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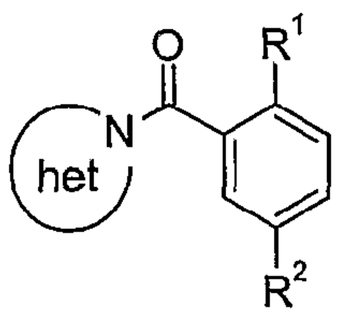
(54) Titre : UTILISATION DE PHENYLMETHANONES SUBSTITUEES BICYCLIQUES ET TRICYCLIQUES COMME INHIBITEURS DES TRANSPORTEURS DE LA GLYCINE I (GLYT-1) POUR TRAITER LA MALADIE D'ALZHEIMER

(54) Title: BI- AND TRICYCLIC SUBSTITUTED PHENYL METHANONES AS GLYCINE TRANSPORTER I (GLYT-1) INHIBITORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE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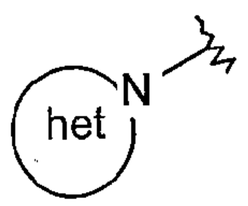
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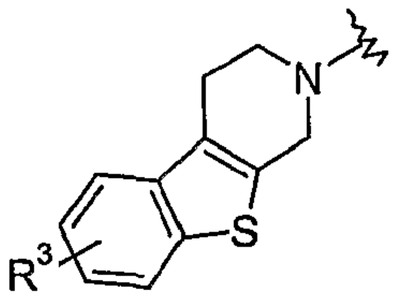
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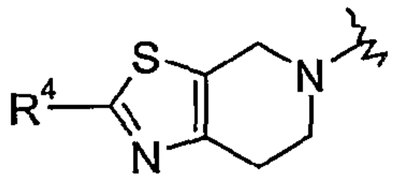
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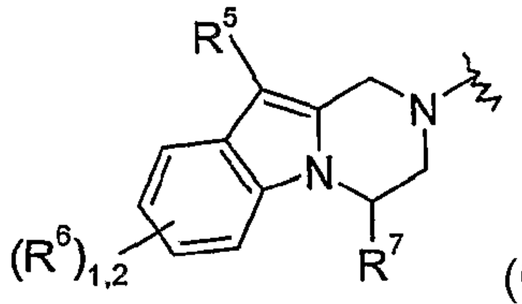
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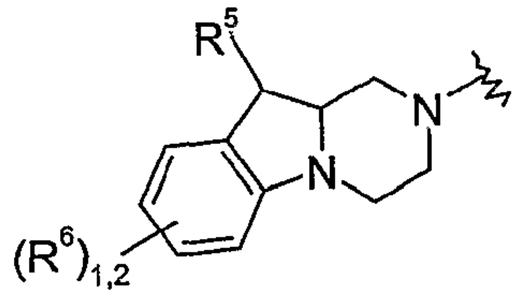
(D)

(E)

(F)

(57) Abrégé/Abstract:
The present invention relates to compounds of the general formula (I), wherein formula (II) is A or B or C or D or E or F. R^1 is a non aromatic heterocycle, or is OR' or $N(R'')_2$; R' is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_{ri}$ cycloalkyl; R'' is lower

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(13) A1

(57) Abrégé(suite)/Abstract(continued):
alkyl; R^2 is NO_2, CN or SO_2R''; R^3 is hydrogen, halogen, lower alkyl, lower alkoxy, or lower alkyl substituted by halogen; R^4 is hydrogen, lower alkyl, phenyl substituted by halogen or CF_3, or is a five or six membered aromatic heterocycle; R^5/R^6 are hydrogen, halogen, lower alkyl, lower alkoxy, or are lower alkyl or lower alkoxy, substituted by halogen; R^7 is hydrogen or lower alkyl; n is 0, 1 or 2; and to pharmaceutically active acid addition salts for the treatment of neurological and neuropsychiatric disorders.

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(74) Agent: **POPPE, Regina**; Grenzacherstrasse 124, CH-4070 Basel (CH).

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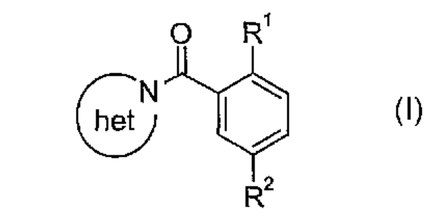
(54) Title: BI- AND TRICYCLIC SUBSTITUTED PHENYL METHANONES AS GLYCINE TRANSPORTER I (GLYT-1) INHIBITORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE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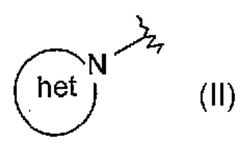
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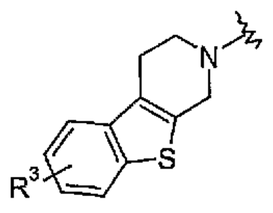
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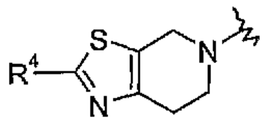
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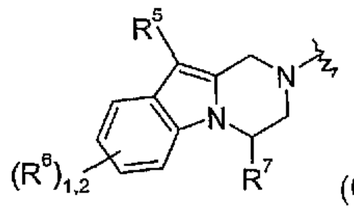
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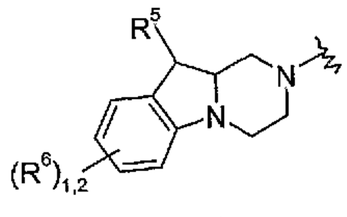
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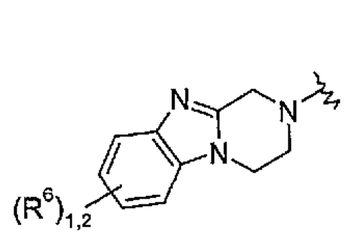
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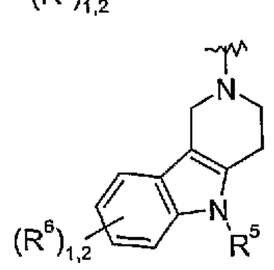
(F)

(57) Abstract: The present invention relates to compounds of the general formula (I), wherein formula (II) is A or B or C or D or E or F. R^1 is a non aromatic heterocycle, or is OR' or $N(R")_2$; R' is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_{ri}$ cycloalkyl; R" is lower alkyl; R^2 is NO_2, CN or $SO_2R"$; R^3 is hydrogen, halogen, lower alkyl, lower alkoxy, or lower alkyl substituted by halogen; R^4 is hydrogen, lower alkyl, phenyl substituted by halogen or CF_3, or is a five or six membered aromatic heterocycle; R^5/R^6 are hydrogen, halogen, lower alkyl, lower alkoxy, or are lower alkyl or lower alkoxy, substituted by halogen; R^7 is hydrogen or lower alkyl; n is 0, 1 or 2; and to pharmaceutically active acid addition salts for the treatment of neurological and neuropsychiatric disorders.

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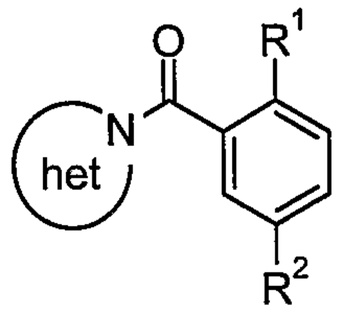
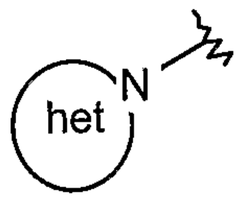
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

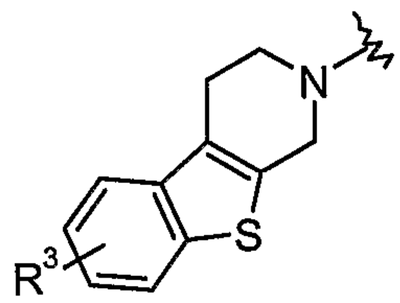
BI- AND TRICYCLIC SUBSTITUTED PHENYL METHANONES AS GLYCINE TRANSPORTER I (GLYT-1) INHIBITORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE.

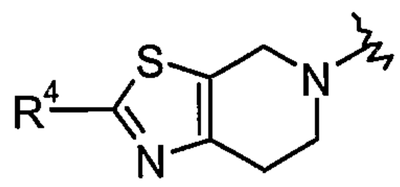
The present invention relates to compounds of the general formula I

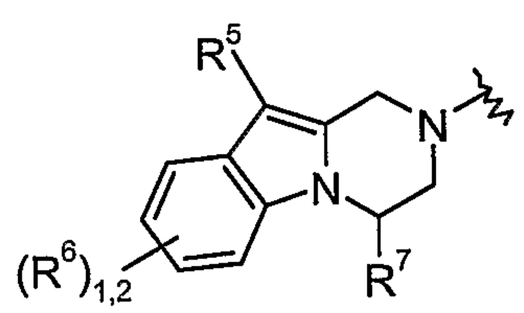


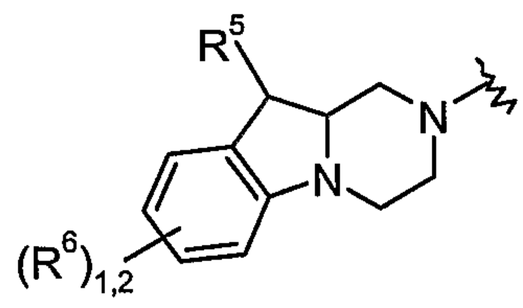
I

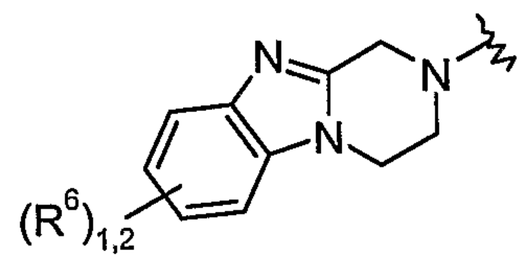
wherein  is

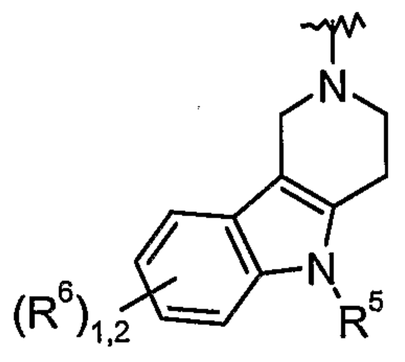


A or 

B or 

C or 

D or 

E or 

F

R^1 is a non aromatic heterocycle, or is OR' or $N(R'')_2$;

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

R'' is lower alkyl;

R^2 is NO_2, CN or SO_2R'';

R^3 is hydrogen, halogen, lower alkyl, lower alkoxy, or lower alkyl substituted by halogen;

R^4 is hydrogen, lower alkyl, phenyl substituted by halogen or CF_3, or is a five or six membered aromatic heterocycle;

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

R^7 is hydrogen or lower alkyl;

n is 0, 1 or 2;

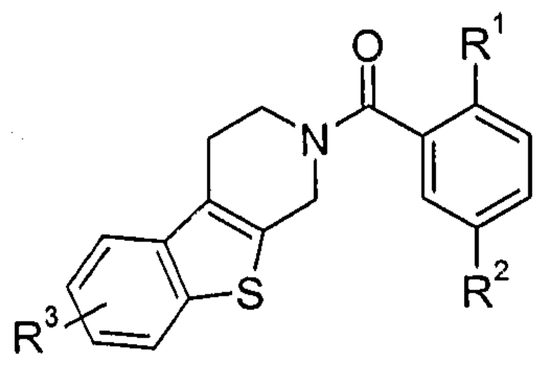
and to pharmaceutically active acid addition salts.

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, ID, IE and IF are encompassed by the present invention:

Compounds of formula IA



IA

wherein

R^1 is a non aromatic heterocycle, or is OR' or $N(R'')_2$;

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

R'' is lower alkyl;

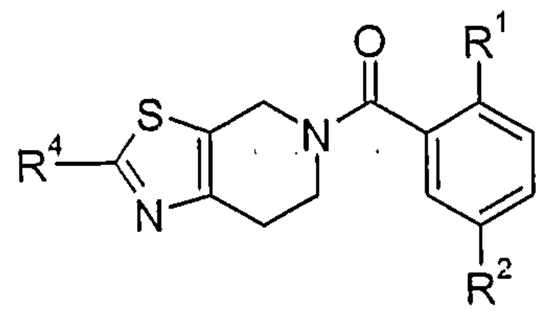
R^2 is NO_2, CN or SO_2R'';

R^3 is hydrogen, halogen, lower alkyl, lower alkoxy, or lower alkyl substituted by halogen;

n is 0, 1 or 2;

and pharmaceutically active acid addition salts.

Compounds of formula IB



IB

wherein

R^1 is a non aromatic heterocycle, or is OR' or $N(R'')_2$;

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

R'' is lower alkyl;

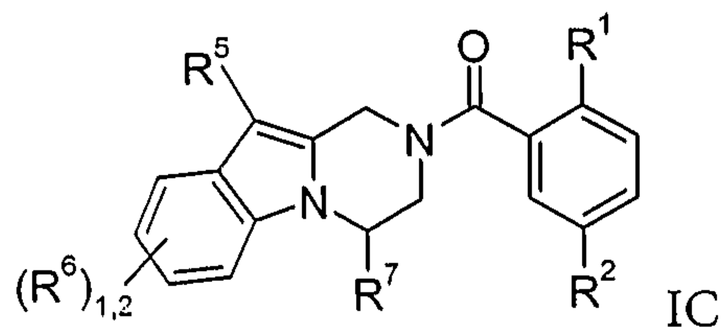
R^2 is NO_2, CN or SO_2R'';

R^4 is hydrogen, lower alkyl, phenyl substituted by halogen or CF_3, or is a five or six membered aromatic heterocycle;

n is 0, 1 or 2;

and pharmaceutically active acid addition salts.

Compounds of formula IC



IC

wherein

R^1 is a non aromatic heterocycle, or is OR' or $N(R'')_2$;

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

R'' is lower alkyl;

R^2 is NO_2, CN or SO_2R'';

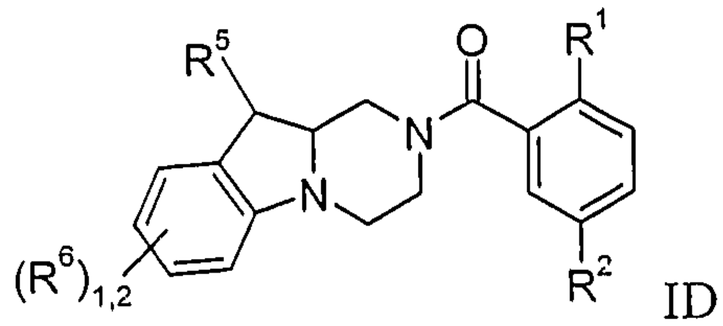
R^5/R^6 are hydrogen, halogen, lower alkyl, lower alkoxy, or are lower alkyl or lower alkoxy, substituted by halogen;

R^7 is hydrogen or lower alkyl;

n is 0, 1 or 2;

and pharmaceutically active acid addition salts.

Compounds of formula ID



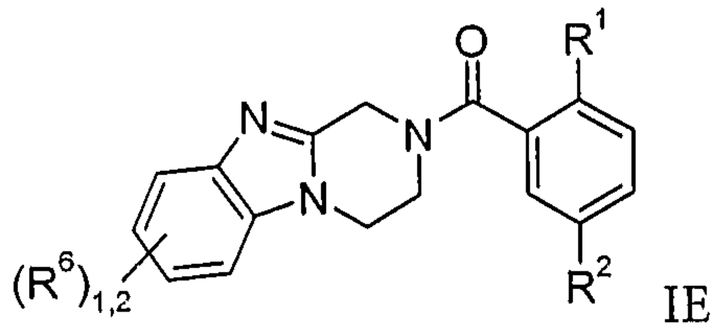
ID

wherein

R^1	is a non aromatic heterocycle, or is OR' or $N(R'')_2$;
R'	is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$-cycloalkyl;
R''	is lower alkyl;
R^2	is NO_2, CN or SO_2R'';
R^5/R^6	are hydrogen, halogen, lower alkyl, lower alkoxy, or are lower alkyl or lower alkoxy, substituted by halogen;
n	is 0, 1 or 2;

and pharmaceutically active acid addition salts.

Compounds of formula IE



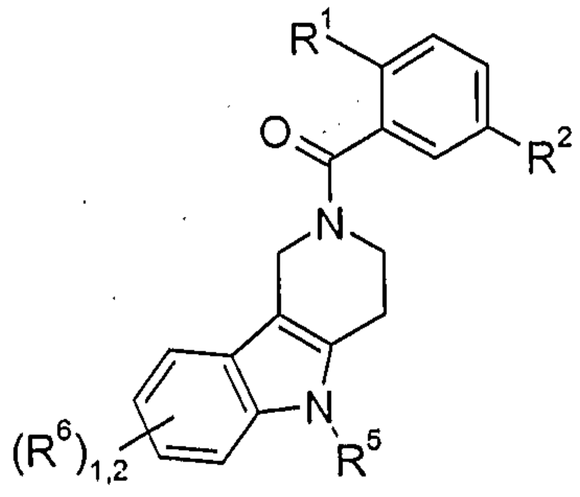
IE

wherein

R^1	is a non aromatic heterocycle, or is OR' or $N(R'')_2$;
R'	is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$-cycloalkyl;
R''	is lower alkyl;
R^2	is NO_2, CN or SO_2R'';
R^6	are hydrogen, halogen, lower alkyl, lower alkoxy, or are lower alkyl or lower alkoxy, substituted by halogen;
n	is 0, 1 or 2;

and pharmaceutically active acid addition salts.

Compounds of formula IF



IF

wherein

R^1	is a non aromatic heterocycle, or is OR' or $N(R'')_2$;
R'	is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$-cycloalkyl;
R''	is lower alkyl;
R^2	is NO_2, CN or SO_2R'';
R^5/R^6	are hydrogen, halogen, lower alkyl, lower alkoxy, or are lower alkyl or lower alkoxy, substituted by halogen;
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 neuroligical 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 "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 "five or six membered aromatic heterocycle" denotes an aromatic ring having one, two or three heteroatoms, furanyl, thiophenyl, pyrrolyl, pyridinyl and the like.

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, $CH(CH_3)CF_3$, 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.

Preferred compounds of formula IA are the followings:

(6-Chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
(6-Chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridin-2-yl)-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone,
3-(6-chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridine-2-carbonyl)-4-isopropoxy-benzonitrile,
(6-chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridin-2-yl)-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone or
(6-chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridin-2-yl)-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone.

Preferred compounds of formula IB are

(2-isobutoxy-5-methanesulfonyl-phenyl)-(2-thiophen-2-yl-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridin-5-yl)-methanone,
(2-isopropoxy-5-methanesulfonyl-phenyl)-(2-thiophen-2-yl-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridin-5-yl)-methanone or
(2-isobutoxy-5-methanesulfonyl-phenyl)-[2-(4-trifluoromethyl-phenyl)-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-5-yl]-methanone.

Preferred compounds of formula IC are

(7-chloro-3,4-dihydro-1H-pyrazino[1,2-a]indol-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone or
(2-isopropoxy-5-methanesulfonyl-phenyl)-(8-trifluoromethoxy-3,4-dihydro-1H-pyrazino[1,2-a]indol-2-yl)-methanone.

A preferred compound of formula ID is

Rac-(2-isopropoxy-5-methanesulfonyl-phenyl)-(8-trifluoromethoxy-3,4,10,10a-tetrahydro-1H-pyrazino[1,2-a]indol-2-yl)-methanone.

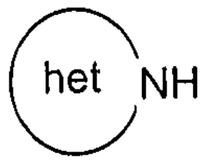
A preferred compound of formula IE is

(2-cyclopentyloxy-5-methanesulfonyl-phenyl)-(3,4-dihydro-1H-benzo[4,5]imidazo[1,2-a]pyrazin-2-yl)-methanone.

Compounds of formula IF are also preferred.

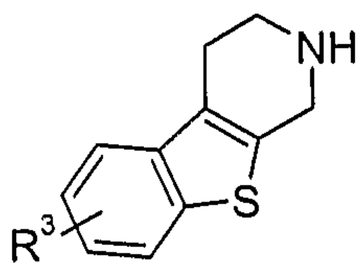
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

a) reacting a compound of formula

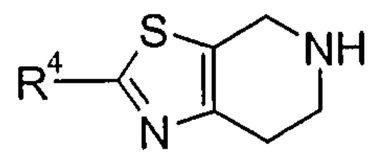


II

selecting from the group consisting of

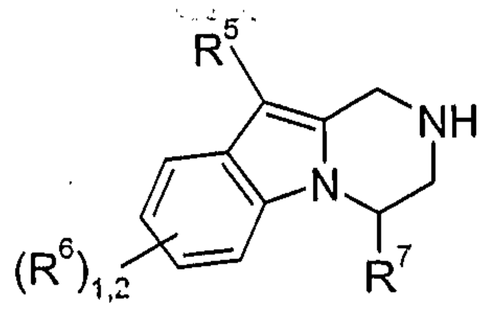


IIA or

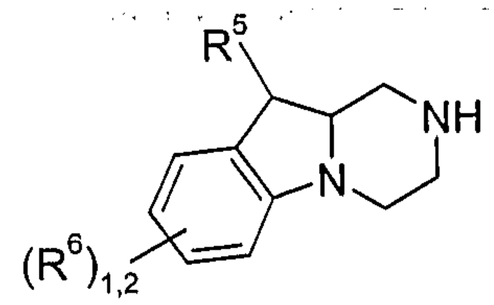


IIB

or

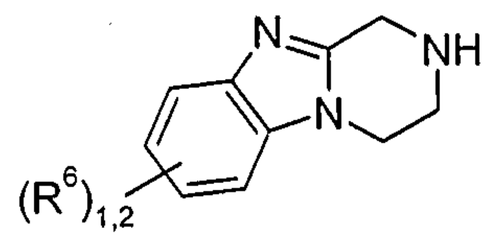


IIC or

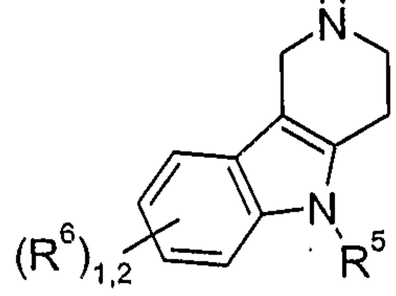


IID

or

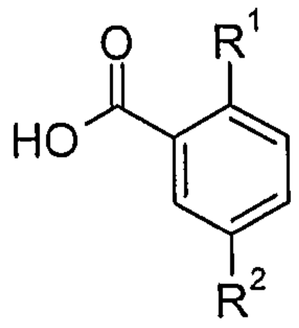


IIE or



IIF

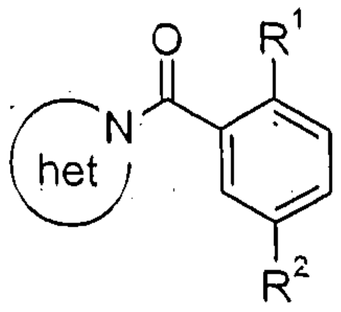
with a compound of formula



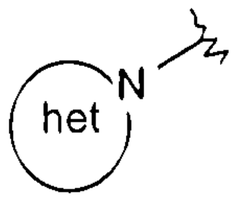
III

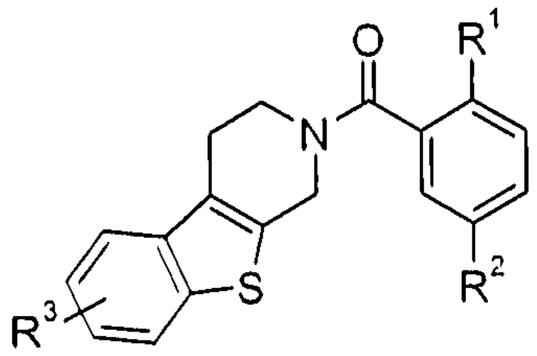
in the presence of an activating agent, such as TBTU,

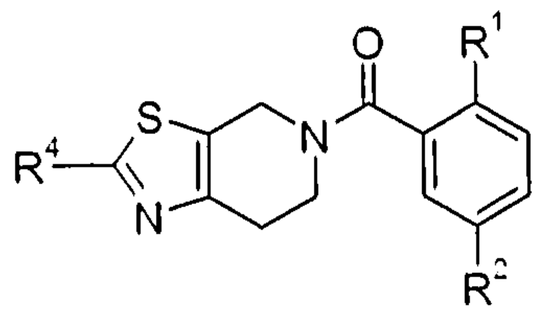
to a compound of formula



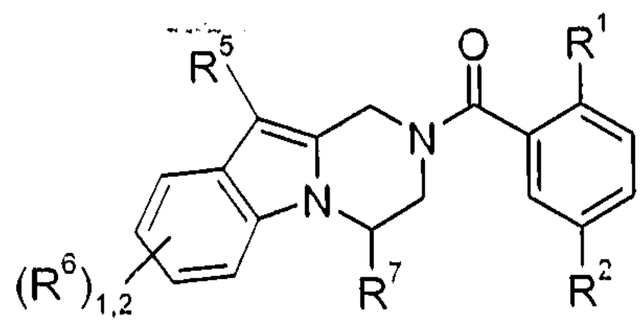
I,

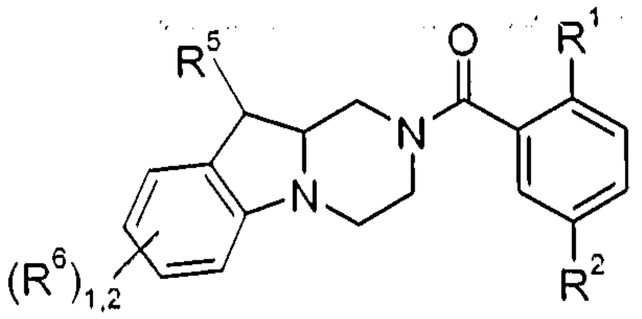
wherein in dependency of  the following structures are encompassed by formula I



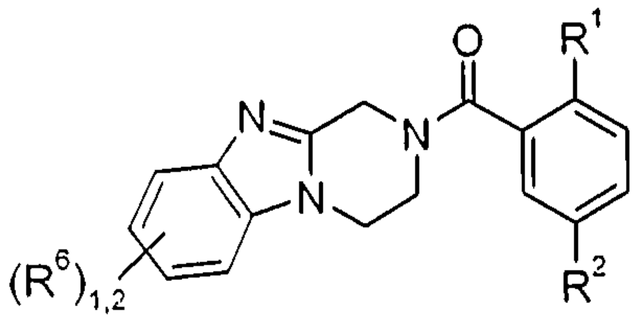
IA or 

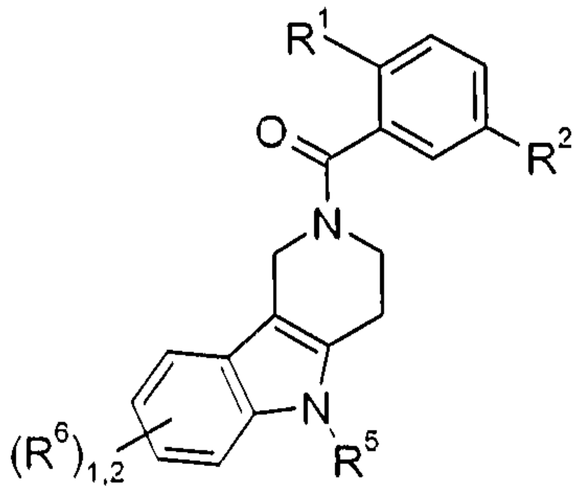
IB or



IC or 

ID or

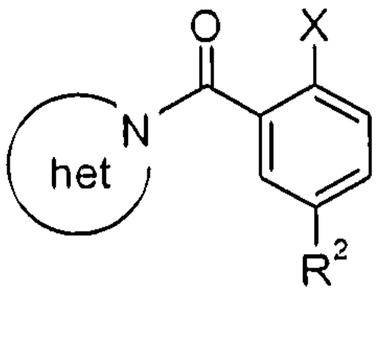


IE or 

IF

wherein the substituents are as defined above, or

b) reacting a compound of formula



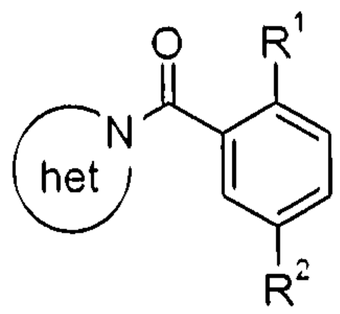
IV

with a compound of formula

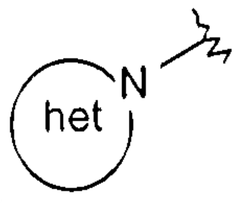
R^1H V

in the presence of a base, such as triethylamine, or a catalyst like Cu(I)Br,

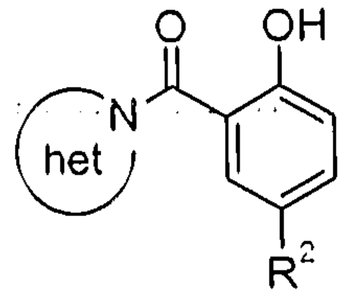
to a compound of formula



I

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

c) reacting a compound of formula

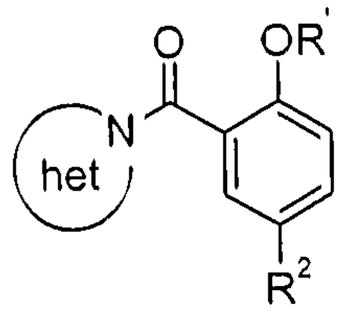


VI

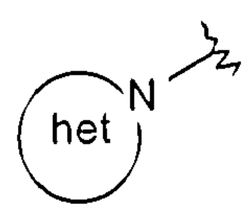
with a compound of formula

$R'X$ VII

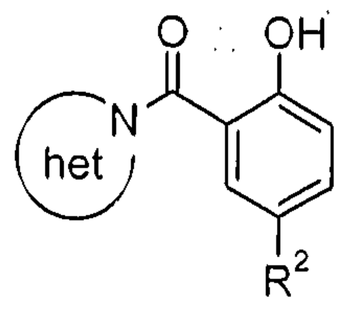
to a compound of formula



I1

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

d) reacting a compound of formula



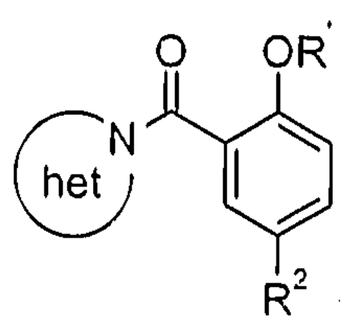
VI

with a compound of formula

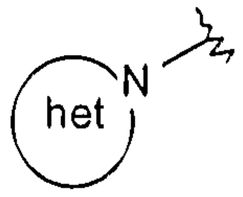
R'OH VIII

under Mitsunobu conditions

to a compound of formula



I1

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

and

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

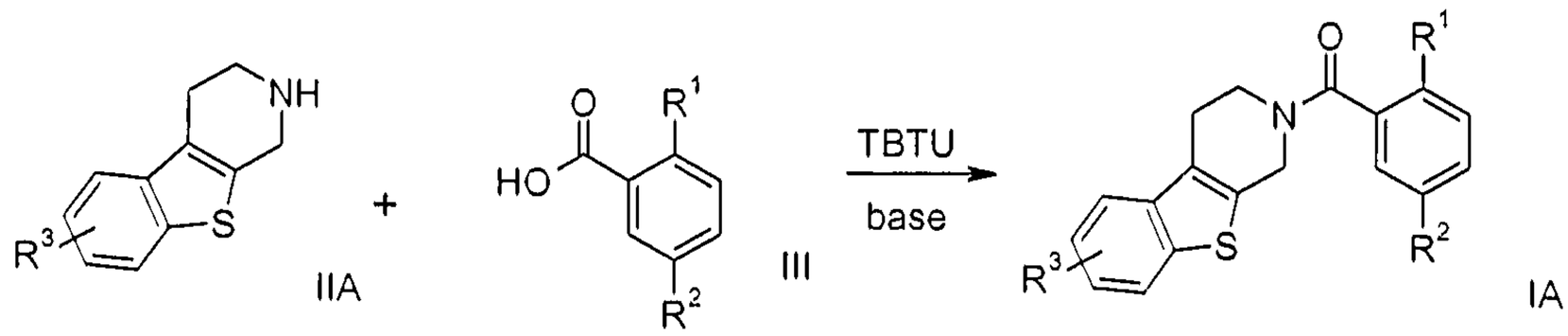
The compounds of formula I may be prepared in accordance with process variants a), b) c) or d) and with the following schemes 1, 2, 3 and 4. All starting materials are either commercially available, described in the literature or can be prepared by methods well known in the art.

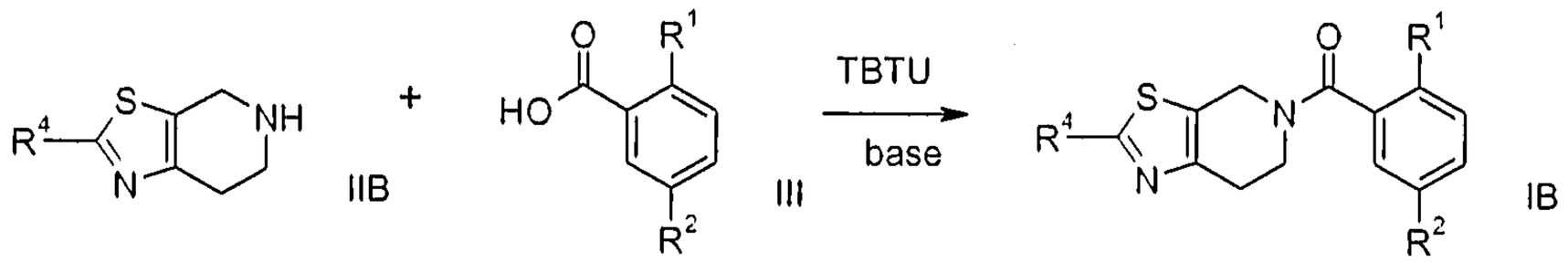
The following abbreviation has been used:

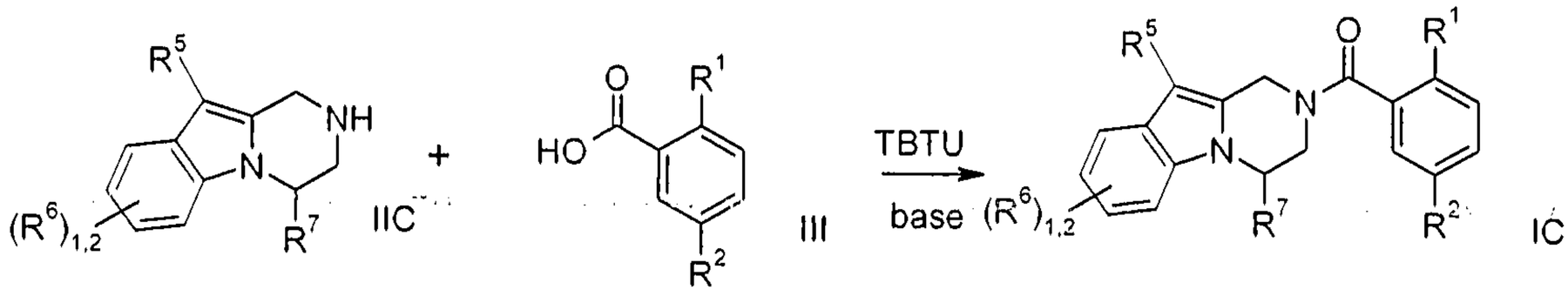
TBTU = (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate)

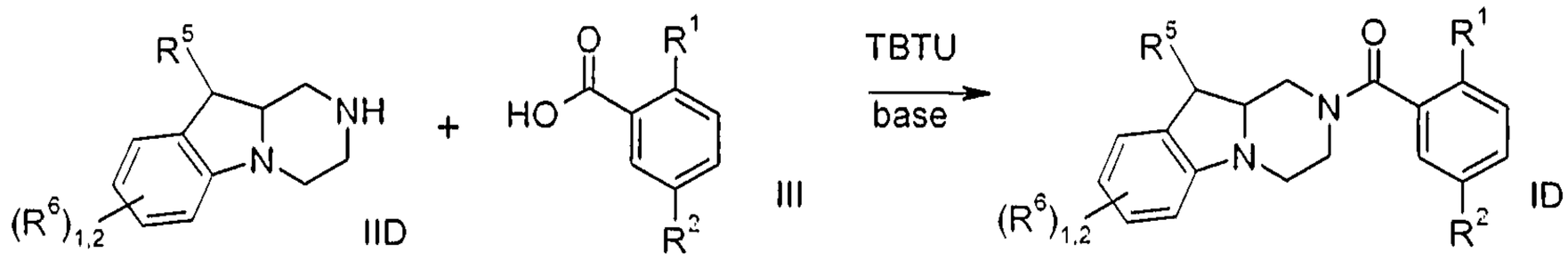
Scheme 1

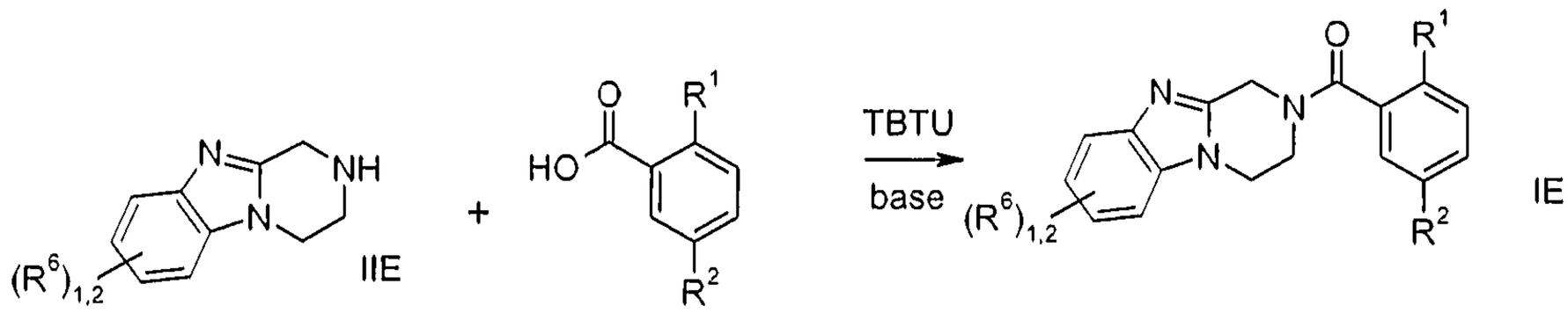
Preparation of compounds of formulas IA, IB, IC, ID, IE and IF

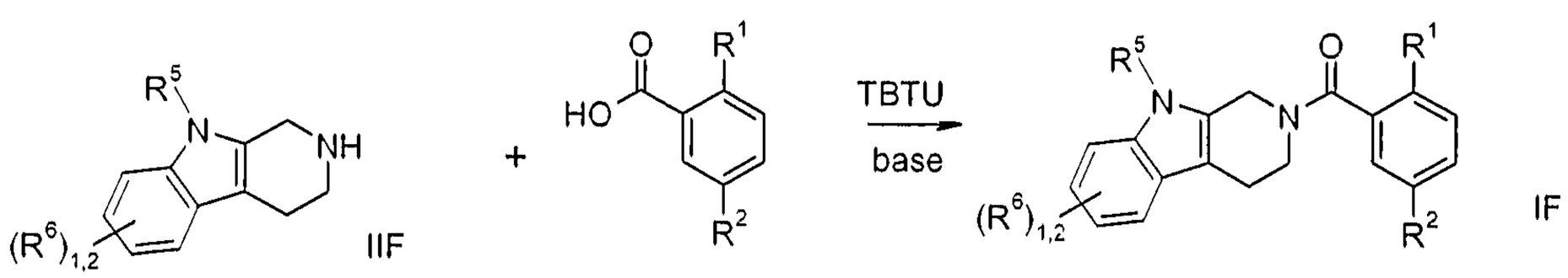










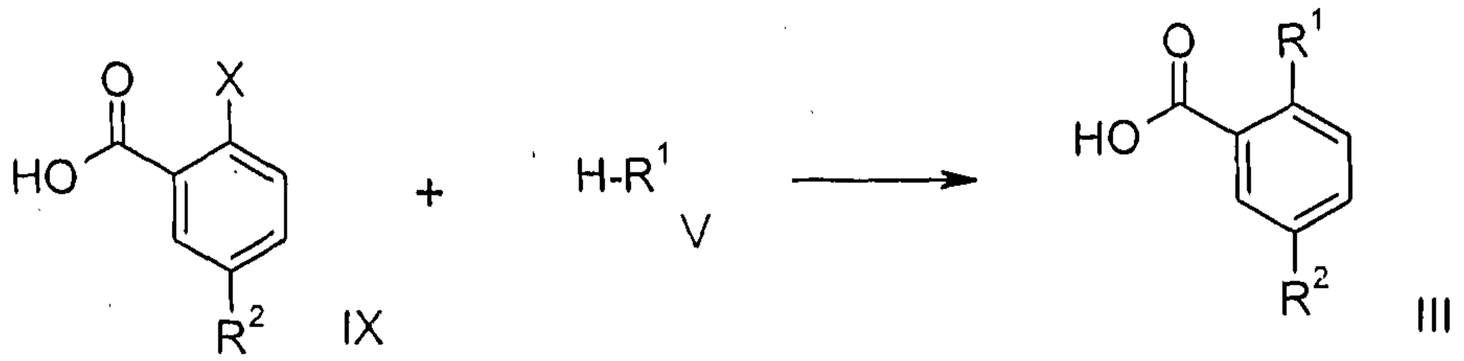


wherein R^1- R^7 are as described above.

A compound of formula II (IIA, IIB, IIC, IID, IIE or IIF) is 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 (IA, IB, IC, ID, IE or IF).

Scheme 2

Preparation of compounds of formula III:



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

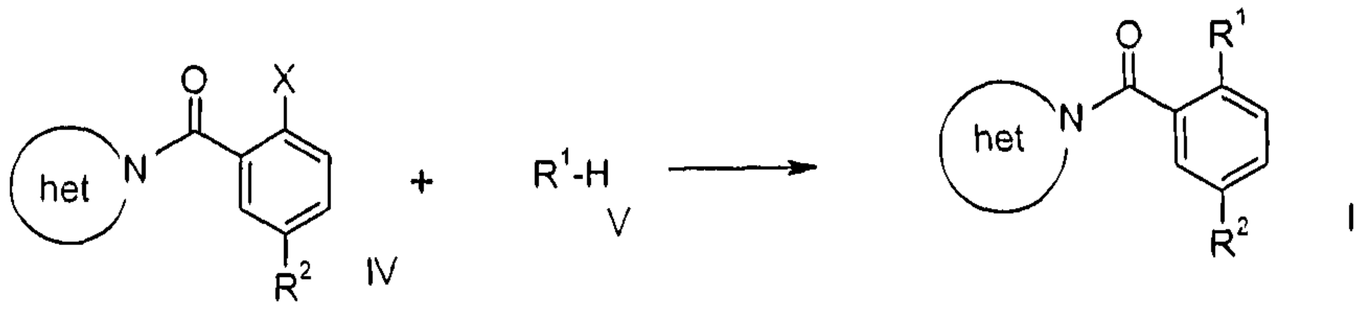
Compounds of formula III may be prepared in conventional manner. If H-R^1 is a non aromatic heterocycle, for example morpholine, the reaction is carried out at room temperature for about 2 hours.

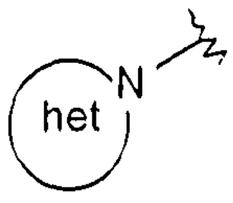
If R^1 is OR' for R' is lower alkyl, lower alkyl, substituted by halogen or -$(CH_2)_n$-cycloalkyl, the reaction is carried out with the corresponding alcohol of formula V by reaction with a mixture of a compound of formula IX and Cu(I)Br in triethylamine.

Compounds of formula IX may be prepared in conventional manner, for example as follows: To a corresponding benzoic acid in methanol at 0 °C oxone® (potassium peroxymonosulfate $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) was added and the mixture was allowed to stir at RT.

Scheme 3

Preparation of compounds of formula I:

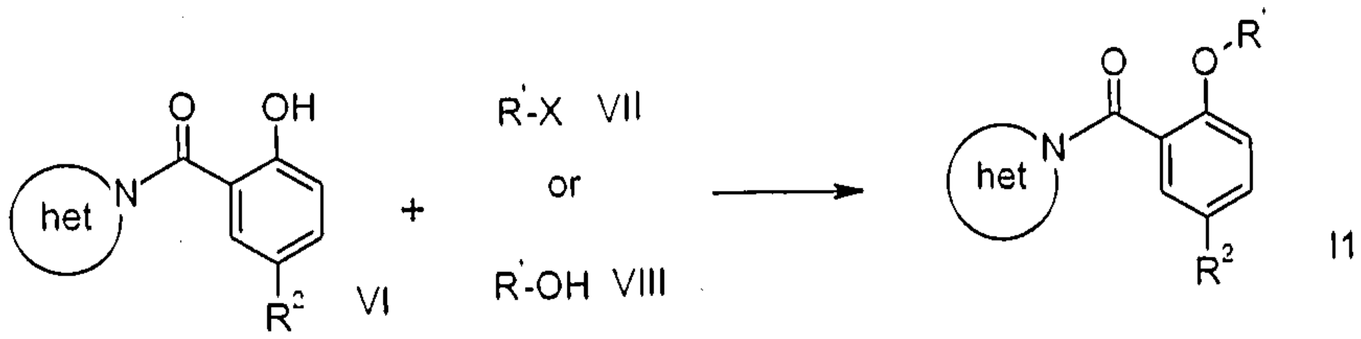


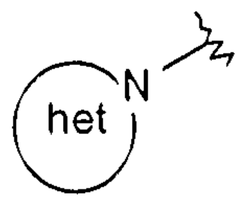
wherein R^1, R^2 and  are as described above and X is halogen.

X may be replaced by R^1 in conventional manner, for example with a base such as triethylamine or with Cu(I)Br.

Scheme 4

Preparation of compounds of formula I1:



wherein R' and R^2 and  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 stoechiometric 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 formula IA	0.019	14 formula ID	0.154
2 formula IA	0.187	15 formula IE	0.367
5 formula IB	0.098	19 formula IA	0.339
6 formula IB	0.407	20 formula A	0.026
9 formula IC	0.134	22 Example A	0.023
11 formula IC	0.088	23 Example B	0.341

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 or can be prepared by methods well known in the art.

Example A

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 (MH^+, 100 %).

Example B

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

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

To 99 mmol 2-chloro-5-(methylthio) benzoic acid in 400 ml methanol at 0 °C 296 mmol oxone® was added and the mixture was allowed to stir at RT for 3.5 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was extracted 3 times with 400 ml ethyl acetate and the combined organic phases were washed twice with 300 mL of 1N HCl then with 300 mL of brine and finally 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 hours 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 1.2.

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

Example C

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

Prepared in analogy to example B from 2-chloro-5-methanesulfonyl-benzoic acid and isobutanol.

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

Example D

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

Prepared in analogy to example B from 2-chloro-5-methanesulfonyl-benzoic acid and morpholine. MS (m/e): 284.1 (MH^-, 100 %).

Example E

2-Thiophen-2-yl-4,5,6,7-tetrahydro-thiazolo[5,4-*c*]pyridine

(a) 1-(2-Thiophen-2-yl-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-5-yl)-ethanone

2.8 mmol of thiophene-2-thiocarboxamide was dissolved in 10 ml acetonitrile. 5.6 mmol of N-ethyl-diisopropylamine was added, followed by 3.4 mmol 1-acetyl-3-bromo-piperidin-4-one hydrobromide (prepared according to patent US 4122083). The reaction mixture was heated to 50 °C for 4 hours, cooled and concentrated. Chromatography of the residue (SiO_2; ethyl acetate) yields the title compound as a yellowish gum. MS (m/e): 265.0 ($M+H^+$).

(b) 2-Thiophen-2-yl-4,5,6,7-tetrahydro-thiazolo[5,4-*c*]pyridine

1 mmol of 1-(2-Thiophen-2-yl-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-5-yl)-ethanone was refluxed for 30 min. in 15 ml of 2 M aqueous hydrochloric acid. The reaction mixture was cooled and made alkaline by addition of sodium carbonate. Extraction with ethyl acetate yields the title compound as a brownish solid. MS (m/e): 223.3 ($M+H^+$).

Example F

2-(4-Fluoro-phenyl)-4,5,6,7-tetrahydro-thiazolo[5,4-*c*]pyridine

(a) 1-[2-(4-Fluoro-phenyl)-6,7-dihydro-4H-thiazolo[5,4]pyridin-5-yl]-ethanone

Prepared in analogy to example E (a) from 4-fluoro-1-benzenecarbothioamide and 1-acetyl-3-bromo-piperidin-4-one hydrobromide as a colorless solid. MS (m/e): 277.1 ($M+H^+$).

(b) 2-(4-Fluoro-phenyl)-4,5,6,7-tetrahydro-thiazolo[5,4-*c*]pyridine

Prepared in analogy to example E (b) from 1-[2-(4-fluoro-phenyl)-6,7-dihydro-4H-thiazolo[5,4]pyridin-5-yl]-ethanone and hydrochloric acid. Chromatography (SiO_2; dichloromethane / methanol 95 :5) yields the title compound as a yellowish solid. MS (m/e): 235.1 ($M+H^+$).

Example G

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

Prepared in analogy to example B from 2-chloro-5-methanesulfonyl-benzoic acid and cyclopentanol, MS (m/e): 283.1 (MH^-, 100 %).

Example H

8-Trifluoromethoxy-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

a) 1-Cyanomethyl-5-trifluoromethoxy-1H-indole-2-carboxylic acid ethyl ester

To a solution of sodium hydride (0.58 g in DMF (12 mL) at 0 °C was slowly added a solution of 5-trifluoromethoxy-1H-indole-2-carboxylic acid ethyl ester (2.64 g) in DMF (12 mL) keeping the temperature below 7.5 °C After gaz evolution ceased chloroacetonitrile was added and the reaction mixture was stirred for 2 hours at 75 °C. After allowing cooling down, water was added and the reaction mixture was extracted with ethyl acetate. The combined organic phases were washed with brine then dried with magnesium sulfate, concentrated *in vacuo* and purified by column chromatography to yield the title compound (2.3 g, 76 %). MS (EI): 312.1 (M^+).

b) 8-Trifluoromethoxy-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole

To a suspension of Lithium Aluminium Hydride (0.68 g) in diethylether (70 mL) was added portionwise 1-cyanomethyl-5-trifluoromethoxy-1H-indole-2-carboxylic acid ethyl ester (2.28 g). The reaction mixture was then stirred for 16 hours at reflux. The solution was then slowly poured into a saturated solution of sodium-potassium tartrate. The mixture was then extracted with ethyl acetate 3 times. The combined organic phases were then washed with brine, dried with magnesium sulfate, concentrated *in vacuo* and purified by column chromatography to yield the desired compound (0.83 g, 45 %). MS (EI): 274.0 (M^+).

Example I

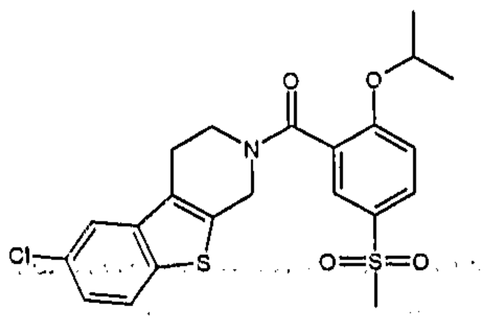
Rac-8-Trifluoromethoxy-1,2,3,4,10,10a-hexahydro-pyrazino[1,2-a]indole

To 8-trifluoromethoxy-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole (0.41 g) in THF (2.2 mL) and TFA (4.4 mL) at 0 °C was added portion wise sodium borohydride (0.124 g) . The reaction mixture was allowed to warm up to room temperature and stirred for 35

minutes. After such time, the reaction mixture was concentrated *in vacuo*, and the residue was dissolved in dichloromethane and poured over water. A sodium hydroxide solution (10M) was the added until reaching pH 13.5. After 15 minutes, the phases were separated. The aqueous phase was extracted with dichloromethane twice. The combined organic layers were then washed with brine, dried with magnesium sulfate, concentrated *in vacuo* and purified by column chromatography to yield the title compound (0.31 g, 76 %). MS (EI): 258.1 (M^+).

Example 1

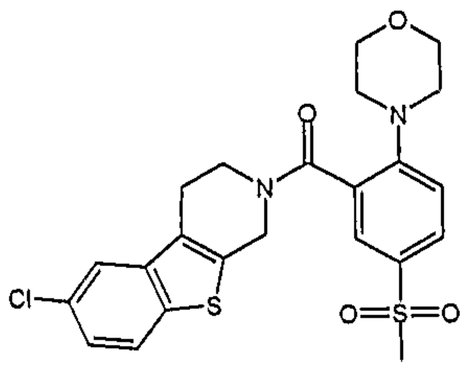
(6-Chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



A solution of 2-isopropoxy-5-methanesulfonyl-benzoic (Example B, 30 mg), and 6-chloro-1,2,3,4-tetrahydro-benzo[4,5]thieno[2,3-c]pyridine ([29078-50-0], 35 mg), *N*-diisopropylethylamine (0.12 m), and TBTU (2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate, 55 mg) in dimethylformamide (2 mL) was stirred at room temperature for 16 hours. The reaction mixture was concentrated and purified by column chromatography (SiO_2, Heptane/EtOAc 0-100 %) to yield the title compound as a white solid (30 mg). MS (m/e): 464.1 ($M+H^+$).

Example 2

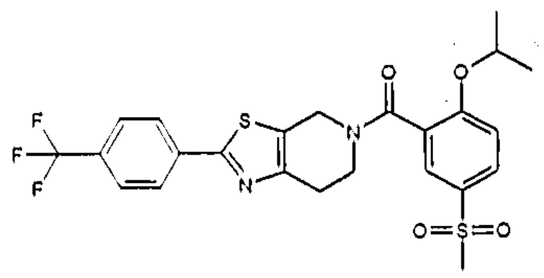
(6-Chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridin-2-yl)-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone



The title compound was prepared in analogy to Example 1 using Example D and 6-chloro-1,2,3,4-tetrahydro-benzo[4,5]thieno[2,3-c]pyridine [29078-50-0].
MS (m/e): 491.1 ($M+H^+$).

Example 3

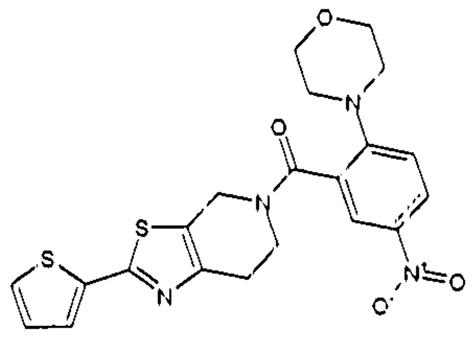
(2-Isopropoxy-5-methanesulfonyl-phenyl)-[2-(4-trifluoromethyl-phenyl)-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridin-5-yl]-methanone



The title compound was prepared in analogy to Example 1 using Example B and 2-[4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydro[1,3]triazolo[5,4-c]pyridine[733757-96-5]. MS (m/e): 525.2 ($M+H^+$).

Example 4

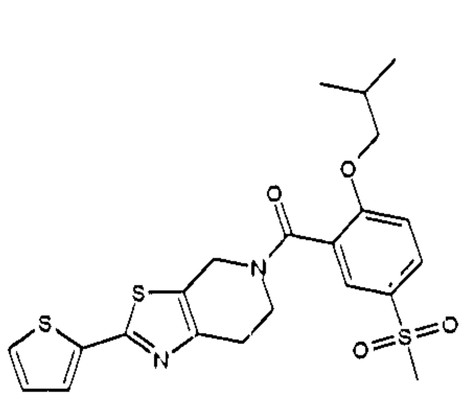
(2-Morpholin-4-yl-5-nitro-phenyl)-(2-thiophen-2-yl-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridin-5-yl)-methanone



The title compound was prepared in analogy to Example 1 using Example A and Example E. MS (m/e): 457.3 ($M+H^+$).

Example 5

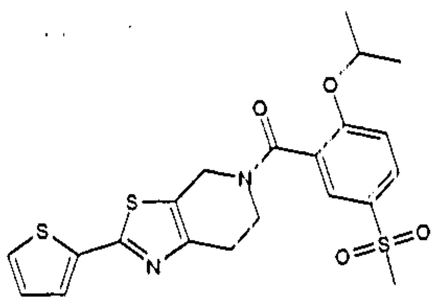
(2-Isobutoxy-5-methanesulfonyl-phenyl)-(2-thiophen-2-yl-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridin-5-yl)-methanone



The title compound was prepared in analogy to Example 1 using Example C and Example E. MS (m/e): 477.0 ($M+H^+$).

Example 6

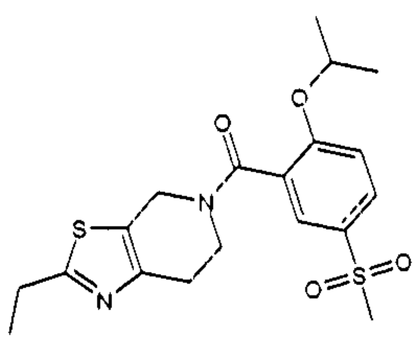
(2-Isopropoxy-5-methanesulfonyl-phenyl)-(2-thiophen-2-yl-6,7-dihydro-4*H*!-thiazolo[5,4-*c*]pyridin-5-yl)-methanone



The title compound was prepared in analogy to Example 1 using Example B and Example E. MS (m/e): 463.3 ($M+H^+$).

Example 7

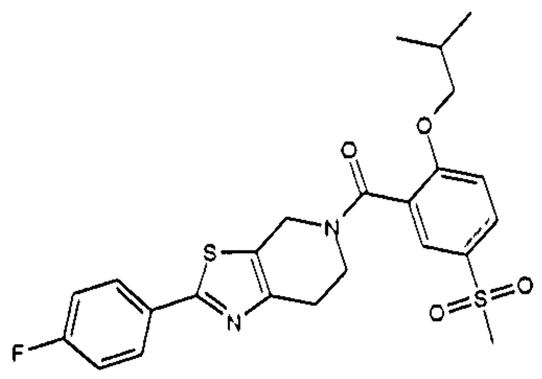
(2-Ethyl-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridin-5-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



The title compound was prepared in analogy to Example 1 using Example B and 2-ethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine [153341-59-4]. MS (m/e): 409.4 ($M+H^+$).

Example 8

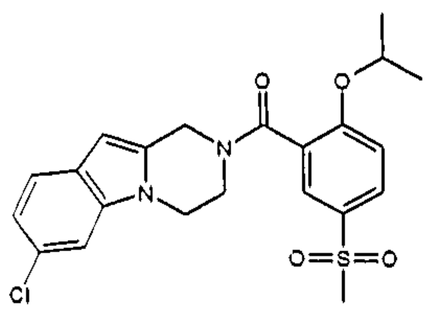
[2-(4-Fluoro-phenyl)-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridin-5-yl]-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone



The title compound was prepared in analogy to Example 1 using Example C and Example F. MS (m/e): 489.0 ($M+H^+$).

Example 9

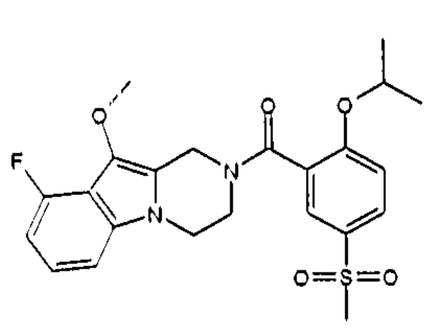
(7-Chloro-3,4-dihydro-1H-pyrazino[1,2-a]indol-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



The title compound was prepared in analogy to Example 1 using Example B and 7-chloro-1,2,3,4-tetrahydro-pyrazino[1,2-a]indole [287384-61-6]. MS (m/e): 447.0 ($M+H^+$).

Example 10

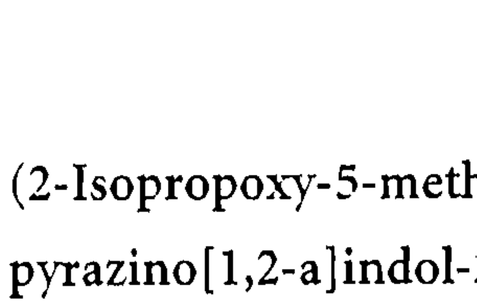
(9-Fluoro-10-methoxy-3,4-dihydro-1H-pyrazino[1,2-a]indol-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



The title compound was prepared in analogy to Example 1 using Example B and 9-fluoro-1,2,3,4-tetrahydro-10-methoxy-pyrazino[1,2-a]indole[153500-96-0]. MS (m/e): 478.1 ($M+NH_4^+$).

Example 11

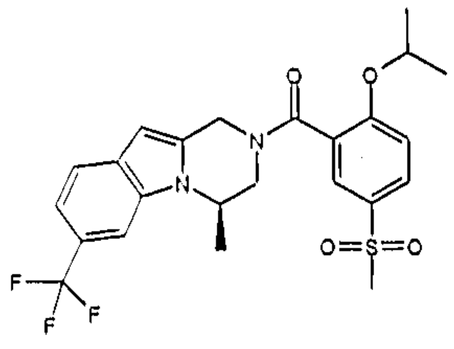
(2-Isopropoxy-5-methanesulfonyl-phenyl)-(8-trifluoromethoxy-3,4-dihydro-1H-pyrazino[1,2-a]indol-2-yl)-methanone



The title compound was prepared in analogy to Example 1 using Example B and Example H. MS (m/e): 497.1 ($M+H^+$).

Example 12

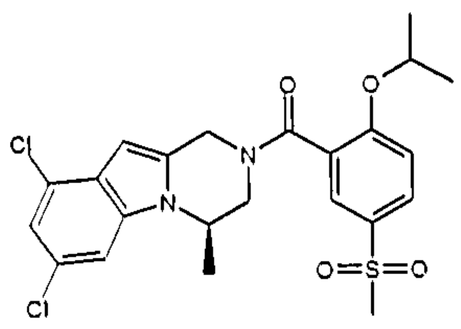
(2-Isopropoxy-5-methanesulfonyl-phenyl)-((R)-4-methyl-7-trifluoromethyl-3,4-dihydro-1H-pyrazino[1,2-a]indol-2-yl)-methanone



The title compound was prepared in analogy to Example 1 using Example B and (R)-4-methyl-7-trifluoromethyl-1,2,3,4-tetrahydropyrazino[1,2-a]indole [396074-54-7]. MS (m/e): 495.3 ($M+H^+$).

Example 13

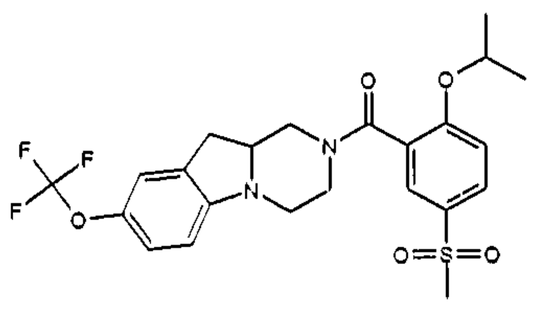
((R)-7,9-Dichloro-4-methyl-3,4-dihydro-1H-pyrazino[1,2-a]indol-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



The title compound was prepared in analogy to Example 1 using Example B and (4R)-7,9-dichloro-1,2,3,4-tetrahydro-4-methyl-pyrazino[1,2-a]indole [763077-49-2]. MS (m/e): 495.4 ($M+H^+$).

Example 14

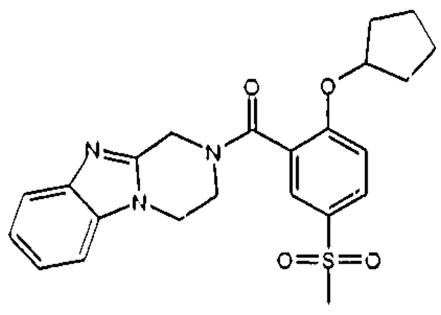
Rac-(2-Isopropoxy-5-methanesulfonyl-phenyl)-(8-trifluoromethoxy-3,4,10,10a-tetrahydro-1H-pyrazino[1,2-a]indol-2-yl)-methanone



The title compound was prepared in analogy to Example 1 using Example B and Example I. MS (m/e): 499.1 ($M+H^+$).

Example 15

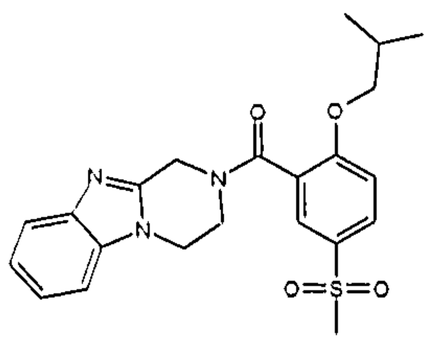
(2-Cyclopentyloxy-5-methanesulfonyl-phenyl)-(3,4-dihydro-1H-benzo[4,5]imidazo[1,2-a]pyrazin-2-yl)-methanone



The title compound was prepared in analogy to Example 1 using Example G and 1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole [4744-53-0]. MS (m/e): 440.4 ($M+H^+$).

Example 16

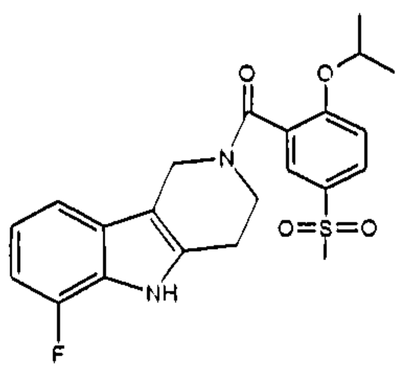
(3,4-Dihydro-1H-benzo[4,5]imidazo[1,2-a]pyrazin-2-yl)-(2-isobutoxy-5-methanesulfonyl-phenyl)-methanone



The title compound was prepared in analogy to Example 1 using Example C and 1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole [4744-53-0]. MS (m/e): 428.5 ($M+H^+$).

Example 17

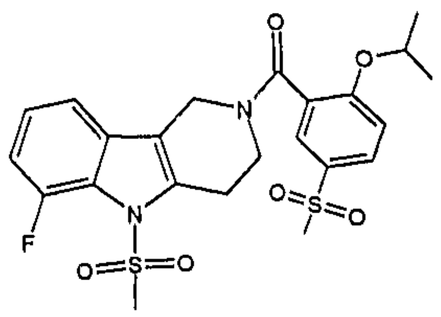
(6-Fluoro-1,3,4,5-tetrahydro-pyrido[4,3-b]indol-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



The title compound was prepared in analogy to Example 1 using Example B and 6-fluoro-2,3,4,5-tetrahydro-1H-pyrido{4,3-b}indole[177858-77-4]. MS (m/e): 431.1 ($M+H^+$).

Example 18

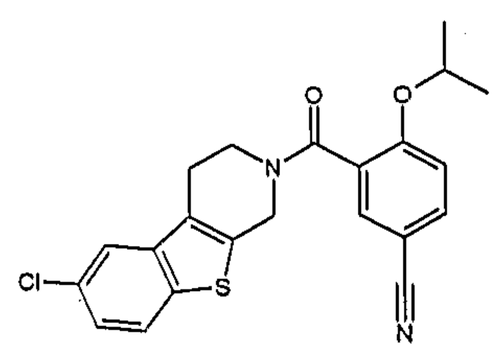
(6-Fluoro-5-methanesulfonyl-1,3,4,5-tetrahydro-pyrido[4,3-b]indol-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



A suspension of 200 mg (6-fluoro-1,3,4,5-tetrahydro-pyrido[4,3-b]indol-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone (Example 17) in 5 ml dichloromethane is treated with 106 mg methane sulfonyl chloride, followed by 118 mg triethylamine. The reaction mixture is stirred overnight. Concentration and chromatography (silica gel; ethyl acetate) yields the title compound as a slightly yellowish solid (17 mg; 7 %). MS (m/e): 509.0 ($M+CH_3COO$).

Example 19

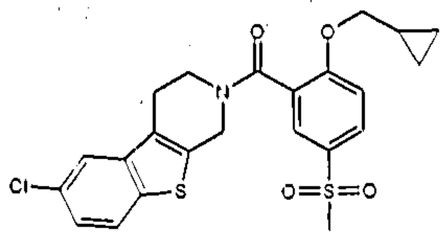
3-(6-Chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridine-2-carbonyl)-4-isopropoxy-benzonitrile



The title compound was prepared in analogy to Example 1 using 6-chloro-1,2,3,4-tetrahydro-[1]benzothieno[2,3-c]pyridine [29078-50-0] and 5-cyano-2-(1-methylethoxy)-benzoic acid[845616-14-0]. MS (m/e): 411.0 ($M+H^+$).

Example 20

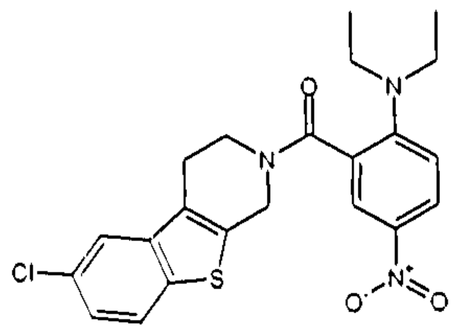
(6-Chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridin-2-yl)-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone



The title compound was prepared in analogy to Example 1 using 6-chloro-1,2,3,4-tetrahydro-[1]benzothieno[2,3-c]pyridine [29078-50-0] and 2-cyclopropylmethoxy-5-methylsulfonylbenzoic acid[845616-03-7]. MS (m/e): 476.0 ($M+H^+$).

Example 21

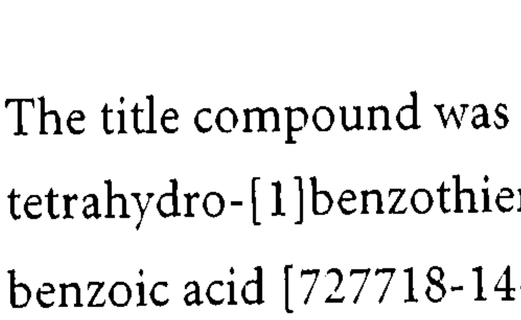
(6-Chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridin-2-yl)-(2-diethylamino-5-nitro-phenyl)-methanone



The title compound was prepared in analogy to Example 1 using 6-chloro-1,2,3,4-tetrahydro-[1]benzothieno[2,3-c]pyridine [29078-50-0] and 2-(diethylamino)-5-nitro-benzoic acid [727718-14-1]. MS (m/e): 444.1 ($M+H^+$).

Example 22

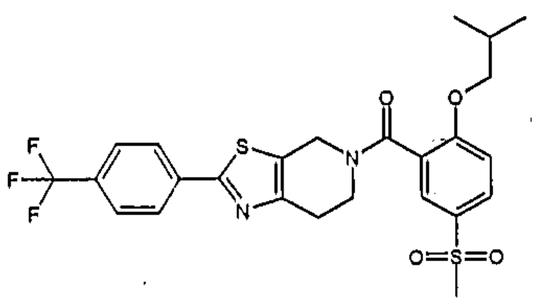
(6-Chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridin-2-yl)-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone



The title compound was prepared in analogy to Example 1 using 6-chloro-1,2,3,4-tetrahydro-[1]benzothieno[2,3-c]pyridine [29078-50-0] and 5-methylsulfonyl-2-[((S)-2,2,2-trifluoro-1-methylethyl)oxy]benzoic acid [845616-82-2]. MS (m/e): 518.1 ($M+H^+$).

Example 23

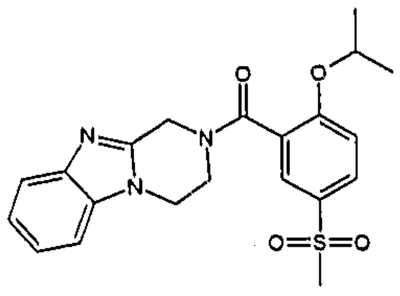
(2-Isobutoxy-5-methanesulfonyl-phenyl)-[2-(4-trifluoromethyl-phenyl)-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-5-yl]-methanone



The title compound was prepared in analogy to Example 1 using 2-[4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydro[1,3]triazolo[5,4-c]pyridine [733757-96-5] and Example C. MS (m/e): 539.3 ($M+H^+$).

Example 24

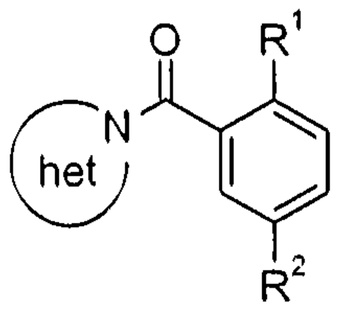
(3,4-Dihydro-1H-benzo[4,5]imidazo[1,2-a]pyrazin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



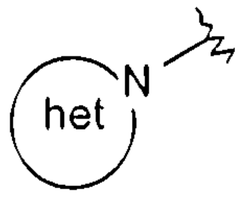
The title compound was prepared in analogy to Example 1 using 1,2,3,4-tetrahydropyrazino[1,2-a]benzimidazole [4744-53-0] and Example B. MS (m/e): 414.3 ($M+H^+$).

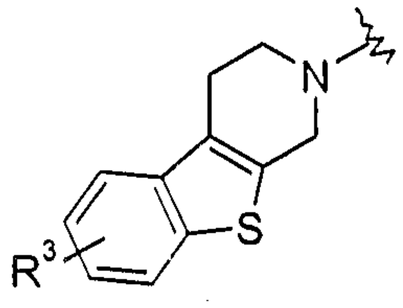
Claims

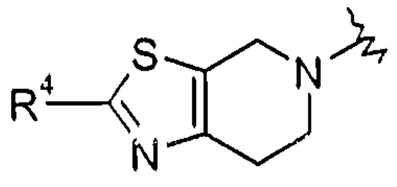
1. Compounds of general formula



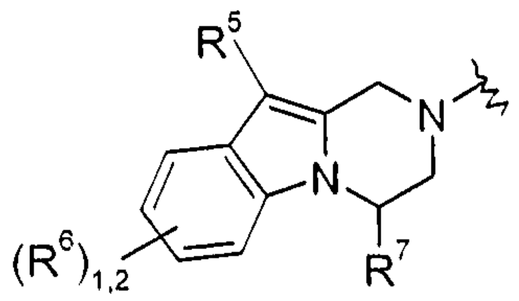
I

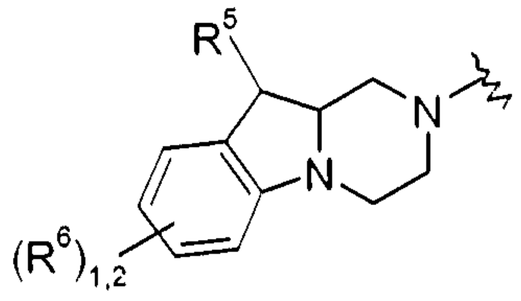
wherein  is



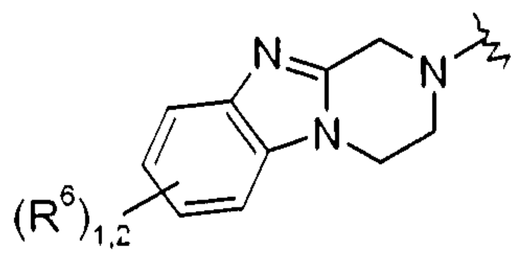
A or 

B

or 

C or 

D

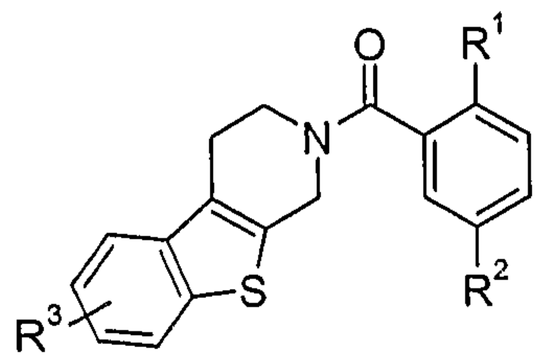
or 

E

	R^1	is a non aromatic heterocycle, or is OR' or $N(R'')_2$;
	R'	is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$-cycloalkyl;
	R''	is lower alkyl;
	R^2	is NO_2, CN or SO_2R'';
	R^3	is hydrogen, halogen, lower alkyl, lower alkoxy, or lower alkyl substituted by halogen;
	R^4	is hydrogen, lower alkyl, phenyl substituted by halogen or CF_3, or is a five or six membered aromatic heterocycle;
	R^5/R^6	are hydrogen, halogen, lower alkyl, lower alkoxy, or are lower alkyl or lower alkoxy, substituted by halogen;
	R^7	is hydrogen or lower alkyl;
	n	is 0, 1 or 2;

and to pharmaceutically active acid addition salts.

2. Compounds of formula IA in accordance with claim 1



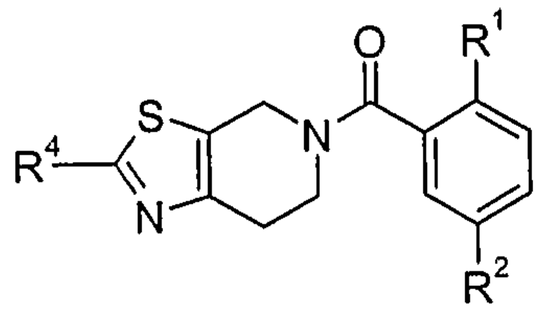
IA

wherein

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

and pharmaceutically active acid addition salts.

3. Compounds of formula IB in accordance with claim 1



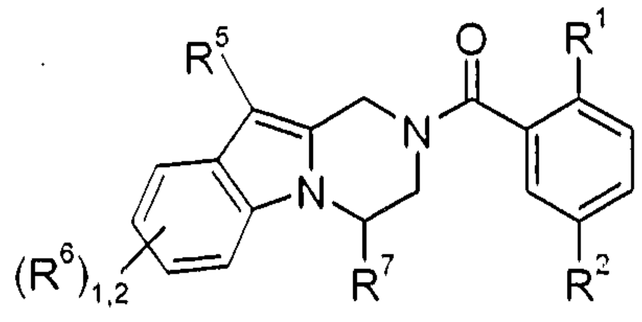
IB

wherein

R^1	is a non aromatic heterocycle, or is OR' or $N(R'')_2$;
R'	is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$-cycloalkyl;
R''	is lower alkyl;
R^2	is NO_2, CN or SO_2R'';
R^4	is hydrogen, lower alkyl, phenyl substituted by halogen or CF_3, or is a five or six membered aromatic heterocycle;
n	is 0, 1 or 2;

and pharmaceutically active acid addition salts.

4. Compounds of formula IC in accordance with claim 1



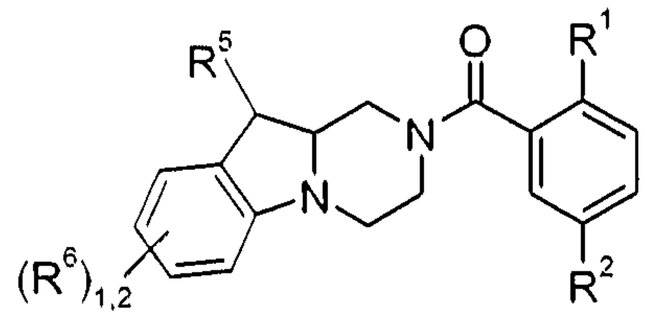
IC

wherein

R^1	is a non aromatic heterocycle, or is OR' or $N(R'')_2$;
R'	is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$-cycloalkyl;
R''	is lower alkyl;
R^2	is NO_2, CN or SO_2R'';
R^5/R^6	are hydrogen, halogen, lower alkyl, lower alkoxy, or are lower alkyl or lower alkoxy, substituted by halogen;
R^7	is hydrogen or lower alkyl;
n	is 0, 1 or 2;

and pharmaceutically active acid addition salts.

5. Compounds of formula ID in accordance with claim 1



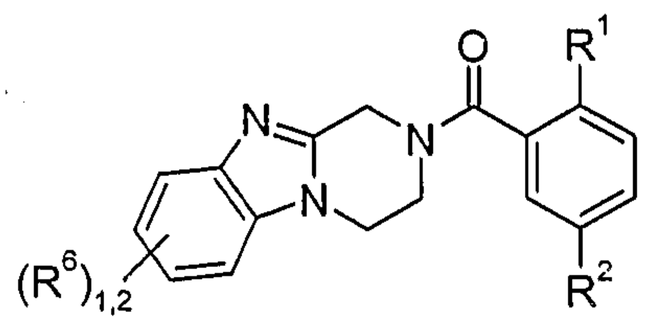
ID

wherein

R^1	is a non aromatic heterocycle, or is OR' or $N(R'')_2$;
R'	is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$-cycloalkyl;
R''	is lower alkyl;
R^2	is NO_2, CN or SO_2R'';
R^5/R^6	are hydrogen, halogen, lower alkyl, lower alkoxy, or are lower alkyl or lower alkoxy, substituted by halogen;
n	is 0, 1 or 2;

and pharmaceutically active acid addition salts.

6. Compounds of formula IE in accordance with claim 1



IE

wherein

R^1 is a non aromatic heterocycle, or is OR' or $N(R'')_2$;

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

R'' is lower alkyl;

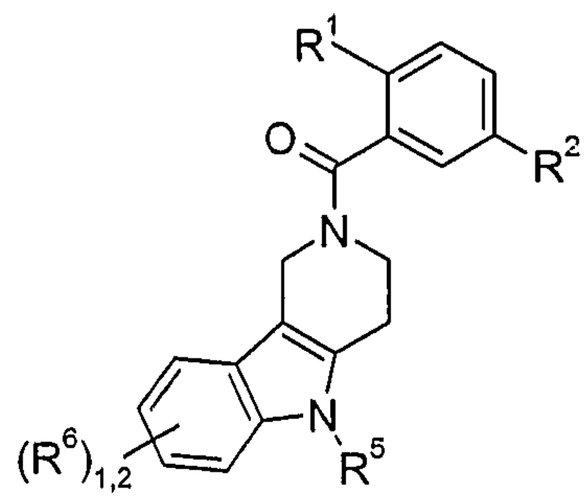
R^2 is NO_2, CN or SO_2R'';

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

n is 0, 1 or 2;

and pharmaceutically active acid addition salts.

7. Compounds of formula IF in accordance with claim 1



IF

wherein

R^1 is a non aromatic heterocycle, or is OR' or $N(R'')_2$;

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

R'' is lower alkyl;

R^2 is NO_2, CN or SO_2R'';

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

n is 0, 1 or 2;

and pharmaceutically active acid addition salts.

8. Compounds of formula IA according to claim 2, which compounds are (6-Chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
(6-Chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridin-2-yl)-(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-methanone,
3-(6-chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridine-2-carbonyl)-4-isopropoxy-benzonitrile,
(6-chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridin-2-yl)-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone or
(6-chloro-3,4-dihydro-1H-benzo[4,5]thieno[2,3-c]pyridin-2-yl)-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone.

9. Compounds of formula IB according to claim 3, which compounds are (2-isobutoxy-5-methanesulfonyl-phenyl)-(2-thiophen-2-yl-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridin-5-yl)-methanone,
(2-isopropoxy-5-methanesulfonyl-phenyl)-(2-thiophen-2-yl-6,7-dihydro-4*H*!-thiazolo[5,4-*c*]pyridin-5-yl)-methanone or
(2-isobutoxy-5-methanesulfonyl-phenyl)-[2-(4-trifluoromethyl-phenyl)-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-5-yl]-methanone.

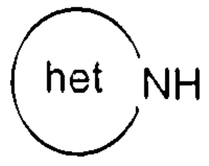
10. Compounds of formula IC according to claim 4, which compounds are (7-chloro-3,4-dihydro-1H-pyrazino[1,2-a]indol-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone or
(2-isopropoxy-5-methanesulfonyl-phenyl)-(8-trifluoromethoxy-3,4-dihydro-1H-pyrazino[1,2-a]indol-2-yl)-methanone.

11. A compounds of formula ID according to claim 5, which compound is Rac-(2-isopropoxy-5-methanesulfonyl-phenyl)-(8-trifluoromethoxy-3,4,10,10a-tetrahydro-1H-pyrazino[1,2-a]indol-2-yl)-methanone.

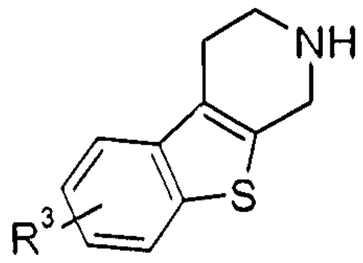
12. A compounds of formula IE according to claim 6, which compound is (2-cyclopentyloxy-5-methanesulfonyl-phenyl)-(3,4-dihydro-1H-benzo[4,5]imidazo[1,2-a]pyrazin-2-yl)-methanone.

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

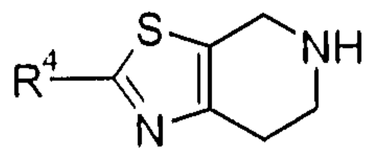
a) reacting a compound of formula


II

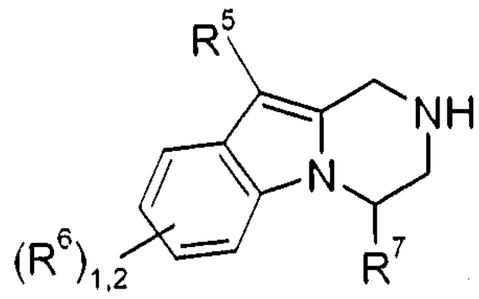
selecting from the group consisting of


IIA

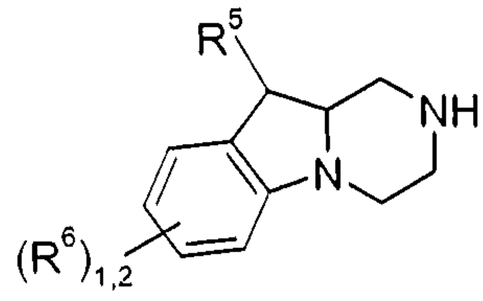
or


IIB

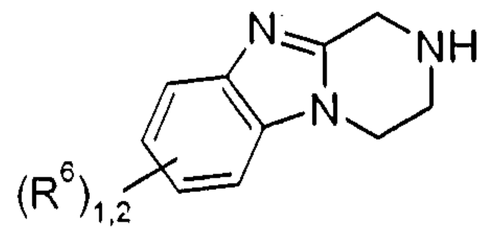
or


IIC

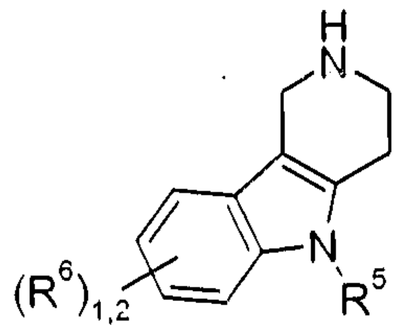
or


IID

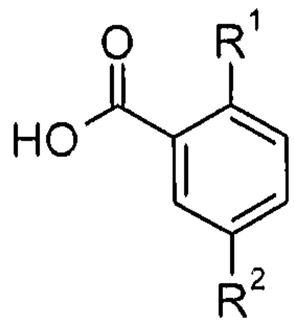
or


IIE

or

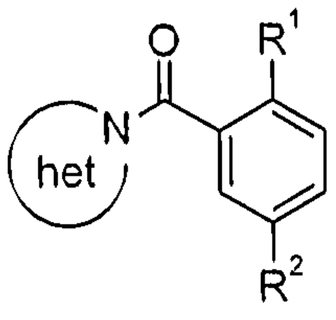

IIF

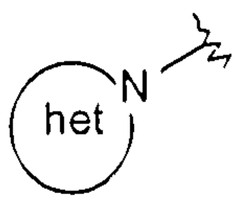
with a compound of formula

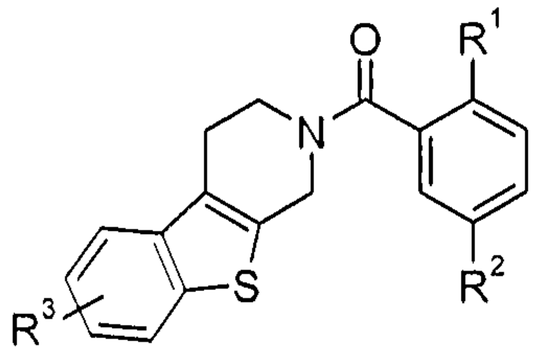

III

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

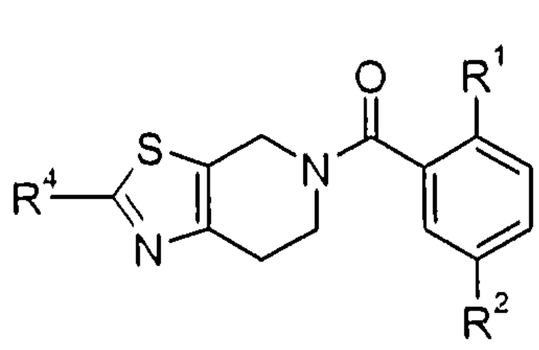
to a compound of formula

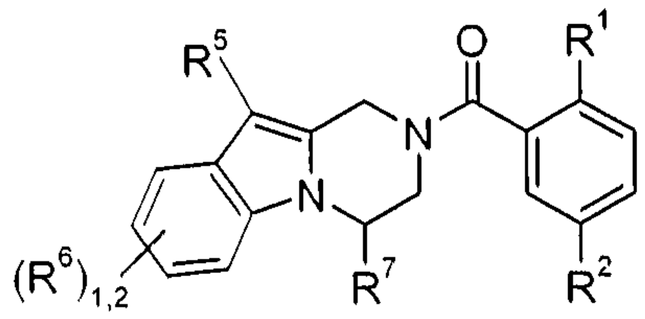

I,

wherein in dependency of  the following structures are encompassed by formula I

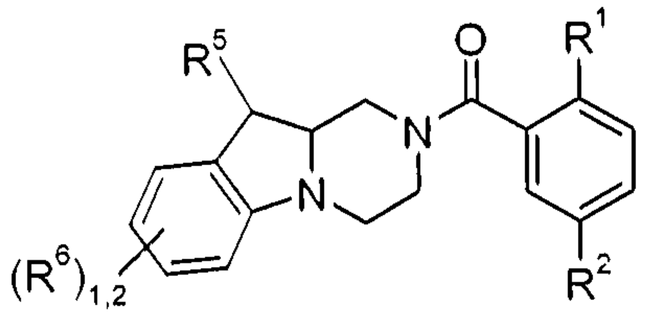

IA

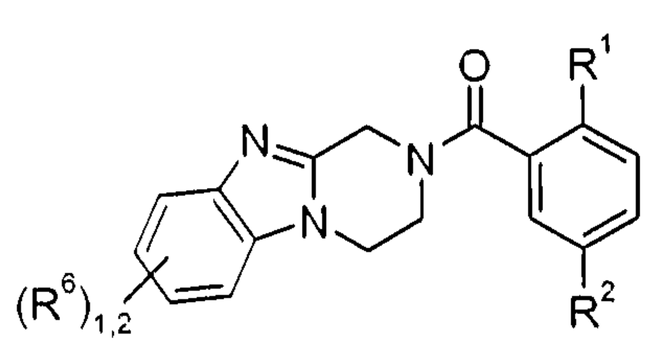
or


IB or

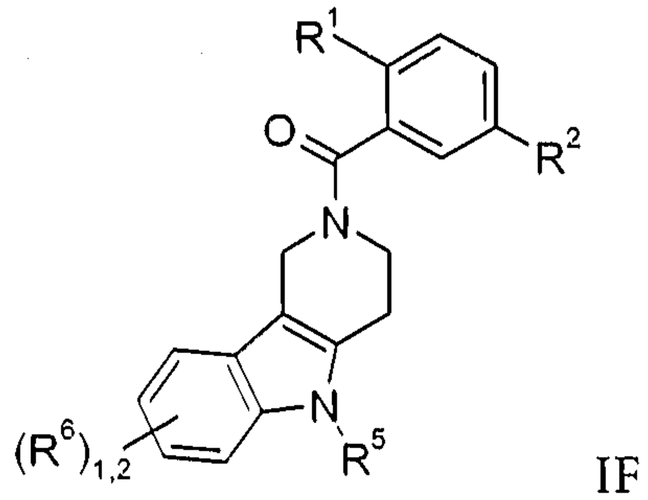

IC

or


ID or

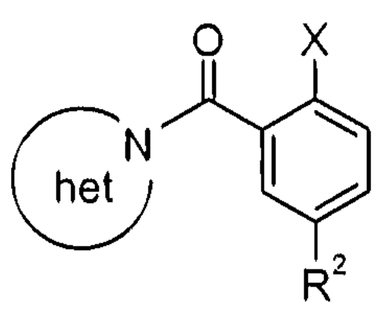

IE

or


IF

wherein the substituents are as defined in claim 1, or

b) reacting a compound of formula

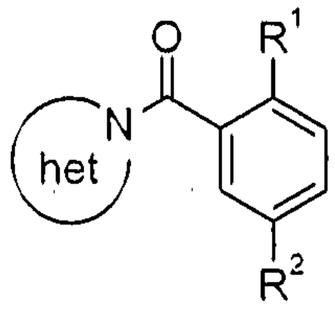

IV

with a compound of formula

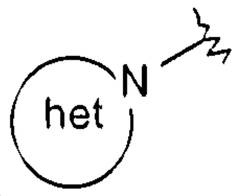
R^1H V

in the presence of a base, such as triethylamine, or a catalyst like Cu(I)Br,

to a compound of formula

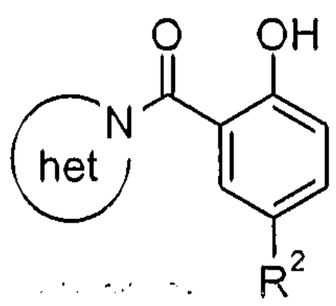


I

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

or

c) reacting a compound of formula

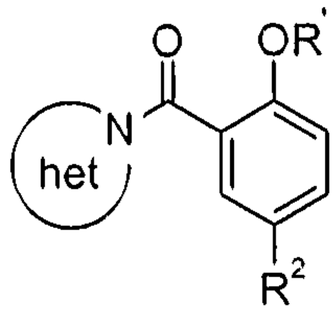


VI

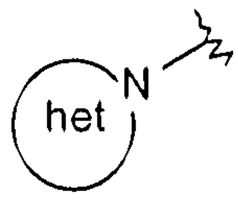
with a compound of formula

VII

to a compound of formula

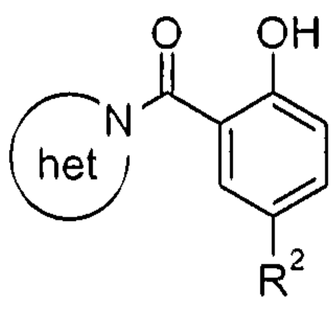


I1

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

or

d) reacting a compound of formula



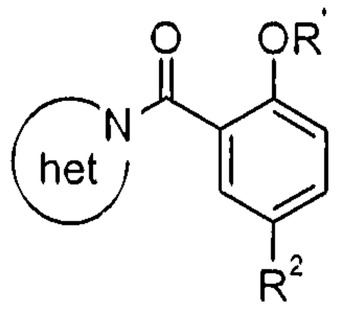
VI

with a compound of formula

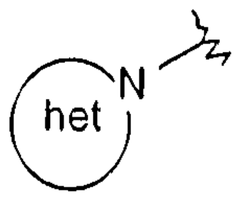
R'OH VIII

under Mitsunobu conditions

to a compound of formula



I1

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

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

14. A compound according to any on of claims 1 – 12, whenever prepared by a process as claimed in claim 13 or by an equivalent method.

15. A medicament containing one or more compounds as claimed in any one of claims 1 – 12 and pharmaceutically acceptable excipients.

16. A medicament according to claim 15 for the treatment of Alzheimer's disease.

17. The use of a compound in any one of claims 1 – 12 for the manufacture of medicaments for the treatment of Alzheimer's disease.

18. The invention as hereinbefore described.

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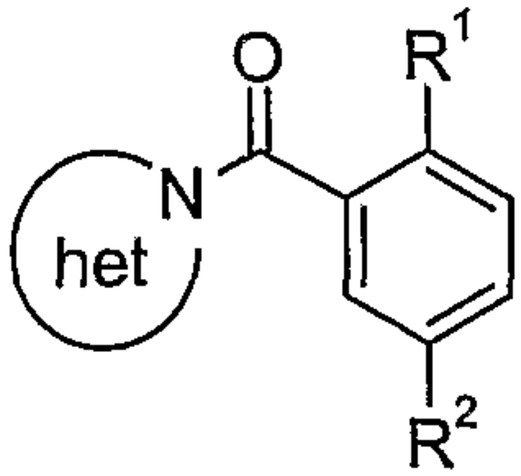
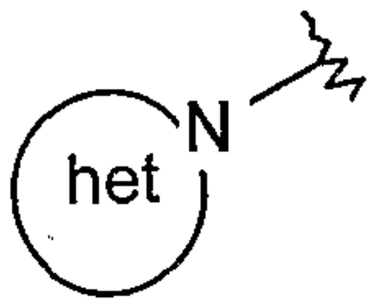
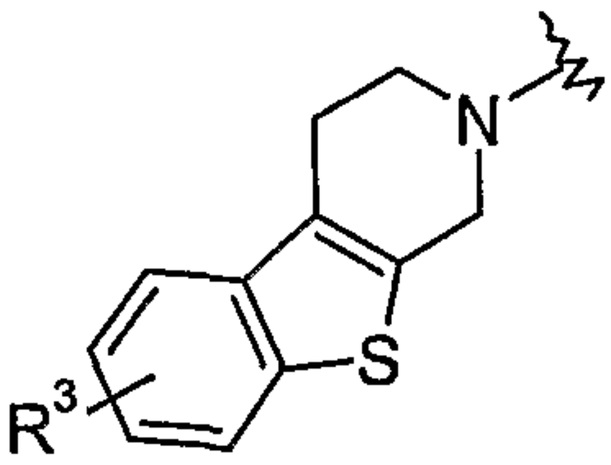


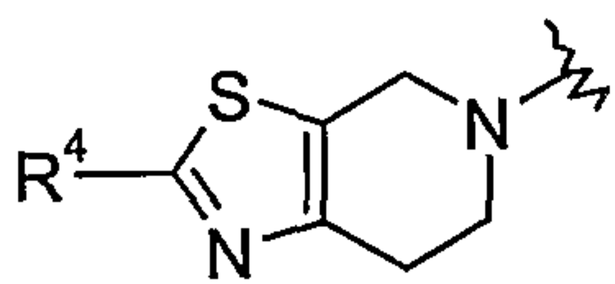
(I)



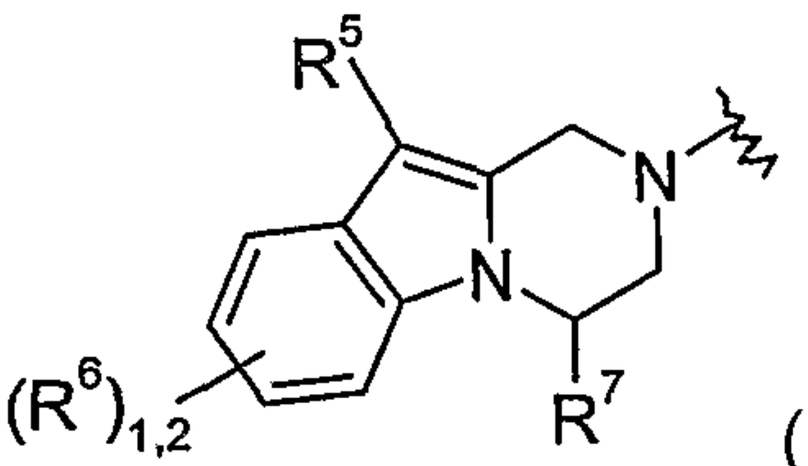
(II)



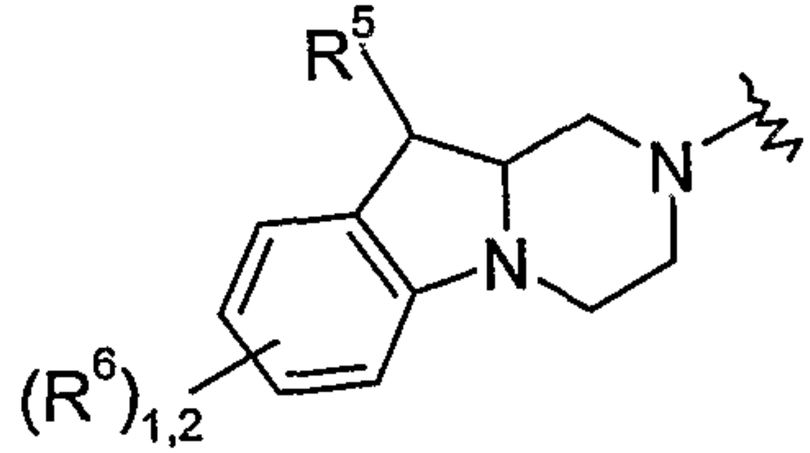
(A)



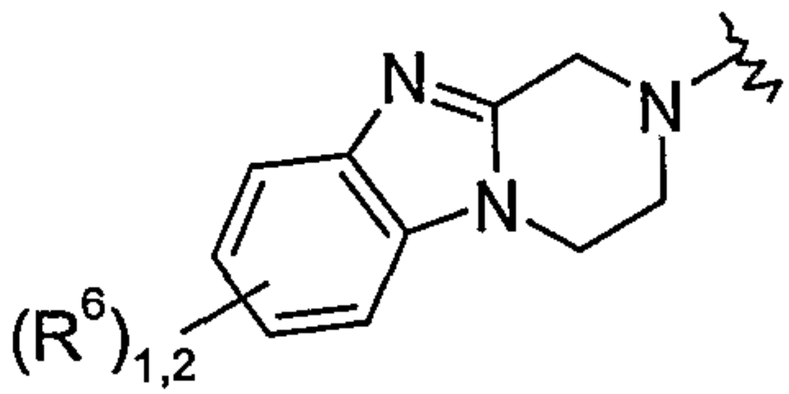
(B)



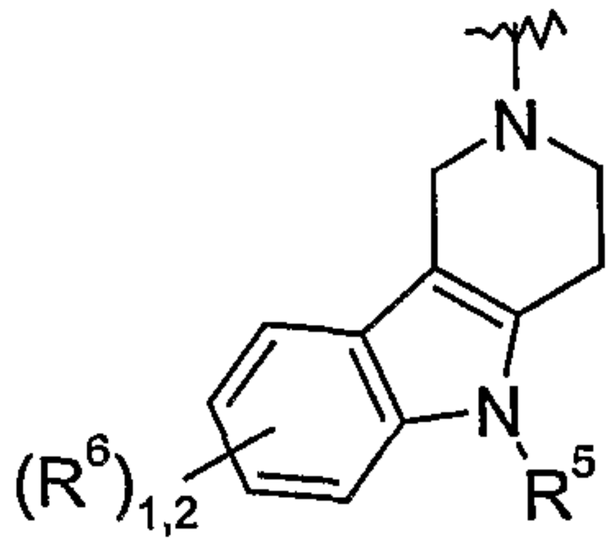
(C)



(D)



(E)



(F)