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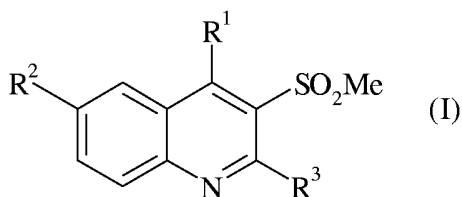
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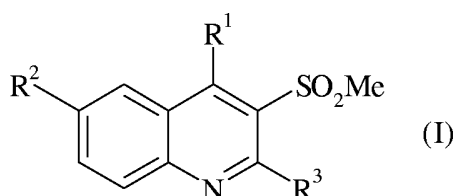
(54) Title: 3-METHANESULFONYLQUINOLINES AS GABA-B ENHANCERS



(57) Abstract: The present invention relates to compounds of formula (I) wherein R¹, R² and R³ are as defined hereinabove which are active at the GABA_B receptor and which can be used for the preparation of medicaments useful in the control or prevention of CNS disorders.

Case 231623-METHANESULFONYLQUINOLINES AS GABA-B ENHANCERS

The present invention relates to compounds of formula I



wherein

- R^1 is phenyl optionally substituted by one or more substituents selected from the group consisting of Cl, F, C₁₋₇-haloalkyl, hydroxy, C₁₋₇-alkoxy, C₁₋₇-haloalkoxy, di(C₁₋₇)alkylamino and C₁₋₇-alkylsulfonyl,
 5 or is 5 or 6 membered heterocycloalkyl optionally substituted by OH;
 R^2 is Br, I, C₁₋₇-alkyl, C₁₋₇-alkoxy, C₁₋₇-haloalkyl, C₁₋₇-haloalkoxy, aryloxy, arylsulfonyl, or C₃₋₆-cycloalkyl optionally substituted by phenyl, or is -NR^aR^b wherein R^a and
 10 R^b are C₁₋₇-alkyl, or R^a and R^b can, together with the nitrogen atom to which they are attached, form a 4 to 8 membered heterocycloalkyl group which can be substituted by one or more substituent(s) selected from the group consisting of halo, C₁₋₇-alkyl, C₁₋₇-alkoxy, hydroxy, phenyl and di(C₁₋₇)alkylamino;
 R^3 is H, C₁₋₇-alkyl, or C₃₋₆-cycloalkyl;
 15 as well as optical isomers and pharmaceutically acceptable salts thereof.

The compounds of formula I and their salts are distinguished by valuable therapeutic properties. It has been found that the compounds are active on the GABA_B receptor.

- γ -Aminobutyric acid (GABA), the most abundant inhibitory neurotransmitter,
 20 activates both ionotropic GABA_A and metabotropic GABA_B receptors (*Hill and Bowery, Nature, 290, 149-152, 1981*). GABA_B receptors that are present in most regions of the mammalian brain on presynaptic terminals and postsynaptic neurons are involved in the fine-tuning of inhibitory synaptic transmission. Presynaptic GABA_B receptors through modulation of high-voltage activated Ca²⁺ channels (P/Q- and N-type) inhibit the release
 25 of many neurotransmitters. Postsynaptic GABA_B receptors activates G-protein coupled inwardly rectifying K⁺ (GIRK) channel and regulates adenylyl cyclase (*Billinton et al.,*
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Trends Neurosci., 24, 277-282, 2001; Bowery et al., *Pharmacol. Rev.* 54, 247-264, 2002). Because the GABA_B receptors are strategically located to modulate the activity of various neurotransmitter systems, GABA_B receptor ligands hence could have potential therapeutic applications in the treatment of anxiety, depression, epilepsy, schizophrenia and cognitive disorders (*Vacher and Bettler, Curr. Drug Target, CNS Neurol. Disord.* 2, 248-259, 2003; *Bettler et al., Physiol Rev.* 84, 835-867, 2004).

Native GABA_B receptors are heteromeric structures composed of two types of subunits, GABA_BR1 and GABA_BR2 subunits (*Kaupmann et al., Nature*, 386, 239-246, 1997 and *Nature*, 396, 683-687, 1998). The structure of GABA_BR1 and R2 show that they belong to a family of G-protein coupled receptors (GPCRs) called family 3. Other members of the family 3 GPCRs include the metabotropic glutamate (mGlu1-8), Calcium-sensing, vomeronasal, pheromone and putative taste receptors (*Pin et al., Pharmacol. Ther.* 98, 325-354, 2003). The family 3 receptors (including GABA_B receptors) are characterized by two distinctly separated topological domains: an exceptionally long extracellular amino-terminal domain (ATD, 500-600 amino acids), which contains a venus flytrap module for the agonist binding (orthosteric site) (*Galvez et al., J. Biol. Chem.*, 275, 41166-41174, 2000) and the 7TM helical segments plus intracellular carboxyl-terminal domain that is involved in receptor activation and G-protein coupling. The mechanism of receptor activation by agonist in GABA_BR1R2 heterodimer is unique among the GPCRs. In the heteromer, only GABA_BR1 subunit binds to GABA, while the GABA_BR2 is responsible for coupling and activation of G-protein (*Havlickova et al., Mol. Pharmacol.* 62, 343-350, 2002; *Kniazeff et al., J. Neurosci.*, 22, 7352-7361, 2002).

Schuler et al., Neuron, 31, 47-58, 2001 have demonstrated that the GABA_BR1 knock-out (KO) mice exhibit spontaneous seizures and hyperalgesia. These KO mice have lost all the biochemical and electrophysiological GABA_B responses. Interestingly, the GABA_BR1 KO mice were more anxious in two anxiety paradigm, namely the light-dark box (decreased time in light) and staircase tests (decreased rears and steps climbed). They showed a clear impairment of passive avoidance performance model indicating impaired memory processes. The GABA_BR1 KO also displayed increased hyperlocomotion and hyperactivity in new environment. The GABA_BR1 gene is mapped to chromosome 6p21.3, which is within the HLA class I, a region with linkage for schizophrenia, epilepsy and dyslexia (*Peters et al., Neurogenetics*, 2, 47-54, 1998). *Mondabon et al., Am. J. Med. Genet* 122B/1, 134, 2003 have reported about a weak association of the Ala20Val polymorphism of GABA_BR1 gene with schizophrenia. Moreover, *Gassmann et al., J*

Neurosci. 24, 6086-6097, 2004 has shown that GABA_BR2KO mice suffer from spontaneous seizures, hyperalgesia, hyperlocomotor activity and severe memory impairment, comparable to GABA_BR1KO mice. Therefore, heteromeric GABA_B R1R2 receptors are responsible for these phenotypes.

- 5 Baclofen (Lioresal[®], β -chlorophenyl GABA), a selective GABA_B receptor agonist with EC₅₀ = 210 nM at native receptor, is the only ligand, which has been used since 1972 in clinical study for the treatment of spasticity and skeletal muscle rigidity in patients following spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy. Most of the preclinical and clinical studies conducted with baclofen and GABA_B
- 10 receptor agonists were for the treatment of neuropathic pain and craving associated with cocaine and nicotine (*Misgeld et al., Prog. Neurobiol.* 46, 423-462, 1995; *Enna et al., Life Sci.* 62, 1525-1530, 1998; *McCarson and Enna, Neuropharmacology*, 38, 1767-1773, 1999; *Brebner et al., Neuropharmacology*, 38, 1797-1804, 1999; *Paterson et al., Psychopharmacology*, 172, 179-186, 2003). In panic disorder patients, Baclofen was shown
- 15 to be significantly effective in reducing the number of panic attacks and symptoms of anxiety as assessed with the Hamilton anxiety scale, Zung anxiety scale and Katz-R nervousness subscale (*Breslow et al., Am. J. Psychiatry*, 146, 353-356, 1989). In a study with a small group of veterans with chronic, combat-related posttraumatic stress disorder (PTSD), baclofen was found to be an effective and well-tolerated treatment. It resulted in
- 20 significant improvements in the overall symptoms of PTSD, most notably the avoidance, emotional numbing and hyperarousal symptoms and also in reduced accompanying anxiety and depression (*Drake et al., Ann. Pharmacother.* 37, 1177-1181, 2003). In preclinical study, baclofen was able to reverse the reduction in prepulse inhibition (PPI) of the acoustic startle response induced by dizocilpine, but not by apomorphine in rat
- 25 PPI model of psychosis (*Bortolato et al., Psychopharmacology*, 171, 322-330, 2004). Therefore, GABA_B receptor agonist has a potential in the pharmacological therapy of psychotic disorders. Unfortunately, Baclofen has a number of side-effects including the poor blood-brain-barrier penetration, very short duration of action and narrow therapeutic window (muscle relaxation, sedation and tolerance) that limit its utility.
- 30 *Urwyler et al., Mol. Pharmacol.*, 60, 963-971, 2001 have reported on a novel class of GABA_B receptor ligands, called positive allosteric modulators, CGP7930 [2,6-di-tert-butyl-4-(3-hydroxy-2,2-dimethyl-propyl)-phenol] and its aldehyde analogue CGP13501. These ligands have no effect on their own at GABA_B receptors, but in concert with

endogenous GABA, they increase both the potency and maximal efficacy of GABA at the GABA_BR1R2 (*Pin et al., Mol. Pharmacol.*, 60, 881-884, 2001). Interestingly, recent study with CGP7930 (*Binet et al., J Biol Chem.*, 279, 29085-29091, 2004) has shown that this positive modulator activates directly the seven transmembrane domains (7TMD) of

5 GABA_BR2 subunit. *Mombereau et al., Neuropsychopharmacology*, 1-13, 2004 have recently reported on the anxiolytic effects of acute and chronic treatment with the GABA_B receptor positive modulator, GS39783 (*N,N*-dicyclopentyl-2-methylsulfanyl-5-nitro-pyrimidine-4,6-diamine) (*Urwyler et al., J. Pharmacol. Exp. Ther.*, 307, 322-330, 2003) in the light-dark box and elevated zero maze test models of anxiety. No tolerance after

10 chronic treatment (21 days) with GS39783 (10 mg/kg, P.O., once daily) was observed. Because the GABA_B enhancers have no effect on receptor activity in the absence of GABA, but do enhance allosterically the affinity of the GABA_B receptor for the endogenous GABA, it is expected that these ligands should have an improved side effect profile as compared to baclofen. Indeed, GS39783 at 0.1-200 mg/kg, PO had no effect on

15 spontaneous locomotor activity, rotarod, body temperature and traction test in comparison to baclofen, which showed these side effects at 2.5-15 mg/kg, PO. GS39783 did not have any effect on cognition performance as assessed by passive avoidance behavioral test in mice and rats. Furthermore, GS39783 exhibited anxiolytic-like effects in the elevated plus maze (rat), elevated zero maze (mice and rats), and the stress-induced

20 hyperthermia (mice) test paradigms. Therefore, GS39783 represents a novel anxiolytic without side-effects associated with baclofen or benzodiazepines (*Cryan et al., J Pharmacol Exp Ther.*, 310, 952-963, 2004). The preclinical investigation with the CGP7930 and GS39783 has shown that both compounds were effective at decreasing cocaine self-administration in rats (*Smith et al., Psychopharmacology*, 173, 105-111, 2004). The positive

25 modulator, CGP7930 has also been preclinically studied for the treatment of Gastro-Esophageal Reflux Disease (GERD) and was found to be effective (WO 03/090731, Use of GABA_B receptor positive modulators in gastro-intestinal disorders).

Positive allosteric modulators have been reported for other family 3 GPCRs including mGlu1 receptor (*Knoflach et al., Proc. Natl. Acad. Sci., USA*, 98, 13402-13407,

30 2001; *Wichmann et al., Farmaco*, 57, 989-992, 2002), Calcium-sensing receptor (NPS R-467 and NPS R-568) (*Hammerland et al., Mol. Pharmacol.*, 53, 1083-1088, 1998) (US 6,313, 146), mGlu2 receptor [LY487379, *N*-(4-(2-methoxyphenoxy)-phenyl)-*N*-(2,2,2-trifluoroethylsulfonyl)-pyrid-3-ylmethylamine and its analogs] (WO 01/56990, Potentiators of glutamate receptors) and mGlu5 receptor (CPPHA, *N*-{4-chloro-2-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl] phenyl}-2-hydroxybenzamide) (*O'Brien et*

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al., *J. Pharmacol. Exp. Ther.*, 27, Jan. 27, 2004). Interestingly, it has been demonstrated that these positive modulators bind to a novel allosteric site located within the 7TMD region, thereby enhancing the agonist affinity by stabilizing the active state of the 7TMD region (*Knoflach et al.*, *Proc. Natl. Acad. Sci., USA* 98, 13402-13407, 2001; *Schaffhauser et al.*, *Mol. Pharmacol.*, 64, 798-810, 2003). Moreover, the NPS R-467, NPS R-568 (Tecalset) and related compounds represent the first positive allosteric modulators that entered the clinical trials due to their allosteric mode of action.

WO 2003080580, WO 2005026125 and WO 2005040124 already described quinoline derivatives for the treatment of CNS disorders. Nevertheless, the compounds disclosed in these patent applications are 3-aryl/heteroarylsulfonyl-8-piperazine-quinoline derivatives, which derivatives differ from the compounds of the instant invention.

Objects of the invention are the compounds of formula I and pharmaceutically acceptable acid addition salts thereof, the preparation of the compounds of formula I and salts thereof, medicaments containing a compound of formula I or a pharmaceutically acceptable acid addition salts thereof.

A further object of the invention is the use of the compound of formula I and acceptable acid addition salts thereof for the manufacture of such medicaments useful in the control or prevention of illnesses, especially of illnesses and disorders of the kind referred to earlier, such as anxiety, depression, epilepsy, schizophrenia, cognitive disorders, spasticity and skeletal muscle rigidity, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy, neuropathic pain and craving associated with cocaine and nicotine, psychosis, panic disorder, posttraumatic stress disorders or gastrointestinal disorders, and, respectively, for the manufacture of corresponding medicaments.

Still a further object of the invention is novel intermediates useful in the preparation of the compounds of the invention.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "Aryl" means a monovalent cyclic aromatic hydrocarbon moiety selected from optionally substituted phenyl or naphthyl. Substituents for aryl

include but are not limited to halo, hydroxy, C₁₋₇-alkyl, C₁₋₇-alkoxy, C₁₋₇-haloalkyl, C₁₋₇-haloalkoxy as well as those groups specifically illustrated by the examples herein below with the examples.

“aryloxy” denotes an aryl group as defined above which is connected via an oxygen atom. Preferred aryloxy is phenyloxy.

“arylsulfonyl” denotes an aryl group as defined above which is connected via a sulfonyl group. Preferred arylsulfonyl is phenylsulfonyl.

“C₁₋₇-alkyl” denotes a straight- or branched-carbon chain group containing from 1 to 7 carbon atoms, preferably 1 to 4 carbon atoms. Examples of such groups are are methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl, n-hexyl as well as those specifically illustrated by the examples herein below.

“C₁₋₇-haloalkyl” denotes a C₁₋₇-alkyl group as defined above which is substituted by one or more halogen. Examples of C₁₋₇-haloalkyl include but are not limited to methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl or n-hexyl substituted by one or more Cl, F, Br or I atom(s) as well as those groups specifically illustrated by the examples herein below. Preferred C₁₋₇-haloalkyl are difluoro- or trifluoro-methyl or ethyl.

“C₁₋₇-alkoxy” denotes a group wherein the alkyl group is as defined above and the alkyl group is connected via an oxygen atom. Preferred alkoxy are MeO- and Et-O as well as those groups specifically illustrated by the examples herein below.

“C₁₋₇-haloalkoxy” denotes a C₁₋₇-alkoxy group as defined above which is substituted by one or more halogen. Examples of C₁₋₇ haloalkyl include but are not limited to methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, substituted by one or more Cl, F, Br or I atom(s) as well as those groups specifically illustrated by the examples herein below. Preferred C₁₋₇-haloalkoxy are difluoro- or trifluoro-methoxy or ethoxy groups.

“Halo” or “halogen” denotes chlorine, iodine, fluorine and/or bromine.

“C₁₋₇-alkylsulfonyl” denotes a sulfonyl group which is substituted by a C₁₋₇-alkyl group as defined herein above. Examples of C₁₋₇-alkylsulfonyl include but are not limited to methylsulfonyl and ethylsulfonyl as well as those groups specifically illustrated by the examples herein below.

“di(C₁₋₇)alkylamino” denotes a -NR^cR^d group, wherein R^c and R^d are C₁₋₇-alkyl groups as defined herein above. Examples of di(C₁₋₇)alkylamino groups include but are not limited to di(methyl)amino, di(ethyl)amino, methylethylamino, as well as those groups specifically illustrated by the examples herein below.

5 “Hydroxy” denotes one, two or three -OH group(s).

“C₃₋₆-cycloalkyl” denotes a saturated carbon cyclic ring having 3 to 6 carbon atoms as ring members and includes but is not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, as well as those groups specifically illustrated by the examples herein below.

“5 or 6 membered heterocycloalkyl” and “4 to 8 membered heterocycloalkyl”
10 denote a saturated mono- or bi-cyclic ring comprising respectively 5 or 6 or 4 to 8 ring atoms and furthermore containing one, two, or three ring heteroatoms selected from N, O, or S, the remaining ring atoms being C. Preferred 4 to 8 membered heterocycloalkyl groups are 5 or 6 membered heterocycloalkyl groups. Examples include but are not limited to optionally substituted azetidiny, piperidiny, piperaziny, homopiperaziny,
15 azepiny, pyrrolidiny, pyrazolidiny, imidazolinyl, imidazolidiny, pyridiny, pyridaziny, pyrimidiny, oxazolidiny, isoxazolidiny, morpholinyl, thiazolidiny, isothiazolidiny, quinuclidiny, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazolylidiny, benzothiazolidiny, benzoazolylidiny, dihydrofuryl, tetrahydrofuryl, dihydropyranly, tetrahydropyranly, thiomorpholinyl, thiomorpholinylsulfoxide, thiomorpholinylsulfone,
20 dihydroquinolinyl, dihydriisoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, 1-oxo- thiomorpholin, 1,1-dioxo-thiomorpholin, 1,4-diazepane, 1,4-oxazepane and 8-oxa-3-aza-bicyclo[3.2.1]oct-3-yl, as well as those groups specifically illustrated by the examples herein below. Preferred 5 or 6 membered heterocycloalkyl are morpholine or piperidine, in particular morpholin-4-yl or piperidin-1-yl. Substituents for these
25 heterocycloalkyl groups include but are not limited to halo, hydroxy, C₁₋₇-alkyl, C₁₋₇-alkoxy, C₁₋₇-haloalkyl, C₁₋₇-haloalkoxy as well as those groups specifically illustrated by the examples herein below.

The term “pharmaceutically acceptable acid addition salts” embraces salts with inorganic and organic acids, which include but are not limited to hydrochloric acid, nitric
30 acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid.

In certain embodiments the compounds of formula I according to the invention are those compounds wherein:

- R¹ is phenyl optionally substituted by one or more substituents selected from the group consisting of Cl, F and C₁₋₇-haloalkyl,
5 or is morpholine or piperidine optionally substituted by OH;
R² is Br, I, C₁₋₇-haloalkoxy, C₃₋₆-cycloalkyl optionally substituted by phenyl, or is morpholine or piperidine;
R³ is C₁₋₇-alkyl;
as well as optical isomers and pharmaceutically acceptable salts thereof.

- 10 In certain embodiments, the compounds of the invention are those compounds of formula I wherein R¹ is phenyl optionally substituted by one or more substituents selected from the group consisting of Cl, F and C₁₋₇-haloalkyl, for example the following compounds:

- 3-Methanesulfonyl-2-methyl-4-phenyl-6-trifluoromethoxy-quinoline;
15 6-Bromo-3-methanesulfonyl-2-methyl-4-phenyl-quinoline;
3-Methanesulfonyl-2-methyl-4-phenyl-6-piperidin-1-yl-quinoline;
3-Methanesulfonyl-2-methyl-6-morpholin-4-yl-4-phenyl-quinoline;
6-Bromo-4-(4-fluoro-phenyl)-3-methanesulfonyl-2-methyl-quinoline;
4-(4-Fluoro-phenyl)-3-methanesulfonyl-2-methyl-6-morpholin-4-yl-quinoline;
20 6-Bromo-4-(4-chloro-phenyl)-3-methanesulfonyl-2-methyl-quinoline;
4-(4-Chloro-phenyl)-3-methanesulfonyl-2-methyl-6-morpholin-4-yl-quinoline;
3-Methanesulfonyl-2-methyl-6-morpholin-4-yl-4-(4-trifluoromethyl-phenyl)-quinoline;
3-Methanesulfonyl-2-methyl-6-morpholin-4-yl-4-(2,4,5-trifluoro-phenyl)-quinoline;
6-Bromo-3-methanesulfonyl-2-methyl-4-(4-trifluoromethyl-phenyl)-quinoline; and
25 6-Bromo-3-methanesulfonyl-2-methyl-4-(2,4,5-trifluoro-phenyl)-quinoline.

In certain embodiments, the compounds of the invention are those compounds of formula I wherein R¹ is morpholine, for example the following compounds:

- 6-Iodo-3-methanesulfonyl-2-methyl-4-morpholin-4-yl-quinoline;
6-Bromo-3-methanesulfonyl-2-methyl-4-morpholin-4-yl-quinoline;
30 3-Methanesulfonyl-2-methyl-4-morpholin-4-yl-6-((1*R*,2*R*)-2-phenyl-cyclopropyl)-quinoline;
3-Methanesulfonyl-2-methyl-4-morpholin-4-yl-6-piperidin-1-yl-quinoline; and
6-Cyclopropyl-3-methanesulfonyl-2-methyl-4-morpholin-4-yl-quinoline.

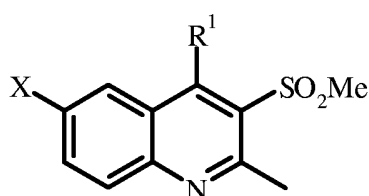
In certain embodiments, the compounds of the invention are those compounds of formula I wherein R^1 is piperidine optionally substituted by OH, for example the following compounds:

- 6-Iodo-3-methanesulfonyl-2-methyl-4-piperidin-1-yl-quinoline;
 5 1-(6-Iodo-3-methanesulfonyl-2-methyl-quinolin-4-yl)-piperidin-4-ol;
 (*R*)-1-(6-Iodo-3-methanesulfonyl-2-methyl-quinolin-4-yl)-piperidin-3-ol; and
 (*S*)-1-(6-Iodo-3-methanesulfonyl-2-methyl-quinolin-4-yl)-piperidin-3-ol.

The invention also encompasses the following novel intermediate compounds, which are useful in the preparation of the compounds of the invention:

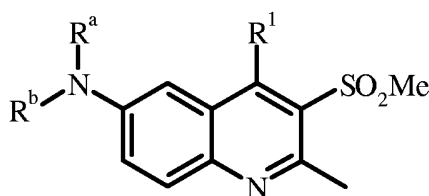
- 10 (2-Amino-5-bromo-phenyl)-(4-trifluoromethyl-phenyl)-methanone;
 (2-Amino-5-bromo-phenyl)-(2,4,5-trifluoro-phenyl)-methanone;
 6-Bromo-2-methyl-4*H*-3,1-benzoxazin-4-one;
 6-Iodo-2-methyl-4*H*-3,1-benzoxazin-4-one;
 6-Bromo-3-methanesulfonyl-2-methyl-quinolin-4-ol;
 15 6-Iodo-3-methanesulfonyl-2-methyl-quinolin-4-ol;
 6-Bromo-4-chloro-3-methanesulfonyl-2-methyl-quinoline; and
 4-Chloro-6-iodo-3-methanesulfonyl-2-methyl-quinoline.

Also encompassed by the compounds of formula I are the compounds of formulae I-a, I-b and I-c as follows:



I - a

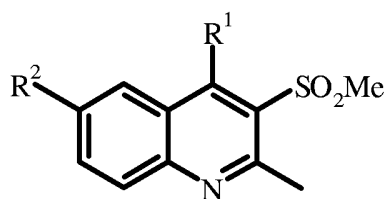
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I - b

and

- 10 -



I - c

wherein

R¹ is a 5 or 6 membered heterocycloalkyl ring optionally substituted by OH, said heterocycloalkyl ring being preferably morpholine or piperidine,

5 R² is as defined hereinabove,

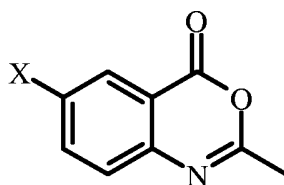
R^a and R^b are as defined hereinabove, and

X is Br or I.

The preparation of said intermediate compounds is described in the examples herein below.

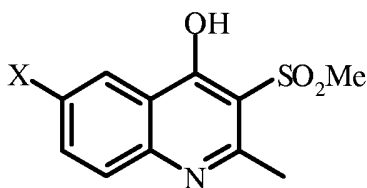
10 The compounds of formula I-a, I-b and I-c can be manufactured by the following process of the invention comprising the step of:

a) reacting a compound of formula IV



IV

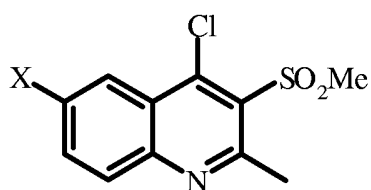
with MeCOCH₂SO₂Me in order to obtain a compound of formula V:



V

- 11 -

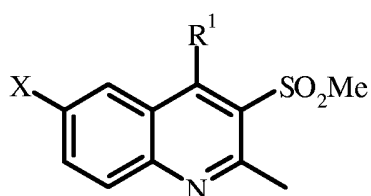
b) reacting the compound of formula V with POCl_3 in order to obtain a compound of formula VI:



VI

c) reacting the compound of formula VI with a compound of formula HR^1 ,

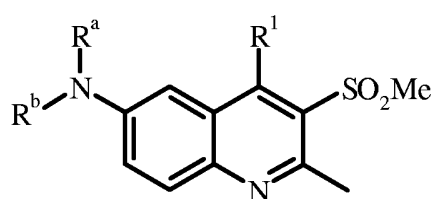
5 in order to obtain a compound of formula I-a:



I - a

and if desired, reacting the compound of formula I-a:

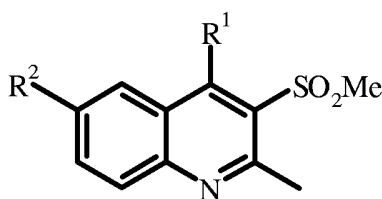
d) either with a compound of formula HNR^aR^b in order to obtain a compound of formula I-b:



I - b

c) or with a compound of formula $\text{R}^2\text{B}(\text{OH})_2$ in order to obtain a compound of formula I-c:

- 12 -



I - c

wherein R¹ is a 5 or 6 membered heterocycloalkyl ring optionally substituted by OH, said heterocycloalkyl ring being preferably morpholine or piperidine,

R² is as defined hereinabove,

5 R^a and R^b are as defined hereinabove, and

X is Br or I, and if desired, converting the compound of formulae I-a, I-b or I-c obtained into a pharmaceutically acceptable acid addition salt. This process of manufacture is further detailed in scheme 4 hereinafter.

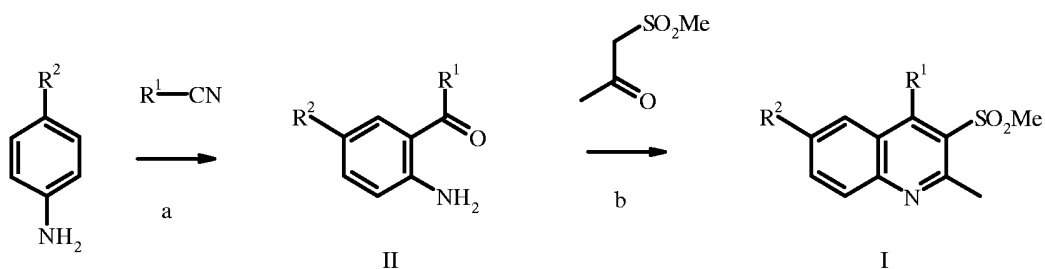
10 The invention also encompasses a compound of formula I, whenever it is prepared according to the above-mentioned process.

The following general schemes 1 to 3 further illustrate certain embodiments of the preparation of the compounds according to the invention. In these schemes, and unless otherwise stated, all starting materials, building blocks and intermediates are commercially available.

15 In certain embodiments, the compounds of formula I wherein R³ is methyl can be prepared according to the general method known in the art as described with scheme1:

Scheme 1:

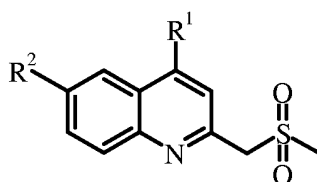
Scheme 1



a) 1. GaCl_3 (1.2 eq), BCl_3 (1.1 eq), DCE, reflux, 12 h; 2. H_2O , 60° , 0.5 h
 b) NaAuCl_4 (2.5 mol%), iPrOH, reflux, 2-4 d

Step a: This step can be performed following a procedure developed by T. Sugasawa, T. Toyoda, M. Adachi, and K. Sasakura, *J. Am. Chem. Soc.* 100, 4842-4852 (1978) and improved by A. W. Douglas, N. L. Abramson, I. N. Houppis, S. Karady, A. Molina, L. C. Xavier, N. Yasuda, *Tetrahedron Lett.* 35, 6807-6810 (1994).

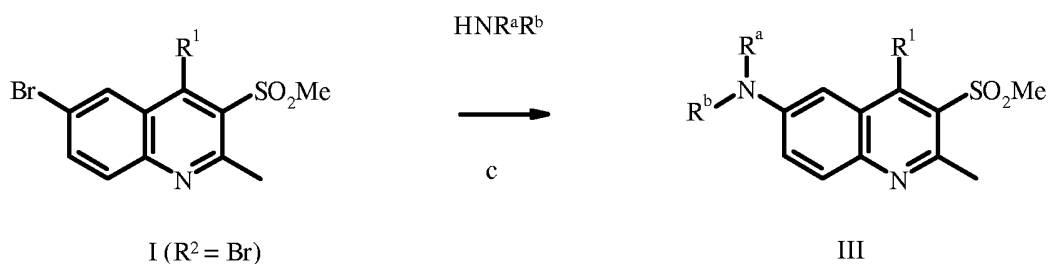
Step b: This step can be conducted according to the procedure developed by A. Arcadi, M. Chiarini, S. Di Giuseppe, and F. Marinelli, *Synlett* 203-206 (2003) for 1,3-diketones and β -ketoesters and was extended to the reaction with β -ketoamides and β -ketosulfones. The latter were prepared by heating intermediates of formula II for several days with about 2 equivalents of methylsulfonyl acetone. The regioisomer shown below is also formed in 5-10 % yield.



In certain embodiments, the compounds of formula I wherein R^3 is methyl can be prepared according to the general method known in the art as described in scheme 2 herein below:

Scheme 2:

Scheme 2

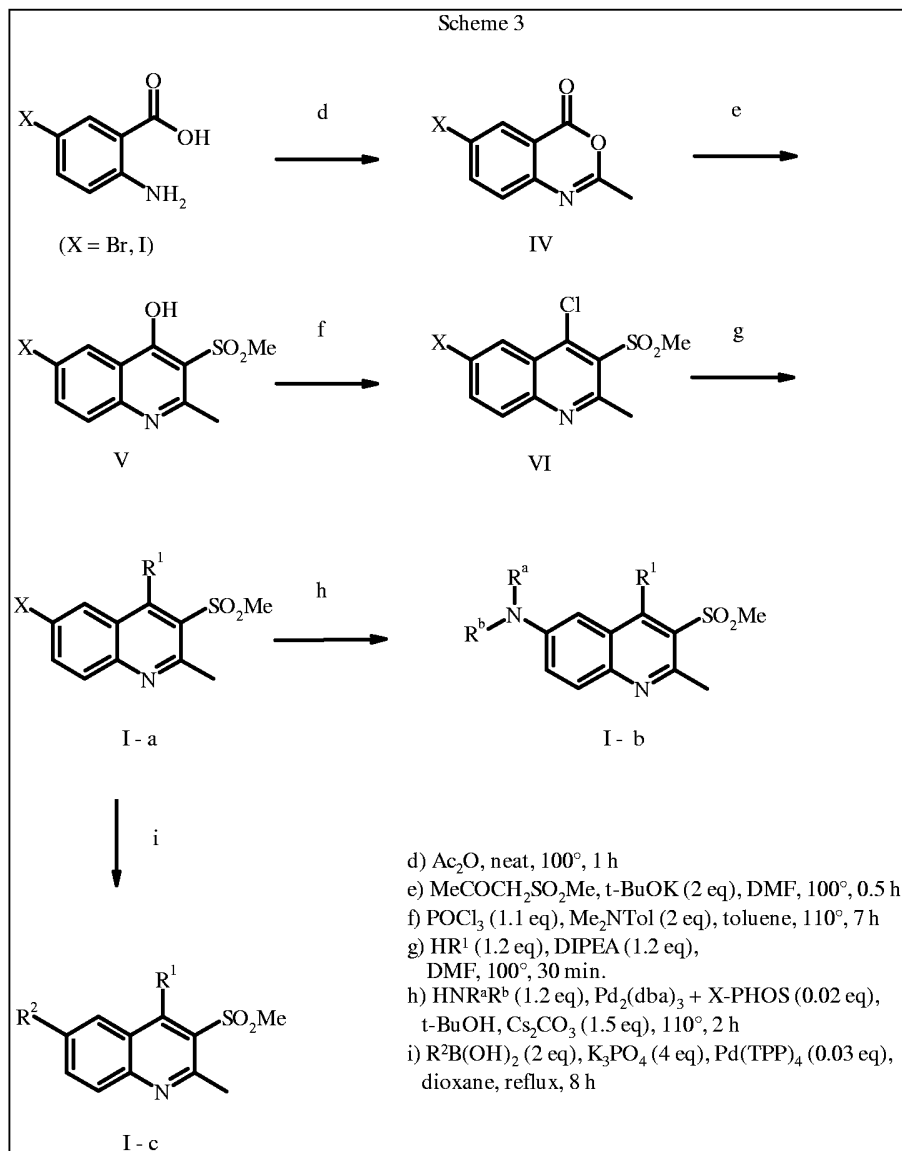


c) HNR^aR^b (1.2 eq), $\text{Pd}_2(\text{dba})_3 + \text{X-PHOS}$ (0.02 eq),
 Cs_2CO_3 (1.5 eq), $t\text{-BuOH}$, 110° , 2 h

Step c: This step can be performed following a methodology developed by J. P. Wolfe and S. L. Buchwald (J. Org. Chem. 2000, 65, 1144-1157). X-PHOS was shown to be superior to BINAP as a catalyst. Preferred solvent was tert.-butanol alone or as mixture
 5 with dioxane.

In certain embodiments, the compounds of formula I wherein R^3 is methyl can be prepared according to the general method of the invention as described in scheme 3 herein below:

Scheme 3:



In this scheme:

R^1 is a 5 or 6 membered heterocycloalkyl ring optionally substituted by OH, said heterocycloalkyl ring being preferably morpholine or piperidine.

5 R^2 is as defined hereinabove.

R^a and R^b are as defined hereinabove.

X is Br or I.

Step d: can be performed following a procedure developed J. B. Jiang, D. P. Hesson, B. A. Dusak, D. L. Dexter, G. J. Kang, E. Hamel, J. Med. Chem. 1990, 33, 1721-1728.

Step e: can be a one-pot transformation under anhydrous basic conditions with e.g. 2 equivalents of sodium hydride or potassium tert.-butoxide in N,N-dimethylformamide which involves the elimination of potassium acetate. No chromatography is needed.

Step f: is an optimized procedure for the formation of the vinylogous sulfonyl chloride with e.g. 2 equivalents of the stable base N,N-dimethyl-toluidine and one equivalent of phosphorous oxy chloride in toluene at reflux for about 6- 9 h. The reaction can also be performed in neat phosphorous oxychloride at reflux for about 0.5 - 1 h with one equivalent of N,N-diethylaniline as base. The product can be directly precipitated and isolated without chromatography.

Step g: can be either nucleophilic substitution with primary and secondary amines in the appropriate solvent, e.g. N,N-dimethylformamide, or a reaction under Buchwald conditions (method c)

Step h: is a reaction under Buchwald conditions (method c).

Step i: Substrates of formula VII (where $R^2 = Br$) reacted smoothly under Suzuki cross-coupling conditions with a base, e.g. tribasic potassium phosphate as in the appropriate solvent, e.g. dioxane at reflux.

The preparation of compounds of formula I is further described in detail in working examples 1 – 21.

As mentioned earlier, the compounds of formula I and their pharmaceutically acceptable addition salts possess valuable pharmacological properties. It has been found that the compounds of the present invention have an affinity to the GABA_B receptor.

The compounds were investigated in accordance with the tests given hereinafter.

Intracellular Ca²⁺ mobilization assay

The Chinese Hamster Ovary (CHO) cells stably expressing human GABA_BR1aR2a and Gα16 were seeded at 5×10^4 cells/well in the poly-D-lysine treated, 96-well, black/clear-bottomed plates (BD Biosciences, Palo Alto, CA). 24 h later, the cells were loaded for 90 min at 37°C with 4 μM Flou-4 acetoxymethyl ester (Catalog No. F-14202, Molecular Probes, Eugene, OR) in loading buffer (1xHBSS, 20 mM HEPES, 2.5 mM Probenecid). Hanks' Balanced Salt Solution (HBSS) (10X) (catalog No. 14065-049) and HEPES (1M) (catalog No. 15630-056) were purchased from Invitrogen, Carlsbad, CA. Probenecid (250 mM) (catalog No. P8761) was from Sigma, Buchs, Switzerland. The cells

- were washed five times with loading buffer to remove excess dye and intracellular calcium mobilization, $[Ca^{2+}]_i$ were measured using a Fluorometric Imaging Plate Reader (FLIPR, Molecular Devices, Menlo Park, CA) as described previously (Porter et al., Br. J. Pharmacol., 128, 13-20, 1999). The enhancers were applied 15 min before the application of the GABA. For GABA shift assay, concentration-response curves of GABA (0.0003-30 μ M) were determined in the absence and presence of 10 μ M enhancer. The GABA-shift is defined as $\text{Log} [EC_{50} (\text{GABA} + 10 \mu\text{M enhancer}) / EC_{50} (\text{GABA alone})]$. The % maximum enhancing effect (% E_{max}) and potency (EC_{50} value) of each enhancer was determined from concentration-response curve of the enhancer (0.001-30 μ M) in the presence of 10 nM GABA (EC_{10}). Responses were measured as peak increase in fluorescence minus basal, normalized to the maximal stimulatory effect induced by 10 μ M GABA alone (considered 100%) and 10 nM GABA alone (considered 0%). The data were fitted with the equation $Y = 100 + (\text{Max} - 100) / (1 + (EC_{50} / [\text{drug}])^n)$ where Max is the maximum effect, EC_{50} the concentration eliciting a half-maximum effect and n the Hill slope.

Example	Intracellular Ca^{2+} mobilization Assay in CHO-GABA _B R1aR2a-G α 16 cell		GABA shift
	E_{max} (%) at 10 nM GABA alone = 0% 10 μ M GABA alone = 100%	EC_{50} (μ M) at 10nM GABA	$\text{Log} [EC_{50}(\text{GABA} + 10 \mu\text{M cp}) / EC_{50}(\text{GABA alone})]$
1	56	0.85	-0.7
5	30	2.1	-0.4
9	48	0.6	-1.2
11	26	0.8	-0.8
14	37	2.1	-0.45

The compounds of formula I as well as their pharmaceutically usable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The

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

5 The compounds of formula I and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragées and hard gelatine capsules.

10 Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols.

Suitable excipients for the manufacture of solutions and syrups include but are not limited to water, polyols, saccharose, invert sugar, glucose.

15 Suitable excipients for injection solutions include but are not limited to water, alcohols, polyols, glycerol, vegetable oils.

Suitable excipients for suppositories include but are not limited to natural or hardened oils, waxes, fats, semi-liquid or liquid polyols.

20 Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

25 The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of general formula I should be appropriate, although the above upper limit can also be exceeded when necessary.

Tablet Formulation (Wet Granulation)

<u>Item</u>	<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

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

EXAMPLESSynthesis of intermediates

Examples A.1 to A.4: intermediates of formula II

Example A.1

5 (2-Amino-5-bromo-phenyl)-(4-fluoro-phenyl)-methanone

In a reactor fitted with magnetic stir bar, rubber septum, thermometer, Hickmann-condenser, nitrogen-inlet and nitrogen-outlet connected to a washing bottle containing 30 % NaOH, anhydrous beads of gallium (III) chloride (11.7 g, 66 mmol) were added at once and then dissolved by the addition of 1,2-dichloroethane (100 mL). This solution
10 was cooled in ice, then 4-bromoaniline (9.5 g, 55 mmol) was added slowly while keeping the temperature below 5 °C. Then the solution was cooled to -10 °C and a fresh 1 M solution of boron trichloride in dichloromethane (61 ml) was added via a syringe fitted with a teflon stop-cock while keeping the temperature below -5 °C. Finally 4-fluorobenzonitrile (6.7 g, 55 mmol) was added and the mixture was allowed to warm to
15 20 °C. The Hickmann-condenser was replaced by a normal reflux condenser and the reaction mixture was heated in an oil-bath (90 °C) over 1-2 h in order to distil off all the dichloromethane (a total of ca. 100 mL of distillate was collected) until the reflux temperature of 80 °C was achieved. Refluxing was continued for 14 h. The reaction mixture was cooled in ice and hydrolyzed slowly with water (100 mL) and then heated at
20 60-80 °C for 20-30 min. in order to hydrolyze the imine. The reaction mixture was cooled again and then extracted twice with dichloromethane and water. The crude product was purified by chromatography with a heptane/ethyl acetate gradient from 100:0 to 80:20 to give a yellow solid (7 g, 43 %). MS: m/z = 294 (M).

Example A.2

25 (2-Amino-5-bromo-phenyl)-(4-chloro-phenyl)-methanone

The title compound was prepared by reacting 4-bromoaniline and 4-chlorobenzonitrile following to the procedure of example A.1. Yield 33 %; MS: m/z = 310 (M).

Example A.3

(2-Amino-5-bromo-phenyl)-(4-trifluoromethyl-phenyl)-methanone

The title compound was prepared by reacting 4-bromoaniline and 4-(trifluoromethyl)benzonitrile following to the procedure of example A.1. Yield 34 %; MS: $m/z = 344$ (M).

Example A.4

5 (2-Amino-5-bromo-phenyl)-(2,4,5-trifluoro-phenyl)-methanone

The title compound was prepared by reacting 4-bromoaniline and 2,4,5-trifluorobenzonitrile following to the procedure of example A.1. Yield 26 %; MS: $m/z = 330$ (M).

Examples B.1 and B.2: intermediates of formula IV

10 Example B.1

6-Bromo-2-methyl-4*H*-3,1-benzoxazin-4-one

2-Amino-5-bromobenzoic acid (25 g, 116 mmol) was added in portions to acetic anhydride (150 mL) giving a slightly exothermic reaction to 30 °C. The suspension was heated at reflux for 2 h. The product crystallized spontaneously upon cooling. After
15 stirring in ice for 30 min, the crystals were filtered off and washed twice with heptane. The crystals were thoroughly dried at 0.1 mbar/50 °C. One obtained 22.4 g (85 %) of beige crystals. MS: $m/z = 239/241$ (M).

Example B.2

6-Iodo-2-methyl-4*H*-3,1-benzoxazin-4-one

20 2-Amino-5-iodobenzoic acid (25.4 g, 96.6 mmol) was added in portions to cold acetic anhydride (100 mL). The suspension was first stirred without cooling then the resulting thick precipitate was heated at reflux for 1 h (red solution). The product crystallized spontaneously upon cooling. After stirring in ice for 30 min, the crystals were filtered off and washed twice with heptane. The crystals were thoroughly dried at 0.1 mbar/50 °C.
25 One obtained 25.1 g (90 %) of beige crystals. MS: $m/z = 287$ (M).

Examples C.1 and C.2: intermediates of formula V

Example C.1

6-Bromo-3-methanesulfonyl-2-methyl-quinolin-4-ol

Methanesulfonylacetone (12.6 g, 92.9 mmol) was dissolved in N,N-dimethylformamide (200 mL) and cooled in ice under nitrogen. Then potassium tert.butylate (11.7 g, 102 mmol) was added (exothermic 20 °C) and stirring without cooling continued for 15 min. Cooled in ice again, then 6-bromo-2-methyl-4*H*-3,1-benzoxazin-4-one (example B.1) (22.3 g, 92.9 mmol) was added and then stirred without cooling for 4 h. Cooled in ice again, then potassium tert.butylate (11.7 g, 102 mmol) was added and the resulting red solution was stirred at 20 °C for 15 min and then heated at 100 °C for 30 min. After cooling, 4 M HCl (30 mL) was added and the mixture was evaporated thoroughly at 0.1 mbar/50 °C. The residue was suspended in water (200 mL) and stirred vigorously for 30 min which led to the formation of a filterable precipitate. This solid was filtered off and washed with water (50 mL). One obtained 14.25 g (48.5 %) of white crystals. MS: $m/z = 315/317$ (M + H).

Example C.2

6-Iodo-3-methanesulfonyl-2-methyl-quinolin-4-ol

Methanesulfonylacetone (13 g, 95 mmol) was dissolved in N,N-dimethylformamide (200 mL) and cooled in ice under nitrogen. Then potassium tert.butylate (11.2 g, 100 mmol) was added (exothermic, 20 °C) and stirring without cooling continued for 15 min. Cooled in ice again, then 6-bromo-2-methyl-4*H*-3,1-benzoxazin-4-one (example B.2) (27.4 g, 95.4 mmol) was added and then stirred without cooling for 4 h. Cooled in ice again, then potassium tert.butylate (11.2 g, 100 mmol) was added and the resulting red solution was stirred at 20 °C for 15 min and then heated at 100 °C for 30 min. After cooling, 4 M HCl (30 mL) was added and the mixture was evaporated thoroughly at 0.1 mbar/50 °C. The residue was suspended in water (200 mL) and stirred vigorously for 30 min which led to the formation of a filterable precipitate. This solid was filtered off and washed with water (50 mL). The crude product was heated to reflux in MeOH (60 mL) in order to dissolve mainly impurities. The suspension was allowed to cool to 20 °C again and the solid was filtered off. One obtained 15.1 g (43 %) of a white solid. MS: $m/z = 363$ (M).

Examples D.1 and D.2: intermediates of formula VI

30

Example D.1

6-Bromo-4-chloro-3-methanesulfonyl-2-methyl-quinoline

6-Bromo-3-methanesulfonyl-2-methyl-quinolin-4-ol (example C.1) (6 g, 19 mmol) and N,N-dimethyl-*p*-toluidine (5.5 mL, 38 mmol) were dissolved in toluene (60 mL) and

heated under argon to reflux. The phosphorous oxychloride (1.9 mL, 20.9 mL) was added and heating at reflux continued for 6.5 h. The product precipitated spontaneously upon cooling to 20 °C, the crystals were filtered off and washed with little toluene. One obtained 4.19 g (66 %) of light brown crystals. Since the product is somewhat soluble in toluene, the mother liquor was extracted with 3 N HCl (2 x), sat. NaCl (2 x). The residue was purified by chromatography on silica gel in dichloromethane. One obtained 1.17 g (18 %) of additional material. MS: $m/z = 333/335$ (M).

Example D.2

4-Chloro-6-iodo-3-methanesulfonyl-2-methyl-quinoline

6-Iodo-3-methanesulfonyl-2-methyl-quinolin-4-ol (example C.2) (14.7 g, 40.5 mmol) and N,N-dimethyl-p-toluidine (11.7 mL, 81 mmol) were dissolved in toluene (150 mL) and heated under argon to reflux. Then phosphorous oxychloride (4.1 mL, 44.5 mmol) was added and heating at reflux continued for 9.5 h. The thick suspension became gradually a dark solution. The reaction mixture was allowed to cool and then extracted with dichloromethane (not soluble in toluene), cold 1 N HCl (2 x), and sat. NaCl (2 x). The product was crystallized from heptane/dichloromethane. One obtained 12 g (78 %) of white crystals. MS: $m/z = 381$ (M).

Synthesis of the compounds of formula I according to the invention

In the following examples, unless otherwise specified, all the starting materials are commercially available.

Example 1

3-Methanesulfonyl-2-methyl-4-phenyl-6-trifluoromethoxy-quinoline

(2-Amino-5-trifluoromethoxy-phenyl)-phenyl-methanone (0.3 g, 1 mmol), methylsulfonylacetone (0.22 g, 2 mmol) and sodium tetrachloroaurate (III) dihydrate (13 mg, 0.036 mmol) were mixed in 2-propanol (3 mL) and heated at reflux under nitrogen for 5 days. 2-propanol was evaporated and the residue was purified by flash chromatography on silica gel in heptane/ethyl acetate 2:1. One obtained 154 mg (34%) of a white solid. MS: $m/z = 382$ (M+H).

Example 2

6-Bromo-3-methanesulfonyl-2-methyl-4-phenyl-quinoline

(2-Amino-5-bromo-phenyl)-phenyl-methanone (10 g, 36 mmol), methanesulfonylacetone (7.4 g, 54 mmol) and sodium tetrachloroaureate(III) dihydrate (720 mg, 1.8 mmol) were heated at reflux in 2-propanol (100 mL) for 4.5 days. The resulting suspension was evaporated to dryness and the residue extracted with
5 dichloromethane (2 x), 1 N NaOH (2 x), which removes excess of methanesulfonylacetone, and sat. NaCl (1 x). The crude product was purified twice by chromatography in dichloromethane and then crystallized from dichloromethane/heptane by evaporation of dichloromethane. One obtained 4.6 g (33 %) of beige crystals. MS: $m/z = 375/377$ (M).

10

Example 3

3-Methanesulfonyl-2-methyl-4-phenyl-6-piperidin-1-yl-quinoline

A tube placed under argon was charged with tris(dibenzylideneacetone)dipalladium chloroform complex (3 mg), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (3 mg) and cesium carbonate (121 mg, 0.37 mmol). 6-Bromo-3-methanesulfonyl-2-methyl-4-
15 phenyl-quinoline (compound of example 2) (100 mg, 0.26 mmol) in dioxane / tert.-butanol 1:1 (15 ml) was added, followed by piperidine (0.027 ml, 0.031 mmol). The tube was sealed and heated at 120 °C for 2 h. The reaction mixture was cooled to 20 °C, diluted with heptane, filtered through dicalite and purified directly by flash chromatography on silica gel in heptane/ethyl acetate 40 : 60 to give a yellow solid (47 mg, 46%). MS: $m/z =$
20 381 (M + H).

Example 4

3-Methanesulfonyl-2-methyl-6-morpholin-4-yl-4-phenyl-quinoline

A tube placed under argon was charged with tris(dibenzylideneacetone)dipalladium chloroform complex (55 mg, 0.053 mmol) , 2-dicyclohexylphosphino-2',4',6'-
25 triisopropylbiphenyl (63 mg, 0.106 mmol) and cesium carbonate (1.3 g, 3.99 mmol). 6-Bromo-3-methanesulfonyl-2-methyl-4-phenyl-quinoline (compound of example 2) (1 g, 2.66 mmol) in tert.-butanol (20 ml) was added, followed by morpholine (0.28 g, 3.19 mmol). The tube was sealed and heated at 110 °C for 2 h. The reaction mixture was cooled to 20 °C, diluted with heptane, filtered through dicalite and purified directly by
30 flash chromatography on silica gel in heptane/ethyl acetate 80 : 20 to give a yellow solid (800 mg, 78%). MS: $m/z = 383$ (M + H).

Example 5

6-Iodo-3-methanesulfonyl-2-methyl-4-morpholin-4-yl-quinoline

4-Chloro-6-iodo-3-methanesulfonyl-2-methyl-quinoline (compound of example D.2) (1 g, 2.62 mmol), morpholine (274 mg, 3.1 mmol) and N,N-diisopropyl ethyl amine (406 mg, 3.1 mmol) were heated at 100 °C in dry N,N-dimethylformamide (10 mL) for 30 min. The reaction mixture was evaporated to dryness, and the residue extracted with dichloromethane, 10 % Na₂CO₃ and sat. NaCl. The crude product was purified by chromatography on silica gel in dichloromethane/ ethyl acetate 5 :1. One obtained 913 mg (80 %) of a yellow foam. MS: m/z = 433 (M + H).

10

Example 6

6-Bromo-3-methanesulfonyl-2-methyl-4-morpholin-4-yl-quinoline

6-Bromo-4-chloro-3-methanesulfonyl-2-methyl-quinoline (compound of example D.1) (11.5 g, 34.4 mmol), morpholine (3.3 mL, 37.8 mmol) and N,N-diisopropyl ethyl amine (6.5 mL, 37.8 mmol) were heated at 100 °C in dry N,N-dimethylformamide (10 mL) for 30 min. The reaction mixture was evaporated to dryness, and the residue extracted with dichloromethane, 10 % Na₂CO₃ and sat. NaCl. The crude product was stirred and heated at 80 °C in ethyl acetate (80 mL) for 10 min, the resulting suspension was cooled in ice, the crystals were filtered off and washed with little cold ethyl acetate. One obtained 10.8 g (81 %) of white crystals. MS: m/z = 385/387 (M + H).

20

Example 7

3-Methanesulfonyl-2-methyl-4-morpholin-4-yl-6-((1*R*,2*R*)-2-phenyl-cyclopropyl)-quinoline

6-Bromo-3-methanesulfonyl-2-methyl-4-morpholin-4-yl-quinoline (compound of example 6) (300 mg, 0.78 mmol), *trans*-2-phenylcyclopropylboronic acid (189 mg, 1.17 mmol), potassium phosphate (496 mg, 2.33 mmol) and tetrakis(triphenylphosphine)-palladium (27 mg, 0.023 mmol) were heated at reflux under argon for 8 h. The crude product was purified by chromatography on silica gel in dichloromethane/ethyl acetate 5 :1 with a gradient from 100:0 to 80:20. One obtained 202 mg (60 %) of white crystals. MS: m/z = 423 (M + H).

30

Example 8

3-Methanesulfonyl-2-methyl-4-morpholin-4-yl-6-piperidin-1-yl-quinoline

A tube placed under argon was charged with tris(dibenzylideneacetone)dipalladium chloroform complex (11 mg, 0.010 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (10 mg, 0.021 mmol) and cesium carbonate (1.3 g, 3.99 mmol). 6-Bromo-3-methanesulfonyl-2-methyl-4-morpholin-4-yl-quinoline (compound of example 6) (200 mg, 0.52 mmol) in tert.-butanol (10 ml) was added, followed by piperidine (0.053 g, 0.62 mmol). The tube was sealed and heated at 110 °C for 2 h. The reaction mixture was cooled to 20 °C, diluted with heptane, filtered through dicalite and purified directly by flash chromatography on silica gel in heptane/ethyl acetate 80 : 20 to give a yellow solid (160 mg, 79 %). MS: $m/z = 390$ (M + H).

10

Example 9

6-Iodo-3-methanesulfonyl-2-methyl-4-piperidin-1-yl-quinoline

4-Chloro-6-iodo-3-methanesulfonyl-2-methyl-quinoline (compound of example D.2) (300 mg, 0.786 mmol), piperidine (74 mg, 0.865 mmol) and N,N-diisopropyl ethyl amine (0.148 mL, 0.865 mmol) were heated in dry N,N-dimethylformamide (3 mL) for 4 h at 100 °C. N,N-Dimethylformamide was evaporated at 40 °C/0.1 mbar, and the residue directly purified by chromatography on silica gel in dichloromethane. One obtained 184 mg (54 %) of white crystals. MS: $m/z = 431$ (M + H).

Example 10

1-(6-Iodo-3-methanesulfonyl-2-methyl-quinolin-4-yl)-piperidin-4-ol

4-Chloro-6-iodo-3-methanesulfonyl-2-methyl-quinoline (compound of example D.2) (300 mg, 0.786 mmol), 4-hydroxypiperidine (87 mg, 0.865 mmol) and N,N-diisopropyl ethyl amine (0.148 mL, 0.865 mmol) were heated in dry N,N-dimethylformamide (3 mL) for 0.5 h at 100 °C. N,N-Dimethylformamide was evaporated at 40 °C/0.1 mbar, and the residue directly purified by chromatography on silica gel in dichloromethane/methanol 20:1. One obtained a yellow oil which was triturated with ethyl acetate and the resulting white crystals were filtered off. One obtained 218 mg (62 %) of white crystals. MS: $m/z = 447$ (M + H).

Example 11

(R)-1-(6-Iodo-3-methanesulfonyl-2-methyl-quinolin-4-yl)-piperidin-3-ol

4-Chloro-6-iodo-3-methanesulfonyl-2-methyl-quinoline (compound of example D.2) (300 mg, 0.786 mmol), (R)-(+)-3-hydroxypiperidine (119 mg, 0.865 mmol) and N,N-

diisopropyl ethyl amine (0.148 mL, 0.865 mmol) were heated in dry N,N-dimethylformamide (3 mL) for 0.5 h at 100 °C. N,N-Dimethylformamide was evaporated at 40 °C/0.1 mbar, the residue was extracted with dichloromethane and 10 % Na₂CO₃, and then purified by chromatography on silica gel in dichloromethane/methanol 20:1.

- 5 One obtained a yellow oil which was triturated with ethyl acetate and the resulting white crystals were filtered off. One obtained 209 mg (60 %) of white crystals. MS: m/z = 447 (M + H).

Example 12

(S)-1-(6-Iodo-3-methanesulfonyl-2-methyl-quinolin-4-yl)-piperidin-3-ol

- 10 4-Chloro-6-iodo-3-methanesulfonyl-2-methyl-quinoline (compound of example D.2) (300 mg, 0.786 mmol), (S)-(+)-3-hydroxypiperidine (119 mg, 0.865 mmol) and N,N-diisopropyl ethyl amine (0.148 mL, 0.865 mmol) were heated in dry N,N-dimethylformamide (3 mL) for 0.5 h at 100 °C. N,N-Dimethylformamide was evaporated at 40 °C/0.1 mbar, the residue was extracted with dichloromethane and 10 % Na₂CO₃, and
- 15 then purified by chromatography on silica gel in dichloromethane/methanol 20:1. One obtained a yellow oil which was triturated with ethyl acetate and the resulting white crystals were filtered off. One obtained 191 mg (54 %) of white crystals. MS: m/z = 447 (M + H).

Example 13

- 20 6-Cyclopropyl-3-methanesulfonyl-2-methyl-4-morpholin-4-yl-quinoline

- 6-Bromo-3-methanesulfonyl-2-methyl-4-morpholin-4-yl-quinoline (compound of example 6) (0.5 g, 1.3 mmol), cyclopropylboronic acid (0.167 g, 1.95 mmol), potassium phosphate tribasic (0.826 g, 3.89 mmol) and tetrakis(triphenylphosphine)palladium(0) (45 mg, 0.039) were mixed together in dioxane (7 mL) and heated at reflux under argon
- 25 for 8 h. After extraction with dichloromethane and half-saturated NaCl solution, the crude product was purified chromatography on silica gel in dichloromethane/ethyl acetate with a gradient from 100:0 to 90:10. One obtained 0.1 g (21 %) of white crystals. MS: m/z = 347 (M + H).

Example 14

- 30 6-Bromo-4-(4-fluoro-phenyl)-3-methanesulfonyl-2-methyl-quinoline

(2-Amino-5-bromo-phenyl)-(4-fluoro-phenyl)-methanone (compound of example A.1) (4 g, 14 mmol), methanesulfonylacetone (2.78g, 20 mmol) and sodium tetrachloroaureate(III) dihydrate (0.27g, 0.7 mmol) were heated at reflux in 2-propanol (50 ml) for 4 days. The resulting mixture was evaporated to dryness and the residue
5 extracted with dichloromethane (2 x), 1 N NaOH (2 x) and NaCl (1 x). The crude product was purified by chromatography in heptane/ethyl acetate with a gradient from 100:0 to 70:30. One obtained a light brown solid (1.5 g, 28%). MS: m/z = 394 (M).

Example 15

4-(4-Fluoro-phenyl)-3-methanesulfonyl-2-methyl-6-morpholin-4-yl-quinoline

10 A tube placed under argon was charged with tris(dibenzylideneacetone)dipalladium chloroform complex (79 mg, 0.076 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (73 mg, 0.152 mmol) and cesium carbonate (1.86 g, 5.7 mmol). 6-Bromo-4-(4-fluoro-phenyl)-3-methanesulfonyl-2-methyl-quinoline (compound of
15 example 14) (200 mg, 0.52 mmol) in tert.-butanol (20 ml) was added, followed by morpholine (0.40 g, 4.56 mmol). The tube was sealed and heated at 110 °C for 2 h. The reaction mixture was cooled to 20 °C, diluted with heptane, filtered through dicalite and purified directly by flash chromatography on silica gel in heptane/ethyl acetate with a gradient from 100:0 to 40:60 to give a yellow solid (850 mg, 56%). MS: m/z = 401 (M + H).

20 Example 16

6-Bromo-4-(4-chloro-phenyl)-3-methanesulfonyl-2-methyl-quinoline

(2-Amino-5-bromo-phenyl)-(4-chloro-phenyl)-methanone (compound of example A.2) (4 g, 12.9 mmol), methanesulfonylacetone (2.63 g, 19.3 mmol) and sodium tetrachloroaureate(III) dihydrate (0.26 g, 0.64 mmol) were heated at reflux in 2-propanol
25 (50 ml) for 4 days. The resulting mixture was evaporated to dryness and the residue extracted with dichloromethane (2 x), 1 N NaOH (2 x) and sat. NaCl (1 x). The crude product was purified by chromatography on silica gel in dichloromethane. The product was crystallized from dichloromethane/heptane by evaporation of dichloromethane. One obtained a light yellow solid (1 g, 19%). MS: m/z = 410 (M).

30 Example 17

4-(4-Chloro-phenyl)-3-methanesulfonyl-2-methyl-6-morpholin-4-yl-quinoline

A tube placed under argon was charged with tris(dibenzylideneacetone)dipalladium chloroform complex (40 mg, 0.039 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (37 mg, 0.078 mmol) and cesium carbonate (952 mg, 2.92 mmol). 6-Bromo-4-(4-chloro-phenyl)-3-methanesulfonyl-2-methyl-quinoline (compound of
5 example 16) (800 mg, 1.95 mmol) in tert.-butanol (20 ml) was added, followed by morpholine (0.204 g, 2.33 mmol). The tube was sealed and heated at 110 °C for 2 h. The reaction mixture was cooled to 20 °C, diluted with heptane, filtered through dicalite and purified directly by flash chromatography on silica gel in heptane/ethyl acetate with a gradient 100:0 to 40:60 to give a yellow solid (350 mg, 43%). MS: m/z = 417 (M + H).

10 Example 18

3-Methanesulfonyl-2-methyl-6-morpholin-4-yl-4-(4-trifluoromethyl-phenyl)-quinoline

A tube placed under argon was charged with tris(dibenzylideneacetone)dipalladium chloroform complex (51 mg, 0.05 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (47 mg, 0.10 mmol) and cesium carbonate (1.21 g, 3.71 mmol). 6-
15 Bromo-3-methanesulfonyl-2-methyl-4-(4-trifluoromethyl-phenyl)-quinoline (compound of example 20) (800 mg, 1.95 mmol) in tert.-butanol (20 ml) was added, followed by morpholine (0.259 g, 2.97 mmol). The tube was sealed and heated at 110 °C for 2 h. The reaction mixture was cooled to 20 °C, diluted with heptane, filtered through dicalite and purified directly by flash chromatography on silica gel in heptane/ethyl
20 acetate with a gradient 100:0 to 40:60 to give a yellow solid (320 mg, 29%). MS: m/z = 451 (M + H).

Example 19

3-Methanesulfonyl-2-methyl-6-morpholin-4-yl-4-(2,4,5-trifluoro-phenyl)-quinoline

A tube placed under argon was charged with tris(dibenzylideneacetone)dipalladium
25 chloroform complex (19 mg, 0.019 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (18 mg, 0.019 mmol) and cesium carbonate (454 mg, 1.4 mmol). 6-Bromo-3-methanesulfonyl-2-methyl-4-(2,4,5-trifluoro-phenyl)-quinoline (compound of example 21) (400 mg, 0.93 mmol) in tert.-butanol (20 ml) was added, followed by morpholine (97 mg, 1.11 mmol). The tube was sealed and heated at 110 °C for 2 h. The
30 reaction mixture was cooled to 20 °C, diluted with heptane, filtered through dicalite and purified directly by flash chromatography on silica gel in heptane/ethyl acetate with a gradient 100:0 to 40:60 to give a yellow solid (250 mg, 62%). MS: m/z = 437 (M + H).

Example 20

6-Bromo-3-methanesulfonyl-2-methyl-4-(4-trifluoromethyl-phenyl)-quinoline

(2-Amino-5-bromo-phenyl)-(4-trifluoromethyl-phenyl)-methanone (compound of example A.3) (4 g, 11.6 mmol), methanesulfonylacetone (2.37 g, 17.4 mmol) and sodium tetrachloroaureate(III) dihydrate (0.23 g, 0.58 mmol) were heated at reflux in ethanol (50 ml) for 4 days. The resulting mixture was evaporated to dryness and the residue extracted with dichloromethane (2 x), NaOH (2 x) and NaCl (1 x). The crude product was purified by chromatography on silica gel in heptane/ ethyl acetate 70:30. One obtained a light yellow solid (1.5 g, 29 %). MS: $m/z = 444$ (M).

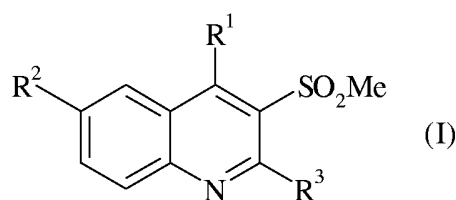
Example 21

10 6-Bromo-3-methanesulfonyl-2-methyl-4-(2,4,5-trifluoro-phenyl)-quinoline

(2-Amino-5-bromo-phenyl)-(2,4,5-trifluoro-phenyl)-methanone (compound of example A.4) (1.9 g, 5.7 mmol), methanesulfonylacetone (1.18 g, 8.6 mmol) and sodium tetrachloroaureate(III) dihydrate (0.12g, 0.28 mmol) were heated at reflux in 2-propanol (50 ml) for 4 days. The resulting mixture was evaporated to dryness and the residue extracted with dichloromethane (2 x), NaOH (2 x) and NaCl (1 x). The crude product was purified by chromatography on silica gel with a heptane/ethyl acetate gradient from 100:0 to 90:10. One obtained a light yellow solid (0.5 g, 20 %). MS: $m/z = 430$ (M).

Claims

1. Compounds of formula I:



wherein

- 5 R^1 is phenyl optionally substituted by one or more substituents selected from the group consisting of Cl, F, C_{1-7} -haloalkyl, hydroxy, C_{1-7} -alkoxy, C_{1-7} -haloalkoxy, di(C_{1-7})alkylamino and C_{1-7} -alkylsulfonyl, or is 5 or 6 membered heterocycloalkyl optionally substituted by OH;
- 10 R^2 is Br, I, C_{1-7} -alkyl, C_{1-7} alkoxy, C_{1-7} -haloalkyl, C_{1-7} -haloalkoxy, aryloxy, arylsulfonyl, or C_{3-6} -cycloalkyl optionally substituted by phenyl, or is $-NR^aR^b$ wherein R^a and R^b are C_{1-7} -alkyl, or R^a and R^b can, together with the nitrogen atom to which they are attached, form a 4 to 8 membered heterocycloalkyl group which can be substituted by one or more substituent(s) selected from the group consisting of halo, C_{1-7} -alkyl, C_{1-7} alkoxy, hydroxy, phenyl and di(C_{1-7})alkylamino;
- 15 R^3 is H, C_{1-7} -alkyl, or C_{3-6} -cycloalkyl;
as well as optical isomers and pharmaceutically acceptable salts thereof.

2. The Compounds of formula I according to claim 1, wherein:

- R^1 is phenyl optionally substituted by one or more substituents selected from the group consisting of Cl, F and C_{1-7} -haloalkyl,
20 or is morpholine or piperidine optionally substituted by OH;
- R^2 is Br, I, C_{1-7} -haloalkoxy, C_{3-6} -cycloalkyl optionally substituted by phenyl, or is morpholine or piperidine;
- R^3 is C_{1-7} -alkyl;
as well as optical isomers and pharmaceutically acceptable salts thereof.

- 25 3. The compounds of formula I according to claim 2, wherein R^1 is phenyl optionally substituted by one or more substituents selected from the group consisting of Cl, F and C_{1-7} -haloalkyl.

4. The compounds of formula I according to claim 3, wherein the compounds are selected from the group consisting of:

- 3-Methanesulfonyl-2-methyl-4-phenyl-6-trifluoromethoxy-quinoline;
6-Bromo-3-methanesulfonyl-2-methyl-4-phenyl-quinoline;
3-Methanesulfonyl-2-methyl-4-phenyl-6-piperidin-1-yl-quinoline;
3-Methanesulfonyl-2-methyl-6-morpholin-4-yl-4-phenyl-quinoline;
5 6-Bromo-4-(4-fluoro-phenyl)-3-methanesulfonyl-2-methyl-quinoline;
4-(4-Fluoro-phenyl)-3-methanesulfonyl-2-methyl-6-morpholin-4-yl-quinoline;
6-Bromo-4-(4-chloro-phenyl)-3-methanesulfonyl-2-methyl-quinoline;
4-(4-Chloro-phenyl)-3-methanesulfonyl-2-methyl-6-morpholin-4-yl-quinoline;
3-Methanesulfonyl-2-methyl-6-morpholin-4-yl-4-(4-trifluoromethyl-phenyl)-quinoline;
10 3-Methanesulfonyl-2-methyl-6-morpholin-4-yl-4-(2,4,5-trifluoro-phenyl)-quinoline;
6-Bromo-3-methanesulfonyl-2-methyl-4-(4-trifluoromethyl-phenyl)-quinoline; and
6-Bromo-3-methanesulfonyl-2-methyl-4-(2,4,5-trifluoro-phenyl)-quinoline.

5. The compounds of formula I according to claim 1, wherein R¹ is morpholine.

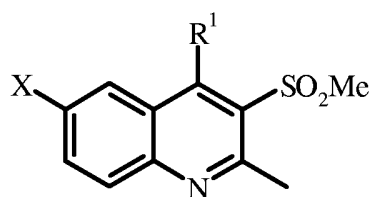
6. The compounds of formula I according to claim 5, wherein the compounds are
15 selected from the group consisting of:
6-Iodo-3-methanesulfonyl-2-methyl-4-morpholin-4-yl-quinoline;
6-Bromo-3-methanesulfonyl-2-methyl-4-morpholin-4-yl-quinoline;
3-Methanesulfonyl-2-methyl-4-morpholin-4-yl-6-((1*R*,2*R*)-2-phenyl-cyclopropyl)-
quinoline;
20 3-Methanesulfonyl-2-methyl-4-morpholin-4-yl-6-piperidin-1-yl-quinoline; and
6-Cyclopropyl-3-methanesulfonyl-2-methyl-4-morpholin-4-yl-quinoline.

7. The compounds of formula I according to claim 1, wherein R¹ is piperidine
optionally substituted by OH.

8. The compounds of formula I according to claim 7, wherein the compounds are
25 selected from the group consisting of:
6-Iodo-3-methanesulfonyl-2-methyl-4-piperidin-1-yl-quinoline;
1-(6-Iodo-3-methanesulfonyl-2-methyl-quinolin-4-yl)-piperidin-4-ol;
(*R*)-1-(6-Iodo-3-methanesulfonyl-2-methyl-quinolin-4-yl)-piperidin-3-ol; and
(*S*)-1-(6-Iodo-3-methanesulfonyl-2-methyl-quinolin-4-yl)-piperidin-3-ol.

- 30 9. The compounds of formula I-a according to claim 1:

- 33 -

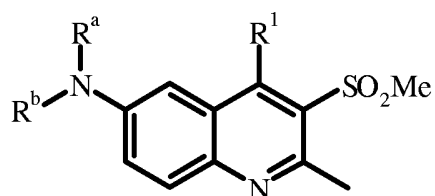


I - a

wherein

R^1 is a 5 or 6 membered heterocycloalkyl ring optionally substituted by OH, and
X is Br or I.

- 5 10. The compounds of formula I-b according to claim 1:

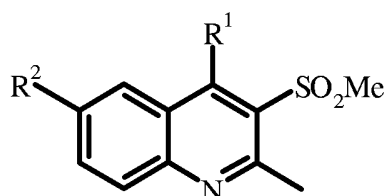


I - b

wherein

R^1 is a 5 or 6 membered heterocycloalkyl ring optionally substituted by OH, and
 R^a and R^b are as defined in claim 1.

- 10 11. The compounds of formula I-c according to claim 1:



I - c

wherein

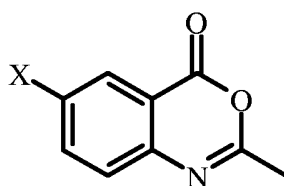
R^1 is a 5 or 6 membered heterocycloalkyl ring optionally substituted by OH, and
 R^2 is as defined in claim 1.

- 15 12. Intermediates useful for the preparation of compounds of formula I according to claim 1, wherein the intermediates are selected from the group consisting of:
(2-Amino-5-bromo-phenyl)-(4-trifluoromethyl-phenyl)-methanone;
(2-Amino-5-bromo-phenyl)-(2,4,5-trifluoro-phenyl)-methanone;
6-Bromo-2-methyl-4*H*-3,1-benzoxazin-4-one;

- 6-Iodo-2-methyl-4*H*-3,1-benzoxazin-4-one;
6-Bromo-3-methanesulfonyl-2-methyl-quinolin-4-ol;
6-Iodo-3-methanesulfonyl-2-methyl-quinolin-4-ol;
6-Bromo-4-chloro-3-methanesulfonyl-2-methyl-quinoline; and
5 4-Chloro-6-iodo-3-methanesulfonyl-2-methyl-quinoline.

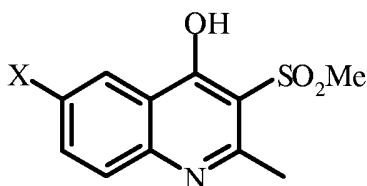
13. A process for the preparation of compounds of formula I-a, I-b and I-c comprising the step of:

a) reacting a compound of formula IV



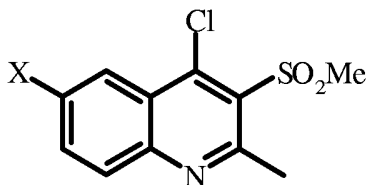
IV

- 10 with $\text{MeCOCH}_2\text{SO}_2\text{Me}$ in order to obtain a compound of formula V:



V

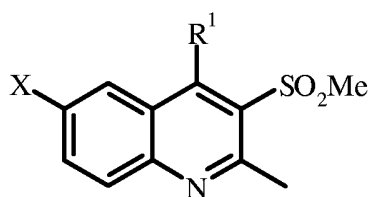
b) reacting the compound of formula V with POCl_3 in order to obtain a compound of formula VI:



VI

- 15 c) reacting the compound of formula VI with a compound of formula HR^1 ,
in order to obtain a compound of formula I-a:

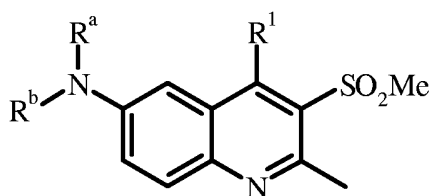
- 35 -



I - a

and if desired, reacting the compound of formula I-a:

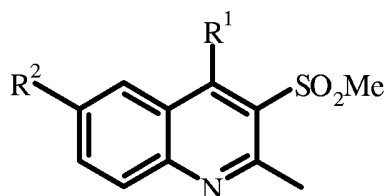
d) either with a compound of formula HNR^aR^b in order to obtain a compound of formula I-b:



I - b

5

c) or with a compound of formula $\text{R}^2\text{B}(\text{OH})_2$ in order to obtain a compound of formula I-c:



I - c

wherein

- 10 R^1 is a 5 or 6 membered heterocycloalkyl ring optionally substituted by OH,
 R^2 and R^a and R^b are as defined in claim 1, and X is Br or I,
 and if desired, converting the compound of formulae I-a, I-b or I-c obtained into a
 pharmaceutically acceptable acid addition salt.

14. A compound prepared according to a process of claim 13.

- 15 15. A medicament containing a compound of formula I according to any one of
 claims 1 to 11.

16. The medicament according to claim 15, wherein the medicament is useful in the control or prevention of illnesses, especially of illnesses and disorders comprising anxiety, depression, epilepsy, schizophrenia, cognitive disorders, spasticity and skeletal muscle rigidity, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy, neuropathic pain and craving associated with cocaine and nicotine, psychosis, panic disorder, posttraumatic stress disorders or gastro-intestinal disorders.

17. The use of a compound according to any one of claims 1 to 11 for the preparation of a medicament.

18. The use according to claim 17, wherein the medicament is useful in the control or prevention of illnesses, especially of illnesses and disorders comprising anxiety, depression, epilepsy, schizophrenia, cognitive disorders, spasticity and skeletal muscle rigidity, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy, neuropathic pain and craving associated with cocaine and nicotine, psychosis, panic disorder, posttraumatic stress disorders or gastro-intestinal disorders.

19. A compound of formula I, a process for the preparation of a compound of formula I, a medicament containing a compound of formula I and a use of a compound of formula I for the manufacture of a medicament as claimed and as described hereinabove.
