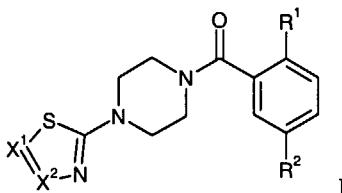


[4-(HETEROARYL) PIPERAZIN-1-YL] - (2, 5-SUBSTITUTED -PHENYL) METHANONE DERIVATIVES
AS GLYCINE TRANSPORTER 1 (GLYT-1) INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL
AND NEUROPSYCHIATRIC DISORDERS

The present invention relates to compounds of the general formula



wherein

- R^1 is $-OR^{1'}$, $-SR^{1'}$ or is a heterocycloalkyl group;
- 5 $R^{1'}$ is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$ -cycloalkyl;
- R^2 is $-S(O)_2$ -lower alkyl, $-S(O)_2NH$ -lower alkyl, NO_2 or CN ;
- X^1 is CR^3 or N ;
- X^2 is $CR^{3'}$ or N ;
- 10 $R^3/R^{3'}$ are independently from each other hydrogen, halogen, lower alkyl, CN , NO_2 , $-S(O)_2$ -phenyl, $-S(O)_2$ -lower alkyl, $-S(O)_2$ -pyridin-2, 3 or 4-yl, phenyl, optionally substituted by one or two substituents selected from the group consisting of NO_2 or halogen, or is lower alkyl substituted by halogen or is $-C(O)$ -lower alkyl;
- n is 0, 1 or 2;
- 15 and to pharmaceutically acceptable acid addition salts thereof.

The present invention relates to compounds of general formula I, to pharmaceutical compositions containing them and their use in the treatment of neurological and neuropsychiatric disorders. It has surprisingly been found that the 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

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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): 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).

10 A complementary model of schizophrenia was proposed in the mid-1960s based 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
15 cognitive dysfunction, thus closely resembling schizophrenia in patients (Javitt DC et al., *Biol. Psychiatry*, 45: 668-679, 1999). Furthermore transgenic mice expressing reduced levels of the NMDAR1 subunit display 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.,
20 *Cell*, 98: 427-236, 1999).

Glutamate neurotransmission, in particular NMDA receptor activity, plays a critical role in synaptic plasticity, learning and memory, such that NMDA receptors appear 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).

25 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, enhancing glutamate transmission, in particular via NMDA receptor activation, would be
30 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 glutamate for N-methyl-D-aspartate (NMDA) receptor function. While glutamate is released in an
35 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

neurotransmitter is to influence their re-uptake at the synapses. Neurotransmitter transporters act by removing neurotransmitters from the extracellular space, and 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).

5 Glycine transporters, which form part of the sodium and chloride family of 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
10 mammalian brain, which give rise to two transporters with ~50 % amino acid sequence 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
15 to be located in CNS and in peripheral tissues, whereas GlyT-2 is specific to the CNS. 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
20 NMDA receptor activity is to elevate the glycine concentration in the local 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 transporter inhibitors are suitable for the treatment of neurological and
25 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 associated with psychotic disorders such as acute mania or depression, associated with bipolar disorders and mood disorders, associated with schizophrenia, (Pralong ET et al.,
30 *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, including a human, attention deficit disorders and pain (Armer RE and Miller DJ, *Exp. Opin. Ther. Patents*, 11 (4): 563-572, 2001).

35 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.

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 the control or prevention of illnesses such as psychoses, 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.

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

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

As used herein, the term "lower alkyl" denotes a saturated straight- or branched-chain group containing from 1 to 7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred alkyl groups are groups with 1 - 4 carbon atoms.

As used herein, the term "cycloalkyl" denotes a saturated carbon ring, containing from 3 to 7 carbon atoms, for example cyclopropyl, cyclopentyl or cycloheptyl.

The term "lower alkyl substituted by halogen" denotes a saturated straight- or branched-chain group containing from 1 to 7 carbon atoms as defined above, wherein one or more hydrogen atoms are replaced by halogen, for example -CF₃, -CH₂CF₃, -CH₂CF₂CF₃, -CH(CH₃)CF₃, -C(CH₃)₂CF₃ or -CH(CF₃)CH₂CH₃;

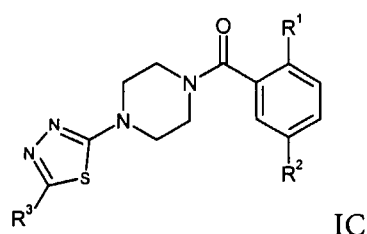
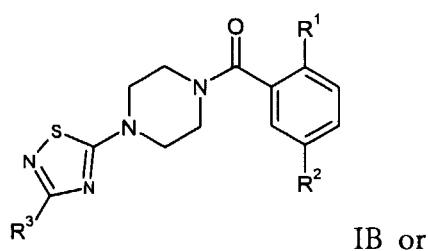
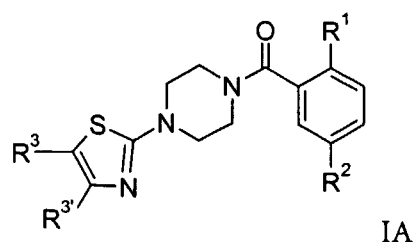
The term "halogen" denotes chlorine, iodine, fluorine and bromine.

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

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.

Encompassed by the present invention are compounds of the following structures

- 5 -



wherein the substituents are as described above.

5 Preferred compounds of the present application are compounds of formula IA.

Especially preferred compounds of formula IA are those, wherein R¹ is OR^{1'} and R^{1'} is lower alkyl, for example the following compounds

[4-(5-benzenesulfonyl-thiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,

10 2-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazole-5-carbonitrile,
2-{4-[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl}-thiazole-5-carbonitrile,

[4-(5-benzenesulfonyl-thiazol-2-yl)-piperazin-1-yl]-[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-phenyl]-methanone,

15 [4-(5-benzenesulfonyl-thiazol-2-yl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone,

{4-[5-(butane-1-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-phenyl]-methanone,

(2-((R)-sec-butoxy)-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone,

20 (2-((S)-sec-butoxy)-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone or

(2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-methyl-5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone.

Further preferred compounds of formula IA are those, wherein R¹ is OR^{1'} and R^{1'} is lower alkyl substituted by halogen, for example the following compounds:

- 5 2-[4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl]-thiazole-5-carbonitrile,
- {4-[5-(butane-1-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone,
- [5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-methyl-4-
- 10 trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone,
- [5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone,
- [5-methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-phenyl]-[4-(5-
- 15 trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone,
- [5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-
- trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone,
- [5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-
- trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone,
- [5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-{4-[5-(2,2,2-trifluoro-
- 20 ethyl)-thiazol-2-yl]-piperazin-1-yl]-methanone,
- [5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-{4-[5-(2,2,2-
- trifluoro-ethyl)-thiazol-2-yl]-piperazin-1-yl}-methanone,
- [5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-{4-[5-(2,2,2-
- trifluoro-ethyl)-thiazol-2-yl]-piperazin-1-yl}-methanone,
- 25 [5-ethanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-
- thiazol-2-yl)-piperazin-1-yl]-methanone,
- [5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-methyl-5-
- trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone,
- [5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-methyl-5-
- 30 trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone or
- [5-methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-phenyl]-[4-(5-trifluoromethyl-
- thiazol-2-yl)-piperazin-1-yl]-methanone.

Further preferred compounds of formula IA are those, wherein R¹ is OR^{1'} and R^{1'} is -(CH₂)_n-cycloalkyl, for example the following compounds:

- 35 2-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazole-5-
- carbonitrile,

- 7 -

- [4-(5-benzenesulfonyl-thiazol-2-yl)-piperazin-1-yl]-(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-methanone,
 {4-[5-(butane-1-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-methanone,
 5 3-[4-(5-cyano-thiazol-2-yl)-piperazine-1-carbonyl]-4-cyclopentyloxy-*N*-methyl-benzenesulfonamide or
 4-cyclopentyloxy-*N*-methyl-3-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine-1-carbonyl]-benzenesulfonamide.

Further preferred compounds of formula IA are those, wherein R¹ is SR^{1'}, for example the
 10 following compound

(2-isopropylsulfanyl-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone.

A compound of formula IB, wherein R¹ is OR^{1'} for R^{1'} being lower alkyl is

(2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(3-phenyl-[1,2,4]thiadiazol-5-yl)-
 15 piperazin-1-yl]-methanone.

A compound of formula IB, wherein R¹ is OR^{1'} for R^{1'} being (CH₂)_n-cycloalkyl is

4-cyclopentyloxy-*N*-methyl-3-[4-(3-phenyl-[1,2,4]thiadiazol-5-yl)-piperazine-1-carbonyl]-benzenesulfonamide.

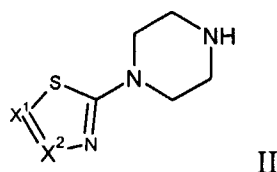
Compounds of formula IC, wherein R¹ is OR^{1'} are, for example the following

- 20 (2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazin-1-yl]-methanone,
 (2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazin-1-yl]-methanone,
 (2-isobutoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-
 25 piperazin-1-yl]-methanone,
 (5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazin-1-yl]-methanone or
 [5-methanesulfonyl-2-((*S*)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazin-1-yl]-methanone.

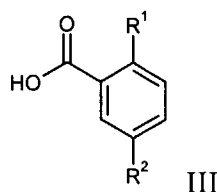
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The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

reacting a compound of formula

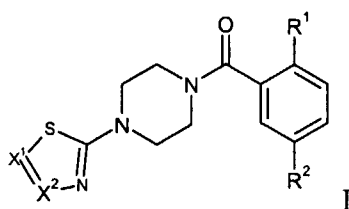


with a compound of formula



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

to a compound of formula



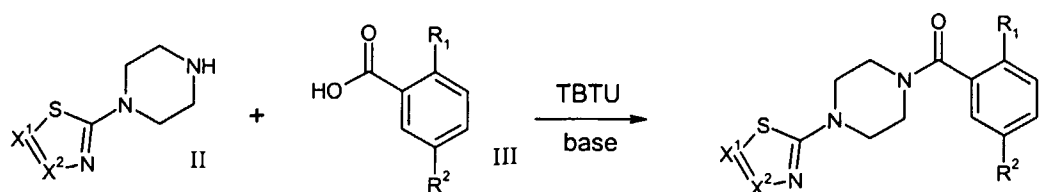
wherein X^1 and X^2 and the substituents R^1 and R^2 are as defined above,

and

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

The compounds of formula I may be prepared in accordance with the process variant as described above and with the following schemes 1 - 7. The starting materials are either commercially available, are otherwise known in the chemical literature, or may be prepared in accordance with methods well known in the art.

Scheme 1



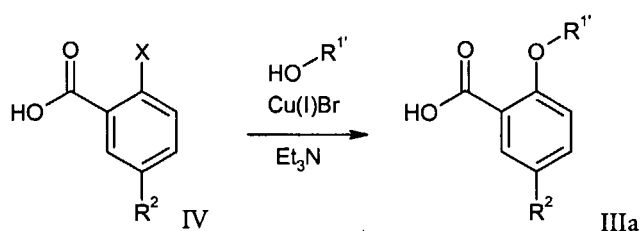
Compounds of general formula I can be prepared by reacting piperazine derivatives of formula II with an appropriately substituted acid of formula III in the presence of an activating agent like TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-

5 tetramethyluroniumtetrafluoroborate) and a base such as N-ethyl-diisopropylamine (Scheme 1).

The acids of formula III can be prepared by various routes as shown in Schemes 2-5.

Scheme 2

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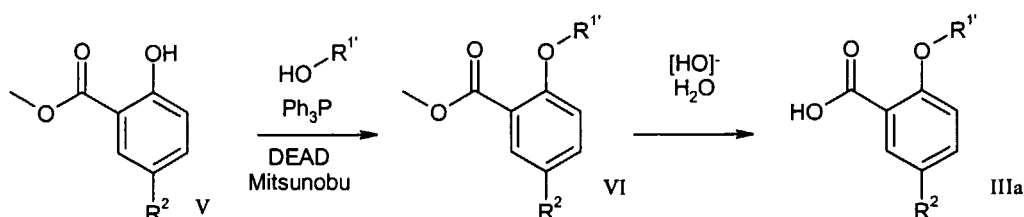


where X = halogen

For example, compounds of formula IIIa where R^{1'} is lower alkyl, lower alkyl, substituted by halogen or -(CH₂)_n-cycloalkyl, can be prepared by reaction of a halogen compound of formula IV with an alcohol of formula R^{1'}OH, optionally in the presence of a copper salt like Cu(I)Br and a base, such as triethylamine (Scheme 2), at elevated temperature.

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Scheme 3

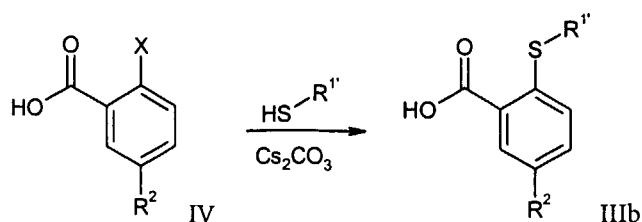


Alternatively, compounds of formula IIIa, where R^{1'} is lower alkyl, lower alkyl, substituted by halogen or -(CH₂)_n-cycloalkyl can be prepared by reacting a hydroxy compound of formula V with an alcohol of formula R^{1'}OH, under Mitsunobu reaction conditions in the presence of a phosphine like triphenylphosphine or diphenyl-2-pyridylphosphine, and a dialkylazodicarboxylate like diethylazodicarboxylate or di-tert-butyl azodicarboxylate, to afford intermediate compounds of formula VI, followed by hydrolysis in the presence of an aqueous base such as potassium hydroxide, sodium hydroxide or lithium hydroxide (Scheme 3).

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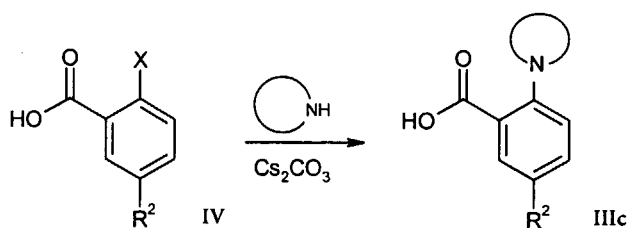
Scheme 4

where X = halogen

Compounds of formula IIIb where R¹ is lower alkyl, lower alkyl, substituted by
 5 halogen or -(CH₂)_n-cycloalkyl, can be prepared by reaction of a halogen compound of
 formula IV with a thiol of formula R¹SH, optionally in the presence of a base, such as
 caesium carbonate, potassium carbonate or sodium carbonate (Scheme 4), at elevated
 temperature.

Scheme 5

10

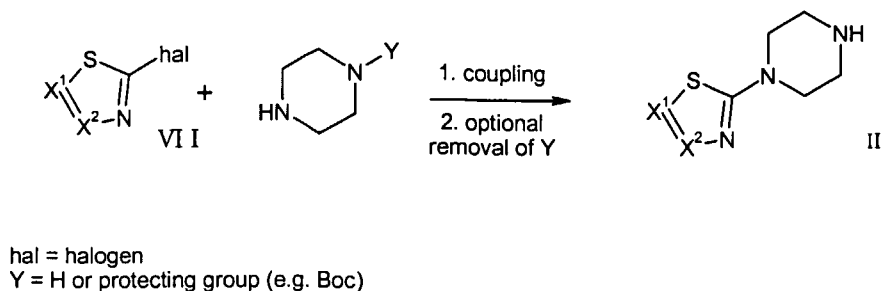


where X = halogen

Compounds of formula IIIc where R¹ is a heterocycloalkyl group, containing a N
 atom, can be prepared by reaction of a halogen compound of formula IV with an amine
 of formula , optionally in the presence of a base, such as caesium carbonate,
 15 potassium carbonate or sodium carbonate (Scheme 5), at elevated temperature.

The halogen-substituted and hydroxyl-substituted starting materials of formula IV
 and V (as shown in Schemes 2-5) are either commercially available, are otherwise known
 in the chemical literature, or may be prepared using a variety of methods well known in
 the art.

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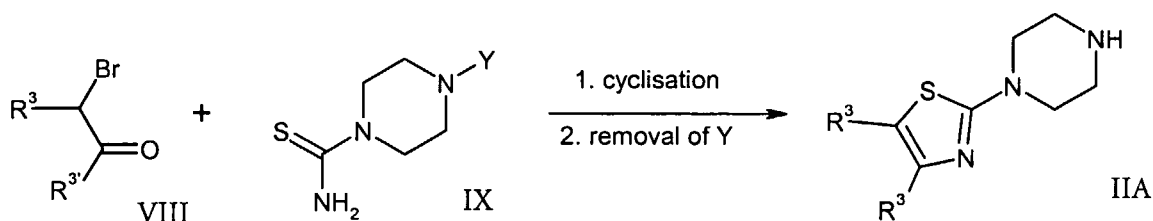
Scheme 6

Piperazine derivatives of formula II can be prepared by heating of piperazine with
 5 the analogous halogen-substituted heterocyclic compound of formula VII, optionally in
 the presence of an organopalladium catalyst (Scheme 6). Alternatively, piperazine
 derivatives of formula II can also be prepared by heating of N-protected piperazine with
 the analogous halogen-substituted heterocyclic compound of formula VII, optionally in
 the presence of an organopalladium catalyst, followed by cleavage of the protective group
 10 (Scheme 6). The protective group is typically tert-butoxycarbonyl (Boc).

The halogen-substituted heterocyclic compounds of formula VII are either
 commercially available, are otherwise known in the chemical literature, or may be
 prepared using a variety of methods well known in the art.

Scheme 7

15



Y = protecting group (e.g. Boc)

In the case where the heterocyclic compound of formula II is a thiazole derivative,
 the compounds can be prepared by an alternative route as shown in Scheme 7. An
 appropriately substituted alpha-bromo-ketone compound of formula VIII is condensed
 20 with an N-protected piperazine-1-carbothioic acid amide compound of formula IX. The
 nitrogen protecting group (e.g. Boc) is then removed to afford the thiazole-substituted
 piperazine compound of formula II.

In the case where compounds of formula II contain reactive functionality (e.g. halogen
 substituents, hydroxyl substituents, or carbonyl substituents) or masked reactive
 25 functionality (e.g. masked carbonyl group or masked hydroxyl group) in R³, further
 reactions may be performed on either the compounds of formula II or on the compounds

of formula I so as to modify the substituent R^3 . Examples of such reactions include functional group interconversions (e.g. change of oxidation state in R^3 , such as from hydroxy to carbonyl substituent, or from thioether to sulphone substituent), nucleophilic substitution reactions (e.g. in case where there is a reactive halogen substituent in R^3),
5 coupling reactions mediated by organometallic catalysts (e.g. Stille or Suzuki coupling reactions, in case where there is a reactive halogen substituent in R^3) or coupling reactions mediated by stoichiometric reagents, (e.g. Wittig reaction, in case where there is a reactive carbonyl substituent in R^3 , or halogen-metal exchange followed by reaction with an electrophile, in case where there is a reactive halogen substituent in R^3). Such
10 reactions may be performed using a variety of methods well known in the art and specific examples may be had by reference to the Examples hereunder described.

Isolation and purification of the compounds

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for
15 example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, thick-layer chromatography, preparative low or high-pressure liquid chromatography or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the preparations and examples herein below. However, other equivalent separation or isolation procedures
20 could, of course, also be used. Racemic mixtures of chiral compounds of formula I can be separated using chiral HPLC.

Salts of compounds of formula I

The compounds of formula I may be basic, for example in cases where the residue R^1 or $R^3/R^{3'}$ contain a basic group such as an aliphatic or aromatic amine moiety. In such
25 cases the compounds of formula I may be converted to a corresponding acid addition salt.

The conversion is accomplished by treatment with at least a stoichiometric amount of an appropriate acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid,
30 glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol or methanol and the like, and the acid added in a

similar solvent. The temperature is maintained between 0 °C and 50 °C. The resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

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 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).

10 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 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)

20 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 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 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 preferred compounds show an IC_{50} (μM) at GlyT-1 in the range of 0.006 – 0.100 as shown in the table below.

Example No.	IC_{50} (μM)	Example No.	IC_{50} (μM)	Example No.	IC_{50} (μM)
4	0.061	55	0.073	79	0.067
10	0.082	59	0.098	80	0.046
14	0.083	66	0.061	81	0.044
16	0.065	67	0.046	84	0.076
19	0.043	68	0.082	93	0.075
29	0.017	69	0.056	99	0.021
30	0.023	70	0.057	100	0.055
31	0.024	71	0.069	101	0.026
39	0.070	74	0.031	103	0.006
41	0.018	77	0.100		
42	0.046	78	0.089		

The compounds of formula I and the pharmaceutically acceptable salts of the
 5 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.

10 The compounds of formula I can be processed with pharmaceutically inert inorganic or organic carriers for the production of pharmaceutical preparations. 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,
 15 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.

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

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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.

The following examples illustrate the invention but are not intended to limit its scope.

20 The following abbreviations were used in the examples:

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

Oxone®: (potassium peroxymonosulfate) 2KHSO₅•KHSO₄•K₂SO₄,

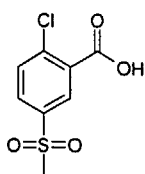
TBTU: 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate;

25 Synthesis of intermediates of formula IIIExample A1

2-Isopropoxy-5-methanesulfonyl-benzoic acid

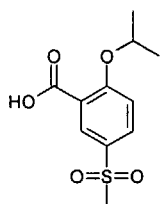
(a) 2-Chloro-5-methanesulfonyl-benzoic acid

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To 99 mmol 2-chloro-5-(methylthio) benzoic acid (purchased from Aldrich) in 400 ml methanol at 0 °C was added 296 mmol Oxone® 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 times with 400 ml ethyl acetate and the combined organic phases washed twice with 300 ml 1 N HCl and with 300 ml saturated aqueous NaCl solution and dried with MgSO₄. Evaporation under reduced pressure yielded the title compound which was used in the next step without further purification.

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

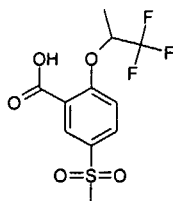


10

A mixture of 2.13 mmol 2-chloro-5-methanesulfonyl-benzoic acid, 0.64 mmol Cu(I)Br in 5 ml triethylamine and 25 ml isopropanol was heated to 120 °C for 16 h in a sealed tube. The volatiles were removed in vacuo and the residue was taken up in 70 ml 1 N 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 compound. MS (m/e): 257.0 ([M-H]⁻, 100%)

Example A2

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



20

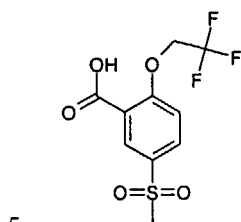
Prepared in analogy to Example A1 (b) from 2-chloro-5-methanesulfonyl-benzoic acid (Example A1(a)) and rac-1,1,1-trifluoro-propan-2-ol. The crude material was

- 18 -

purified by preparative HPLC to yield the title compound as a white solid. MS (m/e): 311.3 ([M-H]⁻, 100%).

Example A3

5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid

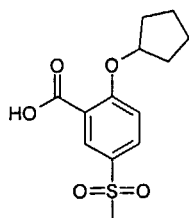


Prepared in analogy to Example A1 (b) from 2-chloro-5-methanesulfonyl-benzoic acid (Example A1(a)) and 2,2,2-trifluoro-ethanol. The crude material was purified by preparative HPLC to yield the title compound as a white solid. MS (m/e): 297.0 ([M-H]⁻, 100%).

10

Example A4

2-Cyclopentyloxy-5-methanesulfonyl-benzoic acid

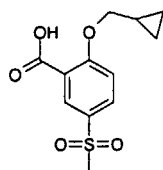


Prepared in analogy to Example A1 (b) from 2-chloro-5-methanesulfonyl-benzoic acid (Example A1(a)) and cyclopentanol. The crude material was purified by flash chromatography to yield the title compound as a yellow solid. MS (m/e): 282.9 ([M-H]⁻, 100%).

15

Example A5

2-Cyclopropylmethoxy-5-methanesulfonyl-benzoic acid



20

Prepared in analogy to Example A1 (b) from 2-chloro-5-methanesulfonyl-benzoic acid (Example A1(a)) and cyclopropyl-methanol. The crude material was purified by

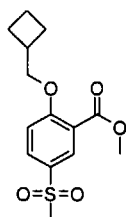
- 19 -

flash chromatography to yield the title compound as a white solid. MS (m/e): 269.1 ($[M-H]^-$, 100%).

Example A6

2-Cyclobutylmethoxy-5-methanesulfonyl-benzoic acid

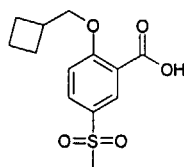
5 (a) 2-Cyclobutylmethoxy-5-methanesulfonyl-benzoic acid methyl ester



A solution of 6.51 mmol 2-hydroxy-5-methanesulfonyl-benzoic acid methyl ester (WO 2002074774), 9.77 mmol triphenylphosphine, 7.17 mmol cyclobutyl methanol and 7.17 mmol di-tert-butyl azodicarboxylate in 20 ml THF was stirred at 60 °C for 2 hours.

10 The reaction mixture was then concentrated *in vacuo* and purified by column chromatography (SiO₂) to yield the title compound as a light yellow oil.

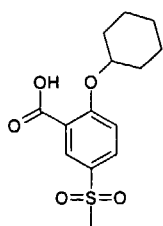
(b) 2-Cyclobutylmethoxy-5-methanesulfonyl-benzoic acid



To 6.51 mmol 2-cyclobutylmethoxy-5-methanesulfonyl-benzoic acid methyl ester
15 in 20 ml tetrahydrofuran was added 40 mmol 2 N aq NaOH solution and the reaction mixture was stirred at 60 °C for 2 hours. After such time the reaction mixture was acidified by addition of concentrated HCl and extracted twice with dichloromethane. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The residue was triturated in ether to give the title compound as a white solid (40% over 2
20 steps). MS (m/e): 283.3 ($[M-H]^-$, 100%).

Example A7

2-Cyclohexyloxy-5-methanesulfonyl-benzoic acid

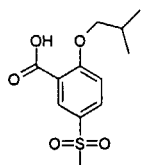


Prepared in analogy to Example A1 (b) from 2-chloro-5-methanesulfonyl-benzoic acid (Example A1(a)) and cyclohexanol. The crude material was purified by preparative HPLC to yield the title compound as a white solid. MS (m/e): 297.3 ([M-H]⁻, 100%).

5

Example A8

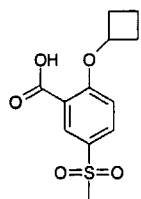
2-Isobutoxy-5-methanesulfonyl-benzoic acid



Prepared in analogy to Example A1 (b) from 2-chloro-5-methanesulfonyl-benzoic acid (Example A1(a)) and isobutanol. The crude material was purified by flash
10 chromatography to yield the title compound as a white solid. MS (m/e): 271.1 ([M-H]⁻, 100%).

Example A9

2-Cyclobutoxy-5-methanesulfonyl-benzoic acid

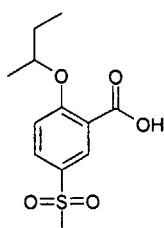


15

Prepared in analogy to Example A1 (b) from 2-chloro-5-methanesulfonyl-benzoic acid (Example A1(a)) and cyclobutanol. The crude material was purified by preparative HPLC to yield the title compound as a white solid. MS (m/e): 269.3 ([M-H]⁻, 100%).

Example A10

Rac-2-sec-Butoxy-5-methanesulfonyl-benzoic acid

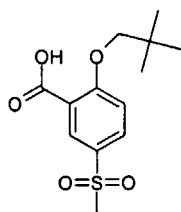


Prepared in analogy to Example A1 (b) from 2-chloro-5-methanesulfonyl-benzoic acid (Example A1(a)) and rac-butan-2-ol. The crude material was purified by preparative HPLC to yield the title compound as a white solid. MS (m/e): 271.4 ([M-H]⁻, 100%).

5

Example A11

2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-benzoic acid



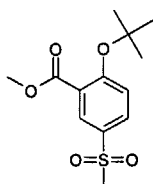
Prepared in analogy to Example A1 (b) from 2-chloro-5-methanesulfonyl-benzoic acid (Example A1(a)) and 2,2-dimethyl-propan-1-ol. The crude material was purified by preparative HPLC to yield the title compound as a white solid. MS (m/e): 285.1 ([M-H]⁻, 100%).

10

Example A12

2-tert-Butoxy-5-methanesulfonyl-benzoic acid

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



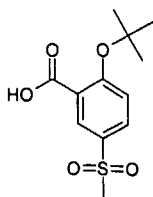
15

To a solution of 2.17 mmol methyl 5-(methanesulfonyl)-salicylate (WO 2002074774) in 5 ml toluene was added 4.78 mmol *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 vacuo* and purified by column chromatography to yield the title compound as colourless oil. MS (m/e): 304.4 (M+NH₄⁺, 100%).

20

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

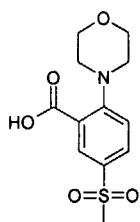
- 22 -



To 5.52 mmol 2-tert-butoxy-5-methanesulfonyl-benzoic acid methyl ester in 25 ml THF was added a solution of 8.34 mmol lithium hydroxide monohydrate in 25 ml water 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 1 N aq HCl leading to precipitation of the compound. The precipitate was filtered off and washed several times with water to yield the title compound (67%) as a white solid. MS (m/e): 289.9 (M+NH₄⁺).

Example A13

10 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid

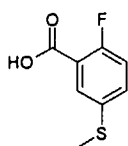


A mixture of 4.26 mmol 2-chloro-5-methanesulfonyl-benzoic acid (Example A1(a)) in 8 ml morpholine was heated at 110 °C for 15 h. After evaporation of all volatiles the residue was acidified by addition of 1 N HCl and extracted three times with ethyl acetate. The combined organic extracts were washed sequentially with 1 N HCl and saturated brine, dried over sodium sulphate, and concentrated *in vacuo* to afford the title compound as a light yellow amorphous solid (58%). MS (m/e): 284.1 ([M-H]⁻, 100%).

Example A14

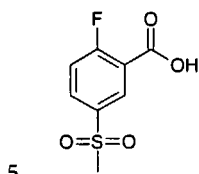
5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-benzoic acid

20 a) 2-Fluoro-5-methylsulfonyl-benzoic acid



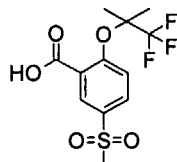
The title compound was prepared by following the procedure described in: Journal of Organometallic Chemistry 1991, 419(1-2), 1-8.

b) 2-Fluoro-5-methanesulfonyl-benzoic acid



To 2.68 mmol 2-fluoro-5-methanesulfonyl-benzoic acid in 5 ml methanol at 0 °C was added 8.05 mmol Oxone® and the mixture was allowed to stir at RT for 72 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was treated with water and extracted 3 times with 400 ml dichloromethane. The combined organic phases were dried over sodium sulfate. Evaporation under reduced pressure yielded the title compound as a white crystalline solid (yield 79%). MS (m/e): 217.2 (M-H⁺, 100%).

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

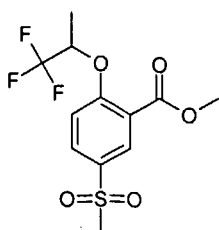


To a solution of 2.75 mmol 2-fluoro-5-methanesulfonyl-benzoic acid in 10 ml N,N-dimethylacetamide were added 14.7 mmol 1,1,1-trifluoro-2-methyl-propan-2-ol and 8.29 mmol cesium carbonate and the mixture was stirred at 170 °C for 72 hours. The reaction mixture was then cooled to room temperature, acidified by addition of formic acid, and then concentrated in vacuo. The residue was purified by preparative HPLC to afford the title compound as a light brown solid (yield 99%). MS (m/e): 325.3. ([M-H]⁻, 100%)

Example A15

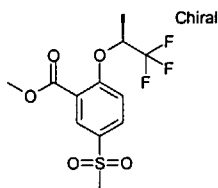
5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid

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



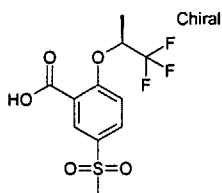
- A mixture of 21.7 mmol 2-hydroxy-5-methanesulfonyl-benzoic acid methyl ester (WO 2002074774), 32.5 mmol rac-trifluoro-methanesulfonic acid 2,2,2-trifluoro-1-methyl-ethyl ester [212556-43-9] and 43.4 mmol potassium carbonate in 87 ml DMF was stirred at 80 °C for 48 hours. After cooling to room temperature, the mixture was concentrated in vacuo, resuspended in water and stirred for 1 hour. Filtration yielded the title compound.

(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 min⁻¹, 220 nm, retention time: 86 min.).

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



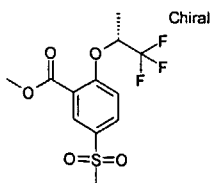
- Prepared in analogy to Example A6(b) from 5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid methyl ester. MS (m/e): 311.0 ([M-H]⁺, 100%)

Example A16

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

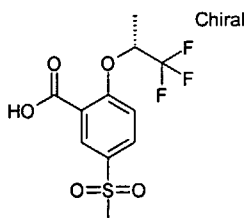
(a) 5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid methyl ester

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The title compound was obtained by separation of rac-5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid methyl ester (Example A15(a)) by chiral HPLC (Chiralcel OD, 15 % ethanol/ Heptane, flow 35 ml min⁻¹, 220 nm, retention time: 74 min.).

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



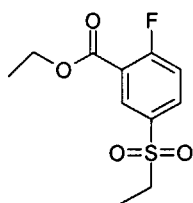
Prepared in analogy to Example A6(b) from 5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid methyl ester. MS (m/e): 311.0 ([M-H]⁻, 100%)

10

Example A17

Rac-5-Ethanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid

(a) 5-Ethanesulfonyl-2-fluoro-benzoic acid ethyl ester

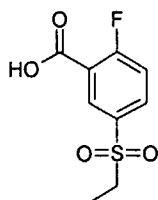


To a solution of 1.98 mol sodium sulfite in 1 l water was added portionwise during 20 min, 0.264 mol 5-chlorosulfonyl-2-fluoro-benzoic acid (CAS: 37098-75-2). The reaction mixture was stirred at room temperature for 2.5 hours then cooled to 0 °C and acidified with 230 ml sulfuric acid (20%) to pH 2. Water was evaporated, and residue was taken up in 200 ml DMF. 73 mmol potassium carbonate and 86 mmol iodoethane were added and the reaction mixture was stirred at room temperature for 50 hours. The solvent was removed in vacuo. The white solid was dissolved in 100 ml water. The aqueous phase was extracted with ethylacetate. The combined extracts were dried over sodium sulfate. Evaporation under reduced pressure and flash chromatography (SiO₂,

- 26 -

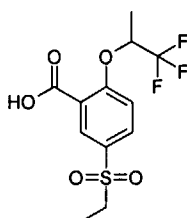
heptane/ethylacetate1/1) yielded the title compound as a colorless oil (yield 37%). MS (m/e): 261.1 ($M+H^+$, 100%).

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



- 5 To 10.8 mmol 5-ethanesulfonyl-2-fluoro-benzoic acid ethyl ester in 26 ml tetrahydrofuran was added 26 ml water and 16.1 mmol lithium hydroxide monohydrate and the reaction mixture was stirred at room temperature for 45 minutes. After such time, the reaction mixture was acidified with 1N HCl, tetrahydrofuran was evaporated and the aqueous phase was extracted twice with dichloromethane. The combined organic
10 phases were dried over sodium sulfate and concentrated *in vacuo* to give the title compound as a white solid (96%). MS (m/e): 232.1 ($[M^+]$, 100%).

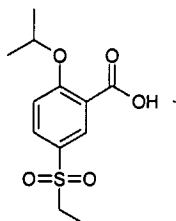
(c) rac-5-Ethanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid



- Prepared in analogy to Example A14(c) from 5-ethanesulfonyl-2-fluoro-benzoic
15 acid and rac-1,1,1-trifluoro-propan-2-ol. MS (m/e): 325.1 ($[M-H]^-$, 100%)

Example A18

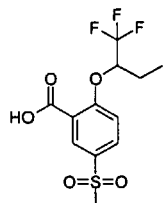
5-Ethanesulfonyl-2-isopropoxy-benzoic acid



- Prepared in analogy to Example A14(c) from 5-ethanesulfonyl-2-fluoro-benzoic
20 acid (Example A17(b)) and isopropanol. MS (m/e): 271.1 ($[M-H]^-$, 100%)

Example A19

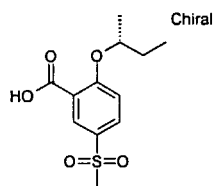
Rac-5-Methanesulfonyl-2-(1-trifluoromethyl-propoxy)-benzoic acid



Prepared in analogy to Example A14(c) from 2-fluoro-5-methanesulfonyl-benzoic acid (Example A14(b)) and rac-1,1,1-trifluoro-butan-2-ol. MS (m/e): 325.0 ([M-H]⁻, 100%)

Example A20

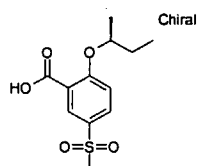
2-((R)-sec-Butoxy)-5-methanesulfonyl-benzoic acid



Prepared in analogy to Example A14(c) from 2-fluoro-5-methanesulfonyl-benzoic acid (Example A14(b)) and (R)-butan-2-ol. MS (m/e): 271.1 ([M-H]⁻, 100%)

Example A21

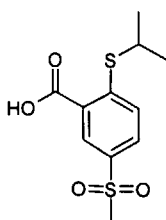
2-((S)-sec-Butoxy)-5-methanesulfonyl-benzoic acid



Prepared in analogy to Example A14(c) from 2-fluoro-5-methanesulfonyl-benzoic acid (Example A14(b)) and (S)-butan-2-ol. MS (m/e): 271.1 ([M-H]⁻, 100%)

Example A22

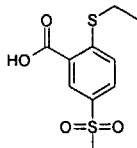
2-Isopropylsulfonyl-5-methanesulfonyl-benzoic acid



To a solution of 4.58 mmol 2-fluoro-5-methanesulfonyl-benzoic acid (Example A14(b)) in 6 ml N,N-dimethylacetamide were added 15.2 mmol cesium carbonate and 10.1 mmol 2-propanethiol and the mixture was stirred at 90 °C for 3 h. The reaction mixture was then cooled to room temperature and acidified to pH1 by addition of hydrochloric acid before being extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated in vacuo to afford the title compound as a light yellow liquid which was used in the next step without further purification (yield 99%). EI-MS (m/e): 274.1 (M^+ , 35%), 232.1 ($[M-C_3H_6]^+$, 30%), 214.1 ($[M-C_3H_6-H_2O]^+$, 100%).

Example A23

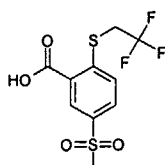
2-Ethylsulfanyl-5-methanesulfonyl-benzoic acid



To a solution of 4.58 mmol 2-fluoro-5-methanesulfonyl-benzoic acid (Example A14(b)) in 6 ml N,N-dimethylformamide were added 13.8 mmol cesium carbonate and 9.25 mmol ethanethiol and the mixture was stirred at 90 °C for 30 min. The reaction mixture was then cooled to room temperature and acidified to pH1 by addition of hydrochloric acid before being extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated in vacuo to afford the title compound as a white solid which was used in the next step without further purification (yield 99%). MS (m/e): 259.0 ($[M-H]^+$, 100%).

Example A24

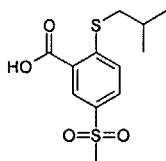
5-Methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-benzoic acid



To a solution of 4.58 mmol 2-fluoro-5-methanesulfonyl-benzoic acid (Example A14(b)) in 6 ml N,N-dimethylformamide were added 13.8 mmol cesium carbonate and 9.16 mmol 2,2,2-trifluoro-ethanethiol and the mixture was stirred at 90 °C for 30 min. The reaction mixture was then cooled to room temperature and acidified to pH1 by addition of hydrochloric acid before being extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated in vacuo to afford the title compound as a red-brown solid which was used in the next step without further purification (yield 99%). MS (m/e): 312.9 ($[M-H]^-$, 100%).

Example A25

2-Isobutylsulfanyl-5-methanesulfonyl-benzoic acid

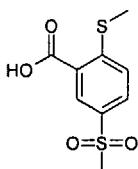


To a solution of 4.58 mmol 2-fluoro-5-methanesulfonyl-benzoic acid (Example A14(b)) in 6 ml N,N-dimethylformamide were added 13.8 mmol cesium carbonate and 9.97 mmol 2-methyl-1-propanethiol and the mixture was stirred at 90 °C for 30 min. The reaction mixture was then cooled to room temperature and acidified to pH1 by addition of hydrochloric acid before being extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated in vacuo to afford the title compound as a white solid which was used in the next step without further purification (yield 99%). MS (m/e): 287.0 ($[M-H]^-$, 100%).

20

Example A26

5-Methanesulfonyl-2-methylsulfanyl-benzoic acid



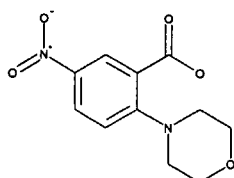
To a solution of 4.58 mmol 2-fluoro-5-methanesulfonyl-benzoic acid (Example A14(b)) in 6 ml N,N-dimethylformamide were added 13.8 mmol cesium carbonate and 10.0 mmol sodium methanethiolate and the mixture was stirred at 90 °C for 30 min. The reaction mixture was then cooled to room temperature and acidified to pH1 by addition of hydrochloric acid before being extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated in vacuo to afford the

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title compound as a colourless oil which was used in the next step without further purification (yield 99%). MS (m/e): 244.9 ($[M-H]^-$, 100%).

Example A27

5 2-Morpholin-4-yl-5-nitro-benzoic acid

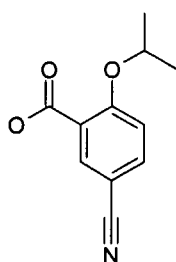


5

To a solution of 12.2 mmol 2-fluoro-5-nitrobenzoic acid (CAS 7304-32-7; commercially available, e.g. from Fluorochem) in 40 ml THF was added 18.2 mmol morpholine and the mixture was stirred at room temperature for 16 h. The volatiles were removed *in vacuo* and the residue was resuspended in 25 ml water and acidified to pH 4
10 by dropwise addition of aqueous HCl. The resulting mixture was stirred at room temperature for 30 min, and the resulting crystals were then collected by filtration and dried *in vacuo* at 50 °C to afford the title compound as a yellow solid (yield 32%). MS (m/e): 251.0 ($[M-H]^-$, 100%)

Example A28

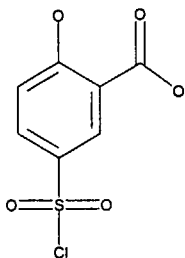
15 5-Cyano-2-isopropoxy-benzoic acid



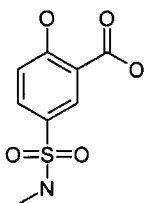
To 198 mmol isopropanol was added 19.8 mmol sodium and the mixture was then heated at 100°C until all the sodium was dissolved (30 min.). Subsequently, 6.59 mmol 5-cyano-2-iodo-benzoic acid [CAS: 219841-92-6; WO9901455] and 1.32 mmol copper
20 (I) bromide were added and the reaction mixture heated at 120 °C for 2 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo. The residue was suspended in 50 ml 1 M aq HCl and extracted 3x with ethyl acetate. The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography on silica gel (eluant: heptane/ethyl acetate) provided the title
25 compound as a white solid (yield 55%). MS (m/e): 204.1 ($[M-H]^-$, 100%).

Example A29

2-Cyclopentyloxy-5-methylsulfamoyl-benzoic acid

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

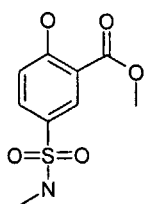
- 5 To 3.26 mol chlorosulfonic acid at 0 °C was added 652 mmol salicylic acid in small portions and the mixture was then allowed to stir at RT for 1 h, then at 50 °C for 1 h, and finally at 70 °C for 1 h. The mixture was then added dropwise to 1000 ml ice-water with stirring and stirring continued for 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
- 10 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
- 15 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
- 20 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%)

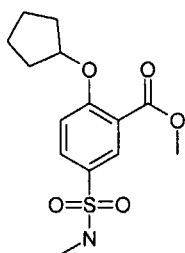
(c) 2-Hydroxy-5-methylsulfamoyl-benzoic acid methyl ester

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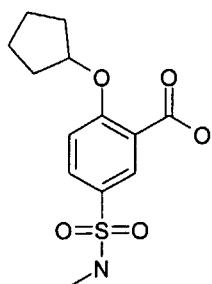
- To 77 mmol 2-hydroxy-5-methylsulfamoyl-benzoic acid in 300 ml THF was added 85 mmol CDI and the mixture heated at 70 °C for 1 h. 770 mmol methanol was then added and the mixture was heated at 70 °C for 16 h. The mixture was then cooled to room temperature and concentrated in vacuo. The residue was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

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



- To 2.85 mmol 2-hydroxy-5-methylsulfamoyl-benzoic acid methyl ester, 3.14 mmol cyclopentanol and 3.28 mmol triphenylphosphine in 10 ml THF was added 3.14 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 2:3) to afford the title compound as a colourless oil. MS (m/e): 312.1 ([M-H]⁻, 100%)

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



To 2.68 mmol 2-cyclopentyloxy-5-methylsulfamoyl-benzoic acid methyl ester in 10 ml THF was added 20 mmol 2 M aq NaOH and the mixture was stirred at RT for 2 h. The

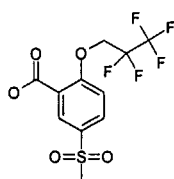
- 33 -

mixture was then 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 as a white solid. MS (m/e): 298.3 ([M-H]⁻, 100%)

5

Example A30

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



Prepared in analogy to Example A14(c) from 2-fluoro-5-methanesulfonyl-benzoic acid (Example A14(b)) and 2,2,3,3,3-pentafluoro-1-propanol. MS (m/e): 346.9 ([M-H]⁻, 100%)

10

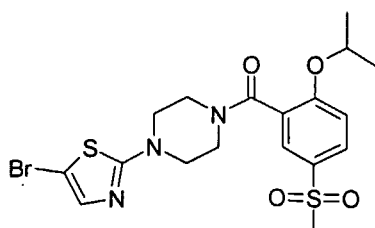
Synthesis of compounds of formula I according to the invention

Example 1

[4-(5-Bromo-thiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone15 a) 1-(5-Bromo-thiazol-2-yl)-piperazine

A mixture of 2.06 mmol 2,5-dibromothiazole, 6.17 mmol piperazine and 6.17 mmol triethylamine in 6 ml tetrahydrofuran in a sealed tube was heated at 160 °C for 10 min under microwave irradiation. The reaction mixture was concentrated and the residue was purified by chromatography (SiO₂, methanol/dichloromethane) to afford the title compound as a white crystalline solid (yield 94%). MS (m/e): 250.0 ({⁸¹Br}M+H⁺, 100%), 248.0 ({⁷⁹Br}M+H⁺, 76%).

20

b) [4-(5-Bromo-thiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

To a solution of 0.31 mmol 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) in 7 ml tetrahydrofuran were added successively 0.46 mmol TBTU, 1.24 mmol N-ethyldiisopropylamine and 0.34 mmol 1-(5-bromo-thiazol-2-yl)-piperazine. The reaction mixture was stirred at RT for 16 h and then concentrated *in vacuo*.

- 5 Chromatography (SiO₂, ethyl acetate/heptane) afforded the title compound as a white foam (yield 87%). MS (m/e): 490.3 (⁸¹Br}M+H⁺, 100%), 488.3 (⁷⁹Br}M+H⁺, 84%).

Example 2

(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-methyl-thiazol-2-yl)-piperazin-1-yl]-methanone

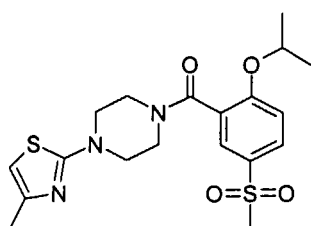
10 a) 2-Iodo-4-methyl-thiazole

- To a solution of 21.7 mmol diisopropylamine in 50 ml tetrahydrofuran was added dropwise 19.7 mmol butylmagnesium chloride solution (2 M in tetrahydrofuran) and the mixture was stirred at room temperature overnight. 10.1 mmol 4-methylthiazole was then added and stirring continued for 1 hour at room temperature. Finally, a solution of
15 25.7 mol iodine in 50 ml tetrahydrofuran was added dropwise and stirring continued for a further 1 h. The reaction mixture was then quenched by addition of 20% aqueous sodium thiosulphate solution and the mixture was extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulphate and concentrated *in vacuo*. Chromatography (SiO₂, ether/heptane) afforded the title compound as a brown
20 solid (yield 83%). MS (m/e): 226.1 (M+H⁺, 100%).

b) 1-(4-Methyl-thiazol-2-yl)-piperazine

- A mixture of 1.33 mmol 2-iodo-4-methyl-thiazole, 4.00 mmol piperazine and 4.00 mmol triethylamine in 4 ml tetrahydrofuran in a sealed tube was heated at 160 °C for 2 h under microwave irradiation. The reaction mixture was concentrated and the residue was
25 purified by chromatography (SiO₂, methanol/dichloromethane) to afford the title compound as a yellow oil (yield 65%). MS (m/e): 184.3 (M+H⁺, 100%).

c) (2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-methyl-thiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-(4-methyl-thiazol-2-yl)-piperazine. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as an amorphous yellow solid (yield 87%). MS (m/e): 424.1 (M+H⁺, 100%).

Example 3

(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-methyl-thiazol-2-yl)-piperazin-1-yl]-methanone

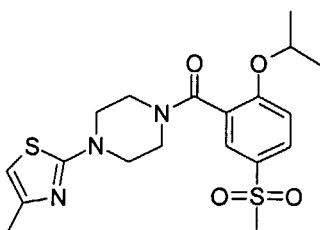
a) 2-Iodo-5-methyl-thiazole

Prepared in analogy to example 2 (a) from 5-methylthiazole. The crude material was purified by chromatography (SiO₂, ether/heptane) to yield the title compound as a brown oil (yield 69%). MS (m/e): 226.3 (M+H⁺, 100%).

b) 1-(5-Methyl-thiazol-2-yl)-piperazine

Prepared in analogy to example 2 (b) from 2-iodo-5-methyl-thiazole and piperazine. The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) to yield the title compound as a yellow oil (yield 32%). MS (m/e): 184.3 (M+H⁺, 100%).

c) (2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-methyl-thiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-(5-methyl-thiazol-2-yl)-piperazine. The crude material

was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as an off-white foam (yield 75%). MS (m/e): 424.3 (M+H⁺, 100%).

Example 4

5 [4-(5-Benzenesulfonyl-thiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

a) 4-(5-Bromo-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

A mixture of 24.7 mmol 2,5-dibromothiazole, 49.4 mmol tert-butyl 1-piperazinecarboxylate and 74.1 mmol triethylamine in 24 ml tetrahydrofuran in a sealed tube was heated at 160 °C for 30 min under microwave irradiation. The reaction mixture
10 was concentrated and the residue was purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title compound as a white crystalline solid (yield 68%). MS (m/e): 350.2 ({⁸¹Br}M+H⁺, 100%), 348.2 ({⁷⁹Br}M+H⁺, 98%).

b) 4-(5-Phenylsulfanyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

To a solution of 1.44 mmol 4-(5-bromo-thiazol-2-yl)-piperazine-1-carboxylic acid
15 tert-butyl ester in 6 ml tetrahydrofuran at -78 °C was added dropwise 1.44 mmol n-butyllithium solution (1.6 M in hexane) and the mixture was stirred at -78 °C for 10 min. A solution of 1.58 mmol diphenyl disulphide in 1 ml tetrahydrofuran was then added dropwise over 15 min and the reaction mixture was then allowed to warm to room temperature. The reaction mixture was then poured onto saturated brine and the mixture
20 was extracted three times with ethyl acetate/tetrahydrofuran (1:1). The combined organic phases were dried over sodium sulphate and concentrated in vacuo. Chromatography (SiO₂, ethyl acetate/heptane) afforded the title compound as a yellow crystalline solid (yield 76%). MS (m/e): 378.3 (M+H⁺, 100%).

c) 4-(5-Benzenesulfonyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

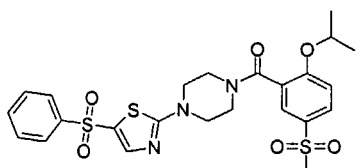
To a solution of 1.06 mmol 4-(5-phenylsulfanyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in 10 ml dichloroethane was added 2.65 mmol meta-chloroperbenzoic acid and the mixture was stirred at room temperature for 16 h. The reaction mixture was then diluted with dichloromethane and was washed with saturated aqueous sodium bicarbonate solution and then with water. The organic phase was dried
30 over sodium sulfate and concentrated in vacuo to afford the title compound as a yellow crystalline solid (yield 77%). MS (m/e): 410.3 (M+H⁺, 100%).

d) 1-(5-Benzenesulfonyl-thiazol-2-yl)-piperazine hydrochloride

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To a solution of 0.73 mmol 4-(5-benzenesulfonyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in 10 ml dioxane was added dropwise 7.32 mmol hydrogen chloride solution (4 M in dioxane) and the mixture was stirred at 80 °C for 2.5 h. The reaction mixture was then cooled to 0 °C and diluted with ether. The resulting
 5 crystals were collected by filtration and washed with ether to afford the title compound as a light brown crystalline solid (yield 81%). MS (m/e): 309.9 (M+H⁺, 100%).

e) [4-(5-Benzenesulfonyl-thiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

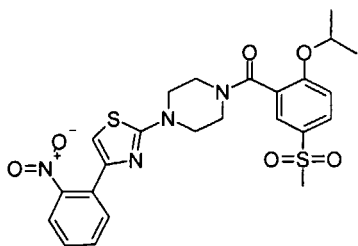


10 Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-(5-benzenesulfonyl-thiazol-2-yl)-piperazine hydrochloride. The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) to yield the title compound as a white crystalline solid (yield 47%). MS (m/e): 550.2 (M+H⁺, 100%), 567.2 (M+NH₄⁺, 100%).

15

Example 5

(2-Isopropoxy-5-methanesulfonyl-phenyl)-{4-[4-(2-nitro-phenyl)-thiazol-2-yl]-piperazin-1-yl}-methanone



20 Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-[4-(2-nitro-phenyl)-thiazol-2-yl]-piperazine dihydrochloride. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a yellow crystalline solid (yield 61%). MS (m/e): 531.3 (M+H⁺, 100%).

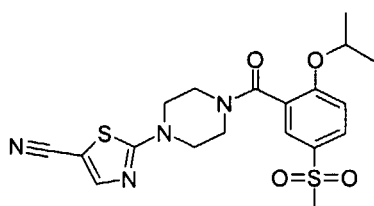
Example 6

25 2-[4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazole-5-carbonitrile

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a) 2-Piperazin-1-yl-thiazole-5-carbonitrile

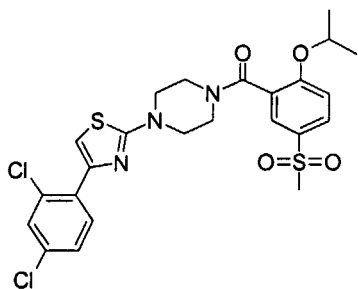
Prepared in analogy to example 2 (b) from 2-chloro-1,3-thiazole-5-carbonitrile and piperazine. The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) to yield the title compound as a white crystalline solid (yield 86%). MS (m/e): 194.9 (M+H⁺, 100%).

b) 2-[4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazole-5-carbonitrile

Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 2-piperazin-1-yl-thiazole-5-carbonitrile. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 69%). MS (m/e): 435.4 (M+H⁺, 100%).

Example 7

15 {4-[4-(2,4-Dichloro-phenyl)-thiazol-2-yl]-piperazin-1-yl}-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



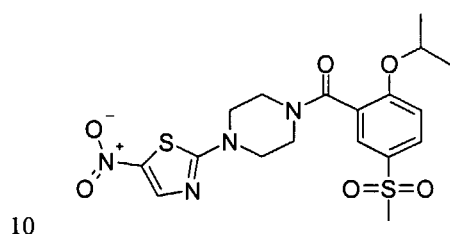
Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-[4-(2,4-dichloro-phenyl)-thiazol-2-yl]-piperazine dihydrochloride. The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) (yield 17%). MS (m/e): 558.1 ({³⁷Cl}M+H⁺, 19%), 555.9 ({³⁷Cl³⁵Cl}M+H⁺, 58%), 554.1 ({³⁵Cl}M+H⁺, 100%).

Example 8

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

Prepared in analogy to example 2 (b) from 2-bromo-5-nitrothiazole and
 5 piperazine. The crude material was purified by chromatography (SiO₂,
 methanol/dichloromethane) to yield the title compound as a light yellow crystalline solid
 (yield 50%). MS (m/e): 215.3 (M+H⁺, 100%).

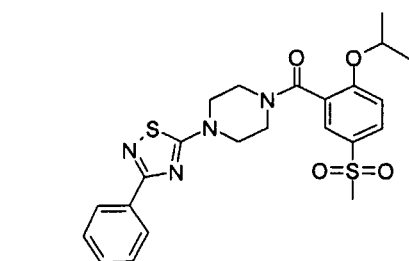
b) (2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-nitro-thiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-
 benzoic acid (Example A1) and 1-(5-nitro-thiazol-2-yl)-piperazine. The crude material
 was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in
 ether to yield the title compound as a yellow crystalline solid (yield 67%). MS (m/e):
 15 455.4 (M+H⁺, 100%), 472.0 (M+NH₄⁺, 100%).

Example 9

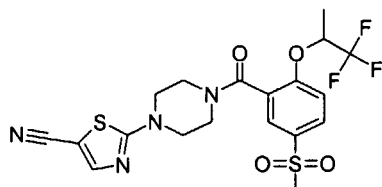
(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(3-phenyl-[1,2,4]thiadiazol-5-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-
 benzoic acid (Example A1) and 3-phenyl-5-piperazino-1,2,4-thiadiazole. The crude
 material was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title
 compound as a white crystalline solid (yield 69%). MS (m/e): 487.3 (M+H⁺, 100%).

Example 10

2-{4-[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl}-thiazole-5-carbonitrile

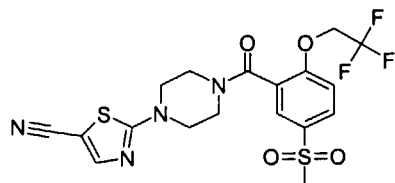


- 5 Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A2) and 2-piperazin-1-yl-thiazole-5-carbonitrile (Example 6(a)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 59%). MS (m/e): 489.1 (M+H⁺, 100%), 506.1 (M+NH₄⁺, 78%).

10

Example 11

2-{4-[5-Methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoyl]-piperazin-1-yl}-thiazole-5-carbonitrile



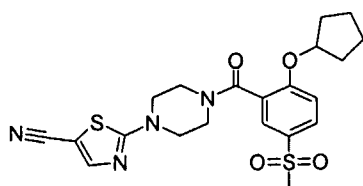
- 15 Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (Example A3) and 2-piperazin-1-yl-thiazole-5-carbonitrile (Example 6(a)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a light brown crystalline solid (yield 57%). MS (m/e): 475.0 (M+H⁺, 100%), 492.3 (M+NH₄⁺, 90%).

20

Example 12

2-[4-(2-Cyclopentylloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazole-5-carbonitrile

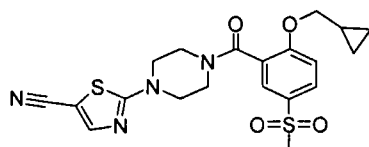
- 41 -



Prepared in analogy to example 1 (b) from 2-cyclopentyloxy-5-methanesulfonyl-benzoic acid (Example A4) and 2-piperazin-1-yl-thiazole-5-carbonitrile (Example 6(a)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as an off-white crystalline solid (yield 64%). MS (m/e): 461.3 (M+H⁺, 100%).

Example 13

2-[4-(2-Cyclopropylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazole-5-carbonitrile



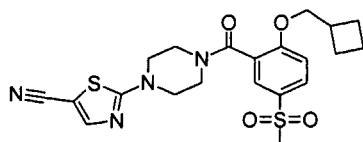
10

Prepared in analogy to example 1 (b) from 2-cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (Example A5) and 2-piperazin-1-yl-thiazole-5-carbonitrile (Example 6(a)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 75%). MS (m/e): 447.3 (M+H⁺, 100%).

15

Example 14

2-[4-(2-Cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazole-5-carbonitrile

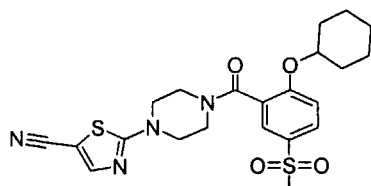


20

Prepared in analogy to example 1 (b) from 2-cyclobutylmethoxy-5-methanesulfonyl-benzoic acid (Example A6) and 2-piperazin-1-yl-thiazole-5-carbonitrile (Example 6(a)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 61%). MS (m/e): 461.3 (M+H⁺, 100%).

Example 15

2-[4-(2-Cyclohexyloxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazole-5-carbonitrile

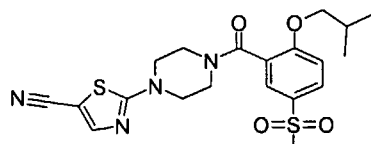


- 5 Prepared in analogy to example 1 (b) from 2-cyclohexyloxy-5-methanesulfonyl-benzoic acid (Example A7) and 2-piperazin-1-yl-thiazole-5-carbonitrile (Example 6(a)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 49%). MS (m/e): 475.4 (M+H⁺, 100%).

10

Example 16

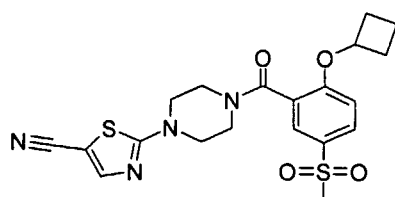
2-[4-(2-Isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazole-5-carbonitrile



- 15 Prepared in analogy to example 1 (b) from 2-isobutoxy-5-methanesulfonyl-benzoic acid (Example A8) and 2-piperazin-1-yl-thiazole-5-carbonitrile (Example 6(a)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 61%). MS (m/e): 449.4 (M+H⁺, 100%).

Example 17

- 20 2-[4-(2-Cyclobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazole-5-carbonitrile

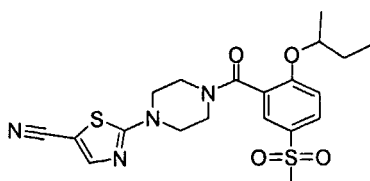


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Prepared in analogy to example 1 (b) from 2-cyclobutoxy-5-methanesulfonyl-benzoic acid (Example A9) and 2-piperazin-1-yl-thiazole-5-carbonitrile (Example 6(a)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as an off-white crystalline solid (yield 54%). MS (m/e): 447.2 (M+H⁺, 100%).

Example 18

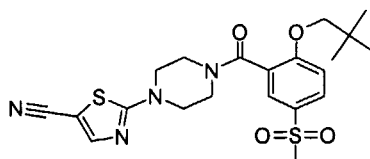
2-[4-(2-sec-Butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazole-5-carbonitrile



Prepared in analogy to example 1 (b) from 2-sec-butoxy-5-methanesulfonyl-benzoic acid (Example A10) and 2-piperazin-1-yl-thiazole-5-carbonitrile (Example 6(a)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 34%). MS (m/e): 449.4 (M+H⁺, 100%).

Example 19

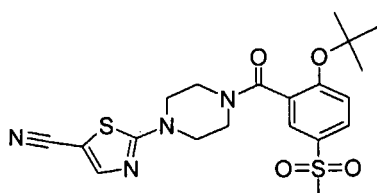
2-[4-[2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl]-thiazole-5-carbonitrile



Prepared in analogy to example 1 (b) from 2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-benzoic acid (Example A11) and 2-piperazin-1-yl-thiazole-5-carbonitrile (Example 6(a)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 68%). MS (m/e): 463.3 (M+H⁺, 100%).

Example 20

2-[4-(2-tert-Butoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazole-5-carbonitrile



- Prepared in analogy to example 1 (b) from 2-tert-butoxy-5-methanesulfonyl-benzoic acid (Example A12) and 2-piperazin-1-yl-thiazole-5-carbonitrile (Example 6(a)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 52%). MS (m/e): 449.3 (M+H⁺, 50%), 466.4 (M+NH₄⁺, 100%).

Example 21

(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-methanesulfonyl-thiazol-2-yl)-piperazin-1-yl]-methanone

- 10 a) 4-(5-Methylsulfonyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

Prepared in analogy to example 4 (b) from 4-(5-bromo-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester (Example 4(a)) and dimethyl disulphide. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title compound as a yellow crystalline solid (yield 78%). MS (m/e): 316.3 (M+H⁺, 100%).

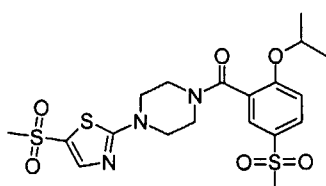
- 15 b) 4-(5-Methanesulfonyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

Prepared in analogy to example 4 (c) from 4-(5-methylsulfonyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester and meta-chloroperbenzoic acid. The title compound was obtained as a yellow crystalline solid (yield 86%). MS (m/e): 348.3 (M+H⁺, 100%).

- 20 c) 1-(5-Methanesulfonyl-thiazol-2-yl)-piperazine hydrochloride

Prepared in analogy to example 4 (d) from 4-(5-methanesulfonyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester and hydrogen chloride solution. The crude material was purified by recrystallisation from ether to afford the title compound as a light brown crystalline solid (yield 99%). MS (m/e): 248.1 (M+H⁺, 100%).

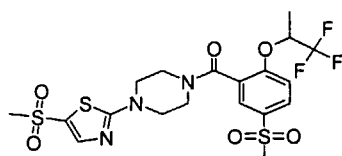
- 25 d) (2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-methanesulfonyl-thiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-(5-methanesulfonyl-thiazol-2-yl)-piperazine hydrochloride. The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) to yield the title compound as a white crystalline solid (yield 43%). MS (m/e): 488.1 (M+H⁺, 100%), 505.0 (M+NH₄⁺, 75%).

Example 22

[4-(5-Methanesulfonyl-thiazol-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone



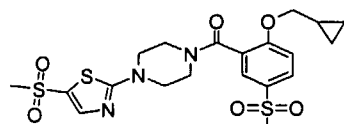
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Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A2) and 1-(5-methanesulfonyl-thiazol-2-yl)-piperazine hydrochloride (Example 21(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 29%). MS (m/e): 542.2 (M+H⁺, 100%), 559.2 (M+NH₄⁺, 65%).

15

Example 23

(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(5-methanesulfonyl-thiazol-2-yl)-piperazin-1-yl]-methanone



20

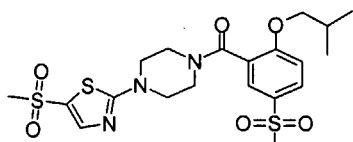
Prepared in analogy to example 1 (b) from 2-cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (Example A5) and 1-(5-methanesulfonyl-thiazol-2-yl)-piperazine hydrochloride (Example 21(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the

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title compound as a yellow crystalline solid (yield 36%). MS (m/e): 500.1 ($M+H^+$, 100%), 517.2 ($M+NH_4^+$, 69%).

Example 24

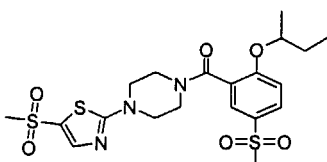
(2-Isobutoxy-5-methanesulfonyl-phenyl)-[4-(5-methanesulfonyl-thiazol-2-yl)-
5 piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 2-isobutoxy-5-methanesulfonyl-benzoic acid (Example A8) and 1-(5-methanesulfonyl-thiazol-2-yl)-piperazine hydrochloride (Example 21(c)). The crude material was purified by chromatography (SiO_2 , ethyl
10 acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 40%). MS (m/e): 502.0 ($M+H^+$, 100%).

Example 25

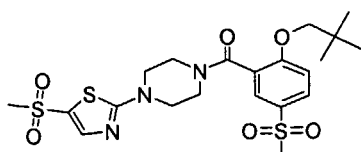
Rac-(2-sec-Butoxy-5-methanesulfonyl-phenyl)-[4-(5-methanesulfonyl-thiazol-2-yl)-
piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from rac-2-sec-butoxy-5-methanesulfonyl-benzoic acid (Example A10) and 1-(5-methanesulfonyl-thiazol-2-yl)-piperazine hydrochloride (Example 21(c)). The crude material was purified by chromatography (SiO_2 , ethyl acetate/heptane) followed by trituration in ether to yield the title compound
20 as an off-white crystalline solid (yield 44%). MS (m/e): 502.1 ($M+H^+$, 99%), 519.3 ($M+NH_4^+$, 100%).

Example 26

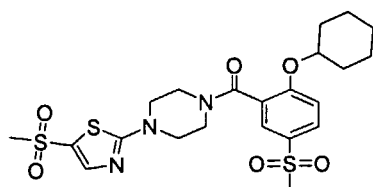
[2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(5-methanesulfonyl-thiazol-
2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-benzoic acid (Example A11) and 1-(5-methanesulfonyl-thiazol-2-yl)-piperazine hydrochloride (Example 21(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 36%). MS (m/e): 516.2 (M+H⁺, 100%).

Example 27

(2-Cyclohexyloxy-5-methanesulfonyl-phenyl)-[4-(5-methanesulfonyl-thiazol-2-yl)-piperazin-1-yl]-methanone



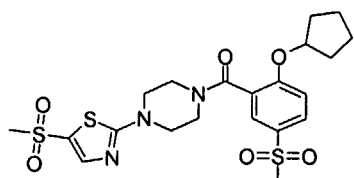
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Prepared in analogy to example 1 (b) from 2-cyclohexyloxy-5-methanesulfonyl-benzoic acid (Example A7) and 1-(5-methanesulfonyl-thiazol-2-yl)-piperazine hydrochloride (Example 21(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a light red crystalline solid (yield 38%). MS (m/e): 528.3 (M+H⁺, 100%).

15

Example 28

(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(5-methanesulfonyl-thiazol-2-yl)-piperazin-1-yl]-methanone



20

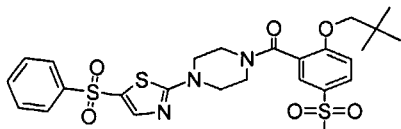
Prepared in analogy to example 1 (b) from 2-cyclopentyloxy-5-methanesulfonyl-benzoic acid (Example A4) and 1-(5-methanesulfonyl-thiazol-2-yl)-piperazine hydrochloride (Example 21(c)). The crude material was purified by chromatography

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(SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as an off-white crystalline solid (yield 38%). MS (m/e): 514.3 (M+H⁺, 100%).

Example 29

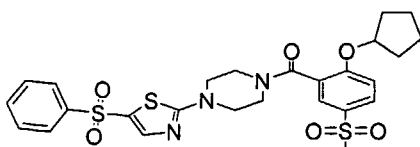
5 [4-(5-Benzenesulfonyl-thiazol-2-yl)-piperazin-1-yl]-[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-phenyl]-methanone



Prepared in analogy to example 1 (b) from 2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-benzoic acid (Example A11) and 1-(5-benzenesulfonyl-thiazol-2-yl)-piperazine hydrochloride (Example 4(d)). The crude material was purified by
10 chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 57%). MS (m/e): 578.2 (M+H⁺, 100%), 595.3 (M+NH₄⁺, 92%).

Example 30

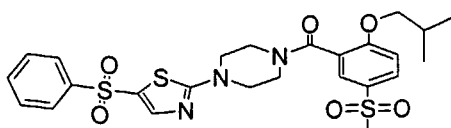
15 [4-(5-Benzenesulfonyl-thiazol-2-yl)-piperazin-1-yl]-(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-methanone



Prepared in analogy to example 1 (b) from 2-cyclopentyloxy-5-methanesulfonyl-benzoic acid (Example A4) and 1-(5-benzenesulfonyl-thiazol-2-yl)-piperazine hydrochloride (Example 4(d)). The crude material was purified by chromatography
20 (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as an off-white crystalline solid (yield 57%). MS (m/e): 576.0 (M+H⁺, 100%), 593.3 (M+NH₄⁺, 94%).

Example 31

25 [4-(5-Benzenesulfonyl-thiazol-2-yl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone



Prepared in analogy to example 1 (b) from 2-isobutoxy-5-methanesulfonyl-benzoic acid (Example A8) and 1-(5-benzenesulfonyl-thiazol-2-yl)-piperazine hydrochloride (Example 4(d)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as an off-white crystalline solid (yield 45%). MS (m/e): 564.3 (M+H⁺, 100%), 581.3 (M+NH₄⁺, 94%).

Example 32

[2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(5-ethanesulfonyl-thiazol-2-yl)-piperazin-1-yl]-methanone

a) 4-(5-Ethylsulfonyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

Prepared in analogy to example 4 (b) from 4-(5-bromo-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester (Example 4(a)) and diethyl disulphide. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title compound as a white crystalline solid (yield 86%). MS (m/e): 330.3 (M+H⁺, 100%).

b) 4-(5-Ethanesulfonyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

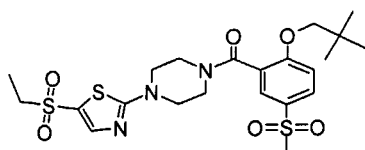
Prepared in analogy to example 4 (c) from 4-(5-ethylsulfonyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester and meta-chloroperbenzoic acid. The title compound was obtained as a yellow crystalline solid (yield 99%). MS (m/e): 362.3 (M+H⁺, 100%), 362.3 (M+NH₄⁺, 70%).

c) 1-(5-Ethanesulfonyl-thiazol-2-yl)-piperazine hydrochloride

Prepared in analogy to example 4 (d) from 4-(5-ethanesulfonyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester and hydrogen chloride solution. The crude material was purified by recrystallisation from ether to afford the title compound as a light brown crystalline solid (yield 86%). MS (m/e): 262.0 (M+H⁺, 100%).

d) [2-(2,2-Dimethyl-propoxy)-5-methanesulfonyl-phenyl]-[4-(5-ethanesulfonyl-thiazol-2-yl)-piperazin-1-yl]-methanone

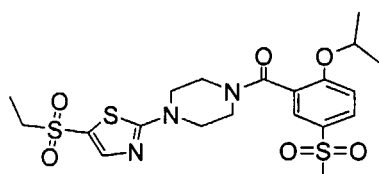
- 50 -



Prepared in analogy to example 1 (b) from 2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-benzoic acid (Example A11) and 1-(5-ethanesulfonyl-thiazol-2-yl)-piperazine hydrochloride. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 63%). MS (m/e): 530.2 (M+H⁺, 64%), 547.2 (M+NH₄⁺, 100%).

Example 33

[4-(5-Ethanesulfonyl-thiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-(5-ethanesulfonyl-thiazol-2-yl)-piperazine hydrochloride (Example 32(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 71%). MS (m/e): 502.3 (M+H⁺, 100%), 519.3 (M+NH₄⁺, 82%).

Example 34

[4-(4,5-Dimethyl-thiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

a) 2-Iodo-4,5-dimethyl-thiazole

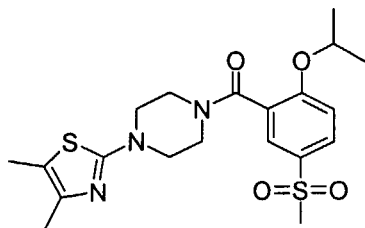
Prepared in analogy to example 2 (a) from 4,5-dimethylthiazole. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as a light brown crystalline solid (yield 66%). MS (m/e): 240.1 (M+H⁺, 100%).

b) 1-(4,5-Dimethyl-thiazol-2-yl)-piperazine

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Prepared in analogy to example 2 (b) from 2-iodo-4,5-dimethyl-thiazole and piperazine. The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) to yield the title compound as a yellow crystalline solid (yield 25%). MS (m/e): 198.3 (M+H⁺, 100%).

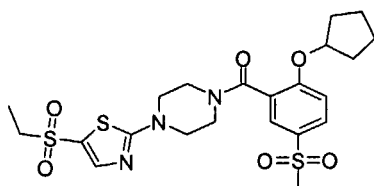
- 5 c) [4-(4,5-Dimethyl-thiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



- 10 Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-(4,5-dimethyl-thiazol-2-yl)-piperazine. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as an off-white crystalline solid (yield 65%). MS (m/e): 584.3 (M+H⁺, 100%), 601.4 (M+NH₄⁺, 60%).

Example 35

- 15 (2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(5-ethanesulfonyl-thiazol-2-yl)-piperazin-1-yl]-methanone

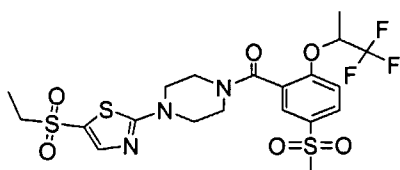


- 20 Prepared in analogy to example 1 (b) from 2-cyclopentyloxy-5-methanesulfonyl-benzoic acid (Example A4) and 1-(5-ethanesulfonyl-thiazol-2-yl)-piperazine hydrochloride (Example 32(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 77%). MS (m/e): 528.3 (M+H⁺, 35%), 545.4 (M+NH₄⁺, 100%).

Example 36

- 25 [4-(5-Ethanesulfonyl-thiazol-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone

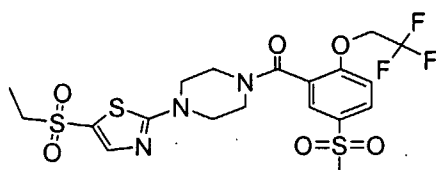
- 52 -



Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A2) and 1-(5-ethanesulfonyl-thiazol-2-yl)-piperazine hydrochloride (Example 32(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 61%). MS (m/e): 556.3 (M+H⁺, 100%), 573.3 (M+NH₄⁺, 55%).

Example 37

10 [4-(5-Ethanesulfonyl-thiazol-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone



Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoroethoxy)-benzoic acid (Example A3) and 1-(5-ethanesulfonyl-thiazol-2-yl)-piperazine hydrochloride (Example 32(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 72%). MS (m/e): 542.2 (M+H⁺, 100%), 559.3 (M+NH₄⁺, 60%).

Example 38

20 {4-[5-(Butane-1-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

a) 4-(5-Butylsulfonyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

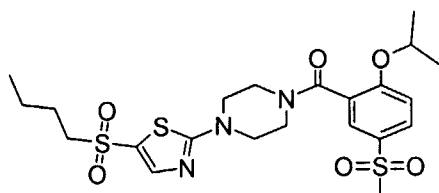
Prepared in analogy to example 4 (b) from 4-(5-bromo-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester (Example 4(a)) and dibutyl disulphide. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title compound as a colourless oil (yield 93%). MS (m/e): 358.3 (M+H⁺, 100%).

b) 4-[5-(Butane-1-sulfonyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester

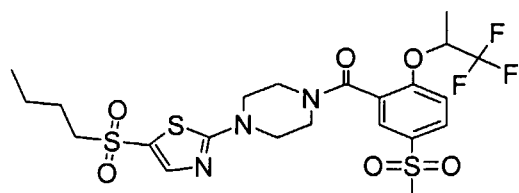
Prepared in analogy to example 4 (c) from 4-(5-butylsulfanyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester and meta-chloroperbenzoic acid. The title compound was obtained as a yellow crystalline solid (yield 82%). MS (m/e): 390.3 (M+H⁺, 100%), 407.3 (M+NH₄⁺, 80%).

c) 1-[5-(Butane-1-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride

Prepared in analogy to example 4 (d) from 4-[5-(butane-1-sulfonyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester and hydrogen chloride solution. The crude material was purified by recrystallisation from ether to afford the title compound as an off-white crystalline solid (yield 92%). MS (m/e): 290.0 (M+H⁺, 100%).

d) {4-[5-(Butane-1-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-[5-(butane-1-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 54%). MS (m/e): 530.3 (M+H⁺, 35%), 547.5 (M+NH₄⁺, 100%).

Example 3920 {4-[5-(Butane-1-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone

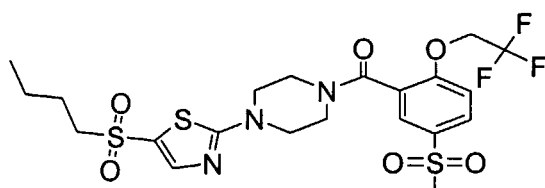
Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A2) and 1-[5-(butane-1-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride (Example 38(c)). The crude material was purified by

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chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 65%). MS (m/e): 584.3 (M+H⁺, 100%), 601.4 (M+NH₄⁺, 60%).

Example 40

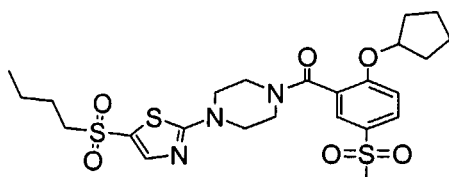
- 5 {4-[5-(Butane-1-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-phenyl]-methanone



- Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-ethoxy)-benzoic acid (Example A3) and 1-[5-(butane-1-sulfonyl)-thiazol-2-yl]-
 10 piperazine hydrochloride (Example 38(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 63%). MS (m/e): 570.4 (M+H⁺, 15%), 587.3 (M+NH₄⁺, 100%).

Example 41

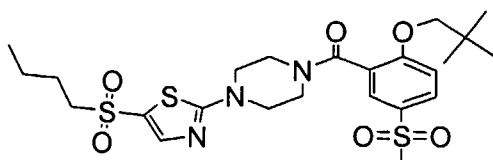
- 15 {4-[5-(Butane-1-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-methanone



- Prepared in analogy to example 1 (b) from 2-cyclopentyloxy-5-methanesulfonyl-benzoic acid (Example A4) and 1-[5-(butane-1-sulfonyl)-thiazol-2-yl]-piperazine
 20 hydrochloride (Example 38(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 71%). MS (m/e): 556.3 (M+H⁺, 35%), 573.5 (M+NH₄⁺, 100%).

Example 42

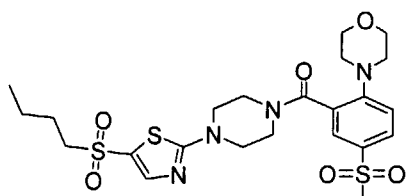
{4-[5-(Butane-1-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-phenyl]-methanone



- 5 Prepared in analogy to example 1 (b) from 2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-benzoic acid (Example A11) and 1-[5-(butane-1-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride (Example 38(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 69%). MS (m/e): 558.4 (M+H⁺, 20%),
 10 575.4 (M+NH₄⁺, 100%).

Example 43

{4-[5-(Butane-1-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone



- 15 Prepared in analogy to example 1 (b) from 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid (Example A13) and 1-[5-(butane-1-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride (Example 38(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a light red crystalline solid (yield 60%). MS (m/e): 557.2 (M+H⁺, 65%), 574.4
 20 (M+NH₄⁺, 100%).

Example 44

(2-Isopropoxy-5-methanesulfonyl-phenyl)-{4-[5-(propane-2-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-methanone

a) 4-[5-(Propane-2-sulfonyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester

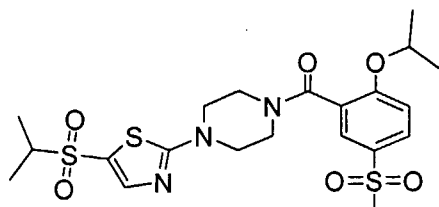
- 56 -

To a solution of 0.83 mmol 4-(5-ethanesulfonyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester (Example 32(b)) in 3 ml tetrahydrofuran at -78 °C was added dropwise 1.08 mmol potassium bis(trimethylsilylamide) solution (0.91 M in tetrahydrofuran). After 3 min, a solution of 1.24 mmol iodomethane in 2 ml
 5 tetrahydrofuran was added dropwise and stirring continued for 10 min at -78 °C. The reaction mixture was then allowed to warm to room temperature and poured onto tetrahydrofuran/ethyl acetate (1:1). The mixture was washed with brine and the organic phase was dried over sodium sulphate and concentrated in vacuo. Chromatography (SiO₂, ethyl acetate/heptane) afforded the title compound as a white crystalline solid
 10 (yield 30%). MS (m/e): 376.1 (M+H⁺, 100%).

b) 1-[5-(Propane-2-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride

Prepared in analogy to example 4 (d) from 4-[5-(propane-2-sulfonyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester and hydrogen chloride solution. The crude material was purified by recrystallisation from ether to afford the title compound as
 15 a white crystalline solid (yield 97%). MS (m/e): 276.4 (M+H⁺, 100%).

c) (2-Isopropoxy-5-methanesulfonyl-phenyl)-{4-[5-(propane-2-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-methanone



Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-[5-(propane-2-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 67%). MS (m/e): 516.3 (M+H⁺, 100%), 533.3 (M+NH₄⁺, 85%).
 20

Example 45

25 (2-Isopropoxy-5-methanesulfonyl-phenyl)-{4-[5-(pyridine-2-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-methanone

a) 4-[5-(Pyridin-2-ylsulfonyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester

Prepared in analogy to example 4 (b) from 4-(5-bromo-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester (Example 4(a)) and 2,2'-dithiodipyridine. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title compound as a yellow crystalline solid (yield 94%). MS (m/e): 379.1 (M+H⁺, 100%).

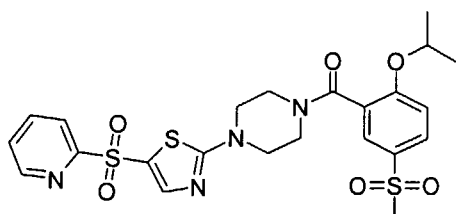
5 b) 4-[5-(Pyridine-2-sulfonyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester

Prepared in analogy to example 4 (c) from 4-[5-(pyridin-2-ylsulfanyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester and meta-chloroperbenzoic acid. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title compound as a white crystalline solid (yield 54%). MS (m/e): 411.3 (M+H⁺,
10 100%).

c) 1-[5-(Pyridine-2-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride

Prepared in analogy to example 4 (d) from 4-[5-(pyridine-2-sulfonyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester and hydrogen chloride solution. The crude material was purified by recrystallisation from ether to afford the title compound as
15 an off-white crystalline solid (yield 99%). MS (m/e): 311.0 (M+H⁺, 100%).

d) (2-Isopropoxy-5-methanesulfonyl-phenyl)-{4-[5-(pyridine-2-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-methanone



Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-[5-(pyridine-2-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 90%). MS (m/e): 551.2 (M+H⁺, 100%).
20

Example 46

25 (2-Isopropoxy-5-methanesulfonyl-phenyl)-{4-[5-(pyridine-3-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-methanone

a) 4-[5-(Pyridin-3-ylsulfanyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester

Prepared in analogy to example 4 (b) from 4-(5-bromo-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester (Example 4(a)) and 3,3'-dithiodipyridine. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title compound as an orange oil (yield 55%). MS (m/e): 379.1 (M+H⁺, 100%).

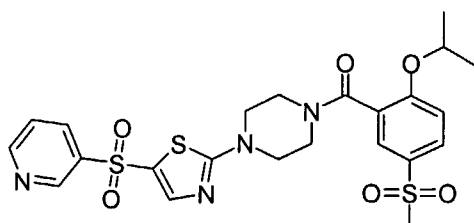
5 b) 4-[5-(Pyridine-3-sulfonyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester

Prepared in analogy to example 4 (c) from 4-[5-(pyridin-3-ylsulfanyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester and meta-chloroperbenzoic acid. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title compound as a white crystalline solid (yield 41%). MS (m/e): 411.1 (M+H⁺,
10 100%).

c) 1-[5-(Pyridine-3-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride

Prepared in analogy to example 4 (d) from 4-[5-(pyridine-3-sulfonyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester and hydrogen chloride solution. The crude material was purified by recrystallisation from ether to afford the title compound as
15 an off-white crystalline solid (yield 99%). MS (m/e): 311.0 (M+H⁺, 100%).

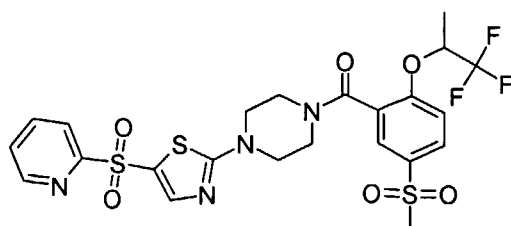
d) (2-Isopropoxy-5-methanesulfonyl-phenyl)-{4-[5-(pyridine-3-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-methanone



Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-[5-(pyridine-3-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as an off-white crystalline solid (yield 87%). MS (m/e): 551.3 (M+H⁺, 100%).
20

Example 47

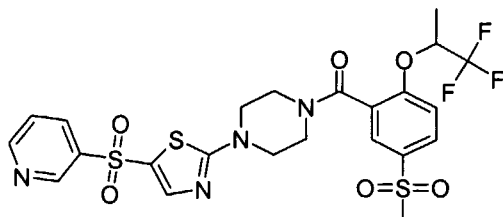
25 [5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-{4-[5-(pyridine-2-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-methanone



Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A2) and 1-[5-(pyridine-2-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride (Example 45(c)). The crude material was purified by
 5 chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as an off-white crystalline solid (yield 68%). MS (m/e): 605.0 (M+H⁺, 100%).

Example 48

[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-{4-[5-(pyridine-3-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-methanone
 10



Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A2) and 1-[5-(pyridine-3-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride (Example 46(c)). The crude material was purified by
 15 chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a light brown crystalline solid (yield 49%). MS (m/e): 605.2 (M+H⁺, 100%).

Example 49

(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone
 20

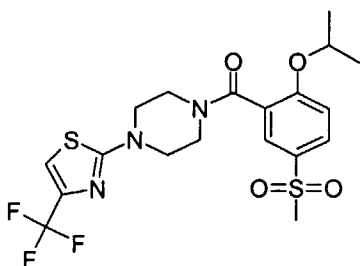
a) 1-(4-Trifluoromethyl-thiazol-2-yl)-piperazine

To a solution of 6.89 mmol 1-piperazinecarbothioamide in 10 ml ethanol was added 8.26 mmol 3-bromo-1,1,1-trifluoroacetone and the mixture was heated at 70 °C for 2 h. The mixture was then concentrated in vacuo and the residue resuspended in

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dichloromethane. Insoluble material was removed by filtration and the filtrate was concentrated in vacuo. Chromatography (SiO₂, methanol/dichloromethane) afforded the title compound as a yellow crystalline solid (yield 41%). MS (m/e): 238.1 (M+H⁺, 100%).

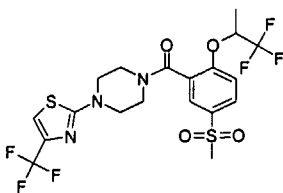
5 b) (2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-(4-trifluoromethyl-thiazol-2-yl)-piperazine. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by
 10 trituration in pentane to yield the title compound as a crystalline white solid (yield 55%). MS (m/e): 478.0 (M+H⁺, 100%).

Example 50

[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone

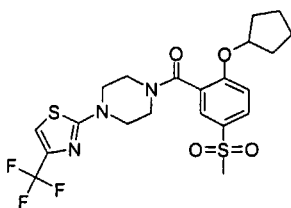


15

Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A2) and 1-(4-trifluoromethyl-thiazol-2-yl)-piperazine (Example 49(a)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in pentane to yield the title compound as a
 20 crystalline white solid (yield 48%). MS (m/e): 531.8 (M+H⁺, 100%).

Example 51

(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 2-cyclopentyloxy-5-methanesulfonylbenzoic acid (Example A4) and 1-(4-trifluoromethyl-thiazol-2-yl)-piperazine (Example 49(a)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in pentane to yield the title compound as a crystalline white solid (yield 71%). MS (m/e): 504.0 (M+H⁺, 100%).

Example 52

(2-Isopropoxy-5-methanesulfonyl-phenyl)-{4-[5-(pyridine-4-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-methanone

a) 4-[5-(Pyridin-4-ylsulfanyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester

Prepared in analogy to example 4 (b) from 4-(5-bromo-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester (Example 4(a)) and 4,4'-dithiodipyridine. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title compound as a yellow oil (yield 79%). MS (m/e): 379.3 (M+H⁺, 100%).

b) 4-[5-(Pyridine-4-sulfonyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester

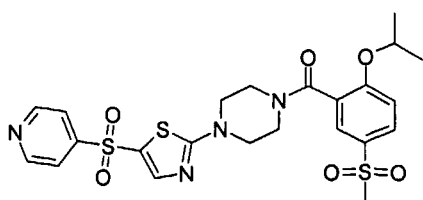
Prepared in analogy to example 4 (c) from 4-[5-(pyridin-4-ylsulfanyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester and meta-chloroperbenzoic acid. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title compound as a yellow crystalline solid (yield 37%). MS (m/e): 411.3 (M+H⁺, 100%).

c) 1-[5-(Pyridine-4-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride

Prepared in analogy to example 4 (d) from 4-[5-(pyridine-4-sulfonyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester and hydrogen chloride solution. The crude material was purified by recrystallisation from ether to afford the title compound as a light yellow crystalline solid (yield 99%). MS (m/e): 311.0 (M+H⁺, 100%).

d) (2-Isopropoxy-5-methanesulfonyl-phenyl)-{4-[5-(pyridine-4-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-methanone

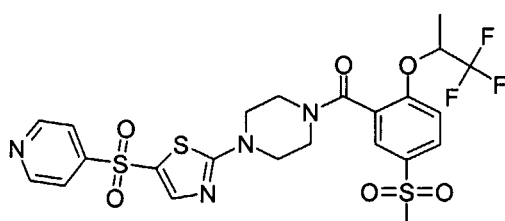
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Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-[5-(pyridine-4-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a light red crystalline solid (yield 32%). MS (m/e): 551.2 (M+H⁺, 100%).

Example 53

[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-{4-[5-(pyridine-4-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-methanone



10

Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A2) and 1-[5-(pyridine-4-sulfonyl)-thiazol-2-yl]-piperazine hydrochloride (Example 52(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a light yellow crystalline solid (yield 32%). MS (m/e): 551.2 (M+H⁺, 100%).

Example 54

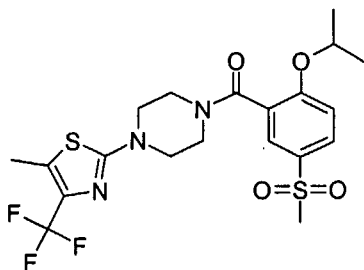
(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-methyl-4-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone

20 a) 1-(5-Methyl-4-trifluoromethyl-thiazol-2-yl)-piperazine

Prepared in analogy to example 49 (a) from 1-piperazinecarbothioamide and 3-bromo-1,1,1-trifluoro-2-butanone. The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) to yield the title compound as a white crystalline solid (yield 25%). MS (m/e): 252.1 (M+H⁺, 100%).

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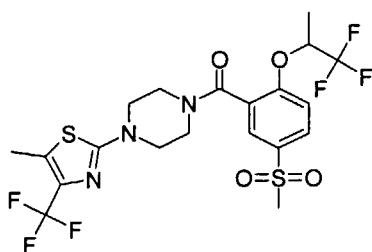
b) (2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-methyl-4-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-
5 benzoic acid (Example A1) and 1-(5-methyl-4-trifluoromethyl-thiazol-2-yl)-piperazine. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in ether to yield the title compound as a white crystalline solid (yield 60%). MS (m/e): 492.3 (M+H⁺, 100%).

Example 55

10 [5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-methyl-4-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A2) and 1-(5-methyl-4-trifluoromethyl-thiazol-2-yl)-piperazine (Example 54(a)). The crude material was purified by chromatography
15 (SiO₂, ethyl acetate/heptane) followed by trituration in pentane to yield the title compound as a white crystalline solid (yield 61%). MS (m/e): 546.3 (M+H⁺, 100%).

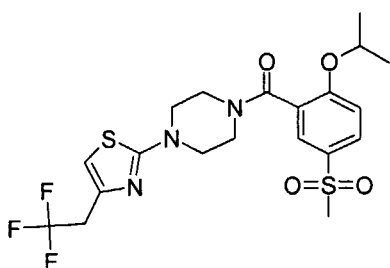
Example 56

(2-Isopropoxy-5-methanesulfonyl-phenyl)-{4-[4-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-
20 piperazin-1-yl}-methanone

a) 1-[4-(2,2,2-Trifluoro-ethyl)-thiazol-2-yl]-piperazine

Prepared in analogy to example 49 (a) from 1-piperazinecarbothioamide and 1-bromo-4,4,4-trifluoro-butan-2-one. The crude material was purified by chromatography (SiO_2 , methanol/dichloromethane) to yield the title compound as a brown oil (yield 24%). MS (m/e): 252.3 ($\text{M}+\text{H}^+$, 100%).

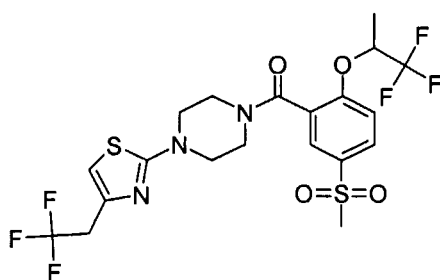
- 5 b) (2-Isopropoxy-5-methanesulfonyl-phenyl)-{4-[4-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazin-1-yl}-methanone



- 10 Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonylbenzoic acid (Example A1) and 1-[4-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazine. The crude material was purified by chromatography (SiO_2 , ethyl acetate/heptane) followed by trituration in pentane to yield the title compound as a white crystalline solid (yield 28%). MS (m/e): 492.1 ($\text{M}+\text{H}^+$, 100%).

Example 57

- 15 [5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-{4-[4-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazin-1-yl}-methanone



- 20 Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A2) and 1-[4-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazine (Example 56(a)). The crude material was purified by chromatography (SiO_2 , ethyl acetate/heptane) followed by trituration in pentane to yield the title compound as a white crystalline solid (yield 29%). MS (m/e): 546.3 ($\text{M}+\text{H}^+$, 100%).

Example 58

(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone

a) 2-Benzenesulfonyl-3-trifluoromethyl-oxirane

5 To a solution of 25.4 mmol 3,3,3-trifluoro-1-(phenylsulphonyl)prop-1-ene in 80 ml acetonitrile were added 30.5 mmol peracetic acid (39% solution in acetic acid) and 101 mmol potassium carbonate. The mixture was heated at 60 °C for 4 h. The reaction mixture was then diluted with ethyl acetate/tetrahydrofuran (1:1) and was washed with brine. The organic phase was dried over sodium sulfate and concentrated in vacuo to
10 afford the title compound as a light yellow crystalline solid (yield 90%). EI-MS (m/e): 252.0 (M⁺, 15%), 125.1 (PhSO⁺, 100%), 77.2 (Ph⁺, 37%).

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

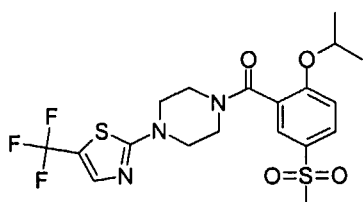
To a solution of 17.5 mmol 2-benzenesulfonyl-3-trifluoromethyl-oxirane in 20 ml N,N-dimethylformamide was added 15.9 mmol 4-thiocarbamoyl-piperazine-1-carboxylic
15 acid tert-butyl ester (prepared from tert-butyl 1-piperazinecarboxylate, 1,1'-thiocarbonyldiimidazole and ammonia according to the procedure of J. Med. Chem. 1998, 41, 5037-5054). The mixture was heated at 90 °C for 10 h. The reaction mixture was then concentrated in vacuo and the residue purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title compound as an orange crystalline solid (yield 26%).
20 MS (m/e): 338.1 (M+H⁺, 100%).

c) 1-(5-Trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride

To a solution of 3.59 mmol 4-(5-trifluoromethyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in 20 ml dioxane was added dropwise 53.8 mmol
hydrogen chloride solution (4 M in dioxane) and the mixture was stirred at 90 °C for 4 h.
25 The reaction mixture was then cooled to 0 °C and diluted with ether. The resulting crystals were collected by filtration and washed with ether to afford the title compound as an off-white crystalline solid (yield 99%). MS (m/e): 238.1 (M+H⁺, 100%).

d) (2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone

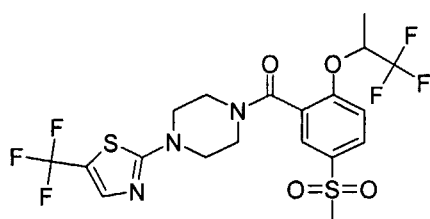
- 66 -



Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in pentane to yield the title compound as a white crystalline solid (yield 28%). MS (m/e): 478.3 (M+H⁺, 100%).

Example 59

[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



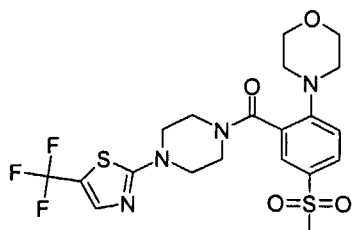
10

Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A2) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in pentane to yield the title compound as an off-white crystalline solid (yield 64%). MS (m/e): 532.0 (M+H⁺, 100%).

15

Example 60

(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



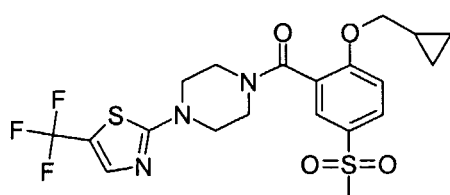
20

- 67 -

Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-morpholin-4-yl-benzoic acid (Example A13) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in pentane to yield the title compound as an off-white crystalline solid (yield 71%). MS (m/e): 505.3 (M+H⁺, 100%).

Example 61

(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 2-cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (Example A5) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in pentane to yield the title compound as a white crystalline solid (yield 22%). MS (m/e): 490.3 (M+H⁺, 100%).

Example 62

(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazin-1-yl]-methanone

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

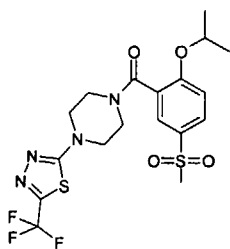
A mixture of 2.2 mmol 2-bromo-5-trifluoromethyl-[1,3,4]thiadiazole (CA 37461-6-3; prepared according to DE2533605), 2.3 mmol piperazine-1-carboxylic acid tert-butyl ester and 4.3 mmol potassium carbonate in 10 ml acetonitrile was refluxed for 4 hours. The reaction mixture was cooled, poured into water and extracted 3 times with ethyl acetate. Concentration and recrystallisation of the crude material from diethyl ether yielded the title compound as a colorless solid. MS (m/e): 397.2 ([M+CH₃COO]⁻, 100%).

b) 1-(5-Trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine trifluoroacetate

- 68 -

0.83 mmol 4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in 10 ml of dichloromethane was treated with 6.6 mmol trifluoroacetic acid and stirred for 2 hours at room temperature. The reaction mixture is concentrated to give the title compound as yellowish gum. MS (m/e): 239.1 (M+H⁺, 100%).

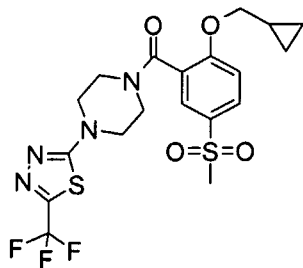
c) (2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine trifluoroacetate. The crude material was purified by chromatography (SiO₂, dichloromethane / methanol 99 : 1) to yield the title compound as a colorless solid. MS (m/e): 479.2 (M+H⁺, 100%).

Example 63

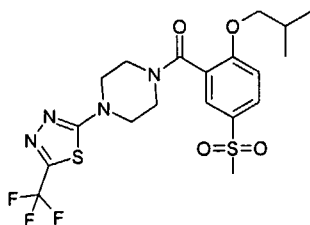
(2-Cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 2-cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (Example A5) and 1-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine trifluoroacetate (Example 62(b)). The crude material was purified by chromatography (SiO₂, dichloromethane / methanol 98 : 2) to yield the title compound as a colorless solid. MS (m/e): 491.2 (M+H⁺, 100%).

Example 64

(2-Isobutoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazin-1-yl]-methanone

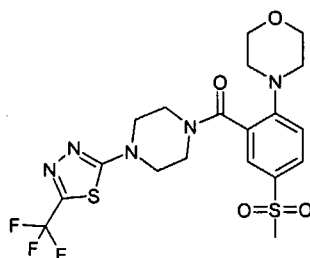


- 5 Prepared in analogy to example 1 (b) from 2-isobutoxy-5-methanesulfonyl-benzoic acid (Example A8) and 1-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine trifluoroacetate (Example 62(b)). The crude material was purified by chromatography (SiO₂, dichloromethane / methanol 98 : 2) to yield the title compound as a colorless solid. MS (m/e): 493.4 (M+H⁺, 100%).

10

Example 65

(5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazin-1-yl]-methanone

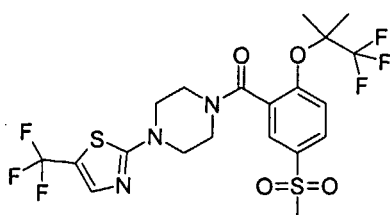


- 15 Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-morpholin-4-yl-benzoic acid (Example A13) and 1-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine trifluoroacetate (Example 62(b)). The crude material was purified by chromatography (SiO₂, dichloromethane / methanol 99 : 1) to yield the title compound as a colorless solid. MS (m/e): 506.3 (M+H⁺, 100%).

Example 66

- 20 [5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone

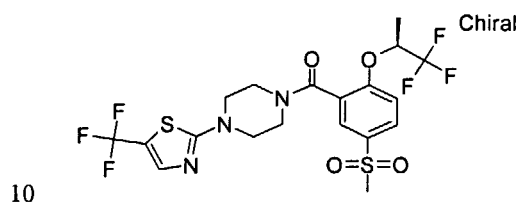
- 70 -



Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-benzoic acid (Example A14) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by chromatography (ethyl acetate/heptane) to yield the title compound as a white solid (yield 52%). MS (m/e): 546.3(M+H⁺, 100%). B.p. = 182-183°C.

Example 67

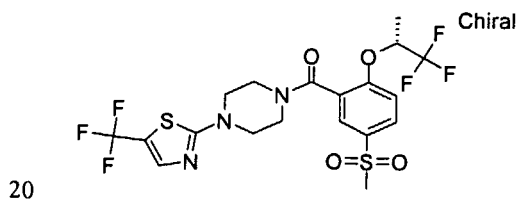
[5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A15) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in pentane to yield the title compound as an off-white crystalline solid (yield 52%). MS (m/e): 532.3 (M+H⁺, 100%).

Example 68

[5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A16) and 1-(5-trifluoromethyl-

thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in pentane to yield the title compound as an off-white crystalline solid (yield 57%). MS (m/e): 532.0 (M+H⁺, 100%).

5

Example 69

[5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-{4-[5-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazin-1-yl}-methanone

a) 4-(5-Hydroxymethyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

To a solution of 179 mmol 30% aqueous hydrogen peroxide in 60 ml water was
10 added 1 N aqueous sodium hydroxide solution until the pH was 9. The reaction mixture was then cooled to 10 °C and 163 mmol acrolein was added dropwise. Further amounts of 1 N aqueous sodium hydroxide solution were added during the addition in order to maintain the pH of the reaction mixture between pH 8 and 9. The mixture was stirred for 30 min at 0 °C and then 40.8 mmol thiocarbamoyl-piperazine-1-carboxylic acid tert-
15 butyl ester (prepared from tert-butyl 1-piperazinecarboxylate, 1,1'-thiocarbonyldiimidazole and ammonia according to the procedure of J. Med. Chem. 1998, 41, 5037-5054) was added. To the resulting suspension was added 25 ml ethanol and the mixture was heated at 80 °C for 30 min. The resulting solution was diluted with ethyl acetate/tetrahydrofuran (1:1) and the mixture was washed twice with brine. The
20 organic phase was dried over sodium sulphate and concentrated in vacuo to afford the title compound as a yellow oil (yield 99%). MS (m/e): 300.3 (M+H⁺, 100%).

b) 4-(5-Formyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

To a solution of 40.0 mmol 4-(5-hydroxymethyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in 300 ml dichloromethane was added 289 mmol
25 manganese(IV) oxide and the mixture was heated at reflux for 3 h. The mixture was then filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title compound as a light brown crystalline solid (yield 40%). MS (m/e): 298.3 (M+H⁺, 100%).

c) 4-[5-(2,2-Difluoro-vinyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester

To a solution of 6.73 mmol triphenylphosphine in 13 ml N,N-dimethylformamide
30 was added 6.73 mmol dibromodifluoromethane and the mixture was stirred at room temperature for 1 h. 3.36 mmol 4-(5-formyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester was added and the mixture was then cooled to 0 °C. 6.73 mmol zinc dust

was added in small portions and stirring continued for 10 min at 0 °C. The mixture was then allowed to warm to room temperature and stirring continued for a further 2 h. The reaction mixture was then filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title

- 5 compound as a white crystalline solid (yield 19%). MS (m/e): 332.3 (M+H⁺, 100%), 276.0 ([M+2H-'Bu]⁺, 100%).

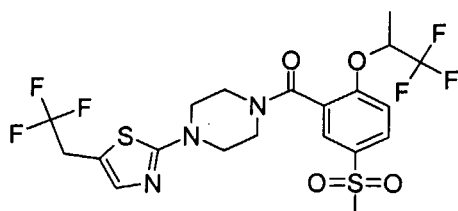
d) 4-[5-(2,2,2-Trifluoro-ethyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester

- To a solution of 1.03 mmol 4-[5-(2,2-difluoro-vinyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester in 7.5 dimethylsulphoxide and 0.3 ml water was added
 10 7.18 mmol potassium fluoride and the mixture was heated at 120 °C for 2 h. The mixture was then diluted with ethyl acetate and washed sequentially with water and brine. The organic phase was dried over sodium sulphate and concentrated in vacuo. The residue was purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title compound as a yellow crystalline solid (yield 90%). MS (m/e): 352.3 (M+H⁺, 100%).

- 15 e) 1-[5-(2,2,2-Trifluoro-ethyl)-thiazol-2-yl]-piperazine hydrochloride

- To a solution of 0.91 mmol 4-[5-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester in 30 ml dioxane was added dropwise 18.2 mmol hydrogen chloride solution (4 M in dioxane) and the mixture was stirred at 90 °C for 90 min. The reaction mixture was then cooled to 0 °C and diluted with ether. The resulting
 20 crystals were collected by filtration and washed with ether to afford the title compound as a light brown crystalline solid (yield 73%). MS (m/e): 252.3 (M+H⁺, 100%).

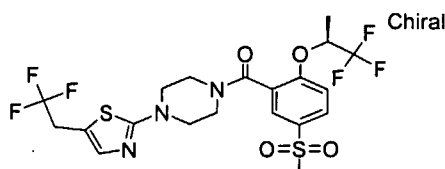
f) [5-Methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-[5-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazin-1-yl]-methanone



- 25 Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A2) and 1-[5-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazine hydrochloride. The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) to yield the title compound as a white crystalline solid (yield 32%). MS (m/e): 546.3 (M+H⁺, 100%).

Example 70

[5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-{4-[5-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazin-1-yl}-methanone

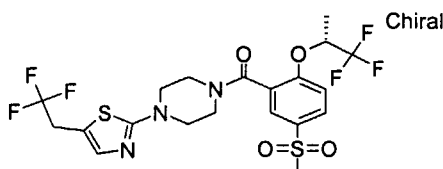


- 5 Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A15) and 1-[5-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazine hydrochloride (Example 69(e)). The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) to yield the title compound as a white crystalline solid (yield 54%). MS (m/e): 546.3 (M+H⁺, 100%).

10

Example 71

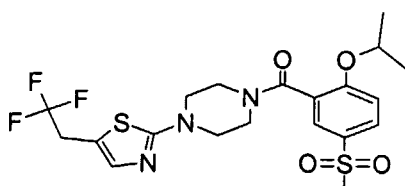
[5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-{4-[5-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazin-1-yl}-methanone



- 15 Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A16) and 1-[5-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazine hydrochloride (Example 69(e)). The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) to yield the title compound as a white crystalline solid (yield 41%). MS (m/e): 546.3 (M+H⁺, 100%).

Example 72

- 20 (2-Isopropoxy-5-methanesulfonyl-phenyl)-{4-[5-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazin-1-yl}-methanone

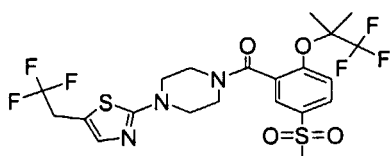


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Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 1-[5-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazine hydrochloride (Example 69(e)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as a white crystalline solid (yield 36%). MS (m/e): 492.4 (M+H⁺, 100%).

Example 73

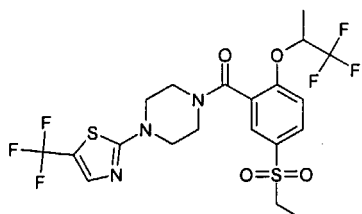
[5-Methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-phenyl]-{4-[5-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazin-1-yl}-methanone



Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-benzoic acid (Example A14) and 1-[5-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazine hydrochloride (Example 69(e)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as a white crystalline solid (yield 27%). MS (m/e): 560.3 (M+H⁺, 100%).

Example 74

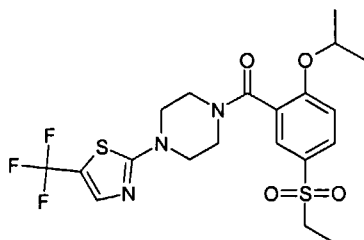
[5-Ethanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 5-ethanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A17) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by reversed phase HPLC (acetonitrile/water) followed by trituration in ether to yield the title compound as an off-white crystalline solid (yield 82%). MS (m/e): 546.4 (M+H⁺, 100%).

Example 75

(5-Ethanesulfonyl-2-isopropoxy-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone

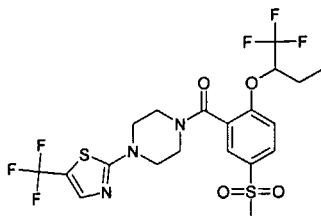


- 5 Prepared in analogy to example 1 (b) from 5-ethanesulfonyl-2-isopropoxy-benzoic acid (Example A18) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by reversed phase HPLC (acetonitrile/water) followed by trituration in ether to yield the title compound as an off-white crystalline solid (yield 21%). MS (m/e): 492.1 (M+H⁺, 100%).

10

Example 76

[5-Methanesulfonyl-2-(1-trifluoromethyl-propoxy)-phenyl]-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone

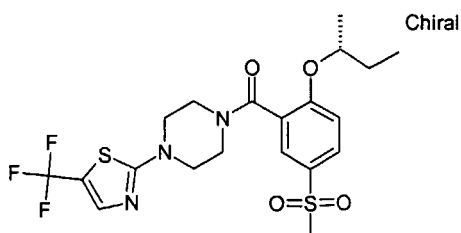


- 15 Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(1-trifluoromethyl-propoxy)-benzoic acid (Example A19) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by reversed phase HPLC (acetonitrile/water) followed by trituration in ether to yield the title compound as an off-white crystalline solid (yield 11%). MS (m/e): 546.3 (M+H⁺, 100%).

Example 77

- 20 (2-((R)-sec-Butoxy)-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone

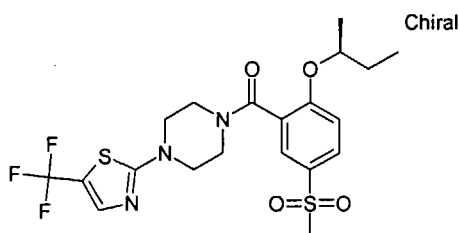
- 76 -



Prepared in analogy to example 1 (b) from 2-((R)-sec-butoxy)-5-methanesulfonyl-benzoic acid (Example A20) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by reversed phase
 5 HPLC (acetonitrile/water) followed by trituration in ether to yield the title compound as an off-white crystalline solid (yield 10%). MS (m/e): 492.4 (M+H⁺, 100%).

Example 78

(2-((S)-sec-Butoxy)-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



10

Prepared in analogy to example 1 (b) from 2-((S)-sec-butoxy)-5-methanesulfonyl-benzoic acid (Example A21) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by reversed phase
 HPLC (acetonitrile/water) followed by trituration in ether to yield the title compound as
 15 an off-white crystalline solid (yield 13%). MS (m/e): 492.4 (M+H⁺, 100%).

Example 79

(2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-methyl-5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone

a) Rac-(3,3,3-Trifluoro-1-methyl-propylsulfanyl)-benzene

20 To a solution of 54.9 mmol 3-iodo-1,1,1-trifluorobutane in 50 ml N,N-dimethylformamide were added 49.9 mmol thiophenol and 74.9mmol potassium carbonate. The mixture was ultrasonicated at room temperature for 90 min. The reaction mixture was then diluted with ether and was washed three times with water. The organic

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phase was dried over sodium sulfate and concentrated in vacuo to afford the title compound as a colourless oil (yield 79%). MS (m/e): 221.3 (M^+ , 15%).

b) Rac-(4,4,4-Trifluoro-butane-2-sulfonyl)-benzene

To a solution of 39.5 mmol rac-(3,3,3-trifluoro-1-methyl-propylsulfanyl)-benzene in 80 ml dichloromethane was added 178 mmol trifluoroacetic acid. 148 mmol urea hydrogen peroxide was then added in small portions and the mixture was subsequently heated at reflux for 4 h. The reaction mixture was then diluted with dichloromethane and was washed sequentially with water, 1 N aqueous sodium hydroxide, and again with water. The organic phase was then dried over sodium sulfate and concentrated in vacuo to afford the title compound as a colourless oil (yield 80%). EI-MS (m/e): 252.1 (M^+ , 3%), 142.1 (PhSO_2H^+ , 100%), 91.1 ($\text{H}_3\text{CCH}=\text{CHCF}_3^+$, 20%; 78.2 (PhH^+ , 74%), 77.2 (Ph^+ , 45%).

c) Rac-(4,4,4-Trifluoro-2-iodo-butane-2-sulfonyl)-benzene

To a solution of 28.5 mmol diisopropylamine in 18 ml tetrahydrofuran at -78°C was added dropwise 28.5 mmol n-butyllithium solution (1.6 M in hexane) and the mixture was then warmed to room temperature. The resulting solution was then added dropwise over 50 min to a solution of 19.0 mmol rac-(4,4,4-trifluoro-butane-2-sulfonyl)-benzene in 30 ml tetrahydrofuran at -78°C and stirring continued for a further 15 min at -78°C . Finally, a solution of 20.9 mol iodine in 15 ml tetrahydrofuran was added dropwise over 15 min and stirring continued for a further 15 min at -78°C and then the reaction mixture was allowed to warm to -20°C . The reaction mixture was quenched by addition of 1 M hydrochloric acid and the mixture was extracted three times with ethyl acetate. The combined organic phases were washed sequentially with aqueous sodium thiosulfite solution and with brine and then dried over sodium sulphate and concentrated in vacuo to afford the title compound as a yellow oil (yield 87%). EI-MS (m/e): 377.9 (M^+ , 4%), 237.0 ($[\text{M}-\text{PhSO}_2]^+$, 40%), 142.0 (PhSO_2H^+ , 100%), 125.1 (PhSO^+ , 93%), 78.2 (PhH^+ , 40%), 77.2 (Ph^+ , 31%).

d) ((E)-4,4,4-Trifluoro-but-2-ene-2-sulfonyl)-benzene

To a solution of 14.0 mmol rac-(4,4,4-trifluoro-2-iodo-butane-2-sulfonyl)-benzene in 25 ml tetrahydrofuran and 2.5 ml water were added 42.1 mmol triethylamine and 42.1 mmol potassium carbonate. The mixture was heated at 70°C for 6 h. The reaction mixture was then diluted with ethyl acetate and was washed sequentially with 1 N hydrochloric acid and brine. The organic phase was dried over sodium sulfate and concentrated in vacuo. The residue was purified by chromatography (SiO_2 , ethyl

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acetate/heptane) to afford the title compound as a yellow oil (yield 72%). EI-MS (m/e): 250.1 (M^+ , 15%), 186.1 ($[M-SO_2]^+$, 38%), 125.0 ($PhSO^+$, 100%), 77.1 (Ph^+ , 38%).

e) Rac-2-Benzenesulfonyl-2-methyl-3-trifluoromethyl-oxirane

To a solution of 15.2 mmol n-butyllithium solution (1.6 M in hexane) in 20 ml tetrahydrofuran at -78 °C was added dropwise 15.2 mmol tert-butyl hydroperoxide solution (5.5 M in nonane) and the mixture was stirred at -78 °C for 10 min, then warmed to -50 °C and re-cooled to -78 °C. A solution of 10.1 mmol ((E)-4,4,4-trifluorobut-2-ene-2-sulfonyl)-benzene in 6 ml tetrahydrofuran was then added dropwise and stirring continued for a further 30 min at -78 °C and then the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with ethyl acetate and washed sequentially with 1 M hydrochloric acid and with brine. The organic phase was then dried over sodium sulphate and concentrated in vacuo. The residue was purified by chromatography (SiO_2 , ethyl acetate/heptane) to afford the title compound as a colourless oil (yield 49%). EI-MS (m/e): 251.1 ($[M-CH_3]^+$, 6%), 250.1 ($[M-O]^+$, 20%), 126.1 ($PhSOH^+$, 61%), 125.0 ($[M-PhSO_2]^+$, 100%), 78.2 (PhH^+ , 21%), 77.2 (Ph^+ , 44%), 43.3 ($CH_3CHCH_3^+$, 73%).

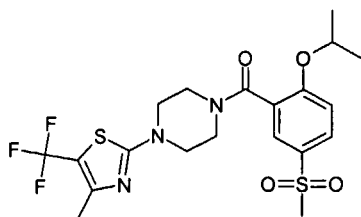
f) 4-(4-Methyl-5-trifluoromethyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

A mixture of 4.92 mmol rac-2-benzenesulfonyl-2-methyl-3-trifluoromethyl-oxirane and 5.41 mmol 4-thiocarbamoyl-piperazine-1-carboxylic acid tert-butyl ester (prepared from tert-butyl 1-piperazinecarboxylate, 1,1'-thiocarbonyldiimidazole and ammonia according to the procedure of J. Med. Chem. 1998, 41, 5037-5054) in 15 ml N,N-dimethylformamide was heated at 100 °C for 4.5 h. The reaction mixture was then concentrated in vacuo and the residue purified by chromatography (SiO_2 , ethyl acetate/heptane) to afford the title compound as a yellow crystalline solid (yield 30%). MS (m/e): 352.3 ($M+H^+$, 100%).

g) 1-(4-Methyl-5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride

To a solution of 1.45 mmol 4-(4-methyl-5-trifluoromethyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in 10 ml dioxane was added dropwise 21.8 mmol hydrogen chloride solution (4 M in dioxane) and the mixture was stirred at 90 °C for 2 h. The reaction mixture was then cooled to 0 °C and diluted with ether. The resulting crystals were collected by filtration and washed with ether to afford the title compound as a white crystalline solid (yield 68%). MS (m/e): 252.3 ($M+H^+$, 100%).

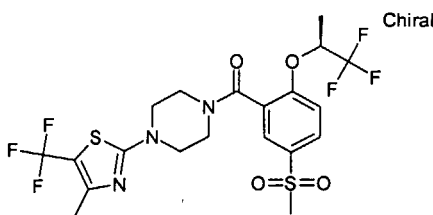
h) (2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-methyl-5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



- Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-
 5 benzoic acid (Example A1) and 1-(4-methyl-5-trifluoromethyl-thiazol-2-yl)-piperazine
 hydrochloride. The crude material was purified by chromatography (SiO₂, ethyl
 acetate/heptane) to yield the title compound as a white foam (yield 52%). MS (m/e):
 492.0 (M+H⁺, 100%).

Example 80

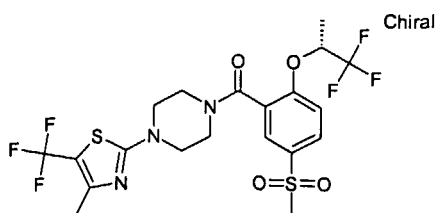
- 10 [5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-methyl-5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



- Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-((S)-2,2,2-
 trifluoro-1-methyl-ethoxy)-benzoic acid (Example A15) and 1-(4-methyl-5-
 15 trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 79(g)). The crude
 material was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title
 compound as a white crystalline solid (yield 56%). MS (m/e): 546.0 (M+H⁺, 100%).

Example 81

- 20 [5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-methyl-5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A16) and 1-(4-methyl-5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 79(g)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as a white crystalline solid (yield 57%). MS (m/e): 546.0 (M+H⁺, 100%).

Example 82

1-{2-[4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazol-5-yl}-propan-1-one

10 a) 4-(Dimethylaminomethylene-thiocarbamoyl)-piperazine-1-carboxylic acid tert-butyl ester

A mixture of 122 mmol N,N-dimethylformamide dimethyl acetal and 6.11 mmol 4-thiocarbamoyl-piperazine-1-carboxylic acid tert-butyl ester (prepared from tert-butyl 1-piperazinecarboxylate, 1,1'-thiocarbonyldiimidazole and ammonia according to the procedure of J. Med. Chem. 1998, 41, 5037-5054) was heated at 110 °C for 3 h. The reaction mixture was then concentrated in vacuo and the residue was resuspended in ethyl acetate/tetrahydrofuran (1:1) and washed with brine. The organic phase was dried over sodium sulphate and concentrated in vacuo to afford the title compound as a light yellow crystalline solid (yield 95%). MS (m/e): 301.4 (M+H⁺, 100%).

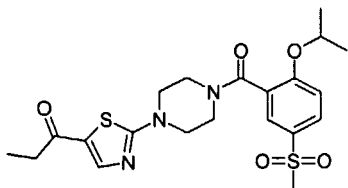
b) 4-(5-Propionyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester

20 To a solution of 0.83 mmol 4-(dimethylaminomethylene-thiocarbamoyl)-piperazine-1-carboxylic acid tert-butyl ester in 6 ml ethanol were added 2.50 mmol triethylamine and 1.00 mmol 1-bromo-2-butanone. The mixture was heated at 90 °C for 16 h. The reaction mixture was then concentrated in vacuo and the residue was purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title compound as a white crystalline solid (yield 72%). MS (m/e): 326.1 (M+H⁺, 100%).

c) 1-(2-Piperazin-1-yl-thiazol-5-yl)-propan-1-one hydrochloride

30 To a solution of 0.58 mmol 4-(5-propionyl-thiazol-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in 6 ml dioxane was added dropwise 8.76 mmol hydrogen chloride solution (4 M in dioxane) and the mixture was stirred at 90 °C for 90 min. The reaction mixture was then cooled to 0 °C and diluted with ether. The resulting crystals were collected by filtration and washed with ether to afford the title compound as a white crystalline solid (yield 99%). MS (m/e): 226.4 (M+H⁺, 100%).

d) 1-{2-[4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazol-5-yl}-propan-1-one



Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-
 5 benzoic acid (Example A1) and 1-(2-piperazin-1-yl-thiazol-5-yl)-propan-1-one
 hydrochloride. The crude material was purified by chromatography (SiO₂,
 methanol/dichloromethane) to yield the title compound as a light brown crystalline solid
 (yield 24%). MS (m/e): 466.0 (M+H⁺, 100%).

Example 83

10 1-{2-[4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazol-5-yl}-2,2-dimethyl-propan-1-one

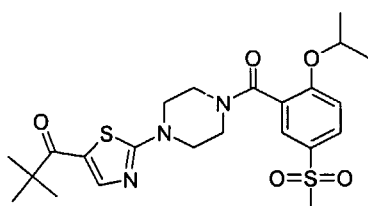
a) 4-[5-(2,2-Dimethyl-propionyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl ester

Prepared in analogy to example 82 (b) from 4-(dimethylaminomethylene-
 15 thiocarbonyl)-piperazine-1-carboxylic acid tert-butyl ester (Example 82(a)) and 1-bromo-pinacolone. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to afford the title compound as a white crystalline solid (yield 87%). MS (m/e): 354.3 (M+H⁺, 100%).

b) 2,2-Dimethyl-1-(2-piperazin-1-yl-thiazol-5-yl)-propan-1-one hydrochloride

20 Prepared in analogy to example 82 (c) from 4-[5-(2,2-dimethyl-propionyl)-thiazol-2-yl]-piperazine-1-carboxylic acid tert-butyl. The crude material was purified by recrystallisation from ether to afford the title compound as a white crystalline solid (yield 93%). MS (m/e): 254.4 (M+H⁺, 100%).

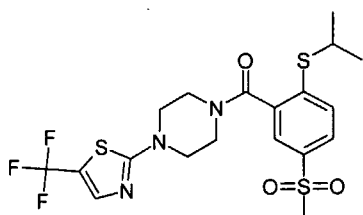
25 c) 1-{2-[4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazol-5-yl}-2,2-dimethyl-propan-1-one



Prepared in analogy to example 1 (b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example A1) and 2,2-dimethyl-1-(2-piperazin-1-yl-thiazol-5-yl)-propan-1-one hydrochloride. The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) to yield the title compound as a light brown crystalline solid (yield 28%). MS (m/e): 494.1 (M+H⁺, 100%).

Example 84

(2-Isopropylsulfanyl-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



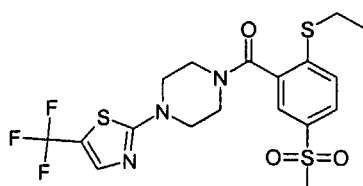
10

Prepared in analogy to example 1 (b) from 2-isopropylsulfanyl-5-methanesulfonyl-benzoic acid (Example A22) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) followed by trituration in pentane to yield the title compound as a white foam (yield 50%). MS (m/e): 494.4 (M+H⁺, 100%).

15

Example 85

(2-Ethylsulfanyl-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



20

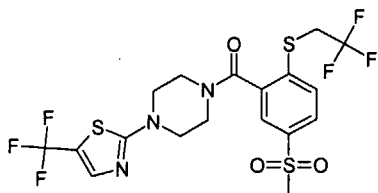
Prepared in analogy to example 1 (b) from 2-ethylsulfanyl-5-methanesulfonyl-benzoic acid (Example A23) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by chromatography

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(SiO₂, ethyl acetate/heptane) to yield the title compound as a white foam (yield 41%). MS (m/e): 479.8 (M+H⁺, 100%).

Example 86

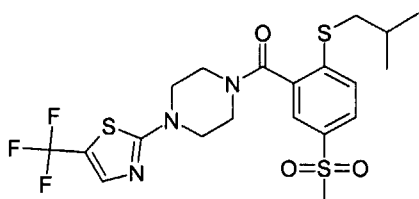
5 [5-Methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-phenyl]-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-benzoic acid (Example A24) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by
10 chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as a light yellow solid (yield 49%). MS (m/e): 534.0 (M+H⁺, 100%).

Example 87

(2-Isobutylsulfanyl-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone

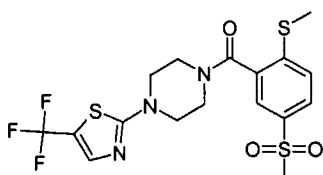


15 Prepared in analogy to example 1 (b) from 2-isobutylsulfanyl-5-methanesulfonyl-benzoic acid (Example A25) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as a light yellow solid (yield
20 88%). MS (m/e): 508.3 (M+H⁺, 100%).

Example 88

(5-Methanesulfonyl-2-methylsulfanyl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone

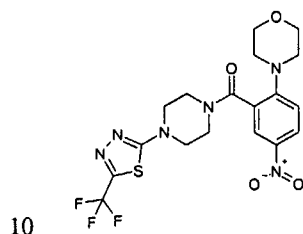
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Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-methylsulfanyl-benzoic acid (Example A26) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as a light brown solid (yield 18%). MS (m/e): 466.0 (M+H⁺, 100%).

Example 89

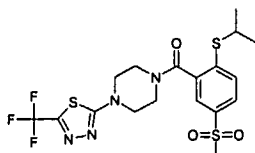
(2-Morpholin-4-yl-5-nitro-phenyl)-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 2-morpholin-4-yl-5-nitro-benzoic acid (Example A27) and 1-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine trifluoroacetate (Example 62(b)). The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) to yield the title compound as a brown solid (yield 34%). MS (m/e): 473.4 (M+H⁺, 100%).

Example 90

(2-Isopropylsulfanyl-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazin-1-yl]-methanone



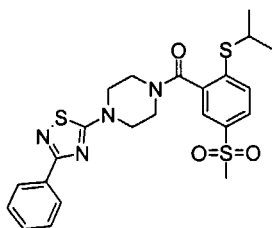
Prepared in analogy to example 1 (b) from 2-isopropylsulfanyl-5-methanesulfonyl-benzoic acid (Example A22) and 1-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine trifluoroacetate (Example 62(b)). The crude material was purified by chromatography

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(SiO₂, ethyl acetate/heptane) to yield the title compound as a white solid (yield 34%). MS (m/e): 495.0 (M+H⁺, 100%).

Example 91

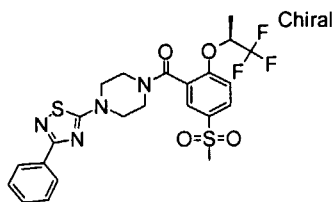
(2-Isopropylsulfanyl-5-methanesulfonyl-phenyl)-[4-(3-phenyl-[1,2,4]thiadiazol-5-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1 (b) from 2-isopropylsulfanyl-5-methanesulfonyl-benzoic acid (Example A22) and 3-phenyl-5-piperazino-1,2,4-thiadiazole. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as an off-white solid (yield 83%). MS (m/e): 503.1 (M+H⁺, 100%).

Example 92

[5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(3-phenyl-[1,2,4]thiadiazol-5-yl)-piperazin-1-yl]-methanone

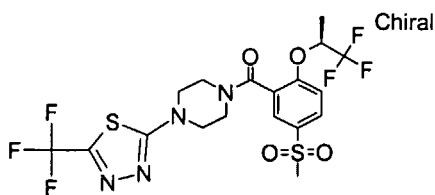


Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A15) and 3-phenyl-5-piperazino-1,2,4-thiadiazole. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as a light brown solid (yield 60%). MS (m/e): 541.3 (M+H⁺, 100%).

Example 93

[5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazin-1-yl]-methanone

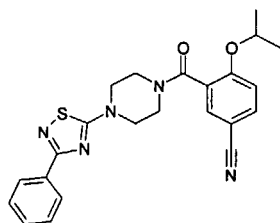
- 86 -



Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-((*S*)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example A15) and 1-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine trifluoroacetate (Example 62(b)). The crude material
 5 was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as an off-white solid (yield 52%). MS (m/e): 533.0 (M+H⁺, 100%).

Example 94

4-Isopropoxy-3-[4-(3-phenyl-[1,2,4]thiadiazol-5-yl)-piperazine-1-carbonyl]-benzonitrile



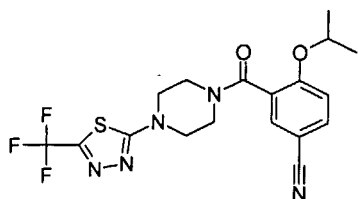
10

Prepared in analogy to example 1 (b) from 5-cyano-2-isopropoxy-benzoic acid (Example A28) and 3-phenyl-5-piperazino-1,2,4-thiadiazole. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as a white solid (yield 74%). MS (m/e): 434.1 (M+H⁺, 100%).

15

Example 95

4-Isopropoxy-3-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine-1-carbonyl]-benzonitrile



Prepared in analogy to example 1 (b) from 5-cyano-2-isopropoxy-benzoic acid
 20 (Example A28) and 1-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine trifluoroacetate (Example 62(b)). The crude material was purified by chromatography

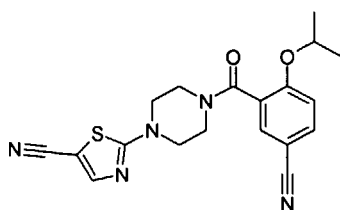
- 87 -

(SiO₂, ethyl acetate/heptane) to yield the title compound as a white solid (yield 80%). MS (m/e): 426.0 (M+H⁺, 100%).

Example 96

2-[4-(5-Cyano-2-isopropoxy-benzoyl)-piperazin-1-yl]-thiazole-5-carbonitrile

5

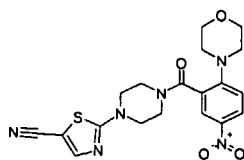


Prepared in analogy to example 1 (b) from 5-cyano-2-isopropoxy-benzoic acid (Example A28) and 2-piperazin-1-yl-thiazole-5-carbonitrile (Example 6(a)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as a white solid (yield 70%). MS (m/e): 382.3 (M+H⁺, 100%).

10

Example 97

2-[4-(2-Morpholin-4-yl-5-nitro-benzoyl)-piperazin-1-yl]-thiazole-5-carbonitrile

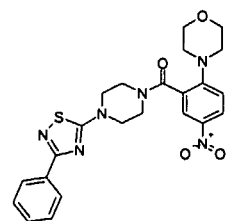


Prepared in analogy to example 1 (b) from 2-morpholin-4-yl-5-nitro-benzoic acid (Example A27) and 2-piperazin-1-yl-thiazole-5-carbonitrile (Example 6(a)). The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) to yield the title compound as a yellow solid (yield 24%). MS (m/e): 429.5 (M+H⁺, 100%).

15

Example 98

(2-Morpholin-4-yl-5-nitro-phenyl)-[4-(3-phenyl-[1,2,4]thiadiazol-5-yl)-piperazin-1-yl]-methanone



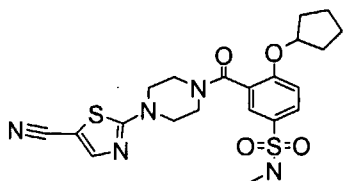
20

Prepared in analogy to example 1 (b) from 2-morpholin-4-yl-5-nitro-benzoic acid (Example A27) and 3-phenyl-5-piperazino-1,2,4-thiadiazole. The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as a yellow solid (yield 18%). MS (m/e): 481.0 (M+H⁺, 100%).

5

Example 99

3-[4-(5-Cyano-thiazol-2-yl)-piperazine-1-carbonyl]-4-cyclopentyloxy-*N*-methyl-benzenesulfonamide



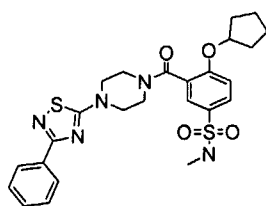
Prepared in analogy to example 1 (b) from 2-cyclopentyloxy-5-methylsulfamoyl-benzoic acid (Example A29) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) to yield the title compound as a white solid (yield 48%). MS (m/e): 476.3 (M+H⁺, 100%).

10

Example 100

4-Cyclopentyloxy-*N*-methyl-3-[4-(3-phenyl-[1,2,4]thiadiazol-5-yl)-piperazine-1-carbonyl]-benzenesulfonamide

15

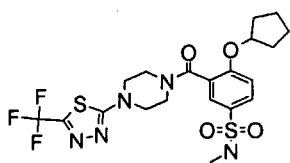


Prepared in analogy to example 1 (b) from 2-cyclopentyloxy-5-methylsulfamoyl-benzoic acid (Example A29) and 3-phenyl-5-piperazino-1,2,4-thiadiazole. The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) to yield the title compound as an off-white solid (yield 72%). MS (m/e): 528.5 (M+H⁺, 100%).

20

Example 101

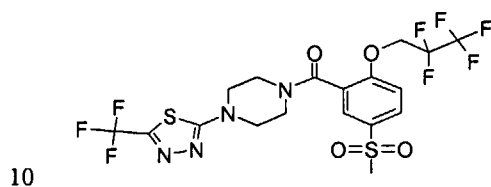
4-Cyclopentyloxy-*N*-methyl-3-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine-1-carbonyl]-benzenesulfonamide



Prepared in analogy to example 1 (b) from 2-cyclopentyloxy-5-methylsulfamoyl-benzoic acid (Example A29) and 1-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine trifluoroacetate (Example 62(b)). The crude material was purified by chromatography
 5 (SiO₂, ethyl acetate/heptane) to yield the title compound as a white solid (yield 46%). MS (m/e): 520.3 (M+H⁺, 100%).

Example 102

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

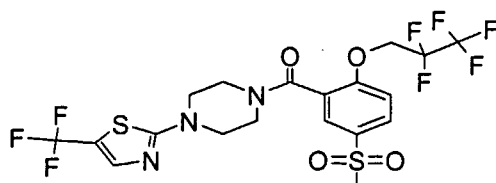


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Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-benzoic acid (Example A30) and 1-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine trifluoroacetate (Example 62(b)). The crude material was purified by chromatography (SiO₂, methanol/dichloromethane) to yield the title
 15 compound as an off-white solid (yield 56%). MS (m/e): 569.3 (M+H⁺, 100%).

Example 103

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



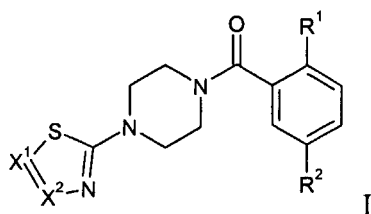
Prepared in analogy to example 1 (b) from 5-methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-benzoic acid (Example A30) and 1-(5-trifluoromethyl-thiazol-2-yl)-piperazine hydrochloride (Example 58(c)). The crude material was purified by chromatography (SiO₂, ethyl acetate/heptane) to yield the title compound as a brown solid (yield 68%).
 MS (m/e): 568.2 (M+H⁺, 100%).

20

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Claims

1. Compounds of general formula



5 wherein

R^1 is $-OR^{1'}$, $-SR^{1'}$ or is a heterocycloalkyl group;

$R^{1'}$ is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$ -cycloalkyl;

R^2 is $-S(O)_2$ -lower alkyl, $-S(O)_2NH$ -lower alkyl, NO_2 or CN ;

X^1 is CR^3 or N ;

10 X^2 is $CR^{3'}$ or N ;

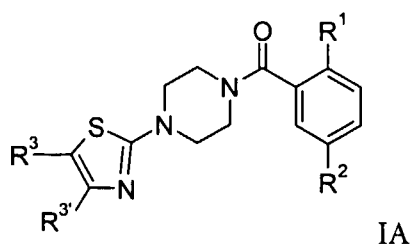
$R^3/R^{3'}$ are independently from each other hydrogen, halogen, lower alkyl, CN , NO_2 , $-S(O)_2$ -phenyl, $-S(O)_2$ -lower alkyl, $-S(O)_2$ -pyridin-2, 3 or 4-yl, phenyl, optionally substituted by one or two substituents selected from the group consisting of NO_2 or
 15 halogen, or is lower alkyl substituted by halogen or is $-C(O)$ -lower alkyl;

n is 0, 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

2. Compounds of formula IA according to formula I in claim 1

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wherein

R^1 is $-OR^{1'}$, $-SR^{1'}$ or is a heterocycloalkyl group;

$R^{1'}$ is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$ -cycloalkyl;

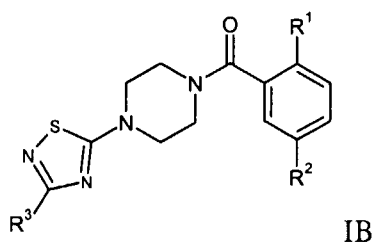
5 R^2 is $-S(O)_2$ -lower alkyl, $-S(O)_2NH$ -lower alkyl, NO_2 or CN;

$R^3/R^{3'}$ are independently from each other hydrogen, halogen, lower alkyl, CN, NO_2 , $-S(O)_2$ -phenyl, $-S(O)_2$ -lower alkyl, $-S(O)_2$ -pyridin-2, 3 or 4-yl, phenyl, optionally substituted by one or two substituents selected from the group consisting of NO_2 or halogen, or is lower alkyl substituted by halogen or is $-C(O)$ -lower alkyl;

10 n is 0, 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

3. Compounds of formula IB according to formula I in claim 1



wherein

15 R^1 is $-OR^{1'}$, $-SR^{1'}$ or is a heterocycloalkyl group;

$R^{1'}$ is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$ -cycloalkyl;

R^2 is $-S(O)_2$ -lower alkyl, $-S(O)_2NH$ -lower alkyl, NO_2 or CN;

R^3 is hydrogen, halogen, lower alkyl, CN, NO_2 , $-S(O)_2$ -phenyl, $-S(O)_2$ -lower alkyl, $-S(O)_2$ -pyridin-2, 3 or 4-yl, phenyl, optionally substituted by one or two substituents

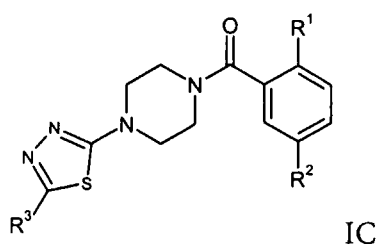
- 92 -

selected from the group consisting of NO₂ or halogen, or is lower alkyl substituted by halogen or is -C(O)-lower alkyl;

n is 0, 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

5 4. Compounds of formula IC according to formula I in claim 1



wherein

R¹ is -OR^{1'}, -SR^{1'} or is a heterocycloalkyl group;

R^{1'} is lower alkyl, lower alkyl substituted by halogen or is -(CH₂)_n-cycloalkyl;

10 R² is -S(O)₂-lower alkyl, -S(O)₂NH-lower alkyl, NO₂ or CN;

R³ is hydrogen, halogen, lower alkyl, CN, NO₂, -S(O)₂-phenyl, -S(O)₂-lower alkyl, -S(O)₂-pyridin-2, 3 or 4-yl, phenyl, optionally substituted by one or two substituents selected from the group consisting of NO₂ or halogen, or is lower alkyl substituted by halogen or is -C(O)-lower alkyl;

15 n is 0, 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

5. Compounds of formula IA according to claim 2, wherein R¹ is OR^{1'} and R^{1'} is lower alkyl.

6. Compounds of formula IA according to claim 5, which compounds are

20 [4-(5-benzenesulfonyl-thiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
 2-[4-(2-isobutoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazole-5-carbonitrile,
 2-[4-[2-(2,2-dimethyl-propoxy)-5-methanesulfonyl-benzoyl]-piperazin-1-yl]-thiazole-5-carbonitrile,

25 [4-(5-benzenesulfonyl-thiazol-2-yl)-piperazin-1-yl]-[2-(2,2-dimethyl-propoxy)-5-

- methanesulfonyl-phenyl]-methanone,
 [4-(5-benzenesulfonyl-thiazol-2-yl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone,
 {4-[5-(butane-1-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-[2-(2,2-dimethyl-propoxy)-5-
 5 methanesulfonyl-phenyl]-methanone,
 (2-((R)-sec-butoxy)-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone,
 (2-((S)-sec-butoxy)-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone or
 10 (2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-methyl-5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone.

7. Compounds of formula IA according to claim 2, wherein R¹ is OR^{1'} and R^{1'} is lower alkyl substituted by halogen.

8. Compounds of formula IA according to claim 7, which compounds are
 15 2-{4-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-piperazin-1-yl}-thiazole-5-carbonitrile,
 {4-[5-(butane-1-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-[5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone,
 [5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-methyl-4-
 20 trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone,
 [5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone,
 [5-methanesulfonyl-2-(2,2,2-trifluoro-1,1-dimethyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone,
 25 [5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone,
 [5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone,
 [5-methanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-[5-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazin-1-yl]-methanone,
 30 [5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-[5-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazin-1-yl]-methanone,
 [5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-[5-(2,2,2-trifluoro-ethyl)-thiazol-2-yl]-piperazin-1-yl]-methanone,
 35 [5-ethanesulfonyl-2-(2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone,
 [5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-methyl-5-

trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone,
 [5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(4-methyl-5-
 trifluoromethyl-thiazol-2-yl)-piperazin-1-yl]-methanone or
 [5-methanesulfonyl-2-(2,2,3,3,3-pentafluoro-propoxy)-phenyl]-[4-(5-trifluoromethyl-
 5 thiazol-2-yl)-piperazin-1-yl]-methanone.

9. Compounds of formula IA according to claim 2, wherein R^1 is $OR^{1'}$ and $R^{1'}$ is $-(CH_2)_n$ -cycloalkyl.

10. Compounds of formula IA according to claim 9, which compounds are
 2-[4-(2-cyclobutylmethoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-thiazole-5-
 10 carbonitrile,
 [4-(5-benzenesulfonyl-thiazol-2-yl)-piperazin-1-yl]-(2-cyclopentyloxy-5-
 methanesulfonyl-phenyl)-methanone,
 {4-[5-(butane-1-sulfonyl)-thiazol-2-yl]-piperazin-1-yl}-(2-cyclopentyloxy-5-
 methanesulfonyl-phenyl)-methanone,
 15 3-[4-(5-cyano-thiazol-2-yl)-piperazine-1-carbonyl]-4-cyclopentyloxy-N-methyl-
 benzenesulfonamide or
 4-cyclopentyloxy-N-methyl-3-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazine-
 1-carbonyl]-benzenesulfonamide.

11. Compounds of formula IA according to claim 2, wherein R^1 is $SR^{1'}$.

20 12. Compounds of formula IA according to claim 11, which compound is
 (2-isopropylsulfanyl-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-thiazol-2-yl)-
 piperazin-1-yl]-methanone.

13. A compound of formula IB according to claim 3, wherein R^1 is $OR^{1'}$ for $R^{1'}$
 being lower alkyl.

25 14. Compounds of formula IB according to claim 13, which compound is
 (2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(3-phenyl-[1,2,4]thiadiazol-5-yl)-
 piperazin-1-yl]-methanone.

15. A compound of formula IB according to claim 3, wherein R^1 is $OR^{1'}$ for $R^{1'}$
 being $(CH_2)_n$ -cycloalkyl.

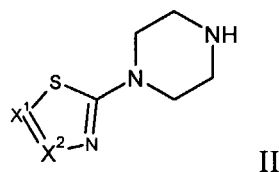
30 16. Compounds of formula IB according to claim 15, which compound is
 4-cyclopentyloxy-N-methyl-3-[4-(3-phenyl-[1,2,4]thiadiazol-5-yl)-piperazine-1-
 carbonyl]-benzenesulfonamide.

17. Compounds of formula IC according to claim 4, wherein R^1 is $OR^{1'}$.

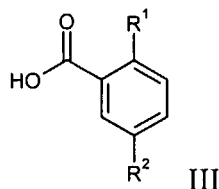
18. Compounds of formula IC according to claim 17, which compound is
 (2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-
 piperazin-1-yl]-methanone,
 (2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-
 5 [1,3,4]thiadiazol-2-yl)-piperazin-1-yl]-methanone,
 (2-isobutoxy-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-2-yl)-
 piperazin-1-yl]-methanone,
 (5-methanesulfonyl-2-morpholin-4-yl-phenyl)-[4-(5-trifluoromethyl-[1,3,4]thiadiazol-
 2-yl)-piperazin-1-yl]-methanone or
 10 [5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-[4-(5-
 trifluoromethyl-[1,3,4]thiadiazol-2-yl)-piperazin-1-yl]-methanone.

19. A process for preparing a compound of formula I as defined in claims 1 to 18,
 which process comprises

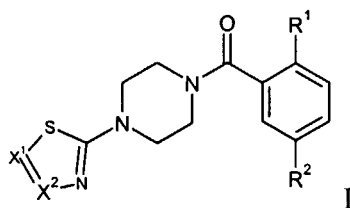
reacting a compound of formula



with a compound of formula



in the presence of an activating agent to a compound of formula



wherein X^1 and X^2 and the substituents R^1 and R^2 are as defined in claim 1,

and

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

- 25 20. A compound according to any one of claims 1 to 18, whenever prepared by a
 process as claimed in claim 19 or by an equivalent method.

21. A medicament containing one or more compounds as claimed in any one of claims 1 to 18 and pharmaceutically suitable excipients.

22. A medicament according to claim 21 for the treatment of illnesses based on the glycine uptake inhibitor.

5 23. A medicament according to claim 22, wherein the illnesses are psychoses, pain, 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.

10 24. The use of a compound as claimed in any one of claims 1 to 18 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.

25. The invention as herein before described.