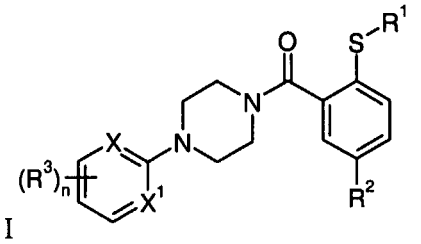
SULFANYL SUBSTITUTED PHENYL METHANONES AS GLYCINE TRANSPORTER 1 (GLYT-1) INHIBITORS FOR THE TREATMENT OF NEUROLOGICAL AND NEUROPSYCHIATRIC DISORDERS

The present invention relates to compounds of the general formula



I

wherein

R^1 is lower alkyl or lower alkyl substituted by halogen;

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

R^3 is halogen, CN, lower alkyl, lower alkyl substituted by halogen, NO_2, -C(O)-lower alkyl or $S(O)_2$-lower alkyl;

X/X^1 are independently from each other CR^4 or N;

R^4 is hydrogen or halogen;

n is 0, 1 or 2;

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 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).*

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 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., *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). 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 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 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*).

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 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 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 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).

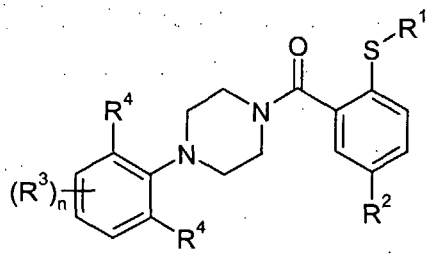
Glycine transporters inhibitors are suitable for the treatment of neurological and neuropsychiatric disorders. The majority of diseases states implicated are psychoses, schizophrenia (Armer RE and Miller DJ, *Exp. Opin. Ther. Patents, 11 (4): 563-572, 2001),* psychotic mood disorders such as severe major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

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

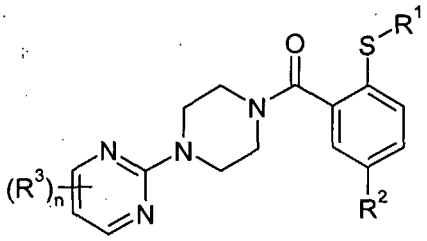
Objects of the present invention are the compounds of formula I per se, the use of compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases related to activation of NMDA receptors via Glyt-1 inhibition, their manufacture, medicaments 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.

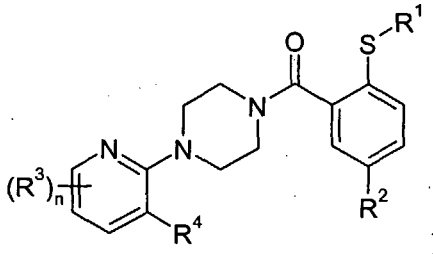
Objects of the present invention are further substructures of formula I as follows:



I-A



I-B or



IC,

wherein

R^1 is lower alkyl or lower alkyl substituted by halogen;

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

R^3 is halogen, CN, lower alkyl, lower alkyl substituted by halogen, NO_2, -C(O)-lower alkyl or $S(O)_2$-lower alkyl;

R^4 is hydrogen or halogen;

n is 0, 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

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

The term "alkyl, substituted by halogen" denotes for example the following groups: CF_3, CHF_2, CH_2F, CH_2CF_3, CH_2CHF_2, CH_2CH_2F, $CH_2CH_2CF_3$, $CH_2CH_2CH_2CF_3$,

CH_2CH_2Cl, $CH_2CF_2CF_3$, $CH_2CF_2CHF_2$, CF_2CHFCF_3, $C(CH_3)_2CF_3$, $CH(CH_3)CF_3$ or $CH(CH_2F)CH_2F$. Preferred are CH_2CF_3 or CF_3.

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.

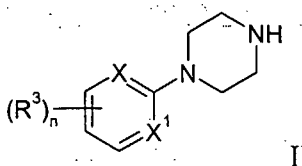
Preferred compounds of the present application are compounds of formula I, wherein R^1 is lower alkyl. Such compounds are
[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-isopropylsulfanyl-5-methanesulfonyl-phenyl)-methanone,
[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isopropylsulfanyl-5-methanesulfonyl-phenyl)-methanone,
(2-ethylsulfanyl-5-methanesulfonyl-phenyl)-[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone,
[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isobutylsulfanyl-5-methanesulfonyl-phenyl)-methanone,
1-{3-fluoro-4-[4-(2-isopropylsulfanyl-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,
[4-(2-chloro-4-nitro-phenyl)-piperazin-1-yl]-(2-isopropylsulfanyl-5-methanesulfonyl-phenyl)-methanone,
4-isopropylsulfanyl-*N*-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide or
(2-isopropylsulfanyl-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone.

Preferred compounds of the present application are further compounds of formula I, wherein R^1 is lower alkyl substituted by halogen. Such compounds are
[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-phenyl]-methanone or

[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-phenyl]-methanone.

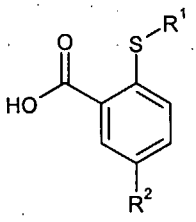
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

a) reacting a compound of formula



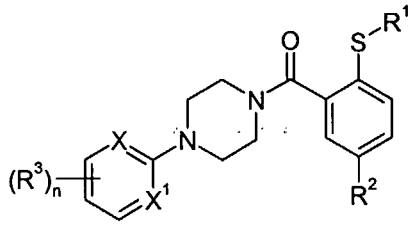
II

with a compound of formula



III

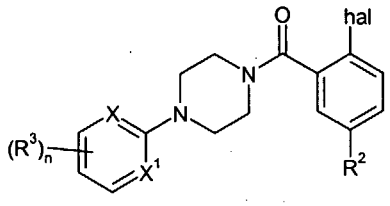
in the presence of an activating agent such as TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate)
to a compound of formula



I

wherein the substituents R^1, R^2, R^3, n, X and X^1 are as defined above, or

b) reacting a compound of formula

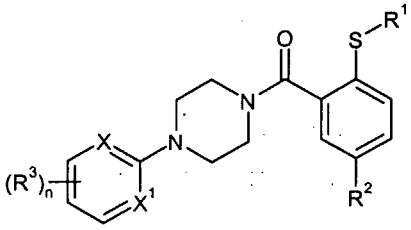


IV

with a compound of formula

R^1SH

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



I

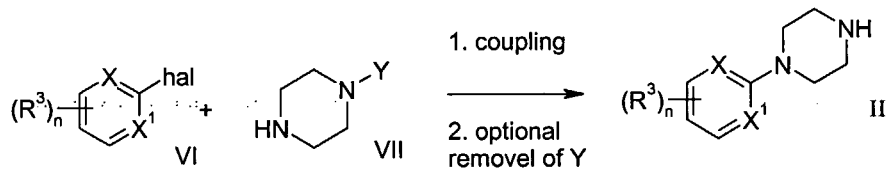
wherein hal is halogen, and the other substituents R^1, R^2, R^3, n, X and X^1 are as defined above,

and

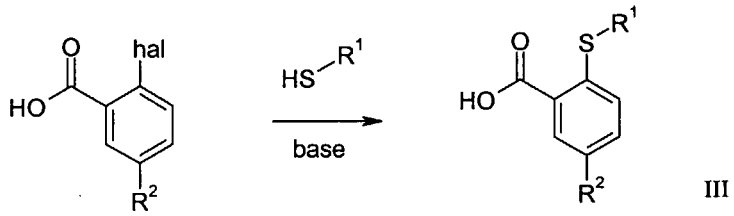
if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

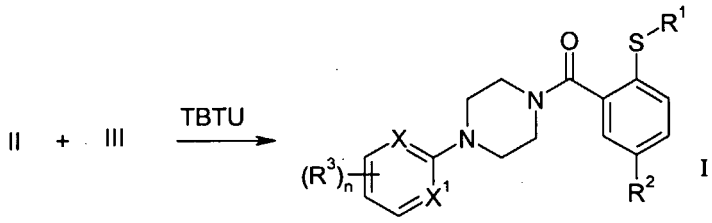
The compounds of formula I may be prepared in accordance with process variant a) or b) and with the following schemes 1 and 2. The starting materials are either commercially available, are otherwise known in the chemical literature, or may be prepared in accordance with methods well known in the art.

Scheme 1



Y = H or protecting group (e.g. Boc)

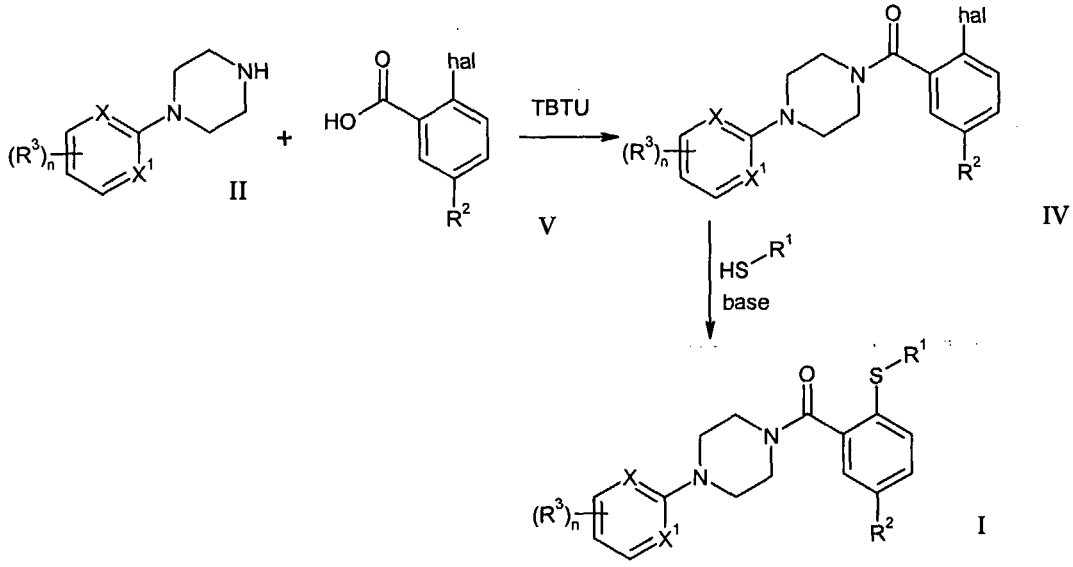




Compounds of general formula I can be prepared by reacting piperazine derivatives of formula II with a corresponding acid of formula III in the presence of an activating agent like TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate). The acid of formula III can be prepared by reaction of an acid of formula V with a thiol of formula R^1SH, optionally in the presence of a catalyst, such as Cu(I)I or Cu(I)Br and a base like potassium carbonate, cesium carbonate or sodium. Piperazine derivatives of formula II can be prepared by heating of

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

Scheme 2



Alternatively, compounds of general formula I can be prepared by reaction of an acyl piperazine of formula IV and a thiol of formula R^1SH, optionally in the presence of a catalyst, such as Cu(I)I or Cu(I)Br and a base like potassium carbonate, cesium carbonate or sodium. Acylpiperazine derivatives of formula IV can be prepared by reaction of an acid of formula V with piperazine derivatives of formula II in the presence of an activating agent like TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate).

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 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

could, of course, also be used. Racemic mixtures of chiral compounds of formula I can be separated using preparativechiral HPLC.

Salts of compounds of formula I

The compounds of formula I may be basic, for example in cases where the compounds contain a basic group such as an aliphatic or aromatic amine moiety. In such 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, 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).

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/Streptomycin1 % (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 $CaCl_2$, 2.5 mM KCl, 2.5 mM $MgSO_4$, 10 mM (+) D-glucose.

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

Glycine uptake inhibition assay (mGlyT-1b)

On day 1 mammalian cells, (Flp-in™-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. IC_{50}, the concentration of the competitor inhibiting glycine uptake of 50 %). A solution was then immediately added containing [^{3}H]-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 prepared compounds show good IC_{50} (µM) at GlyT-1. The preferred compounds show an IC_{50} (µM) at GlyT-1 in the range of 0.006 – 0.1, as shown in the table below.

Example No.	IC_{50} (µM)	Example No.	IC_{50} (µM)	Example No.	IC_{50} (µM)
3	0.03	14	0.10	25	0.006
6	0.04	18	0.10	27	0.007
7	0.08	22	0.015		
11	0.07	23	0.018		

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

The compounds of formula I can be processed with pharmaceutically inert inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used,

for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are however usually required in the case of soft gelatine capsules. 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	mg/tablet			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30

4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Manufacturing Procedure

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

Capsule Formulation

Item	Ingredients	mg/capsule			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
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

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.

The following abbreviations were used in the examples:

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

Oxone®: (potassium peroxymonosulfate) $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$,

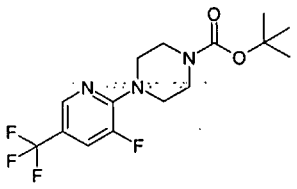
TBTU: 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate;

Synthesis of intermediates of formula II

Example A1

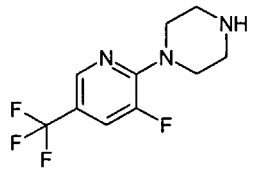
1-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine

(a) 4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester



To a mixture of 120 mmol *N*-Boc-piperazine and 229 mmol potassium carbonate in 300 ml acetonitrile was slowly added a solution of 115 mmol 2,3-difluoro-5-trifluoromethyl-pyridine (EP0104715) in 15 ml acetonitrile. The reaction mixture was refluxed for 2 hours. After such time, the mixture was filtered and the filtrate was concentrated *in vacuo*. The resulting white solid was dissolved in ethyl acetate, washed with water, dried over sodium sulfate and concentrated to yield the title compound as white solid (94% yield). MS (m/e): 294.2 ($M-C_4H_8$, 100%)

(b) 1-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine



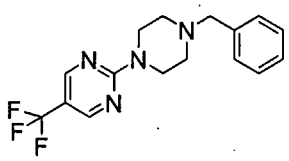
To a solution of 107.3 mmol 4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid tert-butyl ester in 376 ml dichloromethane was added 41 ml trifluoroacetic acid and the reaction mixture was refluxed for 16 hours. After such time the reaction mixture was concentrated *in vacuo* and the residue was dissolved in water. The aqueous phase was basified with 5N NaOH and extracted with dichloromethane. The

combined extracts were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to yield the title compound as a light yellow solid (99% yield). MS (m/e): 250.2 (MH^+, 100%).

Example A2

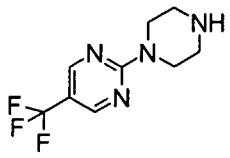
2-Piperazin-1-yl-5-trifluoromethyl-pyrimidine

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



To a solution of 2.60 mmol (3-dimethylamino-2-trifluoromethyl-allylidene)-dimethyl-ammonium chloride (prepared as in Tetrahedron. Lett. 1996, 37, 1829) in 10 ml acetonitrile was added 3.03 mmol 4-benzyl-piperazine-1-carboxamidine hydrochloride (prepared as in Tetrahedron. Lett. 2002, 43, 7105) and 6.25 mmol triethylamine and the reaction mixture was stirred for 3 hours at room temperature. After such time the reaction mixture was concentrated *in vacuo* and purified by column chromatography to yield the title compound as a light yellow solid (0.79 g). MS (m/e): 323.4 ($M+H^+$).

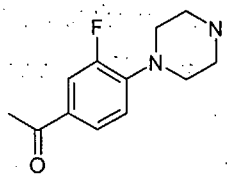
b) 2-Piperazin-1-yl-5-trifluoromethyl-pyrimidine



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

Example A3

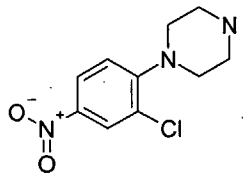
1-(3-Fluoro-4-piperazin-1-yl-phenyl)-ethanone



This compound (CAS: 189763-57-3) was prepared according to WO 9714690. MS (m/e): 223.2 ($M+H^+$).

Example A4

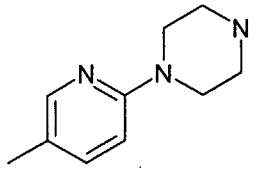
1-(2-Chloro-4-nitro-phenyl)-piperazine



To a mixture of 43.4 mmol of piperazine in 11 ml DMF was slowly added a solution of 8.6 mmol of 1,2-dichloro-4-nitrobenzene in 15 ml DMF. The reaction mixture was heated at 100°C for 2.5 hours. After such time, the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was diluted with dichloromethane (25 mL) and washed with saturated aqueous solution of $NaHCO_3$. The organic phase was then dried over sodium sulfate and concentrated *in* vacuo. The residue was then purified by column chromatography (SiO_2, CH_2Cl_2-MeOH 0-10%) to yield the title compound as yellow solid (766 mg, 37% yield). MS (m/e): 242.3 ($M+H^+$, 100%).

Example A5

1-(5-Methyl-pyridin-2-yl)-piperazine



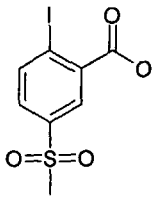
To a solution of 23 mmol 6-chloro-3-methyl pyridine in 12 ml DMA and 30 ml water was added 115 mmol piperazine. The reaction mixture was refluxed for 4 days. After such time, 2 N aq sodium carbonate was added, the reaction mixture was extracted with dichloromethane and concentrated *in vacuo*. The residue was purified on silica gel (dichloromethane/MeOH 1/1) to yield the title compound as white solid (17% yield). MS (m/e): 178 ($M+H^+$, 100%)

Synthesis of compounds of formula I

Example 1

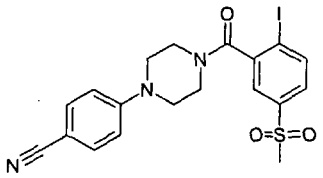
4-[4-(5-Methanesulfonyl-2-methylsulfanyl-benzoyl)-piperazin-1-yl]-benzonitrile

a) 2-Iodo-5-methanesulfonyl-benzoic acid



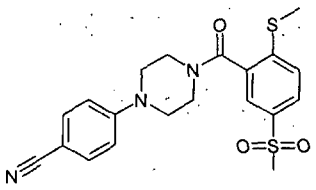
To a suspension of 3.0 mmol 2-amino-5-methanesulfonyl-benzoic acid (WO2003091245) in a mixture of 1.7 ml sulfuric acid and 1.7 ml water was added dropwise a solution of 3.92 mmol sodium nitrite in 1.7 ml water at such a rate that the temperature did not exceed 3 °C. The mixture was stirred at 0 °C for 1 hour. A solution of 3.0 mmol potassium iodide in 1.7 ml water was added dropwise at 0 °C. The brown suspension was allowed to warm to room temperature and stirred for 30 minutes. Excess iodine was destroyed by addition of a few drops of a sodium hydrogensulfite solution. The solid was filtered, washed with water and dried (HV, 50 °C, 1 hour) to yield the title compound. MS (m/e): 325.0 ([M-H]$^-$, 100%)

b) 4-[4-(2-Iodo-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile



To a solution of 6.1 mmol 2-iodo-5-methanesulfonyl-benzoic acid in 20 ml dimethyl formamide were added successively 6.75 mmol TBTU, 43 mmol N-ethyldiisopropylamine and 6.75 mmol 4-piperazin-1-yl-benzonitrile (commercially available, e.g. from Fluka). The reaction mixture was stirred at 20 °C for 1.5 h and then concentrated in vacuo. Addition of 200 ml water followed by filtration yielded the crude product which was recrystallized from methanol to afford the title compound as a white solid (yield 87%). MS (m/e): 495.9 (M+H$^+$, 100%).

c) 4-[4-(5-Methanesulfonyl-2-methylsulfanyl-benzoyl)-piperazin-1-yl]-benzonitrile

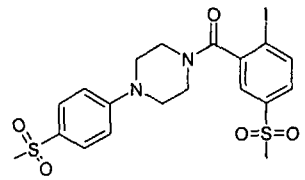


A solution of 0.2 mmol 4-[4-(2-iodo-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzonitrile in 2 ml dimethylformamide was treated with 0.2 mmol of sodium methanethiolate and held at 50 ° C for 2 h, at 80 ° C for 2 h and at 140 ° C for 1 h. The reaction mixture was then concentrated and the product purified by chromatography (dichloromethane/methanol) to afford the title compound as a colorless foam. MS (m/e): 474.2 ([M+CH_3COO^-]$^-$, 100%).

Example 2

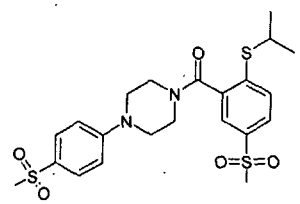
(2-Isopropylsulfanyl-5-methanesulfonyl-phenyl)-[4-(4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone

a) (2-Iodo-5-methanesulfonyl-phenyl)-[4-(4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1b) from 1-(4-methanesulfonyl-phenyl)-piperazine (commercially available, e.g. from Peakdale) and 2-iodo-5-methanesulfonyl-benzoic acid (Example 1a). White solid. MS (m/e): 566.2 (M+NH_4^+, 100%).

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



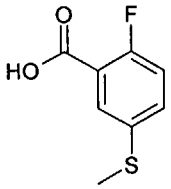
A solution of 0.9 mmol of (2-iodo-5-methanesulfonyl-phenyl)-[4-(4-methanesulfonyl-phenyl)-piperazin-1-yl]-methanone in 10 ml dimethylformamide was treated with 1.2 mmol of 2-propanethiol, 1.6 mmol of potassium carbonate, 0.1 mmol of copper powder and 1 mg of copper(I)-iodide and refluxed for 4 h. Concentration followed by dilution with 100 ml water yielded a dark solid which was purified by

chromatography (ethyl acetate) to give the title compound as a colorless foam. MS (m/e): 555.2 ([M+CH_3COO^-]$^-$, 100%).

Example 3

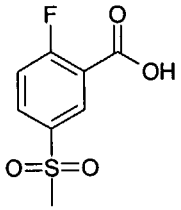
[4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-isopropylsulfanyl-5-methanesulfonyl-phenyl)-methanone

a) 2-Fluoro-5-methylsulfanyl-benzoic acid



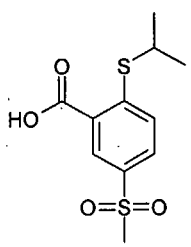
The title compound was prepared by following the procedure described in: Journal of Organometallic Chemistry 1991, 419(1-2), 1-8.

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



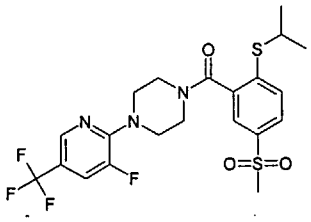
To 2.68 mmol 2-fluoro-5-methanesulfanyl-benzoic acid in 5 ml methanol at 0 °C was added 8.05 mmol Oxone® and the mixture was allowed to stir at RT for 72 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was treated with water and extracted 3 times 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) 2-Isopropylsulfanyl-5-methanesulfonyl-benzoic acid



To a solution of 4.58 mmol 2-fluoro-5-methanesulfonyl-benzoic acid in 6 ml N,N-dimethylacetamide were added 15.2 mol 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%).

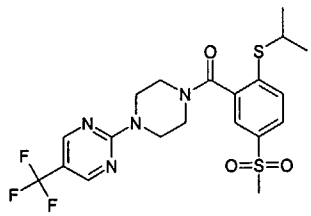
d) [4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-isopropylsulfanyl-5-methanesulfonyl-phenyl)-methanone



To a solution of 0.51 mmol 2-isopropylsulfanyl-5-methanesulfonyl-benzoic acid in 5 ml tetrahydrofuran were added successively 0.38 mmol TBTU, 1.02 mmol N-ethyldiisopropylamine and 0.30 mmol 1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine (Example A1). The reaction mixture was stirred at 45 °C for 16 h and then concentrated in vacuo. Chromatography (SiO_2, ethyl acetate/heptane) afforded the title compound as a light yellow gum (yield 56%). MS (m/e): 506.1 ($M+H^+$, 100%).

Example 4

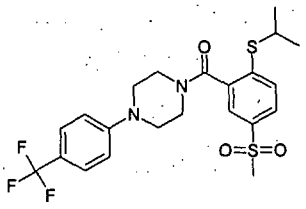
(2-Isopropylsulfanyl-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 3 (d) from 2-isopropylsulfanyl-5-methanesulfonyl-benzoic acid and 2-piperazin-1-yl-5-trifluoromethyl-pyrimidine (Example A2). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) to yield the title compound as a brown solid (yield 55%). MS (m/e): 489.0 ($M+H^+$, 100%).

Example 5

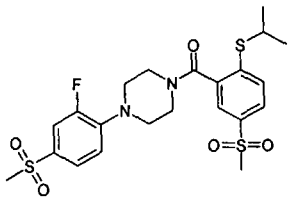
(2-Isopropylsulfanyl-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone



Prepared in analogy to example 3 (d) from 2-isopropylsulfanyl-5-methanesulfonyl-benzoic acid and 1-(4-trifluoromethyl-phenyl)-piperazine (commercially available, e.g. from Fluorochem). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) followed by trituration in pentane to yield the title compound as a light yellow foam (yield 40%). MS (m/e): 487.3 ($M+H^+$, 100%).

Example 6

[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isopropylsulfanyl-5-methanesulfonyl-phenyl)-methanone

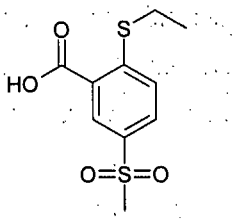


Prepared in analogy to example 3 (d) from 2-isopropylsulfanyl-5-methanesulfonyl-benzoic acid and 1-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine (commercially available, e.g. from Peakdale). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) to yield the title compound as a yellow solid (yield 28%). MS (m/e): 515.0 ($M+H^+$, 100%).

Example 7

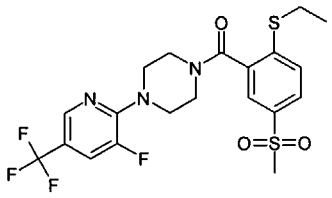
(2-Ethylsulfanyl-5-methanesulfonyl-phenyl)-[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone

a) 2-Ethylsulfanyl-5-methanesulfonyl-benzoic acid



To a solution of 4.58 mmol 2-fluoro-5-methanesulfonyl-benzoic acid in 6 ml N,N-dimethylformamide were added 13.8 mol 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%).

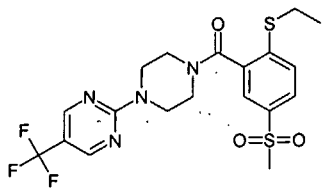
b) (2-Ethylsulfanyl-5-methanesulfonyl-phenyl)-[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone



To a solution of 0.27 mmol 2-ethylsulfanyl-5-methanesulfonyl-benzoic acid in 5 ml tetrahydrofuran were added successively 0.40 mmol TBTU, 1.08 mmol N-ethyldiisopropylamine and 0.32 mmol 1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine (Example A1). The reaction mixture was stirred at 45 °C for 16 h and then concentrated in vacuo. Chromatography (SiO_2, ethyl acetate/heptane) afforded the title compound as a light yellow solid (yield 61%). MS (m/e): 492.0 ($M+H^+$, 100%).

Example 8

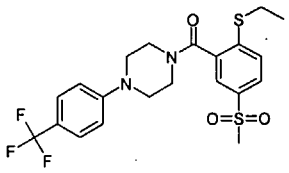
(2-Ethylsulfanyl-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 7 (b) from 2-ethylsulfanyl-5-methanesulfonyl-benzoic acid and 2-piperazin-1-yl-5-trifluoromethyl-pyrimidine (Example A2). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) to yield the title compound as a light yellow solid (yield 52%). MS (m/e): 475.0 ($M+H^+$, 100%).

Example 9

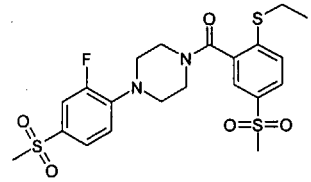
(2-Ethylsulfanyl-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone



Prepared in analogy to example 7 (b) from 2-ethylsulfanyl-5-methanesulfonyl-benzoic acid and 1-(4-trifluoromethyl-phenyl)-piperazine (commercially available, e.g. from Fluorochem). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) to yield the title compound as a white solid (yield 60%). MS (m/e): 473.0 ($M+H^+$, 100%).

Example 10

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

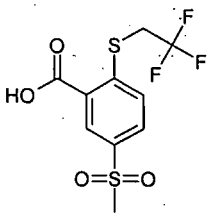


Prepared in analogy to example 7 (b) from 2-ethylsulfanyl-5-methanesulfonyl-benzoic acid and 1-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine (commercially available, e.g. from Peakdale). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) to yield the title compound as a light brown solid (yield 74%). MS (m/e): 501.0 ($M+H^+$, 100%).

Example 11

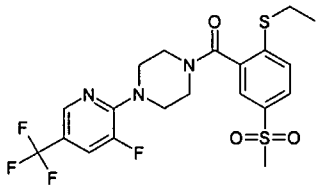
[4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-phenyl]-methanone

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



To a solution of 4.58 mmol 2-fluoro-5-methanesulfonyl-benzoic acid in 6 ml N,N-dimethylformamide were added 13.8 mol 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%).

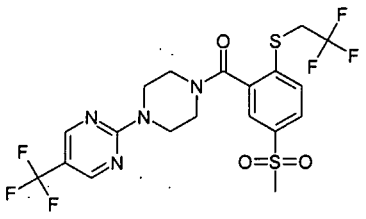
b) [4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-phenyl]-methanone



To a solution of 0.22 mmol 5-methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-benzoic acid in 5 ml tetrahydrofuran were added successively 0.33 mmol TBTU, 0.89 mmol N-ethyldiisopropylamine and 0.27 mmol 1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine (Example A1). The reaction mixture was stirred at 40 °C for 16 h and then concentrated in vacuo. Chromatography (SiO_2, ethyl acetate/heptane) afforded the title compound as a white foam (yield 47%). MS (m/e): 546.0 ($M+H^+$, 100%).

Example 12

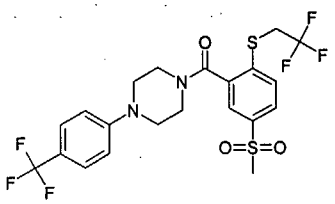
[5-Methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-phenyl]-[4-(5-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 11 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-benzoic acid and 2-piperazin-1-yl-5-trifluoromethyl-pyrimidine (Example A2). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) to yield the title compound as a white foam (yield 58%). MS (m/e): 529.0 ($M+H^+$, 100%).

Example 13

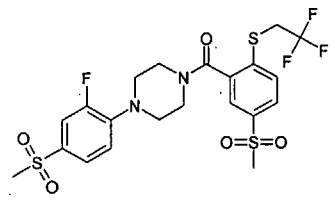
[5-Methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-phenyl]-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone



Prepared in analogy to example 11 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-benzoic acid and 1-(4-trifluoromethyl-phenyl)-piperazine (commercially available, e.g. from Fluorochem). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) to yield the title compound as a brown solid (yield 76%). MS (m/e): 527.2 ($M+H^+$, 100%).

Example 14

[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-phenyl]-methanone

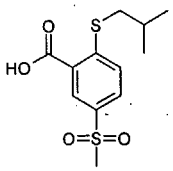


Prepared in analogy to example 11 (b) from 5-methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-benzoic acid and 1-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine (commercially available, e.g. from Peakdale). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) to yield the title compound as a light brown solid (yield 74%). MS (m/e): 555.0 ($M+H^+$, 100%).

Example 15

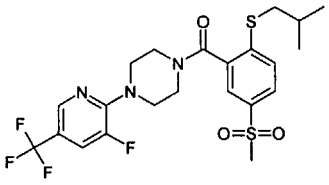
[4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-isobutylsulfanyl-5-methanesulfonyl-phenyl)-methanone

a) 2-Isobutylsulfanyl-5-methanesulfonyl-benzoic acid



To a solution of 4.58 mmol 2-fluoro-5-methanesulfonyl-benzoic acid in 6 ml N,N-dimethylformamide were added 13.8 mol 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%).

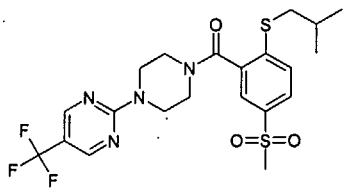
b) [4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-isobutylsulfanyl-5-methanesulfonyl-phenyl)-methanone



To a solution of 0.24 mmol 2-isobutylsulfanyl-5-methanesulfonyl-benzoic acid in 5 ml tetrahydrofuran were added successively 0.36 mmol TBTU, 0.97 mmol N-ethyldiisopropylamine and 0.29 mmol 1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine (Example A1). The reaction mixture was stirred at 45 °C for 16 h and then concentrated in vacuo. Chromatography (SiO_2, ethyl acetate/heptane) afforded the title compound as a light brown solid (yield 57%). MS (m/e): 520.0 ($M+H^+$, 100%).

Example 16

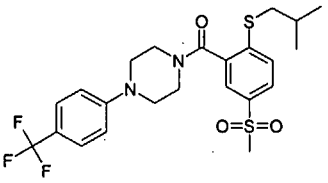
(2-Isobutylsulfanyl-5-methanesulfonyl-phenyl)-[4-(5-trifluoromethyl-pyrimidin-2-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 15 (b) from 2-isobutylsulfanyl-5-methanesulfonyl-benzoic acid and 2-piperazin-1-yl-5-trifluoromethyl-pyrimidine (Example A2). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) to yield the title compound as a white foam (yield 77%). MS (m/e): 503.0 ($M+H^+$, 100%).

Example 17

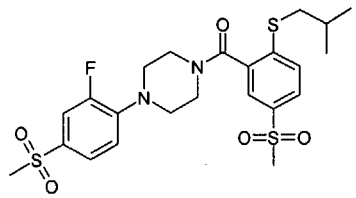
(2-Isobutylsulfanyl-5-methanesulfonyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone



Prepared in analogy to example 15 (b) from 2-isobutylsulfanyl-5-methanesulfonyl-benzoic acid and 1-(4-trifluoromethyl-phenyl)-piperazine (commercially available, e.g. from Fluorochem). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) to yield the title compound as a brown solid (yield 99%). MS (m/e): 501.0 ($M+H^+$, 100%).

Example 18

[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isobutylsulfanyl-5-methanesulfonyl-phenyl)-methanone

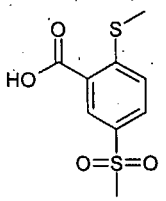


Prepared in analogy to example 15 (b) from 2-isobutylsulfanyl-5-methanesulfonyl-benzoic acid and 1-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine (commercially available, e.g. from Peakdale). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) to yield the title compound as an orange foam (yield 99%). MS (m/e): 529.0 ($M+H^+$, 100%).

Example 19

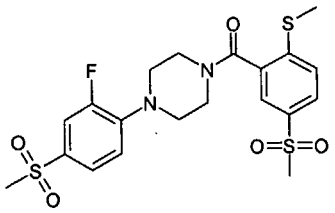
[4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-methylsulfanyl-phenyl)-methanone

a) 5-Methanesulfonyl-2-methylsulfanyl-benzoic acid



To a solution of 4.58 mmol 2-fluoro-5-methanesulfonyl-benzoic acid in 6 ml N,N-dimethylformamide were added 13.8 mol 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 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%).

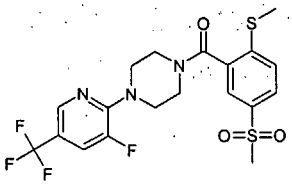
b) [4-(2-Fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(5-methanesulfonyl-2-methylsulfanyl-phenyl)-methanone



To a solution of 0.28 mmol 5-methanesulfonyl-2-methylsulfanyl-benzoic acid in 5 ml tetrahydrofuran were added successively 0.43 mmol TBTU, 1.14 mmol N-ethyldiisopropylamine and 0.34 mmol 1-(2-fluoro-4-methanesulfonyl-phenyl)-piperazine (commercially available, e.g. from Peakdale). The reaction mixture was stirred at 45 °C for 16 h and then concentrated in vacuo. Chromatography (SiO_2, ethyl acetate/heptane) afforded the title compound as a light brown solid (yield 77%). MS (m/e): 487.3 ($M+H^+$, 100%).

Example 20

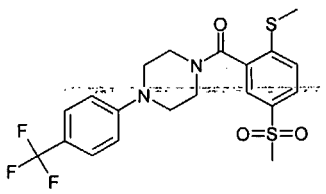
[4-(3-Fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(5-methanesulfonyl-2-methylsulfanyl-phenyl)-methanone



Prepared in analogy to example 19 (b) from 5-methanesulfonyl-2-methylsulfanyl-benzoic acid and 1-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazine (Example A1). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) to yield the title compound as an orange foam (yield 99%). MS (m/e): 478.0 ($M+H^+$, 100%).

Example 21

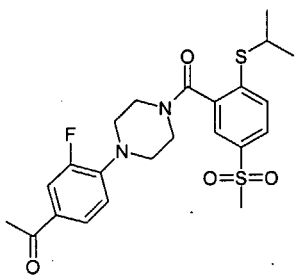
(5-Methanesulfonyl-2-methylsulfanyl-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone



Prepared in analogy to example 19 (b) from 5-methanesulfonyl-2-methylsulfanyl-benzoic acid and 1-(4-trifluoromethyl-phenyl)-piperazine (commercially available, e.g. from Fluorochem). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) to yield the title compound as brown foam (yield 99%). MS (m/e): 459.1 ($M+H^+$, 100%).

Example 22

1-{3-Fluoro-4-[4-(2-isopropylsulfanyl-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone

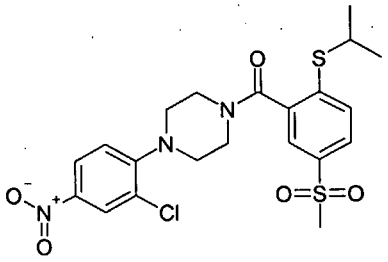


Prepared in analogy to example 3 (d) from 2-isopropylsulfanyl-5-methanesulfonyl-benzoic acid and 1-(3-fluoro-4-piperazin-1-yl-phenyl)-ethanone (Example A3). The

crude material was purified by chromatography (SiO_2, methanol/dichloromethane) to yield the title compound as a white solid (yield 13%). MS (m/e): 479.3 ($M+H^+$, 100%).

Example 23

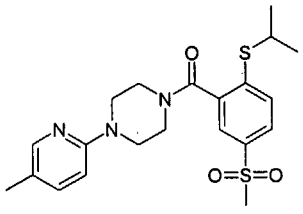
[4-(2-Chloro-4-nitro-phenyl)-piperazin-1-yl]-(2-isopropylsulfanyl-5-methanesulfonyl-phenyl)-methanone



Prepared in analogy to example 3 (d) from 2-isopropylsulfanyl-5-methanesulfonyl-benzoic acid and 1-(2-chloro-4-nitro-phenyl)-piperazine (Example A4). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) to yield the title compound as an orange solid (yield 86%). MS (m/e): 500.2 ({^{37}Cl]M+H$^+$, 59%), 498.2 ({^{35}Cl]M+H$^+$, 100%).

Example 24

(2-Isopropylsulfanyl-5-methanesulfonyl-phenyl)-[4-(5-methyl-pyridin-2-yl)-piperazin-1-yl]-methanone

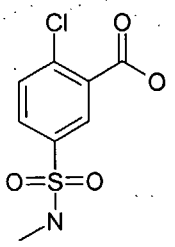


Prepared in analogy to example 3 (d) from 2-isopropylsulfanyl-5-methanesulfonyl-benzoic acid and 1-(5-methyl-pyridin-2-yl)-piperazine (Example A5). The crude material was purified by chromatography (SiO_2, ethyl acetate/heptane) to yield the title compound as an off-white solid (yield 24%). MS (m/e): 434.1 ($M+H^+$, 100%).

Example 25

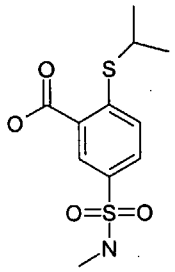
4-Isopropylsulfanyl-*N*-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide

a) 2-Chloro-5-methylsulfamoyl-benzoic acid



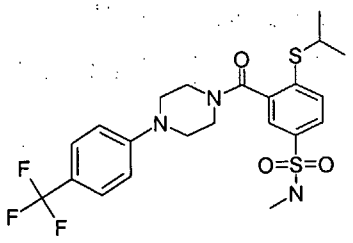
To 41.9 mmol 2-chloro-5-(fluorosulfonyl)sulfanyl-benzoic acid in 100 ml dioxane was added dropwise 420 mmol methylamine solution (41% aqueous) and the mixture was stirred at RT for 2 h. An excess of 2 M aqueous hydrochloric acid was then added to the reaction mixture and the resulting mixture was then concentrated *in vacuo*. The residue was treated with water and extracted 3 times with ethyl acetate. The combined organic phases were dried over sodium sulfate. Evaporation under reduced pressure yielded the title compound as a white crystalline solid (yield 96%). MS (m/e): 248.1 ([M-H]$^-$, 100%).

b) 2-Isopropylsulfanyl-5-methylsulfamoyl-benzoic acid



To a solution of 1.99 mmol 2-chloro-5-methylsulfamoyl-benzoic acid in 3 ml N,N-dimethylacetamide were added 6.37 mmol cesium carbonate and 4.39 mmol 2-propanethiol and the mixture was stirred at 100 °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 an off-white solid which was used in the next step without further purification (yield 85%). MS (m/e): 288.1 ([M-H]$^-$, 100%).

c) 4-Isopropylsulfanyl-*N*-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide

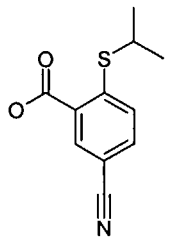


To a solution of 0.17 mmol 2-isopropylsulfanyl-5-methylsulfamoyl-benzoic acid in 3 ml tetrahydrofuran were added successively 0.16 mmol TBTU, 0.42 mmol N-ethyldiisopropylamine and 0.11 mmol 1-(4-trifluoromethylphenyl)-piperazine (commercially available, e.g. from Fluorochem). The reaction mixture was stirred at 35 °C for 16 h and then concentrated in vacuo. Chromatography (SiO_2, ethyl acetate/heptane) followed by trituration in pentane afforded the title compound as a white solid (yield 66%). MS (m/e): 502.1 ($M+H^+$, 100%).

Example 26

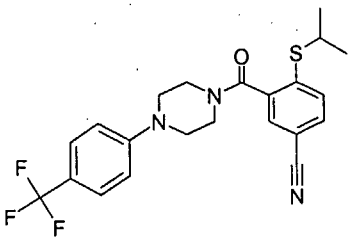
4-Isopropylsulfanyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzonitrile

a) 5-Cyano-2-isopropylsulfanyl-benzoic acid



To a solution of 1.45 mmol 5-cyano-2-iodo-benzoic acid (CAS: 219841-92-6, prepared as described in WO2005014563) in 3 ml N,N-dimethylacetamide were added 4.91 mmol cesium carbonate and 3.19 mmol 2-propanethiol and the mixture was stirred at 120 °C for 4 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 an off-white solid which was used in the next step without further purification (yield 97%). MS (m/e): 220.1 ($[M-H]^-$, 100%).

b) 4-Isopropylsulfanyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzonitrile

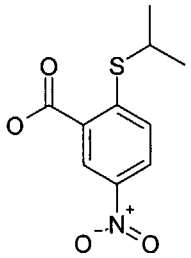


To a solution of 0.32 mmol 5-cyano-2-isopropylsulfanyl-benzoic acid in 5 ml tetrahydrofuran were added successively 0.31 mmol TBTU, 0.84 mmol N-ethyldiisopropylamine and 0.22 mmol 1-(4-trifluoromethylphenyl)-piperazine (commercially available, e.g. from Fluorochem). The reaction mixture was stirred at 35 °C for 16 h and then concentrated in vacuo. Chromatography (SiO_2, ethyl acetate/heptane) followed by trituration in pentane afforded the title compound as an off-white solid (yield 94%). MS (m/e): 434.4 ($M+H^+$, 100%).

Example 27

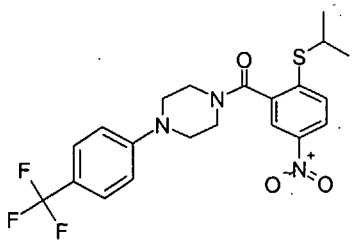
(2-Isopropylsulfanyl-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone

a) 2-Isopropylsulfanyl-5-nitro-benzoic acid



To a solution of 2.67 mmol 5-fluoro-2-nitro-benzoic acid (commercially available, e.g. from Aldrich) in 3 ml N,N-dimethylacetamide were added 8.58 mmol cesium carbonate and 5.83 mmol 2-propanethiol and the mixture was stirred at 35 °C for 4 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 an off-white solid which was used in the next step without further purification (yield 74%). MS (m/e): 240.3 ($[M-H]^-$, 100%).

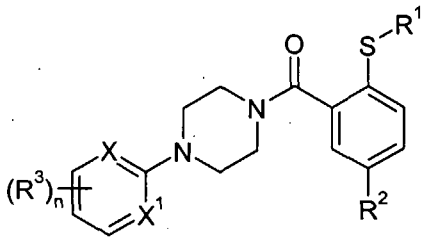
b) (2-Isopropylsulfanyl-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone



To a solution of 0.31 mmol 2-isopropylsulfanyl-5-nitro-benzoic acid in 5 ml tetrahydrofuran were added successively 0.31 mmol TBTU, 0.84 mmol N-ethyldiisopropylamine and 0.22 mmol 1-(4-trifluoromethylphenyl)-piperazine (commercially available, e.g. from Fluorochem). The reaction mixture was stirred at 35 °C for 16 h and then concentrated in vacuo. Chromatography (SiO_2, ethyl acetate/heptane) followed by trituration in pentane afforded the title compound as a yellow solid (yield 83%). MS (m/e): 454.4 ($M+H^+$, 100%).

Claims

1. Compounds of general formula



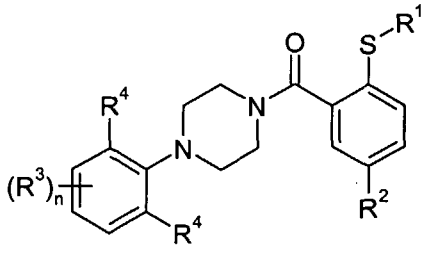
I

wherein

R^1 is lower alkyl or lower alkyl substituted by halogen;
R^2 is $-S(O)_2$-lower alkyl, $-S(O)_2NH$-lower alkyl, NO_2 or CN;
R^3 is halogen, CN, lower alkyl, lower alkyl substituted by halogen, NO_2, -C(O)-lower alkyl or $S(O)_2$-lower alkyl;
X/X^1 are independently from each other CR^4 or N;
R^4 is hydrogen or halogen;
n is 0, 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

2. Compounds of formula I-A in accordance with claim 1,



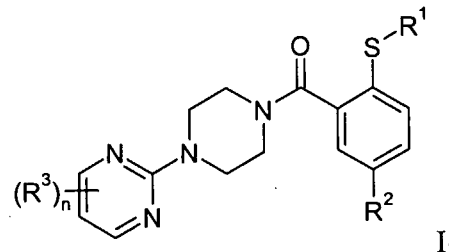
I-A

wherein

R^1 is lower alkyl or lower alkyl substituted by halogen;
R^2 is $-S(O)_2$-lower alkyl, $-S(O)_2NH$-lower alkyl, NO_2 or CN;
R^3 is halogen, CN, lower alkyl, lower alkyl substituted by halogen, NO_2, -C(O)-lower alkyl or $S(O)_2$-lower alkyl;
R^4 is hydrogen or halogen;
n is 0, 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

3. Compounds of formula I-B in accordance with claim 1



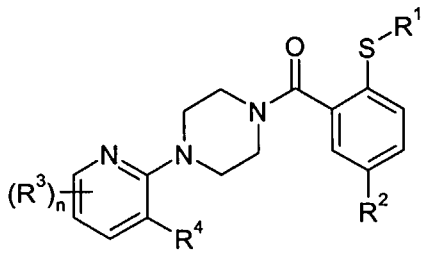
I-B

wherein

R^1 is lower alkyl or lower alkyl substituted by halogen;
R^2 is $-S(O)_2$-lower alkyl, $-S(O)_2NH$-lower alkyl, NO_2 or CN;
R^3 is halogen, CN, lower alkyl, lower alkyl substituted by halogen, NO_2, -C(O)-lower alkyl or $S(O)_2$-lower alkyl;
n is 0, 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

4. Compounds of formula I-C in accordance with claim 1



IC

wherein

R^1 is lower alkyl or lower alkyl substituted by halogen;
R^2 is $-S(O)_2$-lower alkyl, $-S(O)_2NH$-lower alkyl, NO_2 or CN;
R^3 is halogen, CN, lower alkyl, lower alkyl substituted by halogen, NO_2, -C(O)-lower alkyl or $S(O)_2$-lower alkyl;
R^4 is hydrogen or halogen;
n is 0, 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

5. Compounds of formula I in accordance with claim 1, wherein R^1 is lower alkyl.

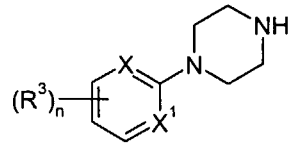
6. Compounds of formula I according to claim 5, which compounds are

[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-(2-isopropylsulfanyl-5-methanesulfonyl-phenyl)-methanone,
[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isopropylsulfanyl-5-methanesulfonyl-phenyl)-methanone,
(2-ethylsulfanyl-5-methanesulfonyl-phenyl)-[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-methanone,
[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-(2-isobutylsulfanyl-5-methanesulfonyl-phenyl)-methanone,
1-{3-fluoro-4-[4-(2-isopropylsulfanyl-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-phenyl}-ethanone,
[4-(2-chloro-4-nitro-phenyl)-piperazin-1-yl]-(2-isopropylsulfanyl-5-methanesulfonyl-phenyl)-methanone,
4-isopropylsulfanyl-*N*-methyl-3-[4-(4-trifluoromethyl-phenyl)-piperazine-1-carbonyl]-benzenesulfonamide or
(2-isopropylsulfanyl-5-nitro-phenyl)-[4-(4-trifluoromethyl-phenyl)-piperazin-1-yl]-methanone.

7. Compounds of formula I in accordance with claim 1, wherein R^1 is lower alkyl substituted by halogen.

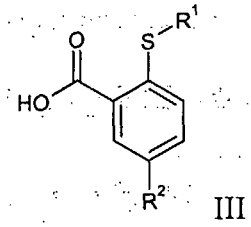
8. Compounds of formula I according to claim 7, which compounds are
[4-(3-fluoro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-phenyl]-methanone or
[4-(2-fluoro-4-methanesulfonyl-phenyl)-piperazin-1-yl]-[5-methanesulfonyl-2-(2,2,2-trifluoro-ethylsulfanyl)-phenyl]-methanone.

9. A process for preparing a compound of formula I as defined in claim 1, which process comprises
a) reacting a compound of formula



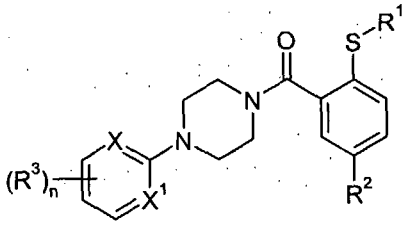
II

with a compound of formula



III

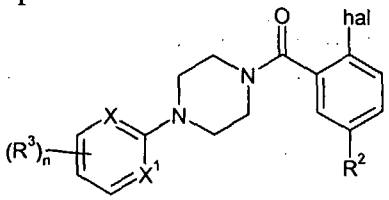
in the presence of an activating agent to a compound of formula



I

wherein the substituents R^1, R^2, R^3, n, X and X^1 are as defined above, or

b) reacting a compound of formula



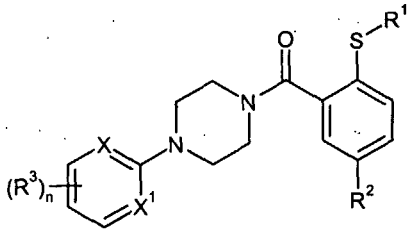
IV

with a compound of formula

R^1SH

optionally in the presence of a catalyst and a base

to a compound of formula



I

wherein hal is halogen, and the other substituents R^1, R^2, R^3, n, X and X^1 are as defined above,

and

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

10. A compound according to claim 1, whenever prepared by a process as claimed in claim 9 or by an equivalent method.

11. A medicament containing one or more compounds as claimed in claim 1 and pharmaceutically acceptable excipients.

12. A medicament according to claim 8 for the treatment of illnesses based on the glycine uptake inhibitor.

13. A medicament according to claim 12, wherein the illnesses are psychoses, pain, neurodegenerative disfunction in memory and learning, schizophrenia, dementia attention deficit disorders or Alzheimer's disease.

14. The use of a compound as claimed in claim 1 for the manufacture of medicaments for the treatment of psychoses, pain, neurodegenerative disfunction in memory and learning, schizophrenia, dementia and attention deficit disorders or Alzheimer's disease.

15. The invention as herein before described.

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