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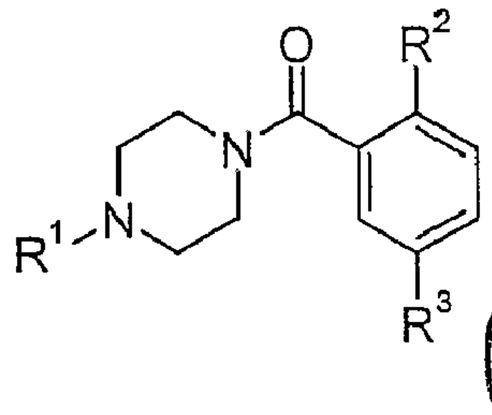
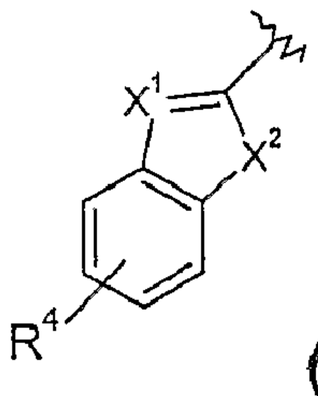
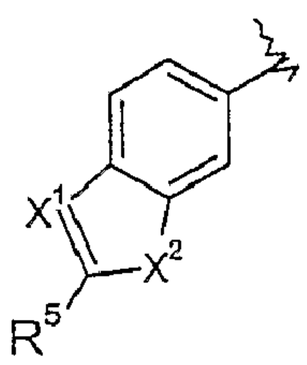
(54) Titre : DERIVES DE LA PHENYL-PIPERAZINE METHANONE
(54) Title: PHENYL-PIPERAZIN METHANONE DERIVATIVES



(I)



(A)



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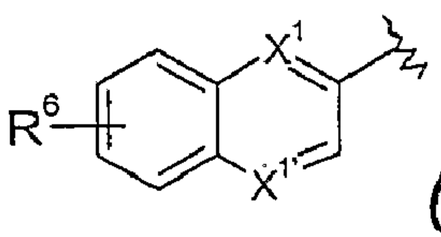

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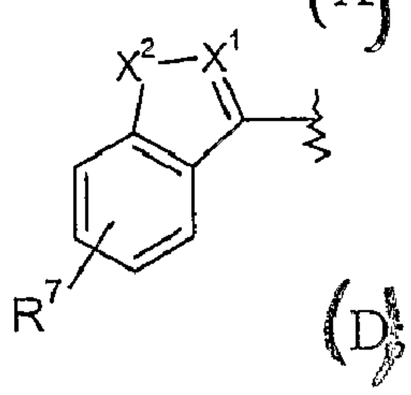

(D)

(57) Abrégé/Abstract:
The present invention relates to compounds of the general formula I (see formula I) wherein R^1 is the group (see formula A) or (see formula B) or (see formula C) or (see formula D); R^2 is a non aromatic heterocycle, or is OR' or $N(R'')_2$; R' is lower alkyl, lower

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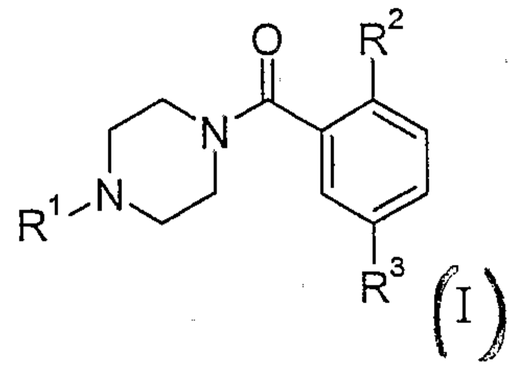
(13) C

(57) Abrégé(suite)/Abstract(continued):
alkyl substituted by halogen or -$(CH_2)_n$-cycloalkyl; R'' is lower alkyl; R^3 is NO_2, CN or SO_2R'; R^4 is hydrogen, hydroxy, halogen, NO_2, lower alkyl, lower alkyl, substituted by halogen, lower alkoxy, SO_2R' or C(O)R''; $R^5/R^6/R^7$ are hydrogen, halogen, lower alkyl or lower alkyl, substituted by halogen; $X^1/X^{1'}$ are CH or N, with the proviso that $X^1/X^{1'}$ are not simultaneously CH; X^2 is O, S, NH or N(lower alkyl); n is 0, 1 or 2; and to pharmaceutically active acid addition salts and to their use in the treatment of neurological and neuropsychiatric disorders.

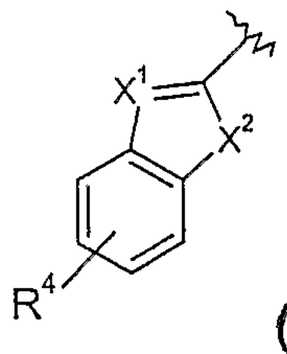
Abstract

The present invention relates to compounds of the general formula I


(I)

wherein

R^1 is the group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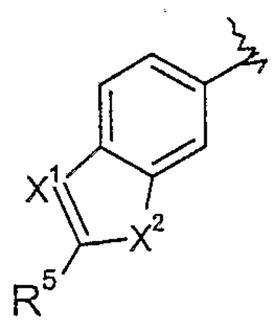
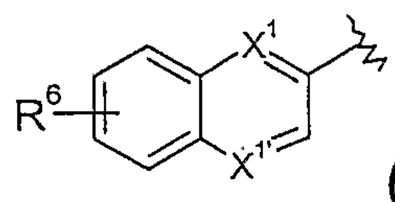
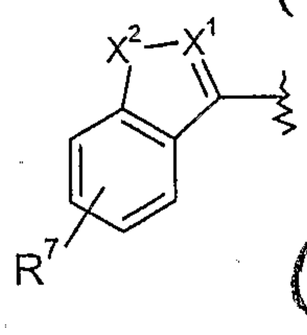

(B) or


(C) or


(D)

R^2 is a non aromatic heterocycle, or is OR' or $N(R'')_2$;

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

R'' is lower alkyl;

R^3 is NO_2, CN or SO_2R';

R^4 is hydrogen, hydroxy, halogen, NO_2, lower alkyl, lower alkyl, substituted by halogen, lower alkoxy, SO_2R' or C(O)OR'';

$R^5/R^6/R^7$ are hydrogen, halogen, lower alkyl or lower alkyl, substituted by halogen;

$X^1/X^{1'}$ are CH or N, with the proviso that $X^1/X^{1'}$ are not simultaneously CH;

X^2 is O, S, NH or N(lower alkyl);

n is 0, 1 or 2;

and to pharmaceutically active acid addition salts and to their use in the treatment of neurological and neuropsychiatric disorders.

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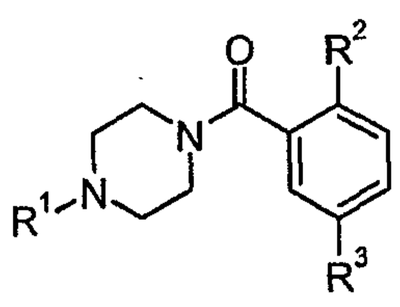
Phenyl-piperazin methanone derivatives

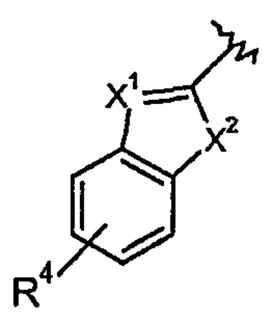
The present invention relates to compounds of the general formula I



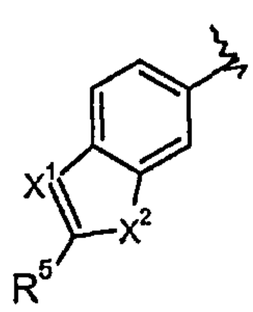
I

wherein

R^1 is the group



A or



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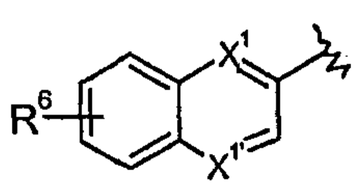

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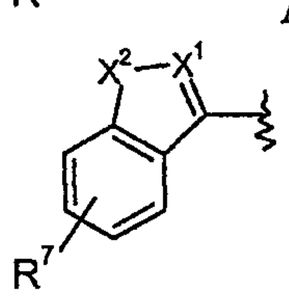


D;

R^2 is a non aromatic heterocycle, or is OR' or $N(R'')_2$;

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

R'' is lower alkyl;

R^3 is NO_2, CN or SO_2R';

R^4 is hydrogen, hydroxy, halogen, NO_2, lower alkyl, lower alkyl, substituted by halogen, lower alkoxy, SO_2R' or C(O)OR'';

$R^5/R^6/R^7$ are hydrogen, halogen, lower alkyl or lower alkyl, substituted by halogen;

$X^1/X^{1'}$ are CH or N, with the proviso that $X^1/X^{1'}$ are not simultaneously CH;

X^2 is O, S, NH or N(lower alkyl);

n is 0, 1 or 2;

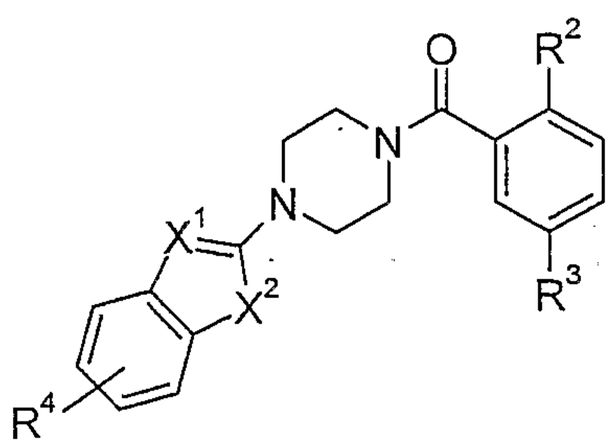
and to pharmaceutically active acid addition salts.

The present invention relates to compounds of general formula I, to processes for preparation of those compounds, to pharmaceutical composition containing them and to 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.

The following compounds of formulae IA, IB, IC and ID are encompassed by the present invention:

The compound of formula



IA

wherein

R^2 is a non aromatic heterocycle, or is OR' or $N(R'')_2$;

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

R'' is lower alkyl;

R^3 is NO_2, CN or SO_2R';

R^4 is hydrogen, hydroxy, halogen, NO_2, lower alkyl, lower alkyl, substituted by halogen, lower alkoxy, SO_2R' or C(O)OR'';

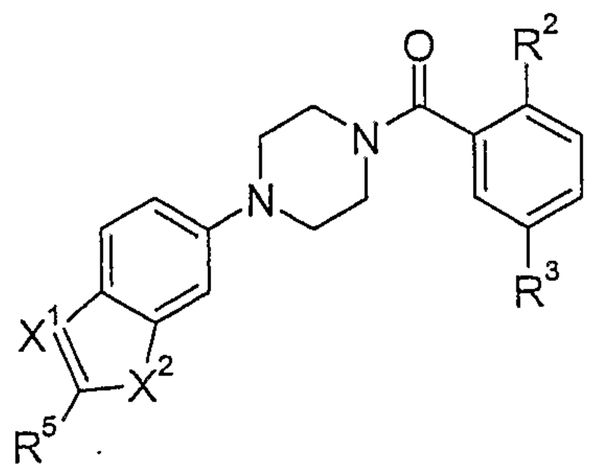
X^1 is CH or N;

X^2 is O, S, NH or N(lower alkyl);

n is 0, 1 or 2;

and pharmaceutically active acid addition salts.

The compound of formula



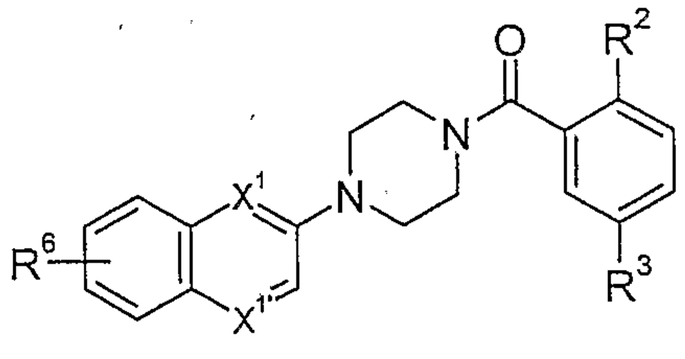
IB

wherein

R^2	is a non aromatic heterocycle, or is OR' or $N(R'')_2$;
R'	is lower alkyl, lower alkyl, substituted by halogen or $-(CH_2)_n$-cycloalkyl;
R''	is lower alkyl;
R^3	is NO_2, CN or SO_2R';
R^5	is hydrogen, halogen, lower alkyl or lower alkyl, substituted by halogen;
X^1	is CH or N;
X^2	is O, S, NH or N(lower alkyl);
n	is 0, 1 or 2;

and pharmaceutically active acid addition salts.

The compound of formula



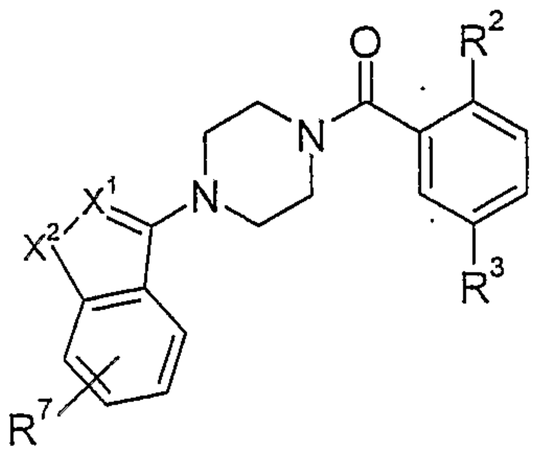
IC

wherein

R^2	is a non aromatic heterocycle, or is OR' or $N(R'')_2$;
R'	is lower alkyl, lower alkyl, substituted by halogen or $-(CH_2)_n$-cycloalkyl;
R''	is lower alkyl;
R^3	is NO_2, CN or SO_2R';
R^6	is hydrogen, halogen, lower alkyl or lower alkyl, substituted by halogen;
$X^1/X^{1'}$	are CH or N, with the proviso that $X^1/X^{1'}$ are not simultaneously CH;
n	is 0, 1 or 2;

and pharmaceutically active acid addition salts.

The compound of formula



ID

wherein

R^2 is a non aromatic heterocycle, or is OR' or $N(R'')_2$;

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

R'' is lower alkyl;

R^3 is NO_2, CN or SO_2R';

R^7 is hydrogen, halogen, lower alkyl or lower alkyl, substituted by halogen;

X^1 is CH or N;

X^2 is O, S, NH or N(lower alkyl);

n is 0, 1 or 2;

and pharmaceutically active acid addition salts.

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*, 2000, 28:325-33). 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*, 2001, 5(4): 507-518; Nakazato A and Okuyama S, et al., 2000, *Exp. Opin. Ther. Patents*, 10(1): 75-98). This pharmacological approach poorly address negative and cognitive symptoms which are the best predictors of functional outcome (Sharma T., *Br.J. Psychiatry*, 1999, 174(suppl. 28): 44-51).

A complementary model of schizophrenia was proposed in the mid-1960' 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., 1999, *Biol. Psychiatry*, 45: 668-679 and refs. herein). Furthermore transgenic mice expressing reduced levels of the NMDAR1 subunit displays behavioral abnormalities similar to those observed in pharmacologically induced models of schizophrenia, supporting a model in which reduced NMDA receptor activity results in schizophrenia-like behavior (Mohn AR et al., 1999, *Cell*, 98: 427-236).

Glutamate neurotransmission, in particular NMDA receptor activity, plays a critical role in synaptic plasticity, learning and memory, such as the NMDA receptors appears to serve as a graded switch for gating the threshold of synaptic plasticity and memory formation (Hebb DO, 1949, *The organization of behavior*, Wiley, NY; Bliss TV and Collingridge GL, 1993, *Nature*, 361: 31-39). Transgenic mice overexpressing the NMDA NR2B subunit exhibit enhanced synaptic plasticity and superior ability in learning and memory (Tang JP et al., 1999, *Nature*: 401- 63-69).

Thus, if a glutamate deficit is implicated 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 by removing neurotransmitters from the extracellular space, can control their extracellular lifetime and thereby modulate the magnitude of the synaptic transmission (Gainetdinov RR et al, 2002, Trends in Pharm. Sci., 23(8): 367-373) .

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., 2001, *Mol. Mem. Biol.*, 18: 13-20). 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., 1998, *Proc. Natl. Acad. Sci. USA*, 95: 15730-15734; Chen L et al., 2003, *J. Neurophysiol.*, 89 (2): 691-703).

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, 2001, *Exp. Opin. Ther. Patents*, 11 (4): 563-572), 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., 2002, *Prog. Neurobiol.*, 67: 173-202), autistic disorders (Carlsson ML, 1998, *J. Neural Transm.* 105: 525-535), 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, 2001, *Exp. Opin. Ther. Patents*, 11 (4): 563-572).

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, disfunction in memory and learning, schizophrenia, dementia and other diseases in which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's disease.

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

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 "lower alkoxy" denotes a saturated straight- or branched-chain group containing from 1 to 7 carbon atoms as defined above, and which is attached via an oxygen atom.

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

As used herein the term "non aromatic heterocycle" denotes a five or six membered heterocyclic ring, containing one or two heteroatoms, selected from the group consisting of O, N or S. Preferred rings are 1-pyrrolidine, 1-piperidine, 1-piperazine or 1-morpholine.

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

As used herein the term "lower alkyl, substituted by halogen" denotes an alkyl group as defined above, wherein at least one hydrogen atom is replaced by halogen, for example CF_3, CHF_2, CH_2F, CH_2CF_3 and the like.

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.

Most preferred compounds of formula I are those of formulas IA and IC.

Preferred compounds of formula IA are the followings:

[4-(6-chloro-benzothiazol-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone,
[4-(6-chloro-benzothiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
(4-benzooxazol-2-yl-piperazin-1-yl)-(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-methanone,
(4-benzooxazol-2-yl-piperazin-1-yl)-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone,
(2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(6-methoxy-benzothiazol-2-yl)-piperazin-1-yl]-methanone,
(2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(6-nitro-benzothiazol-2-yl)-piperazin-1-yl]-methanone,
(2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-methoxy-benzothiazol-2-yl)-piperazin-1-yl]-methanone,
(2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-nitro-benzothiazol-2-yl)-piperazin-1-yl]-methanone,
[4-(4-hydroxy-benzothiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
[4-(5-chloro-benzothiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
[4-(6-ethoxy-benzothiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
[4-(6-chloro-benzothiazol-2-yl)-piperazin-1-yl]-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone or
[4-(6-chloro-benzothiazol-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone.

Preferred compounds of formula IC are

(2-isobutoxy-5-methanesulfonyl-phenyl)-(4-quinolin-2-yl-piperazin-1-yl)-methanone,
[4-(6-chloro-quinolin-2-yl)-piperazin-1-yl]-(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-methanone,
(2-isobutoxy-5-methanesulfonyl-phenyl)-(4-quinoxalin-2-yl-piperazin-1-yl)-methanone,

(2-isopropoxy-5-methanesulfonyl-phenyl)-(4-quinoxalin-2-yl-piperazin-1-yl)-methanone,
(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-(4-quinoxalin-2-yl-piperazin-1-yl)-methanone,
(2-isobutoxy-5-methanesulfonyl-phenyl)-(4-quinolin-3-yl-piperazin-1-yl)-methanone or
(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-(4-quinolin-3-yl-piperazin-1-yl)-methanone.

A preferred compound of formula IB is

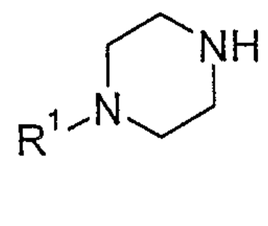
(2-isobutoxy-5-methanesulfonyl-phenyl)-[4-(2-methyl-benzothiazol-5-yl)-piperazin-1-yl]-methanone.

Preferred compounds of formula ID are

(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone or
(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone.

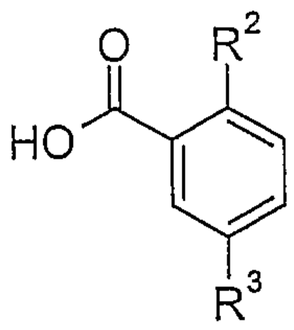
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

a) reacting a compound of formula



II

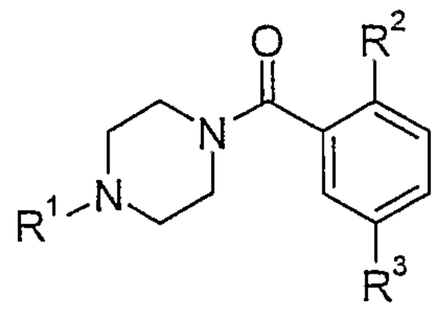
with a compound of formula



III

in the presence of an activating agent, such as TBTU,

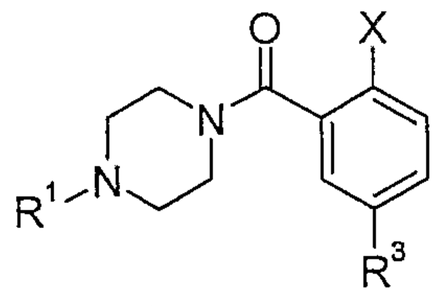
to a compound of formula



I

wherein the substituents are as defined above, or

b) reacting a compound of formula



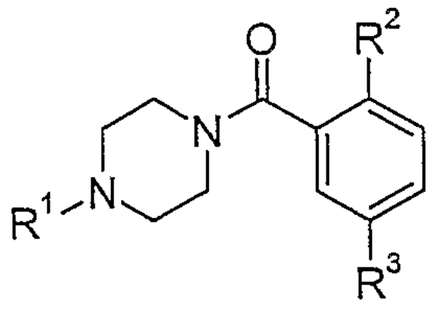
IV

with a compound of formula

R^2H V

in the presence of a base like potassium carbonate, or with addition of a catalyst like Cu(I)I

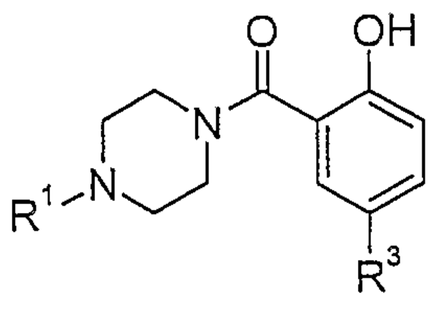
to a compound of formula



I

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

c) reacting a compound of formula

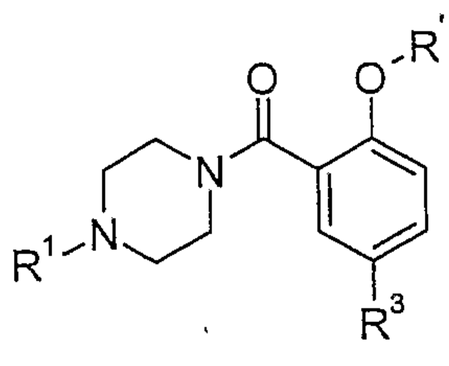


I1

with a compound of formula

R'X VI

to a compound of formula

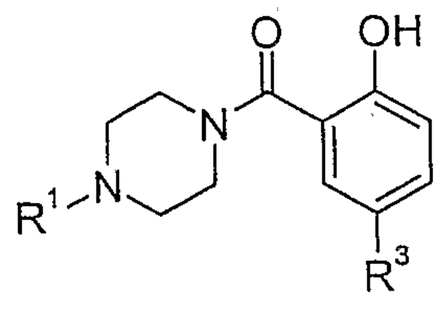


I2

wherein the substituents R^1 and R^3 are as defined above, and R' is lower alkyl, lower alkyl, substituted by halogen or $-(CH_2)_n$-cycloalkyl and X is halogen;

or

d) reacting a compound of formula



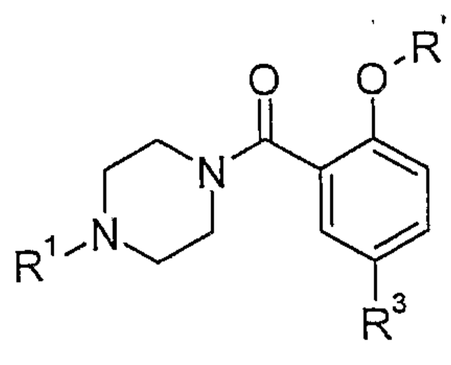
I1

with a compound of formula

R'OH VII

under Mitsunobu conditions

to a compound of formula



I2

wherein the substituents R^1 and R^3 are as defined above, and R' is lower alkyl, lower alkyl, substituted by halogen or $-(CH_2)_n$-cycloalkyl,

and

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

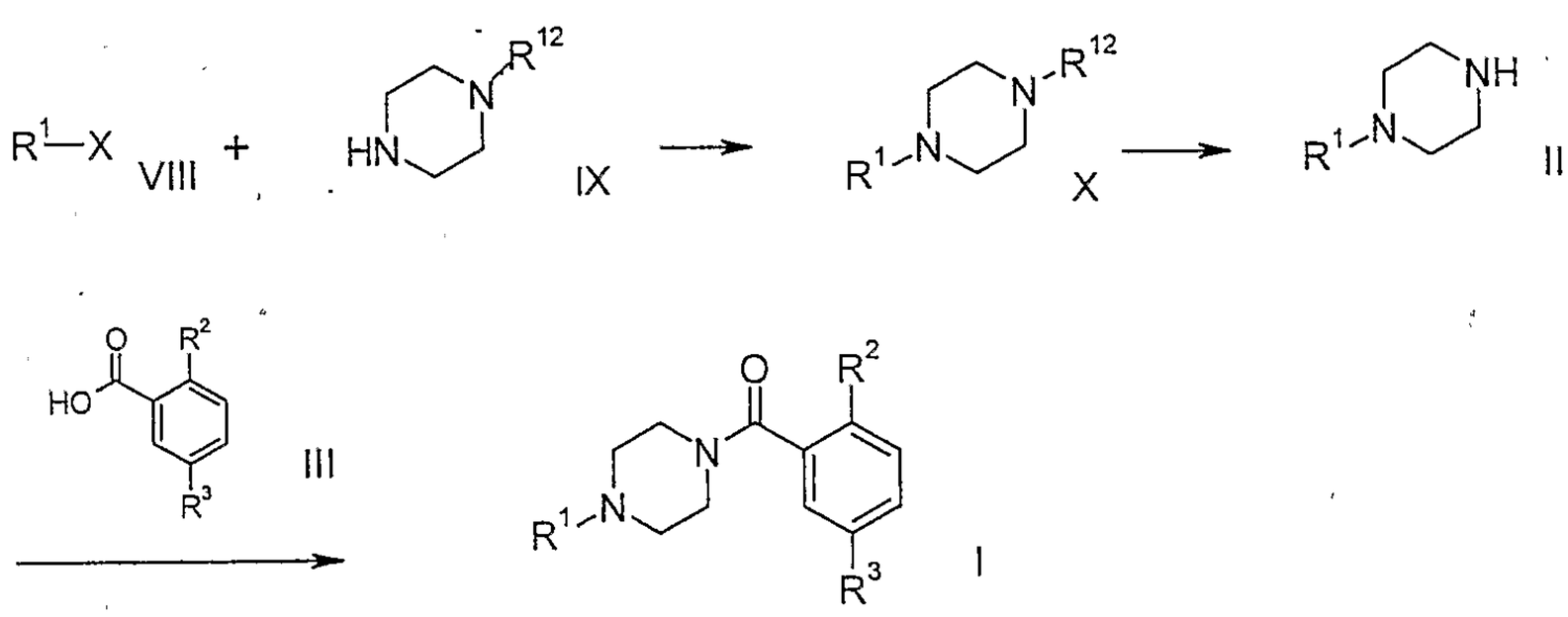
The compounds of formula I may be prepared in accordance with process variants a), b) c) or d) and with the following schemes 1, 2, 3 and 4. All starting materials are either commercially available, described in the literature or can be prepared by methods well known in the art.

The following abbreviation has been used:

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

Scheme 1

Preparation of compounds of formulas II and I



wherein R^1, R^2 and R^3 are as described above, R^{12} is hydrogen or a protecting group, such as tert-butyloxycarbonyl or benzyloxycarbonyl, and X is halogen, mesylate or triflate.

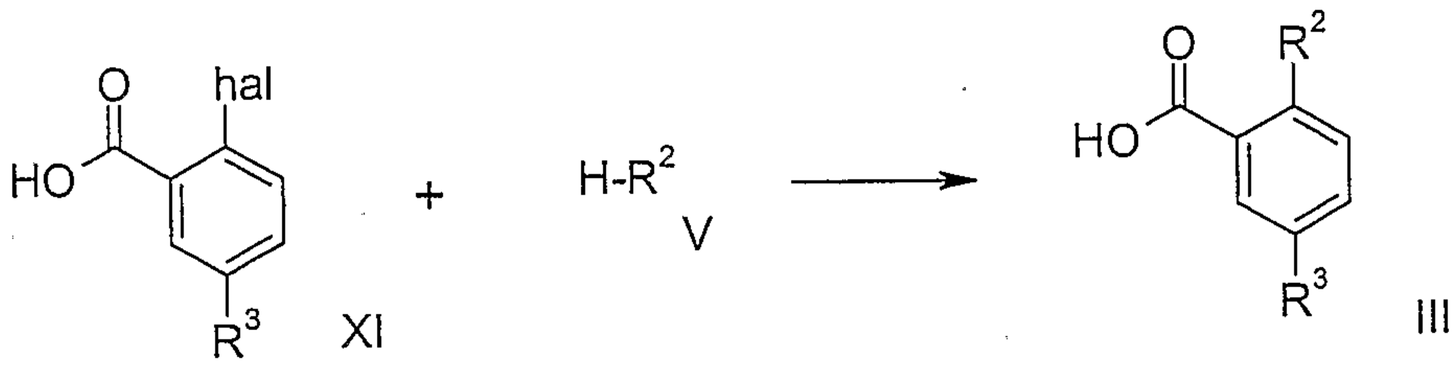
When X is an activated leaving group (for examples in o-position to a nitrogen atom), the compounds of formula X are obtained by heating a compound of formula VIII in the presence of a compound of formula IX and a base like potassium- or sodium carbonate in a suitable solvent like alcohol, acetone or acetonitrile.

When X is an unactivated leaving group, compounds X are obtained by known Pd- or Cu- catalyzed coupling reactions between compounds of formulas VIII and IX (see for example S.L.Buchwald ea., Org. Lett. 4, 581 (2002) or J.F. Hartwig ea., JOC 67, 6479 (2002)).

When R^{12} is a protective group, deprotection by methods known in the art yields compounds of formula II. A compound of formula II is then treated with a compound of formula III in the presence of TBTU and a base, such as N-ethyldiisopropylamine to obtain a compound of formula I.

Scheme 2

Preparation of compounds of formula III:



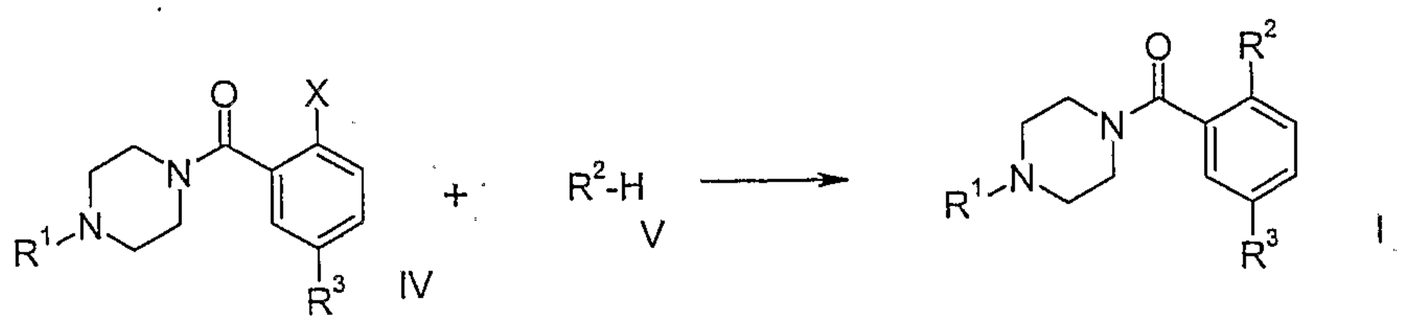
wherein R^2 and R^3 are as described above and hal is halogen.

Compounds of formula III may be prepared in conventional manner. If H-R^2 is a non aromatic heterocycle, for example morpholine, the reaction is carried out at room temperature for about 2 hours.

If R^2 is OR' for R' is lower alkyl, lower alkyl, substituted by halogen or -$(CH_2)_n$-cycloalkyl, the reaction is carried out with the corresponding alcohol of formula V by reaction with a mixture of a compound of formula XI and Cu(I)Br in triethylamine.

Scheme 3

Preparation of compounds of formula I:

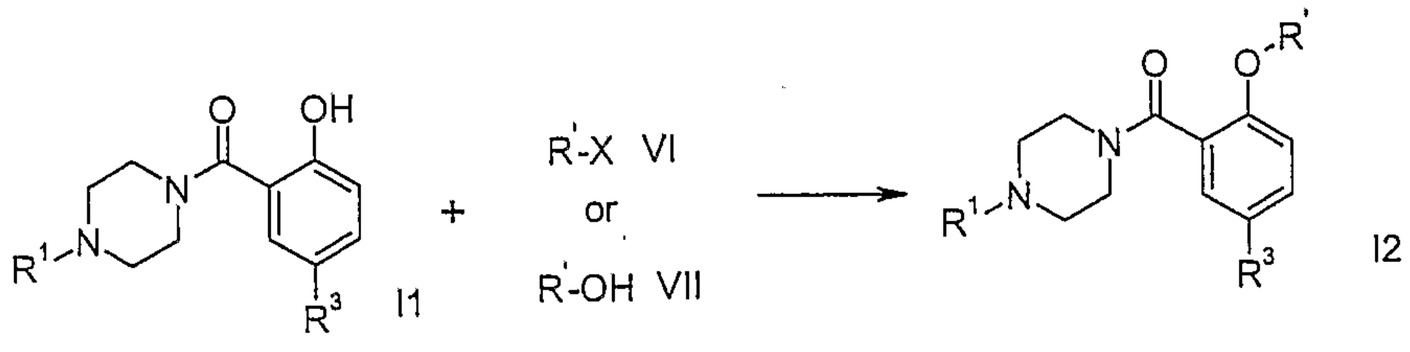


wherein R^1, R^2 and R^3 are as described above and X is halogen.

X may be replaced by R^2 in conventional manner, in presence of a base such as triethylamine or with addition of a catalyst like Cu(I)Br.

Scheme 4

Preparation of compounds of formula I2:



wherein R', R^1 and R^3 are as described above and X is halogen.

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 preferred compounds show an IC_{50} (μM) at GlyT-1 < 0.5.

Example No.	IC_{50} (μM)	Example No.	IC_{50} (μM)
1.1 formula IA	0.271	1.15 formula IA	0.339
1.2 formula IA	0.398	1.17 formula IB	0.440
1.4 formula IA	0.097	1.23 formula IC	0.167
1.5 formula IA	0.144	1.24 formula IC	0.287
1.8 formula IA	0.174	1.25 formula IC	0.067
1.9 formula IA	0.206	1.27 formula IC	0.082
1.11 formula IA	0.148	1.28 formula IC	0.149
1.12 formula IA	0.375	1.29 formula ID	0.500
1.13 formula IA	0.158	1.31 formula ID	0.467
1.14 formula IA	0.218	1.33 formula ID	0.055
1.19 formula IC	0.078	1.39 formula IA	0.230

1.22 formula IC	0.399	1.40 formula IA	0.039

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

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

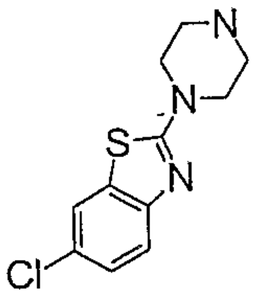
The following examples illustrate the present invention without limiting it. All temperatures are given in degree Celsius.

All starting materials are either commercially available, described in the literature (CA-abstract-numbers are given) or or can be prepared by methods well known in the art.

Example 1.1

Preparation of [4-(6-Chloro-benzothiazol-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

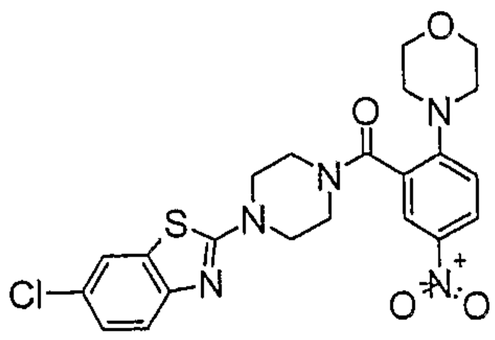
(a) 6-Chloro-2-piperazin-1-yl-benzothiazole



A mixture of 10 mmol 2,6-dichlorobenzothiazole, 12.3 mmol of piperazine and 20 mmol of potassium carbonate in 50 ml of acetonitrile was refluxed for 3 hours. The reaction mixture was concentrated and treated with 25 ml of water. Extraction with ethyl acetate, drying over magnesium sulfate and evaporation of the solvent yielded the title compound as a colorless solid.

MS (m/e): 254.7 (MH^+)

(b) [4-(6-Chloro-benzothiazol-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone



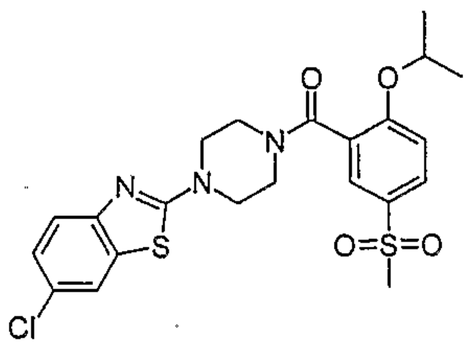
To a solution of 0.25 mmol 2-morpholin-4-yl-5-nitro-benzoic acid (Example 2.1) in 0.7 ml dimethylformamide 0.26 mmol TBTU, 1.6 mmol N-ethyldiisopropylamine and 0.25 mmol 6-chloro-2-piperazin-1-yl-benzothiazole were successively added. The reaction was then stirred at RT for two hours, concentrated in vacuo and treated with 5 ml water. The

solid is filtered off and recrystallized form methanol to yield the title compound as a yellow solid.

MS (m/e): 488.1 ($M+H^+$)

Example 1.2

Preparation of [4-(6-Chloro-benzothiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



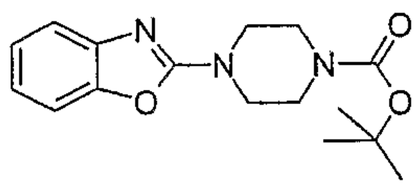
Prepared in analogy to example 1.1 b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.2) and 6-chloro-2-piperazin-1-yl-benzothiazole. The crude material was purified by chromatography (SiO_2, CH_2Cl_2/MeOH = 95/5) to yield the title compound as a yellowish solid.

MS (m/e): 552.3 ($M+CH_3COOH^+$)

Example 1.3

Preparation of (4-Benzoxazol-2-yl-piperazin-1-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

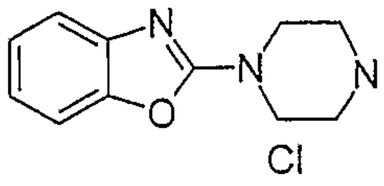
(a) 4-Benzoxazol-2-yl-piperazine-1-carboxylic acid tert.-butyl ester



A mixture of 52.5 mmol 2-chlorobenzoxazol, 53.6 mmol piperazine-1-carboxylic acid tert-butyl ester and 63 mmol of potassium carbonate in 60 ml of acetonitrile was refluxed for 16 hours. The reaction mixture was conentrated, diluted with water and extracted with ethyl acetate. The organic phase was dried and concentrated to yield the title compounds as a slightly orange solid.

MS (m/e): 304.2 ($M+H^+$)

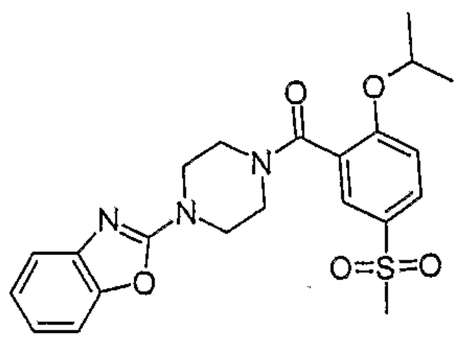
(b) 2-Piperazin-1-yl-benzoxazole hydrochloride



10.8 mmol of 4-benzoxazol-2-yl-piperazine-1-carboxylic acid tert.-butyl ester were treated with 30 ml of a dioxane, saturated with gaseous hydrochloric acid. The heterogenous mixture was stirred at room temperature for 1 hour, before evaporation of the solvent. This yielded the title compound as a colorless solid.

MS (m/e): 204.1 ($M+H^+$)

(c) 4-Benzoxazol-2-yl-piperazin-1-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

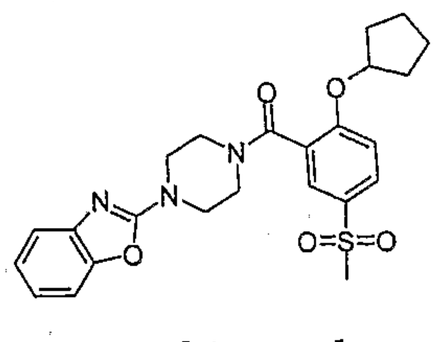


Prepared in analogy to example 1.1 b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.2) and 2-piperazin-1-yl-benzoxazole hydrochloride. The crude material was triturated with diethyl ether to yield the title compound as a colorless solid.

MS (m/e): 444.1 ($M+H^+$)

Example 1.4

Preparation of (4-Benzoxazol-2-yl-piperazin-1-yl)-(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-methanone

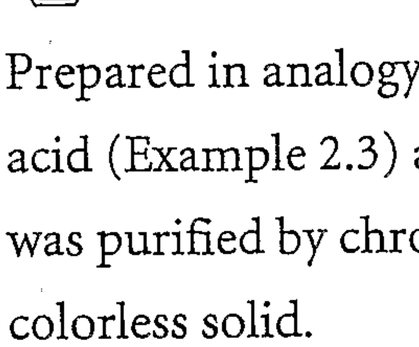


Prepared in analogy to example 1.1 b) from 2-cyclopentyloxy-5-methanesulfonyl-benzoic acid (Example 2.3) and 2-piperazin-1-yl-benzoxazole hydrochloride. The crude material was purified by chromatography (SiO_2, ethyl acetate) to yield the title compound as a colorless solid.

MS (m/e): 470.1 ($M+H^+$)

Example 1.5

Preparation of (4-Benzoxazol-2-yl-piperazin-1-yl)-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone



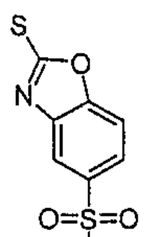
Prepared in analogy to example 1.1 b) from 2-isobutoxy-5-methanesulfonyl-benzoic acid (Example 2.4) and 2-piperazin-1-yl-benzoxazole hydrochloride. The crude material was purified by chromatography (SiO_2, ethyl acetate) to yield the title compound as a slightly yellow solid.

MS (m/e): 458.1 ($M+H^+$)

Example 1.6

Preparation of (2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-[4-(5-ethanesulfonyl-benzoxazol-2-yl)-piperazin-1-yl]-methanone

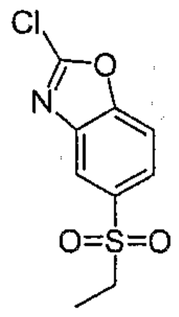
(a) 5-Ethanesulfonyl-benzoxazole-2-thiol



100 mmol 1-amino-5-ethylsulfonyl-2-hydroxybenzene were dissolved in 200 ml of ethanol and 150 ml of carbon disulfide. 120 mmol of potassium hydroxide was added and the mixture refluxed over night. The solvent was evaporated, the residue treated with 1 M hydrochloric acid, extracted with ethyl acetate and dried. Evaporation gave the crude product which was recrystallized from ethyl acetate to yield the title compound as yellowish solid.

MS (m/e): 242.4 (M-H)

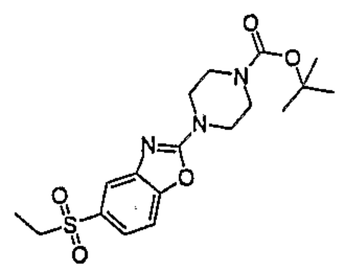
(b) 2-Chloro-5-ethanesulfonyl-benzoxazole



8 mmol of 5-Ethanesulfonyl-benzooxazole-2-thiol were dissolved in 10 ml of thionyl chloride. 1 drop of N,N-dimethylformamide is added and the reaction mixture hold at 65° for 45 min. Evaporation of the solvent yields the title compound as brownish solid.

MS (m/e): 262.9 ($M+NH_4^+$)

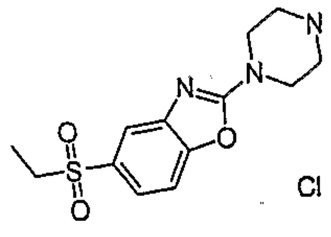
(c) 4-(5-Ethanesulfonyl-benzoxazol-2-yl)-piperazine-1-carboxylic acid tert.-butyl ester



A mixture of 8.1 mmol of 2-chloro-5-ethanesulfonyl-benzoxazole, 8.3 mmol piperazine-1-carboxylic acid tert-butyl ester and 9.8 mmol of potassium carbonate in 20 ml of acetonitrile was refluxed for 16 hours. The reaction mixture was cooled, concentrated in vacuo and treated with 50 ml water. Extraction with ethyl acetate and recrystallisation from a concentrated ethyl acetate solution yielded the title compound as a brownish solid.

MS (m/e): 454.4 ($M+CH_3COO$)

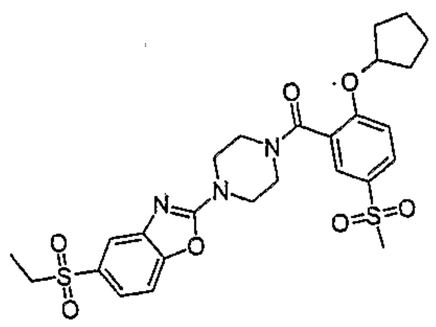
(d) 5-Ethanesulfonyl-2-piperazin-1-yl-benzoxazole hydrochloride



10.8 mmol of -(5-Ethanesulfonyl-benzoxazol-2-yl)-piperazine-1-carboxylic acid tert.-butyl ester were treated with 256 ml of a dioxane, saturated with gaseous hydrochloric acid. The heterogenous mixture was stirred overnight at room temperature. Evaporation of the solvent yielded the title compound as a colorless solid.

MS (m/e): 296.4 ($M+H^+$)

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

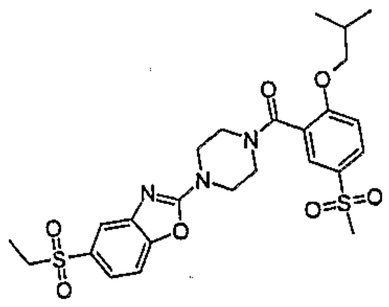


Prepared in analogy to example 1.1 b) from 2-cyclopentyloxy-5-methanesulfonyl-benzoic acid (Example 2.3) and 5-ethanesulfonyl-2-piperazin-1-yl-benzoxazole hydrochloride. The crude material was purified by chromatography (SiO_2, ethyl acetate) to yield the title compound as a colorless solid.

MS (m/e): 562.3 ($M+H^+$)

Example 1.7

Preparation of [4-(5-Ethanesulfonyl-benzoxazol-2-yl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone



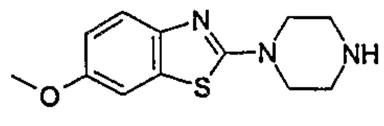
Prepared in analogy to example 1.1 b) from 2-isobutoxy-5-methanesulfonyl-benzoic acid (Example 2.4) and 5-ethanesulfonyl-2-piperazin-1-yl-benzoxazole hydrochloride. The crude material was purified by chromatography (SiO_2, ethyl acetate) to yield the title compound as a colorless solid.

MS (m/e): 550.2 ($M+H^+$)

Example 1.8

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

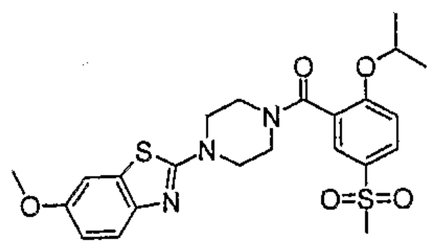
(a) 6-Methoxy-2-piperazin-1-yl-benzothiazole



A mixture of 1.50 mmol 2-chloro-6-methoxybenzothiazole (CA = [2605-14-3]), 4.51 mmol of piperazine and 4.51 mmol of triethylamine in 5 ml of tetrahydrofuran in a sealed tube was heated at 160 °C for 5 min under microwave irradiation. The reaction mixture was concentrated and the residue was purified by chromatography (SiO_2, methanol/dichloromethane) to yield the title compound as a white solid.

MS (m/e): 250.3 ($M+H^+$)

(b) (2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(6-methoxy-benzothiazol-2-yl)-piperazin-1-yl]-methanone



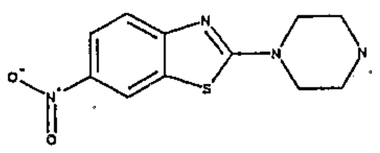
Prepared in analogy to example 1.1 b) from 2-Isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.2) and 6-Methoxy-2-piperazin-1-yl-benzothiazole in tetrahydrofuran. The crude material was purified by chromatography (SiO_2, heptane/ethyl acetate) to yield the title compound as a white foam.

MS (m/e): 490.3 ($M+H^+$)

Example 1.9

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

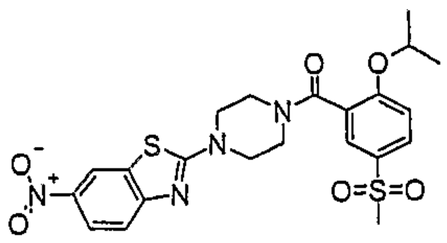
(a) 6-Nitro-2-piperazin-1-yl-benzothiazole



A mixture of 1.40 mmol 2-chloro-6-nitrobenzothiazole (CA = [2407-11-6]), 4.19 mmol of piperazine and 4.19 mmol of triethylamine in 5 ml of 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 (SiO_2, methanol/dichloromethane) to yield the title compound as a yellow solid.

MS (m/e): 264.9 ($M+H^+$)

(b) (2-Isopropoxy-5-methanesulfonyl-phenyl)-[4-(6-nitro-benzothiazol-2-yl)-piperazin-1-yl]-methanone

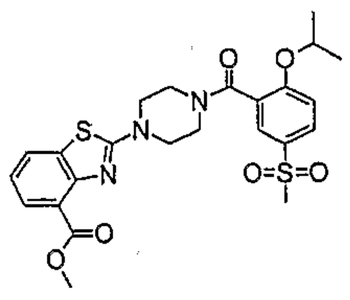


Prepared in analogy to example 1.1 b) from 2-Isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.2) and 6-Nitro-2-piperazin-1-yl-benzothiazole in tetrahydrofuran. The crude material was purified by chromatography (SiO_2, heptane/ethyl acetate) and the residue was then triturated in ether to yield the title compound as a yellow solid.

MS (m/e): 505.3 ($M+H^+$)

Example 1.10

Preparation of (2-[4-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-piperazin-1-yl]-benzothiazole-4-carboxylic acid methyl ester

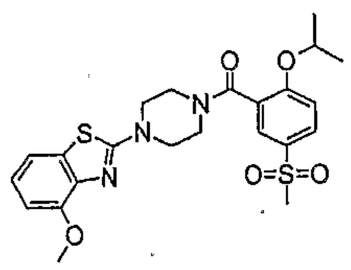


Prepared in analogy to example 1.1 b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.2) and 2-Piperazin-1-yl-benzothiazole-4-carboxylic acid methyl ester hydrochloride in tetrahydrofuran. The crude material was purified by chromatography (SiO_2, heptane/ethyl acetate) and the residue was then triturated in ether to yield the title compound as a white solid.

MS (m/e): 518.5 ($M+H^+$)

Example 1.11

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

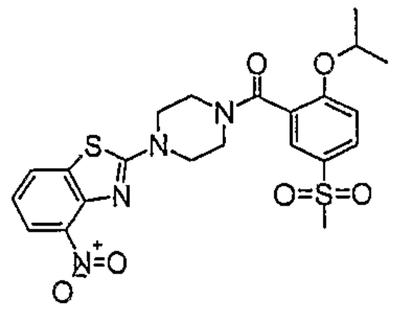


Prepared in analogy to example 1.1 b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.2) and 4-Methoxy-2-piperazin-1-yl-benzothiazole hydrochloride in tetrahydrofuran. The crude material was purified by chromatography (SiO_2, heptane/ethyl acetate) and the residue was then triturated in ether to yield the title compound as a white solid.

MS (m/e): 490.5 ($M+H^+$)

Example 1.12

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

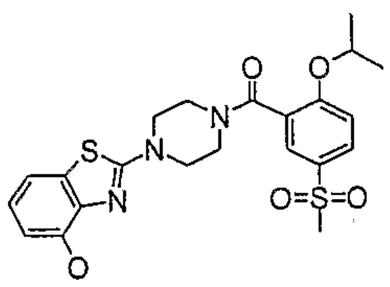


Prepared in analogy to example 1.1 b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.2) and 4-Nitro-2-piperazin-1-yl-benzothiazole hydrochloride in tetrahydrofuran. The crude material was purified by chromatography (SiO_2, heptane/ethyl acetate) and the residue was then triturated in ether to yield the title compound as a white solid.

MS (m/e): 505.3 ($M+H^+$)

Example 1.13

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



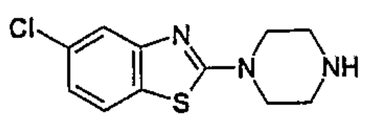
Prepared in analogy to example 1.1 b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.2) and 2-Piperazin-1-yl-benzothiazol-4-ol hydrochloride in tetrahydrofuran. The crude material was purified by chromatography (SiO_2, heptane/ethyl acetate) and the residue was then triturated in ether to yield the title compound as a white solid.

MS (m/e): 476.0 ($M+H^+$)

Example 1.14

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

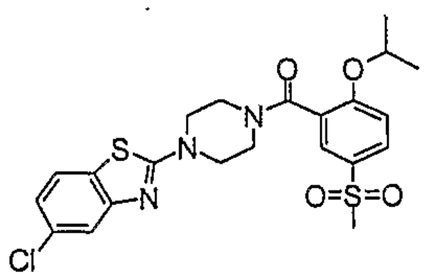
(a) 5-Chloro-2-piperazin-1-yl-benzothiazole



A mixture of 0.49 mmol 2,5-dichlorobenzothiazole (CA = [2941-48-2]), 1.47 mmol of piperazine and 1.47 mmol of triethylamine in 5 ml of tetrahydrofuran in a sealed tube was heated at 160 °C for 5 min under microwave irradiation. The reaction mixture was concentrated and the residue was purified by chromatography (SiO_2, methanol/dichloromethane) to yield the title compound as a white solid.

MS (m/e): 254.1 ($\{^{35}Cl\}M+H^+$), 256.2 ($\{^{37}Cl\}M+H^+$)

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



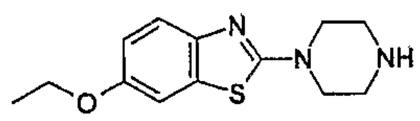
Prepared in analogy to example 1.1 b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.2) and 5-chloro-2-piperazin-1-yl-benzothiazole in tetrahydrofuran. The crude material was purified by chromatography (SiO_2, heptane/ethyl acetate) and the residue was then triturated in ether to yield the title compound as a white solid.

MS MS (m/e): 494.3 ({^{35}Cl}M+H$^+$), 496.2 ({^{37}Cl}M+H$^+$)

Example 1.15

Preparation of [4-(6-Ethoxy-benzothiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

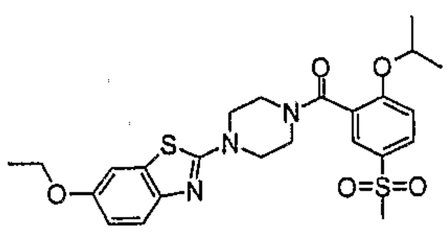
(a) 6-Ethoxy-2-piperazin-1-yl-benzothiazole



A mixture of 1.36 mmol 2-chloro-6-ethoxy-benzothiazole (CA = [79071-17-3]), 3.00 mmol of piperazine and 3.00 mmol of triethylamine in 5 ml of tetrahydrofuran in a sealed tube was heated at 160 °C for 5 min under microwave irradiation. The reaction mixture was concentrated and the residue was purified by chromatography (SiO_2, methanol/dichloromethane) to yield the title compound as a white solid.

MS (m/e): 264.3 (M+H$^+$)

(b) [4-(6-Ethoxy-benzothiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



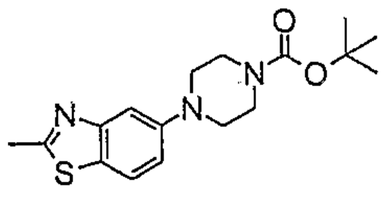
Prepared in analogy to example 1.1 b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.2) and 6-ethoxy-2-piperazin-1-yl-benzothiazole in tetrahydrofuran. The crude material was purified by chromatography (SiO_2, heptane/ethyl acetate) and the residue was then triturated in ether to yield the title compound as a white solid.

MS MS (m/e): 504.1 (M+H$^+$)

Example 1.16

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

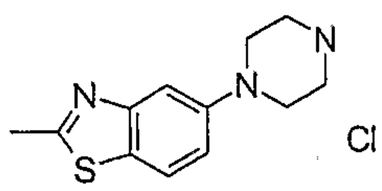
(a) 4-(2-Methyl-benzothiazol-5-yl)-piperazine-1-carboxylic acid tert.-butyl ester



To a mixture of 1.3 mmol 5-bromo-2-methylbenzothiazole, 1.4 mmol piperazine-1-carboxylic acid, 2.0 mmol potassium hydroxide, 0.01 mmol bis(tri-tert.butylphosphine)palladium and 0.01 mmol cetyltrimethylammonium bromide in 1 ml toluene 1 drop of water is added. The reaction mixture is heated overnight under argon at 90° C. Addition of water and extraction with ethyl acetate gives a brownish oil which is purified by chromatography (SiO_2; cyclohexane / ethyl acetate 7:3) to yield the title compound as a yellowish solid.

MS (m/e): 334.4 ($M+H^+$)

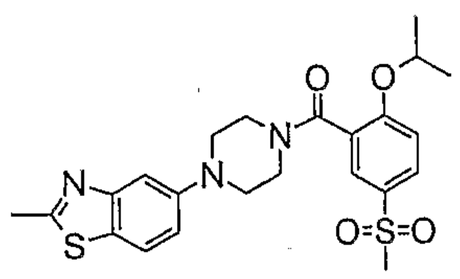
(b) 2-Methyl-5-piperazin-1-yl-benzothiazole hydrochloride



Prepared in analogy to example 1.6 (d) from 4-(2-methyl-benzothiazol-5-yl)-piperazine-1-carboxylic acid tert.-butyl ester and dioxane saturated with gaseous hydrochloric acid.

MS (m/e): 234.1 ($M+H^+$)

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



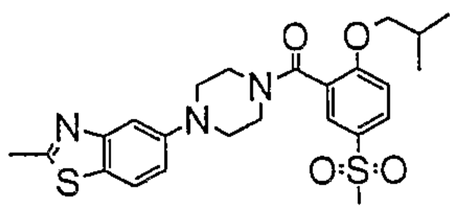
Prepared in analogy to example 1.1 (b) from 2-methyl-5-piperazin-1-yl-benzothiazole hydrochloride and 2-isopropoxy-5-methanesulfonyl-benzoic acid (example 2.2) in acetonitrile.

Trituration in diethyl ether yields the title compound as a yellowish solid.

MS (m/e): 474.1 ($M+H^+$)

Example 1.17

Preparation of (2-Isobutoxy-5-methanesulfonyl-phenyl)-[4-(2-methyl-benzothiazol-5-yl)-piperazin-1-yl]-methanone



Prepared in analogy to example 1.1 (b) from 2-methyl-5-piperazin-1-yl-benzothiazole hydrochloride and 2-isobutoxy-5-methanesulfonyl-benzoic acid (example 2.4) in acetonitrile.

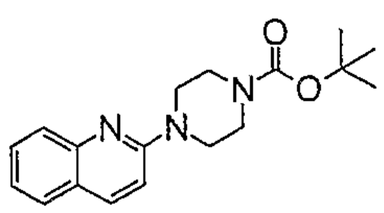
Chromatography (SiO_2; ethyl acetate) yields the title compound as a brownish solid.

MS (m/e): 488.4 ($M+H^+$)

Example 1.18

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(4-quinolin-2-yl-piperazin-1-yl)-methanone

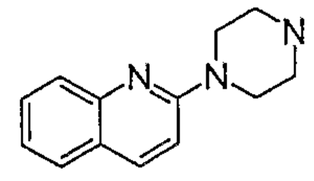
(a) 4-Quinolin-2-yl-piperazine-1-carboxylic acid tert.-butyl ester



A mixture of 6.1 mmol 2-chloroquinoline, 6.7 mmol piperazine-1-carboxylic acid tert-butyl ester and 12.2 mmol potassium carbonate in 15 ml acetonitrile was refluxed overnight. The reaction mixture is concentrated, water is added and the compound extracted with ethyl acetate. Chromatography (SiO_2; cyclohexane / ethyl acetate 9/1) gave the title compound as a colorless solid.

MS (m/e): 314.3 ($M+H^+$)

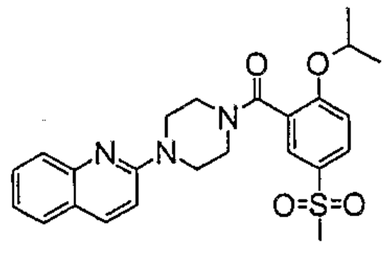
(b) 2-Piperazin-1-yl-quinoline hydrochloride



Prepared in analogy to example 1.6 (d) from 4-quinolin-2-yl-piperazine-1-carboxylic acid tert.-butyl ester and dioxane saturated with gaseous hydrochloric acid.

MS (m/e): 214.4 ($M+H^+$)

(c) (2-Isopropoxy-5-methanesulfonyl-phenyl)-(4-quinolin-2-yl-piperazin-1-yl)-methanone



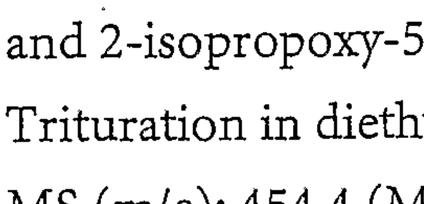
Prepared in analogy to example 1.1 (b) from 2-piperazin-1-yl-quinoline hydrochloride and 2-isopropoxy-5-methanesulfonyl-benzoic acid (example 2.2) in acetonitrile.

Trituration in diethyl ether yields the title compound as a yellowish foam.

MS (m/e): 454.4 ($M+H^+$)

Example 1.19

Preparation of (2-Isobutoxy-5-methanesulfonyl-phenyl)-(4-quinolin-2-yl-piperazin-1-yl)-methanone

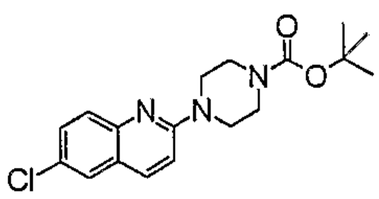


Prepared in analogy to example 1.1 (b) from 2-piperazin-1-yl-quinoline hydrochloride and 2-isobutoxy-5-methanesulfonyl-benzoic acid (example 2.4) in acetonitrile.
Chromatography (SiO_2; ethyl acetate) yields the title compound as a yellowish solid.
MS (m/e): 468.4 ($M+H^+$)

Example 1.20

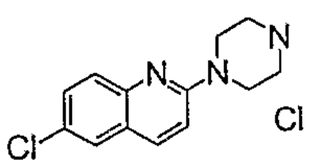
Preparation of [4-(6-Chloro-quinolin-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

(a) 4-(6-Chloro-quinolin-2-yl)-piperazine-1-carboxylic acid tert.-butyl ester



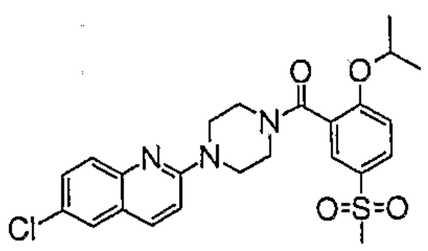
Prepared in analogy to example 1.18 (a) from 2,6-dichloroquinoline and piperazine-1-carboxylic acid tert-butyl ester. Crystallisation from methanol yields the title compound as a colorless solid.
MS (m/e): 348.5 ($M+H^+$)

(b) 6-Chloro-2-piperazin-1-yl-quinoline hydrochloride



Prepared in analogy to example 1.6 (d) from 4-(6-chloro-quinolin-2-yl)-piperazine-1-carboxylic acid tert.-butyl ester and dioxane saturated with gaseous hydrochloric acid.
MS (m/e): 248.1 ($M+H^+$)

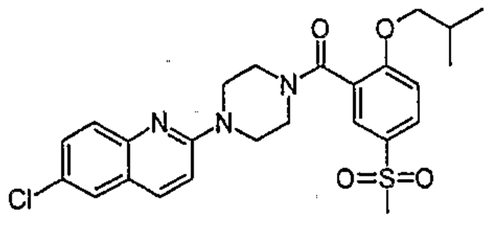
(c) [4-(6-Chloro-quinolin-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



Prepared in analogy to example 1.1 (b) from 6-chloro-2-piperazin-1-yl-quinoline hydrochloride and 2-isopropoxy-5-methanesulfonyl-benzoic acid (example 2.2) in acetonitrile.
Chromatography (SiO_2; ethyl acetate) yields the title compound as a yellowish foam.
MS (m/e): 488.1 ($M+H^+$)

Example 1.21

Preparation of [4-(6-Chloro-quinolin-2-yl)-piperazin-1-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone



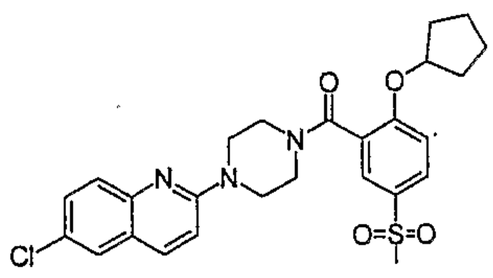
Prepared in analogy to example 1.1 (b) from 6-chloro-2-piperazin-1-yl-quinoline hydrochloride and 2-isobutoxy-5-methanesulfonyl-benzoic acid (example 2.4) in acetonitrile.

Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless solid.

MS (m/e): 503.1 ($M+H^+$)

Example 1.22

Preparation of [4-(6-Chloro-quinolin-2-yl)-piperazin-1-yl]-(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-methanone



Prepared in analogy to example 1.1 (b) from 6-chloro-2-piperazin-1-yl-quinoline hydrochloride and 2-cyclopentyloxy-5-methanesulfonyl-benzoic acid (example 2.3) in acetonitrile.

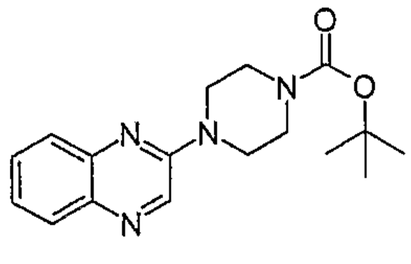
Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless solid.

MS (m/e): 515.1 ($M+H^+$)

Example 1.23

Preparation of (2-Isobutoxy-5-methanesulfonyl-phenyl)-(4-quinoxalin-2-yl-piperazin-1-yl)-methanone

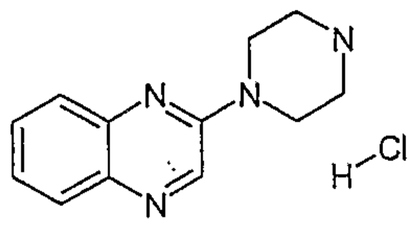
(a) 4-Quinoxalin-2-yl-piperazine-1-carboxylic acid tert.-butyl ester



A mixture of 9.1 mmol 2-chloroquinoxaline, 10.0 mmol piperazine-1-carboxylic acid tert-butyl ester, 22.8 mmol potassium carbonate and 2.1 mmol potassium iodide in 20 ml of toluene was refluxed overnight. The reaction mixture was cooled, poured into water and extracted 3 times with ethyl acetate. The organic phase was dried, evaporated and the title compound was crystallised from methanol. Yellowish solid.

MS (m/e): 315.0 ($M+H^+$)

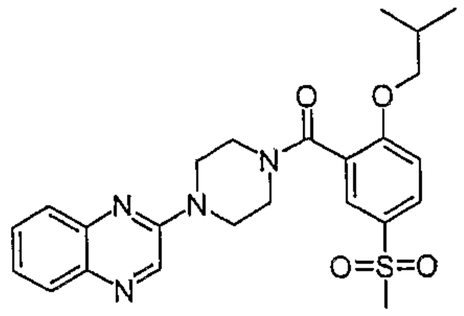
(b) 2-Piperazin-1-yl-quinoxaline hydrochloride



Prepared in analogy to example 1.6 (d) from 4-quinoxalin-2-yl-piperazine-1-carboxylic acid tert.-butyl ester and dioxane saturated with gaseous hydrochloric acid.

MS (m/e): 215.4 ($M+H^+$)

(c) 2-Isobutoxy-5-methanesulfonyl-phenyl)-(4-quinoxalin-2-yl-piperazin-1-yl)-methanone

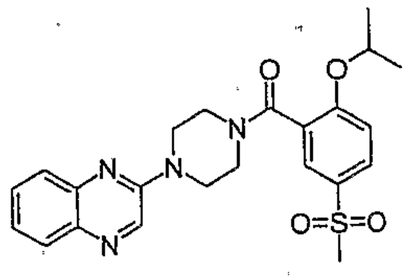


Prepared in analogy to example 1.1 (b) from 2-piperazin-1-yl-quinoxaline hydrochloride and 2-isobutoxy-5-methanesulfonyl-benzoic acid (example 2.4) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a yellowish foam.

MS (m/e): 527.3 ($M+CH_3COO$)

Example 1.24

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(4-quinoxalin-2-yl-piperazin-1-yl)-methanone

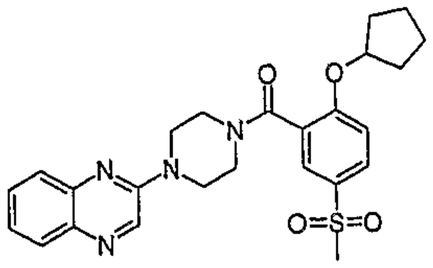


Prepared in analogy to example 1.1 (b) from 2-piperazin-1-yl-quinoxaline hydrochloride and 2-isopropoxy-5-methanesulfonyl-benzoic acid (example 2.2) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a yellowish foam.

MS (m/e): 455.5 ($M+H^+$)

Example 1.25

Preparation of (2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-(4-quinoxalin-2-yl-piperazin-1-yl)-methanone



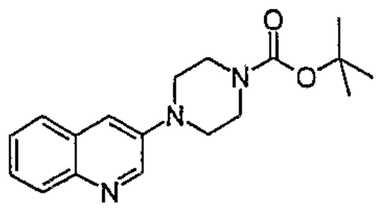
Prepared in analogy to example 1.1 (b) from 2-piperazin-1-yl-quinoxaline hydrochloride and 2-cyclopentyloxy-5-methanesulfonyl-benzoic acid (example 2.3) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a yellowish foam.

MS (m/e): 481.5 ($M+H^+$)

Example 1.26

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(4-quinolin-3-yl-piperazin-1-yl)-methanone

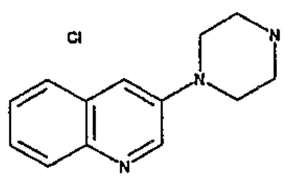
(a) 4-Quinolin-3-yl-piperazine-1-carboxylic acid tert.-butyl ester



Prepared in analogy to example 1.16 (a) from 3-bromoquinoline and piperazine-1-carboxylic acid tert-butyl ester. Chromatography (SiO_2; cyclohexane / ethyl acetate 1/1) followed by cristallisation from diethyl ether / cyclohexane yields the title product as a colorless solid.

MS (m/e): 314.2 ($M+H^+$)

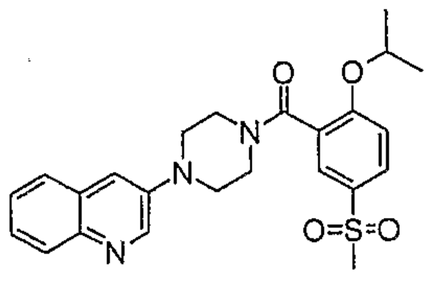
(b) 3-Piperazin-1-yl-quinoline hydrochloride



Prepared in analogy to example 1.6 (d) from 4-quinolin-3-yl-piperazine-1-carboxylic acid tert.-butyl ester and dioxane saturated with gaseous hydrochloric acid. Yellow solid.

MS (m/e): 214.4 ($M+H^+$)

(c) (2-Isopropoxy-5-methanesulfonyl-phenyl)-(4-quinolin-3-yl-piperazin-1-yl)-methanone

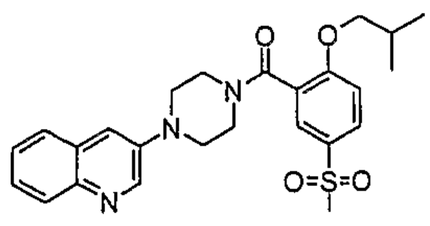


Prepared in analogy to example 1.1 (b) from 3-piperazin-1-yl-quinoline hydrochloride and 2-isopropoxy-5-methanesulfonyl-benzoic acid (example 2.2) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless foam.

MS (m/e): 454.5 ($M+H^+$)

Example 1.27

Preparation of (2-Isobutoxy-5-methanesulfonyl-phenyl)-(4-quinolin-3-yl-piperazin-1-yl)-methanone

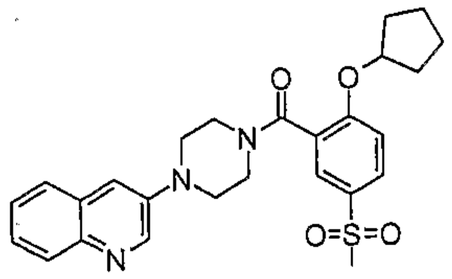


Prepared in analogy to example 1.1 (b) from 3-piperazin-1-yl-quinoline hydrochloride and 2-isobutoxy-5-methanesulfonyl-benzoic acid (example 2.4) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless solid.

MS (m/e): 468.3 ($M+H^+$)

Example 1.28

Preparation of (2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-(4-quinolin-3-yl-piperazin-1-yl)-methanone

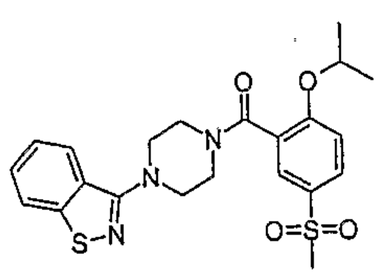


Prepared in analogy to example 1.1 (b) from 3-piperazin-1-yl-quinoline hydrochloride and 2-cyclopentyloxy-5-methanesulfonyl-benzoic acid (example 2.3) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless solid.

MS (m/e): 480.3 ($M+H^+$)

Example 1.29

Preparation of (4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

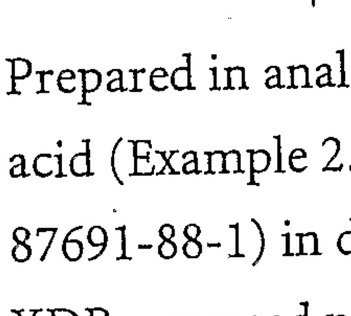


Prepared in analogy to example 1.1 b) from 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.2) and 3-piperazin-1-yl-benzo[d]isothiazole hydrochloride (CA = 87691-88-1) in dimethylformamide. The crude material was purified by HPLC (Zorbax XDB, reversed phase, water/acetonitrile) to yield the title compound as a white foam.

MS (m/e): 460.3 ($M+H^+$)

Example 1.30

Preparation of (4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-(2-diethylamino-5-methanesulfonyl-phenyl)-methanone

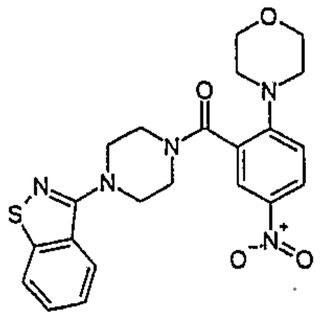


Prepared in analogy to example 1.1 b) from 2-diethylamino-5-methanesulfonyl-benzoic acid (Example 2.5) and 3-piperazin-1-yl-benzo[d]isothiazole hydrochloride (CA = 87691-88-1) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless solid.

MS (m/e): 473.4 ($M+H^+$; 100%)

Example 1.31

Preparation of (4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

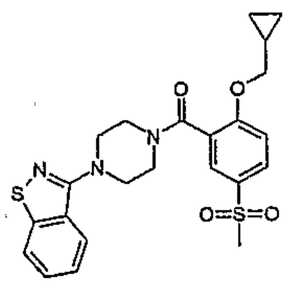


Prepared in analogy to example 1.1 b) from 2-morpholin-4-yl-5-nitro-benzoic acid (Example 2.1) and 3-piperazin-1-yl-benzo[d]isothiazole hydrochloride (CA = 87691-88-1) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless solid.

MS (m/e): 454.2 ($M+H^+$; 100%)

Example 1.32

Preparation of (4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone

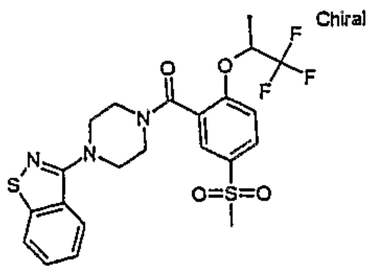


Prepared in analogy to example 1.1 b) from 2-cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (Example 2.6) and 3-piperazin-1-yl-benzo[d]isothiazole hydrochloride (CA = 87691-88-1) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless solid.

MS (m/e): 472.1 ($M+H^+$; 100%)

Example 1.33

Preparation of (4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone



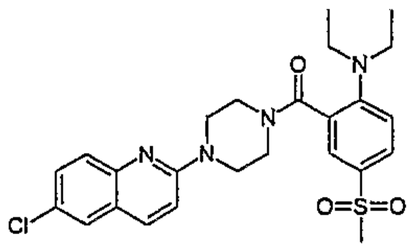
Prepared in analogy to example 1.1 b) from 5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example 2.7) and 3-piperazin-1-yl-benzo[d]isothiazole

hydrochloride (CA = 87691-88-1) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless solid.

MS (m/e): 514.1 ($M+H^+$; 37%)

Example 1.34

Preparation of [4-(6-Chloro-quinolin-2-yl)-piperazin-1-yl]-(2-diethylamino-5-methanesulfonyl-phenyl)-methanone

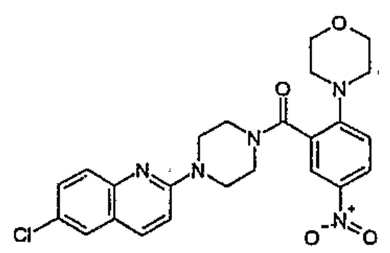


Prepared in analogy to example 1.1 b) from 6-chloro-2-piperazin-1-yl-quinoline hydrochloride (Example 1.20b) and 2-diethylamino-5-methanesulfonyl-benzoic acid (Example 2.5) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless solid.

MS (m/e): 501.4 ($M+H^+$; 100%)

Example 1.35

Preparation of [4-(6-Chloro-quinolin-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

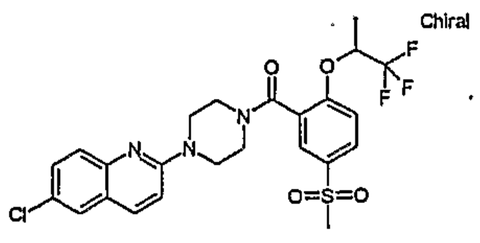


Prepared in analogy to example 1.1 b) from 6-chloro-2-piperazin-1-yl-quinoline hydrochloride (Example 1.20b) and 2-morpholin-4-yl-5-nitro-benzoic acid (Example 2.1) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless solid.

MS (m/e): 482.2 ($M+H^+$; 100%)

Example 1.36

Preparation of [4-(6-Chloro-quinolin-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone



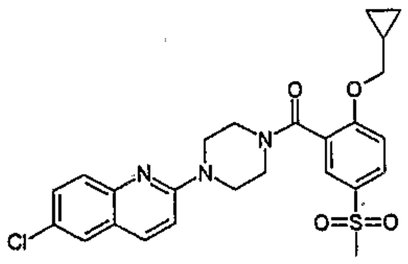
Prepared in analogy to example 1.1 b) from 6-chloro-2-piperazin-1-yl-quinoline hydrochloride (Example 1.20b) and 5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-

ethoxy)-benzoic acid (Example 2.7) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless solid.

MS (m/e): 542.3 ($M+H^+$; 100%)

Example 1.37

Preparation of [4-(6-Chloro-quinolin-2-yl)-piperazin-1-yl]-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone

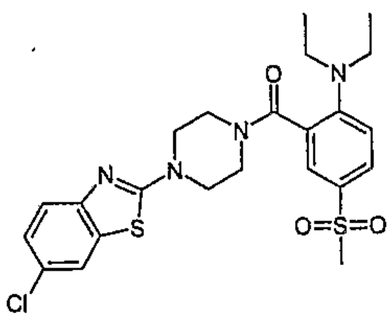


Prepared in analogy to example 1.1 b) from 6-chloro-2-piperazin-1-yl-quinoline hydrochloride (Example 1.20b) and 2-cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (Example 2.6) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless solid.

MS (m/e): 500.3 ($M+H^+$; 100%)

Example 1.38

Preparation of [4-(6-Chloro-benzothiazol-2-yl)-piperazin-1-yl]-(2-diethylamino-5-methanesulfonyl-phenyl)-methanone

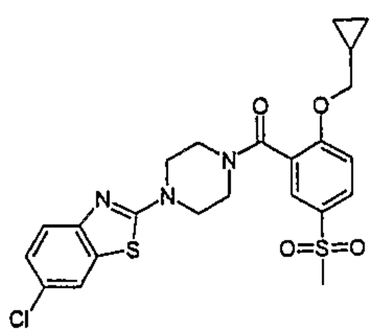


Prepared in analogy to example 1.1 b) from 5-chloro-2-piperazin-1-yl-benzothiazole (Example 1.14a) and 2-diethylamino-5-methanesulfonyl-benzoic acid (Example 2.5) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless solid.

MS (m/e): 507.5 ($M+H^+$; 100%)

Example 1.39

Preparation of [4-(6-Chloro-benzothiazol-2-yl)-piperazin-1-yl]-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone

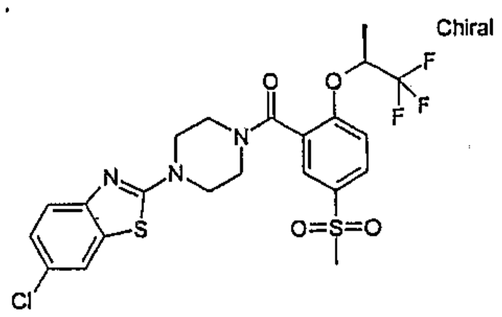


Prepared in analogy to example 1.1 b) from 5-chloro-2-piperazin-1-yl-benzothiazole (Example 1.14a) and 2-cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (Example 2.6) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless solid.

MS (m/e): 506.3 ($M+H^+$; 100%)

Example 1.40

Preparation of [4-(6-Chloro-benzothiazol-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone

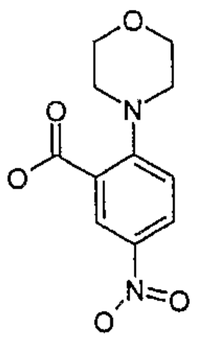


Prepared in analogy to example 1.1 b) from 5-chloro-2-piperazin-1-yl-benzothiazole (Example 1.14a) and 5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (Example 2.7) in acetonitrile. Chromatography (SiO_2; ethyl acetate) yields the title compound as a colorless solid.

MS (m/e): 548.2 ($M+H^+$; 100%)

Example 2.1

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

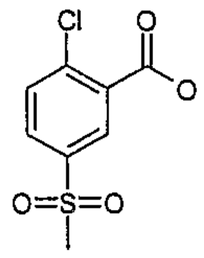


To a solution of 2-fluoro-5-nitrobenzoic acid (4.86 g, 26.2 mmol) in dioxane (50 ml) was added morpholine (11.5 ml). The mixture was stirred at room temperature for 2 hours. The solvent was removed in vacuo. The residue was dissolved in water and the mixture was acidified with HCl 2N. The solid was filtered, washed with water and dried to provide the title compound (6.2 g, 93%) as a yellow solid, MS (m/e): 251.2 (M-H, 100%).

Example 2.2

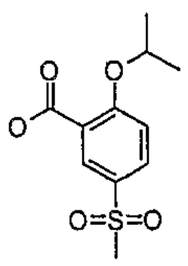
Preparation of 2-Isopropoxy-5-methanesulfonyl-benzoic acid

(a) <u>2-Chloro-5-methanesulfonyl-benzoic acid</u>



To 99 mmol 2-chloro-5-(methylthio) benzoic acid in 400 ml methanol at 0 °C 296 mmol oxone® was added and the mixture was allowed to stir at RT for 3.5 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was extracted 3 x with 400 ml ethyl acetate and the combined organic phases washed 2 x with 300 ml 1N HCl and with 300 ml saturated aqueous NaCl solution and dried with $MgSO_4$. Evaporation under reduced pressure yielded the title compound.

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

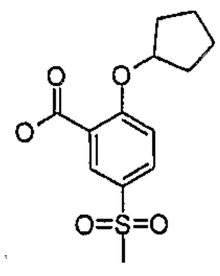


A mixture of 2.13 mmol 2-chloro-5-methanesulfonyl-benzoic acid, 0.64 mmol Cu(I)Br in 5 ml NEt_3 and 25 ml isopropanol was heated to 120 °C for 16 h in a sealed tube. The volatiles were removed under vacuum and the residue was taken up in 70 ml 1N HCl. Extraction with ethyl acetate drying of the combined organic fractions and evaporation yielded a residue which was purified by reversed phase preparative HPLC eluting with an acetonitrile / water gradient. Evaporation of the product fractions yielded the title compound

MS (m/e): 257.0 (MH^-, 100%).

Example 2.3

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

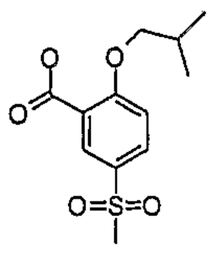


Prepared in analogy to example 2.2 (b) from 2-chloro-5-methanesulfonyl-benzoic acid and cyclopentanol.

MS (m/e): 282.9 (MH^-, 100 %)

Example 2.4

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



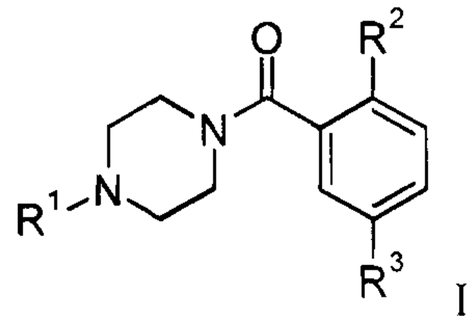
Prepared in analogy to example 2.2 (b) from from 2-chloro-5-methanesulfonyl-benzoic acid and isobutanol.

MS (m/e): 271.1 (MH^-, 100 %)

5

CLAIMS:

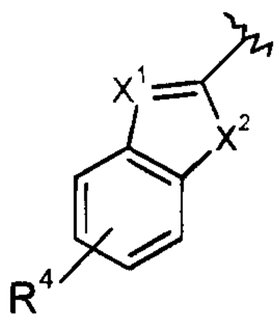
1. A compound of general formula



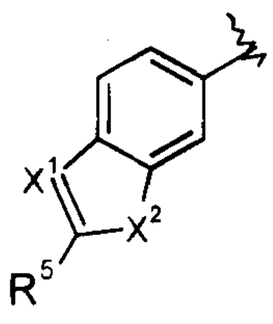
I

wherein

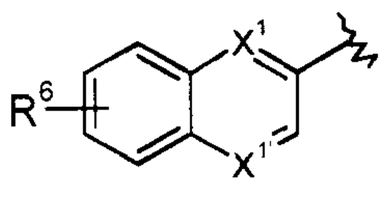
R^1 is the group



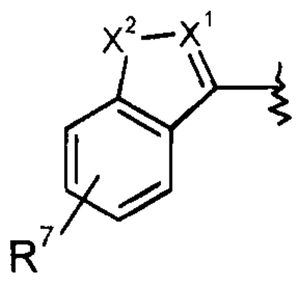
A or



B or



C or



D;

R^2 is a morpholino, OR', or $N(R'')_2$;

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

R'' is lower alkyl;

R^3 is NO_2, CN or SO_2R';

R^4 is hydrogen, hydroxy, halogen, NO_2, lower alkyl, lower alkyl, substituted by halogen, lower alkoxy, SO_2R' or C(O)OR'';

$R^5/R^6/R^7$ are hydrogen, halogen, lower alkyl or lower alkyl, substituted by halogen;

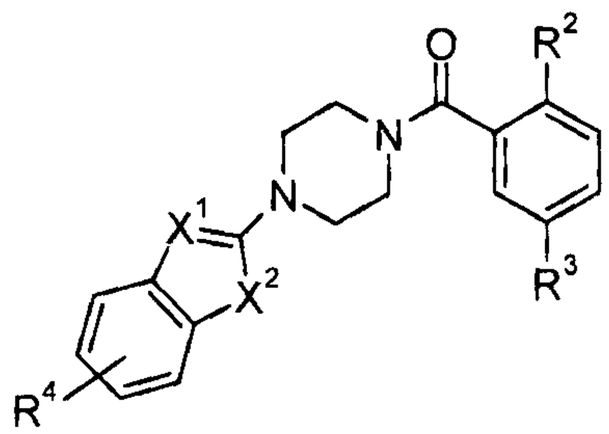
$X^1/X^{1'}$ are CH or N, with the proviso that $X^1/X^{1'}$ are not simultaneously CH;

X^2 is O, S, NH or N(lower alkyl);

n is 0, 1 or 2;

and pharmaceutically active acid addition salts.

2. Compound of formula IA according to claim 1 for R^1 is A,



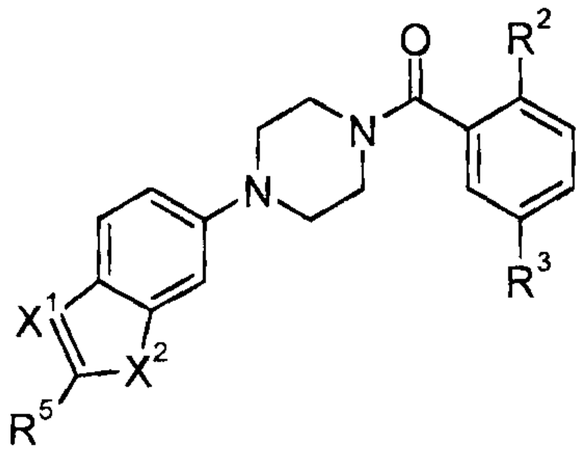
IA

wherein

R^2	is a morpholino, OR', or $N(R'')_2$;
R'	is lower alkyl, lower alkyl, substituted by halogen or $-(CH_2)_n$-cycloalkyl;
R''	is lower alkyl;
R^3	is NO_2, CN or SO_2R';
R^4	is hydrogen, hydroxy, halogen, NO_2, lower alkyl, lower alkyl, substituted by halogen, lower alkoxy, SO_2R' or C(O)OR'';
X^1	is CH or N;
X^2	is O, S, NH or N(lower alkyl);
n	is 0, 1 or 2;

and pharmaceutically active acid addition salts.

3. Compound of formula IB according to claim 1 for R^1 is B,



IB

wherein

R^2	is a morpholino, OR', or $N(R'')_2$;
R'	is lower alkyl, lower alkyl, substituted by halogen or $-(CH_2)_n$-cycloalkyl;
R''	is lower alkyl;
R^3	is NO_2, CN or SO_2R';

R^5 is hydrogen, halogen, lower alkyl or lower alkyl, substituted by halogen;

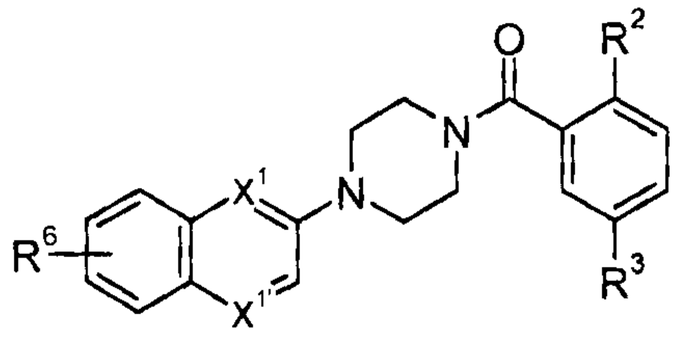
X^1 is CH or N;

X^2 is O, S, NH or N(lower alkyl);

n is 0, 1 or 2;

and pharmaceutically active acid addition salts.

4. Compound of formula IC according to claim 1 for R^1 is C,



IC

wherein

R^2 is a morpholino, OR', or $N(R'')_2$;

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

R'' is lower alkyl;

R^3 is NO_2, CN or SO_2R';

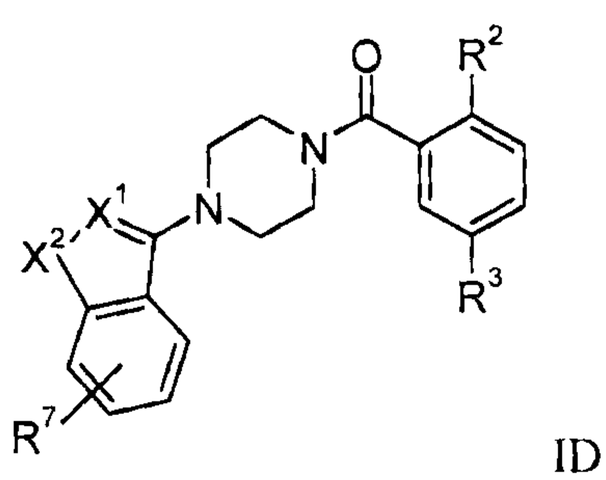
R^6 is hydrogen, halogen, lower alkyl or lower alkyl, substituted by halogen;

$X^1/X^{1'}$ are CH or N, with the proviso that $X^1/X^{1'}$ are not simultaneously CH;

n is 0, 1 or 2;

and pharmaceutically active acid addition salts.

5. Compound of formula ID according to claim 1 for R^1 is D,



ID

wherein

R^2	is a morpholino, OR', or $N(R'')_2$;
R'	is lower alkyl, lower alkyl, substituted by halogen or $-(CH_2)_n$-cycloalkyl;
R''	is lower alkyl;
R^3	is NO_2, CN or SO_2R';
R^7	is hydrogen, halogen, lower alkyl or lower alkyl, substituted by halogen;
X^1	is CH or N;
X^2	is O, S, NH or N(lower alkyl);
n	is 0, 1 or 2;

and pharmaceutically active acid addition salts.

6. Compound of formula IA according to claim 2, which compound is [4-(6-chloro-benzothiazol-2-yl)-piperazin-1-yl]-(2-morpholin-4-yl-5-nitro-phenyl)-methanone.

7. Compound of formula IA according to claim 2, which compound is [4-(6-chloro-benzothiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone.

8. Compound of formula IA according to claim 2, which compound is (4-benzooxazol-2-yl-piperazin-1-yl)-(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-methanone.

9. Compound of formula IA according to claim 2, which compound is (4-benzooxazol-2-yl-piperazin-1-yl)-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone.

10. Compound of formula IA according to claim 2, which compound is (2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(6-methoxy-benzothiazol-2-yl)-piperazin-1-yl]-methanone.

11. Compound of formula IA according to claim 2, which compound is (2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(6-nitro-benzothiazol-2-yl)-piperazin-1-yl]-methanone.

12 Compound of formula IA according to claim 2, which compound is (2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-methoxy-benzothiazol-2-yl)-piperazin-1-yl]-methanone.

13. Compound of formula IA according to claim 2, which compound is (2-isopropoxy-5-methanesulfonyl-phenyl)-[4-(4-nitro-benzothiazol-2-yl)-piperazin-1-yl]-methanone.

14. Compound of formula IA according to claim 2, which compound is [4-(4-hydroxy-benzothiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone.

15. Compound of formula IA according to claim 2, which compound is [4-(5-chloro-benzothiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone.

16. Compound of formula IA according to claim 2, which compound is [4-(6-ethoxy-benzothiazol-2-yl)-piperazin-1-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone.

17. Compound of formula IA according to claim 2, which compound is [4-(6-chloro-benzothiazol-2-yl)-piperazin-1-yl]-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone.

18. Compound of formula IA according to claim 2, which compound is [4-(6-chloro-benzothiazol-2-yl)-piperazin-1-yl]-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone.

19. Compound of formula IB according to claim 3, which compound is (2-isobutoxy-5-methanesulfonyl-phenyl)-[4-(2-methyl-benzothiazol-5-yl)-piperazin-1-yl]-methanone.

20. Compound of formula IC according to claim 4, which compound is (2-isobutoxy-5-methanesulfonyl-phenyl)-(4-quinolin-2-yl-piperazin-1-yl)-methanone.

21. Compound of formula IC according to claim 4, which compound is [4-(6-chloro-quinolin-2-yl)-piperazin-1-yl]-(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-methanone.

22. Compound of formula IC according to claim 4, which compound is (2-isobutoxy-5-methanesulfonyl-phenyl)-(4-quinoxalin-2-yl-piperazin-1-yl)-methanone.

23. Compound of formula IC according to claim 4, which compound is (2-isopropoxy-5-methanesulfonyl-phenyl)-(4-quinoxalin-2-yl-piperazin-1-yl)-methanone.

24. Compound of formula IC according to claim 4, which compound is (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-(4-quinoxalin-2-yl-piperazin-1-yl)-methanone.

25. Compound of formula IC according to claim 4, which compound is (2-isobutoxy-5-methanesulfonyl-phenyl)-(4-quinolin-3-yl-piperazin-1-yl)-methanone.

26. Compound of formula IC according to claim 4, which compound is (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-(4-quinolin-3-yl-piperazin-1-yl)-methanone.

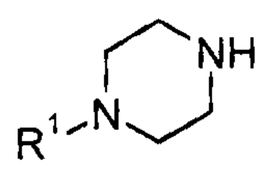
27. Compound of formula ID according to claim 5, which compound is (4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone.

28. Compound of formula ID according to claim 5, which compound is (4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone.

29. Compound of formula ID according to claim 5, which compound is (4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone.

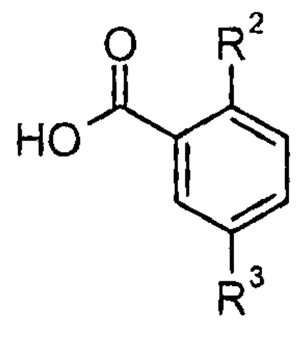
30. A process for preparing a compound of formula I as defined in claim 1, which process comprises

a) reacting a compound of formula



II

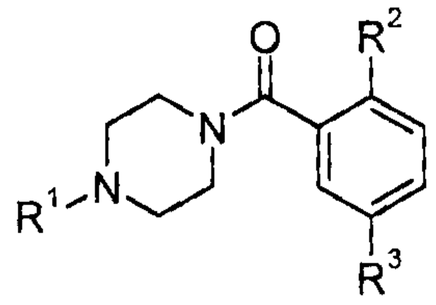
with a compound of formula



III

in the presence of an activating agent

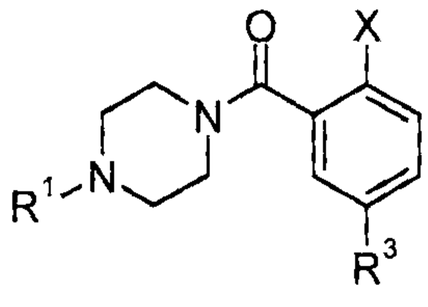
to a compound of formula



I

wherein the substituents are as defined in claim 1, or

b) reacting a compound of formula



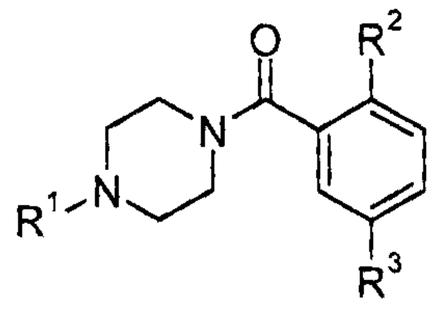
IV

with a compound of formula

R^2H V

in the presence of a base or with addition of a catalyst

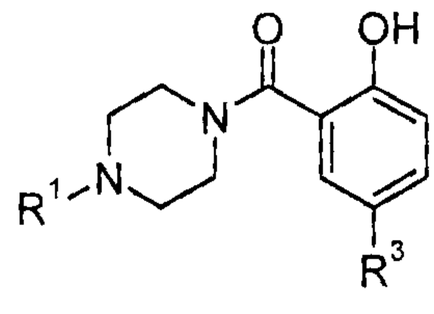
to a compound of formula



I

wherein the substituents R^1, R^2 and R^3 are as defined in claim 1, and X is halogen, or

c) reacting a compound of formula

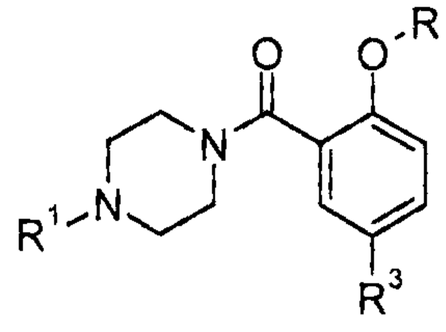


II

with a compound of formula

R'X VI

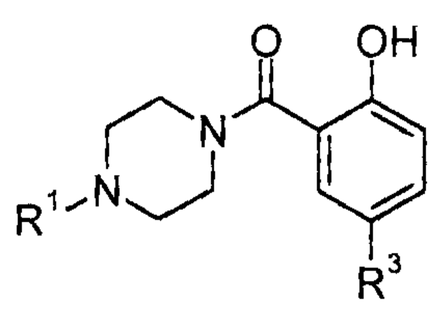
to a compound of formula



I2

wherein the substituents R^1, R' and R^3 are as defined in claim 1 and X is halogen;
or

d) reacting a compound of formula



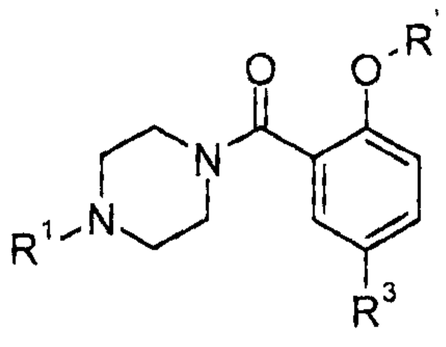
I1

with a compound of formula

R'OH VII

under Mitsunobu conditions

to a compound of formula



I2

wherein the substituents R^1, R' and R^3 are as defined above,
and

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

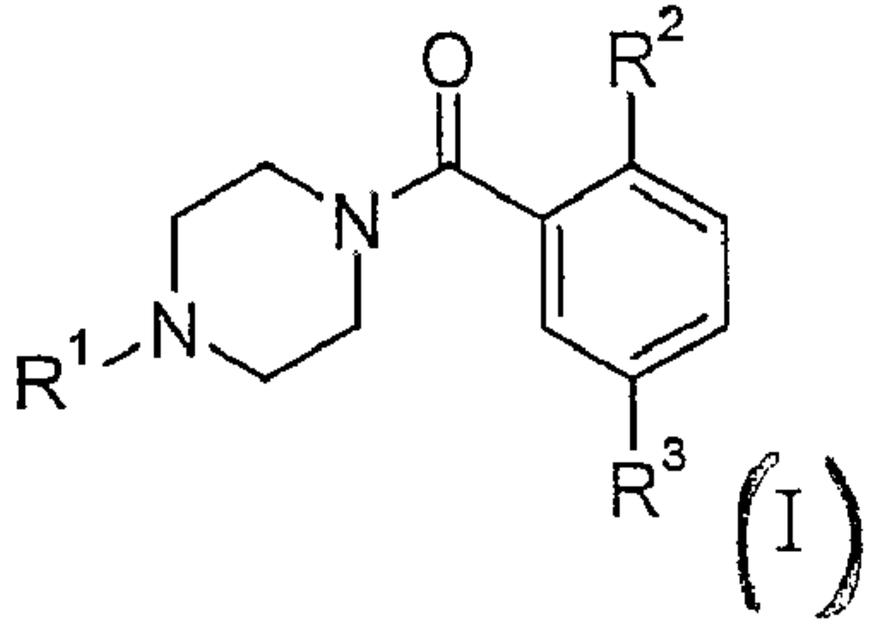
31. A pharmaceutical composition containing one or more compounds as claimed in any one of claims 1 to 29 and pharmaceutically acceptable excipients.

32. A pharmaceutical composition according to claim 31 for the treatment of Alzheimer's disease.

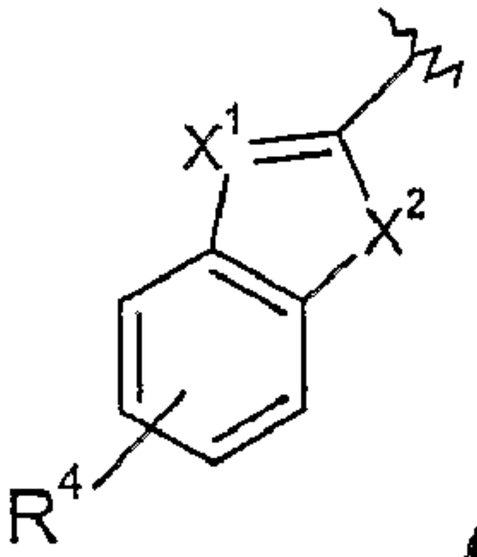
33. The use of a compound in any one of claims 1 to 29 for the manufacture of a medicament for the treatment of Alzheimer's disease.

34. The use of a compound in any one of claims 1 to 29, for the treatment of Alzheimer's disease.

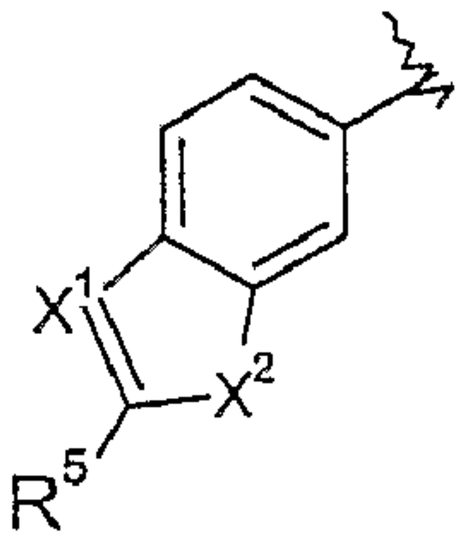
35. A commercial package comprising the compound according to any one of claims 1 to 29 together with instructions for its use for the treatment of Alzheimer's disease.



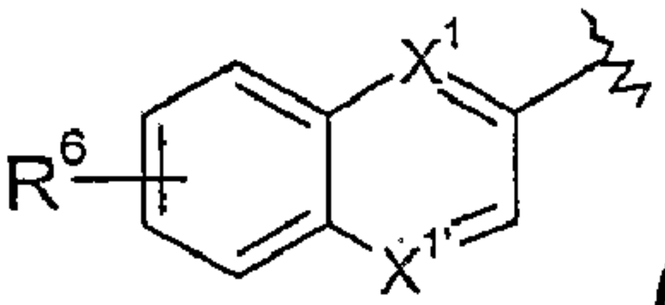
(I)



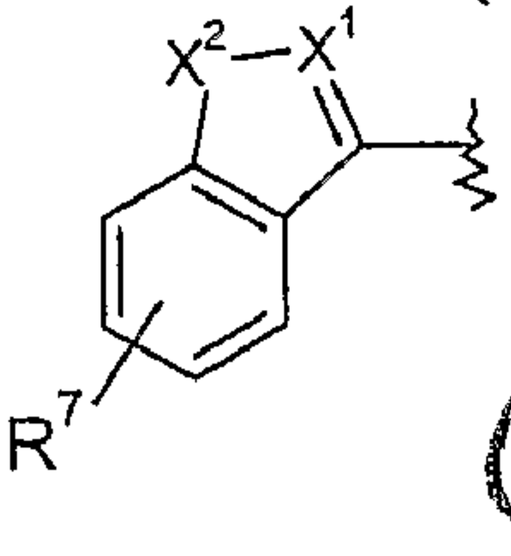
(A)



(B)



(C)



(D)