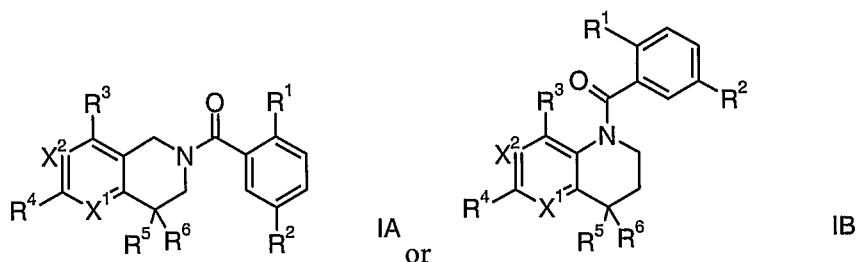


PHENYL METHANONE DERIVATIVES AND THEIR USE AS GLYCINE TRANSPORTER 1 INHIBITORS

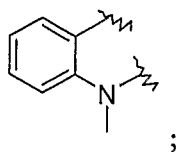
The present invention relates to compounds of general formula IA or IB



5 wherein

- R^1 is aryl, a cyclic amine, or is OR^{11} , SR^{11} or $N(R^{12})_2$;
 10 R^{11} is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$ -cycloalkyl;
 R^{12} is independently from each other hydrogen or lower alkyl;
 R^2 is NO_2 , CN or $S(O)_2$ -lower alkyl;
 R^3 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or is lower alkoxy;
 15 R^4 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen, non cyclic amine, lower alkoxy or benzyloxy, optionally substituted by halogen;
 R^5/R^6 are independently from each other hydrogen, halogen, lower alkyl, lower alkoxy, aryl or form together the keto group $=O$;
 X^1 is N or C- R' ;
 20 X^2 is N or C- R'' ;
 R' is hydrogen, halogen, lower alkyl, lower alkoxy, or benzyloxy optionally substituted by halogen;
 R'' is hydrogen, alkyl substituted by halogen, halogen, nitro, lower alkoxy, cyano, COO -lower alkyl, benzyloxy optionally substituted by halogen or $S(O)_2$ -cyclic
 25 amine;
 or

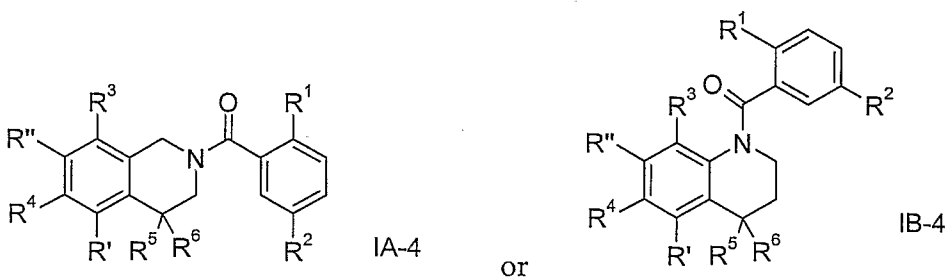
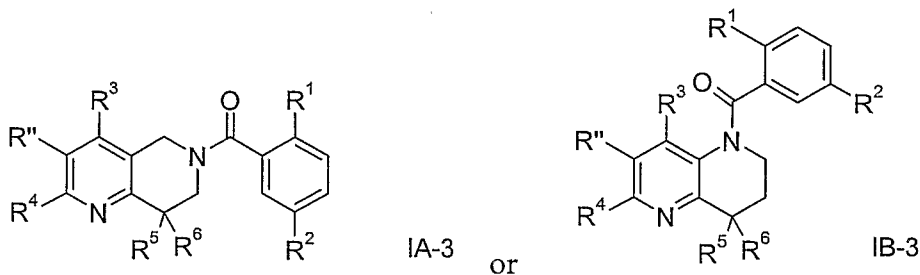
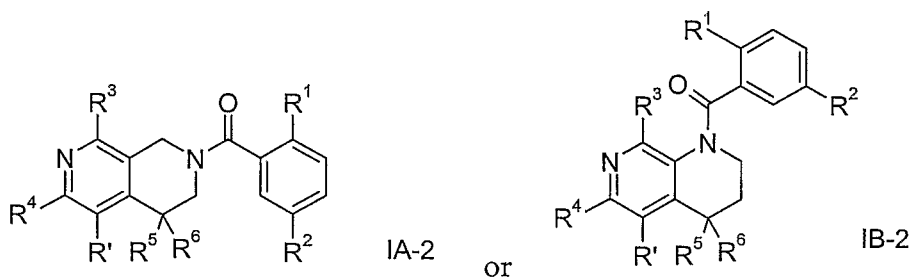
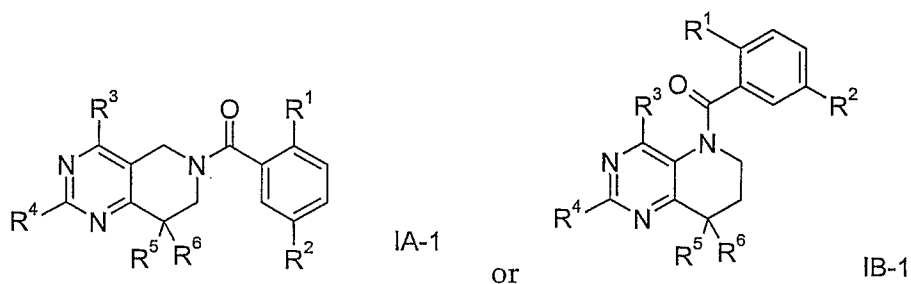
R^3 and R'' or R^4 and R' or R'' and R^4 are together with the carbon atom to which they are attached $-O-(CH_2)_{1,2}-O-$ or $-O-(CH_2)_{2,3}-$ or $-(CH_2)_{2,3}-O-$, or



n is 1 or 2;

5 and to pharmaceutically acceptable acid addition salts thereof.

The following groups of compounds relate to compounds of formula I:



wherein

R^1 is aryl, a cyclic amine, or is OR^{11} , SR^{11} or $N(R^{12})_2$;

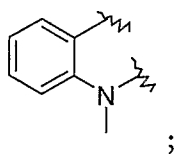
R^{11} is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$ -cycloalkyl;

15 R^{12} is independently from each other hydrogen or lower alkyl;

- R^2 is NO_2 , CN or $\text{S}(\text{O})_2$ -lower alkyl;
 R^3 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or is lower alkoxy;
 R^4 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen, non
 5 cyclic amine, lower alkoxy or benzyloxy, optionally substituted by halogen;
 R^5/R^6 are independently from each other hydrogen, halogen, lower alkyl, lower alkoxy, aryl or form together the keto group $=\text{O}$;
 R' is hydrogen, halogen, lower alkyl, lower alkoxy, or benzyloxy optionally substituted by halogen;
 10 R'' is hydrogen, alkyl substituted by halogen, halogen, nitro, lower alkoxy, cyano, COO -lower alkyl, benzyloxy optionally substituted by halogen or $\text{S}(\text{O})_2$ -cyclic amine;

or

- R^3 and R'' or R^4 and R' or R'' and R^4 are together with the carbon atom to which they are
 15 attached $-\text{O}-(\text{CH}_2)_{1,2}-\text{O}-$ or $-\text{O}-(\text{CH}_2)_{2,3}-$ or $-(\text{CH}_2)_{2,3}-\text{O}-$, or



n is 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

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

25 Schizophrenia is a progressive and devastating neurological disease characterized by episodic positive symptoms such as delusions, hallucinations, thought disorders and psychosis and persistent negative symptoms such as flattened affect, impaired attention and social withdrawal, and cognitive impairments (Lewis DA and Lieberman JA, *Neuron*, 28:325-33, 2000). For decades research has focused on the "dopaminergic hyperactivity" hypothesis which has led to therapeutic interventions involving blockade of the
 30 dopaminergic system (Vandenberg RJ and Aubrey KR., *Exp. Opin. Ther. Targets*, 5(4): 507-518, 2001; Nakazato A and Okuyama S, et al., *Exp. Opin. Ther. Patents*, 10(1): 75-98, 2000). This pharmacological approach poorly address negative and cognitive symptoms which are the predictors of functional outcome (Sharma T., *Br.J. Psychiatry*,
 35 174(suppl. 28): 44-51, 1999).

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

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

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

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

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

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

Two distinct glycine transporter genes have been cloned (GlyT-1 and GlyT-2) from

mammalian brain, which give rise to two transporters with ~50 % amino acid sequence homology. GlyT-1 presents four isoforms arising from alternative splicing and alternative promoter usage (1a, 1b, 1c and 1d). Only two of these isoforms have been found in rodent brain (GlyT-1a and GlyT-1b). GlyT-2 also presents some degree of heterogeneity.

5 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-

10 Corcuera B et al., *Mol. Mem. Biol.*, 18: 13-20, 2001). Thus, one strategy to enhance NMDA receptor activity is to elevate the glycine concentration in the local microenvironment of synaptic NMDA receptors by inhibition of GlyT-1 transporter (Bergereon R. et al., *Proc. Natl. Acad. Sci. USA*, 95: 15730-15734, 1998; Chen L. et al., *J. Neurophysiol.*, 89(2): 691-703, 2003).

15 Glycine transporters inhibitors are suitable for the treatment of neurological and neuropsychiatric disorders. The majority of diseases states implicated are psychoses, schizophrenia (Armer RE and Miller DJ, *Exp. Opin. Ther. Patents*, 11 (4): 563-572, 2001), psychotic mood disorders such as severe major depressive disorder, mood disorders associated with psychotic disorders such as acute mania or depression, associated with

20 bipolar disorders and mood disorders, associated with schizophrenia, (Pralong ET et al., *Prog. Neurobiol.*, 67: 173-202, 2002), autistic disorders (Carlsson ML, *J. Neural Trans.*, 105: 525-535, 1998), cognitive disorders such as dementias, including age related dementia and senile dementia of the Alzheimer type, memory disorders in a mammal, including a human, attention deficit disorders and pain (Armer RE and Miller DJ, *Exp.*

25 *Opin. Ther. Patents*, 11 (4): 563-572, 2001).

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

Objects of the present invention are the compounds of formula I per se, the use of

30 compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases related to activation of NMDA receptors via Glyt-1 inhibition, their manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I in the control or prevention of illnesses such as psychoses, dysfunction in memory and

35 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.

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

As used herein, the term "cycloalkyl" denotes a saturated carbon ring, containing
10 from 3 to 6 carbon atoms.

The term "alkyl, substituted by halogen" denotes a saturated straight- or branched-chain group containing from 1 to 6 carbon atoms as defined above for "alkyl" and wherein at least one hydrogen atom is replaced by a halogen atom, for example CF₃, CHF₂, CH₂F, CH₂CF₃, CH₂CHF₂, CH₂CH₂F, CH₂CH₂CF₃, CH₂CH₂CH₂CF₃, CH₂CH₂Cl,
15 CH₂CF₂CF₃, CH₂CF₂CHF₂, CF₂CHF₂CF₃, C(CH₃)₂CF₃, CH(CH₃)CF₃ or CH(CH₂F)CH₂F. Preferred are CH₂CF₃ or CF₃.

The term "lower alkoxy" denotes a saturated straight- or branched-chain group containing from 1 to 6 carbon atoms as described above and which groups are connected via an oxygen atom.

20 The term "cyclic amine" denotes a 5 – 7 membered non aromatic cyclic group, containing at least one N-atom and may contain in addition to the N atom a further heteroatom, selected from N, O or S, for example pyrrol-1-yl, piperidin-1-yl, piperazin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, 1-oxo-thiomorpholin-4-yl or 1,1-dioxo-thiomorpholin-4-yl.

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

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid,
30 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 I are those, wherein R^1 is OR^{11} and R^2 is SO_2CH_3 .
Most preferred compounds of formula I are those of formula IA-4.

Especially preferred are compounds of this group, wherein at least one of R^3 , R'' , R^4 or R' is halogen, for example

- 5 (6-chloro-3,4-dihydro-1H-isoquinolin-2-yl)-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone,
(6-chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
(7-chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-
10 methanone,
(7,8-dichloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone or
(8-chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone.

- 15 Further preferred are compounds of this group, wherein at least one of R^3 , R'' , R^4 or R' is alkyl substituted by halogen, for example
(2-isopropoxy-5-methanesulfonyl-phenyl)-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone,
(5-methanesulfonyl-2-morpholin-4-yl-phenyl)-(6-trifluoromethyl-3,4-dihydro-1H-
20 isoquinolin-2-yl)-methanone,
[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone or
(4-methanesulfonyl-biphenyl-2-yl)-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone.

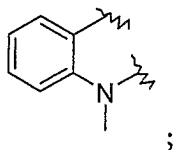
- 25 Further preferred are compounds of this group, wherein at least one of R^3 , R'' , R^4 or R' is CN, for example
2-(2-isopropoxy-5-methanesulfonyl-benzoyl)-1,2,3,4-tetrahydro-isoquinoline-6-carbonitrile.

- Further preferred are compounds of this group, wherein at least one of R^3 , R'' , R^4 or
30 R' is lower alkoxy, for example
(2-isopropoxy-5-methanesulfonyl-phenyl)-(6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-methanone.

A further preferred group of compounds of formula IA-4 are those, wherein R^1 is S-lower alkyl, for example

- 35 (6-chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropylsulfonyl-5-methanesulfonyl-phenyl)-methanone.

Preferred are further compounds, wherein one of R³ and R'' or R⁴ and R' or R'' and R⁴ are together with the carbon atom to which they are attached -O-CH₂-O- or



for example the following compounds:

- 5 (2-isopropoxy-5-methanesulfonyl-phenyl)-(11-methyl-1,2,4,11-tetrahydro-pyrido[4,3-a]carbazol-3-yl)-methanone or
 ((4,9-dimethyl-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-6-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone.

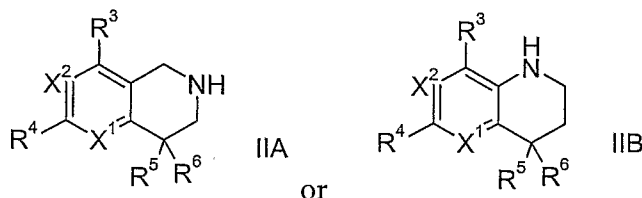
A preferred group of compounds are those from formula IA-3, for example

- 10 (4-methanesulfonyl-biphenyl-2-yl)-(2-trifluoromethyl-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-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

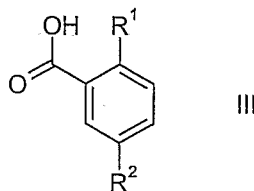
- 15 below, which process comprises

a) reacting a compound of formula IIA or IIB



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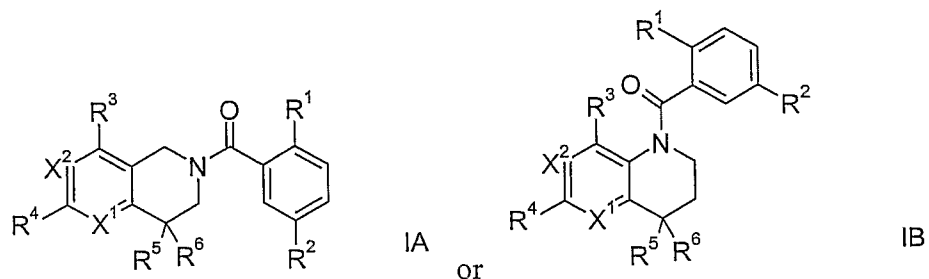
with a compound of formula III



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

- 25 to a compound of formula IA or IB

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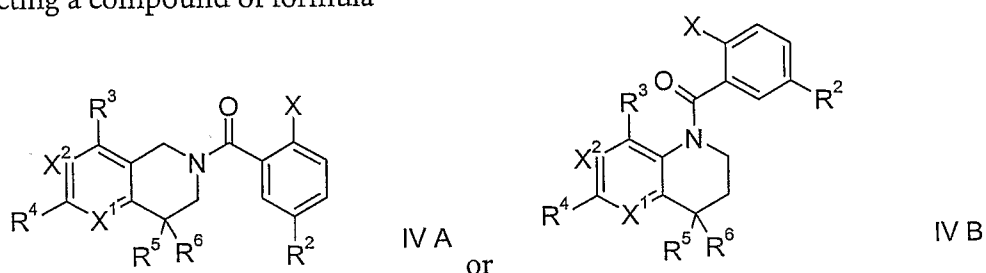


wherein the substituents are as defined above,

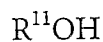
or

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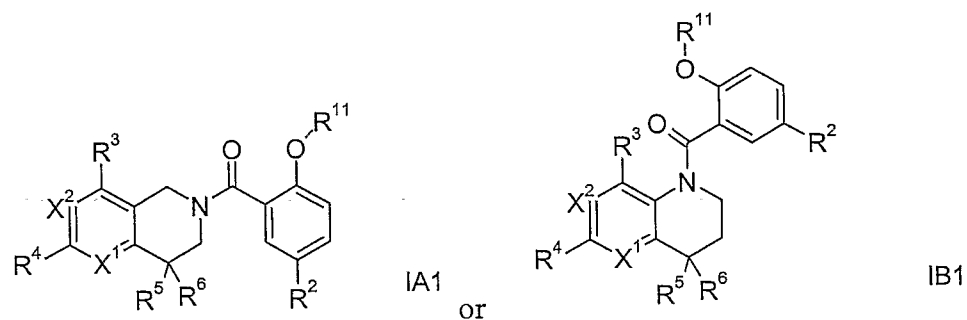
b) reacting a compound of formula



10 with a compound of formula



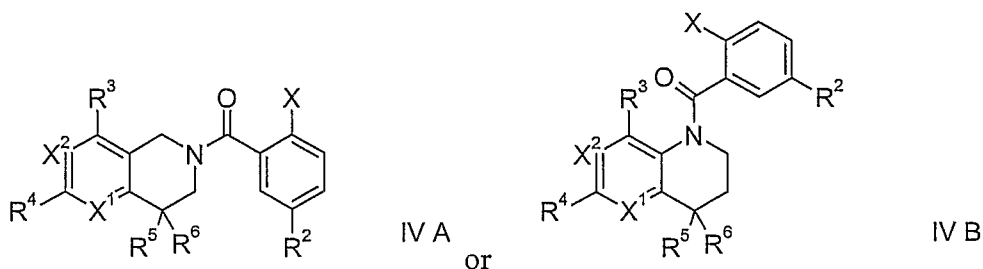
optionally in the presence of a catalyst, such as Cu(I)I and a base like potassium carbonate, cesium carbonate or sodium, to a compound of formula IA1 or IB1



15

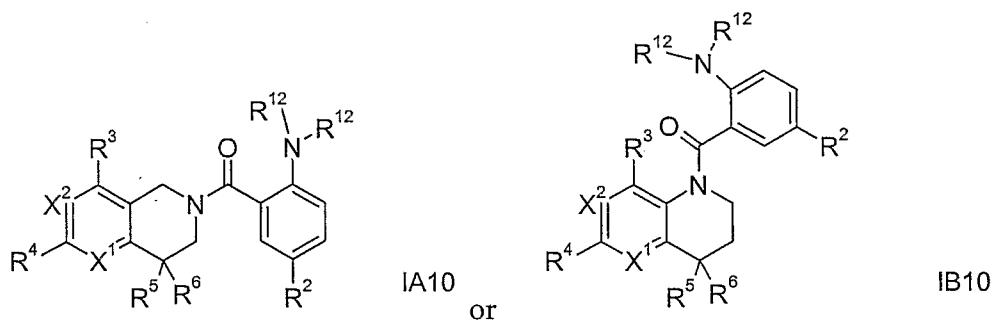
wherein X is halogen, the other substituents are as defined above, or

20 c) reacting a compound of formula



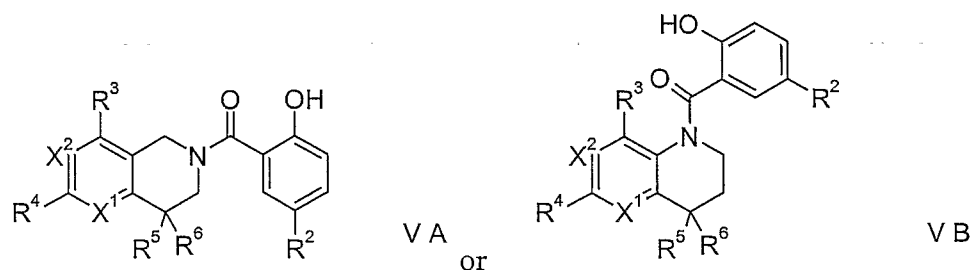
with a compound of formula

5 $\text{NH}(\text{R}^{12})_2$ or with a cyclic amine
optionally in the presence of a catalyst, such as Cu(I)I and a base like potassium
carbonate, cesium carbonate or sodium,
to a compound of formula IA10 or IB10



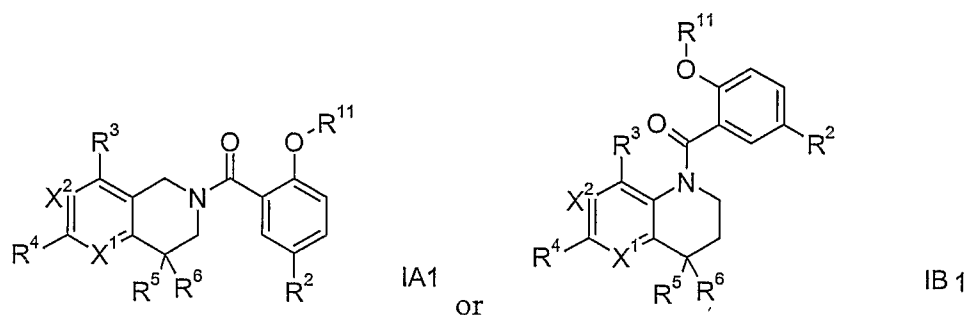
wherein X is halogen, R¹² is as defined above or the two R¹² together with the N-atom may form a cyclic amine and the other substituents are as defined above, or

15 d) reacting a compound of formula



with a compound of formula

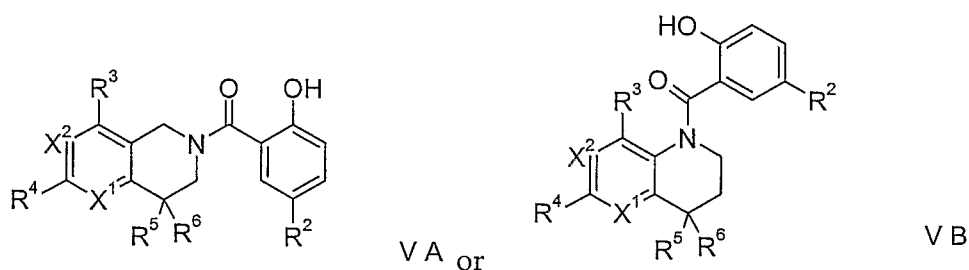
20 R^{11}X
in the presence of a base and optionally in the presence of microwaves
to a compound of formula IA1 or IB1



wherein X is halogen, mesylate or triflate and R^{11} is lower alkyl, lower alkyl substituted by halogen or $(CH_2)_n$ -cycloalkyl:

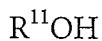
5 or

e) reacting a compound of formula

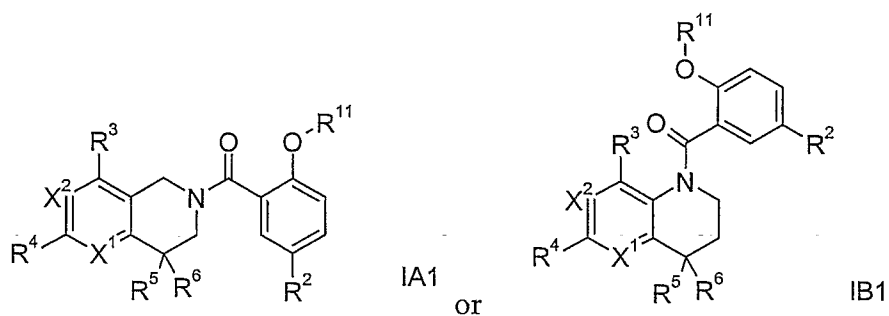


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with a compound of formula



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



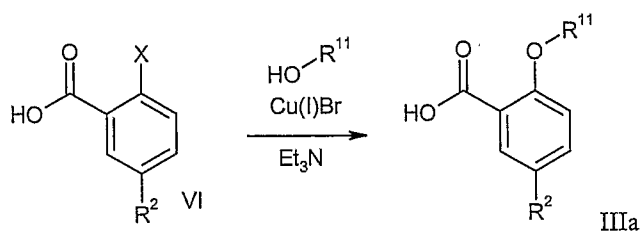
15

wherein the substituents are as defined above.

Compounds of the formula IIA or IIB are either commercially available, their preparation is described in the chemical literature or they can be prepared by methods known in the art.

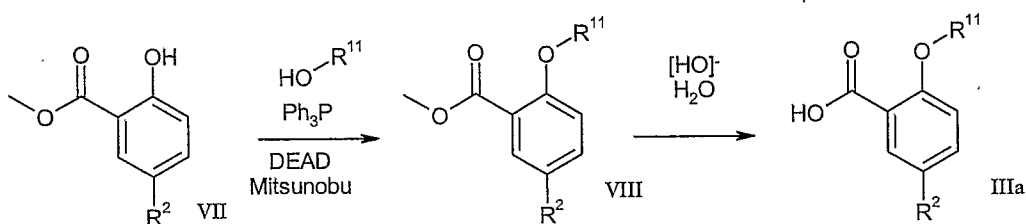
Compounds of formula III may be prepared as follow:

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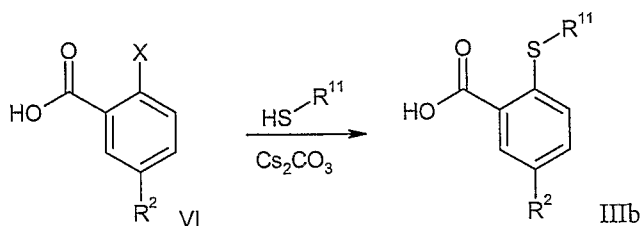
Scheme 1

where X = halogen

For example, compounds of formula IIIa where R¹¹ is lower alkyl, lower alkyl,
 5 substituted by halogen or -(CH₂)_n-cycloalkyl, can be prepared by reaction of a halogen
 compound of formula VI with an alcohol of formula R¹¹OH, optionally in the presence of
 a copper salt like Cu(I)Br and a base, such as triethylamine (Scheme 1), at elevated
 temperature.

Scheme 2

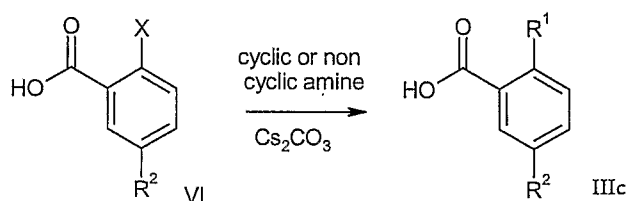
Alternatively, compounds of formula IIIa, where R¹¹ is lower alkyl, lower alkyl,
 substituted by halogen or -(CH₂)_n-cycloalkyl can be prepared by reacting a hydroxy
 compound of formula VII with an alcohol of formula R¹¹OH, under Mitsunobu reaction
 15 conditions in the presence of a phosphine like triphenylphosphine or diphenyl-2-
 pyridylphosphine, and a dialkylazodicarboxylate like diethylazodicarboxylate or di-tert-
 butyl azodicarboxylate, to afford intermediate compounds of formula VIII, followed by
 hydrolysis in the presence of an aqueous base such as potassium hydroxide, sodium
 hydroxide or lithium hydroxide (Scheme 2).

Scheme 3

where X = halogen

Compounds of formula IIIb where R^{11} is lower alkyl, lower alkyl, substituted by halogen or $-(CH_2)_n$ -cycloalkyl, can be prepared by reaction of a halogen compound of formula VI with a thiol of formula $R^{11}SH$, optionally in the presence of a base, such as cesium carbonate, potassium carbonate or sodium carbonate (Scheme 3), at elevated temperature.

Scheme 4



where X = halogen

10

Compounds of formula IIIc where R^1 is a cyclic amine or $NH(R^{12})_2$, can be prepared by reaction of a halogen compound of formula VI with an amine, optionally in the presence of a base, such as cesium carbonate, potassium carbonate or sodium carbonate (Scheme 4), at elevated temperature.

The halogen-substituted and hydroxy-substituted starting materials of formula VI are either commercially available, are otherwise known in the chemical literature, or may be prepared using a variety of methods well known in the art.

Isolation and purification of the compounds

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

Salts of compounds of formula I

The compounds of formula I may be basic, for example in cases where the residue R¹ contains a basic group such as an aliphatic or aromatic amine moiety. In such cases the compounds of formula I may be converted to a corresponding acid addition salt.

5 The conversion is accomplished by treatment with at least a stoichiometric amount of an appropriate acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid,
10 methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol or methanol and the like, and the acid added in a similar solvent. The temperature is maintained between 0 °C and 50 °C. The resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

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

20 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

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

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

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

Glycine uptake inhibition assay (mGlyT-1b)

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

15 The preferred compounds show an IC₅₀ (μM) at GlyT-1 in the range of 0.040 – 0.500 as shown in the table below.

Example No.	IC ₅₀ (μM)	Example No.	IC ₅₀ (μM)	Example No.	IC ₅₀ (μM)
1.8	0.082	1.18	0.157	1.30	0.344
1.12	0.046	1.19	0.359	1.40	0.481
1.13	0.321	1.20	0.454	1.47	0.159
1.14	0.175	1.25	0.215	1.53	0.483
1.15	0.168	1.26	0.163	1.57	0.160

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
 20 preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I can be processed with pharmaceutically inert
 25 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
5 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,
10 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
15 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,
20 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
25 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	<u>Ingredients</u>	<u>mg/tablet</u>			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
5 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

10 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.

15 Capsule Formulation

Item	<u>Ingredients</u>	<u>mg/capsule</u>			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
20 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

- 25 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.

EXPERIMENTAL PART :

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

The following abbreviations have been used:

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

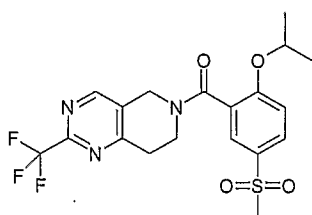
DIPEA = Ethyl-diisopropyl-amine

Oxone® = potassium peroxymonosulfate $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$

5

Example 1.1

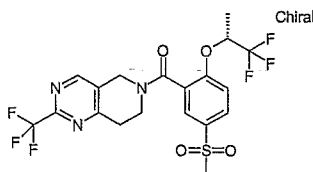
Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(2-trifluoromethyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-methanone



- 10 A solution of 0.23 mmol 2-trifluoromethyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine (CA [74737-17-7]; WO2004069162), 0.23 mmol 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1) and 1.1 mmol of DIPEA in 5 ml of acetonitrile was treated with 0.25 mmol TBTU. The reaction mixture was stirred at room temperature for one hour, concentrated and hydrolyzed with 5 ml of water. Extraction with ethyl acetate
- 15 yields a crude product which is purified by chromatography (SiO_2 ; ethyl acetate) to give, after trituration in diethyl ether, the title compound as a colorless solid. Yield = 83%. MS (m/e): 444.4 ($\text{M}+\text{H}^+$).

Example 1.2

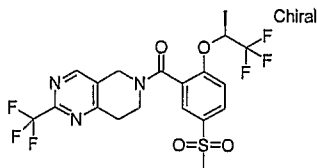
- 20 Preparation of [5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-(2-trifluoromethyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-methanone



- Prepared in analogy to example 1.1 from 2-trifluoromethyl-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine (CA [74737-17-7]; WO2004069162) and 5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (example 2.3). MS (m/e): 498.4 ($\text{M}+\text{H}^+$).
- 25

Example 1.3

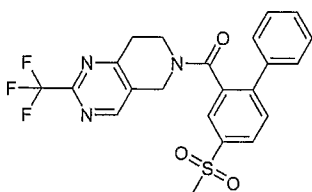
- Preparation of [5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-(2-trifluoromethyl-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-methanone
- 30



Prepared in analogy to example 1.1 from 2-trifluoromethyl-5,6,7,8-tetrahydro-
pyrido[4,3-d]pyrimidine (CA [74737-17-7]; WO2004069162) and 5-methanesulfonyl-2-
((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (example 2.2). MS (m/e): 498.4
5 (M+H⁺).

Example 1.4

Preparation of (4-Methanesulfonyl-biphenyl-2-yl)-(2-trifluoromethyl-7,8-dihydro-5H-
pyrido[4,3-d]pyrimidin-6-yl)-methanone



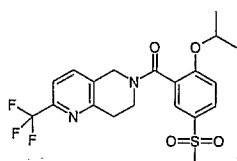
10

Prepared in analogy to example 1.1 from 2-trifluoromethyl-5,6,7,8-tetrahydro-
pyrido[4,3-d]pyrimidine (CA [74737-17-7]; WO2004069162) and 4-methanesulfonyl-
biphenyl-2-carboxylic acid (example 2.5). MS (m/e): 462.0 (M+H⁺).

15

Example 1.5

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(2-trifluoromethyl-7,8-
dihydro-5H-[1,6]naphthyridin-6-yl)-methanone



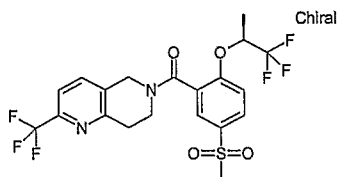
Prepared in analogy to example 1.1 from 2-trifluoromethyl-5,6,7,8-tetrahydro-
[1,6]naphthyridine hydrochloride (CA [741736-98-1]; WO2004069162) and 2-
isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 443.5 (M+H⁺).

20

Example 1.6

Preparation of [5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-(2-
trifluoromethyl-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-methanone

25

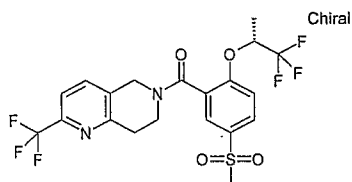


Prepared in analogy to example 1.1 from 2-trifluoromethyl-5,6,7,8-tetrahydro-[1,6]naphthyridine hydrochloride (CA [741736-98-1]; WO2004069162) and 5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (example 2.2).

5 MS (m/e): 497.5 (M+H⁺).

Example 1.7

Preparation of [5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-(2-trifluoromethyl-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-methanone



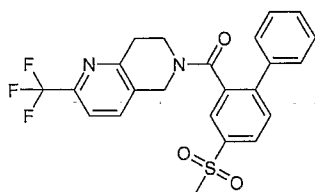
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Prepared in analogy to example 1.1 from 2-trifluoromethyl-5,6,7,8-tetrahydro-[1,6]naphthyridine hydrochloride (CA [741736-98-1]; WO2004069162) and 5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (example 2.3).
MS (m/e): 497.5 (M+H⁺).

15

Example 1.8

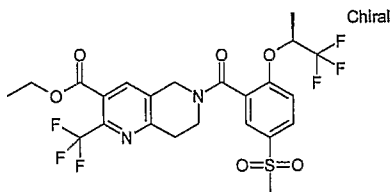
Preparation of (4-Methanesulfonyl-biphenyl-2-yl)-(2-trifluoromethyl-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-methanone



20 Prepared in analogy to example 1.1 from 2-trifluoromethyl-5,6,7,8-tetrahydro-[1,6]naphthyridine hydrochloride (CA [741736-98-1]; WO2004069162) and 4-methanesulfonyl-biphenyl-2-carboxylic acid (example 2.5). MS (m/e): 461.3 (M+H⁺).

Example 1.9

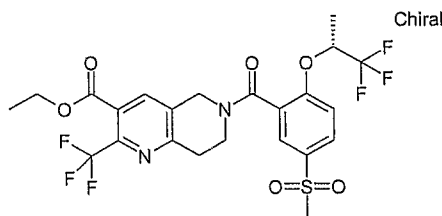
25 Preparation of 6-[5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-2-trifluoromethyl-5,6,7,8-tetrahydro-[1,6]naphthyridine-3-carboxylic acid ethyl ester



Prepared in analogy to example 1.1 from 2-trifluoromethyl-5,6,7,8-tetrahydro-[1,6]naphthyridine-3-carboxylic acid ethyl ester hydrochloride (CA [741736-90-3]; WO2004069162) and 5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (example 2.2). MS (m/e): 569.0 (M+H⁺).

Example 1.10

Preparation of 6-[5-Methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoyl]-2-trifluoromethyl-5,6,7,8-tetrahydro-[1,6]naphthyridine-3-carboxylic acid ethyl ester



10

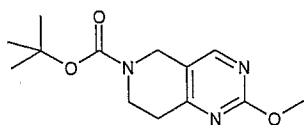
Prepared in analogy to example 1.1 from 2-trifluoromethyl-5,6,7,8-tetrahydro-[1,6]naphthyridine-3-carboxylic acid ethyl ester hydrochloride (CA [741736-90-3]; WO2004069162) and 5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (example 2.3). MS (m/e): 569.0 (M+H⁺).

15

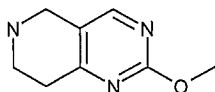
Example 1.11

Preparation of [5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-(2-methoxy-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-methanone

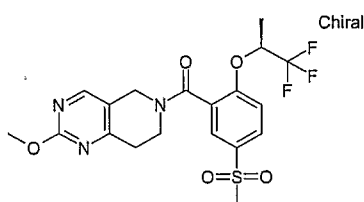
20 (a) 2-Methoxy-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylic acid tert-butyl ester



A mixture of 8.0 mmol 3-dimethylaminomethylene-4-oxo-piperidine-1-carboxylic acid tert-butyl ester (CA [157327-41-8]) and 10 mmol O-methylisourea hydrochloride in 25 ml ethanol is treated with 11 mmol triethylamine and 5 drops of water. The suspension is refluxed overnight, concentrated and diluted with 100 ml water. Extraction with ethyl acetate and chromatography (SiO₂; ethyl acetate / n-heptane 1:1) gives the title compound as a yellowish oil. Yield = 28%. MS (m/e): 266.3 (M+H⁺).

(b) 2-Methoxy-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine

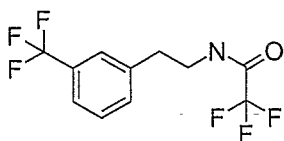
2 mmol 2-Methoxy-7,8-dihydro-5H-pyrido[4,3-d]pyrimidine-6-carboxylic acid tert-butyl ester is dissolved in 15 ml dichloromethane and 10 mmol trifluoroacetic acid is added. The reaction mixture is stirred for 30 minutes at 40° C, concentrated and neutralized by addition of aqueous sodium carbonate. Extraction with ethyl acetate yields the crude title compound as a brownish oil. MS (m/e): 166.4 (M+H⁺).

(c) [5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-(2-methoxy-7,8-dihydro-5H-pyrido[4,3-d]pyrimidin-6-yl)-methanone

Prepared in analogy to example 1.1 from 2-methoxy-5,6,7,8-tetrahydro-pyrido[4,3-d]pyrimidine and 5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (example 2.2). MS (m/e): 460.4 (M+H⁺).

Example 1.12

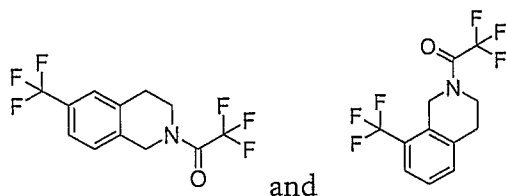
Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

(a) 2,2,2-Trifluoro-N-[2-(3-trifluoromethyl-phenyl)-ethyl]-acetamide

A solution of 14 mmol 2-(3-trifluoromethylphenyl)-ethylamine in 10 ml dichloromethane is slowly added with stirring over 15 minutes to an ice-cooled solution of 42 mmol trifluoroacetic anhydride in 10 ml dichloromethane. After completion of the addition, the reaction mixture is stirred for additional 2 hours at room temperature, then poured into 100 ml of water. The pH is carefully adjusted to 7 by addition of solid sodium hydrogencarbonate. The organic layer is dried and concentrated to give the title compound as a colorless oil which solidifies upon standing. Yield = 94%. MS (m/e): 284.1 (M-H⁺).

(b) 2,2,2-Trifluoro-1-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

and

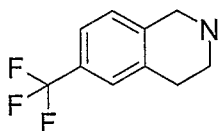
2,2,2-Trifluoro-1-(8-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

15 ml of acetic acid are slowly added to 20 ml of concentrated (97%) sulfuric acid; the reaction is strongly exothermic. After cooling to room temperature, 11 mmol of 2,2-trifluoro-N-[2-(3-trifluoromethyl-phenyl)-ethyl]-acetamide and 16 mmol of paraformaldehyde is added. The solution is stirred overnight at room temperature, then poured into 100ml of an ice water mixture. Extraction with ethyl acetate yields the crude product, consisting of a mixture of the two title regioisomers. Chromatography (SiO₂; ethyl acetate / cyclohexane 1:9) yields 2,2,2-trifluoro-1-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone as the most rapidly eluting fraction. Yield of the colorless solid = 43%. MS (m/e): 297.1 (M-H⁺).

The compound with longer elution times is the 2,2,2-trifluoro-1-(8-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone. Colorless solid. Yield = 30%.

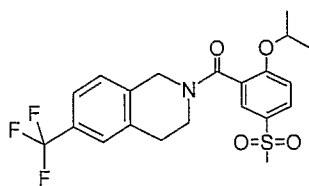
MS (m/e): 297.1 (M+H⁺).

15 (c) 6-Trifluoromethyl-1,2,3,4-tetrahydro-isoquinoline



A solution of 4 mmol 2,2,2-trifluoro-1-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone in 12 ml ethanol is treated with 11 ml of 2M aqueous sodium hydroxide. The reaction mixture is stirred for 1 hour at room temperature, concentrated, diluted with water and extracted 3 times with ethyl acetate to give the title compound as a yellowish oil. Yield = 83%. MS (m/e): 202.2 (M+H⁺).

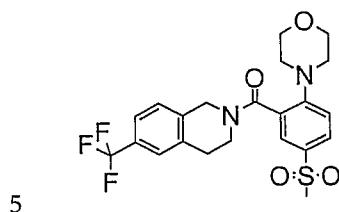
(d) (2-Isopropoxy-5-methanesulfonyl-phenyl)-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone



25 Prepared in analogy to example 1.1 from 6-trifluoromethyl-1,2,3,4-tetrahydro-isoquinoline and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 442.1 (M+H⁺).

Example 1.13

Preparation of (5-Methanesulfonyl-2-morpholin-4-yl-phenyl)-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

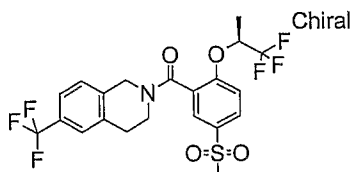


Prepared in analogy to example 1.1 from 6-trifluoromethyl-1,2,3,4-tetrahydro-isoquinoline and 5-methanesulfonyl-2-morpholin-4-yl-benzoic acid (Example 2.4).
MS (m/e): 469.5 (M+H⁺).

10

Example 1.14

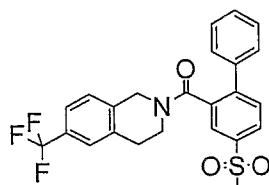
Preparation of [5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone



15 Prepared in analogy to example 1.1 from 6-trifluoromethyl-1,2,3,4-tetrahydro-isoquinoline and 5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (example 2.2). MS (m/e): 496.0 (M+H⁺).

Example 1.15

20 Preparation of (4-Methanesulfonyl-biphenyl-2-yl)-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone



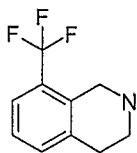
Prepared in analogy to example 1.1 from 6-trifluoromethyl-1,2,3,4-tetrahydro-isoquinoline and 4-methanesulfonyl-biphenyl-2-carboxylic acid (example 2.5).
MS (m/e): 460.1 (M+H⁺).

25

Example 1.16

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(8-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

(a) 8-Trifluoromethyl-1,2,3,4-tetrahydro-isoquinoline

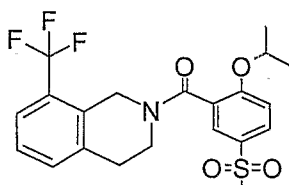


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Prepared in analogy to example 1.12 (c) from 2,2,2-trifluoro-1-(8-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone (example 1.12 (b)) and sodium hydroxide.

MS (m/e): 202.2 (M+H⁺).

10 (b) (2-Isopropoxy-5-methanesulfonyl-phenyl)-(8-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

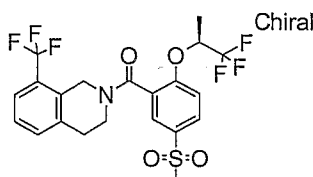


Prepared in analogy to example 1.1 from 8-trifluoromethyl-1,2,3,4-tetrahydro-isoquinoline and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).

15 MS (m/e): 460.1 (M+CH₃COO⁺).

Example 1.17

Preparation of [5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-(8-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone



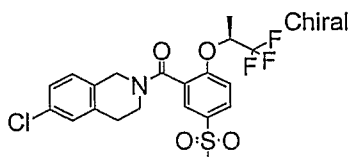
20

Prepared in analogy to example 1.1 from 8-trifluoromethyl-1,2,3,4-tetrahydro-isoquinoline and 5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (example 2.2). MS (m/e): MS (m/e): 496.4 (M+H⁺).

25

Example 1.18

Preparation of (6-Chloro-3,4-dihydro-1H-isoquinolin-2-yl)-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone

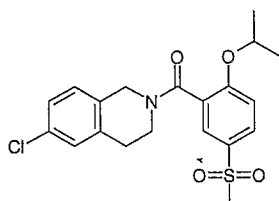


Prepared in analogy to example 1.1 from 6-chloro-1,2,3,4-tetrahydro-isoquinoline (CA [33537-99-4]) and 5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid (example 2.2). MS (m/e): MS (m/e): 462.0 (M+H⁺).

5

Example 1.19

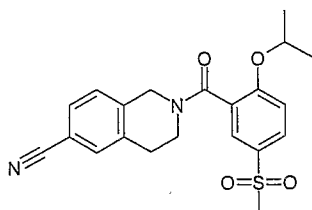
Preparation of (6-Chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



- 10 Prepared in analogy to example 1.1 from 6-chloro-1,2,3,4-tetrahydro-isoquinoline (CA [33537-99-4]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 408.0 (M+H⁺).

Example 1.20

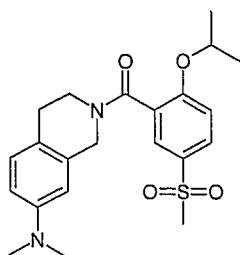
- 15 Preparation of 2-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-1,2,3,4-tetrahydro-isoquinoline-6-carbonitrile



- Prepared in analogy to example 1.1 from 6-cyano-1,2,3,4-tetrahydro-isoquinoline (CA [166398-34-1]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
20 MS (m/e): 399.4 (M+H⁺).

Example 1.21

Preparation of (7-Dimethylamino-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



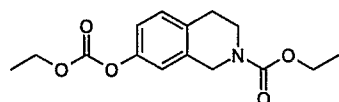
Prepared in analogy to example 1.1 from dimethyl-(1,2,3,4-tetrahydro-isoquinolin-7-yl)-amine (CA [138276-84-3]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 417.4 (M+H⁺).

5

Example 1.22

Preparation of [7-(4-Chloro-benzyloxy)-3,4-dihydro-1H-isoquinolin-2-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

(a) 7-Ethoxycarbonyloxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethyl ester



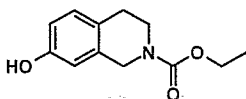
10

A solution of 20 mmol 1,2,3,4-tetrahydro-isoquinolin-7-ol and 140 mmol triethylamine in 300 ml tetrahydrofuran is cooled to 5° C and treated dropwise 120 mmol chloroethyl formate. The reaction mixture is stirred overnight at room temperature, hydrolyzed with 50 ml water and extracted 3 times with diethyl ether. The organic phase is concentrated and the crude mixture purified by chromatography (SiO₂; ethyl acetate / cyclohexane 1:9) to give the title compound.

15

Yield = 54%.

(b) 7-Hydroxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethyl ester

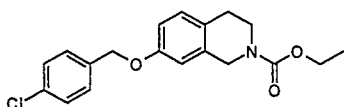


20

A mixture of 11 mmol 7-ethoxycarbonyloxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethyl ester, 14 mmol potassium carbonate, 0.6 ml water and 200 ml ethanol is stirred for 5 hours at room temperature. The reaction mixture is concentrated, diluted with 100 ml water and the pH adjusted to 7 by addition of diluted hydrochloric acid. Extraction with diethyl ether and purification by chromatography (SiO₂; ethyl acetate / cyclohexane 1:1) gives the title compound. Yield = 92%.

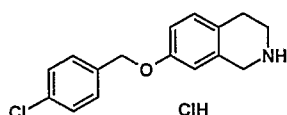
25

(c) 7-(4-Chloro-benzyloxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethyl ester

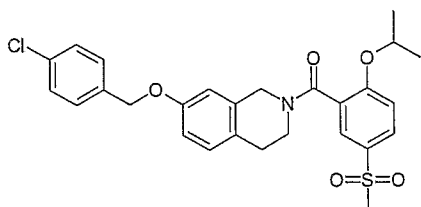


- A solution of 10 mmol 7-hydroxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethyl ester in 25 ml N,N-dimethylformamide is treated with 20 mmol potassium carbonate, cooled to 5° C and 12.5 mmol of 4-chlorobenzyl bromide is added. The reaction mixture is stirred for 4 hours at room temperature, quenched with water and extracted 3 times with ethyl acetate. The organic phase is dried, concentrated and purified by chromatography (SiO₂; ethyl acetate / cyclohexane 1:9) to give the title compound. Yield = 71%.

(d) 7-(4-Chloro-benzyloxy)-1,2,3,4-tetrahydro-isoquinoline hydrochloride



- 10 A solution of 7.2 mmol 7-(4-chloro-benzyloxy)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid ethyl ester in 100 ml ethanol and 35 ml 5M aqueous sodium hydroxide is refluxed overnight. The reaction mixture is concentrated, diluted with water and acidified with conc. hydrochloric acid. The precipitate is filtered off and dried to give the title compound. Yield = 77%.
- 15 (e) [7-(4-Chloro-benzyloxy)-3,4-dihydro-1H-isoquinolin-2-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

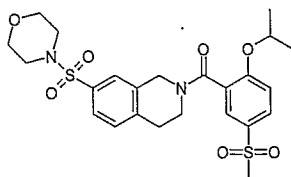


Prepared in analogy to example 1.1 from 7-(4-chloro-benzyloxy)-1,2,3,4-tetrahydro-isoquinoline and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).

- 20 MS (m/e): 514.2 (M+H⁺).

Example 1.23

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-[7-(morpholine-4-sulfonyl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone

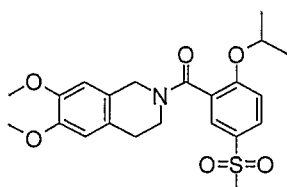


25

Prepared in analogy to example 1.1 from 7-(morpholine-4-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline (CA [185059-05-6]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 523.2 (M+H⁺).

Example 1.24

Preparation of (6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



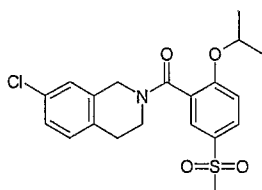
5

Prepared in analogy to example 1.1 from 6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (CA [1745-07-9]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
MS (m/e): 434.1 (M+H⁺).

10

Example 1.25

Preparation of (7-Chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



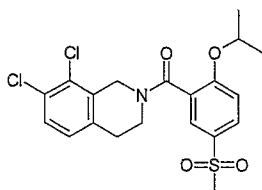
15

Prepared in analogy to example 1.1 from 7-chloro-1,2,3,4-tetrahydro-isoquinoline (CA [82771-60-6]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
MS (m/e): 408.1 (M+H⁺).

20

Example 1.26

Preparation of (7,8-Dichloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



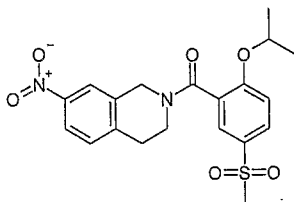
25

Prepared in analogy to example 1.1 from 7,8-dichloro-1,2,3,4-tetrahydro-isoquinoline (CA [61563-24-4]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
MS (m/e): 442.3 (M+H⁺).

5

Example 1.27

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(7-nitro-3,4-dihydro-1H-isoquinolin-2-yl)-methanone



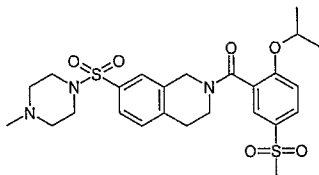
Prepared in analogy to example 1.1 from 7-nitro-1,2,3,4-tetrahydro-isoquinoline (CA [42923-79-5]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
MS (m/e): 419.3 (M+H⁺).

10

Example 1.28

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-[7-(4-methyl-piperazine-1-sulfonyl)-3,4-dihydro-1H-isoquinolin-2-yl]-methanone

15

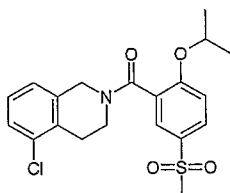


Prepared in analogy to example 1.1 from 7-(4-methyl-piperazine-1-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline (CA [741674-53-3]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 536.3 (M+H⁺).

20

Example 1.29

Preparation of (5-Chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

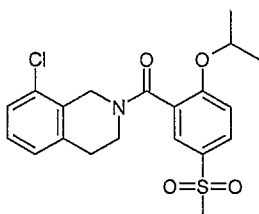


Prepared in analogy to example 1.1 from 5-chloro-1,2,3,4-tetrahydro-isoquinoline (CA [73075-43-1]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
MS (m/e): 408.0 (M+H⁺).

25

Example 1.30

Preparation of (8-Chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



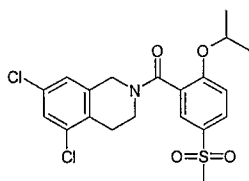
5

Prepared in analogy to example 1.1 from 8-chloro-1,2,3,4-tetrahydro-isoquinoline (CA [61563-33-5]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
MS (m/e): 408.3 (M+H⁺).

10

Example 1.31

Preparation of (5,7-Dichloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



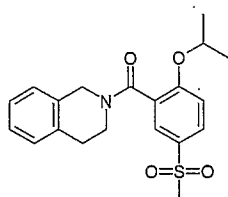
15

Prepared in analogy to example 1.1 from 5,7-dichloro-1,2,3,4-tetrahydro-isoquinoline (CA [89315-56-0]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
MS (m/e): 442.1 (M+H⁺).

20

Example 1.32

Preparation of (3,4-Dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

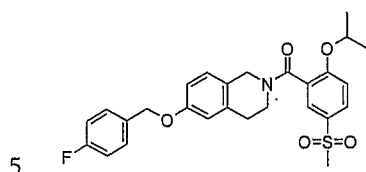


25

Prepared in analogy to example 1.1 from 1,2,3,4-tetrahydro-isoquinoline (CA [473443-13-9]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
MS (m/e): 374.4 (M+H⁺).

Example 1.33

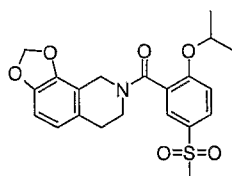
Preparation of [6-(4-Fluoro-benzyloxy)-3,4-dihydro-1H-isoquinolin-2-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



Prepared in analogy to example 1.1 from 6-(4-fluoro-benzyloxy)-1,2,3,4-tetrahydro-isoquinoline (CA [620606-78-2]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 498.4 ($M+H^+$).

Example 1.34

Preparation of (6,9-Dihydro-7H-[1,3]dioxolo[4,5-h]isoquinolin-8-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

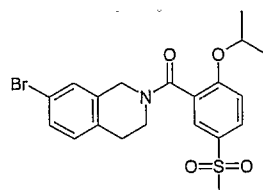


Prepared in analogy to example 1.1 from 6,7,8,9-tetrahydro-[1,3]dioxolo
 15 [4,5-h]isoquinoline (CA [87091-23-4]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 418.1 ($M+H^+$).

Example 1.35

Preparation of (7-Bromo-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

20

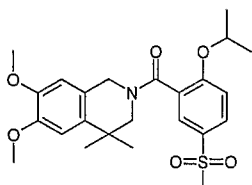


Prepared in analogy to example 1.1 from 7-bromo-1,2,3,4-tetrahydro-isoquinoline (CA [17680-55-6]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 454.2 ($\{^{81}\text{Br}\}M+H^+$), 452.1 ($\{^{79}\text{Br}\}M+H^+$).

25

Example 1.36

Preparation of (6,7-Dimethoxy-4,4-dimethyl-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



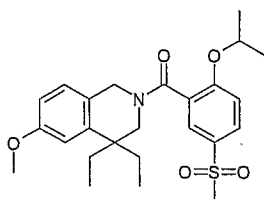
5

Prepared in analogy to example 1.1 from 6,7-dimethoxy-4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (CA [57553-25-0]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 462.5 (M+H⁺).

10

Example 1.37

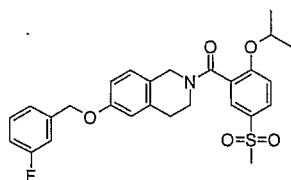
Preparation of (4,4-Diethyl-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



15 Prepared in analogy to example 1.1 from 4,4-diethyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 460.5 (M+H⁺).

Example 1.38

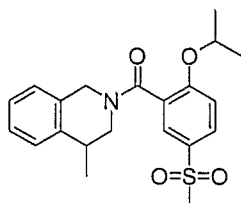
20 Preparation of [6-(3-Fluoro-benzyloxy)-3,4-dihydro-1H-isoquinolin-2-yl]-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



25 Prepared in analogy to example 1.1 from 6-(3-fluoro-benzyloxy)-1,2,3,4-tetrahydroisoquinoline ((CA [620606-74-8]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 498.4 (M+H⁺).

Example 1.39

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(4-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

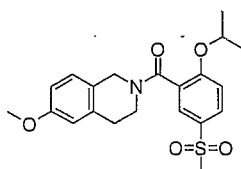


- 5 Prepared in analogy to example 1.1 from 4-methyl-1,2,3,4-tetrahydro-isoquinoline (CA [110841-71-9]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
MS (m/e): 388.4 (M+H⁺).

Example 1.40

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

10

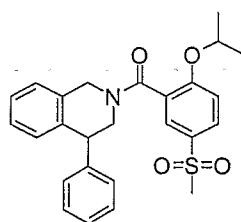


Prepared in analogy to example 1.1 from 6-methoxy-1,2,3,4-tetrahydro-isoquinoline (CA [42923-77-3]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
MS (m/e): 404.5 (M+H⁺).

15

Example 1.41

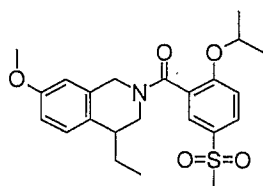
Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(4-phenyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone



- 20 Prepared in analogy to example 1.1 from 4-phenyl-1,2,3,4-tetrahydro-isoquinoline (CA [42923-77-3]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
MS (m/e): 450.4 (M+H⁺).

Example 1.42

- 25 Preparation of (4-Ethyl-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



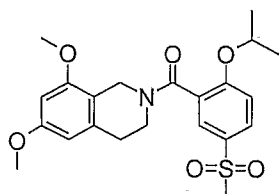
Prepared in analogy to example 1.1 from 4-ethyl-7-methoxy-1,2,3,4-tetrahydro-isoquinoline and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).

MS (m/e): 432.5 (M+H⁺).

5

Example 1.43

Preparation of (6,8-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

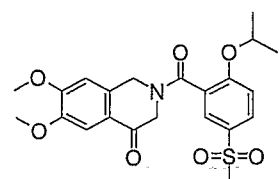


10 Prepared in analogy to example 1.1 from 6,8-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (CA [88207-92-5]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).

MS (m/e): 434.4 (M+H⁺).

Example 1.44

15 Preparation of 2-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-6,7-dimethoxy-2,3-dihydro-1H-isoquinolin-4-one

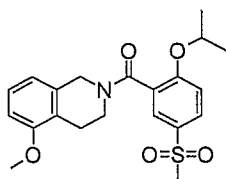


Prepared in analogy to example 1.1 from 6,7-dimethoxy-2,3-dihydro-1H-isoquinolin-4-one (CA [206763-75-9]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example

20 2.1). MS (m/e): 448.3 (M+H⁺).

Example 1.45

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(5-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

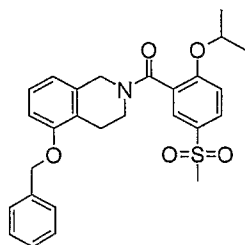


Prepared in analogy to example 1.1 from 5-methoxy-1,2,3,4-tetrahydro-isoquinoline (CA [103030-70-2]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
MS (m/e): 404.4 (M+H⁺).

5

Example 1.46

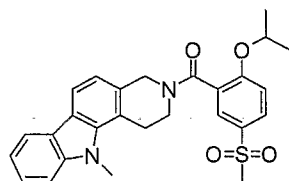
Preparation of (5-Benzyloxy-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



- 10 Prepared in analogy to example 1.1 from 6-benzyloxy-1,2,3,4-tetrahydro-isoquinoline (CA [189745-29-7]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
MS (m/e): 480.5 (M+H⁺).

Example 1.47

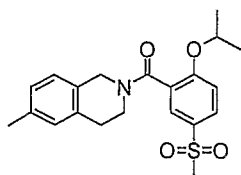
- 15 Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(11-methyl-1,2,4,11-tetrahydro-pyrido[4,3-a]carbazol-3-yl)-methanone



- Prepared in analogy to example 1.1 from 11-methyl-2,3,4,11-tetrahydro-1H-pyrido[4,3-a]carbazole and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
20 MS (m/e): 477.4 (M+H⁺).

Example 1.48

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(6-methyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone

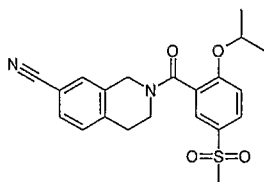


Prepared in analogy to example 1.1 from 6-methyl-1,2,3,4-tetrahydro-isoquinoline (CA [42923-76-2]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 388.4 (M+H⁺).

5

Example 1.49

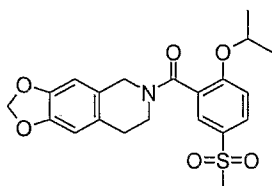
Preparation of 2-(2-Isopropoxy-5-methanesulfonyl-benzoyl)-1,2,3,4-tetrahydro-isoquinoline-7-carbonitrile



- 10 Prepared in analogy to example 1.1 from 7-cyano-1,2,3,4-tetrahydro-isoquinoline (CA [149355-52-2]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 399.1 (M+H⁺).

Example 1.50

- 15 Preparation of (7,8-Dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-6-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

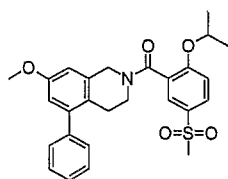


- Prepared in analogy to example 1.1 from 5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (CA [94143-83-6]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 418.4 (M+H⁺).

20

Example 1.51

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(7-methoxy-5-phenyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone



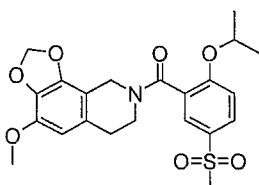
Prepared in analogy to example 1.1 from 7-methoxy-5-phenyl-1,2,3,4-tetrahydroisoquinoline and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).

MS (m/e): 480.5 (M+H⁺).

5

Example 1.52

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(4-methoxy-6,9-dihydro-7H-[1,3]dioxolo[4,5-h]isoquinolin-8-yl)-methanone

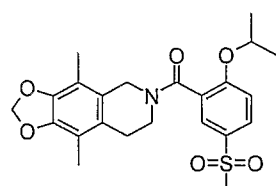


- 10 Prepared in analogy to example 1.1 from 4-methoxy-6,7,8,9-tetrahydro-[1,3]dioxolo[4,5-h]isoquinoline (CA [110103-21-4]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 448.3 (M+H⁺).

15

Example 1.53

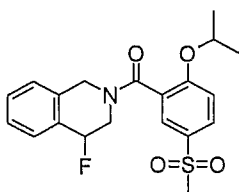
Preparation of ((4,9-Dimethyl-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-6-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone



- 20 Prepared in analogy to example 1.1 from 4,9-dimethyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 446.3 (M+H⁺).

Example 1.54

- 25 Preparation of (4-Fluoro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

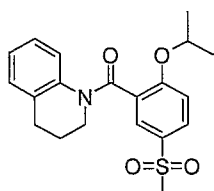


Prepared in analogy to example 1.1 from 4-fluoro-1,2,3,4-tetrahydro-isoquinoline (CA [537033-79-7]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 392.0 (M+H⁺).

5

Example 1.55

Preparation of (3,4-Dihydro-2H-quinolin-1-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

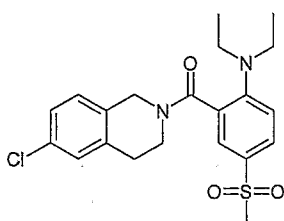


10

Prepared in analogy to example 1.1 from 1,2,3,4-tetrahydro-quinoline (CA [635-46-1]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 373.3 (M⁺).

Example 1.56

15 Preparation of (6-Chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-diethylamino-5-methanesulfonyl-phenyl)-methanone

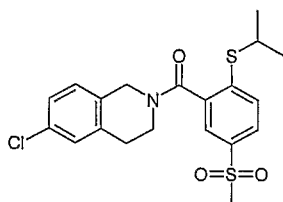


Prepared in analogy to example 1.1 from 6-chloro-1,2,3,4-tetrahydro-isoquinoline (CA [33537-99-4]) and 2-diethylamino-5-methanesulfonyl-benzoic acid (example 2.6).

20 MS (m/e): 421.1 (M+H⁺).

Example 1.57

Preparation of (6-Chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropylsulfanyl-5-methanesulfonyl-phenyl)-methanone

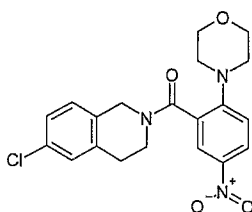


Prepared in analogy to example 1.1 from 6-chloro-1,2,3,4-tetrahydro-isoquinoline (CA [33537-99-4]) and 2-isopropylsulfanyl-5-methanesulfonyl-benzoic acid (example 2.7).
MS (m/e): 424.1 (M+H⁺).

5

Example 1.58

Preparation of (6-Chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-morpholin-4-yl-5-nitro-phenyl)-methanone

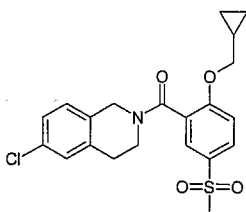


10 Prepared in analogy to example 1.1 from 6-chloro-1,2,3,4-tetrahydro-isoquinoline (CA [33537-99-4]) and 2-morpholin-4-yl-5-nitro-benzoic acid (example 2.8).
MS (m/e): 402.3 (M+H⁺).

15

Example 1.59

Preparation of (6-Chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-cyclopropylmethoxy-5-methanesulfonyl-phenyl)-methanone

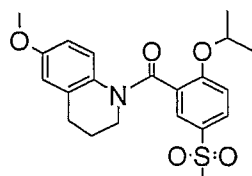


20 Prepared in analogy to example 1.1 from 6-chloro-1,2,3,4-tetrahydro-isoquinoline (CA [33537-99-4]) and 2-cyclopropylmethoxy-5-methanesulfonyl-benzoic acid (example 2.9). MS (m/e): 420.1 (M+H⁺).

Example 1.60

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(6-methoxy-3,4-dihydro-2H-quinolin-1-yl)-methanone

25



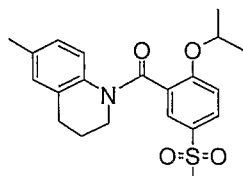
Prepared in analogy to example 1.1 from 6-methoxy-1,2,3,4-tetrahydro-quinoline (CA [120-15-0]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).

MS (m/e): 404.2 (M+H⁺).

5

Example 1.61

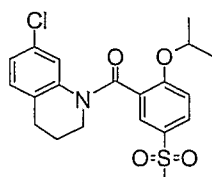
Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(6-methyl-3,4-dihydro-2H-quinolin-1-yl)-methanone



- 10 Prepared in analogy to example 1.1 from 6-methyl-1,2,3,4-tetrahydro-quinoline (CA [91-61-2]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1). MS (m/e): 445.9 (M+CH₃COOH).

Example 1.62

- 15 Preparation of (7-Chloro-3,4-dihydro-2H-quinolin-1-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone

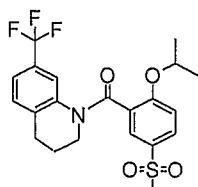


Prepared in analogy to example 1.1 from 7-chloro-1,2,3,4-tetrahydro-quinoline (CA [90562-35-9]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).

- 20 MS (m/e): 408.1 (M+H⁺).

Example 1.63

Preparation of (2-Isopropoxy-5-methanesulfonyl-phenyl)-(7-trifluoromethyl-3,4-dihydro-2H-quinolin-1-yl)-methanone



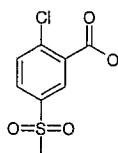
Prepared in analogy to example 1.1 from 7-trifluoromethyl-1,2,3,4-tetrahydro-quinoline (CA [450-62-4]) and 2-isopropoxy-5-methanesulfonyl-benzoic acid (Example 2.1).
MS (m/e): 500.1 (M+CH₃COOH).

5

Example 2.1

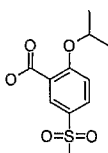
Preparation of 2-Isopropoxy-5-methanesulfonyl-benzoic acid

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



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

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



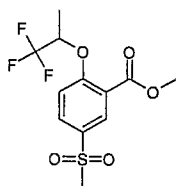
- A mixture of 2.13 mmol 2-chloro-5-methanesulfonyl-benzoic acid, 0.64 mmol Cu(I)Br in 5 ml NEt₃ and 25 ml isopropanol was heated to 120 °C for 16 h in a sealed tube. The vola-
- 20 tiles were removed under vacuum and the residue was taken up in 70 ml 1N HCl. Extraction with ethyl acetate drying of the 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 (M-H⁺, 100%)

25

Example 2.2

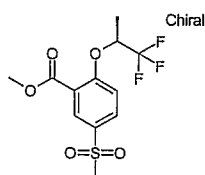
Preparation of 5-Methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid

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



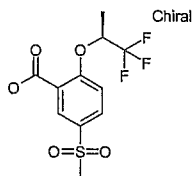
A mixture of 21.7 mmol 2-hydroxy-5-methanesulfonyl-benzoic acid methyl ester [68029-77-6], 32.5 mmol trifluoro-methanesulfonic acid 2,2,2-trifluoro-1-methyl-ethyl ester [212556-43-9], 43.4 mmol potassium carbonate in 87 ml DMF was stirred at 80 °C for 48 hours. After cooling to RT, the mixture was concentrated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

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



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

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

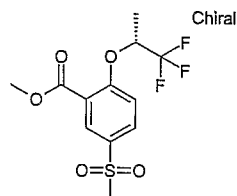


Prepared from 5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid methyl ester by saponification with excess 1N NaOH at 60° for 15 minutes. Acidification of the reaction mixture with 1N HCl yields the title compound.

MS (m/e): 311.0 (M-H⁺, 100%)

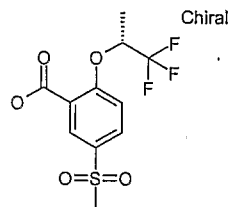
Example 2.3

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



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

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

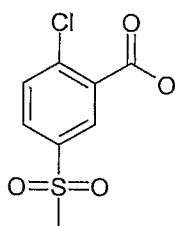


The compound was prepared in analogy to compound 2.2 (c) from 5-methanesulfonyl-2-((R)-2,2,2-trifluoro-1-methyl-ethoxy)-benzoic acid methyl ester
MS (m/e): 311.0 (M-H⁺, 100%)

Example 2.4

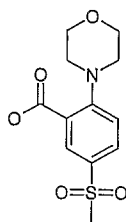
Preparation 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid

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



A solution of 2-chloro-5-(methylthio)benzoic acid (CAS: 51546-12-4; 2.5 g, 11.8 mmol) was dissolved in methanol (50 ml) and cooled to 0°C. Oxone® (21.9 g, 35.5 mmol) was added portionwise within 5 minutes. The mixture was stirred at 0°C for 30 minutes and then at room temperature for 22 hours. The mixture was filtered. The filtrate was poured onto water (200 ml). The aqueous layer was extracted with dichloromethane (5x50 ml). The combined extracts were dried over Na₂SO₄, filtered and the solvent was removed in vacuo. The solid was stirred in ether (30 ml), filtered and dried to provide the title compound (1.96 g, 70%) as a beige solid, MS (m/e): 232.9 (M-H⁺, 100%).

(b) 5-Methanesulfonyl-2-morpholin-4-yl-benzoic acid

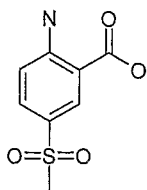


A mixture of 163.8 mg (0.7 mmol) 2-chloro-5-methanesulfonyl-benzoic acid in 2 ml morpholine was heated for 16 h to 100 °C. After evaporation of all volatiles the residue was taken up in 2 ml methanol/formic acid 3/1 and subjected to reversed phase HPLC purification eluting with an acetonitrile / water gradient to yield the title compound after
5 evaporation of the product fractions. MS (m/e): 284.1 (MH⁺, 100%).

Example 2.5

Preparation 4-Methanesulfonyl-biphenyl-2-carboxylic acid

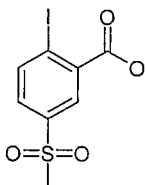
(a) 2-Amino-5-methanesulfonyl-benzoic acid



10

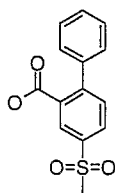
A mixture of 4.26 mmol 2-chloro-5-methanesulfonyl-benzoic acid, 0.39 mmol Copper powder and 10 ml ammonium hydroxide 25% was heated at 125-130°C with stirring for 18 hours. Mixture was cooled to room temperature and filtered. The solid was washed with methanol. The filtrate was concentrated in vacuo.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

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



To a suspension of 3.0 mmol 2-amino-5-methanesulfonyl-benzoic acid in a mixture of
20 1.7 ml sulfuric acid and 1.7 ml water was added dropwise a solution of 3.92 mmol sodium nitrite in 1.7 ml water at such rate that the temperature did not exceed 3°C. The mixture was stirred at 0°C for 1 hour. A solution of 3.0 mmol KI in 1.7 ml water was added dropwise at 0°C. The brown suspension was allowed to warm to rt and stirred for 30 minutes. Excess iodine was destroyed by addition of a few drops of a sodium
25 hydrogensulfite solution. The solid was filtered, washed with water and dried (HV, 50°C, 1 hour) to yield the title compound. MS (m/e): 325.0 (M-H, 100%)

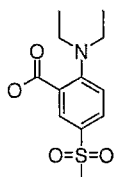
(c) 4-Methanesulfonyl-biphenyl-2-carboxylic acid



A mixture of 15 mmol 2-iodo-5-methanesulfonyl-benzoic acid, 31 mmol phenylboronic acid, 45 mmol sodium carbonate and 34 mg palladium(II)-acetate in 100 ml water is stirred at room temperature for 60 hours. The reaction mixture is acidified by careful
 5 addition of concentrated hydrochloric acid and extracted 3 times with ethyl acetate. The organic phase is dried, concentrated and the residue crystallized from diethyl ether to yield the title compound (3.87 g, 91%) as a slightly yellow solid, MS (m/e): 275.0 ($M-H^+$, 100%).

Example 2.6

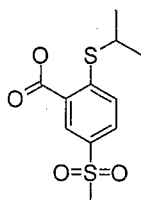
10 Preparation of 2-Diethylamino-5-methanesulfonyl-benzoic acid



3.0 g of 2-fluoro-5-methanesulfonyl-benzoic acid (CA 247569-56-8; WO200501453) was dissolved in 30 ml of diethylamine and refluxed overnight. The reaction mixture was diluted with water, acidified by addition of diluted hydrochloric acid and extracted with
 15 ethyl acetate. The organic phase was dried and concentrated to give the title compound as a slightly brownish solid. MS (m/e): 272.1 ($M+H^+$; 100%)

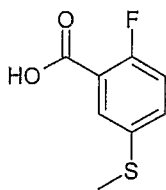
Example 2.7

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



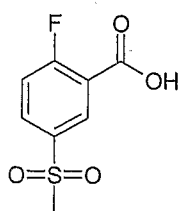
20

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



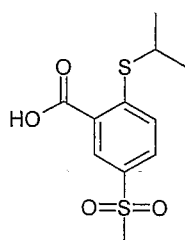
The title compound was prepared by following the procedure described in: Journal of Organometallic Chemistry 1991, 419(1-2), 1-8.

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



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

c) 2-Isopropylsulfonyl-5-methanesulfonyl-benzoic acid

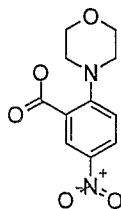


15

To a solution of 4.58 mmol 2-fluoro-5-methanesulfonyl-benzoic acid in 6 ml N,N-dimethylacetamide were added 15.2 mmol cesium carbonate and 10.1 mmol 2-propanethiol and the mixture was stirred at 90 °C for 3 h. The reaction mixture was then cooled to room temperature and acidified to pH1 by addition of hydrochloric acid before being extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated in vacuo to afford the title compound as a light yellow liquid which was used in the next step without further purification (yield 99%). EI-MS (m/e): 274.1 (M⁺, 35%), 232.1 ([M-C₃H₆]⁺, 30%), 214.1 (M-C₃H₆-H₂O)⁺, 100%).

Example 2.8

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

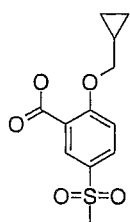


- 5 To a solution of 2-fluoro-5-nitrobenzoic acid (4.86 g, 26.2 mmol) in dioxane (50 ml) was added morpholine (11.5 ml). The mixture was stirred at room temperature for 2 hours. The solvent was removed in vacuo. The residue was dissolved in water and the mixture was acidified with HCl 2N. The solid was 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%).

10

Example 2.9

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

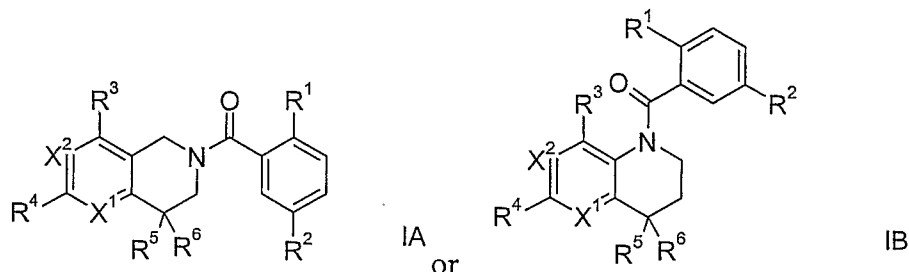


This compound (CA 845616-03-7) was prepared as described in WO2005014563.

- 15 MS (m/e): 269.1 (MH⁺, 89%)

Claims

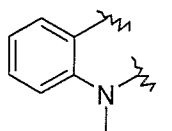
1. Compounds of general formula



5

wherein

- R^1 is aryl, a cyclic amine, or is OR^{11} , SR^{11} or $N(R^{12})_2$;
 10 R^{11} is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$ -cycloalkyl;
 R^{12} is independently from each other hydrogen or lower alkyl;
 R^2 is NO_2 , CN or $S(O)_2$ -lower alkyl;
 R^3 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or is lower alkoxy;
 15 R^4 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen, non cyclic amine, lower alkoxy or benzyloxy, optionally substituted by halogen;
 R^5/R^6 are independently from each other hydrogen, halogen, lower alkyl, lower alkoxy, aryl or form together the keto group $=O$;
 X^1 is N or C- R' ;
 20 X^2 is N or C- R'' ;
 R' is hydrogen, halogen, lower alkyl, lower alkoxy, or benzyloxy optionally substituted by halogen;
 R'' is hydrogen, alkyl substituted by halogen, halogen, nitro, lower alkoxy, cyano, COO-lower alkyl, benzyloxy optionally substituted by halogen or $S(O)_2$ -cyclic amine;
 25 or
 R^3 and R'' or R^4 and R' or R'' and R^4 are together with the carbon atom to which they are attached $-O-(CH_2)_{1,2}-O-$ or $-O-(CH_2)_{2,3}-$ or $-(CH_2)_{2,3}-O-$, or

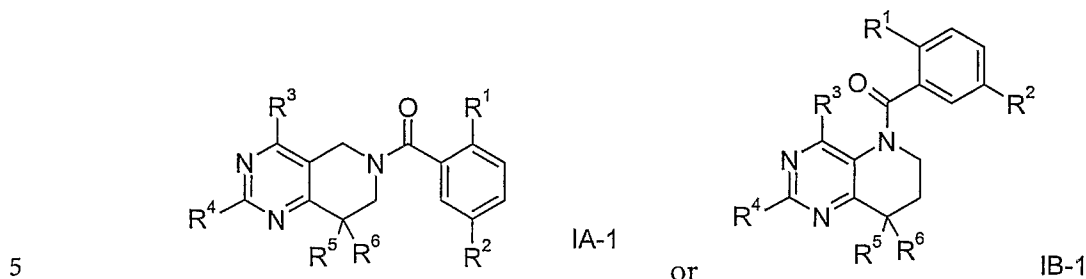


30 n

is 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

2. Compounds of formula IA-1 and IB-1 in accordance with claim 1,

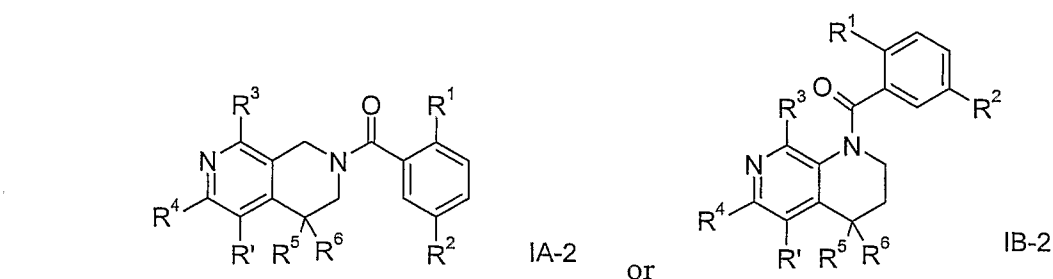


wherein

- 10 R^1 is aryl, a cyclic amine, or is OR^{11} , SR^{11} , or $N(R^{12})_2$;
 R^{11} is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$ -cycloalkyl;
 R^{12} is independently from each other hydrogen or lower alkyl;
 R^2 is NO_2 , CN or $S(O)_2$ -lower alkyl;
 R^3 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or is
 15 lower alkoxy;
 R^4 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen, non
 cyclic amine, lower alkoxy or benzyloxy, optionally substituted by halogen;
 R^5/R^6 are independently from each other hydrogen, halogen, lower alkyl, lower
 alkoxy, aryl or form together the keto group $=O$;
 20 n is 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

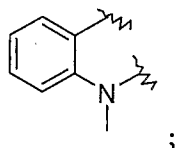
3. Compounds of formula IA-2 and IB-2 in accordance with claim 1,



wherein

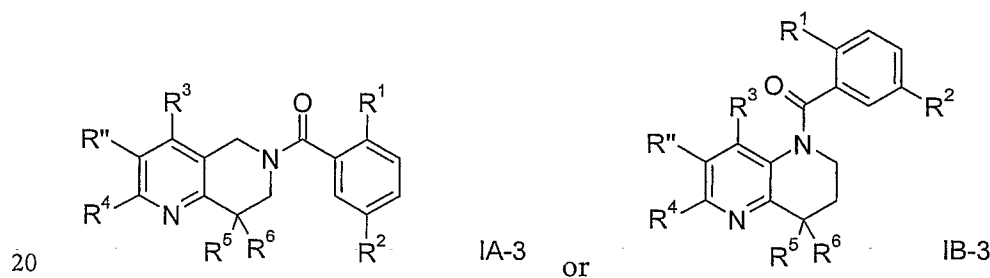
- R^1 is aryl, a cyclic amine, or is OR^{11} , SR^{11} , or $N(R^{12})_2$;
 R^{11} is lower alkyl, lower alkyl substituted by halogen or is $-(CH_2)_n$ -cycloalkyl;

- R^{12} is independently from each other hydrogen or lower alkyl;
 R^2 is NO_2 , CN or $\text{S}(\text{O})_2$ -lower alkyl;
 R^3 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or is lower alkoxy;
 5 R^4 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen, non cyclic amine, lower alkoxy or benzyloxy, optionally substituted by halogen;
 R^5/R^6 are independently from each other hydrogen, halogen, lower alkyl, lower alkoxy, aryl or form together the keto group $=\text{O}$;
 R' is hydrogen, halogen, lower alkyl, lower alkoxy, or benzyloxy optionally substituted by halogen;
 10 or
 R^4 and R' are together with the carbon atom to which they are attached $-\text{O}-(\text{CH}_2)_{1,2}-\text{O}-$ or $-\text{O}-(\text{CH}_2)_{2,3}-\text{O}-$ or $-(\text{CH}_2)_{2,3}-\text{O}-$, or



- 15 n is 1 or 2;
 and pharmaceutically acceptable acid addition salts thereof.

4. Compounds of formula IA-3 and IB-3 in accordance with claim 1,



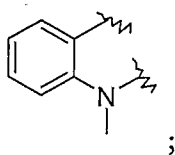
wherein

- R^1 is aryl, a cyclic amine, or is OR^{11} , SR^{11} , or $\text{N}(\text{R}^{12})_2$;
 25 R^{11} is lower alkyl, lower alkyl substituted by halogen or is $-(\text{CH}_2)_n$ -cycloalkyl;
 R^{12} is independently from each other hydrogen or lower alkyl;
 R^2 is NO_2 , CN or $\text{S}(\text{O})_2$ -lower alkyl;
 R^3 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or is lower alkoxy;
 30 R^4 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen, non cyclic amine, lower alkoxy or benzyloxy, optionally substituted by halogen;

R^5/R^6 are independently from each other hydrogen, halogen, lower alkyl, lower alkoxy, aryl or form together the keto group =O;
 R'' is hydrogen, alkyl substituted by halogen, halogen, nitro, lower alkoxy, cyano, COO-lower alkyl, benzyloxy optionally substituted by halogen or S(O)₂-cyclic amine;

or

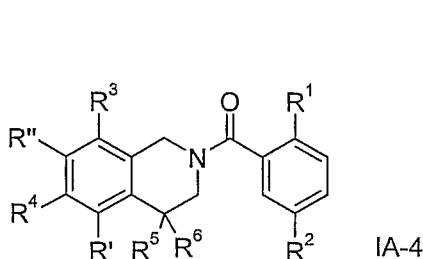
R^3 and R'' or R'' and R^4 are together with the carbon atom to which they are attached -O-(CH₂)_{1,2}-O- or -O-(CH₂)_{2,3}- or -(CH₂)_{2,3}-O-, or



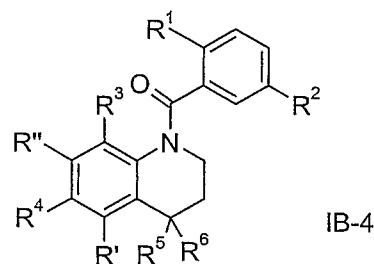
n is 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

5. Compounds of formula IA-4 and IB-4 in accordance with claim 1,



or



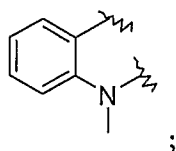
wherein

R^1 is aryl, a cyclic amine, or is OR¹¹, SR¹¹, or N(R¹²)₂;
 R^{11} is lower alkyl, lower alkyl substituted by halogen or is -(CH₂)_n-cycloalkyl;
 R^{12} is independently from each other hydrogen or lower alkyl;
 R^2 is NO₂, CN or S(O)₂-lower alkyl;
 R^3 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen or is lower alkoxy;
 R^4 is hydrogen, halogen, lower alkyl, lower alkyl substituted by halogen, non cyclic amine, lower alkoxy or benzyloxy, optionally substituted by halogen;
 R^5/R^6 are independently from each other hydrogen, halogen, lower alkyl, lower alkoxy, aryl or form together the keto group =O;
 R' is hydrogen, halogen, lower alkyl, lower alkoxy, or benzyloxy optionally substituted by halogen;

R'' is hydrogen, alkyl substituted by halogen, halogen, nitro, lower alkoxy, cyano, COO-lower alkyl, benzyloxy optionally substituted by halogen or S(O)₂-cyclic amine;

or

- 5 R³ and R'' or R⁴ and R' or R'' and R⁴ are together with the carbon atom to which they are attached -O-(CH₂)_{1,2}-O- or -O-(CH₂)_{2,3}- or -(CH₂)_{2,3}-O-, or



n is 1 or 2;

and pharmaceutically acceptable acid addition salts thereof.

10

6. Compounds of formula I according to claim 1, wherein R¹ is OR¹¹ and R² is SO₂CH₃.

7. Compounds of formula IA-4 according to claim 5, wherein at least one of R³, R'', R⁴ or R' is halogen.

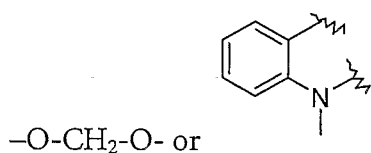
- 15 8. Compounds of formula IA-4 according to claim 7, wherein the compounds are
 (6-chloro-3,4-dihydro-1H-isoquinolin-2-yl)-[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-methanone,
 (6-chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
 20 (7-chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone,
 (7,8-dichloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone or
 (8-chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-
 25 methanone.

9. Compounds of formula IA-4 according to claim 5, wherein at least one of R³, R'', R⁴ or R' is alkyl substituted by halogen.

10. Compounds of formula IA-4 according to claim 9, wherein the compounds are
 (2-isopropoxy-5-methanesulfonyl-phenyl)-(6-trifluoromethyl-3,4-dihydro-1H-
 30 isoquinolin-2-yl)-methanone,
 (5-methanesulfonyl-2-morpholin-4-yl-phenyl)-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone,

[5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methyl-ethoxy)-phenyl]-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone or
(4-methanesulfonyl-biphenyl-2-yl)-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-methanone.

- 5 11. Compounds of formula IA-4 according to claim 5, wherein at least one of R^3 , R'' , R^4 or R' is CN.
12. Compounds of formula IA-4 according to claim 11, wherein the compound is 2-(2-isopropoxy-5-methanesulfonyl-benzoyl)-1,2,3,4-tetrahydro-isoquinoline-6-carbonitrile.
- 10 13. Compounds of formula IA-4 according to claim 5, wherein at least one of R^3 , R'' , R^4 or R' is lower alkoxy.
14. Compounds of formula IA-4 according to claim 13, wherein the compound is (2-isopropoxy-5-methanesulfonyl-phenyl)-(6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-methanone.
- 15 15. Compounds of formula IA-4 according to claim 5, wherein R^1 is S-lower alkyl.
16. A compound of formula IA-4 according to claim 15, wherein the compound is (6-chloro-3,4-dihydro-1H-isoquinolin-2-yl)-(2-isopropylsulfanyl-5-methanesulfonyl-phenyl)-methanone.
17. Compounds of formula I according to claim 1, wherein one of R^3 and R'' or R^4 and R' or R'' and R^4 are together with the carbon atom to which they are attached

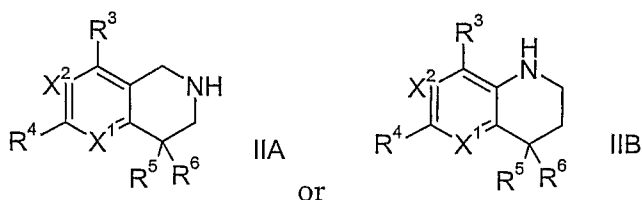


18. Compounds of formula I according to claim 17, wherein the compounds are (2-isopropoxy-5-methanesulfonyl-phenyl)-(11-methyl-1,2,4,11-tetrahydro-pyrido[4,3-a]carbazol-3-yl)-methanone or
- 25 ((4,9-dimethyl-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-6-yl)-(2-isopropoxy-5-methanesulfonyl-phenyl)-methanone.
19. Compounds of formula IA-3 according to claim 4, wherein the compound is

(4-methanesulfonyl-biphenyl-2-yl)-(2-trifluoromethyl-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-methanone.

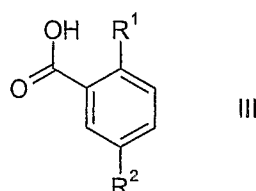
20. A process for preparing a compound of formula IA or IB as defined in claim 1, which
5 process comprises

a) reacting a compound of formula IIA or IIB



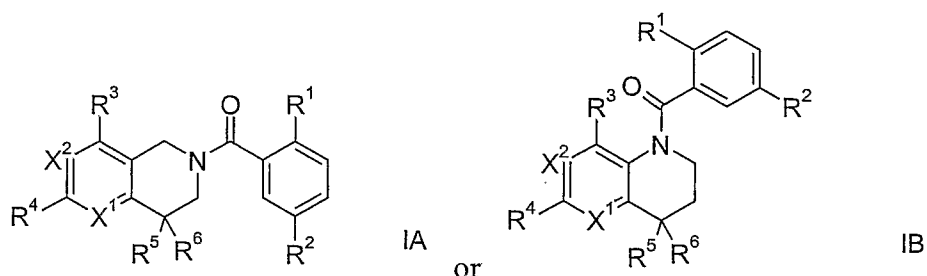
10

with a compound of formula III



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

- 15 to a compound of formula IA or IB

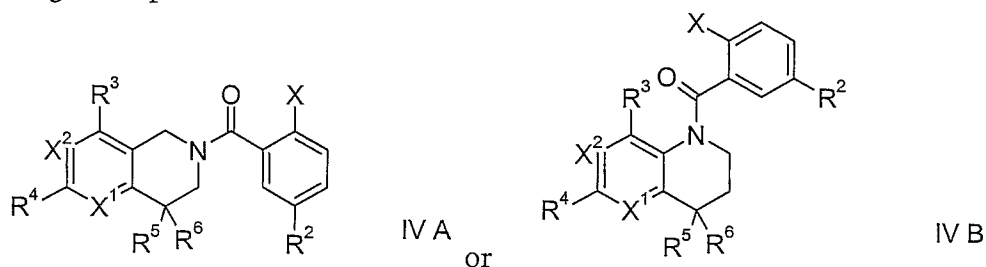


wherein the substituents are as defined in claim 1,

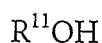
or

20

b) reacting a compound of formula

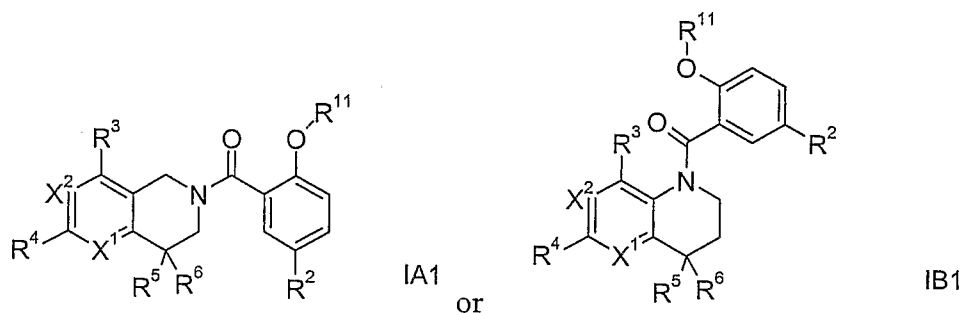


with a compound of formula



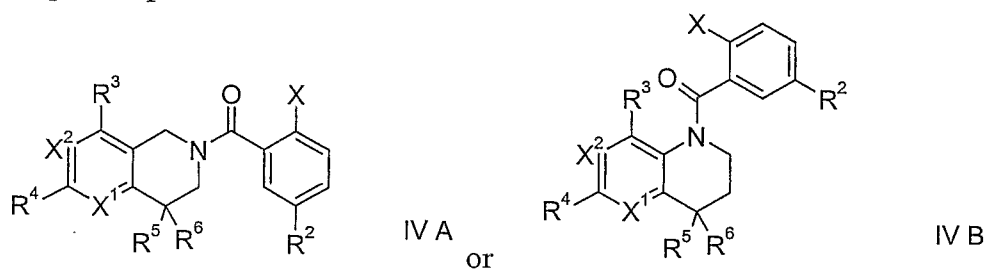
optionally in the presence of a catalyst, such as Cu(I)I and a base like potassium carbonate, cesium carbonate or sodium,

- 5 to a compound of formula IA1 or IB1



wherein X is halogen, the other substituents are as defined in claim 1, or

- 10 c) reacting a compound of formula

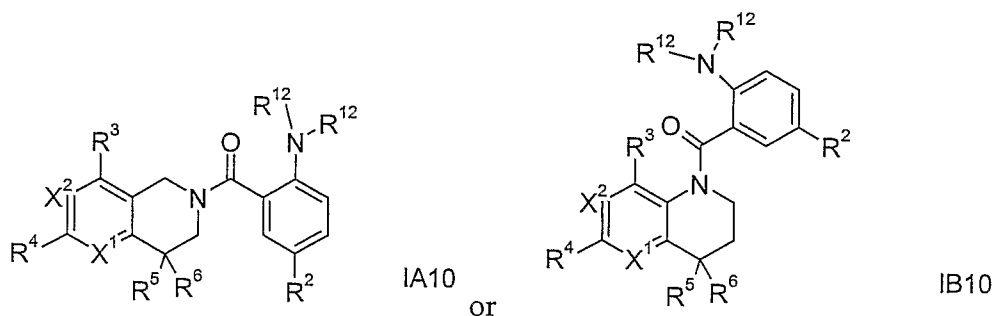


with a compound of formula

- 15 $NH(R^{12})_2$ or with a cyclic amine

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

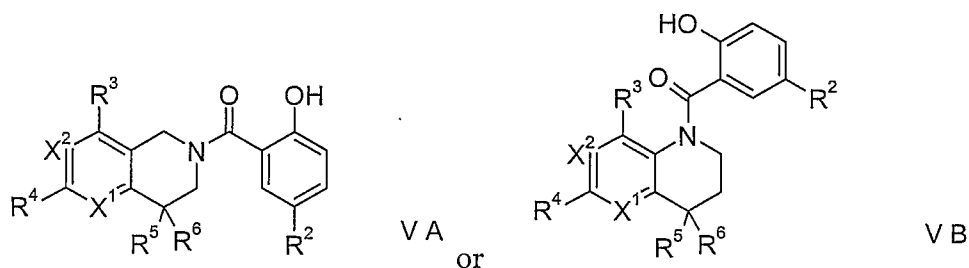
to a compound of formula IA10 or IB10



wherein X is halogen, R¹² is as defined in claim 1 or the two R¹² together with the N-atom may form a cyclic amine and the other substituents are as defined in claim 1, or

d) reacting a compound of formula

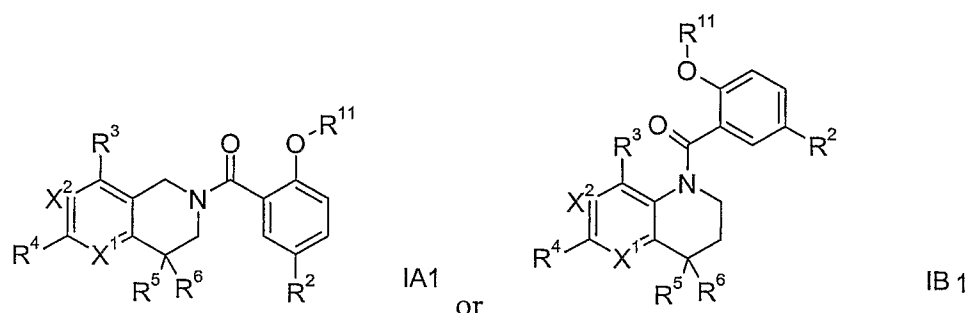
5



with a compound of formula

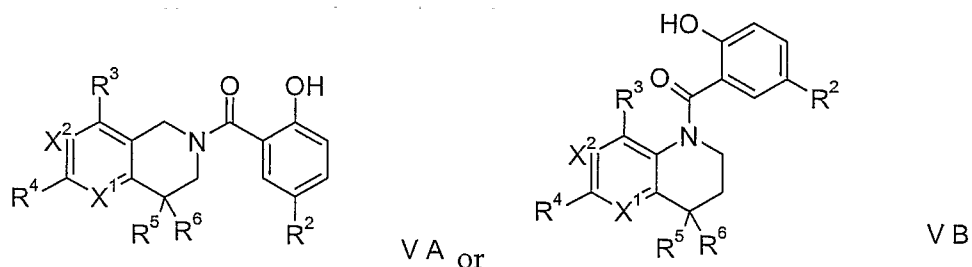


10 in the presence of a base and optionally in the presence of microwaves to a compound of formula IA1 or IB1



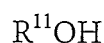
wherein X is halogen, mesylate or triflate and R¹¹ is lower alkyl, lower alkyl substituted by
15 halogen or (CH₂)_n-cycloalkyl :
or

e) reacting a compound of formula

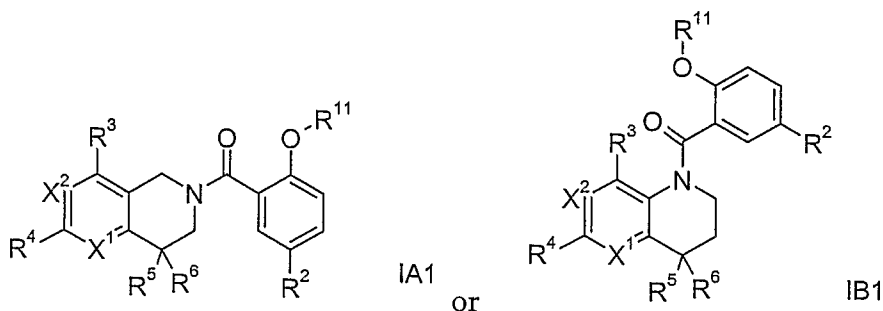


20

with a compound of formula



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



wherein the substituents are as defined above, and, if desired, converting the compound
 5 obtained into a pharmaceutically active acid addition salt.

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

22. A medicament containing one or more compounds as claimed in any one of claims 1
 10 to 19 and pharmaceutically suitable excipients.

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

24. A medicament according to claim 23, wherein the illnesses are psychoses, pain,
 15 dysfunction in memory and learning, schizophrenia, dementia and other diseases in
 which cognitive processes are impaired, such as attention deficit disorders or Alzheimer's
 disease.

25. The use of a compound as claimed in any one of claims 1 to 19 for the manufacture of
 20 medicaments for the treatment of psychoses, pain, neurodegenerative dysfunction in
 memory and learning, schizophrenia, dementia and other diseases in which cognitive
 processes are impaired, such as attention deficit disorders or Alzheimer's disease.

26. The invention as herein before described.

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