylmethoxy-benzoic acid	cyclopropyl-methanol	216.1 (M-H ⁻ , 100 %)
1.15	5-Cyano-2-isobutoxy-benzoic acid	isobutyl alcohol	218.3 (M-H ⁻ , 100 %)
1.16	5-Cyano-2-cyclopentyloxy-benzoic acid	cyclopentanol	230.1 (M-H ⁻ , 100 %)

In analogy to Example 5 compounds 55 to 61 of the following table were prepared from the acid derivatives and piperazine derivatives:

Expl.- No.	Systematic Name	Starting materials	MW found (MH ⁺)
55	1-(3-Fluoro-4-{4-[5-methanesulfonyl-2-(2-methoxy-ethoxy)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 5-Methanesulfonyl-2-(2-methoxy-ethoxy)-benzoic acid (compound 1.10)	479.5
56	4-(2-Methoxy-ethoxy)-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzonitrile	1-(4-Trifluoromethyl-phenyl)-piperazine and 5-cyano-2-(2-methoxy-ethoxy)-benzoic acid (compound 1.11)	434.5
57	4-(2,2,2-Trifluoro-ethoxy)-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzonitrile	1-(4-trifluoromethylphenyl)piperazine and 5-Cyano-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.12)	458.4
58	4-Isopropoxy-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzonitrile	1-(4-trifluoromethylphenyl)piperazine and 5-Cyano-2-isopropoxy-benzoic acid (compound 1.13)	418.3
59	4-Cyclopropylmethoxy-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzonitrile	1-(4-trifluoromethylphenyl)piperazine and 5-Cyano-2-cyclopropylmethoxy-benzoic acid (compound 1.14)	430.6

60	4-Isobutoxy-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzonitrile	1-(4-trifluoromethylphenyl)piperazine and 5-Cyano-2-isobutoxy-benzoic acid (compound 1.15)	432.5
61	4-Cyclopentyloxy-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzonitrile	1-(4-trifluoromethylphenyl)piperazine and 5-Cyano-2-cyclopentyloxy-benzoic acid (compound 1.16)	444.5

Example 2.1

Preparation of (2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

- 5 Compound 2.1 was prepared in analogy to Example 5 using 2-hydroxy-5-nitrobenzoic acid [96-97-9] and 1-(4-trifluoromethyl-phenyl)-piperazine. MS (m/e): 394.0 (M-H, 100%)

Example 2.2

10 Preparation of (2-Hydroxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

Compound 2.2 was prepared in analogy to Example 5 using 2-hydroxy-5-(methylsulfonyl)benzoic acid [68029-77-6] and 1-(4-trifluoromethyl-phenyl)-piperazine. MS (m/e): 427.5 (M-H, 100%)

Example 66

15 Preparation of (2-Butoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

A solution of (2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (50 mg), potassium carbonate (87 mg) and 1-bromobutane (0.15 mL) in dimethylacetamide (0.3 mL) was heated at 150°C for 15 minutes in a microwave oven.

The reaction mixture was then concentrated and purified by column chromatography (SiO₂) to give the title compound (55 mg).

In analogy to Example 66, compounds 62 to 97 of the following table were prepared from the acid derivatives and piperazine derivatives:

Expl.- No.	Systematic Name	Starting materials	MW found (MH ⁺)
62	(2-Isopropoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 2-bromopropane	438.4
63	(2-Cyclopropylmethoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and cyclopropylmethylbromide	450.5
64	(2-Cyclobutylmethoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and Cyclobutylmethylbromide	464.5
65	(2-Allyloxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.2) and cyclopropylbromide	469.5
66	(2-Butoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and bromobutane	452.4

67	Rac-[2-(2-Hydroxy-propoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and rac-1-Bromo-2-propanol	454.6
68	[2-(2,2-Dimethyl-propoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 1-Bromo-2,2-Dimethylpropane	466.6
69	[2-(3-Methyl-butoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 1-Bromo-3-methylbutane	466.5
70	(2-Isobutoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 1-Bromo-3-methylpropan	452.5
71	(2-Cyclopentyloxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and Cyclopentyl bromide	464.5
72	(5-Nitro-2-propoxy-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 1-Bromopropane	438.5

73	(2-Cycloheptyloxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and Bromocycloheptane	492.5
74	(2-Cyclobutoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and Bromocyclobutane	450.4
75	[2-(2-Ethoxy-ethoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 2-Bromoethyl-ethylether	468.5
76	[2-((R)-3-Hydroxy-2-methyl-propoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and (R)-(-)-3-bromo-2-methyl-1-propanol	468.4
77	(2-Ethoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 2-Bromo-1-ethoxy-1,1,2-trifluoro-ethane	424.4
78	Rac-(2-sec-Butoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	Rac-(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 2-Bromobutane	452.5

79	[2-(2-Hydroxy-ethoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 2-Bromo-1-ethanol	440.4
80	[5-Nitro-2-(2,2,3,3-tetrafluoro-propoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 1-Iodo-2,2,3,3,-tetrafluoropropane	510.5
81	[5-Nitro-2-(4,4,4-trifluorobutoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 1-Bromo-4,4,4,-trifluorobutane	506.5
82	[2-(2-Fluoro-ethoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 1-Bromo-2-fluoroethane	442.5
83	[2-(3-Hydroxy-2,2-dimethyl-propoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 3-Bromo-2,2-Dimethyl-2-propan-1-ol	482.6
84	[5-Nitro-2-(2,2,2-trifluoroethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 1,1,1-Trifluoro-2-jodo-ethane	478.3

85	[2-(1-Ethyl-propoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 3-Bromopentane	466.5
86	[5-Nitro-2-(oxetan-3-yloxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and Toluene-4-sulfonic acid oxetan-3-yl ester (CAS: 26272-83-3)	452.4
87	[2-(3-Hydroxy-propoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and Bromopropanole	454.6
88	[2-(Bicyclo[2.2.1]hept-2-yloxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and exo-2-Bromonorbornane	490.5
89	[2-(2-Methoxy-ethoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 2-bromoethylmethylether	454.5
90	[2-(3,3-Dimethyl-butoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 1-bromo-3,3-dimethylbutane	480.8

91	[2-(1-Ethoxy-cyclopropoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 1-Bromo-1-ethoxy-cyclopropane	480.6
92	[2-(2-Chloro-ethoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 2-Chloroethanol	458.4
93	{4-Nitro-2-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-phenoxy}-acetonitrile	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and bromoacetonitrile	435.4
94	[5-Nitro-2-(3,3,3-trifluoropropoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 1,1,1-Trifluoro-1-Iodopropan	492.4
95	[5-Nitro-2-(tetrahydropyran-4-yloxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 4-chloro-tetrahydropyrane	480.4
96	[2-(2,2-Difluoro-ethoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 1-bromo-2,2-difluoroethane	460.5

97	[2-(1,1,2,3,3,3-Hexafluoropropoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and 3-Hexafluoropropane	546.3
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Example 98

Preparation of (2-Difluoromethoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

5 In analogy to a procedure published in WO9749710, a solution of (2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (50 mg), potassium carbonate (1 eq), and ethyl chlorofluoroacetate (1 eq) in DMF (1 mL) was stirred at 65°C for 16 hours. After such time the reaction mixture was concentrated *in vacuo* and purified by column chromatography (SiO₂) to yield the title compound (26 mg). MS
 10 (m/e): 446.0 (M+H⁺, 100%).

Example 99

Preparation of 5-Nitro-2-(2,2,3,3-tetrafluoro-cyclobutylmethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

Example 99 was prepared in analogy to Example 66 using 1-(chloromethyl)-2,2,3,3-tetrafluorocyclobutane [356-80-9]. MS (m/e): 536.3 (M+H⁺, 100%).
 15

Example 100

Preparation of [5-Nitro-2-(2,2,3,3,3-pentafluoro-propoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

To a refluxing solution of 50 mg of (2-hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone in acetone (2 mL) containing potassium carbonate (35 mg) was added 2,2,3,3,3-pentafluoropropyl trifluoromethanesulfonate (54 mg) over 10 min. The reaction mixture was refluxed for 20 hours before being concentrated *in vacuo* and purified by column chromatography (SiO₂, CH₂Cl₂/MeOH) to yield the title compound as a colorless solid (66 mg). MS (m/e): 569.0 (M+H⁺, 100%).
 20

25

Example 101

Preparation of [2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

A solution of (2-hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (50 mg), 1,3-difluoro-2-propanol [453-13-4] (27 mg), triphenylphosphine (76 mg) and diisopropylazodicarboxylate (48mg) was refluxed overnight, concentrated in *vacuo* and purified by column chromatography (SiO₂) to yield the title compound as a colorless solid (68 mg). MS (m/e): 474.1 (M+H⁺, 100%).

In analogy to Example 48, compounds 102 to 104 of the following table were prepared from (2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 1.9) and an alcohol:

Expl.-No.	Systematic Name	Starting materials	MW found (MH ⁺)
102	[2-(1-Ethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 1.9) and 3-Pentanol	499.5
103	[5-Methanesulfonyl-2-(3-methyl-oxetan-3-ylmethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 1.9) and Methyloxethanemethanol	513.4
104	Rac-[2-(1-Cyclopropylethoxy)-5-methanesulfonyl-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	(2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 1.9) and rac-1-cyclopropylethanol	497.4

Example 2.3

Preparation of (2-Fluoro-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone

Compound 2.3 was prepared in analogy to Example 5 using 2-fluoro-5-(methylsulfonyl)benzoic acid [247569-56-8] and 1-(5-trifluoromethyl-2-pyridyl)piperazine [132834-58-3]. MS (m/e): 432.4 (M+H⁺, 100%).

Example 105

5 **Preparation of [5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone**

A solution of (2-fluoro-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone (compound 2.3) (20 mg), 2-trifluoromethyl-2-propanol (0.053 mL), potassium carbonate or cesium carbonate (3 equivalents) in
10 dimethylacetamide was heated at 150°C for 30 min and then at 180°C for 1h in a microwave oven. After such time the reaction mixture was concentrated and purified by column chromatography (SiO₂) to yield the title compound as a light yellow solid (4.9 mg). MS (m/e): 540.3 (M+H⁺, 100%).

Example 2.4

15 **Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-piperazin-1-yl-methanone trifluoro-acetic acid**

A solution of 2-isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2, 1.0 g), tert-butyl 1-piperazinecarboxylate (0.78 g), TBTU (1.4 g) and N-ethyl-diisopropylamine (4 mL) was stirred at room temperature for 2 hours. After such time, the reaction mixture
20 was concentrated *in vacuo* and purified by column chromatography (SiO₂) to give 4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-piperazine-1-carboxylic acid tert-butyl ester as a colorless foam (1.6 g). The latter was dissolved in dichloromethane (11 mL) and treated with trifluoroacetic acid (4.2 mL) for 30 minutes. After such time the reaction mixture was concentrated *in vacuo* to yield the title compound (1.6 g) as light yellow oil.
25 MS (m/e): 327.1 (M+H⁺, 100%).

Example 2.5

Preparation of 4-Chloro-6-trifluoromethyl-pyrimidine

6-Trifluoromethyl-pyrimidin-4-ol ([1546-78-7], 5 g) was refluxed in phosphorus oxychloride (17 mL) for 2 hours. The reaction mixture was carefully concentrated *in*
30 *vacuo* and the residue was distilled (Kugelrohr) under reduced pressure (bp = 30-55°C @ 10 mbar) to yield the title compound ([37552-81-1], 1.4 g). MS (EI): 182.0 (M).

Example 106

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-nitro-pyridin-2-yl)-piperazin-1-yl]-methanone

A solution of (2-isopropoxy-5-methanesulfonyl-phenyl)-piperazin-1-yl-methanone
5 trifluoro-acetic acid (compound 2.4, 80 mg) 2-chloro-5-nitro-pyridine (29 mg),
potassium carbonate (50 mg) in 1-butanol (3 mL) was stirred at 120°C for 20 hours.
After such time the solution was concentrated *in vacuo*, and purified by column
chromatography (SiO₂) to yield the title compound as white foam (81 mg). MS (m/e):
449.1 (M+H⁺, 100%).

10

Example 107

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(6-trifluoromethyl-pyrimidin-4-yl)-piperazin-1-yl]-methanone

Example 107 was prepared in analogy to example 106 using 4-chloro-6-trifluoromethyl-pyrimidine [37552-81-1]. MS (m/e): 473.1 (M+H⁺, 100%).

15

Example 2.6

Preparation of 2-(4-fluorophenoxy)-5-nitrobenzoic acid

2-(4-Fluoro-phenoxy)-5-nitro-benzoic acid can be prepared by a similar method to that
described in the literature (e.g. WO9938845) by reaction of 2-Chloro-5-nitro-benzoic
acid ethyl ester [16588-17-3] with 4-Fluoro-phenol [371-35-7] yielding 2-(4-Fluoro-
20 phenoxy)-5-nitro-benzoic acid ethyl ester. 2-(4-Fluoro-phenoxy)-5-nitro-benzoic acid
ethyl ester can then be hydrolysed with sodium hydroxide for example to yield the title
compound. MS (m/e): 276.1 (M+H⁺, 100%).

Example 2.7

Preparation of 2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoro-acetic acid

25 (a) 4-(4-Cyano-2,3-difluoro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

To a solution of *N*-Boc-Piperazine (0.65 g) in DMA (20 mL) was slowly added a solution
of 2,3,4-trifluorobenzonitrile (0.49 g) in DMA (10 mL). The reaction mixture was stirred
for 2 hours at 80°C. After such time the solvent was removed *in vacuo* and purified by
column chromatography (SiO₂) to yield the title compound as white solid (0.76 g).

30 (b) 2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoro-acetic acid

To a solution of 4-(4-Cyano-2,3-difluoro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (0.72 g) in dichloromethane (5 mL) was added trifluoroacetic acid and the reaction mixture was stirred at room temperature for 30 minutes. After such time the reaction mixture was concentrated *in vacuo* to yield the title compound (0.63 g). MS (m/e): 224.3 (M+H⁺, 100%).

Example 2.8

Preparation of 2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoro-acetic acid

Example 2.8 was prepared in analogy to Example 2.7 using 2,4,5-trifluorobenzonitrile. MS (m/e): 224.3 (M+H⁺, 100%).

Example 2.9

Preparation of 5-Methylsulfamoyl-2-trifluoromethoxy-benzoic acid

(a) 5-Chlorosulfonyl-2-trifluoromethoxy-benzoic acid

A solution of 2-trifluoromethoxy benzoic acid [1979-29-9] (1.0 g) was added in small batches to chlorosulfonic acid (3.2 mL) at 0°C. After completion of the addition, the reaction mixture was stirred at 70°C for 4 hours then left at room temperature overnight and heated at 75°C for another 3 hours. After such time the reaction was slowly poured onto ice, and the precipitate was then filtered, washed with water and dried to yield the title compound as a white solid (1.2 g). MS (m/e): 303.3 (M-H, 100%).

(b) 5-Methylsulfamoyl-2-trifluoromethoxy-benzoic acid

To a solution of 5-Chlorosulfonyl-2-trifluoromethoxy-benzoic acid (0.15 g) in dichloromethane (1.5 mL) was added a solution of methylamine in methanol (8M, 0.31 mL) and the reaction mixture was stirred for 2 minutes after precipitation was complete. The reaction mixture was then concentrated *in vacuo* and the residue was dissolved in 1N NaOH (2 mL) and extracted with diethylether. The aqueous phase was then acidified using 3 N hydrochloric acid solution (2 mL) and the solution was extracted with dichloromethane (2 x 10 mL). The combined organic phases were dried with sodium sulfate and concentrated *in vacuo* to yield the title compound as a white solid (0.12 g). MS (m/e): 298.0 (M-H, 100%).

Example 2.10

Preparation of 5-Methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-benzoic acid

(a) 5-Methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-benzoic acid methyl ester

A solution of methyl 5-(methanesulfonyl)-salicylate [101371-44-2] (50 mg), triphenylphosphine (65 mg) 3,3,3-trifluoro-1-propanol and di-tert-butyl azodicarboxylate (55 mg) in THF (3 mL) was stirred at room temperature for 1 hour.

- 5 The reaction mixture was then concentrated *in vacuo* purified by column chromatography (SiO₂) to yield the title compound as a white solid (65 mg). MS (m/e): 327.5 (M+H⁺, 100%).

(b) 5-Methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-benzoic acid

- 10 To 5-methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-benzoic acid methyl ester (620 mg) in ethanol at 60°C was added 1N NaOH solution (3.8 mL) and the reaction mixture was stirred for 15 minutes. After such time 3.8 ml of 1N HCl was slowly added to the reaction mixture and the ethanol was evaporated *in vacuo*. The precipitate was then washed with water several times to give the title compound (497 mg). MS (m/e): 311.0, M-H⁺, 100%.

Example 2.11

- 15 Preparation of 5-Methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoic acid

Compound 2.11 was prepared in analogy to compound 2.10 using tetrahydro-2H-pyran-4-ol. MS (m/e): 299.4 (M-H, 100%).

Example 2.12

Preparation of 2-Cyclobutylmethoxy-5-methanesulfonyl-benzoic acid

- 20 Compound 2.12 was prepared in analogy to compound 2.10 using cyclobutyl methanol. MS (m/e): 299.4 (M-H, 100%).

Example 2.13

Preparation of 3,5-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid

- 25 Compound 2.13 was prepared in analogy to compound 2.7 using 3,4,5-trifluorobenzonitrile. MS (m/e): 224.1 (M+H⁺, 100%).

Example 2.14

Preparation of 2,6-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid

Compound 2.14 was prepared in analogy to compound 2.7 using 2,4,6-trifluorobenzonitrile. MS (m/e): 224.1 (M+H⁺, 100%).

Example 2.15

Preparation of 5-Methanesulfonyl-2-trifluoromethoxy-benzoic acid

5 (a) 5-Sulfinoyl-2-trifluoromethoxy-benzoic acid

5-chlorosulfonyl-2-trifluoromethoxy-benzoic acid (1.0 g, compound 2.9.a) was added portionwise onto a solution of sodium sulfite (3.1 g) in 16 mL of water. The reaction mixture was kept under basic conditions by the addition of the proper amount of 20% NaOH and was stirred at room temperature for 45 minutes. After such time the reaction mixture was cooled down with an ice bath and was then acidified by the addition of 20% H₂SO₄ solution until reaching pH 2. The solution was then extracted several times with diethyl ether and ethyl acetate. The combined organic phases were dried (sodium sulfate) and concentrated *in vacuo* to yield the title compound as a white solid (0.88 g).

(b) 5-Methanesulfonyl-2-trifluoromethoxy-benzoic acid

15 To 5-Sulfinoyl-2-trifluoromethoxy-benzoic acid (0.82 g) in DMF (5 mL) was added 1.3 g of potassium carbonate and the reaction mixture was stirred for 5 minutes before methyl iodide (0.66 mL) was added. The reaction mixture was then stirred at room temperature for 60 hours. After such time the reaction mixture was concentrated *in vacuo* and the residue was treated with 1N NaOH (10 mL) and THF (4 mL). The reaction mixture was stirred for a further 2 hours at room temperature. After such time the solution was acidified with concentrated HCl solution. THF was then removed *in vacuo* and the precipitate was isolated by filtration and washed several times with water to yield the title compound. MS (m/e): 283.0 (M-H, 100%).

Example 2.16

25 Preparation of 2,4-Difluoro-6-piperazin-1-yl-benzonitrile trifluoro-acetic acid

Compound 2.16 was prepared in analogy to compound 2.7 using 2,4,6-trifluorobenzonitrile of . MS (m/e): 224.1 (M+H⁺, 100%).

Example 2.17

Preparation of 2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoic acid

Compound 2.17 was prepared in analogy to compound 2.10 using 1,3-difluoro-2-propanol. MS (m/e): 293.1 (M-H, 100%).

Example 2.18

Preparation of 5-Methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-benzoic acid

5 (a) 5-Methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-benzoic acid methyl ester

A solution of methyl 5-(methanesulfonyl)salicylate [101371-44-2] (0.50 g), trifluoromethanesulfonic acid 2,2,3,3,3-pentafluoro-propyl ester (0.67 g) and potassium carbonate (0.60 g) in acetone was stirred at 60°C for 5 hours. The reaction mixture was then concentrated *in vacuo* and purified by column chromatography (SiO₂) to yield the
10 title compound as a white solid (0.44 g). MS (m/e): 363.1 (M+H⁺, 100%).

(b) 5-Methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-benzoic acid

To 5-methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-benzoic acid methyl ester (414 mg) in THF (5 mL) was added a solution of lithium hydroxide monohydrate (72 mg) in water (5 mL), and the reaction mixture was stirred at room temperature for 1 hour. After
15 such time 1.72 mL of 1N aqueous hydrochloric acid solution was added. The reaction mixture was then concentrated *in vacuo* and the resulting precipitate was then washed several times with water to yield the title compound as a white solid (367 mg). MS (m/e): 347.1 (M-H, 100%).

Example 2.19

20 Preparation of 2-tert-Butoxy-5-methanesulfonyl-benzoic acid

(a) 2-tert-Butoxy-5-methanesulfonyl-benzoic acid methyl ester

To a solution of methyl 5-(methanesulfonyl)salicylate [101371-44-2] (0.50 g) in toluene (5 mL) was added *N,N*-dimethylformamide-di-*tert*-butylacetal and the reaction mixture was stirred at 80°C for 1 hour. After such time the reaction mixture was concentrated *in*
25 *vacuo* and purified by column chromatography to yield the title compound as colourless oil (258 mg). MS (m/e): 304.4 (M+NH₄⁺, 100%).

(b) 2-tert-Butoxy-5-methanesulfonyl-benzoic acid

To 2-tert-Butoxy-5-methanesulfonyl-benzoic acid methyl ester (1.58 g) in THF (25 mL) was added a solution lithium hydroxide monohydrate (0.35 g) in water (25 mL) and the

reaction mixture was stirred at room temperature for 4 hours. After such time the THF was removed *in vacuo* and to the remaining aqueous solution was added 8 mL of 1N HCl solution leading to precipitation of the compound. The precipitate was filtered off and washed several times with water to yield the title compound (1.00 g) as a white solid. MS (m/e): 289.9 (M+NH₄⁺).

Example 2.20

Preparation of 1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid

(a) 2,4,5-Trifluoro-benzenesulfinic acid

2,4,5-Trifluoro-benzenesulfonyl chloride ([220227-21-4], 2.5 g) was added portionwise onto a solution of sodium sulfite (10.3 g) in 50 mL of water. The reaction mixture was kept under basic conditions by the addition of the proper amount of 20% NaOH and was stirred at room temperature for 1 hour. Methanol was added to the reaction mixture and the reaction mixture was stirred at room temperature for another hour. After such time the reaction mixture was cooled down with an ice bath and was then acidified by the addition of 20% H₂SO₄ solution until reaching pH 2. The aqueous solution was then extracted several times with diethyl ether and ethyl acetate. The aqueous solution was further extracted with ethyl acetate using a Kutscher-Steudel apparatus (continuous extraction). The combined organic phases were dried (sodium sulfate) and concentrated *in vacuo* to yield the title compound as a white solid (2.1 g).

(b) 1,2,4-Trifluoro-5-methanesulfonyl-benzene

To 2,4,5-trifluoro-benzenesulfinic acid (2.0 g) in DMF (17 mL) was added 4.3 g of potassium carbonate and the reaction mixture was stirred for 5 minutes before methyl iodide (2.2 mL) was added. The reaction mixture was then stirred at room temperature for 60 hours. After such time water (30 mL) was poured onto the reaction mixture and the reaction mixture was extracted with diethylether several times. The combined organic phases were dried with sodium sulfate and the remaining mixture was distilled to yield the title compound as a light yellow oil (2.1 g).

(c) 1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid

The title compound was obtained in analogy to example 2.7 using 1,2,4-Trifluoro-5-methanesulfonyl-benzene. MS (m/e): 277.1 (M+H⁺).

Example 2.21**Preparation of 1-(3,5-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid**

Compound 2.21 was prepared in analogy to compound 2.20 using 2,4,6-trifluoro-
5 benzenesulfonyl chloride [172326-59-9]. MS (m/e): 277.1 (M+H⁺).

Example 2.22**Preparation of 5-Methanesulfonyl-2-(2,2,3,3-tetrafluoro-propoxy)-benzoic acid**

Compound 2.22 was prepared in analogy to compound 2.18 using 2,2,3,3-tetrafluoro-1-propyl triflate. MS (m/e): 329.1 (M-H).

10 **Example 2.23**

Preparation of 1-(2,6-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid

Compound 2.23 was prepared in analogy to compound 2.20 using 3,4,5-trifluoro-benzenesulfonyl chloride [351003-43-5]. MS (m/e): 277.1 (M+H⁺).

15 **Example 2.24**

Preparation of 4-Piperazin-1-yl-6-trifluoromethyl-pyrimidine trifluoro-acetic acid

Compound 2.24 was prepared in analogy to compound 2.7 using 4-chloro-6-trifluoromethyl-pyrimidine [37552-81-1]. MS (m/e): 233.1 (M+H⁺).

Example 2.25

20 **Preparation of 2-Piperazin-1-yl-5-trifluoromethyl-pyrimidine**

(a) 2-(4-Benzyl-piperazin-1-yl)-5-trifluoromethyl-pyrimidine

To a solution of (3-Dimethylamino-2-trifluoromethyl-allylidene)-dimethyl-ammonium chloride ([176214-18-9], 0.60 g) in acetonitrile (10 mL) was added 4-Benzyl-piperazine-1-carboxamide hydrochloride ([7773-69-5], 0.66 g) and triethylamine (0.87 mL) and
25 the reaction mixture was stirred for 3 hours at room temperature. After such time the reaction mixture was concentrated *in vacuo* and purified by column chromatography to yield the title compound as a light yellow solid (0.79 g). MS (m/e): 323.4 (M+H⁺).

(b) 2-Piperazin-1-yl-5-trifluoromethyl-pyrimidine

To a solution of 2-(4-Benzyl-piperazin-1-yl)-5-trifluoromethyl-pyrimidine (0.63 g) in methanol was added Palladium-C (Degussa E101N; 5%) and the reaction mixture was heated at 60°C under hydrogen atmosphere. The reaction mixture was then allowed to cool down to room temperature, the catalyst was filtered off and solvent was removed *in vacuo* to yield the title compound as a colorless solid (0.41 g). MS (m/e): 233.1 (M+H⁺).

In analogy to Example 5 compounds 108 to 280 of the following table were prepared from the acid derivatives and piperazine derivatives:

Expl.- No.	Systematic Name	Starting materials	MW found (MH ⁺)
108	[2-(4-Fluoro-phenoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-trifluoromethyl-phenyl)piperazine and 2-(4-fluorophenoxy)-5-nitrobenzoic acid (compound 2.6)	490.5
109	2,3-Difluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoro-acetic acid (compound 2.7) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	464.3
110	2,5-Difluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoro-acetic acid (compound 2.8) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	464.1
111	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-trifluoromethoxy-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 5-Methylsulfamoyl-2-trifluoromethoxy-benzoic acid (compound 2.9)	487.1

112	3-Fluoro-4-{4-[5-methanesulfonyl-2-(3,3,3-trifluoropropoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Methanesulfonyl-2-(3,3,3-trifluoropropoxy)-benzoic acid (compound 2.10)	500.3
113	4-{4-[5-Methanesulfonyl-2-(3,3,3-trifluoropropoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	4-Piperazin-1-yl-benzonitrile (commercial) and 5-Methanesulfonyl-2-(3,3,3-trifluoropropoxy)-benzoic acid (compound 2.10)	482.3
114	2-Fluoro-4-{4-[5-methanesulfonyl-2-(3,3,3-trifluoropropoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 5-Methanesulfonyl-2-(3,3,3-trifluoropropoxy)-benzoic acid (compound 2.10)	500.3
115	[5-Methanesulfonyl-2-(3,3,3-trifluoropropoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-(3,3,3-trifluoropropoxy)-benzoic acid (compound 2.10)	525.2
116	[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(3,3,3-trifluoropropoxy)-phenyl]-methanone	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 5.1) and 5-Methanesulfonyl-2-(3,3,3-trifluoropropoxy)-benzoic acid (compound 2.10)	543.3

117	[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-phenyl]-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 1.1) and 5-Methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-benzoic acid (compound 2.10)	543.2
118	1-(3-Fluoro-4-{4-[5-methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 5-Methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-benzoic acid (compound 2.10)	517.3
119	[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-phenyl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-benzoic acid (compound 2.10)	553.2
120	4-{4-[5-Methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoyl]-piperazin-1-yl}-benzonitrile	4-Piperazin-1-yl-benzonitrile (commercial) and 5-Methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoic acid (compound 2.11)	470.0
121	2-Fluoro-4-{4-[5-methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 5-Methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoic acid (compound 2.11)	488.1

122	3-Fluoro-4-{4-[5-methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoyl]-piperazin-1-yl}-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoic acid (compound 2.11)	488.0
123	[5-Methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoic acid (compound 2.11)	513.3
124	[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-phenyl]-methanone	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 5.1) and 5-Methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoic acid (compound 2.11)	531.0
125	[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-phenyl]-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 1.1) and 5-Methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoic acid (compound 2.11)	531.2
126	1-(3-Fluoro-4-{4-[5-methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 5-Methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoic acid (compound 2.11)	505.1

127	[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-phenyl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoic acid (compound 2.11)	541.3
128	2,3-Difluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoro-acetic acid (compound 2.7) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	478.1
129	4-[4-(2-Cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,3-difluoro-benzonitrile	2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoro-acetic acid (compound 2.7) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	476.3
130	2,3-Difluoro-4-{4-[5-methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoro-acetic acid (compound 2.7) and 5-Methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoic acid (compound 2.11)	506.4
131	4-[4-(2-Cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,3-difluoro-benzonitrile	2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoro-acetic acid (compound 2.7) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	490.5

132	2,5-Difluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoro-acetic acid (compound 2.8) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	478.4
133	4-[4-(2-Cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,5-difluoro-benzonitrile	2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoro-acetic acid (compound 2.8) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	476.3
134	2,5-Difluoro-4-{4-[5-methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoro-acetic acid (compound 2.8) and 5-Methanesulfonyl-2-(tetrahydro-pyran-4-yloxy)-benzoic acid (compound 2.11)	506.4
135	4-[4-(2-Cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,5-difluoro-benzonitrile	2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoro-acetic acid (compound 2.8) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	490.5
136	4-[4-(2-Cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	4-Piperazin-1-yl-benzonitrile (commercial) and 2-Cyclobutylmethoxy-5-methanesulfonyl-benzoic acid (compound 2.12)	454.6

137	4-[4-(2-Cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-Cyclobutylmethoxy-5-methanesulfon-yl-benzoic acid (compound 2.12)	472.3
138	4-[4-(2-Cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 2-Cyclobutylmethoxy-5-methanesulfon-yl-benzoic acid (compound 2.12)	472.3
139	(2-Cyclobutylmethoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-pipera-zine (commercial) and 2-Cyclobutylmethoxy-5-methanesulfon-yl-benzoic acid (compound 2.12)	497.3
140	(2-Cyclobutylmethoxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 5.1) and 2-Cyclobutylmethoxy-5-methanesulfon-yl-benzoic acid (compound 2.12)	515.4
141	(2-Cyclobutylmethoxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-trifluoromethyl-pheny-l)-piperazine (compound 1.1) and 2-Cyclobutylmethoxy-5-methanesulfon-yl-benzoic acid (compound 2.12)	515.4

142	1-[4-[4-(2-Cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl]-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 2-Cyclobutylmethoxy-5-methanesulfonyl-benzoic acid (compound 2.12)	489.5
143	(2-Cyclobutylmethoxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-Cyclobutylmethoxy-5-methanesulfonyl-benzoic acid (compound 2.12)	525.3
144	2-[4-(2-Cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile	2-Piperazin-1-yl-5-trifluoromethyl-benzonitrile (compound 5.2) and 2-Cyclobutylmethoxy-5-methanesulfonyl-benzoic acid (compound 2.12)	522.4
145	4-[4-(2-Cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,3-difluoro-benzonitrile	2,3-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoro-acetic acid (compound 2.7) and 2-Cyclobutylmethoxy-5-methanesulfonyl-benzoic acid (compound 2.12)	490.5
146	4-[4-(2-Cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,5-difluoro-benzonitrile	2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoro-acetic acid (compound 2.8) and 2-Cyclobutylmethoxy-5-methanesulfonyl-benzoic acid (compound 2.12)	490.5

147	4-[4-(2-Cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3,5-difluoro-benzonitrile	3,5-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.13) and 2-Cyclobutylmethoxy-5-methanesulfonyl-benzoic acid (compound 2.12)	490.5
148	4-[4-(2-Cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,6-difluoro-benzonitrile	2,6-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.14) and 2-Cyclobutylmethoxy-5-methanesulfonyl-benzoic acid (compound 2.12)	490.5
149	2,5-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoro-acetic acid (compound 2.8) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	504.0
150	2,3-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoro-acetic acid (compound 2.7) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	504.1
151	2,5-Difluoro-4-[4-(5-trifluoromethoxy-benzoyl)-piperazin-1-yl]-benzonitrile	2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoro-acetic acid (compound 2.8) and 5-Methanesulfonyl-2-trifluoromethoxy-benzoic acid (compound 2.15)	490.0

152	4-[4-(5-Methanesulfonyl-2-trifluoromethoxy-benzoyl)-piperazin-1-yl]-benzonitrile	4-Piperazin-1-yl-benzonitrile (commercial) and 5-Methanesulfonyl-2-trifluoromethoxy-benzoic acid (compound 2.15)	454.3
153	2-Fluoro-4-[4-(5-methanesulfonyl-2-trifluoromethoxy-benzoyl)-piperazin-1-yl]-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 5-Methanesulfonyl-2-trifluoromethoxy-benzoic acid (compound 2.15)	472.1
154	3-Fluoro-4-[4-(5-methanesulfonyl-2-trifluoromethoxy-benzoyl)-piperazin-1-yl]-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Methanesulfonyl-2-trifluoromethoxy-benzoic acid (compound 2.15)	472.0
155	(5-Methanesulfonyl-2-trifluoromethoxy-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-trifluoromethoxy-benzoic acid (compound 2.15)	514.2 (M+NH ₄ ⁺)
156	[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-trifluoromethoxy-phenyl)-methanone	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 5.1) and 5-Methanesulfonyl-2-trifluoromethoxy-benzoic acid (compound 2.15)	532.2 (M+NH ₄ ⁺)
157	[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-trifluoromethoxy-phenyl)-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 1.1) and 5-Methanesulfonyl-2-trifluoromethoxy-benzoic acid (compound 2.15)	515.3

158	2,3-Difluoro-4-[4-(5-methanesulfonyl-2-trifluoromethoxy-benzoyl)-piperazin-1-yl]-benzonitrile	2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoro-acetic acid (compound 2.7) and 5-Methanesulfonyl-2-trifluoromethoxy-benzoic acid (compound 2.15)	507.4 (M+NH ₄ ⁺)
159	3,5-Difluoro-4-[4-(5-methanesulfonyl-2-trifluoromethoxy-benzoyl)-piperazin-1-yl]-benzonitrile	3,5-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.13) and 5-Methanesulfonyl-2-trifluoromethoxy-benzoic acid (compound 2.15)	507.3 (M+NH ₄ ⁺)
160	2,6-Difluoro-4-[4-(5-methanesulfonyl-2-trifluoromethoxy-benzoyl)-piperazin-1-yl]-benzonitrile	2,6-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.14) and 5-Methanesulfonyl-2-trifluoromethoxy-benzoic acid (compound 2.15)	507.4 (M+NH ₄ ⁺)
161	[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-trifluoromethoxy-phenyl)-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-trifluoromethoxy-benzoic acid (compound 2.15)	542.0 (M+NH ₄ ⁺)
162	2-[4-(5-Methanesulfonyl-2-trifluoromethoxy-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile	2-Piperazin-1-yl-5-trifluoromethyl-benzonitrile (compound 5.2) and 5-Methanesulfonyl-2-trifluoromethoxy-benzoic acid (compound 2.15)	539.2 (M+NH ₄ ⁺)

163	3,5-Difluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	3,5-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.13) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	464.1
164	3,5-Difluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	3,5-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.13) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	478.0
165	4-[4-(2-Cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3,5-difluoro-benzonitrile	3,5-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.13) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	476.1
166	3,5-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	3,5-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.13) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	504.1
167	4-[4-(2-Cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3,5-difluoro-benzonitrile	3,5-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.13) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	490.3

168	2,6-Difluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	2,6-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.14) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	481.1 (M+NH ₄ ⁺)
169	2,6-Difluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	2,6-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.14) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	495.0 (M+NH ₄ ⁺)
170	4-[4-(2-Cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,6-difluoro-benzonitrile	2,6-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.14) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	493.0 (M+NH ₄ ⁺)
171	2,6-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2,6-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.14) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	521.3 (M+NH ₄ ⁺)
172	4-[4-(2-Cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,6-difluoro-benzonitrile	2,6-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.14) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	507.3 (M+NH ₄ ⁺)

173	2,4-Difluoro-6-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	2,4-Difluoro-6-piperazin-1-yl-benzonitrile trifluoroacetic acid (compound 2.16) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	581.4 (M+NH ₄ ⁺)
174	2-Fluoro-4-{4-[2-(2-fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoic acid (compound 2.17)	482.3
175	3-Fluoro-4-{4-[2-(2-fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoic acid (compound 2.17)	482.4
176	2,3-Difluoro-4-{4-[2-(2-fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile	2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoroacetic acid (compound 2.7) and 2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoic acid (compound 2.17)	500.3
177	2,5-Difluoro-4-{4-[2-(2-fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile	2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoroacetic acid (compound 2.8) and 2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoic acid (compound 2.17)	500.3

178	3,5-Difluoro-4-{4-[2-(2-fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile	3,5-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.13) and 2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoic acid (compound 2.17)	500.3
179	2,6-Difluoro-4-{4-[2-(2-fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile	2,6-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.14) and 2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoic acid (compound 2.17)	500.3
180	2-Fluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 5-Methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-benzoic acid (compound 2.18)	536.3
181	3-Fluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-benzoic acid (compound 2.18)	536.3
182	[5-Methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-benzoic acid (compound 2.18)	561.3

183	[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-phenyl]-methanone	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 5.1) and 5-Methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-benzoic acid (compound 2.18)	579.0
184	2,3-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2,3-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoroacetic acid (compound 2.7) and 5-Methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-benzoic acid (compound 2.18)	554.0
185	2,5-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoroacetic acid (compound 2.8) and 5-Methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-benzoic acid (compound 2.18)	554.0
186	3,5-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	3,5-Difluoro-4-piperazin-1-yl-benzonitrile trifluoroacetic acid (compound 2.13) and 5-Methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-benzoic acid (compound 2.18)	554.0
187	2,6-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2,6-Difluoro-4-piperazin-1-yl-benzonitrile trifluoroacetic acid (compound 2.14) and 5-Methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-benzoic acid (compound 2.18)	571.2 (M+NH ₄ ⁺)

188	[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-phenyl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-(2,2,3,3,3-pentafluoropropoxy)-benzoic acid (compound 2.18)	589.3
189	4-{4-[2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile	4-Piperazin-1-yl-benzonitrile (commercial) and 2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoic acid (compound 2.17)	464.1
190	[2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoic acid (compound 2.17)	507.3
191	[2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-phenyl]-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 5.1) and 2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoic acid (compound 2.17)	525.2
192	[2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-phenyl]-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 1.1) and 2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoic acid (compound 2.17)	525.0

193	[2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-phenyl]-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoic acid (compound 2.17)	535.3
194	2-{4-[2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-5-trifluoromethyl-benzonitrile	2-Piperazin-1-yl-5-trifluoromethyl-benzonitrile (compound 5.2) and 2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoic acid (compound 2.17)	532.2
195	[4-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[2-(2-fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-phenyl]-methanone	1-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazine (compound 5.3) and 2-(2-Fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoic acid (compound 2.17)	553.2
196	4-[4-(2-tert-Butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,3-difluoro-benzonitrile	2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoro-acetic acid (compound 2.7) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	478.3
197	[4-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid (compound 2.20) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	534.3 (M+NH ₄ ⁺)

198	[4-(3,5-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(3,5-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid (compound 2.21) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	534.3 (M+NH ₄ ⁺)
199	2-[4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	2-Piperazin-1-yl-benzonitrile (commercial) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	428.5
200	[4-(2-Fluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(2-Fluoro-phenyl)-piperazine (commercial) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	421.3
201	[4-(4-Chloro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Chloro-phenyl)-piperazine (commercial) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	437.3
202	5-Chloro-2-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	5-Chloro-2-piperazin-1-yl-benzonitrile (WO9625414) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	462.1
203	[4-(4-Chloro-2-fluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Chloro-2-fluoro-phenyl)-piperazine hydrochloride (commercial) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	455.4

204	[4-(4-Chloro-3-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Chloro-3-trifluoromethyl-phenyl)-piperazine (commercial) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	505.3
205	[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(3,4-Dichloro-phenyl)-piperazine (commercial) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	471.0
206	[4-(2-Fluoro-4-methyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(2-Fluoro-4-methyl-phenyl)-piperazine (compound 5.4) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	435.3
207	rac-2,3-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoro-acetic acid (compound 2.7) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	535.3 (M+NH ₄ ⁺)
208	(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethoxy-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethoxy-phenyl)-piperazine (WO03007954) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	487.3

209	2-Fluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 5-Methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-benzoic acid (compound 2.22)	535.3 (M+NH ₄ ⁺)
210	3-Fluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-benzoic acid (compound 2.22)	535.5 (M+NH ₄ ⁺)
211	[5-Methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-benzoic acid (compound 2.22)	560.3 (M+NH ₄ ⁺)
212	[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-phenyl]-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 1.1) and 5-Methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-benzoic acid (compound 2.22)	578.2 (M+NH ₄ ⁺)
213	2,3-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoroacetic acid (compound 2.7) and 5-Methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-benzoic acid (compound 2.22)	553.2 (M+NH ₄ ⁺)

214	2,5-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoroacetic acid (compound 2.8) and 5-Methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-benzoic acid (compound 2.22)	553.2 (M+NH ₄ ⁺)
215	3,5-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	3,5-Difluoro-4-piperazin-1-yl-benzonitrile trifluoroacetic acid (compound 2.13) and 5-Methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-benzoic acid (compound 2.22)	553.0 (M+NH ₄ ⁺)
216	2,6-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2,6-Difluoro-4-piperazin-1-yl-benzonitrile trifluoroacetic acid (compound 2.14) and 5-Methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-benzoic acid (compound 2.22)	553.2 (M+NH ₄ ⁺)
217	[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-phenyl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-(2,2,3,3-tetrafluoropropoxy)-benzoic acid (compound 2.22)	588.3 (M+NH ₄ ⁺)
218	[4-(2,6-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(2,6-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoroacetic acid (compound 2.23) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	517.3

219	3-Chloro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	3-Chloro-4-piperazin-1-yl-benzonitrile (WO 9625414) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	462.3
220	[4-(2-Chloro-4-nitro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(2-Chloro-4-nitro-phenyl)-piperazine (EP 257864) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	482.3
221	3-[4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	3-Piperazin-1-yl-benzonitrile (WO02068399) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	428.4
222	[4-(3,5-Dichloro-pyridin-4-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(3,5-Dichloro-pyridin-4-yl)-piperazine (commercial) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	474.0
223	5-Chloro-2-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	5-Chloro-2-piperazin-1-yl-benzonitrile (WO9625414) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	502.1

224	[4-(4-Chloro-2-fluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(4-Chloro-2-fluoro-phenyl)-piperazine hydrochloride (commercial) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	495.4
225	[4-(4-Chloro-3-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(4-Chloro-3-trifluoromethyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	545.3
226	[4-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid (compound 2.20) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	574.3 (M+NH ₄ ⁺)
227	[4-(2,6-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(2,6-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid (compound 2.23) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	557.4

228	5-Chloro-2-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	5-Chloro-2-piperazin-1-yl-benzonitrile (WO9625414) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	474.1
229	[4-(4-Chloro-2-fluorophenyl)-piperazin-1-yl]-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Chloro-2-fluorophenyl)-piperazine hydrochloride (commercial) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	467.3
230	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(3,4-dichloro-phenyl)-piperazin-1-yl]-methanone	1-(3,4-Dichloro-phenyl)-piperazine (commercial) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	483.3
231	[4-(4-Chloro-3-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Chloro-3-trifluoromethyl-phenyl)-piperazine (commercial) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	517.0

232	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(2,5-difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid (compound 2.20) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	546.3 (M+NH ₄ ⁺)
233	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(2,6-difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2,6-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid (compound 2.23) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	546.3 (M+NH ₄ ⁺)
234	4-[4-(2-tert-Butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,5-difluoro-benzonitrile	2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoro-acetic acid (compound 2.8) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	478.1
235	4-[4-(2-tert-Butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3,5-difluoro-benzonitrile	3,5-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.13) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	478.1
236	4-[4-(2-tert-Butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,6-difluoro-benzonitrile	2,6-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.14) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	478.1

237	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	530.2 (M+NH ₄ ⁺)
238	2-[4-(2-tert-Butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile	2-Piperazin-1-yl-5-trifluoromethyl-benzonitrile (compound 5.2) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	527.3 (M+NH ₄ ⁺)
239	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(2,3-difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazine (compound 5.3) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	548.3 (M+NH ₄ ⁺)
240	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazine (commercial) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	520.3
241	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(5-chloro-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(5-Chloro-pyridin-2-yl)-piperazine (WO01062751) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	452.3

242	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(5-Trifluoromethyl-pyridin-2-yl)-piperazine (commercial) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	486.4
243	4-[4-(2-tert-Butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	460.3
244	4-[4-(2-tert-Butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	460.3
245	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	485.5
246	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 5.1) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	503.1
247	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 1.1) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	503.3

248	6-[4-(2-tert-Butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-nicotinonitrile	6-Piperazin-1-yl-nicotinonitrile (commercial) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	443.4
249	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(2,5-difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid (compound 2.20) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	548.3 (M+NH ₄ ⁺)
250	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(2,6-difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2,6-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid (compound 2.23) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	548.3 (M+NH ₄ ⁺)
251	[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(3,4-Dichloro-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	511.0
252	2-[4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-nicotinonitrile	2-Piperazin-1-yl-nicotinonitrile (commercial) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	429.5

253	(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone	2-Piperazin-1-yl-4-trifluoromethyl-pyrimidine (commercial) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	473.0
254	rac-[4-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid (compound 2.20) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	571.0
255	rac-[4-(2,6-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(2,6-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid (compound 2.23) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	571.2
256	rac-5-Chloro-2-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	5-Chloro-2-piperazin-1-yl-benzonitrile (WO9625414) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	516.2

257	rac-[4-(4-Chloro-2-fluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(4-Chloro-2-fluoro-phenyl)-piperazine hydrochloride (commercial) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	509.3
258	rac-[4-(3,4-Dichloro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(3,4-Dichloro-phenyl)-piperazine (commercial) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	525.2
259	rac-[4-(4-Chloro-3-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(4-Chloro-3-trifluoromethyl-phenyl)-piperazine (commercial) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	559.0
260	rac-3,5-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	3,5-Difluoro-4-piperazin-1-yl-benzonitrile trifluoroacetic acid (compound 2.13) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	518.2
261	rac-2,5-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoroacetic acid (compound 2.8) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	518.0

262	rac-2,6-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2,6-Difluoro-4-piperazin-1-yl-benzonitrile trifluoro-acetic acid (compound 2.14) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	517.8
263	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone	2-Piperazin-1-yl-4-trifluoromethyl-pyrimidine (commercial) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	485.1
264	(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(2-trifluoromethyl-pyrimidin-4-yl)-piperazin-1-yl]-methanone	4-Piperazin-1-yl-2-trifluoromethyl-pyrimidine trifluoro-acetic acid (WO030249) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	473.1
265	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine (compound 5.5) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	504.0
266	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone	2-Piperazin-1-yl-4-trifluoromethyl-pyrimidine (commercial) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	487.1

267	[5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-[4-(4-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone	2-Piperazin-1-yl-4-trifluoromethyl-pyrimidine (commercial) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	513.3
268	rac-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone	2-Piperazin-1-yl-4-trifluoromethyl-pyrimidine (commercial) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	527.0
269	[4-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid and 5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 5.6)	571.0
270	[4-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid (compound 2.20) and 5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 5.7)	571.0

271	[4-(2,6-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(2,6-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid (compound 2.23) and 5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 5.6)	571.2
272	[4-(2,6-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(2,6-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid (compound 2.23) and 5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 5.7)	571.2
273	rac-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(2-trifluoromethyl-pyrimidin-4-yl)-piperazin-1-yl]-methanone	4-Piperazin-1-yl-2-trifluoromethyl-pyrimidine trifluoro-acetic acid (WO030249) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	527.0
274	rac-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(6-trifluoromethyl-pyrimidin-4-yl)-piperazin-1-yl]-methanone	4-Piperazin-1-yl-6-trifluoromethyl-pyrimidine trifluoro-acetic acid (compound 2.24) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	527.2

275	rac-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone	2-Piperazin-1-yl-5-trifluoromethyl-pyrimidine (compound 2.25) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	527.2
276	(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone	2-Piperazin-1-yl-5-trifluoromethyl-pyrimidine (compound 2.25) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	473.1
277	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(2-trifluoromethyl-pyrimidin-4-yl)-piperazin-1-yl]-methanone	4-Piperazin-1-yl-2-trifluoromethyl-pyrimidine trifluoro-acetic acid (WO030249) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	485.1
278	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(6-trifluoromethyl-pyrimidin-4-yl)-piperazin-1-yl]-methanone	4-Piperazin-1-yl-6-trifluoromethyl-pyrimidine trifluoro-acetic acid (compound 2.24) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	485.5

279	[5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-[4-(2-trifluoromethyl-pyrimidin-4-yl)-piperazin-1-yl]-methanone	4-Piperazin-1-yl-2-trifluoromethyl-pyrimidine trifluoro-acetic acid (WO030249) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	513.3
280	[5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-[4-(6-trifluoromethyl-pyrimidin-4-yl)-piperazin-1-yl]-methanone	4-Piperazin-1-yl-6-trifluoromethyl-pyrimidine trifluoro-acetic acid (compound 2.24) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	513.3

In analogy to Example 1.2 (b) compounds 3.1 to 3.5 of the following table were prepared from 2-chloro-5-methanesulfonyl-benzoic acid and the appropriate alcohol:

Expl. No	Compound name	Alcohol	MS (m/e)
3.1	rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl ethoxy)-benzoic acid (compound 3.1)	rac-1,1,1-Trifluoro-propan-2-ol	311.3 (MH-)
3.2	2-Cyclohexyloxy-5-methanesulfonyl-benzoic acid (compound 3.2)	Cyclohexanol	297.3 (MH-)

3.3	2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-benzoic acid (compound 3.3)	2,2-Dimethyl-propan-1-ol	285.1 (MH-)
3.4	2-Cyclobutoxy-5-methanesulfonyl-benzoic acid (compound 3.4)	cyclobutanol	269.3 (MH-)
3.5	rac-2-sec-Butoxy-5-methanesulfonyl-benzoic acid (compound 3.5)	Butan-2-ol	271.4 (MH-)

In analogy to Example 5 compounds 281 to 326 of the following table were prepared from the acid derivatives and piperazine derivatives.

Expl.-No.	Systematic Name	Starting materials	MW found (MH ⁺)
281	1-{4-[4-(2-cyclohexyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluorophenyl}-ethanone	1-(3-Fluoro-4-piperazin-1-phenyl)-ethanone (WO9714690) and 2-cyclohexyloxy-5-methanesulfonyl-benzoic acid (compound 3.2)	503.5
282	4-[4-(2-Cyclohexyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	4-Piperazin-1-yl-benzonitrile (commercial) and 2-cyclohexyloxy-5-methanesulfonyl-benzoic acid (compound 3.2)	468.5
283	4-[4-(2-Cyclohexyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluorobenzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 2-cyclohexyloxy-5-methanesulfonyl-benzoic acid (compound 3.2)	486.5

284	4-[4-(2-Cyclohexyloxy-ethanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-nzonitrile	2-Fluoro-4-piperazin-1-yl-nzonitrile (WO 9808835) and 2-Cyclohexyloxy-5-ethanesulfonyl-benzoic acid (compound 3.2)	486.5
285	(2-Cyclohexyloxy-5-ethanesulfonyl-phenyl)-[4-(4-fluoromethyl-phenyl)-piperazin-1-yl]-ethanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 2-Cyclohexyloxy-5-ethanesulfonyl-benzoic acid (compound 3.2)	511.5
286	(2-Cyclohexyloxy-5-ethanesulfonyl-phenyl)-[4-(2-fluoro-4-fluoromethyl-phenyl)-piperazin-1-yl]-ethano	1-(2-Fluoro-4-fluoromethyl-phenyl)-piperazine (compound 1.1) and 2-Cyclohexyloxy-5-ethanesulfonyl-benzoic acid (compound 3.2)	529.5
287	(2-Cyclohexyloxy-5-ethanesulfonyl-phenyl)-[4-(3-fluoro-4-fluoromethyl-phenyl)-piperazin-1-yl]-ethano	1-(3-Fluoro-4-fluoromethyl-phenyl)-piperazine (compound 5.1) and 2-Cyclohexyloxy-5-ethanesulfonyl-benzoic acid (compound 3.2)	529.3

288	(2-Cyclohexyloxy-5-ethanesulfonyl-phenyl)-[4-(2-fluoro-4-ethanesulfonyl-phenyl)-piperazin-1-yl]-ethano	1-(2-Fluoro-4-ethanesulfonyl-phenyl)piperazine (commercial) and Cyclohexyloxy-5-ethanesulfonyl-benzoic acid compound 3.2)	539.5
289	1-(4-{4-[2-(2,2-Dimethyl-propoxy)-5-ethanesulfonyl-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone	1-(3-Fluoro-4-piperazin-1-phenyl)-ethanone (WO9714690) and 2-(2,2-dimethyl-propoxy)-5-ethanesulfonyl-benzoic acid compound 3.3)	491.5
290	4-{4-[2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile	4-Piperazin-1-yl-benzonitrile (commercial) and 2-(2,2-dimethyl-propoxy)-5-ethanesulfonyl-benzoic acid compound 3.3)	456.6
291	4-{4-[2-(2,2-Dimethyl-propoxy)-5-ethanesulfonyl-benzoyl]-piperazin-1-yl}-3-fluoro-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 2-(2,2-Dimethyl-propoxy)-5-ethanesulfonyl-benzoic acid compound 3.3)	474.4
292	4-{4-[2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-2-fluoro-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-(2,2-Dimethyl-propoxy)-5-ethanesulfonyl-benzoic acid compound 3.3)	474.5

293	[2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(2,2,2-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-benzoic acid (compound 3.3)	499.4
294	[2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 1.1) and 2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-benzoic acid (compound 3.3)	517.5
295	[2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 5.1) and 2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-benzoic acid (compound 3.3)	517.5
296	[2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-benzoic acid (compound 3.3)	527.3
297	rac-1-(3-Fluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone	1-(3-Fluoro-4-piperazin-1-phenyl)-ethanone (WO9714690) and rac-5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	517.5

298	rac-4-{4-[5-methanesulfonyl-2-(2,2,2-fluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	4-Piperazin-1-yl-benzonitrile (commercial) and rac-5-methanesulfonyl-2-(2,2,2-fluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	482.5
299	rac-3-Fluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-fluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	500.4
300	rac-2-Fluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-fluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	500.4
301	rac-5-Methanesulfonyl-2-(2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-fluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and rac-5-methanesulfonyl-2-(2,2,2-fluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	525.3
302	rac-[4-(2-Fluoro-4-fluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-fluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(2-Fluoro-4-fluoromethyl-phenyl)-piperazine (compound 1.1) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	543.5

303	rac-[4-(3-Fluoro-4-fluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(3-Fluoro-4-fluoromethyl-phenyl)-piperazine (compound 5.1) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	543.5
304	rac-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-fluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	553.0
305	4-{4-[5-Methanesulfonyl-2-methoxy-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	4-Piperazin-1-yl-benzonitrile (commercial) and 5-Methanesulfonyl-2-(2-methoxy-ethoxy)-benzoic acid (compound 1.10)	444.3
306	3-Fluoro-4-{4-[5-methanesulfonyl-2-methoxy-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Methanesulfonyl-2-(2-methoxy-ethoxy)-benzoic acid (compound 1.10)	462.5
307	2-Fluoro-4-{4-[5-methanesulfonyl-2-methoxy-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 5-Methanesulfonyl-2-(2-methoxy-ethoxy)-benzoic acid (compound 1.10)	462.5

308	[4-(2-Fluoro-4-fluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2-methoxy-ethoxy)-phenyl]-methanone	1-(2-Fluoro-4-fluoromethyl-phenyl)-piperazine (compound 1.1) and 5-Methanesulfonyl-2-(2-methoxy-ethoxy)-benzoic acid (compound 1.10)	505.5
309	[4-(3-Fluoro-4-fluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2-methoxy-ethoxy)-phenyl]-methanone	1-(3-Fluoro-4-fluoromethyl-phenyl)-piperazine (compound 5.1) and 5-Methanesulfonyl-2-(2-methoxy-ethoxy)-benzoic acid (compound 1.10)	505.5
310	[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2-methoxy-ethoxy)-phenyl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-(2-methoxy-ethoxy)-benzoic acid (compound 1.10)	515.5
311	1-{4-[4-(2-Cyclobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluorophenyl}-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 2-(2-cyclobutoxy-5-methanesulfonyl-benzoic acid (compound 3.4)	475.4
312	4-[4-(2-Cyclobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	4-Piperazin-1-yl-benzonitrile (commercial) and 2-(2-cyclobutoxy-5-methanesulfonyl-benzoic acid (compound 3.4)	440.5

313	4-[4-(2-Cyclobutoxy-5-ethanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluorobenzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and Cyclobutoxy-5-ethanesulfonyl-benzoic acid compound 3.4)	458.5
314	4-[4-(2-Cyclobutoxy-5-ethanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluorobenzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-Cyclobutoxy-5-ethanesulfonyl-benzoic acid compound 3.4)	458.5
315	(2-Cyclobutoxy-5-ethanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 2-Cyclobutoxy-5-ethanesulfonyl-benzoic acid compound 3.4)	483.5
316	(2-Cyclobutoxy-5-ethanesulfonyl-phenyl)-[4-(2-fluoro-4-fluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-fluoromethyl-phenyl)-piperazine (compound 1.1) and 2-Cyclobutoxy-5-ethanesulfonyl-benzoic acid compound 3.4)	501.5
317	(2-Cyclobutoxy-5-ethanesulfonyl-phenyl)-[4-(3-fluoro-4-fluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(3-Fluoro-4-fluoromethyl-phenyl)-piperazine (compound 5.1) and Cyclobutoxy-5-ethanesulfonyl-benzoic acid compound 3.4)	501.5
318	(2-Cyclobutoxy-5-ethanesulfonyl-phenyl)-[4-(2-fluoro-4-fluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-fluoromethyl-phenyl)-piperazine (commercial) and Cyclobutoxy-5-ethanesulfonyl-benzoic acid compound 3.4)	511.5

319	rac-1-{4-[4-(2-sec-butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluorophenyl}-ethanone	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and rac-2-sec-butoxy-5-methanesulfonyl-benzonitrile acid (compound 3.5)	477.4
320	rac-4-[4-(2-sec-Butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	4-Piperazin-1-yl-benzonitrile (commercial) and rac-2-sec-butoxy-5-methanesulfonyl-benzonitrile acid (compound 3.5)	442.5
321	rac-4-[4-(2-sec-Butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluorobenzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and rac-2-sec-Butoxy-5-methanesulfonyl-benzonitrile acid (compound 3.5)	460.5
322	rac-4-[4-(2-sec-Butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluorobenzonitrile	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and rac-2-sec-Butoxy-5-methanesulfonyl-benzonitrile acid (compound 3.5)	460.5
323	rac-(2-sec-Butoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and rac-2-sec-Butoxy-5-methanesulfonyl-benzonitrile acid (compound 3.5)	485.5
324	rac-(2-sec-Butoxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-fluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-fluoromethyl-phenyl)-piperazine (compound 1.1) and rac-2-sec-Butoxy-5-methanesulfonyl-benzonitrile acid (compound 3.5)	503.3

325	rac-(2-sec-Butoxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-fluoromethyl-phenyl)-piperazin-1-yl]-ethanone	1-(3-Fluoro-4-fluoromethyl-phenyl)-piperazine (compound 5.1) and 2-sec-Butoxy-5-methanesulfonyl-benzic acid (compound 3.5)	503.3
326	rac-(2-sec-Butoxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-ethanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-sec-Butoxy-5-methanesulfonyl-benzic acid (compound 3.5)	513.5

Example 4.1

Preparation of 6-Ethoxy-2-fluoro-3-methanesulfonyl-benzoic acid

(a) 3-Chlorosulfonyl-2,6-difluoro-benzoic acid

95 mmol of 2,6-difluorobenzoic acid in 19 ml of chlorosulfonic acid was stirred for 2 h at 150°. The mixture was poured into 200 ml of ice and stirred for 20 min. The resulting slurry was filtered, washed with water and dried (20° overnight in the dessicator) to yield the title compound as a colorless solid. MS (m/e): 279.4 (MNa⁺, 81%)

(b) 2,6-Difluoro-3-sulfinic-benzoic acid

41 mmol of 3-chlorosulfonyl-2,6-difluoro-benzoic acid was slowly added over 20 min. to a solution of 310 mmol sodium sulfite in 200 ml of water. The resulting mixture was stirred for one hour at room temperature, cooled to 0° C and acidified with 20% aqueous sulfuric acid. The sulfinic acid was extracted with ethyl acetate, dried over MgSO₄ and concentrated to yield the title compound as a colorless solid. MS (m/e): 220.9 (M-H, 100%)

(c) 6-Ethoxy-2-fluoro-3-methanesulfonyl-benzoic acid

A mixture of 27 mmol 2,6-difluoro-3-sulfinic-benzoic acid and 9 mmol Na₂CO₃ in 110 ml methanol was treated with 72 mmol of methyl iodide. The resulting mixture was stirred overnight at 60°, concentrated and the dark residue dissolved in 100 ml of ethanol. 100 ml of 2 molar aqueous NaOH is added and the mixture was refluxed for 2 hours. Concentration to about 100 ml precipitated a yellowish solid which was filtered and

trituated with diethyl ether to give the crude title compound, which was used without further purification.

Example 4.2

Preparation of 1-(4-Trifluoromethanesulfonyl-phenyl)-piperazine

- 5 A mixture of 1 mmol 1-Bromo-4-trifluoromethanesulfonyl-benzene [Nodiff et al., J.Org.Chem. 25, 60 (1960)], 3 mmol of piperazine and 2 mmol of potassium carbonate in 5 ml of acetonitrile was refluxed for 2 hours. The resulting mixture was poured into water, extracted with ethyl acetate, dried, concentrated and purified by column chromatography (SiO₂; Et₂O / cyclohexane) to yield the title compound as a colorless
10 solid. MS (m/e): 295.2 (MH⁺, 100%)

Example 4.3

Preparation of 1-(2,4-Bis-trifluoromethyl-phenyl)-piperazine hydrochloride

(a) 4-(2,4-Bis-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

- A mixture of 5 mmol 2,4-bis(trifluoromethyl)bromobenzene, 6 mmol N-BOC-
15 piperazine, 8 mmol NaOtBu, 0.5 mmol rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and 1 mmol tris-(dibenzylideneacetone)dipalladium chloroform complex in 20 ml toluene was stirred at 80° C for 3 hours. The mixture was then diluted with water, extracted with ethyl acetate, dried and purified by column chromatography (SiO₂; cyclohexane / ethyl acetate 9:1) to yield the title compound as a yellowish oil.
20 MS (m/e): 399.1 (MH⁺, 100%)

(b) 1-(2,4-Bis-trifluoromethyl-phenyl)-piperazine hydrochloride

- 3 mmol of 4-(2,4-Bis-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester was stirred in 10 ml of 1,4-dioxane saturated with gaseous HCl. After 4 h at room temperature, the reaction mixture was evaporated to dryness to yield the title compound
25 as a colorless solid. MS (m/e): 299.3 (MH⁺, 100%)

Example 4.4

Preparation of 1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-piperazine hydrochloride

(a) 4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester

A well stirred mixture of 0.015 mmol of bis(tri-*t*-butylphosphine)palladium, 0.01 mmol of cetyltrimethylammonium bromide, 2 mmol of powdered potassium hydroxide, 2 mmol of 3-(4-bromo-phenyl)-5-methyl-[1,2,4]oxadiazole and 2.1 mmol of N-BOC-piperazine in 1 ml of toluene was heated under Ar to 90° C for 17 hours. The resulting reaction mixture was diluted with water, extracted with ethyl acetate and the product purified by column chromatography (SiO₂; cyclohexane / ethyl acetate 7:3) to yield the title compound as a yellowish solid. MS (m/e): 345.3 (MH⁺, 100%)

(b) 1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-piperazine hydrochloride

1 mmol of 4-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester was stirred in 3 ml of 1,4-dioxane saturated with gaseous HCl. After 2 h at room temperature, the reaction mixture was evaporated to dryness to yield the title compound as a colorless solid. MS (m/e): 245.1 (MH⁺, 100%)

Example 4.5

Preparation of 1-(4-Oxazol-2-yl-phenyl)-piperazine hydrochloride

(a) 4-Bromo-N-(2,2-dimethoxy-ethyl)-benzamide

A solution of 24 mmol aminoacetaldehyde dimethylacetal was dissolved in 30 ml of water and treated with 25 mmol of potassium hydrogencarbonate. A solution of 23 mmol of 4-bromobenzoyl chloride in 50 ml of acetone was slowly added under stirring over a period of 30 min. The acetone was evaporated and the aqueous phase extracted 3 times with ethyl acetate to yield the crude title compound as a slightly brown solid.

MS (m/e): 287.1 (M-H, 43%)

(b) 2-(4-Bromo-phenyl)-oxazole

A solution of 21 mmol of phosphorous pentoxide in 20 ml of methanesulfonic acid was treated with 7 mmol of 4-Bromo-N-(2,2-dimethoxy-ethyl)-benzamide. The reaction mixture was heated for 5 hours at 130°, cooled to room temperature and poured into ice-water. The resulting solid was filtered off and dried to yield the crude title compound as a brownish solid. MS (m/e): 224.0 (MH⁺, 24%)

(c) 4-(4-Oxazol-2-yl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

Prepared in analogy to example 4.4 (a) from 2-(4-Bromo-phenyl)-oxazole and N-BOC-piperazine. MS (m/e): 330.3 (MH⁺, 100%)

(d) 1-(4-Oxazol-2-yl-phenyl)-piperazine hydrochloride

Prepared in analogy to example 4.4 (b) from 4-(4-Oxazol-2-yl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester and hydrochloric acid in dioxane. MS (m/e): 230.1 (MH⁺, 100%)

5

Example 4.6

Preparation of 1-[4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-piperazine hydrochloride

(a) 2-(4-Bromo-phenyl)-[1,3,4]oxadiazole

12.3 mmol of 4-bromo-benzoic acid hydrazide were dissolved in 26 ml of triethyl orthoformate. The reaction mixture was stirred overnight at 140°, evaporated and the
10 residue crystallized from ethanol to give the title compound as a colorless solid. MS (m/e): 225.0 (MH⁺, 100%)

(b) 4-(4-[1,3,4]Oxadiazol-2-yl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

Prepared in analogy to example 4.4 (a) from 2-(4-Bromo-phenyl)-[1,3,4]oxadiazole and N-BOC-piperazine.

15 MS (m/e): 342.2 (MH⁺, 100%)

(c) 1-[4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-piperazine hydrochloride

Prepared in analogy to example 4.4 (b) from 4-(4-[1,3,4]Oxadiazol-2-yl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester and hydrochloric acid in dioxane. MS (m/e): 245.3 (MH⁺, 100%)

20

Example 4.7

Preparation of 1-[4-(2-Methyl-2H-tetrazol-5-yl)-phenyl]-piperazine hydrochloride

(a) 5-(4-Bromo-phenyl)-2-methyl-2H-tetrazole

A mixture of 3.5 mmol of 5-(4-bromo-phenyl)-2H-tetrazole, 0.2 mmol of tetrabutyl ammonium bromide, 4.4 mmol of methyl iodide, 6 ml of 1M aqueous sodium hydroxide
25 and 6 ml of dichloromethane were stirred at room temperature for 24 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was dried, evaporated and the product purified by column chromatography (SiO₂; cyclohexane / ethyl acetate 7:3). MS (m/e): 239.1 (MH⁺, 29%)

(b) 4-[4-(2-Methyl-2H-tetrazol-5-yl)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester

Prepared in analogy to example 4.4 (a) from 5-(4-Bromo-phenyl)-2-methyl-2H-tetrazole and N-BOC-piperazine. MS (m/e): 345.1 (MH⁺, 41%)

5 (c) 1-[4-(2-Methyl-2H-tetrazol-5-yl)-phenyl]-piperazine hydrochloride

Prepared in analogy to example 4.4 (b) from 4-[4-(2-Methyl-2H-tetrazol-5-yl)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester and hydrochloric acid in dioxane. MS (m/e): 245.1 (MH⁺, 100%)

Example 4.8

10 Preparation of 3,4,5,6-Tetrahydro-2H-[1,2']bipyrazinyl-5'-carboxylic acid methyl ester hydrochloride

(a) 2,3,5,6-Tetrahydro-[1,2']bipyrazinyl-4,5'-dicarboxylic acid 4-tert-butyl ester 5'-methyl ester

15 A mixture of 17 mmol methyl-5-chloropyrazine-2-carboxylate, 18 mmol of N-BOC-piperazine and 20 mmol of K₂CO₃ in 20 ml of acetonitrile was heated under reflux for 3 hours. The reaction mixture was concentrated, diluted with water and extracted with ethyl acetate. The title compound was recrystallized from ethyl acetate to yield a colorless solid. MS (m/e): 323.4 (MH⁺, 100%)

20 (b) 3,4,5,6-Tetrahydro-2H-[1,2']bipyrazinyl-5'-carboxylic acid methyl ester hydrochloride

Prepared in analogy to example 4.4 (b) from 2,3,5,6-Tetrahydro-[1,2']bipyrazinyl-4,5'-dicarboxylic acid 4-tert-butyl ester 5'-methyl ester and 1,4-dioxane saturated with gaseous HCl. MS (m/e): 223.1 (MH⁺, 100%)

Example 4.9

25 Preparation of 6'-Chloro-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl trifluoroacetate

(a) 6'-Chloro-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-carboxylic acid tert-butyl ester

A mixture of 10 mmol 2,6-dichloropyrazine and 21 mmol of N-BOC-piperazine in 15 ml acetonitrile was heated under reflux for 1.5 hours. The reaction mixture was concentrated and purified by chromatography (SiO₂; dichloromethane / methanol 95:5) to yield the title compound as a colorless solid. MS (m/e): 299.2 (MH⁺, 100%)

30

(b) 6'-Chloro-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl trifluoroacetate

A solution of 2 mmol 6'-Chloro-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-carboxylic acid tert-butyl ester in 10 ml of dichloromethane was treated with 3 mmol of trifluoroacetic acid and stirred at room temperature for 17 hours. Concentration and crystallisation
5 from diethylether yielded the title compound as a colorless solid.

MS (m/e): 198.0 (M^+ , 100%)

Example 4.10

Preparation of 3,4,5,6-Tetrahydro-2H-[1,2']bipyrazinyl-5'-carboxylic acid amide hydrochloride

10 (a) 5'-Carbamoyl-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-carboxylic acid tert-butyl ester

3 mmol of 2,3,5,6-Tetrahydro-[1,2']bipyrazinyl-4,5'-dicarboxylic acid 4-tert-butyl ester 5'-methyl ester (example 1.13 (a)) was dissolved in a 7 molar solution of gaseous ammonia in methanol. The reaction vessel was tightly closed and heated overnight at 60° C. Cooling of the reaction mixtures led to crystallisation of the title compound. MS
15 (m/e): 308.4 (MH^+ , 100%)

(b) 3,4,5,6-Tetrahydro-2H-[1,2']bipyrazinyl-5'-carboxylic acid amide hydrochloride

0.25 mmol of 5'-Carbamoyl-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-carboxylic acid tert-butyl ester was stirred for 1 hour in 1 ml of dioxane saturated with gaseous HCl. Concentration of the reaction mixture led to the title compound, as a colorless solid. MS
20 (m/e): 208.3 (MH^+ , 100%)

Example 4.11

Preparation of Dimethyl-(4-piperazin-1-yl-[1,3,5]triazin-2-yl)-amine

(a) 4-(4-Chloro-[1,3,5]triazin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

A solution of 11 mmol of 2,4-dichlorotriazine (WO 02/083654) in 20ml of acetonitrile
25 was chilled and treated with 11 mmol of triethylamine and 11 mmol of N-BOC-piperazine. The reaction mixture was stirred for 2 hours at 0° C then for 2 hours at room temperature. Addition of 100ml brine and extraction with ethyl acetate yielded the crude product which was purified through trituration in ethyl acetate. MS (m/e): 300.3 (MH^+ , 100%)

(b) 4-(4-Dimethylamino-[1,3,5]triazin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

A solution of 2 mmol of 4-(4-Chloro-[1,3,5]triazin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in 15 ml of 2M dimethylamine in methanol was stirred at room temperature for 1 hour. Concentration and purification by chromatography (SiO₂; ethyl acetate / cyclohexane 1:1) yielded the title compound as a colorless solid. MS (m/e): 309.1 (MH⁺, 100%)

(c) Dimethyl-(4-piperazin-1-yl-[1,3,5]triazin-2-yl)-amine

A solution of 1 mmol of 4-(4-Dimethylamino-[1,3,5]triazin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in 10 ml dichloromethane was chilled and treated with 14 mmol of trifluoroacetic acid. The reaction mixture was heated to 40° C for 30 min. After cooling, 50ml of 2M aqueous sodium hydroxide is added. The organic layer was separated, dried and concentrated to yield the title compound as a yellowish oil. MS (m/e): 267.0 (M+CH₃COO⁺, 100%)

Example 4.12

15 Preparation of 6'-Methoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl

(a) 6'-Methoxy-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-carboxylic acid tert-butyl ester

1 mmol of 6'-Chloro-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-carboxylic acid tert-butyl ester [example 4.9 (a)] was dissolved in a solution of sodium methanolate (prepared by dissolving 1 mmol of sodium in 10 ml of methanol). The mixture was heated overnight to 70°, concentrated and the product purified by chromatography (SiO₂; dichloromethane / methanol 99:1) to yield the title compound as a colorless foam. MS (m/e): 295.3 (MH⁺, 100%)

(b) 6'-Methoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl

Prepared in analogy to example 4.10 (c) from 6'-Methoxy-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-carboxylic acid tert-butyl ester and trifluoroacetic acid. MS (m/e): 195.1 (MH⁺, 80%)

Example 4.13

Preparation of 2-Methoxy-4-piperazin-1-yl-[1,3,5]triazine

(a) 4-(4-Methoxy-[1,3,5]triazin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

1 mmol of 4-(4-Chloro-[1,3,5]triazin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester [example 4.11 a)] was dissolved in a solution of sodium methanolate (prepared by dissolving 1 mmol of sodium in 5 ml of methanol). The mixture was stirred at room temperature for 1 hour, concentrated and the title compound purified by
5 recrystallisation from ethyl acetate / cyclohexane. MS (m/e): 296.3 (MH^+ , 100%)

(b) 2-Methoxy-4-piperazin-1-yl-[1,3,5]triazine

Prepared in analogy to example 4.10 (c) from 4-(4-Methoxy-[1,3,5]triazin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester and trifluoroacetic acid. MS (m/e): 196.4 (MH^+ , 100%)

10

Example 4.14

Preparation of 2-Dimethylcarbamoyloxy-5-methanesulfonyl-benzoic acid

(a) 2-Hydroxy-5-methanesulfonyl-benzoic acid benzyl ester

5 mmol of N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimid-hydrochloride was slowly added to a stirred suspension of 5 mmol 2-hydroxy-5-methanesulfonyl-benzoic acid, 5
15 mmol of benzyl alcohol and 0.5 mmol of 4-dimethylaminopyridine in 10 ml acetonitrile. The mixture was stirred overnight at room temperature, concentrated and treated with 10 ml of water. A few drops of diluted hydrochloric acid were added to acidify the solution. The resulting solid was filtered and the purified by chromatography (SiO_2 ; ethyl acetate / cyclohexane 3:7) to yield the title compound as a colorless solid. MS (m/e):
20 305.0 (M-H, 100%)

(b) 2-Dimethylcarbamoyloxy-5-methanesulfonyl-benzoic acid benzyl ester

A mixture of 1 mmol 2-hydroxy-5-methanesulfonyl-benzoic acid benzyl ester, 1.5 mmol of N-methylmorpholine and 0.2 mmol of 4-dimethylaminopyridine in 4 ml of dimethylformamide was treated with 1.3 mmol of N,N-dimethyl-carbamoylchloride. The
25 reaction mixture was stirred at 60° for 48 hours, concentrated in vacuo and the residue taken up in 5 ml of water. Acidification with diluted hydrochloric acid and extraction with ethyl acetate yielded a crude product which was purified by chromatography (SiO_2 ; ethyl acetate / cyclohexane 1.1). MS (m/e): 378.3 (MH^+ , 100%)

(c) 2-Dimethylcarbamoyloxy-5-methanesulfonyl-benzoic acid

1 mmol of 2-dimethylcarbamoyloxy-5-methanesulfonyl-benzoic acid benzyl ester was dissolved in 5 ml of methanol. 25 mg of palladium 10% on charcoal was added and the reaction mixture hydrogenated at room temperature to yield the title compound as a slightly yellowish solid. MS (m/e): 288.0 (MH^+ , 66%)

- 5 In analogy to Example 5 compounds 327 to 355 of the following table were prepared from the acid derivatives and piperazine derivatives:

Expl.- No.	Systematic Name	Starting materials	MW found (MH^+)
327	(6-Ethoxy-2-fluoro-3-methanesulfonyl-phenyl)-[4-(4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Methanesulfonyl-phenyl)-piperazine (commercial) and 6-Ethoxy-2-fluoro-3-methanesulfonyl-benzoic acid (compound 4.1)	485.4
328	(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethanesulfonyl-phenyl)-piperazine (compound 4.2) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	552.0 ($M+NH_4^+$)
329	(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethanesulfonyl-phenyl)-piperazine (compound 4.2) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	578.0 ($M+NH_4^+$)

330	(2-Isobutoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethanesulfonyl-phenyl)-piperazine (compound 4.2) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	566.1 (M+NH ₄ ⁺)
331	[4-(2,4-Bis-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(2,4-Bis-trifluoromethyl-phenyl)-piperazine hydrochloride (compound 4.3) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	539.2
332	[4-(2,4-Bis-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-methanone	1-(2,4-Bis-trifluoromethyl-phenyl)-piperazine hydrochloride (compound 4.3) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	565.3
333	[4-(2,4-Bis-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone	1-(2,4-Bis-trifluoromethyl-phenyl)-piperazine hydrochloride (compound 4.3) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	553.2
334	(2-Isobutoxy-5-methanesulfonyl-phenyl)-{4-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-piperazin-1-yl}-methanone	1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-piperazine hydrochloride (compound 4.4) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	499.1

335	(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-{4-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-piperazin-1-yl}-methanone	1-[4-(5-Methyl-[1,2,4]oxadiazol-3-yl)-phenyl]-piperazine hydrochloride (compound 4.4) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	511.4
336	(2-Isobutoxy-5-methanesulfonyl-phenyl)-[4-(4-oxazol-2-yl-phenyl)-piperazin-1-yl]-methanone	1-(4-Oxazol-2-yl-phenyl)-piperazine; hydrochloride (compound 4.5) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	484.4
337	(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-oxazol-2-yl-phenyl)-piperazin-1-yl]-methanone	1-(4-Oxazol-2-yl-phenyl)-piperazine; hydrochloride (compound 4.5) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	496.4
338	(2-Isopropoxy-5-methanesulfonyl-phenyl)-{4-[4-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-piperazin-1-yl}-methanone	1-[4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-piperazine hydrochloride (compound 4.6) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	485.3
339	(2-Isobutoxy-5-methanesulfonyl-phenyl)-{4-[4-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-piperazin-1-yl}-methanone	1-[4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-piperazine hydrochloride (compound 4.6) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	499.2

340	(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-{4-[4-(5-methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-piperazin-1-yl}-methanone	1-[4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-phenyl]-piperazine hydrochloride (compound 4.6) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	511.3
341	(2-Isobutoxy-5-methanesulfonyl-phenyl)-{4-[4-(2-methyl-2H-tetrazol-5-yl)-phenyl]-piperazin-1-yl}-methanone	1-[4-(2-Methyl-2H-tetrazol-5-yl)-phenyl]-piperazine; hydrochloride (compound 4.7) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	499.1
342	4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-5'-carboxylic acid methyl ester	3,4,5,6-Tetrahydro-2H-[1,2']bipyrazinyl-5'-carboxylic acid methyl ester; hydrochloride (compound 4.8) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	463.4
343	4-(2-Isobutoxy-5-methanesulfonyl-benzoyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-5'-carboxylic acid methyl ester	3,4,5,6-Tetrahydro-2H-[1,2']bipyrazinyl-5'-carboxylic acid methyl ester; hydrochloride (compound 4.8) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	477.1

344	(6'-Chloro-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	6'-Chloro-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl; trifluoroacetic acid (compound 4.9) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	439.1
345	4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-5'-carboxylic acid amide	3,4,5,6-Tetrahydro-2H-[1,2']bipyrazinyl-5'-carboxylic acid amide; hydrochloride (compound 4.10) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	448.3
346	4-(2-Isobutoxy-5-methanesulfonyl-benzoyl)-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl-5'-carboxylic acid amide	3,4,5,6-Tetrahydro-2H-[1,2']bipyrazinyl-5'-carboxylic acid amide; hydrochloride (compound 4.10) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	462.3
347	[4-(4-Dimethylamino-[1,3,5]triazin-2-yl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone	Dimethyl-(4-piperazin-1-yl-[1,3,5]triazin-2-yl)-amine (compound 4.11) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	463.3
348	[4-(4-Dimethylamino-[1,3,5]triazin-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	Dimethyl-(4-piperazin-1-yl-[1,3,5]triazin-2-yl)-amine (compound 4.11) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	449.3

349	(2-Isopropoxy-5-methanesulfonyl-phenyl)-(6'-methoxy-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-methanone	6'-Methoxy-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl; trifluoro-acetic acid (compound 4.12) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	435.2
350	(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-methoxy-[1,3,5]triazin-2-yl)-piperazin-1-yl]-methanone	2-Methoxy-4-piperazin-1-yl-[1,3,5]triazine (compound 4.13) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	436.4
351	Dimethyl-carbamic acid 4-methanesulfonyl-2-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-phenyl ester	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 2-Dimethylcarbamoyloxy-5-methanesulfonyl-benzoic acid (compound 4.14)	500.4
352	Dimethyl-carbamic acid 2-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-methanesulfonyl-phenyl ester	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-Dimethylcarbamoyloxy-5-methanesulfonyl-benzoic acid (compound 4.14)	528.3
353	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-(4-phenyl-piperazin-1-yl)-methanone	1-Phenyl-piperazine (commercial) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	415.5

354	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(4-methoxy-phenyl)-piperazin-1-yl]-methanone	1-(4-Methoxy-phenyl)-piperazine (commercial) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	445.3
355	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(4-hydroxy-phenyl)-piperazin-1-yl]-methanone	4-Piperazin-1-yl-phenol (commercial) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	431.4

Example 356

Preparation of 1-{3-Fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone oxime

- 5 0.12 mmol of 1-{3-Fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone was dissolved in 1 ml of a 1:1 mixture of ethanol and water. 0.8 mmol of hydroxylamine hydrochloride was added, followed by 8.4 mmol of sodium acetate. The resulting mixture was stirred overnight at room temperature, diluted with water, filtered, washed and dried to yield the title compound as a colorless solid.
- 10 MS (m/e): 478.2 (MH⁺, 100%)

Example 357

Preparation of 1-{3-Fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone O-methyl-oxime

- 0.12 mmol of 1-{3-Fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone was dissolved in 1 ml of a 1:1 mixture of ethanol and water. 0.8 mmol of O-methyl-hydroxylamine hydrochloride was added, followed by 8.4 mmol of sodium acetate. The slurry was stirred overnight at room temperature, diluted with water, extracted with ethyl acetate, dried and concentrated. The resulting gum was
- 15

trituated with diethyl ether / heptane to yield the title compound as a colorless solid. MS (m/e): 492.3 (MH⁺, 100%)

Example 4.15

Preparation of (2,6-Difluoro-3-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone

5

(a) 3-Chlorosulfonyl-2,6-difluoro-benzoic acid

77 mmol of 2,6-difluorobenzoic acid were dissolved in 15.5 ml of chlorosulfonic acid and stirred for 2 h at 150° C. The reaction mixture was cooled to room temperature and poured into 100 ml of ice / water. The solid was filtered and dried to yield the title
10 compound as a colorless solid. MS (m/e): 255.1 (M-H, 44%)

(b) 2,6-Difluoro-3-sulfinobenzoic acid

240 mmol of sodium sulfite were dissolved in 150 ml of water. 32 mmol of 3-Chlorosulfonyl-2,6-difluoro-benzoic acid was added under stirring over a period of about 20 min. After stirring for an additional hour at room temperature, the mixture was
15 chilled and acidified with 20% aqueous sulfuric acid. The product was extracted with ethyl acetate to yield the title compound as a colorless solid. MS (m/e): 221.3 (M-H, 34%)

(c) 2,6-Difluoro-3-methanesulfonylbenzoic acid

A suspension of 18 mmol sodium carbonate and 9 mmol 2,6-Difluoro-3-sulfinobenzoic acid in 30 ml of methanol was stirred at room temperature for 30 min, then heated to 60°
20 C. 24 mmol of methyl iodide were added and the reaction mixture heated overnight at 60° C. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was discarded and the aqueous phase acidified by addition of concentrated hydrochloric acid. Extraction with ethyl acetate yielded the title compound as a slightly
25 brownish solid. MS (m/e): 235.1 (M-H, 16%)

(d) (2,6-Difluoro-3-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone

This compound was prepared in analogy to example 5 from 1-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine and 2,6-difluoro-3-methanesulfonylbenzoic acid.
30 MS (m/e): 477.0 (MH⁺, 67%)

Example 4.16**Preparation of 4-[4-(2,6-Difluoro-3-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile**

Prepared in analogy to example 5 from 4-piperazin-1-yl-benzonitrile and 2,6-difluoro-3-methanesulfonyl-benzoic acid. MS (m/e): 406.3 (MH⁺, 84%)

Example 358**Preparation of (2-Cyclopentyloxy-6-ethoxy-3-methanesulfonyl-phenyl)-[4-(4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone**

0.12 mmol of (6-Ethoxy-2-fluoro-3-methanesulfonyl-phenyl)-[4-(4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone (example 55) was added to a solution of sodium cyclopentanolate (prepared from 1 mmol sodium dissolved in 1 ml of cyclopentanol). The mixture was heated for 1 hour at 80° C, poured on ice / water and extracted with ethyl acetate. Chromatography (SiO₂; ethyl acetate) yielded the title compound as a slightly yellow solid. MS (m/e): 551.1 (MH⁺, 29%)

Example 359**Preparation of (2, 6-diisopropoxy-3-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone**

0.27 mmol of 2,6-difluoro-3-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone (example 4.15) was added to a solution of sodium isopropanolate (prepared by dissolving 3 mmol of sodium in 2 ml of isopropanol). The reaction mixture was heated under reflux for 5 hours, cooled, diluted with water and extracted with ethyl acetate, yielding the title compound as a slightly yellow solid.

MS (m/e): 557.3 (MH⁺, 66%)

Example 360**Preparation of (2-Fluoro-6-isopropoxy-3-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone**

0.2 mmol of (2,6-difluoro-3-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone were dissolved in a solution of sodium isopropanolate (prepared by dissolving 0.2 mmol of sodium in 1 ml of isopropanol). The reaction mixture was heated to 50° C for 2 hours, then stirred at room temperature for 48 hours. The solution was diluted with water and extracted with ethyl acetate. The product

was purified by chromatography (SiO₂, ethyl acetate / cyclohexane 9:1) to yield the title compound as a colorless solid. MS (m/e): 517.1 (MH⁺, 100%)

Example 361

5 Preparation of (6-Cyclopentyloxy-2-fluoro-3-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone

The compound was prepared in analogy to example 358 from (2,6-difluoro-3-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone and sodium cyclopentanolate. MS (m/e): 560.5 (MNH₄⁺, 43%)

Example 362

10 Preparation of 4-[4-(2-Fluoro-6-isopropoxy-3-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile

The compound was prepared in analogy to example 359 from 4-[4-(2,6-difluoro-3-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile and sodium isopropanolate. MS (m/e): 446.0 (MH⁺, 49%)

15

Example 5.1

Preparation of 1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine

(a) 4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

A mixture of 4.9 mmol 4-chloro-2-fluorobenzotrifluoride, 5.9 mmol n-Boc-piperazine, 0.05 mmol palladium acetate, 6.9 mmol sodium-t-butoxide and 0.49 mmol 2-(di-t-butylphosphino)biphenyl in 10 ml toluene was heated for 16 h at 80 °C. After cooling to RT, the mixture was diluted with ether, the suspension was filtered over decalite and the filtrate evaporated. The residue was purified on silica eluting with a gradient of heptane / EtOAc to yield after evaporation the title compound.

(b) 1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine

25 A mixture of 2.87 mmol 4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester in 10 ml dichloromethane was treated with 14.4 mmol trifluoroacetic acid and refluxed for 3 h. The mixture was concentrated and treated with 10 ml water, NaOH and extracted with dichloromethane. The combined organic phases were dried with MgSO₄ and evaporated to yield the title compound 5.1. MS (m/e): 249.2 (MH⁺,
30 100%)

Example 5.2**Preparation of 2-Piperazin-1-yl-5-trifluoromethyl-benzonitrile**

The compound was prepared in analogy to compound 5.1 from 2-Chloro-5-trifluoromethyl-benzonitrile (DE2550262). MS (m/e): 256.0 (MH⁺, 100%)

5

Example 5.3**Preparation of 1-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazine**

The compound was prepared in analogy to compound 2.20 from 2,3,4-Trifluorobenzenesulfonyl chloride (commercial). MS (m/e): 277.2 (MH⁺, 100%)

Example 5.4

10

Preparation of 1-(2-Fluoro-4-methyl-phenyl)-piperazine

The compound was prepared in analogy to compound 1.1 from 4-bromo-3-fluorotoluene (commercial). MS (m/e): 195.3 (MH⁺, 100%)

Example 5.5**Preparation of 1-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine**

15 The compound was prepared in analogy to compound 2.7 from 2,3-Difluoro-5-trifluoromethyl-pyridine (EP0104715). MS (m/e): 250.2 (MH⁺, 100%)

Example 5.6**Preparation of 5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid****(a) rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid methyl ester**

20 A mixture of 21.7 mmol 2-Hydroxy-5-methanesulfonyl-benzoic acid methyl ester [68029-77-6], 32.5 mmol trifluoro-methanesulfonic acid 2,2,2-trifluoro-1-methyl-ethyl ester [212556-43-9], 43.4 mmol potassium carbonate in 87 ml DMF was stirred at 80 °C for 48 hours. After cooling to RT, the mixture was concentrated in vacuo, taken in water and stirred for 1 hour. Filtration yielded the title compound.

25 **(b) 5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid methyl ester**

The title compound was obtained by separation of rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid methyl ester by chiral HPLC (Chiralcel OD, 15 % ethanol/ Heptane, flow 35 ml, 220 nm, retention time: 86 min.).

(c) 5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid

The compound was prepared in analogy to compound 2.10(b) from 5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid methyl ester MS (m/e): 311.0 (M-H, 100%)

5

Example 5.7

Preparation of 5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid

(a) 5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid methyl ester

The title compound was obtained by separation of rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid methyl ester by chiral HPLC (Chiralcel OD, 15 % ethanol/ Heptane, flow 35 ml, 220 nm, retention time: 74 min.).

10

(c) 5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid

15

The compound was prepared in analogy to compound 2.10(b) from 5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid methyl ester MS (m/e): 311.0 (M-H, 100%)

Example 5.8

Preparation of 2-Chloro-4-piperazin-1-yl-benzonitrile

A mixture of 7.0 mmol 2-chloro-4-fluorobenzonitrile (commercial), 10.5 mmol piperazine in 4 ml N,N-dimethylacetamide was heated for 1 h at 85 °C. After cooling to RT and evaporation in vacuo, the mixture was diluted with dichloromethane and purified on silica eluting with a gradient of dichloromethane / MeOH to yield after evaporation the title compound. MS (m/e): 222.1 (MH⁺, 100%)

20

Example 5.9

Preparation of 1-(2-Fluoro-4-piperazin-1-yl-phenyl)-ethanone

The compound was prepared in analogy to compound 5.8 from 2,4-difluoroacetophenone (commercial). MS (m/e): 223.2 (M-H, 100%)

25

Example 5.10

Preparation of 1-(3-Fluoro-4-methanesulfonyl-phenyl)-piperazine

The compound was prepared in analogy to compound 2.20 from 2,4-difluorobenzenesulfonylchloride (commercial). MS (m/e): 259.1 (MH⁺, 100%)

Example 5.11

Preparation of 1-(4-Fluoro-2-piperazin-1-yl-phenyl)-ethanone

- 5 The compound was prepared in analogy to compound 5.8 from 2,4-difluoroacetophenone (commercial). MS (m/e): 223.2 (M-H, 100%)

Example 5.12

Preparation of 6-Isopropoxy-isophthalamic acid

- 10 The compound was prepared in analogy to compound 2.10 from 6-Hydroxy-isophthalamic acid methyl ester [89366-34-7]. MS (m/e): 222.1 (M-H, 100%)

Example 5.13

Preparation of 5-Ethanesulfonyl-2-isopropoxy-benzoic acid

(a) 5-Ethanesulfonyl-2-hydroxy-benzoic acid methyl ester

- 15 The compound was prepared in analogy to compound 2.20(b) from 2-Hydroxy-5-sulfinobenzoic acid [19479-88-0] and ethyliodide

(b) 5-Ethanesulfonyl-2-isopropoxy-benzoic acid

The compound was prepared in analogy to compound 2.10 from 5-Ethanesulfonyl-2-hydroxy-benzoic acid methyl ester. MS (m/e): 271.1 (M-H, 100%)

Example 5.14

- 20 Preparation of 1-(4-Difluoromethyl-2-fluoro-phenyl)-piperazine

(a) 1-Chloro-4-difluoromethyl-2-fluoro-benzene

- 24.7 mmol 4-Chloro-3-fluorobenzaldehyde was dissolved in DAST (5.1 ml) under nitrogen. The mixture was stirred at room temperature for 3 hours, at 50°C for 2 hours and then at room temperature for 65 hours. The solution was added dropwise to a saturated bicarbonate solution (150 ml) under cooling. The aqueous layer was extracted 3 times with ethyl acetate. The combined extracts were dried over Na₂SO₄, filtered and the solvent was removed in vacuo. The residue was purified on silica eluting with heptane to yield after evaporation the title compound.
- 25

(b) 1-(4-Difluoromethyl-2-fluoro-phenyl)-piperazine

The compound was prepared in analogy to compound 1.1 from 1-Chloro-4-difluoromethyl-2-fluoro-benzene. MS (m/e): 231.2 (M+H⁺, 100%)

Example 5.15

5 **Preparation of 1-(6-Trifluoromethyl-pyridin-3-yl)-piperazine**

The compound was prepared in analogy to compound 1.1 from 5-Bromo-2-trifluoromethyl-pyridine [436799-32-5]. MS (m/e): 232.1 (M+H⁺, 100%)

Example 5.16

Preparation of 3-Fluoro-4-piperazin-1-yl-benzoic acid ethyl ester

- 10 The compound was prepared in analogy to compound 5.8 from Ethyl-3,4-difluorobenzoate (commercial). MS (m/e): 253.2 (M+H⁺, 100%)

Example 5.17

Preparation of 1-(2-Trifluoromethyl-pyridin-4-yl)-piperazine

- 15 The compound can be prepared from 4-Nitro-2-trifluoromethyl-pyridine 1-oxide [147149-97-1] in analogy to the procedure used for the preparation of 4-Bromo-2-methyl-6-trifluoromethyl-pyridine [615579-78-1] (WO03087056). MS (m/e): 227 (M+H⁺, 100%)

Example 5.18

Preparation of 1-(6-Methyl-pyridin-3-yl)-piperazine

- 20 The compound was prepared in analogy to compound 1.1 from 5-Bromo-2-methyl-pyridine (commercial). MS (m/e): 178.1 (M+H⁺, 100%)

In analogy to Example 5 compounds 363 to 461 of the following table were prepared from the acid derivatives and piperazine derivatives:

Expl.- No.	Systematic Name	Starting materials	MW found (MH ⁺)
363	2-[4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile	2-Piperazin-1-yl-5-trifluoromethyl-benzonitrile (compound 5.2) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	496.3
364	4-[4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-trifluoromethyl-benzonitrile	4-Piperazin-1-yl-2-trifluoromethyl-benzonitrile (WO0017163) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	496.3
365	1-{4-[4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-trifluoromethyl-phenyl}-ethanone	1-(4-Piperazin-1-yl-2-trifluoromethyl-phenyl)-ethanone (WO0210277) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	513.4
366	2-Chloro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile	2-Chloro-4-piperazin-1-yl-benzonitrile (compound 5.8) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	462.3

367	1-{2-Fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-(2-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (compound 5.9) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	463.4
368	[4-(3-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(3-Fluoro-4-methanesulfonyl-phenyl)-piperazine (compound 5.10) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	499.3
369	1-{4-[4-(2-Cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-phenyl}-ethanone	1-(2-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (compound 5.9) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	475.4
370	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(3-Fluoro-4-methanesulfonyl-phenyl)-piperazine (compound 5.10) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	511.4
371	[4-(3-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone	1-(3-Fluoro-4-methanesulfonyl-phenyl)-piperazine (compound 5.10) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	513.4

372	1-{2-Fluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-(2-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (compound 5.9) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	477.3
373	2-[4-(2-Cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile	2-Piperazin-1-yl-5-trifluoromethyl-benzonitrile (compound 5.2) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	522.4
374	2-[4-(2-Cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile	2-Piperazin-1-yl-5-trifluoromethyl-benzonitrile (compound 5.2) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	508.6
375	2-[4-(2-Isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile	2-Piperazin-1-yl-5-trifluoromethyl-benzonitrile (compound 5.2) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	510.6
376	2-{4-[5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoyl]-piperazin-1-yl}-5-trifluoromethyl-benzonitrile	2-Piperazin-1-yl-5-trifluoromethyl-benzonitrile (compound 5.2) and 5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoic acid (compound 1.5)	536.5

377	rac-[4-(3-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(3-Fluoro-4-methanesulfonyl-phenyl)-piperazine (compound 5.10) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	553.2
378	rac-1-(2-Fluoro-4-[4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl]-phenyl)-ethanone	1-(2-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (compound 5.9) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	517.4
379	1-{4-Fluoro-2-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone	1-(4-Fluoro-2-piperazin-1-yl-phenyl)-ethanone (compound 5.11) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	463.4
380	3-[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-benzamide	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 1.1) and 6-Isopropoxy-isophthalamide (compound 5.12)	454.6
381	4-Isopropoxy-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 6-Isopropoxy-isophthalamide (compound 5.12)	436.4

382	3-[4-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-benzamide	1-(3-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 5.1) and 6-Isopropoxy-isophthalamic acid (compound 5.12)	454.6
383	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-benzamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 6-Isopropoxy-isophthalamic acid (compound 5.12)	464.4
384	3-[4-(2-Cyano-4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-benzamide	2-Piperazin-1-yl-5-trifluoromethyl-benzonitrile (compound 5.2) and 6-Isopropoxy-isophthalamic acid (compound 5.12)	461.4
385	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-benzamide	4-Piperazin-1-yl-benzonitrile (commercial) and 6-Isopropoxy-isophthalamic acid (compound 5.12)	393.2
386	3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-benzamide	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 6-Isopropoxy-isophthalamic acid (compound 5.12)	411.4
387	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-benzamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 6-Isopropoxy-isophthalamic acid (compound 5.12)	411.4
388	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-benzamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 6-Isopropoxy-isophthalamic acid (compound 5.12)	428.6

389	[4-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazine (compound 5.3) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	517.4
390	(5-Ethanesulfonyl-2-isopropoxy-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 5-Ethanesulfonyl-2-isopropoxy-benzoic acid (compound 5.13)	485.5
391	(5-Ethanesulfonyl-2-isopropoxy-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Ethanesulfonyl-2-isopropoxy-benzoic acid (compound 5.13)	513.4
392	4-[4-(5-Ethanesulfonyl-2-isopropoxy-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Ethanesulfonyl-2-isopropoxy-benzoic acid (compound 5.13)	460.5
393	(5-Ethanesulfonyl-2-isopropoxy-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 1.1) and 5-Ethanesulfonyl-2-isopropoxy-benzoic acid (compound 5.13)	503.3
394	[4-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(5-ethanesulfonyl-2-isopropoxy-phenyl)-methanone	1-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazine (compound 5.3) and 5-Ethanesulfonyl-2-isopropoxy-benzoic acid (compound 5.13)	531.3

395	(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(2,3-difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazine (compound 5.3) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	542.1
396	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(2,3-difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazine (compound 5.3) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	529.3
397	[4-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoroethoxy)-phenyl]-methanone	1-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazine (compound 5.3) and 5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoic acid (compound 1.5)	557.2
398	rac-[4-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazine (compound 5.3) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	571.3
399	[4-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-trifluoromethoxy-phenyl)-methanone	1-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazine (compound 5.3) and 5-Methanesulfonyl-2-trifluoromethoxy-benzoic acid (compound 2.15)	543.2

400	[4-(4-Difluoromethyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Difluoromethyl-2-fluoro-phenyl)-piperazine (compound 5.14) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	471.1
401	[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoroethoxy)-phenyl]-methanone	1-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazine (commercial) and 5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoic acid (compound 1.5)	546.3
402	[5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-phenyl]-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(5-Trifluoromethyl-pyridin-2-yl)-piperazine (commercial) and 5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoic acid (compound 1.5)	512.4
403	6-{4-[5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoyl]-piperazin-1-yl}-nicotinonitrile	6-Piperazin-1-yl-nicotinonitrile (commercial) and 5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoic acid (compound 1.5)	469.3
404	6-[4-(2-Cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-nicotinonitrile	6-Piperazin-1-yl-nicotinonitrile (commercial) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	441.4

405	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(5-Trifluoromethyl-pyridin-2-yl)-piperazine (commercial) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	484.5
406	[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone	1-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazine (commercial) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	518.3
407	rac-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazine (commercial) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	560.3
408	rac-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(5-Trifluoromethyl-pyridin-2-yl)-piperazine (commercial) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	526.2

409	rac-6-{4-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl}-nicotinonitrile	6-Piperazin-1-yl-nicotinonitrile (commercial) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	483.4
410	[4-(6-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone	1-(6-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazine (WO03097636) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	518.3
411	6-[4-(2-Cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-nicotinonitrile	6-Piperazin-1-yl-nicotinonitrile (commercial) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	455.5
412	(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(5-Trifluoromethyl-pyridin-2-yl)-piperazine (commercial) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	498.3
413	[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-methanone	1-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazine (commercial) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	532.3

414	[4-(6-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(6-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazine (WO03097636) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	506.3
415	(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(5-Trifluoromethyl-pyridin-2-yl)-piperazine (commercial) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	472.2
416	6-[4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-nicotinonitrile	6-Piperazin-1-yl-nicotinonitrile (commercial) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	429.5
417	[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazine, (commercial) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	506.3
418	rac-[4-(5-Chloro-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(5-Chloro-pyridin-2-yl)-piperazine (WO01062751) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	492.3

419	[4-(5-Chloro-pyridin-2-yl)-piperazin-1-yl]-(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-methanone	1-(5-Chloro-pyridin-2-yl)-piperazine (WO01062751) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	464.3
420	[4-(5-Chloro-pyridin-2-yl)-piperazin-1-yl]-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone	1-(5-Chloro-pyridin-2-yl)-piperazine (WO01062751) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	450.4
421	[4-(5-Chloro-pyridin-2-yl)-piperazin-1-yl]-(5-methanesulfonyl-2-(2,2,2-trifluoroethoxy)-phenyl)-methanone	1-(5-Chloro-pyridin-2-yl)-piperazine (WO01062751) and 5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoic acid (compound 1.5)	478.2
422	[4-(5-Chloro-pyridin-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(5-Chloro-pyridin-2-yl)-piperazine (WO01062751) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	438.3
423	Rac-[4-(6-Chloro-pyridazin-3-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	3-Chloro-6-piperazin-1-yl-pyridazine (WO02030405) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	493.3

424	[4-(6-Chloro-pyridazin-3-yl)-piperazin-1-yl]-(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-methanone	3-Chloro-6-piperazin-1-yl-pyridazine (WO02030405) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	465.4
425	(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(6-trifluoromethyl-pyridin-3-yl)-piperazin-1-yl]-methanone	1-(6-Trifluoromethyl-pyridin-3-yl)-piperazine (compound 5.15) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	472.2
426	[5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-phenyl]-[4-(6-trifluoromethyl-pyridin-3-yl)-piperazin-1-yl]-methanone	1-(6-Trifluoromethyl-pyridin-3-yl)-piperazine (compound 5.15) and 5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoic acid (compound 1.5)	512.4
427	rac-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(6-trifluoromethyl-pyridin-3-yl)-piperazin-1-yl]-methanone	1-(6-Trifluoromethyl-pyridin-3-yl)-piperazine (compound 5.15) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	526.2
428	3-Fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzoic acid ethyl ester	3-Fluoro-4-piperazin-1-yl-benzoic acid ethyl ester (compound 5.16) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	493.4

429	[4-(5-Bromo-pyridin-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(5-Bromo-pyridin-2-yl)-piperazine (WO 9534555) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	482.4
430	(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(6-trifluoromethyl-pyridin-3-yl)-piperazin-1-yl]-methanone	1-(6-Trifluoromethyl-pyridin-3-yl)-piperazine (compound 5.15) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	498.3
431	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(6-trifluoromethyl-pyridin-3-yl)-piperazin-1-yl]-methanone	1-(6-Trifluoromethyl-pyridin-3-yl)-piperazine (compound 5.15) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	484.5
432	[4-(5-Bromo-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoroethoxy)-phenyl]-methanone	1-(5-Bromo-pyridin-2-yl)-piperazine (WO 9534555) and 5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoic acid (compound 1.5)	522.2
433	[5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-phenyl]-[4-(2-trifluoromethyl-pyridin-4-yl)-piperazin-1-yl]-methanone	1-(2-Trifluoromethyl-pyridin-4-yl)-piperazine (compound 5.17) and 5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoic acid (compound 1.5)	512.4

434	(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(2-trifluoromethyl-pyridin-4-yl)-piperazin-1-yl]-methanone	1-(2-Trifluoromethyl-pyridin-4-yl)-piperazine (compound 5.17) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	472.2
435	rac-[4-(5-Bromo-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(5-Bromo-pyridin-2-yl)-piperazine (WO 9534555) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	536.3
436	[4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine (compound 5.5) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	530.3
437	[4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine (compound 5.5) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	490.4
438	rac-[4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine (compound 5.5) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	544.3

439	(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine (compound 5.5) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	516.4
440	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine (compound 5.5) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	502.3
441	rac-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(2-trifluoromethyl-pyridin-4-yl)-piperazin-1-yl]-methanone	1-(2-Trifluoromethyl-pyridin-4-yl)-piperazine (compound 5.17) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	526.2
442	[5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-[4-(6-methyl-pyridin-3-yl)-piperazin-1-yl]-methanone	1-(6-Methyl-pyridin-3-yl)-piperazine (compound 5.18) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	458.4
443	(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(6-methyl-pyridin-3-yl)-piperazin-1-yl]-methanone	1-(6-Methyl-pyridin-3-yl)-piperazine (compound 5.18) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	418.3

444	(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(6-methyl-pyridin-3-yl)-piperazin-1-yl]-methanone	1-(6-Methyl-pyridin-3-yl)-piperazine (compound 5.18) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	444.4
445	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(6-methyl-pyridin-3-yl)-piperazin-1-yl]-methanone	1-(6-Methyl-pyridin-3-yl)-piperazine (compound 5.18) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	430.5
446	[5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-phenyl]-[4-(5-methyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(5-Methyl-pyridin-2-yl)-piperazine (WO03032996) and 5-Methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoic acid (compound 1.5)	458.0
447	(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-methyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(5-Methyl-pyridin-2-yl)-piperazine (WO03032996) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	418.3
448	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(5-methyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(5-Methyl-pyridin-2-yl)-piperazine (WO03032996) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	430.5

449	rac-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-methyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(5-Methyl-pyridin-2-yl)-piperazine (WO03032996) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	472.3
450	rac-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(6-methyl-pyridin-3-yl)-piperazin-1-yl]-methanone	1-(6-Methyl-pyridin-3-yl)-piperazine (compound 5.18) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	472.2
451	[5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-[4-(4-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-pyridin-2-yl)-piperazine (WO02002529) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	512.4
452	(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-pyridin-2-yl)-piperazine (WO02002529) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	472.3
453	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-pyridin-2-yl)-piperazine (WO02002529) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	486.2

454	[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 5.6)	570.4 (M+NH ₄ ⁺)
455	rac-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-pyridin-2-yl)-piperazine (WO02002529) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	526.0
456	[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 5.7)	570.4 (M+NH ₄ ⁺)
457	(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(4-Trifluoromethyl-pyridin-2-yl)-piperazine (WO02002529) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	498.2
458	(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(6-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(6-Trifluoromethyl-pyridin-2-yl)-piperazine (EP 462638) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	472.1

459	rac-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(6-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(6-Trifluoromethyl-pyridin-2-yl)-piperazine (EP 462638) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	526.0
460	[5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-[4-(6-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	1-(6-Trifluoromethyl-pyridin-2-yl)-piperazine (EP 462638) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	512.2
461	3-Fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzaldehyde	1-(4-Difluoromethyl-2-fluorophenyl)-piperazine (compound 5.14) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	449.1

Example 462

Preparation of rac-{4-[2-Fluoro-4-(1-hydroxy-ethyl)-phenyl]-piperazin-1-yl}-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

- 5 0.086 mmol of 1-{3-Fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone was dissolved in 1 ml ethanol and 0.26 mmol sodium borohydride was added. The mixture was refluxed for 40 min., cooled to room temperature, quenched with water, acidified with HCl 1N and extracted with ethyl acetate. The combined extracts were dried over Na₂SO₄, filtered and the solvent was removed in vacuo. The residue was purified on silica eluting with heptane/ethylacetate to yield after evaporation the title compound. MS (m/e): 465.4 (M+H⁺, 100%)

Example 463

Preparation of {4-[2-Fluoro-4-(1-hydroxy-1-methyl-ethyl)-phenyl]-piperazin-1-yl}-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

To a solution of 0.173 mmol 1-{3-Fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone in tetrahydrofuran (2 ml) was added dropwise 0.190 mmol 1.6M Methyllithium solution in ether at -75°C . The mixture was stirred for 2 hours and then allowed to warm to 0°C . The mixture was quenched with a 20% NH_4Cl solution and extracted 3 times with ethyl acetate. The combined extracts were dried over Na_2SO_4 , filtered and the solvent was removed in vacuo. The residue was purified on silica eluting with dichloromethane/MeOH to yield after evaporation the title compound. MS (m/e): 479.5 ($\text{M}+\text{H}^+$, 100%)

The examples 464-471 have been prepared by separation of the racemic material by chiral HPLC:

Expl.- No.	Systematic Name	Starting materials	Separation Conditions	MW found (MH^+)
464	[5-Methanesulfonyl-2-((S or R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	rac-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone (example 408)	Chiralpak AD, 20 % Isopropanol/ Heptane, flow 35 ml, 254 nm, 170 min.	525.8 (M)
465	[5-Methanesulfonyl-2-((R or S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone	rac-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone (example 408)	Chiralpak AD, 20 % Isopropanol/ Heptane, flow 35 ml, 254 nm, 245 min.	525.3 (M)

466	[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-((S or R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	rac-[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone (example 302)	Chiralpak AD, 25 % Isopropanol/ Heptane, flow 35 ml, 220 nm, 141 min.	543.2
467	[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-((R or S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	rac-[4-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone (example 302)	Chiralpak AD, 25 % Isopropanol/ Heptane, flow 35 ml, 220 nm, 199 min.	543.2
468	[5-Methanesulfonyl-2-((S or R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (example 301)	Chiralpak AD, 25 % Isopropanol/ Heptane, flow 35 ml, 220 nm, 197 min.	525.2
469	[5-Methanesulfonyl-2-((R or S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (example 301)	Chiralpak AD, 25 % Isopropanol/ Heptane, flow 35 ml, 220 nm, 280 min.	525.2

470	[4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	rac-[4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone (example 438)	Chiralpak AD, 20 % Isopropanol/ Heptane, flow 35 ml, 254 nm, 110 min.	544.3
471	[4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	rac-[4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone (example 438)	Chiralpak AD, 20 % Isopropanol/ Heptane, flow 35 ml, 254 nm, 145 min.	544.0

Example 6.1

Preparation of 2-isobutoxy-5-methylsulfamoyl-benzoic acid

(a) 5-Chlorosulfonyl-2-hydroxy-benzoic acid

To 3.26 mol chlorosulfonic acid at 0 °C was added 652 mmol salicylic acid in small portions and the mixture was then allowed to stir at RT for 1 h, then at 50 °C for 1 h, and finally at 70 °C for 1 h. The mixture was then added dropwise to 1000 ml ice-water with stirring and stirring continued for an additional 30 min. The ensuing white crystals were collected by filtration, washed three times with water, and then dried *in vacuo* at 45 °C for 16 h to yield the title compound. MS (m/e): 236.8 ([³⁷Cl]M-H)⁺, 33%), 235.0 ([³⁷Cl]M-H)⁺, 100%)

(b) 2-Hydroxy-5-methylsulfamoyl-benzoic acid

To 63 mmol 5-chlorosulfonyl-2-hydroxy-benzoic acid in 120 ml dichloromethane at RT was added dropwise 317 mmol methylamine (8 M solution in ethanol) and the mixture was allowed to stir at RT for 1 h. The mixture was then concentrated in vacuo. The residue was suspended in 1 M aq NaOH solution and extracted twice with ether. The aqueous phase was acidified with 5 M aq HCl, saturated with NaCl, and extracted 3 times

with THF. The combined THF extracts were washed twice with saturated aqueous NaCl solution and dried with Na₂SO₄. Evaporation in vacuo yielded the title compound. MS (m/e): 249.0 (M+NH₄⁺, 100%), 231.9 (M+H⁺, 63%)

(c) 2-Hydroxy-5-methylsulfamoyl-benzoic acid methyl ester

- 5 To 77 mmol 2-hydroxy-5-methylsulfamoyl-benzoic acid in 300 ml THF was added 85 mmol CDI and the mixture heated at 70 °C for 1 h. 770 mmol methanol was then added and the mixture was heated at 70 °C for 16 h. The mixture was then cooled to room temperature and concentrated in vacuo. The residue was chromatographed on silica gel (eluant: ethyl acetate/heptane/dichloromethane 45:45:10) to afford the title compound.
- 10 MS (m/e): 244.1 ([M-H]⁻, 100%)

(d) 2-Isobutoxy-5-methylsulfamoyl-benzoic acid methyl ester

- To 2.9 mmol 2-hydroxy-5-methylsulfamoyl-benzoic acid methyl ester, 3.1 mmol 2-methyl-1-propanol and 3.3 mmol triphenylphosphine in 10 ml THF was added 3.1 mmol di-tert-butyl azodicarboxylate and the mixture was stirred at RT for 2 h. The mixture was
- 15 then concentrated in vacuo. The residue was chromatographed on silica gel (eluant: ethyl acetate/heptane 2:3) to afford the title compound. MS (m/e): 300.2 ([M-H]⁻, 100%)

(e) 2-Isobutoxy-5-methylsulfamoyl-benzoic acid

- To 3.3 mmol 2-isobutoxy-5-methylsulfamoyl-benzoic acid methyl ester in 10 ml THF was added 20 mmol 2 M aq NaOH and the mixture was heated at 50 °C for 2 h. The
- 20 mixture was then cooled to RT and extracted twice with ether. The aqueous phase was acidified with 10% aq citric acid and extracted 3 times with ethyl acetate. The combined organic phases were dried with Na₂SO₄. Evaporation in vacuo followed by trituration in ether afforded the title compound. MS (m/e): 286.2 ([M-H]⁻, 100%)

- In analogy to Example 6.1(d) and (e), compounds 6.2 to 6.10 of the following table were
- 25 prepared from 2-hydroxy-5-methylsulfamoyl-benzoic acid methyl ester and the appropriate alcohol, followed by hydrolysis with aqueous sodium hydroxide:

Expl. No	Systematic Name	alcohol	MS (M/e)
6.2	2-(2,2-Dimethyl-propoxy)-5-methylsulfamoyl-benzoic acid	2,2-Dimethyl-1-propanol	300.2 (M -H)
6.3	2-Isopropoxy-5-methylsulfamoyl-benzoic acid	2-Propanol	272.2 (M -H)
6.4	2-Cyclopentyloxy-5-methylsulfamoyl-benzoic acid	Cyclopentanol	298.2 (M -H)
6.5	2-Cyclobutoxy-5-methylsulfamoyl-benzoic acid	Cyclobutanol	284.1 (M -H)
6.6	2-Cyclopropylmethoxy-5-methylsulfamoyl-benzoic acid	Cyclopropyl-methanol	284.1 (M -H)
6.7	2-Cyclobutylmethoxy-5-methylsulfamoyl-benzoic acid	Cyclobutyl-methanol	298.2 (M -H)
6.8	5-Methylsulfamoyl-2-(tetrahydro-pyran-4-yloxy)-benzoic acid	Tetrahydro-2H-pyran-4-ol	314.1 (M -H)
6.9	2-(2-Methoxy-ethoxy)-5-methylsulfamoyl-benzoic acid	2-Methoxy-ethanol	288.1 (M -H)
6.10	5-Methylsulfamoyl-2-(3,3,3-trifluoro-propoxy)-benzoic acid	3,3,3-Trifluoro-1-propanol	326.2 (M -H)

Example 6.11

Preparation of 5-methylsulfamoyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid

(a) 5-Methylsulfamoyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid methyl ester

To 3.3 mmol 2-hydroxy-5-methylsulfamoyl-benzoic acid methyl ester and 3.3 mmol potassium carbonate in 50 ml acetone was added dropwise 4.9 mmol 2,2,2-trifluoro-ethyl trifluoromethanesulfonate and the mixture was heated at 60 °C for 16 h. The mixture was then concentrated in vacuo. The residue was suspended in dichloromethane and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (eluant: ethyl acetate/heptane 3:7) to afford the title compound. MS (m/e): 328.0 (M+H⁺, 100%)

(b) 5-Methylsulfamoyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid

To 2.3 mmol 5-methylsulfamoyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid methyl ester in 10 ml THF was added 20 mmol 2 M aq NaOH and the mixture was heated at 50 °C for 2 h. The mixture was then cooled to RT and extracted twice with ether. The aqueous phase was acidified with 10% aq citric acid and extracted 3 times with ethyl acetate. The combined organic phases were dried with Na₂SO₄. Evaporation in vacuo followed by trituration in ether afforded the title compound. MS (m/e): 312.0 ([M-H]⁻, 100%)

Example 6.19

Preparation of rac-5-methylsulfamoyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid

(a) rac-5-Methylsulfamoyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid methyl ester

To 4.1 mmol 2-hydroxy-5-methylsulfamoyl-benzoic acid methyl ester and 4.1 mmol potassium carbonate in 5 ml DMF was added dropwise 6.1 mmol trifluoromethanesulfonic acid 2,2,2-trifluoro-1-methyl-ethyl ester and the mixture was heated at 90 °C for 16 h. The mixture was then cooled to RT, poured onto water and extracted 3 times with ethyl acetate. The combined organic phases were dried with Na₂SO₄. Evaporation in vacuo followed by chromatography on silica gel (eluant: dichloromethane) afforded the title compound.

MS (m/e): 359.2 (M+NH₄⁺, 80%), 342.0 (M+H⁺, 100%)

(b) rac-5-Methylsulfamoyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid

To 1.6 mmol 5-methylsulfamoyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid methyl ester in 10 ml THF was added 20 mmol 2 M aq NaOH and the mixture was heated at 50 °C for 2 h. The mixture was then cooled to RT and extracted twice with ether. The aqueous phase was acidified with 10% aq citric acid and extracted twice with

ethyl acetate. The combined organic phases were dried with Na_2SO_4 . Evaporation in vacuo followed by trituration in ether and hexane afforded the title compound. MS (m/e): 326.2 ($[\text{M}-\text{H}]^-$, 100%)

Example 6.14

5 Preparation of 5-cyclopropanesulfonyl-2-isopropoxy-benzoic acid

(a) 2-Hydroxy-5-sulfinobenzoic acid

To 317 mmol sodium sulfite in 200 ml water at RT was added dropwise over 30 min a solution of 42.3 mmol 5-chlorosulfonyl-2-hydroxy-benzoic acid in 80 ml dioxane and stirring continued for a further 30 min. 5 M aq NaOH was then added dropwise until the
10 reaction mixture was pH 14 and the mixture was then allowed to stir at RT for a further 2 h. The mixture was then cooled to 0 °C and concentrated H_2SO_4 added until the reaction mixture was pH 1. Ethyl acetate was added and the phases were separated. The organic phase was dried with Na_2SO_4 . Evaporation in vacuo yielded the title compound.

MS (m/e): 201.0 ($[\text{M}-\text{H}]^-$, 100%)

15 (b) 5-(3-Chloro-propane-1-sulfonyl)-2-hydroxy-benzoic acid

To 16.7 mmol 2-hydroxy-5-sulfinobenzoic acid and 41.7 mmol triethylamine in 40 ml DMF was added 18.3 mmol 1-chloro-3-iodopropane and the mixture heated at 40 °C for 1 h. The mixture was then cooled to room temperature and concentrated in vacuo. The residue was chromatographed on silica gel (eluant: dichloromethane/methanol/acetic
20 acid gradient) to afford the title compound. MS (m/e): 279.1 ($[\text{M}-\text{H}]^-$, 33%), 277.0 ($[\text{M}-\text{H}]^-$, 100%)

(c) 5-Cyclopropanesulfonyl-2-hydroxy-benzoic acid

To 8.0 mmol 5-(3-chloro-propane-1-sulfonyl)-2-hydroxy-benzoic acid in 30 ml THF at -78 °C was added dropwise over 30 min 23.9 mmol of a 0.9 M solution of potassium
25 bis(trimethylsilyl)amide in toluene. The reaction mixture was then allowed to warm to RT and stirring continued for a further 30 min at RT. The mixture was then diluted with THF/ethyl acetate (1:1) and washed sequentially with 1 M aq HCl and saturated aqueous NaCl solution, dried with Na_2SO_4 , and concentrated in vacuo. The residue was trituated in ether/pentane to afford the title compound. MS (m/e): 241.2 ($[\text{M}-\text{H}]^-$, 100%)

30 (d) 5-Cyclopropanesulfonyl-2-hydroxy-benzoic acid methyl ester

To 7.2 mmol 5-cyclopropanesulfonyl-2-hydroxy-benzoic acid in 20 ml dichloroethane containing a few drops of DMF was added dropwise 8.7 mmol oxalyl chloride. After stirring for 90 min at RT, the reaction mixture was cooled to 0 °C and then 144 mmol methanol was added followed by 72 mmol pyridine and stirring continued at RT for 1 h.

- 5 The mixture was then washed with 1 M aq HCl, dried with Na₂SO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (eluant: ethyl acetate/heptane gradient) to afford the title compound. MS (m/e): 255.2 ([M-H]⁻, 100%)

(e) 5-Cyclopropanesulfonyl-2-isopropoxy-benzoic acid

- 10 To 0.6 mmol 5-cyclopropanesulfonyl-2-hydroxy-benzoic acid methyl ester, 3.7 mmol 2-propanol and 0.9 mmol diphenyl-2-pyridylphosphine in 8 ml THF was added 0.9 mmol di-tert-butyl azodicarboxylate and the mixture was stirred at RT for 3 h. 4 mmol 5 M aq NaOH solution was then added and the mixture heated at 60 °C for 1 h. The mixture was then concentrated in vacuo. The residue was resuspended in ethyl acetate and washed twice with 1 M aq NaOH solution. The combined aqueous phases were then acidified to
- 15 pH 1 by addition of 25% aq HCl and extracted three times with ethyl acetate. The combined organic extracts were then dried with Na₂SO₄, and concentrated in vacuo to afford the title compound. MS (m/e): 282.9 ([M-H]⁻, 100%)

- In analogy to Example 6.14 (e), compounds 6.15 to 6.18 of the following table were prepared from 5-cyclopropanesulfonyl-2-hydroxy-benzoic acid methyl ester and the
- 20 appropriate alcohol, followed by hydrolysis with aqueous sodium hydroxide:

Expl. No	Systematic Name	alcohol	MS (m/e)
6.15	5-Cyclopropanesulfonyl-2-isobutoxy-benzoic acid	2-Methyl-1-propanol	297.1 (M -H)
6.16	2-Cyclopentyloxy-5-cyclopropanesulfonyl-benzoic acid	Cyclopentanol	309.1 (M -H)
6.17	5-Cyclopropanesulfonyl-2-cyclopropylmethoxy-benzoic acid	Cyclopropyl-methanol	295.2 (M -H)

6.18	2-Cyclobutoxy-5-cyclopropanesulfonyl-benzoic acid	Cyclobutanol	295.2 (M-H)
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Example 6.12

Preparation of 1-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazine

(a) 3,4-Difluoro-benzenesulfinic acid

- 5 To 2.47 mol sodium sulfite in 1120 ml water at RT was added dropwise over 20 min a solution of 329 mmol 3,4-difluoro-benzenesulfonyl chloride in 560 ml dioxane and stirring continued for a further 30 min. 1 M aq NaOH was then added dropwise until the reaction mixture was pH 14 and the mixture was then allowed to stir at RT for a further 16 h. The mixture was then cooled to 0 °C and concentrated H₂SO₄ added until the
- 10 reaction mixture was pH 1. The mixture was extracted three times with ethyl acetate and the combined organic phases washed with saturated aq NaCl solution and then dried with Na₂SO₄. Evaporation in vacuo yielded the title compound. MS (m/e): 177.1 ([M-H]⁻, 100%)

(b) 4-Ethanesulfonyl-1,2-difluoro-benzene

- 15 To 3.0 mmol 3,4-difluoro-benzenesulfinic acid and 3.0 mmol triethylamine in 10 ml DMF was added 7.5 mmol iodoethane and the mixture heated at 90 °C for 9 h. The reaction mixture was then poured onto water and extracted three times with ethyl acetate. The combined organic phases were then washed twice with saturated aq. NaCl solution, dried over Na₂SO₄, and concentrated in vacuo. The residue was
- 20 chromatographed on silica gel (eluant: ethyl acetate/heptane 1:7) to afford the title compound. MS (m/e): 206.9 (M+H⁺, 100%)

(c) 1-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazine

- To 2.0 mmol 4-ethanesulfonyl-1,2-difluoro-benzene in 5 ml N,N-dimethylacetamide was added 5.6 mmol piperazine and the mixture was heated at 80 °C for 45 min. The mixture
- 25 was then concentrated in vacuo to afford the title compound. MS (m/e): 273.0 (M+H⁺, 100%)

In analogy to Example 6.12 (b) and (c), compounds 6.13, and 6.21 to 6.23 of the following table were prepared from 3,4-difluoro-benzenesulfinic acid and the indicated alkyl halides, followed by reaction with piperazine:

Expl. No.	Systematic Name	alkyl halide	MW found (M+H ⁺)
6.13	1-[4-(Butane-1-sulfonyl)-2-fluoro-phenyl]-piperazine	Iodobutane	301.1
6.21	1-[2-Fluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine	2-Iodopropane	287.0
6.22	1-(4-Cyclopropylmethanesulfonyl-2-fluoro-phenyl)-piperazine	Bromomethyl-cyclopropane and NaI	299.2
6.23	1-[2-Fluoro-4-(2-methoxy-ethanesulfonyl)-phenyl]-piperazine	1-Iodo-2-methoxy-ethane	303.1

5

Example 6.20

Preparation of 1-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazine

(a) 4-(3-Chloro-propane-1-sulfonyl)-1,2-difluoro-benzene

To 28.3 mmol 3,4-difluoro-benzenesulfinic acid and 36.8 mmol triethylamine in 100 ml DMF was added 70.7 mmol 1-chloro-3-iodopropane and the mixture stirred at RT for 1 h. The reaction mixture was then poured onto water and extracted three times with ethyl acetate. The combined organic phases were then washed with saturated aq. NaCl solution, dried over Na₂SO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (eluant: ethyl acetate/heptane gradient) to afford the title compound.

15 MS (m/e): 257.2 ({³⁷Cl}M+H⁺, 33%), 255.1({³⁵Cl}M+H⁺, 100%),

(b) 4-Cyclopropanesulfonyl-1,2-difluoro-benzene

To 11.8 mmol 4-(3-chloro-propane-1-sulfonyl)-1,2-difluoro-benzene in 400 ml THF at -78 °C was added dropwise over 30 min 14.2 mmol of a 0.9 M solution of potassium bis(trimethylsilyl)amide in THF. The reaction mixture was then allowed to warm to RT and stirring continued for a further 30 min at RT. The mixture was then quenched by addition of 1 M aq HCl and extracted three times with ethyl acetate. The combined organic phases were dried with Na₂SO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (eluant: ethyl acetate/heptane 1:5) to afford the title compound. MS (m/e): 219.2 (M+H⁺, 100%)

(c) 1-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazine

To 0.2 mmol 4-cyclopropanesulfonyl-1,2-difluoro-benzene in 5 ml N,N-dimethylacetamide was added 0.5 mmol piperazine and the mixture was heated at 80 °C for 90 min. The mixture was then concentrated in vacuo to afford the title compound. MS (m/e): 285.0 (M+H⁺, 100%)

Example 6.24

Preparation of 1-(4-cyclobutanesulfonyl-2-fluoro-phenyl)-piperazine hydrochloride

(a) 4-Cyclobutanesulfonyl-1,2-difluoro-benzene

To 5.6 mmol 3,4-difluoro-benzenesulfinic acid and 6.2 mmol triethylamine in 10 ml DMF were added 8.4 mmol bromocyclobutane and 0.2 mmol sodium iodide and the mixture heated at 100 °C for 48 h. The reaction mixture was then poured onto water and extracted three times with ethyl acetate. The combined organic phases were then washed with saturated aq. NaCl solution, dried over Na₂SO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (eluant: ethyl acetate/heptane gradient) to afford the title compound. MS (m/e): 233.1 (M+H⁺, 100%)

(b) 1-(4-Cyclobutanesulfonyl-2-fluoro-phenyl)-piperazine hydrochloride

To 2.8 mmol 4-cyclobutanesulfonyl-1,2-difluoro-benzene in 20 ml N,N-dimethylacetamide was added 8.3 mmol piperazine and the mixture was heated at 80 °C for 45 min. The mixture was then concentrated in vacuo and the residue was chromatographed on silica gel (eluant: ethyl acetate/methanol gradient). The product-containing fractions were combined and concentrated in vacuo. The residue was resuspended in 100 ml dioxane and 6.0 mmol HCl (as a 4 M solution in dioxane) was added. After stirring for 10 min, the ensuing white crystals were collected by filtration, washing twice with ether, to afford the title compound.

MS (m/e): 299.1 (M+H⁺, 100%)

In analogy to Example 6.24 (a) and (b), compound 6.25 of the following table was prepared from the 3,4-difluoro-benzenesulfinic acid, bromocyclobutane and sodium iodide, followed by reaction with piperazine and subsequent treatment with HCl in dioxane:

Expl. No	Systematic Name	Starting Materials	MW found (M+H ⁺)
6.25	1-(4-Cyclopentanesulfonyl-2-fluoro-phenyl)-piperazine hydrochloride)	difluoro-benzenesulfinic acid and bromocyclopentane	313.3

Example 6.26

Preparation of 1-[2-fluoro-4-(3,3,3-trifluoro-propane-1-sulfonyl)-phenyl]-piperazine

(a) 1,2-Difluoro-4-(3,3,3-trifluoro-propylsulfanyl)-benzene

To 3.4 mmol 3,4-difluoro-thiophenol and 5.1 mmol 1-iodo-3,3,3-trifluoropropane in 5 ml acetone was added 3.7 mmol potassium carbonate and the mixture heated at 140 °C for 3 h under microwave irradiation. The reaction mixture was then poured onto water and extracted three times with ethyl acetate. The combined organic phases were then washed with saturated aq. NaCl solution, dried over Na₂SO₄, and concentrated in vacuo to afford the title compound. MS (m/e): 243.1 (M+H⁺, 100%)

(b) 1,2-Difluoro-4-(3,3,3-trifluoro-propane-1-sulfonyl)-benzene

To 3.0 mmol 1,2-difluoro-4-(3,3,3-trifluoro-propylsulfanyl)-benzene in 5 ml dichloromethane was added 8.3 mmol m-chloroperbenzoic acid and the mixture heated at 50 °C for 48 h.. The reaction mixture was then cooled to room temperature and diluted with dichloromethane and washed three times with saturated aq NaHCO₃ solution. The organic phase was then washed with saturated aq. NaCl solution, dried over Na₂SO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (eluant: ethyl acetate/heptane gradient) to afford the title compound. MS (m/e): 275.1 (M+H⁺, 100%)

(c) 1-[2-Fluoro-4-(3,3,3-trifluoro-propane-1-sulfonyl)-phenyl]-piperazine

To 0.5 mmol 1,2-difluoro-4-(3,3,3-trifluoro-propane-1-sulfonyl)-benzene in 5 ml N,N-dimethylacetamide was added 1.5 mmol piperazine and the mixture was heated at 80 °C for 90 min. The mixture was then concentrated in vacuo and the residue was chromatographed on silica gel (eluant: methanol/dichloromethane gradient) to afford the title compound. MS (m/e): 341.2 (M+H⁺, 100%)

In analogy to Example 6.26 (a) to (c), compounds 6.27 and 6.28 of the following table were prepared from 3,4-difluoro-thiophenol and the indicated alkylating agent, followed by oxidation with m-chloroperbenzoic acid and reaction with piperazine:

Expl No	Systematic name	Alkylating agent	MW found (M+H ⁺)
6.27	1-[2-Fluoro-4-(tetrahydro-pyran-4-sulfonyl)-phenyl]-piperazine	Toluene-4-sulfonic acid tetrahydro-pyran-4-yl ester	329.1
6.28	1-(4-Cyclohexanesulfonyl-2-fluoro-phenyl)-piperazine	Iodocyclohexane	327.3

10

Example 6.29

Preparation of 1-[2,3-difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine hydrochloride

(a) 1,2,3-Trifluoro-4-(propane-2-sulfonyl)-benzene

To 20.4 mmol 2,3,4-trifluoro-benzenesulfinic acid (prepared in analogy to example 2.20(a) from 2,3,4-trifluoro-benzenesulfonyl chloride) and 61.2 mmol triethylamine in 20 ml DMF was added 40.8 mmol 2-iodopropane and the mixture stirred at room temperature for 16 h. The reaction mixture was then poured onto water and extracted three times with ethyl acetate. The combined organic phases were then washed twice with saturated aq. NaCl solution, dried over Na₂SO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (eluant: ethyl acetate/heptane 1:4) to afford the title compound. MS (m/e): 239.1 (M+H⁺, 100%)

(b) 4-[2,3-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester

To 7.6 mmol 1,2,3-trifluoro-4-(propane-2-sulfonyl)-benzene in 20 ml N,N-dimethylacetamide was added 15.9 mmol tert-butyl-1-piperazine carboxylate and the mixture was heated at 90 °C for 1 h. The mixture was then cooled to room temperature and concentrated in vacuo. The residue was chromatographed on silica gel (eluant: ethyl acetate/heptane 1:2) to afford the title compound. MS (m/e): 405.2 (M+H⁺, 100%)

(c) 1-[2,3-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine hydrochloride

To 7.5 mmol 4-[2,3-difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester in 100 ml dioxane was added 30.2 mmol HCl (as a 4 M solution in dioxane) and the mixture was heated at 80 °C for 1 h. The mixture was then cooled to room temperature and the ensuing white crystals were collected by filtration, washing twice with ether, to afford the title compound.

MS (m/e): 305.2 (M+H⁺, 100%)

In analogy to Example 6.29 (a) to (c), compounds 6.30, 6.32 and 6.33 of the following table were prepared from the indicated sulfinic acids and alkyl halides, followed by reaction with tert-butyl-1-piperazine carboxylate and hydrolysis with HCl in dioxane:

Expl. No	Systematic Name	starting materials	MW found (M+H)
6.30	1-(4-Ethanesulfonyl-2,3-difluoro-phenyl)-piperazine hydrochloride	2,3,4-trifluoro-benzenesulfinic acid and iodoethane	291.2
6.32	1-[2,5-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine hydrochloride	2,4,5-Trifluoro-benzenesulfinic acid and 2-iodopropane	305.1
6.33	1-(4-Ethanesulfonyl-2,5-difluoro-phenyl)-piperazine hydrochloride	2,4,5-Trifluoro-benzenesulfinic acid and iodoethane	291.1

Example 6.31

Preparation of 1-(4-cyclopropanesulfonyl-2,3-difluoro-phenyl)-piperazine hydrochloride

(a) 1-(3-Chloro-propane-1-sulfonyl)-2,3,4-trifluoro-benzene

- 5 To 30.6 mmol 2,3,4-trifluoro-benzenesulfinic acid (acid (prepared in analogy to example 2.20(a) from 2,3,4-trifluoro-benzenesulfonyl chloride) and 91.8 mmol triethylamine in 20 ml DMF was added 61.2 mmol 1-chloro-3-iodopropane and the mixture stirred at room temperature for 1 h. The reaction mixture was then poured onto water and extracted three times with ethyl acetate. The combined organic phases were then washed
- 10 twice with saturated aq. NaCl solution, dried over Na₂SO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (eluant: ethyl acetate/heptane 1:4) to afford the title compound. MS (m/e): 275.2 (³⁷Cl}M+H⁺, 33%), 273.1(³⁵Cl}M+H⁺, 100%),

(b) 1-Cyclopropanesulfonyl-2,3,4-trifluoro-benzene

- 15 To 5.9 mmol 1-(3-chloro-propane-1-sulfonyl)-2,3,4-trifluoro-benzene in 200 ml THF at -78 °C was added dropwise over 30 min 7.0 mmol of a 0.9 M solution of potassium bis(trimethylsilyl)amide in THF. The reaction mixture was then allowed to warm to RT and stirring continued for a further 30 min at RT. The mixture was then quenched by addition of 1 M aq HCl and extracted three times with ethyl acetate. The combined
- 20 organic phases were dried with Na₂SO₄, and concentrated in vacuo. The residue was chromatographed on silica gel (eluant: ethyl acetate/heptane 1:4) to afford the title compound. MS (m/e): 237.2 (M+H⁺, 100%)

(c) 4-(4-Cyclopropanesulfonyl-2,3-difluoro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

- 25 To 4.2 mmol 1-cyclopropanesulfonyl-2,3,4-trifluoro-benzene in 20 ml N,N-dimethylacetamide was added 8.9 mmol tert-butyl-1-piperazine carboxylate and the mixture was heated at 90 °C for 1 h. The mixture was then cooled to room temperature and concentrated in vacuo. The residue was chromatographed on silica gel (eluant: dichloromethane/ethyl acetate gradient) to afford the title compound. MS (m/e): 403.3
- 30 (M+H⁺, 100%)

(d) 1-(4-Cyclopropanesulfonyl-2,3-difluoro-phenyl)-piperazine hydrochloride

To 3.7 mmol 4-(4-Cyclopropanesulfonyl-2,3-difluoro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester in 100 ml dioxane was added 14.9 mmol HCl (as a 4 M solution in dioxane) and the mixture was heated at 80 °C for 1 h. The mixture was then cooled to room temperature and the ensuing white crystals were collected by filtration, washing
 5 twice with ether, to afford the title compound. MS (m/e): 303.2 (M+H⁺, 100%)

In analogy to Example 6.31 (a) to (d), compound 6.34 of the following table was prepared from the indicated sulfinic acid and alkyl halide, followed by treatment with potassium bis(trimethylsilyl)amide, reaction with tert-butyl-1-piperazine carboxylate and deprotection with HCl in dioxane:

Expl. No	Systematic Name	starting materials	MW found (M+H)
6.34	1-(4-Cyclopropanesulfonyl-2,5-difluoro-phenyl)-piperazine hydrochloride	2,4,5-Trifluoro-benzenesulfinic acid and 2-iodopropane	303.1

10

Example 6.35

Preparation of rac-2-Methyl-1-(4-trifluoromethyl-phenyl)-piperazine hydrochloride

(a) rac-3-Methyl-4-(4-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

15 To 1-bromo-4-trifluoromethyl-benzene (1 g), rac-3-Methyl-piperazine-1-carboxylic acid tert-butyl ester (1 g), in toluene (10 mL) was added sodium *tert*-butylate (0.6 g), 2-(dicyclohexylphosphino)biphenyl (31 mg), and tris(dibenzylideneacetone)Pd-CHCl₃ (23 mg). The reaction mixture was then stirred at 80°C overnight. Ethyl acetate was then added to the reaction mixture. Solids were filtered off. The filtrate was then concentrated
 20 *in vacuo* and the residue was purified by column chromatography to yield 0.46 g of the title compound. MS (m/e): 345.2 (M+H⁺, 100%)

(b) rac-2-Methyl-1-(4-trifluoromethyl-phenyl)-piperazine hydrochloride

To 0.58 mmol rac-3-methyl-4-(4-trifluoromethyl-phenyl)-piperazine-1-carboxylic acid tert-butyl ester in 3 ml dioxane was added 8.7 mmol HCl (as a 4 M solution in dioxane)
 25 and the mixture was heated at 90 °C for 3 h. The mixture was then cooled 0 °C and

diluted with 10 ml ether. The ensuing white crystals were collected by filtration, washing with ether, and dried in vacuo to afford the title compound.

MS (m/e): 245.1 ($M+H^+$, 100%)

Example 6.36

5 Preparation of 5-Acetyl-2-isopropoxy-benzoic acid

(a) 5-Acetyl-2-isopropoxy-benzoic acid methyl ester

To 25.8 mmol methyl-5-acetyl-2-hydroxybenzoate, 28.3 mmol 2-propanol and 29.6 mmol triphenylphosphine in 100 ml THF was added 28.3 mmol di-tert-butyl azodicarboxylate and the mixture was stirred at RT for 90 min. The mixture was then
10 concentrated in vacuo to afford the title compound. MS (m/e): 237.1 ($M+H^+$, 100%)

(b) 5-Acetyl-2-isopropoxy-benzoic acid

To 25.8 mmol 5-acetyl-2-isopropoxy-benzoic acid methyl ester in 100 ml THF was added 400 mmol 2 M aq NaOH and the mixture was heated at 80 °C for 2 h. The mixture was then cooled to RT and extracted twice with ether. The aqueous phase was acidified with
15 15% aq hydrochloric acid and extracted 3 times with ethyl acetate. The combined organic phases were dried with Na_2SO_4 . Evaporation in vacuo followed by trituration in ether afforded the title compound. MS (m/e): 221.2 ($[M-H]^-$, 100%)

In analogy to Example 5 compounds 472 to 619 of the following table were prepared from the acid derivatives and piperazine derivatives:

Expl.- No.	Systematic Name	Starting materials	MW found (MH^+)
472	3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-ethoxy-benzenesulfonamide	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 2-Ethoxy-5-sulfamoyl-benzoic acid (JP53050139)	433.2
473	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-ethoxy-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-Ethoxy-5-sulfamoyl-benzoic acid (JP53050139)	431.3 ($M-H$)

474	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-4-ethoxy-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 2-Ethoxy-5-sulfamoyl-benzoic acid (JP53050139)	413.3 (M -H)
475	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-isobutoxy-N-methyl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-Isobutoxy-5-methylsulfamoyl-benzoic acid (compound 6.1)	475.1
476	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-(2,2-dimethyl-propoxy)-N-methyl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-(2,2-Dimethyl-propoxy)-5-methylsulfamoyl-benzoic acid (compound 6.2)	489.3
477	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-N-methyl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-Isopropoxy-5-methylsulfamoyl-benzoic acid (compound 6.3)	461.2
478	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclopentyloxy-N-methyl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-Cyclopentyloxy-5-methylsulfamoyl-benzoic acid (compound 6.4)	487.3
479	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclobutoxy-N-methyl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-Cyclobutoxy-5-methylsulfamoyl-benzoic acid (compound 6.5)	473.1

480	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclopropylmethoxy-N-methyl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-Cyclopropylmethoxy-5-methylsulfamoyl-benzoic acid (compound 6.6)	473.2
481	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclobutylmethoxy-N-methyl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-Cyclobutylmethoxy-5-methylsulfamoyl-benzoic acid (compound 6.7)	487.3
482	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(tetrahydro-pyran-4-yloxy)-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 5-Methylsulfamoyl-2-(tetrahydro-pyran-4-yloxy)-benzoic acid (compound 6.8)	503.2
483	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-(2-methoxy-ethoxy)-N-methyl-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 2-(2-Methoxy-ethoxy)-5-methylsulfamoyl-benzoic acid (compound 6.9)	477.3
484	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(3,3,3-trifluoro-propoxy)-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 5-Methylsulfamoyl-2-(3,3,3-trifluoro-propoxy)-benzoic acid (compound 6.10)	515.2
485	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-4-(2-methoxy-ethoxy)-N-methyl-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 2-(2-Methoxy-ethoxy)-5-methylsulfamoyl-benzoic acid (compound 6.9)	459.1

486	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(3,3,3-trifluoro-propoxy)-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 5-Methylsulfamoyl-2-(3,3,3-trifluoro-propoxy)-benzoic acid (compound 6.10)	497.0
487	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(tetrahydro-pyran-4-yloxy)-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 5-Methylsulfamoyl-2-(tetrahydro-pyran-4-yloxy)-benzoic acid (compound 6.8)	485.2
488	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-4-isobutoxy-N-methyl-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 2-Isobutoxy-5-methylsulfamoyl-benzoic acid (compound 6.1)	457.3
489	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-4-(2,2-dimethyl-propoxy)-N-methyl-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 2-(2,2-Dimethyl-propoxy)-5-methylsulfamoyl-benzoic acid (compound 6.2)	471.1
490	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-N-methyl-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 2-Isopropoxy-5-methylsulfamoyl-benzoic acid (compound 6.3)	443.2
491	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-4-cyclopentyloxy-N-methyl-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 2-Cyclopentyloxy-5-methylsulfamoyl-benzoic acid (compound 6.4)	469.2
492	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-4-cyclobutoxy-N-methyl-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 2-Cyclobutoxy-5-methylsulfamoyl-benzoic acid (compound 6.5)	455.3

493	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-4-cyclopropylmethoxy-N-methyl-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 2-Cyclopropylmethoxy-5-methylsulfamoyl-benzoic acid (compound 6.6)	455.3
494	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-4-cyclobutylmethoxy-N-methyl-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 2-Cyclobutylmethoxy-5-methylsulfamoyl-benzoic acid (compound 6.7)	469.2
495	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-isobutoxy-N-methyl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-Isobutoxy-5-methylsulfamoyl-benzoic acid (compound 6.1)	528.0
496	4-(2,2-Dimethyl-propoxy)-3-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-N-methyl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-(2,2-Dimethyl-propoxy)-5-methylsulfamoyl-benzoic acid (compound 6.2)	559.2 (M+NH ₄ ⁺)
497	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-N-methyl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-Isopropoxy-5-methylsulfamoyl-benzoic acid (compound 6.3)	514.1
498	4-Cyclopentyloxy-3-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-N-methyl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-Cyclopentyloxy-5-methylsulfamoyl-benzoic acid (compound 6.4)	557.0 (M+NH ₄ ⁺)

499	4-Cyclobutoxy-3-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-N-methyl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-Cyclobutoxy-5-methylsulfamoyl-benzoic acid (compound 6.5)	526.0
500	4-Cyclopropylmethoxy-3-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-N-methyl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-Cyclopropylmethoxy-5-methylsulfamoyl-benzoic acid (compound 6.6)	526.0
501	4-Cyclobutylmethoxy-3-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-N-methyl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-Cyclobutylmethoxy-5-methylsulfamoyl-benzoic acid (compound 6.7)	557.0 (M+NH ₄ ⁺)
502	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-(2-methoxy-ethoxy)-N-methyl-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-(2-Methoxy-ethoxy)-5-methylsulfamoyl-benzoic acid (compound 6.9)	530.1
503	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(3,3,3-trifluoropropoxy)-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Methylsulfamoyl-2-(3,3,3-trifluoropropoxy)-benzoic acid (compound 6.10)	585.0 (M+NH ₄ ⁺)

504	3-[4-(4-Cyano-2-fluorophenyl)-piperazine-1-carbonyl]-4-isobutoxy-N-methylbenzenesulfonamide	3-Fluoro-4-piperazin-1-ylbenzonitrile (WO9625414) and 2-Isobutoxy-5-methylsulfamoylbenzoic acid (compound 6.1)	475.0
505	3-[4-(4-Cyano-2-fluorophenyl)-piperazine-1-carbonyl]-4-(2,2-dimethyl-propoxy)-N-methylbenzenesulfonamide	3-Fluoro-4-piperazin-1-ylbenzonitrile (WO9625414) and 2-(2,2-Dimethyl-propoxy)-5-methylsulfamoylbenzoic acid (compound 6.2)	489.0
506	3-[4-(4-Cyano-2-fluorophenyl)-piperazine-1-carbonyl]-4-isopropoxy-N-methylbenzenesulfonamide	3-Fluoro-4-piperazin-1-ylbenzonitrile (WO9625414) and 2-Isopropoxy-5-methylsulfamoylbenzoic acid (compound 6.3)	478.0 (M+NH ₄ ⁺)
507	3-[4-(4-Cyano-2-fluorophenyl)-piperazine-1-carbonyl]-4-cyclopentyloxy-N-methylbenzenesulfonamide	3-Fluoro-4-piperazin-1-ylbenzonitrile (WO9625414) and 2-Cyclopentyloxy-5-methylsulfamoylbenzoic acid (compound 6.4)	487.1
508	3-[4-(4-Cyano-2-fluorophenyl)-piperazine-1-carbonyl]-4-cyclobutoxy-N-methylbenzenesulfonamide	3-Fluoro-4-piperazin-1-ylbenzonitrile (WO9625414) and -Cyclobutoxy-5-methylsulfamoylbenzoic acid (compound 6.5)	472.8
509	3-[4-(4-Cyano-2-fluorophenyl)-piperazine-1-carbonyl]-4-cyclopropylmethoxy-N-methylbenzenesulfonamide	3-Fluoro-4-piperazin-1-ylbenzonitrile (WO9625414) and 2-Cyclopropylmethoxy-5-methylsulfamoylbenzoic acid (compound 6.6)	472.8

510	3-[4-(4-Cyano-2-fluorophenyl)-piperazine-1-carbonyl]-4-cyclobutylmethoxy-N-methylbenzenesulfonamide	3-Fluoro-4-piperazin-1-ylbenzonitrile (WO9625414) and 2-Cyclobutylmethoxy-5-methylsulfamoyl-benzoic acid (compound 6.7)	487.1
511	3-[4-(4-Cyano-2-fluorophenyl)-piperazine-1-carbonyl]-N-methyl-4-(tetrahydro-pyran-4-yloxy)-benzenesulfonamide	3-Fluoro-4-piperazin-1-ylbenzonitrile (WO9625414) and 5-Methylsulfamoyl-2-(tetrahydropyran-4-yloxy)-benzoic acid (compound 6.8)	503.0
512	3-[4-(4-Cyano-2-fluorophenyl)-piperazine-1-carbonyl]-4-(2-methoxyethoxy)-N-methylbenzenesulfonamide	3-Fluoro-4-piperazin-1-ylbenzonitrile (WO9625414) and 2-(2-Methoxyethoxy)-5-methylsulfamoyl-benzoic acid (compound 6.9)	477.1
513	3-[4-(4-Cyano-2-fluorophenyl)-piperazine-1-carbonyl]-N-methyl-4-(3,3,3-trifluoropropoxy)-benzenesulfonamide	3-Fluoro-4-piperazin-1-ylbenzonitrile (WO9625414) and 5-Methylsulfamoyl-2-(3,3,3-trifluoropropoxy)-benzoic acid (compound 6.10)	515.1
514	3-[4-(4-Acetyl-2-fluorophenyl)-piperazine-1-carbonyl]-4-isobutoxy-N-methylbenzenesulfonamide	1-(3-Fluoro-4-piperazin-1-ylphenyl)-ethanone (WO9714690) and 2-Isobutoxy-5-methylsulfamoylbenzoic acid (compound 6.1)	492.1
515	3-[4-(4-Acetyl-2-fluorophenyl)-piperazine-1-carbonyl]-4-(2,2-dimethylpropoxy)-N-methylbenzenesulfonamide	1-(3-Fluoro-4-piperazin-1-ylphenyl)-ethanone (WO9714690) and 2-(2,2-Dimethylpropoxy)-5-methylsulfamoylbenzoic acid (compound 6.2)	506.3

516	3-[4-(4-Acetyl-2-fluorophenyl)-piperazine-1-carbonyl]-4-isopropoxy-N-methyl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 2-Isopropoxy-5-methylsulfamoyl-benzoic acid (compound 6.3)	478.2
517	3-[4-(4-Acetyl-2-fluorophenyl)-piperazine-1-carbonyl]-4-cyclopentyloxy-N-methyl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 2-Cyclopentyloxy-5-methylsulfamoyl-benzoic acid (compound 6.4)	504.2
518	3-[4-(4-Acetyl-2-fluorophenyl)-piperazine-1-carbonyl]-4-cyclobutoxy-N-methyl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 2-Cyclobutoxy-5-methylsulfamoyl-benzoic acid (compound 6.5)	590.6
519	3-[4-(4-Acetyl-2-fluorophenyl)-piperazine-1-carbonyl]-4-cyclopropylmethoxy-N-methyl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 2-Cyclopropylmethoxy-5-methylsulfamoyl-benzoic acid (compound 6.6)	490.2
520	3-[4-(4-Acetyl-2-fluorophenyl)-piperazine-1-carbonyl]-4-cyclobutylmethoxy-N-methyl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 2-Cyclobutylmethoxy-5-methylsulfamoyl-benzoic acid (compound 6.7)	504.2
521	3-[4-(4-Acetyl-2-fluorophenyl)-piperazine-1-carbonyl]-N-methyl-4-(tetrahydro-pyran-4-yloxy)-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 5-Methylsulfamoyl-2-(tetrahydro-pyran-4-yloxy)-benzoic acid (compound 6.8)	520.3

522	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(2-methoxy-ethoxy)-N-methyl-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 2-(2-Methoxy-ethoxy)-5-methylsulfamoyl-benzoic acid (compound 6.9)	494.2
523	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(3,3,3-trifluoro-propoxy)-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 5-Methylsulfamoyl-2-(3,3,3-trifluoro-propoxy)-benzoic acid (compound 6.10)	532.2
524	4-Isobutoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 2-Isobutoxy-5-methylsulfamoyl-benzoic acid (compound 6.1)	500.2
525	4-(2,2-Dimethyl-propoxy)-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 2-(2,2-Dimethyl-propoxy)-5-methylsulfamoyl-benzoic acid (compound 6.2)	514.2
526	4-Isopropoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 2-Isopropoxy-5-methylsulfamoyl-benzoic acid (compound 6.3)	486.2
527	4-Cyclopentyloxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 2-Cyclopentyloxy-5-methylsulfamoyl-benzoic acid (compound 6.4)	512.3

528	4-Cyclobutoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 2-Cyclobutoxy-5-methylsulfamoyl-benzoic acid (compound 6.5)	498.2
529	4-Cyclopropylmethoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 2-Cyclopropylmethoxy-5-methylsulfamoyl-benzoic acid (compound 6.6)	498.2
530	4-Cyclobutylmethoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 2-Cyclobutylmethoxy-5-methylsulfamoyl-benzoic acid (compound 6.7)	512.3
531	N-Methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-4-(3,3,3-trifluoropropoxy)-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 5-Methylsulfamoyl-2-(3,3,3-trifluoropropoxy)-benzoic acid (compound 6.10)	540.2
532	3-[4-(4-Cyano-3-fluorophenyl)-piperazine-1-carbonyl]-N-methyl-4-(2,2,2-trifluoroethoxy)-benzenesulfonamide	2-Fluoro-4-piperazin-1-yl-benzonitrile (WO 9808835) and 5-Methylsulfamoyl-2-(2,2,2-trifluoroethoxy)-benzoic acid (compound 6.11)	501.1
533	3-[4-(4-Cyano-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(2,2,2-trifluoroethoxy)-benzenesulfonamide	4-Piperazin-1-yl-benzonitrile (commercial) and 5-Methylsulfamoyl-2-(2,2,2-trifluoroethoxy)-benzoic acid (compound 6.11)	483.3

534	3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(2,2,2-trifluoro-ethoxy)-benzenesulfonamide	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Methylsulfamoyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 6.11)	501.1
535	3-[4-(4-Acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(2,2,2-trifluoro-ethoxy)-benzenesulfonamide	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone (WO9714690) and 5-Methylsulfamoyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 6.11)	518.2
536	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(2,2,2-trifluoro-ethoxy)-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Methylsulfamoyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 6.11)	554.1
537	N-Methyl-4-(2,2,2-trifluoro-ethoxy)-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 5-Methylsulfamoyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 6.11)	526.0
538	[4-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.12) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	513.3
539	{4-[4-(Butane-1-sulfonyl)-2-fluoro-phenyl]-piperazin-1-yl}-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-[4-(Butane-1-sulfonyl)-2-fluoro-phenyl]-piperazine (compound 6.13) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	541.0

540	4-[4-(5-Cyclopropanesulfonyl-2-isopropoxy-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Cyclopropanesulfonyl-2-isopropoxy-benzoic acid (compound 6.14)	472.3
541	(5-Cyclopropanesulfonyl-2-isopropoxy-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 1.1) and 5-Cyclopropanesulfonyl-2-isopropoxy-benzoic acid (compound 6.14)	515.4
542	(5-Cyclopropanesulfonyl-2-isobutoxy-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Cyclopropanesulfonyl-2-isobutoxy-benzoic acid (compound 6.15)	539.5
543	4-[4-(5-Cyclopropanesulfonyl-2-isobutoxy-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Cyclopropanesulfonyl-2-isobutoxy-benzoic acid (compound 6.15)	486.5
544	(5-Cyclopropanesulfonyl-2-isobutoxy-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 1.1) and 5-Cyclopropanesulfonyl-2-isobutoxy-benzoic acid (compound 6.15)	529.4

545	(2-Cyclopentyloxy-5-cyclopropanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-Cyclopentyloxy-5-cyclopropanesulfonyl-benzoic acid (compound 6.16)	551.3
546	4-[4-(2-Cyclopentyloxy-5-cyclopropanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 2-Cyclopentyloxy-5-cyclopropanesulfonyl-benzoic acid (compound 6.16)	498.3
547	(2-Cyclopentyloxy-5-cyclopropanesulfonyl-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 1.1) and 2-Cyclopentyloxy-5-cyclopropanesulfonyl-benzoic acid (compound 6.16)	541.3
548	(5-Cyclopropanesulfonyl-2-cyclopropylmethoxy-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Cyclopropanesulfonyl-2-cyclopropylmethoxy-benzoic acid (compound 6.17)	537.4
549	4-[4-(5-Cyclopropanesulfonyl-2-cyclopropylmethoxy-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and 5-Cyclopropanesulfonyl-2-cyclopropylmethoxy-benzoic acid (compound 6.17)	484.5

550	(5-Cyclopropanesulfonyl-2-cyclopropylmethoxy-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-trifluoromethyl-phenyl)-piperazine (compound 1.1) and 5-Cyclopropanesulfonyl-2-cyclopropylmethoxy-benzoic acid (compound 6.17)	527.3
551	(2-Cyclobutoxy-5-cyclopropanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-Cyclobutoxy-5-cyclopropanesulfonyl-benzoic acid (compound 6.18)	537.4
552	(5-Cyclopropanesulfonyl-2-isopropoxy-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 5-Cyclopropanesulfonyl-2-isopropoxy-benzoic acid (compound 6.14)	525.3
553	rac-3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and rac-5-Methylsulfamoyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 6.19)	585.1 (M+NH ₄ ⁺)
554	rac-N-Methyl-4-(2,2,2-trifluoro-1-methyl-ethoxy)-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and rac-5-Methylsulfamoyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 6.19)	557.2 (M+NH ₄ ⁺)

555	rac-3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzenesulfonamide	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414) and rac-5-Methylsulfamoyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 6.19)	532.3 (M+NH ₄ ⁺)
556	[4-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.20) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	542.2 (M+NH ₄ ⁺)
557	rac-3-[4-(4-Cyano-2,5-difluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzenesulfonamide	2,5-Difluoro-4-piperazin-1-yl-benzonitrile-trifluoro-acetic acid (compound 2.8) and rac-5-Methylsulfamoyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 6.19)	550.1 (M+NH ₄ ⁺)
558	rac-3-[4-(4-Cyano-2,3-difluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzenesulfonamide	2,3-Difluoro-4-piperazin-1-yl-benzonitrile- trifluoro-acetic acid (compound 2.7) and rac-5-Methylsulfamoyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 6.19)	550.1 (M+NH ₄ ⁺)
559	{4-[2-Fluoro-4-(propane-2-sulfonyl)-phenyl]-piperazin-1-yl}-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-[2-Fluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine (compound 6.21) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	544.3 (M+NH ₄ ⁺)

560	[4-(4-Cyclopropylmethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Cyclopropylmethanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.22) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	556.2 (M+NH ₄ ⁺)
561	{4-[2-Fluoro-4-(2-methoxy-ethanesulfonyl)-phenyl]-piperazin-1-yl}-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-[2-Fluoro-4-(2-methoxy-ethanesulfonyl)-phenyl]-piperazine (compound 6.23) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	560.3 (M+NH ₄ ⁺)
562	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.12) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	542.2 (M+NH ₄ ⁺)
563	(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.12) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	556.1 (M+NH ₄ ⁺)
564	(2-Cyclohexyloxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.12) and 2-Cyclohexyloxy-5-methanesulfonyl-benzoic acid (compound 3.2)	570.2 (M+NH ₄ ⁺)

565	[2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.12) and 2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-benzoic acid (compound 3.3)	558.2(M+NH ₄ ⁺)
566	[4-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.12) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	544.2(M+NH ₄ ⁺)
567	(2-Cyclobutoxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.12) and 2-Cyclobutoxy-5-methanesulfonyl-benzoic acid (compound 3.4)	542.3 (M+NH ₄ ⁺)
568	rac-(2-sec-Butoxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.12) and rac-2-sec-Butoxy-5-methanesulfonyl-benzoic acid (compound 3.5)	544.2 (M+NH ₄ ⁺)
569	(2-Cyclobutylmethoxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.12) and 2-Cyclobutylmethoxy-5-methanesulfonyl-benzoic acid (compound 2.12)	556.1 (M+NH ₄ ⁺)

570	[4-(4-Cyclobutanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Cyclobutanesulfonyl-2-fluoro-phenyl)-piperazine hydrochloride (compound 6.24) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	556.1 (M+NH ₄ ⁺)
571	[4-(4-Cyclopentanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Cyclopentanesulfonyl-2-fluoro-phenyl)-piperazine hydrochloride (compound 6.25) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	570.3 (M+NH ₄ ⁺)
572	[4-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.20) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	537.2
573	(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.20) and 2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid (compound 1.6)	568.0 (M+NH ₄ ⁺)
574	(2-Cyclohexyloxy-5-methanesulfonyl-phenyl)-[4-(4-cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.20) and 2-Cyclohexyloxy-5-methanesulfonyl-benzoic acid (compound 3.2)	582.1 (M+NH ₄ ⁺)

575	[4-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-phenyl]-methanone	1-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.20) and 2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-benzoic acid (compound 3.3)	570.2 (M+NH ₄ ⁺)
576	(2-Cyclobutoxy-5-methanesulfonyl-phenyl)-[4-(4-cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.20) and 2-Cyclobutoxy-5-methanesulfonyl-benzoic acid (compound 3.4)	536.9
577	{4-[2-Fluoro-4-(3,3,3-trifluoro-propane-1-sulfonyl)-phenyl]-piperazin-1-yl}-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-[2-Fluoro-4-(3,3,3-trifluoro-propane-1-sulfonyl)-phenyl]-piperazine (compound 6.26) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	581.0
578	[4-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.20) and 2-Isobutoxy-5-methanesulfonyl-benzoic acid (compound 1.3)	556.1 (M+NH ₄ ⁺)
579	{4-[2-Fluoro-4-(tetrahydro-pyran-4-sulfonyl)-phenyl]-piperazin-1-yl}-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-[2-Fluoro-4-(tetrahydro-pyran-4-sulfonyl)-phenyl]-piperazine (compound 6.27) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	586.2 (M+NH ₄ ⁺)

580	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-{4-[2-fluoro-4-(propane-2-sulfonyl)-phenyl]-piperazin-1-yl}-methanone	1-[2-Fluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine (compound 6.21) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	558.2 (M+NH ₄ ⁺)
581	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.12) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	544.2 (M+NH ₄ ⁺)
582	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(4-cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.20) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	556.1 (M+NH ₄ ⁺)
583	{4-[2-Fluoro-4-(propane-2-sulfonyl)-phenyl]-piperazin-1-yl}-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-[2-Fluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine (compound 6.21) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	584.1 (M+NH ₄ ⁺)
584	[4-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.12) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	570.3 (M+NH ₄ ⁺)

585	[4-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.20) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	582.1 (M+NH ₄ ⁺)
586	rac{4-[2-Fluoro-4-(propane-2-sulfonyl)-phenyl]-piperazin-1-yl}-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-[2-Fluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine (compound 6.21) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	598.2 (M+NH ₄ ⁺)
587	rac-[4-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(4-Ethanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.12) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	584.1 (M+NH ₄ ⁺)
588	rac-[4-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(4-Cyclopropanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.20) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	596.2 (M+NH ₄ ⁺)

589	[4-(4-Cyclohexanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Cyclohexanesulfonyl-2-fluoro-phenyl)-piperazine (compound 6.28) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	584.3 (M+NH ₄ ⁺)
590	{4-[2,3-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazin-1-yl}-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-[2,3-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine hydrochloride (compound 6.29) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	545.2
591	[4-(4-Ethanesulfonyl-2,3-difluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Ethanesulfonyl-2,3-difluoro-phenyl)-piperazine hydrochloride (compound 6.30) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	531.1
592	[4-(4-Cyclopropanesulfonyl-2,3-difluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Cyclopropanesulfonyl-2,3-difluoro-phenyl)-piperazine hydrochloride (compound 6.31) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	543.3
593	{4-[2,5-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazin-1-yl}-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-[2,5-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine hydrochloride (compound 6.32) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	545.2

594	[4-(4-Ethanesulfonyl-2,5-difluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Ethanesulfonyl-2,5-difluoro-phenyl)-piperazine hydrochloride (compound 6.33) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	531.1
595	[4-(4-Cyclopropanesulfonyl-2,5-difluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	1-(4-Cyclopropanesulfonyl-2,5-difluoro-phenyl)-piperazine hydrochloride (compound 6.34) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	543.3
596	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(4-cyclobutanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Cyclobutanesulfonyl-2-fluoro-phenyl)-piperazine hydrochloride (compound 6.24) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	553.6
597	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-{4-[2,3-difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazin-1-yl}-methanone	1-[2,3-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine hydrochloride (compound 6.29) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	503.1 (M - tBu+H)
598	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2,3-difluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Ethanesulfonyl-2,3-difluoro-phenyl)-piperazine hydrochloride (compound 6.30) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	489.2 (M - tBu+H)

599	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(4-cyclopropanesulfonyl-2,3-difluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Cyclopropanesulfonyl-2,3-difluoro-phenyl)-piperazine hydrochloride (compound 6.31) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	501.1 (M - tBu+H)
600	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-{4-[2,5-difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazin-1-yl}-methanone	1-[2,5-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine hydrochloride (compound 6.32) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	503.2 (M - tBu+H)
601	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2,5-difluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Ethanesulfonyl-2,5-difluoro-phenyl)-piperazine hydrochloride (compound 6.33) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	489.1 (M - tBu+H)
602	(2-tert-Butoxy-5-methanesulfonyl-phenyl)-[4-(4-cyclopropanesulfonyl-2,5-difluoro-phenyl)-piperazin-1-yl]-methanone	1-(4-Cyclopropanesulfonyl-2,5-difluoro-phenyl)-piperazine hydrochloride (compound 6.34) and 2-tert-Butoxy-5-methanesulfonyl-benzoic acid (compound 2.19)	501.3 (M - tBu+H)
603	[4-(4-Cyclobutanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(4-Cyclobutanesulfonyl-2-fluoro-phenyl)-piperazine hydrochloride (compound 6.24) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	579.1

604	{4-[2,3-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazin-1-yl}-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-[2,3-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine hydrochloride (compound 6.29) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	602.2 (M+NH ₄ ⁺)
605	[4-(4-Ethanesulfonyl-2,3-difluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(4-Ethanesulfonyl-2,3-difluoro-phenyl)-piperazine hydrochloride (compound 6.30) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	571.2
606	[4-(4-Cyclopropanesulfonyl-2,3-difluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(4-Cyclopropanesulfonyl-2,3-difluoro-phenyl)-piperazine hydrochloride (compound 6.31) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	600.2 (M+NH ₄ ⁺)
607	{4-[2,5-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazin-1-yl}-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-[2,5-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine hydrochloride (compound 6.32) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	602.3 (M+NH ₄ ⁺)
608	[4-(4-Ethanesulfonyl-2,5-difluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(4-Ethanesulfonyl-2,5-difluoro-phenyl)-piperazine hydrochloride (compound 6.33) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	588.3 (M+NH ₄ ⁺)

609	[4-(4-Cyclopropanesulfonyl-2,5-difluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone	1-(4-Cyclopropanesulfonyl-2,5-difluoro-phenyl)-piperazine hydrochloride (compound 6.34) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	600.2 (M+NH ₄ ⁺)
610	rac-[4-(4-Cyclobutanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(4-Cyclobutanesulfonyl-2-fluoro-phenyl)-piperazine hydrochloride (compound 6.24) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	593.2
611	rac-{4-[2,3-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazin-1-yl}-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-[2,3-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine hydrochloride (compound 6.29) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	599.2
612	rac-[4-(4-Ethanesulfonyl-2,3-difluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(4-Ethanesulfonyl-2,3-difluoro-phenyl)-piperazine hydrochloride (compound 6.30) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	602.2 (M+NH ₄ ⁺)

613	rac-[4-(4-Cyclopropanesulfonyl-2,3-difluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(4-Cyclopropanesulfonyl-2,3-difluoro-phenyl)-piperazine hydrochloride (compound 6.31) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	614.3(M+NH ₄ ⁺)
614	rac-4-[2,5-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-[2,5-Difluoro-4-(propane-2-sulfonyl)-phenyl]-piperazine hydrochloride (compound 6.32) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	616.2 (M+NH ₄ ⁺)
615	rac-[4-(4-Ethanesulfonyl-2,5-difluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(4-Ethanesulfonyl-2,5-difluoro-phenyl)-piperazine hydrochloride (compound 6.33) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	602.3 (M+NH ₄ ⁺)
616	rac-[4-(4-Cyclopropanesulfonyl-2,5-difluoro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(4-Cyclopropanesulfonyl-2,5-difluoro-phenyl)-piperazine hydrochloride (compound 6.34) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	614.3 (M+NH ₄ ⁺)

617	[4-(4-Hydroxy-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone	4-Piperazin-1-yl-phenol (commercial) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	419.1
618	rac-(2-Isopropoxy-5-methanesulfonyl-phenyl)-[3-methyl-4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone	rac-2-Methyl-1-(4-trifluoromethyl-phenyl)-piperazine hydrochloride (compound 6.35) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	485.2
619	1-{4-Isopropoxy-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-phenyl}-ethanone	1-(4-Trifluoromethyl-phenyl)-piperazine (commercial) and 5-Acetyl-2-isopropoxy-benzoic acid (compound 6.36)	435.2

Example 6.37

Preparation of 4-isopropoxy-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzoic acid

5 (a) 4-Isopropoxy-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzonitrile

To a solution of 3.6 mmol 5-cyano-2-isopropoxy-benzoic acid (compound 1.13) in 20 ml THF were added 4.0 mmol TBTU, 21.6 mmol N-ethyldiisopropylamine and 4.0 mmol 1-(4-trifluoromethyl-phenyl)-piperazine (commercial). The reaction was then stirred at RT for 16 h, concentrated in vacuo, and purified by chromatography on silica gel (eluant: ethyl acetate/heptane 1:1) to afford the title compound. MS (m/e): 418.3 (M+H⁺, 100%)

10 (b) 4-Isopropoxy-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzoic acid

To 3.2 mmol 4-isopropoxy-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzonitrile in 15 ml ethanol was added 30 mmol 2 M aq NaOH and the mixture was heated at 85 °C for 16 h. The mixture was then cooled to RT, diluted with water and acidified to pH 1 with conc HCl, and then extracted three times with ethyl acetate. The combined organic phases were dried with Na₂SO₄, concentrated in vacuo, and the

residue purified by chromatography on silica gel (eluant: methanol/dichloromethane 5:95) to afford the title compound. MS (m/e): 435.3 ($[M-H]^-$, 100%)

Example 620

Preparation of 4-isopropoxy-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzoic acid methyl ester

5

To 0.3 mmol 4-isopropoxy-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzoic acid in 2 ml DMF was added 0.4 mmol CDI and the mixture heated at 50 °C for 30 min. 5.2 mmol methanol was then added and the mixture was stirred at RT for 16 h. The mixture was then cooled to room temperature, concentrated in vacuo, and the residue chromatographed on silica gel (eluant: ethyl acetate/heptane 1:4) to afford the title compound. MS (m/e): 451.2 ($M+H^+$, 100%)

10

Example 621

Preparation of 4-isopropoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzamide

To 0.3 mmol 4-isopropoxy-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzoic acid in 2 ml DMF was added 0.4 mmol CDI and the mixture heated at 50 °C for 30 min. 5.2 mmol methylamine (41% aq solution) was then added and the mixture was stirred at RT for 16 h. The mixture was then cooled to room temperature, concentrated in vacuo, and the residue chromatographed on silica gel (eluant: ethyl acetate) to afford the title compound. MS (m/e): 450.1 ($M+H^+$, 100%)

20

Example 6.38

Preparation of 3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-hydroxy-benzenesulfonamide

(a) 2-Hydroxy-5-sulfamoyl-benzoic acid

Ammonia gas was bubbled through a solution of 107 mmol 5-chlorosulfonyl-2-hydroxy-benzoic acid in 250 ml acetone at 0 °C for 2 h. Argon gas was then bubbled through the reaction mixture for 1 h to purge excess ammonia. The mixture was then diluted with water, the pH adjusted to pH 14 by addition of 5 M aq NaOH solution, and the mixture was then extracted with ether/ethyl acetate (1:1). The aqueous phase was acidified with concentrated HCl, saturated with NaCl, and extracted twice with THF. The combined THF extracts were dried with Na_2SO_4 . Evaporation of the solvent in vacuo followed by

30

drying of the residue by heating at 60 °C overnight in vacuo yielded the title compound.
MS (m/e): 216.1 ([M-H]⁺, 100%)

(b) 2-Hydroxy-5-sulfamoyl-benzoic acid methyl ester

To 62 mmol 2-hydroxy-5-sulfamoyl-benzoic acid in 80 ml THF was added 80 mmol CDI
5 and the mixture heated at 50 °C for 1 h. 616 mmol methanol was then added and the
mixture was heated at 50 °C for 16 h. The mixture was then cooled to room temperature,
concentrated in vacuo, and the residue chromatographed on silica gel (eluant:
dichloromethane/methanol 20:1). The product containing fractions were concentrated in
vacuo and the residue suspended in ethyl acetate and washed with aq NaHCO₃ solution.
10 The organic phase was dried with Na₂SO₄ and concentrated in vacuo to afford the
title compound. MS (m/e): 230.2 ([M-H]⁺, 100%)

(c) 2-(4-Methoxy-benzyloxy)-5-sulfamoyl-benzoic acid methyl ester

To 4.8 mmol 2-hydroxy-5-sulfamoyl-benzoic acid methyl ester, 5.2 mmol 4-
methoxybenzyl alcohol and 5.2 mmol triphenylphosphine in 8 ml THF was added 5.2
15 mmol di-tert-butyl azodicarboxylate and the mixture was stirred at RT for 2 h. The
mixture was then concentrated in vacuo. The residue was chromatographed on silica gel
(eluant: ethyl acetate/heptane gradient) to afford the title compound. MS (m/e): 350.2
([M-H]⁺, 100%)

(d) 2-(4-Methoxy-benzyloxy)-5-sulfamoyl-benzoic acid

To 2.5 mmol 2-(4-methoxy-benzyloxy)-5-sulfamoyl-benzoic acid methyl ester in 6 ml
THF was added 5 mmol 2 M aq NaOH and the mixture was heated at 60 °C for 30 min.
The mixture was then cooled to RT and extracted twice with ethyl acetate. The aqueous
phase was acidified to pH 1 with 5 M aq HCl and extracted with ethyl acetate. The
combined organic phases were washed with saturated aq NaCl and dried with Na₂SO₄.
25 Evaporation in vacuo afforded the title compound. MS (m/e): 336.1 ([M-H]⁺, 100%)

(e) (3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-(4-methoxy-benzyloxy)-
benzenesulfonamide

To a solution of 3.5 mmol 2-(4-methoxy-benzyloxy)-5-sulfamoyl-benzoic acid in 4 ml
dimethylformamide and 12 ml THF were added 5.3 mmol TBTU, 17.5 mmol N-
30 ethyldiisopropylamine and 3.5 mmol 3-fluoro-4-piperazin-1-yl-benzonitrile
(WO9625414). The reaction was then stirred at RT for 1 h, concentrated in vacuo, and

purified by chromatography on silica gel (eluant: ethyl acetate/heptane gradient) to afford the title compound. MS (m/e): 525.1 (M+H⁺)

(f) (3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-hydroxy-benzenesulfonamide

- 5 Hydrogen gas was bubbled through a solution of 1.0 mmol (3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-(4-methoxy-benzyloxy)-benzenesulfonamide in 40 ml THF containing 50 mg 10% palladium on charcoal and a few drops of acetic acid for 6 h at RT. The reaction mixture was then purged with argon, filtered through celite, and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica
10 gel (eluant: methanol/dichloromethane gradient) to afford the title compound. MS (m/e): 403.1 ([M-H]⁻, 100%)

In analogy to Example 6.38(e) and (f), compounds 6.39 and 6.40 of the following table were prepared from 2-(4-methoxy-benzyloxy)-5-sulfamoyl-benzoic acid and the appropriate piperazine, followed by hydrogenolysis with catalytic palladium on charcoal:

Expl. No	name	piperazine	MS (m/e)
6.39	3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-hydroxy-benzenesulfonamide	3-Fluoro-4-piperazin-1-yl-benzonitrile (WO9625414)	403.1 (M -H)
6.40	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-hydroxy-benzenesulfonamide	1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial)	456.2 (M -H)

15

Example 622

Preparation of 3-[4-(4-cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-isobutoxy-benzenesulfonamide

- To 0.1 mmol (3-[4-(4-cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-hydroxy-benzenesulfonamide (compound 6.38), 0.5 mmol 2-methyl-1-propanol and 0.3 mmol
20 diphenyl-2-pyridylphosphine in 4 ml THF was added 0.3 mmol di-tert-butyl azodicarboxylate and the mixture was stirred at 60 °C for 4 h. The mixture was then

diluted with ethyl acetate and washed twice with 5 M aq HCl and then with saturated aq NaCl solution. The organic phase was then dried with Na₂SO₄, and concentrated in vacuo. The residue was triturated in ether to afford the title compound. MS (m/e): 459.2 ([M-H]⁺, 100%)

- 5 In analogy to Example 622, compounds 623 to 632 of the following table were prepared from compounds 6.38 to 6.40 and the appropriate alcohol:

Expl. No.	name	Starting materials	MW found (MH ⁺)
623	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclopentyloxy-benzenesulfonamide	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-hydroxy-benzenesulfonamide (compound 6.38) and cyclopentanol	471.3 (M-H)
624	3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-benzenesulfonamide	3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-hydroxy-benzenesulfonamide (compound 6.39) and 2-propanol	445.2 (M-H)
625	3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-isobutoxy-benzenesulfonamide	3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-hydroxy-benzenesulfonamide (compound 6.39) and 2-methyl-1-propanol	459.2 (M-H)
626	3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclopentyloxy-benzenesulfonamide	3-[4-(4-Cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-hydroxy-benzenesulfonamide (compound 6.39) and cyclopentanol	471.3 (M-H)

627	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-isobutoxy-benzenesulfonamide	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-hydroxy-benzenesulfonamide (compound 6.40) and 2-methyl-1-propanol	512.3 (M-H)
628	4-Cyclopentyloxy-3-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-hydroxy-benzenesulfonamide (compound 6.40) and cyclopentanol	524.5 (M-H)
629	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-benzenesulfonamide	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-hydroxy-benzenesulfonamide (compound 6.38) and 2-propanol	445.1 (M-H)
630	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclobutylmethoxy-benzenesulfonamide	3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-hydroxy-benzenesulfonamide (compound 6.38) and cyclobutanemethanol	471.3 (M-H)
631	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-benzenesulfonamide	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-hydroxy-benzenesulfonamide (compound 6.40) and 2-propanol	498.4 (M-H)
632	4-Cyclobutylmethoxy-3-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide	3-[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine-1-carbonyl]-4-hydroxy-benzenesulfonamide (compound 6.40) and cyclobutanemethanol	524.5 (M-H)

Example 7.1:

Preparation of 3-Piperazin-1-yl-5-trifluoromethyl-pyridazine

(a)-3-Chloro-5-trifluoromethyl-pyridazine

5 5-Trifluoromethyl-pyridazin-3-ol [244268-34-6 (1g) was added to a stirred solution of phosphoryloxychloride and the reaction mixture was stirred at 80°C for 1 hour. After such time, the reaction mixture was allowed to cool to room temperature, poured onto ice and after 5 minutes was extracted twice from the aqueous solution with dichloromethane. The combined organic phases were dried with sodium sulfate and concentrated *in vacuo*. The residue was distilled in a Kugelrohr apparatus (bp = 80-100°C
10 @ 12 mBar) to yield the title compound (0.26g). MS (m/e): 182.0

(b) 4-(5-Trifluoromethyl-pyridazin-3-yl)-piperazine-1-carboxylic acid tert-butyl ester

3-Chloro-5-trifluoromethyl-pyridazine (200mg) was added to piperazine-1-carboxylic acid tert-butyl ester (231mg) in dimethylacetamide (3mL) and the reaction mixture was stirred at 100°C for 3 hours. After such time the reaction mixture was allowed to cool
15 down to room temperature and diluted with ethyl acetate. The solid was filtered off and washed with ethyl acetate. The filtrate was then concentrated *in vacuo* and then purified by column chromatography (SiO₂, Heptane/EtOAc) to yield the title compound as a white solid (364mg). MS (m/e): 333.4 (M+H⁺, 100%)

(c) 3-Piperazin-1-yl-5-trifluoromethyl-pyridazine

20 4-(5-Trifluoromethyl-pyridazin-3-yl)-piperazine-1-carboxylic acid tert-butyl ester (45mg) was dissolved in dichloromethane (0.5 mL) and trifluoroacetic acid was added (0.5 mL). The reaction mixture was stirred for 30 minutes before being concentrated *in vacuo* to afford the crude title compound which was used directly in the next step without further purification or analysis.

25

Example 7.2:

Preparation of 5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-benzoic acid

To 2-Fluoro-5-methanesulfonyl-benzoic acid (247569-56-8) (600 mg) in dimethylacetamide (10 mL) was added cesium carbonate at 170°C. 2-trifluoromethyl-propanol (0.94 mL) was first added to the reaction mixture followed by additionally 0.47
30 mL every 24 hours. After a total of 72 hours, the reaction mixture was acidified by

addition of formic acid, concentrated *in vacuo* and purified by preparative HPLC to yield the title compound as a light brown solid (897 mg). MS (m/e): 325.3. (M-H, 100%)

Example 7.3:

Preparation of 5-Methanesulfonyl-2-piperazin-1-yl-pyrimidine

5 (a) 3-Dimethylamino-2-methanesulfonyl-allylidene-dimethyl-ammonium; chloride

To sulfonyl-acetic acid (1.5g) in dimethylformamide was slowly added phosphorus oxychloride over 5 minutes and the reaction was then stirred at 70°C for 1 hour and then at room temperature overnight. The reaction mixture was then directly poured over a short column chromatography (SiO₂, 100 g) eluting successively with 500 mL of EtOAc, THF, EtOAc/EtOH (50/50), EtOH and finally MeOH to yield the title compound (1.58g). MS (m/e): 204.9 (M⁺).

10 (b) 5-Methanesulfonyl-2-piperazin-1-yl-pyrimidine

The title compound was prepared in analogy to Example 2.25 using 3-Dimethylamino-2-methanesulfonyl-allylidene-dimethyl-ammonium; chloride as starting material. MS (m/e): 243.1 (M+H⁺, 100%).

Example 7.4:

Preparation of 1-(5-Methanesulfonyl-pyridin-2-yl)-piperazine trifluoro-acetic acid

The title compound was prepared in analogy to Example 7.1 (b-c) from 2-bromo-5-(methanesulfonyl) pyridine and piperazine-1-carboxylic acid *tert*-butyl ester. MS (m/e): 242.1 (M+H⁺, 100%)

In analogy to Example 5, compounds 633 to 644 of the following table were prepared from the acid derivatives and piperazine derivatives:

Expl.- No.	Systematic Name	Starting materials	MW found (MH ⁺)
633	rac-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyridazin-3-yl)-piperazin-1-yl]-methanone	3-Piperazin-1-yl-5-trifluoromethyl-pyridazine (compound 7.1) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	527.0
634	[5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone	2-Piperazin-1-yl-5-trifluoromethyl-pyrimidine (compound 2.25) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-benzoic acid (compound 7.2)	541.0
635	[5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone	2-Piperazin-1-yl-5-trifluoromethyl-pyrimidine (compound 2.25) and 5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 5.6)	527.2
636	[5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone	2-Piperazin-1-yl-5-trifluoromethyl-pyrimidine (compound 2.25) and 5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 5.7)	527.2

637	[4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-phenyl]-methanone	1-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine (compound 5.5) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-benzoic acid (compound 7.2)	558.2
638	[5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone	2-Piperazin-1-yl-5-trifluoromethyl-pyrimidine (compound 2.25) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (compound 1.5)	513.3
639	(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone	2-Piperazin-1-yl-5-trifluoromethyl-pyrimidine (compound 2.25) and 2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (compound 1.4)	485.4
640	[4-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-phenyl]-methanone	1-(2,5-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid (compound 2.20) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-benzoic acid (compound 7.2)	585.3
641	[4-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-phenyl]-methanone	1-(2,3-Difluoro-4-methanesulfonyl-phenyl)-piperazine (compound 5.3) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-benzoic acid (compound 7.2)	585.3

642	[4-(2,6-Difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-phenyl]-methanone	1-(2,6-Difluoro-4-methanesulfonyl-phenyl)-piperazine trifluoro-acetic acid (compound 2.23) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-benzoic acid (compound 7.2)	585.2
643	rac-[4-(5-Methanesulfonyl-pyrimidin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	5-Methanesulfonyl-2-piperazin-1-yl-pyrimidine (compound 7.3) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	537.3
644	rac-[4-(5-Methanesulfonyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone	1-(5-Methanesulfonyl-pyridin-2-yl)-piperazine trifluoro-acetic acid (compound 7.4) and rac-5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 3.1)	536.3

Example 645

Preparation of (2-Allyloxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

- 5 The title compound was prepared in analogy to example 62 from (2-Hydroxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone (compound 2.1) and cyclopropyl bromide. MS (m/e): 436.5 (MH⁺, 100%)

Example 7.5:

Preparation of 2-Benzoyloxy-5-methanesulfonyl-benzoic acid

- 10 The title compound was prepared in analogy to example 2.10 from methyl 5-(methanesulfonyl)salicylate and benzylalcohol. MS (m/e): 305.3 (M-H, 100%)

Example 646**Preparation of (2-Benzyloxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone**

The title compound was prepared in analogy to example 5 from 1-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine (compound 5.5) and 2-Benzyloxy-5-methanesulfonyl-benzoic acid (compound 7.5). MS (m/e): 538.4 (MH⁺, 100%)

Example 647**Preparation of (2-Benzyloxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone**

The title compound was prepared in analogy to example 5 from 1-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazine (commercial) and 2-Benzyloxy-5-methanesulfonyl-benzoic acid (compound 7.5). MS (m/e): 547.4 (MH⁺, 100%)

Example 648**Preparation of [4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-hydroxy-5-methanesulfonyl-phenyl)-methanone**

A mixture of 0.915 mmol (2-benzyloxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone, 0.05 mmol palladium on charcoal (10%) in 12.5 ml methanol was hydrogenated at atmospheric pressure at room temperature for 2 hours. After addition of chloroform, the mixture was filtered and the solvent was evaporated to provide the title compound. MS (m/e): 474.3 (M+NH₄⁺, 100%)

Example 7.6**Preparation of 5-Piperazin-1-yl-2-trifluoromethyl-pyrimidine****(a) 5-Chloro-2-trifluoromethyl-pyrimidine**

To a solution of 38 mmol trifluoroacetamide in 70 ml acetonitrile was added 37.92 mmol ((Z)-2-Chloro-3-dimethylamino-allylidene)-dimethyl-ammonium hexafluoro phosphate (CAS: 291756-76-8) followed by 45.5 mmol triethylamine. The yellow solution was stirred at room temperature for 5 hours, then poured onto water and extracted 3 times with ether. The combined extracts were dried over sodium sulfate,

filtered and distilled at 760 mm Hg to provide the title compound. MS (m/e): 182.2 (M^+ , 100%)

(b) 4-(2-Trifluoromethyl-pyrimidin-5-yl)-piperazine-1-carboxylic acid tert-butyl ester

- 0.26 mmol 5-Chloro-2-trifluoromethyl-pyrimidine was added to 0.26 mmol piperazine-
5 1-carboxylic acid tert-butyl ester in 1.5 ml dimethylacetamide and the reaction mixture was stirred at 150°C for 10 min. in a microwave oven. After such time the reaction mixture was concentrated and the residue was then purified by column chromatography (SiO_2 , Heptane/EtOAc) to yield the title compound. MS (m/e): 333.2 ($M+H^+$, 100%)

(c) 5-Piperazin-1-yl-2-trifluoromethyl-pyrimidine

- 10 The title compound was prepared in analogy to Example 7.1 (c) from 4-(2-trifluoromethyl-pyrimidin-5-yl)-piperazine-1-carboxylic acid tert-butyl ester MS (m/e): 233.0 ($M+H^+$, 100%)

Example 7.7

Preparation of 5'-Trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl

- 15 (a) 2-Bromo-5-trifluoromethyl-pyrazine

- To a suspension of 0.423 mmol copper (II) bromide in THF (1 ml) was added dropwise 0.51 mmol tert-butylnitrite at 0°C within 2 minutes. 0.37 mmol 5-Trifluoromethyl-pyrazin-2-ylamine (CAS: 69816-38-2; WO9518097) in solution in THF (0.5 ml) was added dropwise within 5 minutes at 0°C. The mixture was stirred at 0°C for 1 hour, at
20 room temperature for 21 hours and quenched with water. The aqueous phase was extracted with ether. The combined extracts were dried over sodium sulfate and filtered and concentrated at atmospheric pressure. The residue was then purified by column chromatography (SiO_2 , ether) to yield the title compound.

(b) 5'-Trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl

- 25 The title compound was prepared in analogy to Example 7.6 (b-c) from 2-Bromo-5-trifluoromethyl-pyrazine MS (m/e): 233.0 ($M+H^+$, 100%)

Example 7.8

Preparation of 3-Piperazin-1-yl-6-trifluoromethyl-pyridazine

- The title compound was prepared in analogy to Example 7.6 (b-c) from 3-Chloro-6-
30 trifluoromethyl-pyridazine (CAS: 258506-68-2). MS (m/e): 233.0 ($M+H^+$, 100%)

In analogy to Example 5, compounds 649 to 660 of the following table were prepared from the acid derivatives and piperazine derivatives:

Expl.- No.	Systematic Name	Starting materials	MW found (MH ⁺)
649	[5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(2-trifluoromethyl-pyrimidin-5-yl)-piperazin-1-yl]-methanone	5-Piperazin-1-yl-2-trifluoromethyl-pyrimidine (compound 7.6) and 5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 5.6)	527.2
650	[5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(2-trifluoromethyl-pyrimidin-5-yl)-piperazin-1-yl]-methanone	5-Piperazin-1-yl-2-trifluoromethyl-pyrimidine (compound 7.6) and 5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 5.7)	527.0
651	(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(2-trifluoromethyl-pyrimidin-5-yl)-piperazin-1-yl]-methanone	5-Piperazin-1-yl-2-trifluoromethyl-pyrimidine (compound 7.6) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	473.0
652	[5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[5'-(2-trifluoromethyl-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-methanone	5'-(2-Trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl (compound 7.7) and 5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 5.6)	527.2

653	[5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-(5'-trifluoromethyl-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-methanone	5'-Trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl (compound 7.7) and 5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 5.7)	527.2
654	(2-Isopropoxy-5-methanesulfonyl-phenyl)-(5'-trifluoromethyl-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-methanone	5'-Trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl (compound 7.7) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	473.4
655	[5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(6-trifluoromethyl-pyridazin-3-yl)-piperazin-1-yl]-methanone	3-Piperazin-1-yl-6-trifluoromethyl-pyridazine (compound 7.8) and 5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 5.6)	527.3
656	(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(6-trifluoromethyl-pyridazin-3-yl)-piperazin-1-yl]-methanone	3-Piperazin-1-yl-6-trifluoromethyl-pyridazine (compound 7.8) and 2-Isopropoxy-5-methanesulfonyl-benzoic acid (compound 1.2)	473.3
657	[5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(6-trifluoromethyl-pyridazin-3-yl)-piperazin-1-yl]-methanone	3-Piperazin-1-yl-6-trifluoromethyl-pyridazine (compound 7.8) and 5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (compound 5.7)	527.3

658	[5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-phenyl]-[4-(2-trifluoromethyl-pyrimidin-5-yl)-piperazin-1-yl]-methanone	5-Piperazin-1-yl-2-trifluoromethyl-pyrimidine (compound 7.6) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-benzoic acid (compound 7.2)	541.3
659	[5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-phenyl]-[4-(6-trifluoromethyl-pyridazin-3-yl)-piperazin-1-yl]-methanone	3-Piperazin-1-yl-6-trifluoromethyl-pyridazine (compound 7.8) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-benzoic acid (compound 7.2)	541.3
660	[5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-phenyl]-(5'-trifluoromethyl-2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-methanone	5'-Trifluoromethyl-3,4,5,6-tetrahydro-2H-[1,2']bipyrazinyl (compound 7.7) and 5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-benzoic acid (compound 7.2)	541.3

The compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. Specifically, it has been found that the compounds of the present invention are good inhibitors of the glycine transporter I (GlyT-1).

- 5 The compounds were investigated in accordance with the test given hereinafter.

Solutions and materials

DMEM complete medium: Nutrient mixture F-12 (Gibco Life-technologies), fetal bovine serum (FBS) 5 %, (Gibco life technologies), Penicillin/Streptomycin 1 % (Gibco life technologies), Hygromycin 0.6 mg/ml (Gibco life technologies), Glutamine 1 mM Gibco

10 life technologies)

Uptake buffer (UB): 150 mM NaCl, 10 mM Hepes-Tris, pH 7.4, 1 mM CaCl₂, 2.5 mM KCl, 2.5 mM MgSO₄, 10 mM (+) D-glucose.

Flp-inTM-CHO (Invitrogen Cat n° R758-07) cells stably transfected with mGlyT1b cDNA.

Glycine uptake inhibition assay (mGlyT-1b)

- 5 On day 1 mammalian cells, (Flp-inTM-CHO), transfected with mGlyT-1b cDNA, were plated at the density of 40,000 cells/well in complete F-12 medium, without hygromycin in 96-well culture plates. On day 2, the medium was aspirated and the cells were washed twice with uptake buffer (UB). The cells were then incubated for 20 min at 22°C with either (i) no potential competitor, (ii) 10 mM non-radioactive glycine, (iii) a
- 10 concentration of a potential inhibitor. A range of concentrations of the potential inhibitor was used to generate data for calculating the concentration of inhibitor resulting in 50 % of the effect (e.g. IC₅₀, the concentration of the competitor inhibiting glycine uptake of 50 %). A solution was then immediately added containing [³H]-glycine 60 nM (11-16 Ci/mmol) and 25 µM non-radioactive glycine. The plates were incubated
- 15 with gentle shaking and the reaction was stopped by aspiration of the mixture and washing (three times) with ice-cold UB. The cells were lysed with scintillation liquid, shaken 3 hours and the radioactivity in the cells was counted using a scintillation counter.

The prepared compounds show an IC₅₀ (µM) at GlyT-1 in the range of 0.006 – 5.0. The preferred compounds show an IC₅₀ (µM) at GlyT-1 in the range of 0.006 – 0.05, as

20 shown in the table below.

Example No.	IC ₅₀ (µM)	Example No.	IC ₅₀ (µM)	Example No.	IC ₅₀ (µM)
1	0.039	213	0.021	430	0.037
5	0.012	215	0.049	435	0.029
15	0.015	228	0.047	437	0.026
28	0.012	234	0.043	438	0.047
54	0.05	244	0.042	439	0.021
62	0.017	247	0.03	459	0.04
63	0.028	249	0.032	461	0.046
64	0.025	250	0.061	464	0.02

66	0.032	251	0.032	465	0.04
68	0.008	256	0.032	466	0.026
70	0.008	258	0.086	468	0.02
71	0.008	260	0.043	469	0.02
72	0.026	261	0.043	470	0.03
74	0.016	262	0.042	475	0.04
78	0.012	281	0.021	481	0.03
80	0.029	282	0.027	488	0.039
84	0.04	283	0.008	491	0.037
88	0.007	284	0.01	494	0.03
92	0.05	285	0.042	504	0.025
95	0.035	287	0.033	505	0.024
100	0.02	288	0.025	506	0.046
104	0.046	289	0.018	507	0.031
105	0.039	290	0.017	408	0.026
109	0.021	291	0.013	509	0.03
111	0.035	292	0.021	510	0.015
112	0.024	293	0.034	514	0.045
116	0.019	294	0.037	515	0.04
117	0.044	295	0.016	517	0.035
118	0.024	296	0.043	518	0.033
128	0.02	298	0.021	519	0.035

131	0.03	299	0.044	524	0.012
132	0.038	300	0.016	525	0.021
135	0.041	301	0.03	526	0.009
136	0.027	302	0.013	527	0.006
137	0.027	303	0.006	528	0.015
138	0.017	311	0.045	529	0.013
139	0.024	313	0.018	530	0.0057
142	0.034	317	0.041	531	0.028
144	0.045	319	0.031	534	0.049
145	0.015	321	0.018	537	0.03
146	0.019	322	0.028	546	0.035
147	0.031	324	0.039	554	0.019
148	0.036	325	0.033	557	0.042
164	0.019	328	0.032	558	0.029
165	0.47	329	0.016	561	0.038
167	0.016	330	0.018	562	0.044
169	0.012	363	0.008	563	0.043
170	0.031	367	0.036	564	0.041
172	0.019	369	0.032	566	0.03
180	0.036	371	0.041	568	0.044
182	0.03	372	0.006	570	0.046
184	0.022	373	0.035	571	0.05

186	0.048	375	0.035	573	0.037
194	0.047	393	0.032	574	0.034
196	0.041	400	0.023	576	0.039
202	0.024	407	0.027	578	0.041
207	0.023	408	0.037	589	0.032
209	0.041	411	0.045	595	0.049
210	0.039	412	0.033	637	0.047
211	0.043	413	0.03		
212	0.029	417	0.046		

The compounds of formula I and the pharmaceutically acceptable salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions.

The compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations.

10 Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are however usually required in the case of soft gelatine capsules.

15 Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying

the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of schizophrenia, cognitive impairment and Alzheimer's disease.

The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

Tablet Formulation (Wet Granulation)

Item	Ingredients	<u>mg/tablet</u>			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
- 5 4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

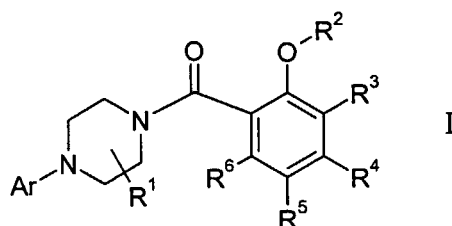
	<u>Item</u>	<u>Ingredients</u>	<u>mg/capsule</u>			
			5 mg	25 mg	100 mg	500 mg
	1.	Compound of formula I	5	25	100	500
10	2.	Hydrous Lactose	159	123	148	---
	3.	Corn Starch	25	35	40	70
	4.	Talc	10	15	10	25
	5.	Magnesium Stearate	1	2	2	5
		Total	200	200	300	600

15 Manufacturing Procedure

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Claims

1. Compounds of general formula



5 wherein

Ar is unsubstituted or substituted aryl or 6-membered heteroaryl, containing one, two or three nitrogen atoms, and wherein the aryl and the heteroaryl groups may be substituted by one or more substituents selected from the group consisting of hydroxy, halogen, NO₂, CN, (C₁-C₆)-alkyl, (C₁-C₆)-alkyl substituted by halogen, (C₁-C₆)-alkyl substituted by hydroxy, (CH₂)_n-(C₁-C₆)-alkoxy, (C₁-C₆)-alkoxy substituted by halogen, NR⁷R⁸, C(O)R⁹, SO₂R¹⁰, -C(CH₃)=NOR⁷, or by a 5-membered aromatic heterocycle, containing 1 – 4 heteroatoms, selected from N and O, which is optionally substituted by (C₁-C₆)-alkyl;

15 R¹ is hydrogen or (C₁-C₆)-alkyl;

R² is hydrogen, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₁-C₆)-alkyl substituted by halogen, (C₁-C₆)-alkyl substituted by hydroxy, (CH₂)_n-(C₃-C₇)-cycloalkyl optionally substituted by (C₁-C₆)-alkoxy or by halogen, or is CH(CH₃)-(C₃-C₇)-cycloalkyl, (CH₂)_{n+1}-C(O)-R⁹, (CH₂)_{n+1}-CN, bicyclo[2.2.1]heptyl, (CH₂)_{n+1}-O-(C₁-C₆)-alkyl, (CH₂)_n-heterocycloalkyl, (CH₂)_n-aryl or (CH₂)_n-5 or 6-membered heteroaryl containing one, two or three heteroatoms, selected from the group consisting of oxygen, sulphur or nitrogen wherein aryl, heterocycloalkyl and heteroaryl are unsubstituted or substituted by one or more substituents selected from the group consisting of hydroxy, halogen, (C₁-C₆)-alkyl or (C₁-C₆)-alkoxy;

R³, R⁴ and R⁶ independently from each other are hydrogen, hydroxy, halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy or O-(C₃-C₆)-cycloalkyl;

R^5 is NO_2 , CN , $\text{C}(\text{O})\text{R}^9$ or SO_2R^{10} ;

R^7 and R^8 independently from each other are hydrogen or $(\text{C}_1\text{-C}_6)\text{-alkyl}$;

5 R^9 is hydrogen, $(\text{C}_1\text{-C}_6)\text{-alkyl}$, $(\text{C}_1\text{-C}_6)\text{-alkoxy}$ or NR^7R^8 ;

R^{10} is $(\text{C}_1\text{-C}_6)\text{-alkyl}$ optionally substituted by halogen, $(\text{CH}_2)_n\text{-(C}_3\text{-C}_6\text{)-cycloalkyl}$,
 $(\text{CH}_2)_n\text{-(C}_3\text{-C}_6\text{)-alkoxy}$, $(\text{CH}_2)_n\text{-heterocycloalkyl}$ or NR^7R^8 ;

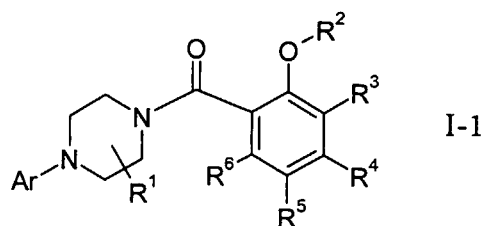
10 n is 0, 1, or 2;

and to pharmaceutically acceptable acid addition salts thereof,

with the proviso that

- 1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-(3-chlorophenyl)-piperazine,
 15 1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-(4-fluorophenyl)-piperazine,
 1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-[3-(trifluoromethyl)phenyl]-piperazine,
 4-(3-amino-4-nitrophenyl)-1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-methyl-piperazine,
 1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-methyl-4-(4-nitrophenyl)-
 20 piperazine,
 4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-methyl-1-(4-nitrophenyl)-piperazine,
 1-(2-chloro-4-nitrophenyl)-4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-piperazine,
 25 1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-4-(2,4-dinitrophenyl)-2-methyl-piperazine,
 1-(4-chloro-2-nitrophenyl)-4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-piperazine and
 4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-1-(2,4-dinitrophenyl)-2-methyl-
 30 piperazine
 are excluded.

2. Compounds of formula



wherein

5 Ar is substituted aryl or unsubstituted or substituted 6-membered heteroaryl, containing one, two or three nitrogen atoms, and wherein the aryl and the heteroaryl groups are substituted by one or more substituents selected from the group consisting of hydroxy, halogen, NO₂, CN, (C₁-C₆)-alkyl, (C₁-C₆)-alkyl substituted by halogen,

10 (C₁-C₆)-alkoxy, (C₁-C₆)-alkoxy substituted by halogen, NR⁷R⁸, C(O)R⁹ or SO₂R¹⁰;

R¹ is hydrogen or (C₁-C₆)-alkyl;

R² is (C₁-C₆)-alkyl, (C₁-C₆)-alkyl substituted by halogen, (C₃-C₆)-cycloalkyl, 15 heterocycloalkyl, (C₁-C₆)-alkyl-(C₃-C₆)-cycloalkyl, (C₁-C₆)-alkyl-heterocycloalkyl, (C₁-C₆)-alkyl-C(O)-R⁹, (C₁-C₆)-alkyl-CN, (C₂-C₆)-alkyl-O-R¹³, (C₂-C₆)-alkyl-NR⁷R⁸, aryl or 6-membered heteroaryl containing one, two or three nitrogen atoms, (C₁-C₆)-alkyl-aryl or (C₁-C₆)-alkyl-5 or 6-membered heteroaryl containing one, two or three heteroatoms, selected from the group consisting of oxygen, sulphur or 20 nitrogen wherein aryl, heterocycloalkyl and heteroaryl are unsubstituted or substituted by one or more substituents selected from the group consisting of hydroxy, halogen, (C₁-C₆)-alkyl or (C₁-C₆)-alkoxy;

R³, R⁴ and R⁶ independently from each other are hydrogen, hydroxy, halogen, CN, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy or NR⁷R⁸;

25

R⁵ is NO₂, CN, C(O)R⁹, SO₂R¹⁰ or NR¹¹R¹²;

R⁷ and R⁸ independently from each other are hydrogen or (C₁-C₆)-alkyl;

30 R⁹ is hydroxy, (C₁-C₆)-alkyl, (C₃-C₆)-cycloalkyl, (C₁-C₆)-alkoxy or NR⁷R⁸;

R¹⁰ is (C₁-C₆)-alkyl, (C₃-C₆)-cycloalkyl or NR⁷R⁸;

R¹¹ and R¹² independently from each other are hydrogen, C(O)-(C₁-C₆)-alkyl, SO₂-(C₁-C₆)-alkyl, or form together with the N-atom a 5-membered heteroaryl group, optionally substituted by halogen, (C₁-C₆)-alkyl, (C₁-C₆)-alkyl substituted by halogen or (C₃-C₆)-cycloalkyl;

R¹³ is hydroxy, (C₁-C₆)-alkyl or (C₃-C₆)-cycloalkyl;

and pharmaceutically acceptable acid addition salts thereof,

with the proviso that

1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-(3-chlorophenyl)-piperazine,
 1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-(4-fluorophenyl)-piperazine,
 1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-[3-(trifluoromethyl)phenyl]-piperazine,
 4-(3-amino-4-nitrophenyl)-1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-methyl-piperazine,
 1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-methyl-4-(4-nitrophenyl)-piperazine,
 4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-methyl-1-(4-nitrophenyl)-piperazine,
 1-(2-chloro-4-nitrophenyl)-4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-piperazine,
 1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-4-(2,4-dinitrophenyl)-2-methyl-piperazine,
 1-(4-chloro-2-nitrophenyl)-4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-piperazine and
 4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-1-(2,4-dinitrophenyl)-2-methyl-piperazine
 are excluded.

3. Compounds of formula I according to claim 1, wherein Ar is substituted phenyl, R² is (C₁-C₆)-alkyl and R⁵ is S(O)₂CH₃ or S(O)₂CH₂CH₃.

4. Compounds of formula I according to claim 3, wherein the compounds are:

1-[3-fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl]-ethanone,

- 3-fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
2-Fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
- 5 1-{3-fluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,
4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
3-fluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
2-fluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
- 10 (2-isobutoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone,
[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone,
- 15 [4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone,
[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
- 20 2,3-difluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
2,3-difluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
2,5-difluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
- 25 2,6-difluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
3,5-difluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
- 30 4-[4-(2-tert-butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,3-difluoro-benzonitrile,
5-chloro-2-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
4-[4-(2-tert-butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,5-difluoro-benzonitrile,
- 35 4-[4-(2-tert-butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile,
(2-tert-butoxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,

- (2-tert-butoxy-5-methanesulfonyl-phenyl)-[4-(2,5-difluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone,
1-(4-{4-[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-3-fluoro-phenyl)-ethanone,
5 4-{4-[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-benzonitrile,
4-{4-[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-3-fluoro-benzonitrile,
4-{4-[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-2-fluoro-
10 benzonitrile,
[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
15 [2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(2-fluoro-4-ethanesulfonyl-phenyl)-piperazin-1-yl]-methanone,
rac-1-{4-[4-(2-sec-butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-
20 phenyl}-ethanone,
rac-4-[4-(2-sec-butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile,
rac-4-[4-(2-sec-butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-benzonitrile,
25 rac-(2-sec-butoxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
rac-(2-sec-butoxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
(2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethanesulfonyl-phenyl)-
30 piperazin-1-yl]-methanone,
(2-isobutoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethanesulfonyl-phenyl)-piperazin-1-yl]-methanone,
2-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-benzonitrile,
35 1-{2-fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,
[4-(3-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-

- methanesulfonyl-phenyl)-methanone,
 1-{2-fluoro-4-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-
 ethanone,
 2-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-
 5 benzonitrile,
 (5-ethanesulfonyl-2-isopropoxy-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-
 piperazin-1-yl]-methanone,
 [4-(4-difluoromethyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-
 methanesulfonyl-phenyl)-methanone,
 10 [4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-
 methanesulfonyl-phenyl)-methanone,
 3-fluoro-4-[4-(2-isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzaldehyde,
 [4-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-
 phenyl)-methanone,
 15 rac-(2-sec-butoxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-
 piperazin-1-yl]-methanone,
 [4-(4-cyclobutanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-
 methanesulfonyl-phenyl)-methanone,
 [4-(4-cyclopentanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-
 20 methanesulfonyl-phenyl)-methanone,
 [4-(4-cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-(2-isobutoxy-5-
 methanesulfonyl-phenyl)-methanone and
 [4-(4-cyclopropanesulfonyl-2,5-difluoro-phenyl)-piperazin-1-yl]-(2-isopropoxy-5-
 methanesulfonyl-phenyl)-methanone.

- 25 5. Compounds of formula I according to claim 1, wherein Ar is substituted phenyl,
 R^2 is $(CH_2)_n-(C_3-C_7)$ -cycloalkyl and R^5 is $S(O)_2CH_3$.

6. Compounds of formula I according to claim 5, wherein the compounds are:

- 1-{4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-
 phenyl}-ethanone,
 30 4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
 4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-
 benzonitrile,
 4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-
 benzonitrile,
 35 (2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-

- piperazin-1-yl]-methanone,
(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
5 1-{4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,
4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-
10 benzonitrile,
4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-benzonitrile,
(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
15 (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
Rac-[2-(1-cyclopropyl-ethoxy)-5-methanesulfonyl-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
20 4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,3-difluoro-benzonitrile,
4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,5-difluoro-benzonitrile,
25 4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-benzonitrile,
4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile,
30 (2-cyclobutylmethoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
1-{4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,
2-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-5-
35 trifluoromethyl-benzonitrile,
4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,3-difluoro-benzonitrile,

- 4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,5-difluoro-benzonitrile,
4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3,5-difluoro-benzonitrile,
5 4-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,6-difluoro-benzonitrile,
4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3,5-difluoro-benzonitrile,
4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3,5-difluoro-
10 benzonitrile,
4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,6-difluoro-benzonitrile,
4-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2,6-difluoro-benzonitrile,
15 5-chloro-2-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
4-[4-(2-cyclohexyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile,
4-[4-(2-cyclohexyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile,
20 4-[4-(2-cyclohexyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-benzonitrile,
(2-cyclohexyloxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
(2-cyclohexyloxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-trifluoromethyl-phenyl)-
25 piperazin-1-yl]-methanone,
(2-cyclohexyloxy-5-methanesulfonyl-phenyl)-[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone,
1-{4-[4-(2-cyclobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-phenyl}-ethanone,
30 4-[4-(2-cyclobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-3-fluoro-benzonitrile,
(2-cyclobutoxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethanesulfonyl-phenyl)-piperazin-1-yl]-methanone,
35 1-{4-[4-(2-cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-2-fluoro-phenyl}-ethanone,
2-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-5-trifluoromethyl-

- benzonitrile,
 (2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone,
 (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-
 5 piperazin-1-yl]-methanone,
 (2-cyclohexyloxy-5-methanesulfonyl-phenyl)-[4-(4-ethanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone,
 (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone,
 10 (2-cyclohexyloxy-5-methanesulfonyl-phenyl)-[4-(4-cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone,
 (2-cyclobutoxy-5-methanesulfonyl-phenyl)-[4-(4-cyclopropanesulfonyl-2-fluoro-phenyl)-piperazin-1-yl]-methanone

7. Compounds of formula I according to claim 1, wherein Ar is substituted phenyl,
 15 R² is (C₁-C₆)-alkyl substituted by halogen and R⁵ is S(O)₂CH₃.

8. Compounds of formula I according to claim 7, wherein the compounds are:

- 1-(3-fluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,
 3-fluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoyl]-piperazin-1-yl}-
 20 benzonitrile,
 [4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone,
 [4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone,
 25 [4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone,
 3-fluoro-4-{4-[5-methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-benzoyl]-piperazin-1-yl}-benzonitrile,
 [4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-phenyl]-methanone,
 30 [4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-phenyl]-methanone,
 1-(3-fluoro-4-{4-[5-methanesulfonyl-2-(3,3,3-trifluoro-propoxy)-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,
 35 2,5-difluoro-4-[4-(5-methanesulfonyl-2-trifluoromethoxy-benzoyl)-piperazin-1-yl]-

- benzonitrile,
2,3-difluoro-4-{4-[2-(2-fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoyl]-
piperazin-1-yl}-benzonitrile,
2-fluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-benzoyl]-
5 piperazin-1-yl}-benzonitrile,
[5-methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-phenyl]-[4-(4-trifluoromethyl-
phenyl)-piperazin-1-yl]-methanone,
2,3-difluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-benzoyl]-
piperazin-1-yl}-benzonitrile,
10 3,5-difluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-benzoyl]-
piperazin-1-yl}-benzonitrile,
2-{4-[2-(2-fluoro-1-fluoromethyl-ethoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-
5-trifluoromethyl-benzonitrile,
rac-2,3-difluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-
15 piperazin-1-yl}-benzonitrile,
2-Fluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoro-propoxy)-benzoyl]-piperazin-
1-yl}-benzonitrile,
3-fluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoro-propoxy)-benzoyl]-piperazin-
1-yl}-benzonitrile,
20 [5-methanesulfonyl-2-(2,2,3,3-tetrafluoro-propoxy)-phenyl]-[4-(4-trifluoromethyl-
phenyl)-piperazin-1-yl]-methanone,
[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,3,3-
tetrafluoro-propoxy)-phenyl]-methanone,
2,3-difluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoro-propoxy)-benzoyl]-
25 piperazin-1-yl}-benzonitrile,
3,5-Difluoro-4-{4-[5-methanesulfonyl-2-(2,2,3,3-tetrafluoro-propoxy)-benzoyl]-
piperazin-1-yl}-benzonitrile,
[4-(3,4-dichloro-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-
phenyl]-methanone,
30 rac-5-chloro-2-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-
piperazin-1-yl}-benzonitrile, ,
rac-3,5-difluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-
piperazin-1-yl}-benzonitrile,
rac-2,5-difluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-
35 piperazin-1-yl}-benzonitrile,
rac-2,6-difluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-
piperazin-1-yl}-benzonitrile,

- rac-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile,
 rac-3-fluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile,
 5 rac-2-fluoro-4-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl}-benzonitrile,
 rac-5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 rac-[4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone,
 10 rac-[4-(3-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone,
 [4-(2-fluoro-4-trifluoromethyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-((S or R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone,
 15 [5-methanesulfonyl-2-((S or R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone and
 [5-methanesulfonyl-2-((R or S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone.

9. Compounds of formula I according to claim 1, wherein Ar is substituted phenyl,
 20 R² is (C₁-C₆)-alkyl, (C₁-C₆)-alkyl substituted by halogen, CH₂)_n-(C₃-C₇)-cycloalkyl, bicycle[2.2.1]heptyl, (CH₂)_n-O-(C₁-C₆)-alkyl or CH₂)_n-heterocycloalkyl and R⁵ is NO₂.

10. Compounds of formula I according to claim 9, wherein the compounds are
 1-(3-fluoro-4-{4-[2-(2-methoxy-ethoxy)-5-nitro-benzoyl]-piperazin-1-yl}-phenyl)-ethanone,
 25 (2-isopropoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 (2-cyclopropylmethoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 (2-cyclobutylmethoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 30 (2-butoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 [2-(2,2-dimethyl-propoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 (2-isobutoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 35 methanone,

- (2-cyclopentyloxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 (5-nitro-2-propoxy-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 (2-cyclobutoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-
 5 methanone,
 Rac-(2-sec-butoxy-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 [5-nitro-2-(2,2,3,3-tetrafluoro-propoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 10 [5-nitro-2-(2,2,2-trifluoro-ethoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 [2-(bicyclo[2.2.1]hept-2-yloxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone,
 [2-(2-chloro-ethoxy)-5-nitro-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-
 15 methanone and
 [5-nitro-2-(2,2,3,3,3-pentafluoro-propoxy)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone.

11. Compounds of formula I according to claim 1, wherein Ar is substituted phenyl, R² is (C₁-C₆)-alkyl, (C₁-C₆)-alkyl substituted by halogen or
 20 (CH₂)_n-(C₃-C₇)-cycloalkyl and R⁵ is S(O)₂NHCH₃.

12. Compounds of formula I according to claim 11, which compounds are

- 3-[4-(4-Cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-trifluoromethoxy-benzenesulfonamide,
 3-[4-(4-cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-isobutoxy-N-methyl-
 25 benzenesulfonamide,
 3-[4-(4-cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclopentyloxy-N-methyl-benzenesulfonamide,
 3-[4-(4-cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclobutoxy-N-methyl-benzenesulfonamide,
 30 3-[4-(4-cyano-3-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclobutylmethoxy-N-methyl-benzenesulfonamide,
 3-[4-(4-cyano-phenyl)-piperazine-1-carbonyl]-4-isobutoxy-N-methyl-benzenesulfonamide,
 3-[4-(4-cyano-phenyl)-piperazine-1-carbonyl]-4-cyclopentyloxy-N-methyl-
 35 benzenesulfonamide,

- 3-[4-(4-cyano-phenyl)-piperazine-1-carbonyl]-4-cyclobutylmethoxy-N-methyl-benzenesulfonamide,
- 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-isobutoxy-N-methyl-benzenesulfonamide,
- 5 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(2,2-dimethyl-propoxy)-N-methyl-benzenesulfonamide,
- 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-isopropoxy-N-methyl-benzenesulfonamide,
- 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclopentyloxy-N-methyl-
- 10 benzenesulfonamide,
- 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclobutoxy-N-methyl-benzenesulfonamide,
- 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclopropylmethoxy-N-methyl-benzenesulfonamide,
- 15 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclobutylmethoxy-N-methyl-benzenesulfonamide,
- 3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-isobutoxy-N-methyl-benzenesulfonamide,
- 3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-(2,2-dimethyl-propoxy)-N-
- 20 methyl-benzenesulfonamide,
- 3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclopentyloxy-N-methyl-benzenesulfonamide,
- 3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclobutoxy-N-methyl-benzenesulfonamide,
- 25 3-[4-(4-acetyl-2-fluoro-phenyl)-piperazine-1-carbonyl]-4-cyclopropylmethoxy-N-methyl-benzenesulfonamide,
- 4-isobutoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
- 4-(2,2-dimethyl-propoxy)-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-
- 30 carbonyl]-benzenesulfonamide,
- 4-isopropoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
- 4-cyclopentyloxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
- 35 4-cyclobutoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,

- 4-cyclopropylmethoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
 4-cyclobutylmethoxy-N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
 5 N-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-4-(3,3,3-trifluoropropoxy)-benzenesulfonamide,
 3-[4-(4-cyano-2-fluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(2,2,2-trifluoroethoxy)-benzenesulfonamide,
 N-methyl-4-(2,2,2-trifluoro-ethoxy)-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
 10 rac-N-methyl-4-(2,2,2-trifluoro-1-methyl-ethoxy)-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide,
 rac-3-[4-(4-cyano-2,5-difluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzenesulfonamide and
 15 rac-3-[4-(4-cyano-2,3-difluoro-phenyl)-piperazine-1-carbonyl]-N-methyl-4-(2,2,2-trifluoro-1-methyl-ethoxy)-benzenesulfonamide.

13. Compounds of formula I according to claim I, wherein Ar is a substituted 6-membered heteroaryl group, containing one, two or three nitrogen atoms, R² is (C₁-C₆)-alkyl or CH₂)_n-(C₃-C₇)-cycloalkyl, and R⁵ is SO₂CH₃.

- 20 14. Compounds of formula I according to claim 13, which compounds are

- [4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone,
 6-[4-(2-cyclopentyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-nicotinonitrile,
 (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-pyridin-2-yl)-
 25 piperazin-1-yl]-methanone,
 [4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-methanone,
 (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(6-trifluoromethyl-pyridin-3-yl)-piperazin-1-yl]-methanone,
 30 [4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone and
 (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone.

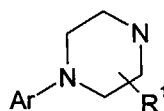
15. Compounds of formula I according to claim 1, wherein, wherein Ar is a substituted 6-membered heteroaryl group, containing one, two or three nitrogen atoms, R² is (C₁-C₆)-alkyl substituted by halogen and R⁵ is SO₂CH₃.

5 16. Compounds of formula I according to claim 15, which compounds are

rac-[4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone,
 rac-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone,
 10 rac-[4-(5-bromo-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone,
 rac-[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone,
 rac-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(6-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone,
 15 [5-methanesulfonyl-2-((S or R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone,
 [5-methanesulfonyl-2-((R or S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone,
 20 [4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone and
 [4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-phenyl]-methanone.

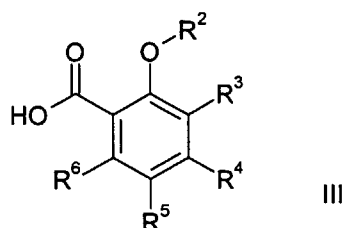
17. A process for preparing a compound of formula I as defined in claim 1, which
 25 process comprises

a) reacting a compound of formula



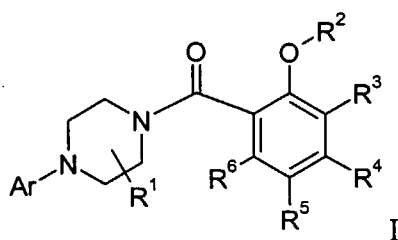
with a compound of formula

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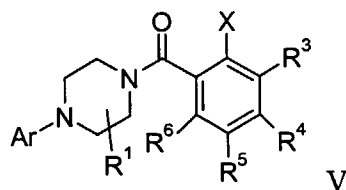
in the presence of an activating agent such as TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate)
to a compound of formula

5



wherein the substituents are as defined above, or

b) reacting a compound of formula

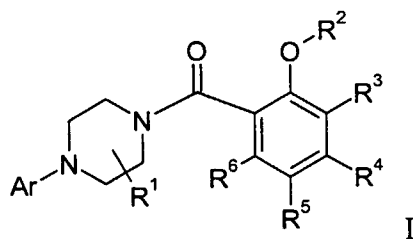


with a compound of formula

10



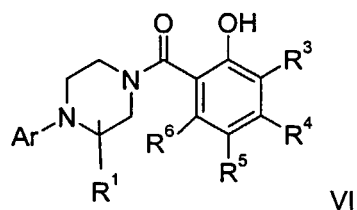
optionally in the presence of a catalyst, such as Cu(I)I and a base like potassium carbonate, cesium carbonate or sodium,
to a compound of formula



15 wherein X is halogen and the other substituents are as defined above, or

c) reacting a compound of formula

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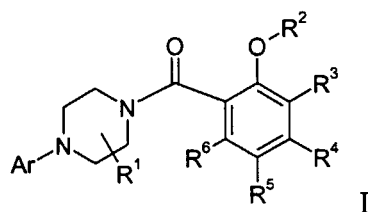


with a compound of formula



in the presence of a base and optionally in the presence of microwaves

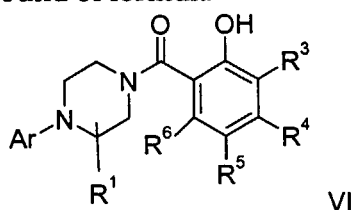
5 to a compound of formula



wherein X is halogen, mesylate or triflate and the other substituents are as defined above,
or

d) reacting a compound of formula

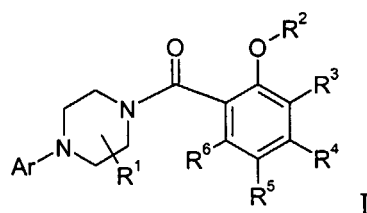
10



with a compound of formula



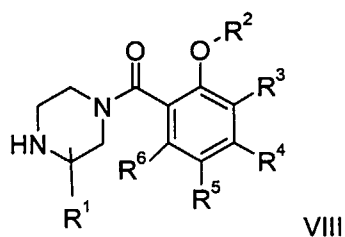
under Mitsunobu conditions in the present of a phosphine to a compound of formula



15 wherein the substituents are as defined above, or

e) reacting a compound of formula

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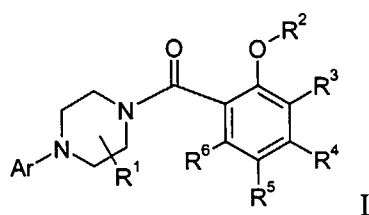


with a compound of formula

ArX

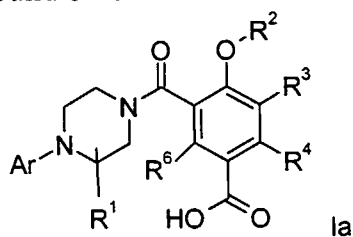
to a compound of formula

5



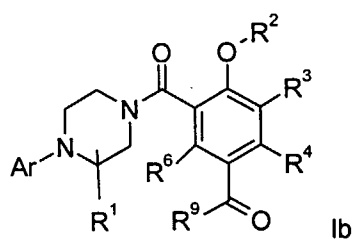
wherein X is halogen and the other substituents are as defined above, or

f) reacting a compound of formula



with a corresponding amine or alcohol in the presence of an activating agent

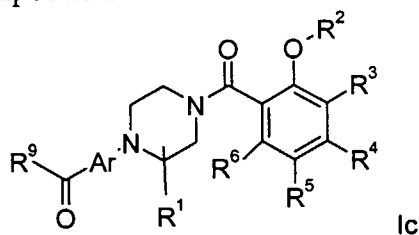
10 to a compound of formula



wherein R⁹ is (C₁-C₆)-alkyl, (C₃-C₆)-cycloalkyl, (C₁-C₆)-alkoxy or NR⁷R⁸;
and the other substituents are as defined above, or

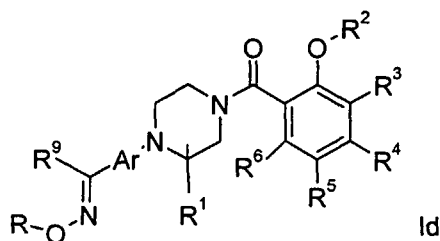
g) reacting a compound of formula

15



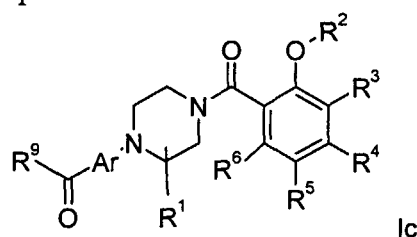
with a compound of formula RONH_2

to a compound of formula



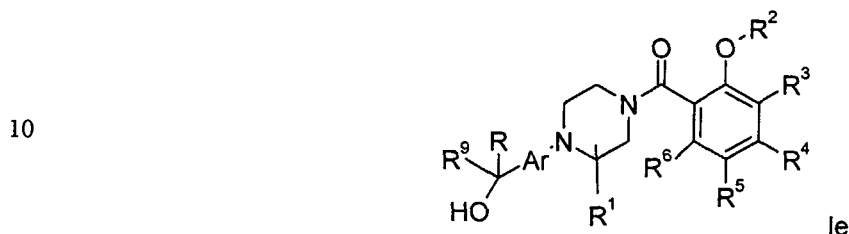
wherein R is H or alkyl and the other substituents are as defined above, or

5 h) reacting a compound of formula



with a reducing agent like sodium borohydride (when R is H) or an alkylating agent like
alkyllithium (when R is alkyl)

to a compound of formula



wherein R is H or alkyl and the other substituents are as defined above, and

if desired, converting the compounds obtained into pharmaceutically acceptable
acid addition salts.

18. A compound according to claim 1, whenever prepared by a process as claimed
15 in claim 17 or by an equivalent method.

19. A medicament containing one or more compounds as claimed in claim 1 or
containing

1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-(3-chlorophenyl)-piperazine,
1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-(4-fluorophenyl)-piperazine,
20 1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-[3-(trifluoromethyl)phenyl]-piperazine,
4-(3-amino-4-nitrophenyl)-1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-

methyl-piperazine,
 1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-methyl-4-(4-nitrophenyl)-
 piperazine,
 4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-methyl-1-(4-nitrophenyl)-
 5 piperazine,
 1-(2-chloro-4-nitrophenyl)-4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-
 piperazine,
 1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-4-(2,4-dinitrophenyl)-2-methyl-
 piperazine,
 10 1-(4-chloro-2-nitrophenyl)-4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-
 piperazine and
 4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-1-(2,4-dinitrophenyl)-2-methyl-
 piperazine.
 and pharmaceutically acceptable excipients.

15 20. A medicament according to claim 19 for the treatment of illnesses based on the
 glycine uptake inhibitor.

21. A medicament according to claim 20, wherein the illnesses are psychoses, pain,
 disfunction in memory and learning, schizophrenia, dementia and other diseases in
 which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's
 20 disease.

22. The use of a compound as claimed in claim 1 or of
 1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-(3-chlorophenyl)-piperazine,
 1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-(4-fluorophenyl)-piperazine,
 1-[5-(aminosulfonyl)-2-methoxybenzoyl]-4-[3-(trifluoromethyl)phenyl]-piperazine,
 25 4-(3-amino-4-nitrophenyl)-1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-
 methyl-piperazine,
 1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-methyl-4-(4-nitrophenyl)-
 piperazine,
 4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-2-methyl-1-(4-nitrophenyl)-
 30 piperazine,
 1-(2-chloro-4-nitrophenyl)-4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-
 piperazine,
 1-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-4-(2,4-dinitrophenyl)-2-methyl-
 piperazine,

1-(4-chloro-2-nitrophenyl)-4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-
piperazine and
4-[4-(dimethylamino)-2-methoxy-5-nitrobenzoyl]-1-(2,4-dinitrophenyl)-2-methyl-
piperazine.

- 5 for the manufacture of medicaments for the treatment of psychoses, pain,
neurodegenerative dysfunction in memory and learning, schizophrenia, dementia and
other diseases in which cognitive processes are impaired, such as attention deficit
disorders or Alzheimer's disease.

23. The invention as herein before described.