QUINOLINE COMPOUNDS SUITABLE FOR TREATING DIDORDERS THAT RESPOND TO MODULATION OF THE SEROTONIN 5-HT6 RECEPTOR

BACKGROUND OF THE INVENTION

The present invention relates to novel quinoline compounds. The compounds possess valuable therapeutic properties and are particularly suitable, for treating diseases that respond to modulation of the serotonin 5-HT_6 receptor.

Serotonin (5-hydroxytryptamine, 5-HT), a monoamine neurotransmitter and local hormone, is formed by the hydroxylation and decarboxylation of tryptophan. The greatest concentration is found in the enterochromaffin cells of the gastrointestinal tract, the remainder being predominantly present in platelets and in the Central Nervous System (CNS). 5-HT is implicated in a vast array of physiological and pathophysiological pathways. In the periphery, it contracts a number of smooth muscles and induces endothelium-dependent vasodilation. In the CNS, it is believed to be involved in a wide range of functions, including the control of appetite, mood, anxiety, hallucinations, sleep, vomiting and pain perception.

Neurons that secrete 5-HT are termed serotonergic. The function of 5-HT is exerted upon its interaction with specific (serotonergic) neurons. Until now, seven types of 5-HT receptors have been identified: 5-HT_1 (with subtypes 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F}), 5-HT_2 (with subtypes 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}), 5-HT_3, 5-HT_4, 5-HT_5 (with subtypes 5-HT_{5A} and 5-HT_{5B}), 5-HT_6 and 5-HT_7. Most of these receptors are coupled to G-proteins that affect the activities of either adenylate cyclase or phospholipase Cγ.

The human 5-HT_6 receptors are positively coupled to adenylyl cyclase. They are distributed throughout the limbic, striatal and cortical regions of the brain and show a high affinity to antipsychotics.

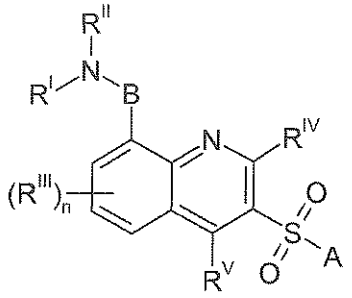
The modulation of the 5-HT_6 receptor by suitable substances is expected to improve certain disorders including cognitive dysfunctions, such as a deficit in memory, cognition and learning, in particular associated with Alzheimer's disease, age-related cognitive decline and mild cognitive impairment, attention deficit disorder/hyperactivity syndrome, personality disorders, such as schizophrenia, in particular cognitive deficits related with schizophrenia, affective disorders such as depression, anxiety and obsessive compulsive disorders, motion or motor disorders such as Parkinson's disease and epilepsy, migraine, sleep disorders (including disturbances of the Circadian rhythm), feeding disorders, such as anorexia and bulimia, certain gastrointestinal disorders such as Irritable Bowl Syndrome, diseases associated with

neurodegeneration, such as stroke, spinal or head trauma and head injuries, such as hydrocephalus, drug addiction and obesity.

Quinoline compounds having an affinity for the 5-HT_6 receptor have been described in the prior art, e.g. in US 2007/0027161, WO 05/026125 and WO 03/080580. The compounds disclosed therein carry a piperazin-1-yl radical in the 8-position of the quinoline moiety. The compounds are mentioned to be useful for the treatment of 5-HT_6 receptor-related disorders.

WO 05/113539 describes quinoline compounds which carry a N-bound heterocyclic radical in the 8-position having an affinity for the 5-HT_6 receptor.

The intermediately published WO 07/039219 describes quinoline compounds of formula (1),



(1)

wherein B is -$(CH_2)_m$- or -$(CR^{IIX}R^{IX})$-, with m being 2 to 4 and R^{IIX} and R^{IX} being H or C_1-C_3-alkyl having an affinity for the 5-HT_6 receptor.

However, there is still an ongoing need for providing compounds having high affinity for the 5-HT_6 receptor and which show high selectivity to this receptor. In particular the compounds should have low affinity to adrenergic receptors, such as α_1-adrenergic receptor, histamine receptors, such as H_1-receptor, and dopaminergic receptors, such as D_2-receptor, in order to avoid or reduce considerable side effects associated with modulation of these receptors, such as postural hypotension, reflex tachycardia, potentiation of the antihypertensive effect of prazosin, terazosin, doxazosin and labetalol or dizziness associated to the blockade of the α_1-adrenergic receptor, weight gain, sedation, drowsiness or potentiation of central depressant drugs associated to the blockade of the H_1-receptor, or extrapyramidal movement disorder, such as dystonia, parkinsonism, akathisia, tardive dyskinesia or rabbit syndrome, or endocrine effects, such as prolactin elevation (galactorrhea, gynecomastia, menstruyl changes, sexual dysfunction in males), associated to the blockade of the D_2-receptor.

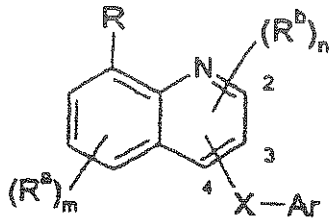
It is an object of the present invention to provide compounds which have a high affinity and selectivity for the 5-HT_6 receptor, thus allowing the treatment of disorders related to or affected by the 5-HT_6 receptor.

The compounds should also have good pharmacological profile, e.g. a good brain plasma ratio, a good bioavailability, good metabolic stability, or a decreased inhibition of the mitochondrial respiration.

SUMMARY

It has now been found that the quinoline compounds of the formula (I) as defined herein, their physiologically tolerated acid addition salts and the N-oxides thereof exhibit to a surprising and unexpected degree, selective binding to the 5-HT_6 receptor.

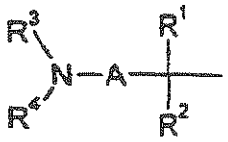
In a first aspect, there is provided quinoline compounds of formula (I)



(I)

wherein

R is a moiety of the formula



(R)

wherein

A is a chemical bond, CHR^5 or CH_2CHR^5;
R^1 is hydrogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C1- C4- haloalkoxy;
R^2 is hydrogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy;
R^3 is hydrogen or C_1-C_4-alkyl;
R^1 and R^3 together may also be linear C_1-C_4-alkylene, which may carry 1 or 2 radicals R^6;
R^4 is hydrogen, C_1-C_6-alkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, C_1-C_6-haloalkoxy-C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_3-C_6-halocycloalkyl, C_3-C_6-cycloalkyl-C_1-C_4-alkyl, aryl-C_1-C_4-alkyl, hetaryl-C_1-C_4-alkyl, C_3-C_6-alkenyl, C_3-C_6-haloalkenyl, formyl, C_1-C_4-alkylcarbonyl or C_1-C_4-alkoxycarbonyl;
R^5 is hydrogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy;
R^1 and R^5 together may also be a single bond, linear C_1-C_4-alkylene, which may carry 1 or 2 radicals R^7; or
R^3 and R^5 together may also be linear C_1-C_4-alkylene, which may carry 1 or 2 radicals R^8;
R^6 is C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy; or
R^5 and R^6 together may also be linear C_1-C_4-alkylene, which may carry 1 or 2 radical R^9;
R^7, R^8 and R^9 are independently selected from the group consisting of C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy and C_1-C_4-haloalkoxy;
n is 0, 1 or 2;
m is 0, 1, 2 or 3;
R^a, R^6 are independently selected from the group consisting of halogen, CN, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, $C(O)R^{aa}$, $C(O)NR^{cc}R^{bb}$ and $NR^{cc}R^{bb}$; wherein R^{aa} is hydrogen, C_1-C_4.-alkyl, C_1-C_4.haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy, and R^{cc}, R^{bb} are independently selected from the group consisting of hydrogen and C_1-C_4-alkyl;
X is CH_2, C(O), S. S(O) or $S(O)_2$; which is located in the 3- or 4-position of the quinoline ring;

Ar is a radical Ar^1, Ar^2–Ar^3 or Ar^2–O- Ar^3, wherein Ar^1, Ar^2 and Ar^3 are each independently selected from the group consisting of aryl or hetaryl wherein aryl or hetaryl moieties may be unsubstituted or may canny 1, 2, 3 substituents R^x, wherein

R^x is halogen, CN, NO_2, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, C_2-C_6-alkenyl, C_2-C_6-haloalkenyl, C_3-C_6-cycloalkyl, C_3-C_6-halocydoalkyl, C_1-C_6-alkoxy, C_1-C_6-hydroxy- alkoxy. C_1-C_6.alkoxy-C_1-C_4-alkoxy, C_1-C_6-haloalkoxy, C_1-C_6-alkylthio, C_1-C_6-haloalkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-haloalkylsulfinyl, C_1-C_6-alkylsulfonyl, C_1-C_6-haloalkylsulfonyl, C_1-C_6-alkylcarbonyl, C_1-C_6-haloalkylcarbonyl, C_1-C_6-alkylcarbonylamino, C_1-C_6-haloalkyl- carbonylamino, carboxy, NH-C(O)-$NR^{x1}R^{x2}$, $NR^{x1}R^{x2}$. $NR^{x1}R^{x2}$-C_1-C_6-alkylene, O-$NR^{x1}R^{x2}$, wherein R^{x1} and R^{x2} in the last 4 mentioned radicals are independently of each other hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl or C_1-C_6-alkoxy or R^{x1} and R^{x2} in the last 4 mentioned radicals together with the nitrogen atom form an N-bound 5-, 6- or 7-membered, saturated heterocycle which is unsubstituted or which carries 1, 2, 3 or 4 radicals selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl and C_1-C_4-alkoxy and wherein 2 radicals R^x, which are bound to adjacent carbon atoms of Ar may form a saturated or unsaturated 5- or 6-membered carbocyclic or heterocyclic ring, which itself may carry a radical R^x;

provided that for X being $S(O)_2$ at least one of the radicals R^1, R^2 and if present R^5 is different from hydrogen and C_1-C_4-alkyl;
and physiologically tolerated acid addition salts and the N-oxides thereof.

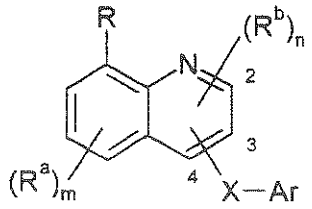
In a second aspect, there is provided a pharmaceutical composition comprising at least one compound as defined above, optionally together with at least one physiologically acceptable carrier or auxiliary substance.

In a third aspect, there is provided the use of a compound as defined above for preparing a pharmaceutical composition.

In a fourth aspect, there is provided the compound as defined above for the use as a medicament.

In a fifth aspect, there is provided the use of the compound as defined above in the manufacture of a medicament for the treatment of a medical disorder which is selected from a disease of the central nervous system, in particular a cognitive dysfunction such as cognitive dysfunction associated with Alzheimer's disease and cognitive dysfunction associated with schizophrenia, addiction disease and obesity.

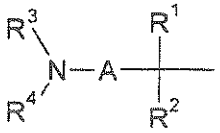
Therefore, the present disclosure relates to the compounds of formula (I)



(I)

wherein

R is a moiety of the formula



(R)

wherein

A is a chemical bond, CHR^5 or CH_2CHR^5;

R^1 is hydrogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy;

R^2 is hydrogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy;

R^3 is hydrogen or C_1-C_4-alkyl;

R^1 and R^3 together may also be linear C_1-C_4-alkylene, which may carry 1 or 2 radicals R^6;

R^4 is hydrogen, C_1-C_6-alkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, C_1-C_6-haloalkoxy-C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_3-C_6-halocycloalkyl, C_3-C_6-cycloalkyl-C_1-C_4-alkyl, aryl-C_1-C_4-alkyl, hetaryl-C_1-C_4-alkyl, C_3-C_6-alkenyl, C_3-C_6-haloalkenyl, formyl, C_1-C_4-alkylcarbonyl or C_1-C_4-alkoxycarbonyl;

R^5 is hydrogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy;

R^1 and R^5 together may also be a single bond or linear C_1-C_4-alkylene, which may carry 1 or 2 radicals R^7; or

R^3 and R^5 together may also be linear C_1-C_4-alkylene, which may carry 1 or 2 radicals R^6;

R^6 is C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy; or
R^5 and R^6 together may also be linear C_1-C_4-alkylene, which may carry 1 or 2 radicals R^9;
R^7, R^8 and R^9 are independently selected from the group consisting of C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy and C_1-C_4-haloalkoxy;

n is 0, 1 or 2;

m is 0, 1, 2 or 3;

R^a, R^b are independently selected from the group consisting of halogen, CN, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, $C(O)R^{aa}$, $C(O)NR^{cc}R^{bb}$ and $NR^{cc}R^{bb}$;
wherein R^{aa} is hydrogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy, and
R^{cc}, R^{bb} are independently selected from the group consisting of hydrogen and C_1-C_4-alkyl;

X is CH_2, C(O), S, S(O) or $S(O)_2$; which is located in the 3- or 4-position of the quinoline ring;

Ar is a radical Ar^1, Ar^2-Ar^3 or Ar^2-O-Ar^3, wherein Ar^1, Ar^2 and Ar^3 are each independently selected from the group consisting of aryl or hetaryl wherein aryl or hetaryl moieties may be unsubstituted or may carry 1, 2, 3 substituents R^x, wherein
R^x is halogen, CN, NO_2, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, C_2-C_6-alkenyl, C_2-C_6-haloalkenyl, C_3-C_6-cycloalkyl, C_3-C_6-halocycloalkyl, C_1-C_6-alkoxy, C_1-C_6-hydroxyalkoxy, C_1-C_6-alkoxy-C_1-C_4-alkoxy, C_1-C_6-haloalkoxy, C_1-C_6-alkylthio, C_1-C_6-haloalkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-haloalkylsulfinyl, C_1-C_6-alkylsulfonyl, C_1-C_6-haloalkylsulfonyl, C_1-C_6-alkylcarbonyl, C_1-C_6-haloalkylcarbonyl, C_1-C_6-alkylcarbonylamino, C_1-C_6-haloalkylcarbonylamino, carboxy, NH-C(O)-$NR^{x1}R^{x2}$, $NR^{x1}R^{x2}$, $NR^{x1}R^{x2}$-C_1-C_6-alkylene, O-$NR^{x1}R^{x2}$, wherein R^{x1} and R^{x2} in the last 4 mentioned radicals are independently of each other hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl or C_1-C_6-alkoxy or R^{x1} and R^{x2} in the last 4 mentioned radicals together with the nitrogen atom form an N-bound 5-, 6- or 7-membered, saturated heterocycle which is unsubstituted or which carries 1, 2, 3 or 4 radicals selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl and C_1-C_4-alkoxy and wherein 2 radicals R^x, which are bound to adjacent carbon atoms of Ar may form a saturated or unsaturated 5- or 6-membered carbocyclic or heterocyclic ring, which itself may carry a radical R^x;

and physiologically tolerated acid addition salts and the N-oxides thereof.

Compounds of formula (I), wherein X is $S(O)_2$, are preferably selected from compounds, wherein at least one of the radicals R^1, R^2 and if present R^5 is different from hydrogen and C_1-C_4-alkyl.

The present disclosure also relates to a pharmaceutical composition which comprises at least one quinoline compound of the formula (I) and/or at least one physiologically tolerated acid addition salt of (I) and/or at least one N-oxide of (I), where appropriate together with physiologically acceptable carriers and/or auxiliary substances.

The present disclosure further relates to the use of a quinoline compound of the formula (I) and/or physiologically tolerated acid addition salts thereof and/or at least one N-oxide of (I), for preparing a pharmaceutical composition, optionally together with at least one physiologically acceptable carrier or auxiliary substance.

The compounds are selective 5-HT_6 receptor ligands. Thus the compounds are particularly suitable for the treatment of disorders of the central nervous system, addiction diseases or obesity, as these disorders and diseases are likely to respond to influencing by 5-HT_6 receptor ligands. Therefore the present disclosure also provides a method for treating disorders in mammals, said method comprising administering an effective amount of at least one compound of the formula (I) and/or at least one physiologically tolerated acid addition salt of (I) and/or at least one N-oxide of (I) to a subject in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

The diseases which are susceptible to treatment with a quinoline compound of the formula I include, e.g., disorders and diseases of the central nervous system, in particular cognitive dysfunctions, such as a deficit in memory, cognition and learning, in particular associated with Alzheimer's disease, age-related cognitive decline and mild cognitive impairment, attention deficit disorder/hyperactivity syndrome (ADHD), personality disorders, such as schizophrenia, in particular cognitive deficits related with schizophrenia, affective disorders such as depression, anxiety and obsessive compulsive disorders, motion or motor disorders such as Parkinson's disease and epilepsy, migraine, sleep disorders (including disturbances of the Circadian rhythm), feeding disorders, such as anorexia and bulimia, certain gastrointestinal disorders such as Irritable Bowl Syndrome, diseases associated with neurodegeneration, such as stroke, spinal or head trauma and head injuries, such as hydrocephalus, drug addiction and obesity.

According to the invention, at least one quinoline compound of the general formula (I) having the meanings mentioned at the outset is used for treating the above mentioned indications. Provided the compounds of the formula (I) of a given constitution may exist

in different spatial arrangements, for example if they possess one or more centers of asymmetry, polysubstituted rings or double bonds, or as different tautomers, it is also possible to use enantiomeric mixtures, in particular racemates, diastereomeric mixtures and tautomeric mixtures, preferably, however, the respective essentially pure enantiomers, diastereomers and tautomers of the compounds of formula (I) and/or of their salts and/or their N-oxides.

It is likewise possible to use physiologically tolerated salts of the compounds of the formula (I), especially acid addition salts with physiologically tolerated acids. Examples of suitable physiologically tolerated organic and inorganic acids are hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, C_1-C_4-alkylsulfonic acids, such as methanesulfonic acid, aromatic sulfonic acids, such as benzenesulfonic acid and toluenesulfonic acid, oxalic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, adipic acid and benzoic acid. Other utilizable acids are described in Fortschritte der Arzneimittelforschung [Advances in drug research], Volume 10, pages 224 ff., Birkhäuser Verlag, Basel and Stuttgart, 1966.

It is likewise possible to use N-oxides of the compounds of the formula (I), if those compounds contain a basic nitrogen atom, such as the nitrogen atom of the quinoline moiety.

The organic moieties mentioned in the above definitions of the variables are - like the term halogen - collective terms for individual listings of the individual group members. The prefix C_n-C_m indicates in each case the possible number of carbon atoms in the group.

The term "halogen" denotes in each case fluorine, bromine, chlorine or iodine, in particular fluorine, chlorine or bromine.

The term "C_1-C_6-alkyl" as used herein and in the alkyl moieties of C_1-C_6-hydroxyalkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, C_1-C_6-alkylcarbonyl, C_1-C_6-alkylcarbonylamino, C_3-C_6-cycloalkyl-C_1-C_4-alkyl, aryl-C_1-C_4-alkyl or hetaryl-C_1-C_4-alkyl denotes in each case a straight-chain or branched alkyl group having from 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms. Examples of an alkyl group are methyl, ethyl, n-propyl, iso-propyl, n-butyl, 2-butyl, iso-butyl, tert-butyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl.

The term "C_1-C_6-haloalkyl" as used herein and in the haloalkyl moieties of C_1-C_6-haloalkylthio, C_1-C_6-haloalkylsulfinyl, C_1-C_6-haloalkylsulfonyl, C_1-C_6-haloalkylcarbonyl, C_1-C_6-haloalkylcarbonylamino denotes in each case a straight-chain or branched alkyl group having from 1 to 6 carbon atoms, wherein the hydrogen atoms of this group are partially or totally replaced with halogen atoms. Preferred haloalkyl moieties are selected from C_1-C_4-haloalkyl, especially preferred from C_1-C_2-haloalkyl, such as chloromethyl, bromomethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, chlorofluoromethyl, dichlorofluoromethyl, chlorodifluoromethyl, 1-chloroethyl, 1-bromethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2-fluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2dichloro-2-fluorethyl, 2,2,2-trichloroethyl, pentafluoroethyl and the like.

The term "C_1-C_4-alkylene" as used herein denotes a straight-chain or branched bivalent alkandiyl group having from 1 to 4 carbon atoms, examples including methylene, 1,1-ethylene (1,1-ethandiyl), 1,2-ethylene (1,2-ethandiyl), 1,1-propandiyl, 1,2-propandiyl, 2,2-propandiyl, 1,3-propandiyl, 1,1-butandiyl, 1,2-butandiyl, 1,3-butandiyl, 1,4-butandiyl, 2,3-butandiyl, 2,2-butanediyl. The term " linear C_1-C_4-alkylene" as used herein denotes a straight-chain bivalent alkandiyl group having from 1 to 4 carbon atoms, examples including methylene, 1,2-ethylene, 1,3-propandiyl and 1,4-butandiyl.

The term "C_1-C_6-alkoxy" as used herein and in the alkoxy moieties of C_1-C_6-alkoxy-C_1-C_4-alkyl denotes in each case a straight-chain or branched alkoxy group having from 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms. Examples of an alkoxy group are methoxy, ethoxy, n-propoxy, iso-propoxy, n-butyloxy, 2-butyloxy, iso-butyloxy, tert-butyloxy, pentyloxy, 1-methylbutyloxy, 2-methylbutyloxy, 3-methylbutyloxy, 2,2-dimethylpropyloxy, 1-ethylpropyloxy, hexyloxy, 1,1-dimethylpropyloxy, 1,2-dimethylpropyloxy, 1-methylpentyloyx, 2-methylpentyloxy, 3-methylpentyloxy, 4-methylpentyloxy, 1,1-dimethylbutyloyx, 1,2-dimethylbutyloxy, 1,3-dimethylbutyloxy, 2,2-dimethylbutyloxy, 2,3-dimethylbutyloyx, 3,3-dimethylbutyloxy, 1-ethylbutyloxy, 2-ethylbutyloxy, 1,1,2-trimethylpropyloxy, 1,2,2-trimethylpropyloxy, 1-ethyl-1-methylpropyloxy and 1-ethyl-2-methylpropyloxy.

The term "C_1-C_6-haloalkoxy" as used herein and in the haloalkoxy moieties of C_1-C_6-haloalkoxy-C_1-C_4-alkyl denotes in each case a straight-chain or branched alkoxy group having from 1 to 6 carbon atoms, wherein the hydrogen atoms of this group are partially or totally replaced with halogen atoms, in particular fluorine atoms. Preferred haloalkoxy moieties include C_1-C_4-haloalkoxy, in particular C_1-C_2-fluoroalkoxy, such as fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-fluoroethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 2-chloro-2-fluoroethoxy, 2-chloro-2,2-difluoroethoxy, 2,2dichloro-2-fluorethoxy, 2,2,2-trichloroethoxy, pentafluoroethoxy and the like.

The term "C_1-C_6-hydroxyalkyl" is a straight-chain or branched alkyl group having from 1 to 6, especially 1 to 4 carbon atoms (= C_1-C_4 hydroxyalkyl), in particular 1 to 3 carbon atoms (= C_1-C_3 hydroxyalkyl), wherein one of the hydrogen atoms is replaced by a hydroxy group, such as in 2-hydroxyethyl or 3-hydroxypropyl.

The term "C_1-C_6-alkoxy-C_1-C_4-alkyl" is a straight-chain or branched alkyl group having from 1 to 4 carbon atoms, wherein one of the hydrogen atoms is replaced by a C_1-C_6-alkoxy group, such as in methoxymethyl, ethoxymethyl, propoxymethyl, 1-methoxyethyl, 1-ethoxyethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-methoxypropyl, 2-ethoxypropyl, 3-methoxypropyl or 3-ethoxypropyl.

The term "C_1-C_6-haloalkoxy-C_1-C_4-alkyl" is a straight-chain or branched alkyl group having from 1 to 4 carbon atoms, wherein one of the hydrogen atoms is replaced by a C_1-C_6-haloalkoxy group.

The term "C_3-C_6-cycloalkyl" as used herein and in the cycloalkyl moieties of C_3-C_6-cycloalkyl-C_1-C_4-alkyl and C_3-C_6-halocycloylkyl denotes in each case a cycloaliphatic radical having from 3 to 6 C atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The cycloalkyl radical may be unsubstituted or may carry 1, 2, 3 or 4 C_1-C_4-alkyl radicals, preferably a methyl radical.

The term "C_3-C_6-halocycloalkyl" as used herein and in the halocycloalkyl moieties of C_3-C_6-halocycloalkyl-C_1-C_4-alkyl denotes in each case a cycloaliphatic radical having from 3 to 6 C atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, wherein at least one hydrogen radical, e.g. 1, 2, 3, 4 or 5 hydrogen radicals are replaced by halogen, in particular fluorine. Examples include 1-fluorocyclopropyl, 2-fluorocyclopropyl, 2,2-difluorocyclopropyl, 1-fluorocyclobutyl, 2-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3-fluorocyclobutyl, 3,3-difluorocyclobutyl, 1,3-difluorocyclobutyl etc,

The term "C_2-C_6-alkenyl" as used herein and in the alkenyl moieties of C_3-C_6-haloalkenyl and aryl-C_2-C_4-alkenyl denotes in each case a singly unsaturated hydrocarbon radical having 2, 3, 4, 5 or 6 C-atoms, e.g. vinyl, allyl (2-propen-1-yl), 1-propen-1-yl, 2-propen-2-yl, methallyl (2-methylprop-2-en-1-yl), 2-buten-1-yl, 3-buten-1-yl, 2-penten-1-yl, 3-penten-1-yl, 4-penten-1-yl, 1-methylbut-2-en-1-yl, 2-ethylprop-2-en-1-yl and the like.

The term "aryl" as used herein denotes in each case a carbocyclic radical selected from the group consisting of phenyl and phenyl fused to a saturated or unsaturated 5- or 6-membered carbocyclic ring, such as naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, indenyl or indanyl, provided that in the fused rings aryl is bound via the phenyl part of the fused rings.

The term "hetaryl" as used herein denotes in each case a heterocyclic radical selected from the group consisting of monocyclic 5- or 6-membered heteroaromatic radicals comprising as ring members 1, 2 or 3 heteroatoms selected from N, O and S and 5- or 6-membered heteroaromatic ring fused to a phenyl ring or to a 5- or 6-membered heteroaromatic radical, where the heterocyclic ring comprises as ring members 1, 2 or 3 heteroatoms selected from N, O and S.

Examples of 5- or 6-membered heteroaromatic radicals include pyridyl, i.e. 2-, 3-, or 4-pyridyl, pyrimidinyl, i.e. 2-, 4- or 5-pyrimidinyl, pyrazinyl, pyridazinyl, i.e. 3- or 4-pyridazinyl, thienyl, i.e. 2- or 3-thienyl, furyl, i.e. 2-or 3-furyl, pyrrolyl, i.e. 2- or 3-pyrrolyl, oxazolyl, i.e. 2-, 3- or 5-oxazolyl, isoxazolyl, i.e. 3-, 4- or 5-isoxazolyl, thiazolyl, i.e. 2-, 3- or 5-thiazolyl, isothiazolyl, i.e. 3-, 4- or 5-isothiazolyl, pyrazolyl, i.e. 1-, 3-, 4- or 5-pyrazolyl, i.e. 1-, 2-, 4- or 5-imidazolyl, oxadiazolyl, e.g. 2- or 5-[1,3,4]oxadiazolyl, 4- or 5-(1,2,3-oxadiazol)yl, 3- or 5-(1,2,4-oxadiazol)yl, 2- or 5-(1,3,4-thiadiazol)yl, thiadiazolyl, e.g. 2- or 5-(1,3,4-thiadiazol)yl, 4- or 5-(1,2,3-thiadiazol)yl, 3- or 5-(1,2,4-thiadiazol)yl, triazolyl, e.g. 1H-, 2H- or 3H-1,2,3-triazol-4-yl, 2H-triazol-3-yl, 1H-, 2H-, or 4H-1,2,4-triazolyl and tetrazolyl, i.e. 1H- or 2H-tetrazolyl.

Examples of a 5- or 6-membered heteroaromatic ring fused to a phenyl ring or to a 5- or 6-membered heteroaromatic radical include benzofuranyl, benzothienyl, indolyl, indazolyl, benzimidazolyl, benzoxathiazolyl, benzoxadiazolyl, benzothiadiazolyl, benzoxazinyl, chinolinyl, isochinolinyl, purinyl, 1,8-naphthyridyl, pteridyl, pyrido[3,2-d]pyrimidyl or pyridoimidazolyl and the like. These fused hetaryl radicals may be bonded to the remainder of the molecule (more precisely to the X group) via any ring atom of 5- or 6-membered heteroaromatic ring or via a carbon atom of the fused phenyl moiety.

Examples of rings Ar, wherein 2 radicals R^x, which are bound to adjacent carbon atoms of Ar, form a saturated or unsaturated 5- or 6-membered carbocyclic or heterocyclic ring include 2,3-dihydrobenzofuranyl, 2,3-dihydroindolyl, dihydroisoindolyl, dihydrobenzoxazinyl, tetrahydroisochinolinyl, benzomorpholinyl, chromenyl, chromanyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, indenyl and indanyl.

The term "saturated or unsaturated heterocyclic ring" in each case denotes a 3- to 7-membered cyclic radical containing at least one hetero atom selected from the group consisting of N, O and S. Examples for such saturated or unsaturated 3- to 7-membered heterocyclic rings comprise saturated or unsaturated, aromatic or non-aromatic heterocyclic rings. Examples therefore include, apart from the above-defined 5- or 6-membered heteroaromatic radicals, aziridyl, diaziridinyl, oxiranyl, azetidinyl, azetinyl, di- and tetrahydrofuranyl, pyrrolinyl, pyrrolidinyl, oxopyrrolidinyl, pyrazolinyl,

pyrazolidinyl, imidazolinyl, imidazolidinyl, oxazolinyl, oxazolidinyl, oxo-oxazolidinyl, isoxazolinyl, isoxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, oxothiomorpholinyl, dioxothiomorpholinyl and the like.

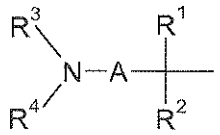
Examples for "N-bound 5- to 7-membered saturated heterocycle" are pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, morpholin-4-yl, imidazolidin-1-yl, oxazolidin-3-yl, thiazolidin-3-yl or hexahydrodiazepin-1-yl, especially piperidin-1-yl and morpholin-4-yl.

With regard to their ability to bind to the 5-HT_6 receptor preference is given to compounds of formula (I), wherein the variables Ar, A, X, n, m, R^1, R^2, R^3, R^4, R^a and R^b have the meanings given below.

The remarks made in the following with respect to preferred aspects of the invention, e.g. to preferred meanings of the variables of compound (I), to preferred compounds (I) and to preferred embodiments of the method or the use according to the invention, apply in each case on their own or to combinations thereof.

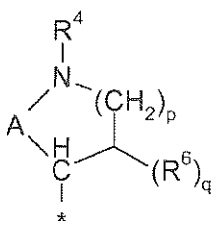
A first preferred embodiment of the invention relates to compounds of the formula (I), wherein R is a cyclic moiety, i.e. R^1 and R^3 together are linear C_1-C_4-alkylene, which may carry 1 or 2 radicals R^6; R^1 and R^5 together are a single bond or linear C_1-C_4-alkylene, which may carry 1 or 2 radicals R^7; or R^3 and R^5 together are linear C_1-C_4-alkylene, which may carry 1 or 2 radicals R^8.

More preferred are compounds of formula (I) wherein the radicals R^1 and R^3 together form a linear C_1-C_4-alkylene moiety, which may carry 1 or 2 radicals R^6, in particular 0 or 1 radicals R^6. Amongst these compounds, preference is given to those compounds of the formula I, wherein the moiety R

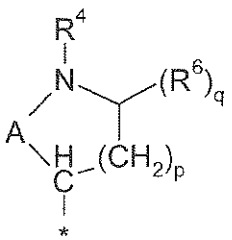


(R)

is a radical of the formulae R^A or R^B:

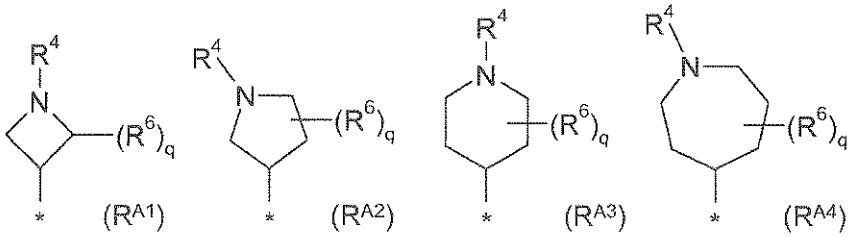


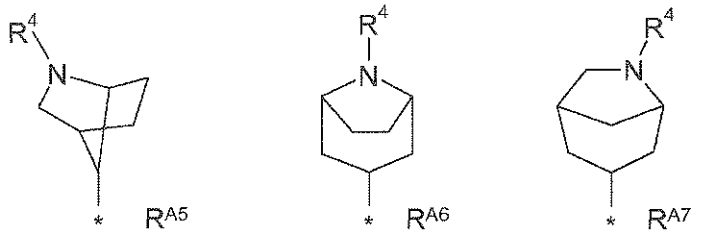
(R^A)



(R^B)

wherein A, R^4 and R^6 are as defined above, * indicates the binding site to the quinolinyl radical, p is 0, 1, 2 or 3 and q is 0 or 1. p is preferably 1 or 2. In the formulae R^A and R^B, the radical A is in particular methylene, 1,2-ethylene, or CH_2-CHR^5. R^5 is preferably methyl. R^6 is preferably methyl or R^5 and R^6 together are 1,2-ethandiyl. R^4 is preferably hydrogen. Examples of radicals R^A and R^B include radicals of the formulae R^{A1}, R^{A2}, R^{A3}, R^{A4}, R^{A5}, R^{A6} and R^{A7}:



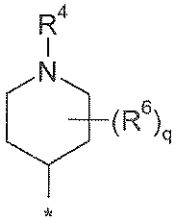


wherein R^4 and R^6 are as defined above, * indicates the binding site to the quinolinyl radical and q is 0 or 1. R^6 is preferably methyl. R^4 is preferably hydrogen.

Particular preference is given to quinoline compounds of the formula I, wherein the moiety R is of the formulae R^{A2}, R^{A3} or R^{A4}, wherein R^4 and R^6 are as defined above, and q is 0 or 1. In the formulae R^{A2}, R^{A3} and R^{A4} the radical R^6, if present, is preferably methyl. In the formulae R^{A2}, R^{A3} and R^{A4} the radical R^4 is preferably hydrogen.

Particular preference is further given to quinoline compounds of the formula I, wherein the moiety R is of the formulae R^{A1}, R^{A2} or R^{A3}, wherein R^4 and R^6 are as defined above, and q is 0 or 1. In the formulae R^{A1}, R^{A2} and R^{A3} the radical R^6, if present, is preferably methyl. In the formulae R^{A1}, R^{A2} and R^{A3} the radical R^4 is preferably hydrogen.

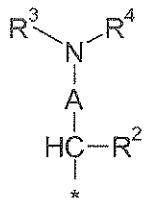
A particular preferred embodiment of the invention relates to compounds of the formula I, wherein the moiety R is a radical of the formula R^{A3}:



(R^{A3})

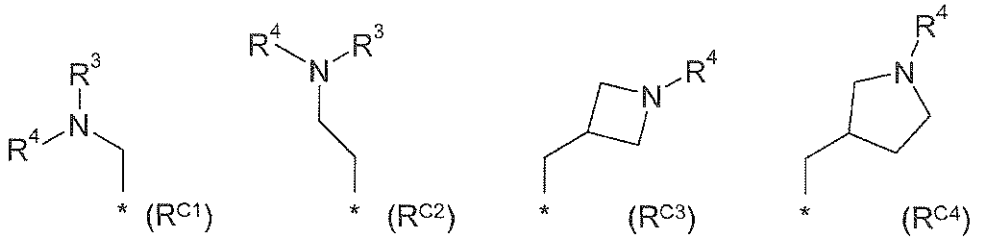
wherein R^4 and R^6 are as defined above, * indicates the binding site to the quinolinyl radical and q is 0 or 1. R^6 is preferably methyl. R^4 is preferably hydrogen.

A second embodiment of the invention relates to compounds of the formula A, wherein the radical R^1 is hydrogen. Amongst these compounds, preference is given to those compounds of the formula I, wherein the moiety R is a radical of the formula R^C:



(R^C)

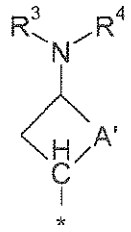
wherein A, R^2, R^3 and R^4 are as defined above, * indicates the binding site to the quinolinyl radical. In the formula R^C, the radical R^2 is preferably hydrogen. In the formula R^C, the radical A is in particular a single bond CH_2 or CH_2CHR^5, wherein R^5 is as defined above or preferably hydrogen or R^3 and R^5 together are CH_2, 1,2-ethandiyl or 1,3-propandiyl. In formula R^C, R^3 is preferably hydrogen or C_1-C_4-alkyl. In formula R^C, R^4 is preferably hydrogen. Examples of radicals R^C include radicals of the formulae R^{C1}, R^{C2}, R^{C3} and R^{C4}:



(R^{C1}) (R^{C2}) (R^{C3}) (R^{C4})

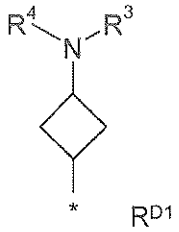
wherein R^3 and R^4 are as defined above. In these formulae, R^4 is preferably hydrogen or C_1-C_4-alkyl, in particular hydrogen.

A third embodiment of the invention relates to compounds of the formula I, wherein the radical R^2 is hydrogen A is a bivalent radical CH_2CHR^5 and wherein R^1 and R^5 are together linear C_1-C_4-alkylene, which may carry 1 or 2 radicals R^7. Amongst the compounds of the third embodiment, preference is given to those compounds of the formula I, wherein the moiety R is a radical of the formula R^D:

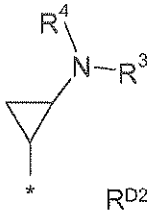


(R^D)

wherein A' is a single bond, CH_2, CH_2CH_2, CHR^7 or CH_2CHR^7, wherein R^7 is as defined above and wherein R^7 is in particular hydrogen. In the formula R^D, the radical A' is in particular a single bond CH_2 or CH_2CH_2. In formula R^D, R^3 is preferably hydrogen or C_1-C_4-alkyl, in particular hydrogen. In formula R^D, R^4 is preferably hydrogen. Examples of radicals R^D include radicals of the formulae R^{D1} and R^{D2}:



R^{D1}



R^{D2}

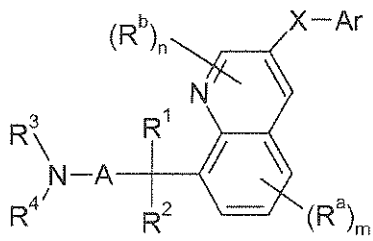
wherein R^3 and R^4 are as defined above and * indicates the binding site to the quinolinyl radical.

A particular preferred embodiment of the invention relates to compounds of the formula I, wherein X is SO_2.

Another embodiment of the invention relates to compounds of the formula I, wherein X is CH_2.

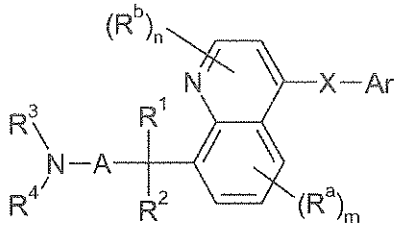
A further embodiment of the invention relates to compounds of the formula I, wherein X is a carbonyl group, i.e. X is C(=O).

In one preferred embodiment of the invention X is located in the 3-position of the quinolinyl moiety, i.e. this embodiment relates to compounds of the following formula Ia:



(Ia)

In another embodiment of the invention X is located in the 4-position of the quinolinyl moiety, i.e. this embodiment relates to compounds of the following formula Ib:



(Ib)

Amongst compounds Ia and Ib, preference is given to those compounds, wherein X is SO_2.

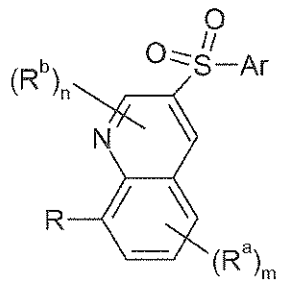
Amongst compounds Ia and Ib, preference is given to those compounds, wherein the moiety R is a moiety of the formula R^A or R^B, in particular a moiety R^{A2}, R^{A3} or R^{A4} and more preferably a moiety R^{A3}, wherein q, R^4 and R^6 are as defined above.

Amongst compounds Ia and Ib, preference is also given to those compounds, wherein the moiety R is a moiety of the formula R^C, in particular a moiety R^{C1}, R^{C2}, R^{C3} or R^{C4}, wherein R^3 and R^4 are as defined above.

Amongst compounds Ia and Ib, preference is also given to those compounds, wherein the moiety R is a moiety of the formula R^D, in particular a moiety R^{D1} or R^{D2}, wherein R^3 and R^4 are as defined above.

Amongst compounds Ia and Ib, particular preference is given to those compounds Ia and Ib, wherein X is SO_2 and wherein R is a moiety of the formula R^A or R^B, in particular a moiety R^{A2}, R^{A3} or R^{A4} and more preferably a moiety R^{A3}, wherein q, R^4 and R^6 are as defined above.

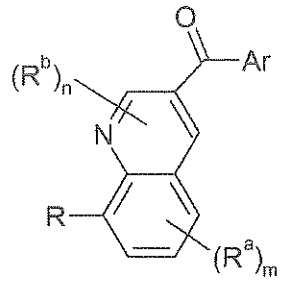
A very preferred embodiment of the invention relates to compounds of the following formula Ia.a:



(Ia.a)

wherein n, m, Ar, R^a and R^b are as defined herein and wherein R is as defined above, e.g. a moiety of the formula R^A, R^B, R^C or R^D, more preferably a moiety R^A or R^B, in particular a moiety R^{A2}, R^{A3} or R^{A4} and most preferably a moiety R^{A3}.

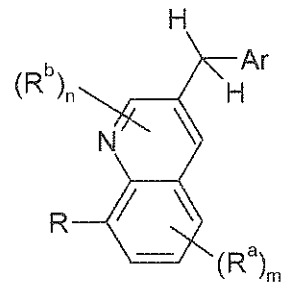
Another preferred embodiment of the invention relates to compounds of the following formula Ia.b:



(Ia.b)

wherein n, m, Ar, R^a and R^b are as defined herein and wherein R is as defined above, e.g. a moiety of the formula R^A, R^B, R^C or R^D, more preferably a moiety R^A or R^B, in particular a moiety R^{A2}, R^{A3} or R^{A4} and most preferably a moiety R^{A3}.

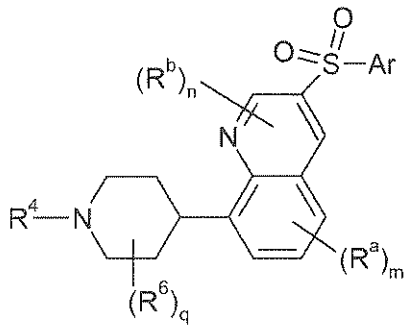
A further preferred embodiment of the invention relates to compounds of the following formula Ia.c:



(Ia.c)

wherein n, m, Ar, R^a and R^b are as defined herein and wherein R is as defined above, e.g. a moiety of the formula R^A, R^B, R^C or R^D, more preferably a moiety R^A or R^B, in particular a moiety R^{A2}, R^{A3} or R^{A4} and most preferably a moiety R^{A3}.

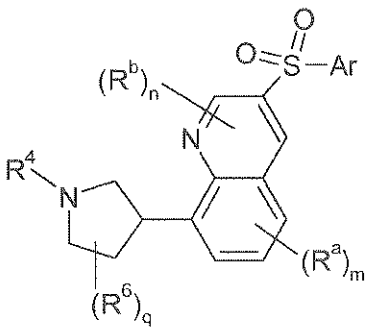
A particularly preferred embodiment of the invention relates to compounds of the following formula Ia.a1:



(Ia.a1)

wherein n, m, q, Ar, R^4, R^6, R^a and R^b are as defined herein. R^4 is in particular hydrogen. The variable q is in particular 0.

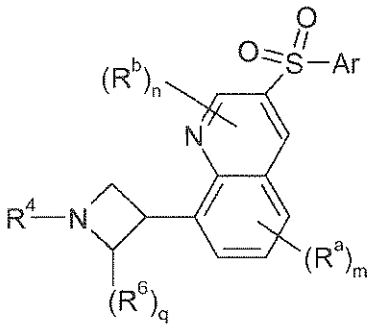
Another particularly preferred embodiment of the invention relates to compounds of the following formula Ia.a2:



(Ia.a2)

wherein n, m, q, Ar, R^4, R^6, R^a and R^b are as defined herein. R^4 is in particular hydrogen. The variable q is in particular 0.

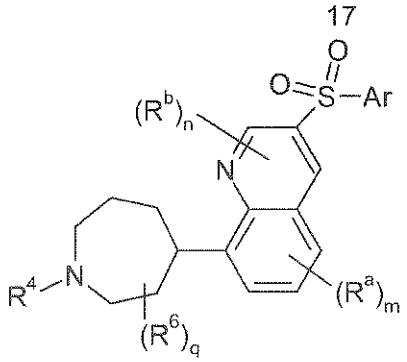
A further particularly preferred embodiment of the invention relates to compounds of the following formula Ia.a3:



(Ia.a3)

wherein n, m, q, Ar, R^4, R^6, R^a and R^b are as defined herein. R^4 is in particular hydrogen. The variable q is in particular 0.

A further particularly preferred embodiment of the invention relates to compounds of the following formula Ia.a4:



(Ia.a4)

wherein n, m, q, Ar, R^4, R^6, R^a and R^b are as defined herein. R^4 is in particular hydrogen. The variable q is in particular 0.

In the compounds of the formula I, and likewise in formulae Ia, Ib, Ia.a, Ia.b, Ia.c, Ia.a1, Ia.a2, Ia.a3 and Ia.a4, Ar is preferably a radical Ar^1, in particular a radical selected from phenyl, naphthyl, thienyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, thiadiazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, benzofuranyl, benzothiophenyl, benzoxazinyl, benzothiazolyl, benzoxadiazolyl, benzothiadiazolyl, benzomorpholinyl or indanyl, wherein the cyclic radical Ar^1 is unsubstituted or may carry 1, 2 or 3 substituents R^x as defined herein. Likewise preferred are compounds of the formula I, wherein Ar is a radical Ar^2-Ar^3, wherein Ar^2 and Ar^3 are independently of each other selected from the group consisting of phenyl, thienyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, thiadiazolyl, wherein the Ar^1 and Ar^2 are unsubstituted or may carry 1, 2 or 3 substituents R^x as defined herein. In the radicals Ar^2-Ar^3, the radical Ar^2 is preferably selected from phenyl, pyridyl and thienyl, and the radical Ar^3 is preferably phenyl, thienyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl or thiadiazolyl, wherein Ar^2 and Ar^3 are unsubstituted or may carry 1, 2 or 3 substituents R^x as defined herein. Likewise preferred are compounds of the formula I, wherein Ar is a radical Ar^2-O-Ar^3, wherein Ar^2 and Ar^3 are independently of each other selected from the group consisting of phenyl, thienyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl or thiadiazolyl, wherein Ar^2 and Ar^3 are unsubstituted or may carry 1, 2 or 3 substituents R^x as defined herein. In the radicals Ar^2-Ar^3, the radical Ar^2 is preferably selected from phenyl, pyridyl and thienyl, and the radical Ar^3 is preferably phenyl, wherein Ar^2 and Ar^3 are unsubstituted or may carry 1, 2 or 3 substituents R^x as defined herein.

In the compounds of the formula I, and likewise in formulae Ia, Ib, Ia.a, Ia.b, Ia.c, Ia.a1, Ia.a2, Ia.a3 and Ia.a4, Ar is more preferably phenyl, which is unsubstituted or may carry 1, 2 or 3 substituents R^x as defined herein.

If R^x is present, R^x is preferably selected from halogen, CN, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_3-C_6-cycloalkyl, and a group $NR^{x1}R^{x2}$.

More preferably R^x is selected from halogen, C_1-C_4-haloalkyl, C_1-C_4-haloalkoxy, and a group $NR^{x1}R^{x2}$. Most preferably R^x is selected from halogen, C_1-C_4-haloalkyl, or C_1-C_4-haloalkoxy.

In one embodiment R^x is phenyl or phenoxy (i.e. Ar is Ar^2-Ar^3 or Ar^2-O-Ar^3 with Ar^3 being phenyl), wherein the phenyl radical in the 2 last-mentioned radicals is unsubstituted or may carry 1, 2 or 3 substituents selected from halogen, CN, NO_2, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy.

In the compounds of the formula I, and likewise in formulae Ia, Ib, Ia.a, Ia.b, Ia.c, Ia.a1, Ia.a2, Ia.a3 and Ia.a4, m is preferably 0. If m is different from 0, R^a is preferably selected from halogen, CN, C_1-C_4-alkyl, in particular methyl, OCH_3, CF_3, CHF_2, $OCHF_2$ and OCF_3.

In the compounds of the formula I, and likewise in formulae Ia, Ib, Ia.a, Ia.a1, Ia.a2 and Ia.a3, n is preferably 0. If m is different from 0, R^b is preferably selected from halogen, CN, C_1-C_4-alkyl, in particular methyl, OCH_3, CF_3, CHF_2, $OCHF_2$ and OCF_3.

Examples of preferred compounds of the formula I are given in the following tables 1 to 6.

Table 1.
Compounds of formula I.a.a, wherein m and n are 0 and R is a moiety of the formula R^{A3} with q being 0, wherein and the variables Ar and R^4 have the meanings given in one of rows 1 to 110 of table A (compounds Ia.a1-1 to Ia.a1-110).

Table A.

	Ar	R^4
1	phenyl	H
2	2-fluorophenyl	H
3	3-fluorophenyl	H
4	2,3-difluorophenyl	H
5	2,4-difluorophenyl	H
6	2,5-difluorophenyl	H
7	2,6-difluorophenyl	H
8	3,4-difluorophenyl	H
9	3,5-difluorophenyl	H
10	2-chlorophenyl	H
11	3-chlorophenyl	H
12	2-tolyl	H

	Ar	R^4
13	3-tolyl	H
14	2-isopropylphenyl	H
15	3-isopropylphenyl	H
16	2-difluoromethylphenyl	H
17	3-difluoromethylphenyl	H
18	2-trifluoromethylphenyl	H
19	3-trifluoromethylphenyl	H
20	biphenyl-2-yl	H
21	biphenyl-3-yl	H
22	2-methoxyphenyl	H
23	3-methoxyphenyl	H
24	2-difluoromethoxyphenyl	H
25	3-difluoromethoxyphenyl	H
26	2-trifluoromethoxyphenyl	H
27	3-trifluoromethoxyphenyl	H
28	2-phenoxyphenyl	H
29	3-phenoxyphenyl	H
30	4-(oxazol-5-yl)phenyl	H
31	3-(pyrrolidin-1-yl)phenyl	H
32	1-naphthyl	H
33	2-naphthyl	H
34	pyridin-2-yl	H
35	pyridin-3-yl	H
36	pyridin-4-yl	H
37	2-(pyrrolidin-1-yl)pyridin-4-yl	H
38	6-morpholinylpyridin-3-yl	H
39	6-phenoxypyridin-3-yl	H
40	thien-2-yl	H
41	5-methylthien-2-yl	H
42	5-(pyridin-2-yl)thien-2-yl	H
43	5-(2-methylthiazol-4-yl)-thien-2-yl	H
44	5-chloro-3-methyl-benzo[b]thien-2-yl	H
45	2-methylthiazol-5-yl	H
46	2,4-dimethyl-thiazol-5-yl	H
47	4-methylthiazol-2-yl	H
48	5-methylthiazol-2-yl	H
49	3,5-dimethylisoxazol-4-yl	H

	Ar	R^4
50	1-methylimidazol-4-yl	H
51	benzothiazol-7-yl	H
52	4-methylbenzomorpholin-8-yl	H
53	quinolin-8-yl	H
54	isoquinolin-4-yl	H
55	2,1,3-benzoxdiazol-4-yl	H
56	phenyl	n-propyl
57	2-fluorophenyl	n-propyl
58	3-fluorophenyl	n-propyl
59	2,3-difluorphenyl	n-propyl
60	2,4-difluorophenyl	n-propyl
61	2,5-difluorophenyl	n-propyl
62	2,6-difluorophenyl	n-propyl
63	3,4-difluorophenyl	n-propyl
64	3,5-difluorophenyl	n-propyl
65	2-chlorophenyl	n-propyl
66	3-chlorophenyl	n-propyl
67	2-tolyl	n-propyl
68	3-tolyl	n-propyl
69	2-isopropylphenyl	n-propyl
70	3-isopropylphenyl	n-propyl
71	2-difluoromethylphenyl	n-propyl
72	3-difluoromethylphenyl	n-propyl
73	2-trifluoromethylphenyl	n-propyl
74	3-trifluoromethylphenyl	n-propyl
75	biphenyl-2-yl	n-propyl
76	biphenyl-3-yl	n-propyl
77	2-methoxyphenyl	n-propyl
78	3-methoxyphenyl	n-propyl
79	2-difluoromethoxyphenyl	n-propyl
80	3-difluoromethoxyphenyl	n-propyl
81	2-trifluoromethoxyphenyl	n-propyl
82	3-trifluoromethoxyphenyl	n-propyl
83	2-phenoxyphenyl	n-propyl
84	3-phenoxyphenyl	n-propyl
85	4-(oxazol-5-yl)phenyl	n-propyl
86	3-(pyrrolidin-1-yl)phenyl	n-propyl
87	1-naphthyl	n-propyl
88	2-naphthyl	n-propyl

	Ar	R^4
89	pyridin-2-yl	n-propyl
90	pyridin-3-yl	n-propyl
91	pyridin-4-yl	n-propyl
92	2-(pyrrolidin-1-yl)pyridin-4-yl	n-propyl
93	6-morpholinylpyridin-3-yl	n-propyl
94	6-phenoxypyridin-3-yl	n-propyl
95	thien-2-yl	n-propyl
96	5-methylthien-2-yl	n-propyl
97	5-(pyridin-2-yl)thien-2-yl	n-propyl
98	5-(2-methylthiazol-4-yl)-thien-2-yl	n-propyl
99	5-chloro-3-methyl-benzo[b]thien-2-yl	n-propyl
100	2-methylthiazol-5-yl	n-propyl
101	2,4-dimethyl-thiazol-5-yl	n-propyl
102	4-methylthiazol-2-yl	n-propyl
103	5-methylthiazol-2-yl	n-propyl
104	3,5-dimethylisoxazol-4-yl	n-propyl
105	1-methylimidazol-4-yl	n-propyl
106	benzothiazol-7-yl	n-propyl
107	4-methylbenzomorpholin-8-yl	n-propyl
108	quinolin-8-yl	n-propyl
109	isoquinolin-4-yl	n-propyl
110	2,1,3-benzoxdiazol-4-yl	n-propyl

Table 2.

Compounds of formula I.a.a, wherein m and n are 0 and R is a moiety of the formula R^{A3} with q being 1 and R^6 being methyl which is located in the 2-position of the piperidine ring, wherein and the variables Ar and R^4 have the meanings given in one of rows 1 to 110 of table A (compounds Ia.a1-111 to Ia.a1-220).

Table 3.

Compounds of formula I.a.a, wherein m and n are 0 and R is a moiety of the formula R^{A3} with q being 1 and R^6 being methyl which is located in the 3-position of the piperidine ring, wherein and the variables Ar and R^4 have the meanings given in one of rows 1 to 110 of table A (compounds Ia.a1-221 to Ia.a1-330).

Table 4.

Compounds of formula I.a.a, wherein m and n are 0 and R is a moiety of the formula R^{A2} with q being 0, wherein and the variables Ar and R^4 have the meanings given in one of rows 1 to 110 of table A (compounds Ia.a2-1 to Ia.a2-110).

Table 5.
Compounds of formula I.a.a, wherein m and n are 0 and R is a moiety of the formula R^{A1} with q being 0, wherein and the variables Ar and R^4 have the meanings given in one of rows 1 to 110 of table A (compounds Ia.a3-1 to Ia.a3-110).

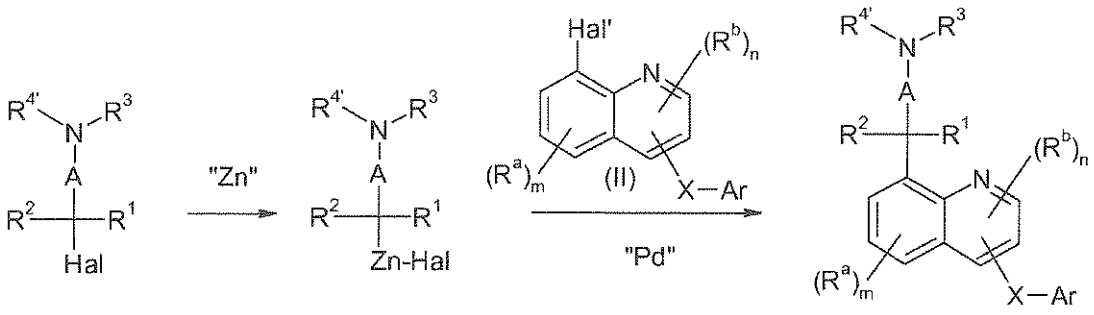
Table 6.
Compounds of formula I.a.a, wherein m and n are 0 and R is a moiety of the formula R^{A4} with q being 0, wherein and the variables Ar and R^4 have the meanings given in one of rows 1 to 110 of table A (compounds Ia.a4-1 to Ia.a4-110).

Compounds of the formula I according to the present invention can be obtained as outlined in the synthetic routes below.

1. General synthetic pathways

Compounds of the formula I can be prepared e.g. starting from suitable 8-halo substituted quinoline compounds of the formula II and amines III by a transition metal catalyzed cross-coupling as depicted in scheme 1:

Scheme 1:



(III) (IIIa) (I')

In scheme 1 the variables R^1, R^2, R^3, A, R^a, R^b, X, Ar, m and n are as defined herein. $R^{4'}$ has one of the meanings given for R^4 different from hydrogen or a suitable N-protecting group, e.g. Boc, and Hal and Hal' are Br or I. According to scheme 1 the halogen compound III is converted into a organozinc compound IIIa according to standard processes, e.g. by the process described in Tetrahedron 1987, 43, 2203-2212; J. Org. Chem. 1988, 53, 2390-2392. The organozinc compound is subsequently reacted in a Negeshi type Pd(0)-mediated cross coupling reaction with an appropriate 8-haloquinoline compound II to give the 8-substituted compound I' by analogy to the

method described in Synlett 1998, 4, 379-380; J. Am. Chem. Soc. 2003, 125, 12527-12530. Alternatively, the intermediately generated organozinc compound IIIa can be transmetallized, e. g. with CuCN*2LiCl, and subsequent reacted with a 8-haloquinoline compound of formula II.

If $R^{4'}$ is a suitable N-protecting group, compounds of the formula I, wherein R^4 is hydrogen can be obtained from compounds of the formula I' by cleavage of the N-$R^{R4'}$-bond, In case of $R^{4'}$ being Boc, cleavage can be achieved by treatment with trifluoroacetic acid.

If in the resulting quinoline compound I' the radical $R^{4'}$ is not the desired radical R^4 but a precursor thereof, the compound can be modified as outlined below to obtain the desired substituent R^4. A precursor is a radical which can be easily removed and replaced by the desired group R^4 or which can be modified to give R^4. The precursor can also be an N-protective group (PG), such as butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), 9-fluorenylmethoxycarbonyl (Fmoc), triphenylmethyl (Trt), nitrobenzenesulfenyl (Nps), allyl and benzyl.

If $R^{4'}$ is allyl, the allyl group can be cleaved to obtain a compound of the formula I, wherein R^4 is hydrogen. The cleavage of the allyl group is achieved, for example, by reacting a compound I' with $R^{4'}$ = allyl with an allyl trapping agent, such as mercaptobenzoic acid or 1,3-dimethylbarbituric acid, in the presence of catalytic quantities of palladium (0) compounds or palladium compounds which are able to form a palladium(0) compound under reaction conditions, e.g. palladium dichloride, tetrakis(triphenylphosphine)palladium(0) or tris(dibenzylideneacetone)dipalladium(0), advantageously in combination with phosphine ligands, e.g. triarylphosphines, such as triphenylphosphine, trialkylphosphines, such as tributylphosphine, and cycloalkylphosphines, such as tricyclohexylphosphine, and especially with phosphine chelate ligands, such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl or 1,4-bis(diphenylphosphino)butane, applying methods known to a skilled person (with regard to eliminating N-allyl in the presence of mercaptobenzoic acid, see WO 94/24088; with regard to eliminating in the presence of 1,3-dimethylbarbituric acid, see J. Am. Chem. Soc. 2001, 123 (28), pp. 6801-6808 and J. Org. Chem. 2002, 67(11) pp. 3718-3723). Alternatively, the cleavage of N-allyl can also be effected by reacting compound I' with $R^{4'}$ being allyl in the presence of rhodium compounds, such as tris(triphenylphosphine)chlororhodium(I), by analogy to the methods described in J. Chem. Soc., Perkin Transaction I: Organic and Bio-Organic Chemistry 1999 (21) pp. 3089-3104 and Tetrahedron Asymmetry 1997, 8(20), pp. 3387 - 3391).

If $R^{4'}$ is benzyl, this substituent may also be cleaved to obtain a compound I wherein R^4 is H. The reaction conditions for the cleavage are known in the art. Typically, the benzyl

group is removed by a hydrogenation reaction in the presence of a suitable Pd catalyst, such as Pd on carbon or palladium hydroxide.

$R^{4'}$ can also be a protective group. The protective group may be removed to yield a compound I, wherein $R^{4'}$ is hydrogen. Suitable protective groups are known in the art and are, for example, selected from tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), 9-fluorenylmethoxycarbonyl (Fmoc), triphenylmethyl (Trt) and nitrobenzenesulfenyl (Nps). A preferred protective group is Boc. The protective groups can be removed by known methods, such as treatment of the protected amine with an acid, e.g. halogen acid, such as HCl or HBr, formic acid or trifluoroacetic acid, or by hydrogenation, optionally in the presence of a Pd catalyst.

The resulting compound I, wherein R^4 is H, can then be reacted, in a known manner, in the sense of an alkylation, with a compound R^4-X. In this compound, R^4 is C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy-C_1-C_4-alkyl, aryl-C_1-C_4-alkyl, hetaryl-C_1-C_4-alkyl or C_3-C_6-cycloalkyl-C_1-C_4-alkyl and X is a nucleophilically displaceable leaving group, e.g. halogen, trifluoromethylsulfonate, alkylsulfonate, arylsulfonate, alkyl sulfate and the like. The reaction conditions which are required for the alkylation have been disclosed, e.g. in Bioorganic and Medicinal Chemistry Lett. 2002, 12(7), pp. 2443-2446 and also 2002, 12(5), pp. 1917-1919.

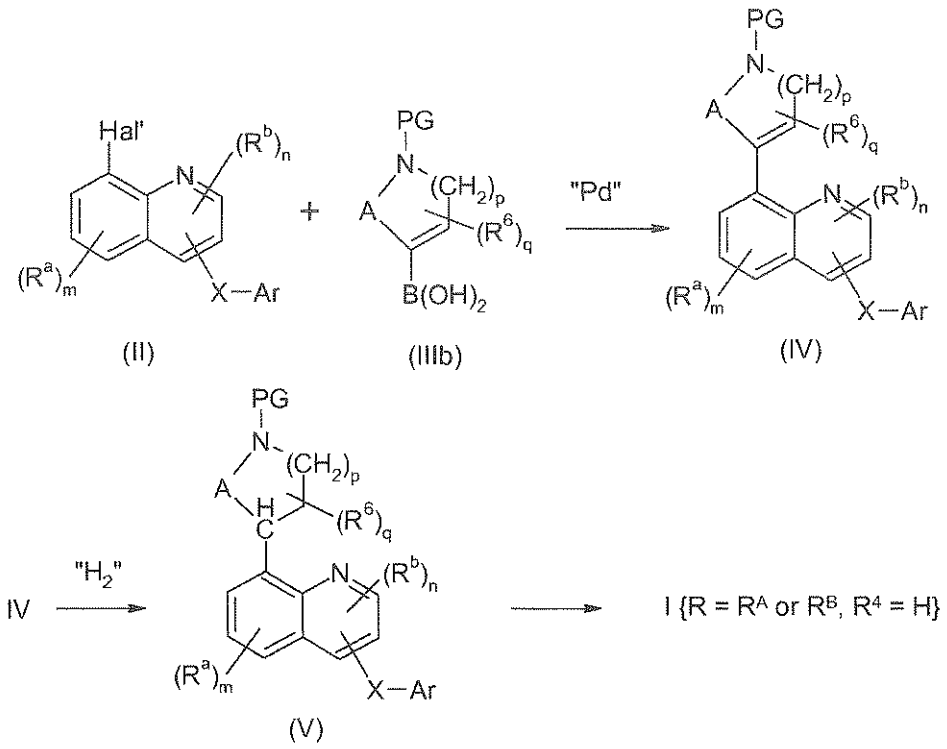
The alkylation can also be achieved, in the sense of a reductive amination, by reacting the compound I, wherein R^4 = H, with a suitable ketone or aldehyde in the presence of a reducing agent, e.g. in the presence of a borohydride such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride. The skilled person is familiar with the reaction conditions which are required for a reductive amination, e.g. from Bioorganic and Medicinal Chemistry Lett. 2002, 12(5), pp. 795-798 and 12(7) pp. 1269-1273.

In case R^4 is hydrogen, the compound I can also be reacted with an acyl halide to obtain a compound of the formula I wherein R^4 is formyl or C_1-C_4-alkylcarbonyl. The carbonyl group in these compounds can be reduced with diborane to obtain compounds of the general formula I, wherein R^4 is C_2-C_5-alkyl. The carbonyl group can also be reacted with a fluorinating agent to obtain a compound I wherein R^4 is 1,1-difluoroalkyl. Acylation and reduction can be achieved by standard methods, which are discussed in Jerry March, Advanced Organic Chemistry, 3rd ed. J. Wiley & Sons, New York 1985, p.370 and 373 (acylation) and p. 1099 f. and in the literature cited in this publication (with regard to acylation, see also Synth. Commun. 1986, 16, p. 267, and with regard to reduction, see also J. Heterocycl. Chem. 1979, 16, p. 1525).

Compounds of the formula I, wherein the moiety R is a radical of the formula R^A or R^B with R^4 being hydrogen can be prepared e.g. starting from suitable 8-halo substituted

quinoline compounds of the formula II by a transition metal catalyzed cross-coupling with a boronic compound IIIa and subsequent hydrogenation and deprotection, as depicted in scheme 2:

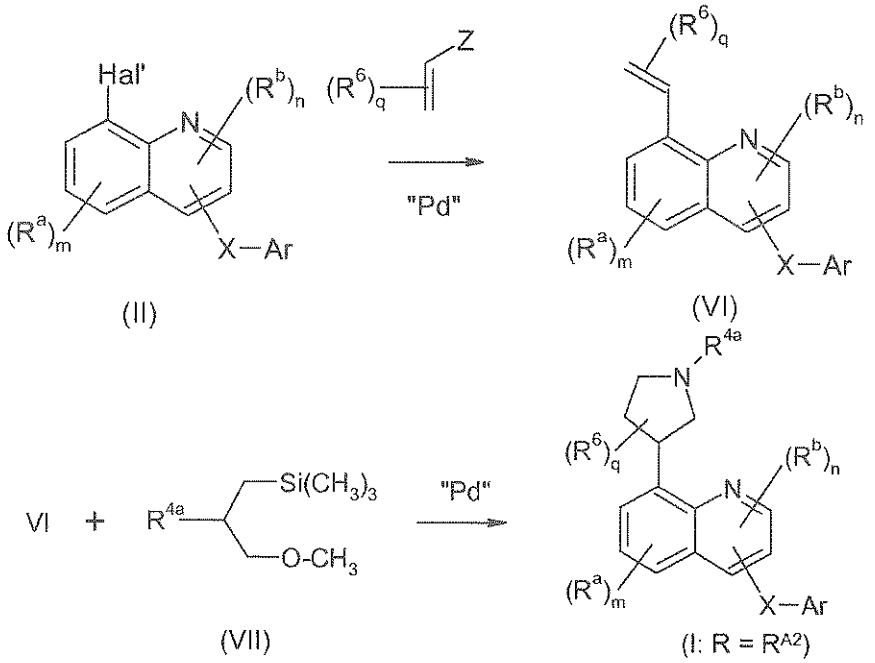
Scheme 2:



In scheme 2, the variables R^6, A, p, q, R^a, R^b, X, Ar, m and n are as defined herein. PG is suitable N-protecting group, e.g. BOC, and Hal and Hal' are Br or I. The 8-quinoline compound II is reacted under conditions of Suzuki coupling reaction with a boronic acid IIIb in the presence of a palladium catalyst to give a compound IV intermediate. Compound IV can then be reduced under conditions of catalytic hydrogenation to give the compound V. If the hydrogenation is carried out under chiral conditions, e.g. by using chiral catalysts, the enantiomerically pure phenylpyrrolidine compounds can be obtained. Chiral hydrogenation catalysts are well known in the art and are e.g. described in Jerry March, Advanced Organic Chemistry, John Wiley, 3rd edition. Dependent on the choice of protecting group PG, the free amino compound I (R^4 = H) can be obtained by subsequent deprotection (e.g. TFA for BOC).

Compounds of the formula I, wherein the moiety R is a radical of the formula R^{A2} can be prepared according to the method depicted in scheme 3:

Scheme 3:



In scheme 3, the variables R^6, q, R^a, R^b, X, Ar, m and n are as defined herein. Z is a radical SnR_3 with R being C_1-C_4-alkyl. R^{4a} has one of the meanings of R^4 different from H or is cleavable group, e.g. benzyl, and Hal' is Br or I. Key step is a [3+2] dipolar cycloaddition of a non-stabilized azomethine ylid to an 8-alkenylquinoline derivative VI to yield compound V. This procedure is generally described in J. Org. Chem 1987, 52, 235. The precursor of the ylid, the amine VII, is commercially available or can be synthesized from NH_2(PG), $(CH_3)_3SiCH_2Cl$ and HCHO in the presence of methanol.

The 8-alkenyl-quinoline compound (VI) can be synthesized e.g. by a Stille coupling of an 8-halogeno quinoline II, e.g. iodo, with the corresponding alkenyl tributyl stannate, such as vinyl or isobutenyl tributyl stannate, in the presence of an appropriate Pd coupling catalyst, e.g. tetrakistriphenylphosphine palladium(0) (see, e.g. Tetrahedron, 2003, 59(34), 6545 and Bioorg. Med. Chem. 1999, 7(5), 665). By choosing a special Stille isomer (e.g. cis- or trans-isobutenyl tributyl stannate), the corresponding cis- or trans alkyl phenyl pyrrolidine can be prepared selectively.

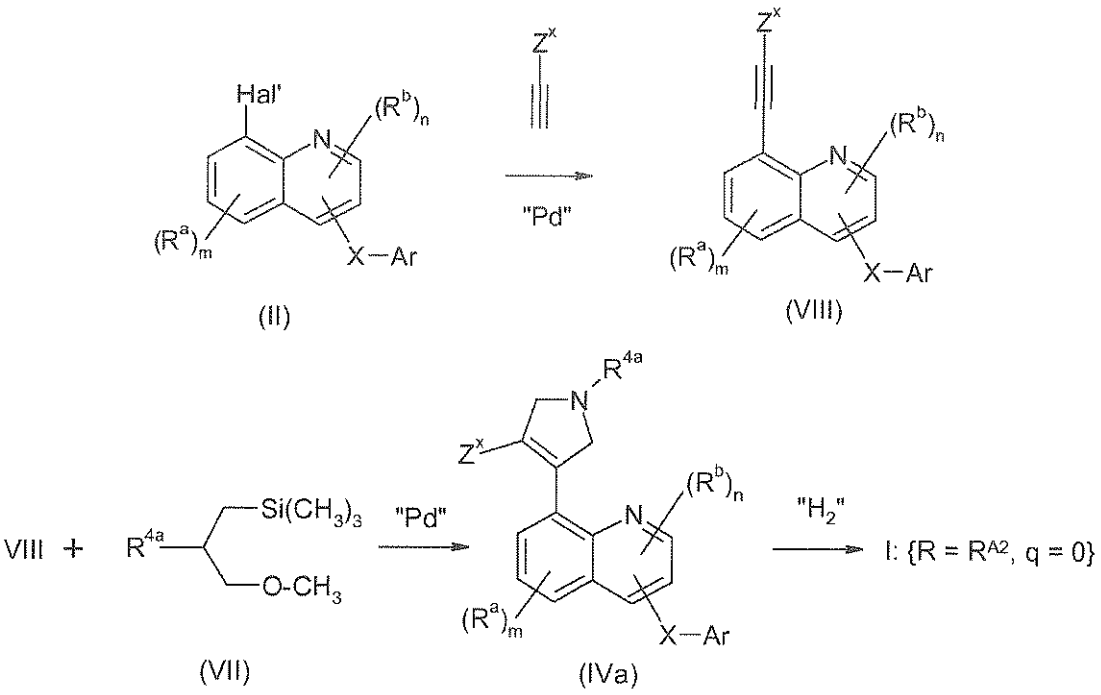
Alternatively, the 8-alkenyl-aromatic compound (VI) can be prepared by a Wittig reaction of the corresponding 8-formylquinoline derivative with a Wittig reagent such as PPh_3=CHR (R is H, or C_1-C_3-alkyl). Conditions for the Wittig reaction are well known in the art and are, e.g. discussed in Jerry March, Advanced Organic Chemistry, John Wiley, 3rd edition, page 845 ff.

The group R^{4a} of the precursor amine VII advantageously corresponds either to the desired group R^4 of the final compound I or is alternatively a cleavable group, such as

benzyl, which can be removed by catalytic hydrogenation to give the compound I with R = R^{A2} and R^4 = H.

Compounds of the formula I, wherein the moiety R is a radical of the formula R^{A2} can also be prepared according to the method depicted in scheme 4:

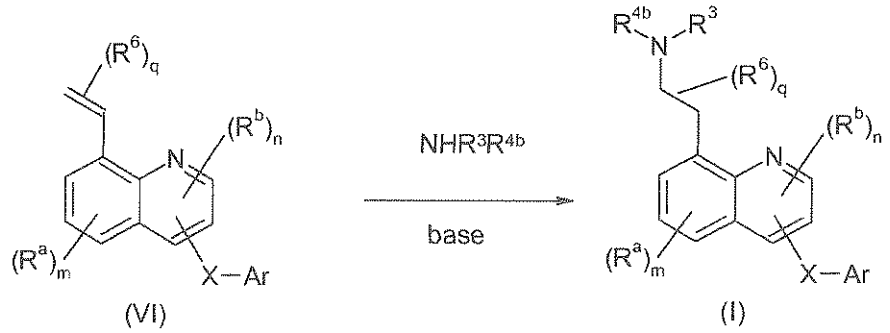
Scheme 4:



In scheme 4, the variables R^a, R^b, X, Ar, m and n are as defined herein. Z^X is hydrogen, C_1-C_4-alkyl or SiR_3 with R being C_1-C_4-alkyl. R^{4a} has one of the meanings of R^4 different from H or is cleavable group, e.g. benzyl, and Hal' is Br or I. Key step is a [3+2] dipolar cycloaddition of a non-stabilized azomethine ylid to an 8-alkynylquinoline derivative VIII to yield compound IVa (see, e.g., Tetrahedron 1996, 52, 59). IVa is then hydrogenated to the corresponding pyrrolidine compound I (R = R^{A2}). Optionally the moiety Z^x is removed. If the hydrogenation is carried out under chiral conditions, e.g. by using chiral catalysts, the enantiomerically pure phenylpyrrolidine compounds can be obtained. Chiral hydrogenation catalysts are well known in the art and are e.g. described in Jerry March, Advanced Organic Chemistry, John Wiley, 3rd edition.

Compounds of the formula I, wherein the moiety R is a radical of the formula R^{C2} can be prepared starting from the compound VI according to the method depicted in scheme 5:

Scheme 5:

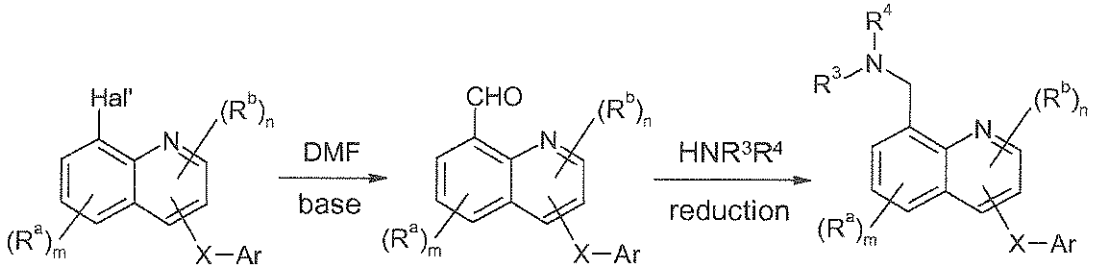


(VI) (I)

In scheme 5, the variables R^6, q, R^a, R^b, X, Ar, m and n are as defined herein. R^{4b} has one of the meanings of R^4 different from H or is N-protecting group, e.g. benzyl or Boc. According to scheme 5, the 8-alkenyl-quinoline compound VI is treated with an appropriate amine HNR^3R^{4b} in the presence of a strong base such n-butyl lithium (BuLi) or sodium hydride in an aprotic polar solvent such as tetrahydrofuran (THF) or N,N-dimethyl formamide (DMF) to give after workup the desired Michael addition product I.

Compounds of the formula I, wherein the moiety R is a radical of the formula R^{C1} can be prepared starting from the compound II according to the method depicted in scheme 6:

Scheme 6:

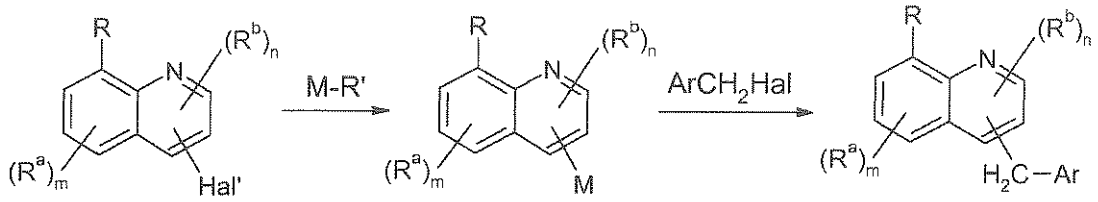


(II) (IX) (I)

In scheme 6, the variables R^3, R^4, R^a, R^b, X, Ar, m and n are as defined herein. Hal' is bromine or iodine. According to scheme 6, the 8-halo-quinoline compound II is reacted with DMF and appropriate base such BuLi or NaH in a aprotic solvent solvent such as THF or DMF to give the formyl compound IX. Compound IX is then subjected to a reductive amination with amine HNR^3R^4 to give the desired amino methyl quinoline compound. Reductive amination is usually performed in the presence of a suitable base (e.g. Na_2CO_3) and reduction can be achieved by a variety of chemical reduction or catalytic hydrogenation techniques familiar to those skilled in the art.

Compounds of the formula I, wherein X is CH_2 may also be prepared starting from 3- or 4-haloquinoline compounds of the formula X as depicted in scheme 7:

Scheme 7:

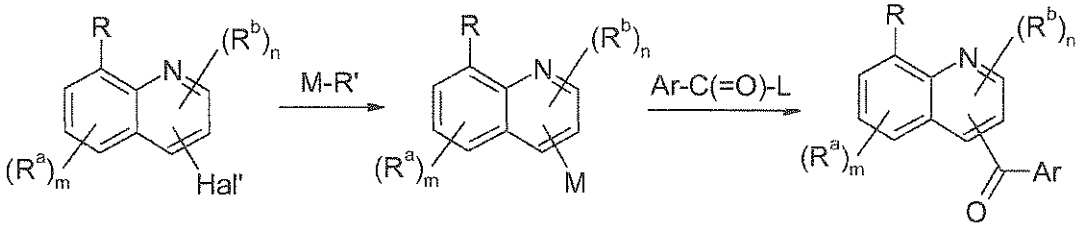


(X) (XI) (I)

In scheme 7, the variables R, R^a, R^b, Ar, m and n are as defined herein. Hal and Hal' are bromine or iodine. R' is alkyl. M is lithium or Mg-Hal. According to scheme 7, a 3- or 4-haloquinoline compound X is treated with an alkyl metal compound M-R such as BuLi or MeMgBr in an aprotic ether solvent such as diethylether, methyl-tert.-butylether, THF or dioxan to give an intermediate metallated compound XI. Compound XI is then subjected to an alkylation with a suitable arylmethyl halide $ArCH_2Hal$ to give the desired 3- or 4-substituted quinoline. This reaction sequence can also be accomplished earlier in the synthetic route prior to the introduction of the 8-alkyl amino substituent. Compound X can be prepared by a rearrangement of the chemical transformations outlined in Schemes 1 to 6 in a manner well known to a person skilled in the art.

Compounds of the formula I, wherein X is C(=O) may also be prepared starting from 3- or 4-haloquinoline compounds of the formula X as depicted in scheme 7:

Scheme 8:



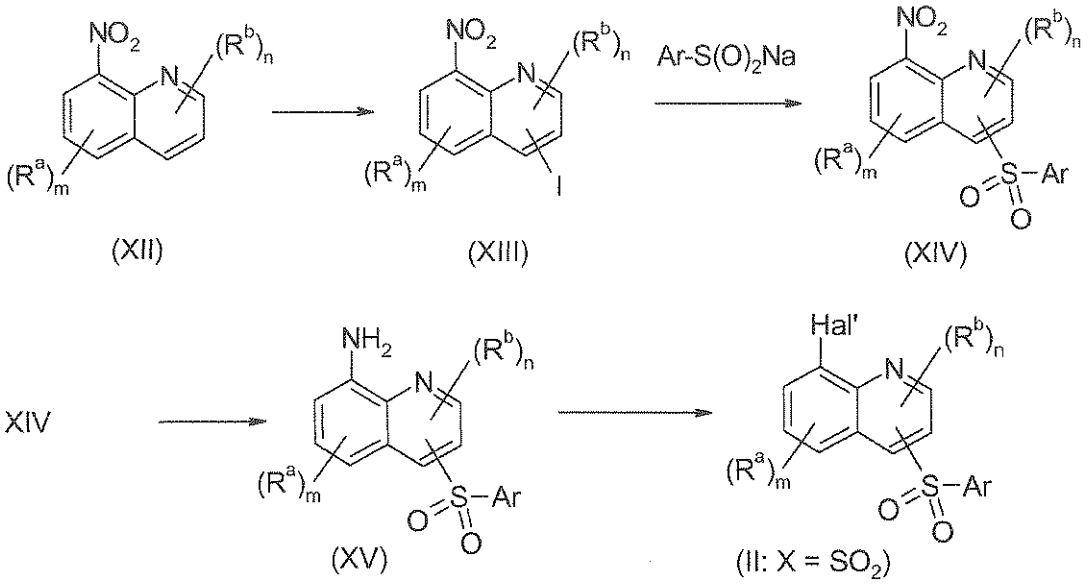
(X) (XI) (I)

In scheme 8, the variables R, R^a, R^b, Ar, m and n are as defined herein. Hal' is bromine or iodine. R' is alkyl. M is lithium or Mg-Hal. L is a suitable leaving group, e.g. halogen (aroyl halide), O-alkyl (aroyl ester) or a Weinreb amide residue. According to scheme 8, a 3- or 4-haloquinoline compound X is treated with an alkyl metal compound M-R such as BuLi or MeMgBr in an aprotic ether solvent such as diethylether, methyl-tert.-butylether, THF or dioxane to give an intermediate metallated compound XI.

Compound XI is then subjected to an acylation with a suitable aroyl compound Ar-C(=O)-L to give the desired 3- or 4-substituted quinoline. This reaction sequence can also be accomplished earlier in the synthetic route prior to the introduction of the 8-alkyl amino substituent.

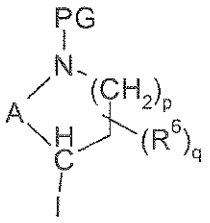
The 8-haloquinoline compounds of the formula II are commercially available or they can be prepared according to routine techniques of organic synthesis, which are well known to a person skilled in the art. Compounds of the formula II, wherein X is $S(O)_2$ can be prepared e.g. starting from 8-nitroquinoline compounds of the formula XII as depicted in scheme 9.

Scheme 9:



Commercially available nitroquinolines such as XII can be converted to the 3-iodo derivatives XIII by treatment with an iodinating reagent such as N-iodosuccinimide in a solvent such as acetic acid to yield the 3- or 4-iodoquinoline compound XIII. The 3- and 4-isomers can be separated at this stage or a later stage. Compound XIII is then reacted with an alkali metal salt of a sulfinic acid Ar-S(O)OH, e.g. the sodium salt $Ar\text{-}S(O)_2Na$, in the presence of a copper (I) salt such as Cu (I) triflate in a polar solvent such as N,N-dimethyl acetamide (DMA) or DMF. Reduction of the nitro group of XIV gives the amino compound XV. Reduction can be achieved by a variety methods, including reduction with "non-hydrogen" reducing agent such as $SnCl_2$ or by catalytic hydrogenation techniques familiar to those skilled in the art. The amino group of XV is then converted to the iodo group by a Sandmeyer reaction using a nitrosonium source (e.g. $NaNO_2$, n-$BuNO_2$) and a iodide (e.g. CuI or n-Bu_4NI) in a suitable solvent such water or CH_3CN.

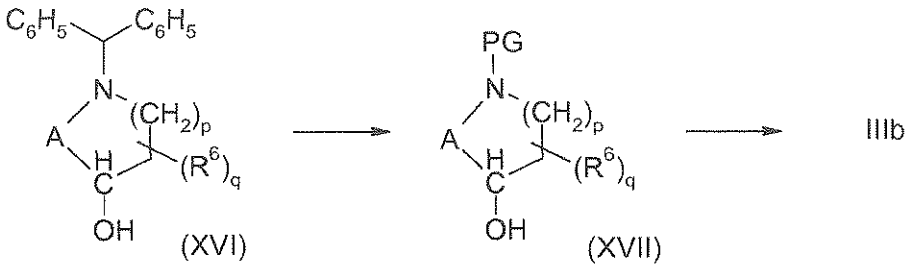
Compounds of the formula IIIb,



(IIIb)

in particular compounds of the formula IIIb, wherein p is 0 and A is CH_2 can be prepared by the reaction sequence depicted in scheme 10.

Scheme 10.



Starting from a benzhydryl compound XVI, e.g. 1-benzhydryl-azetidin-3-ol compound, a Pd-mediated deprotection is performed to yield the free amine (Tetrahedron 2002, 58, 9865-9870), Then, a protective group PG is introduced (e.g. carbamate formation if PG is BOC) to yield compound XVII. Subsequent halogenation generates the iodine compound IIIb that is susceptible to undergo Zn insertion (Tetrahedron 1987, 43, 2203-2212; J. Org. Chem. 1988, 53, 2390-2392). The thus obtainable organozinc compound can be used in synthetic routes as outlined above in scheme 1. The synthesis of azetidin-3-ol compounds has for instance been described in J. Med. Chem. 1994, 37, 4195-4210 or Helvetica Chimica Acta 1995, 78, 1238-1246.

If not indicated otherwise, the above-described reactions are generally carried out in a solvent at temperatures between room temperature and the boiling temperature of the solvent employed. Alternatively, the activation energy which is required for the reaction can be introduced into the reaction mixture using microwaves, something which has proved to be of value, in particular, in the case of the reactions catalyzed by transition metals (with regard to reactions using microwaves, see Tetrahedron 2001, 57, p. 9199 ff. p. 9225 ff. and also, in a general manner, "Microwaves in Organic Synthesis", André Loupy (Ed.), Wiley-VCH 2002.

The acid addition salts of compounds I are prepared in a customary manner by mixing the free base with a corresponding acid, where appropriate in solution in an organic

solvent, for example acetonitrile, a lower alcohol, such as methanol, ethanol or propanol, an ether, such as diethyl ether, methyl tert-butyl ether or diisopropyl ether, a ketone, such as acetone or methyl ethyl ketone, an ester, such as ethyl acetate, mixtures thereof as well as mixtures thereof with water.

The compound of the invention can be a 5-HT_6 receptor agonist, including partial agonistic activity, or a 5-HT_6 receptor antagonist, including inverse agonist activity.

The compounds of formula I according to the present invention have a surprisingly high affinity for 5-HT_6 receptors. The high affinity of the compounds according to the invention for 5-HT_6 receptors is reflected in very low in-vitro receptor binding constants (K_i(5-HT_6) values) of as a rule less than 50 nM (nmol/l), preferably of less than 10 nM and, in particular of less than 5 nM. The displacement of ^{3}H-LSD can, for example, be used in receptor binding studies for determining binding affinities to 5-HT_6 receptors.

Furthermore the compounds of formula I are highly selective 5-HT_6 receptor ligands which, because of their low affinity for other receptors such as dopamine receptors, adrenergic receptors, muscarinic receptors, histamine receptors, opiate receptors, in particular dopamine D_2, α_1-adrenergic and histamine H_1 receptors, give rise to fewer side-effects than other, less selective 5-HT_6 ligands.

For instance the 5-HT_6/D_2, 5-HT_6/α_1-adrenergic or 5-HT_6/H_1selectivities of the compounds according to the present invention, i.e. the ratios $K_i(D_2)/K_i$(5-HT_6), $K_i(\alpha_1$-adrenergic)/K_i(5-HT_6) or $K_i(H_1)/K_i$(5-HT_6) of the receptor binding constants, is as a rule at least 25, preferably at least 50, even better at least 100.

The displacement of [^{3}H]SCH23390 or [^{125}I]spiperone can be used, for example, for carrying out receptor binding studies on D_1, D_2 and D_4 receptors.

Furthermore the compounds of formula I because of their structural features are susceptible to display an enhanced brain penetration than other known 5-HT_6 receptor ligands.

Because of their binding profile, the compounds can be used for treating diseases which respond to 5-HT_6 receptor ligands (or which are susceptible to treatment with a 5-HT_6 receptor ligand), i.e. they are effective for treating those medical disorders or diseases in which exerting an influence on (modulating) the 5-HT_6 receptors leads to an improvement in the clinical picture or to the disease being cured. Examples of these diseases are disorders or diseases of the central nervous system.

Disorders or diseases of the central nervous system are understood as meaning disorders which affect the spinal cord and, in particular, the brain. Within the meaning

of the invention, the term "disorder" denotes disturbances and/or anomalies which are as a rule regarded as being pathological conditions or functions and which can manifest themselves in the form of particular signs, symptoms and/or malfunctions. While the treatment according to the invention can be directed toward individual disorders, i.e. anomalies or pathological conditions, it is also possible for several anomalies, which may be causatively linked to each other, to be combined into patterns, i.e. syndromes, which can be treated in accordance with the invention.

The disorders which can be treated in accordance with the invention are in particular disorders which respond to a modulation of the 5-HT_6 receptor. They include cognitive dysfunctions, such as a deficit in memory, cognition and learning, in particular associated with Alzheimer's disease, age-related cognitive decline and mild cognitive impairment, attention deficit disorder/hyperactivity syndrome, personality disorders, such as schizophrenia, in particular cognitive deficits related with schizophrenia, affective disorders such as depression, anxiety and obsessive compulsive disorders, motion or motor disorders such as Parkinson's disease and epilepsy, migraine, sleep disorders (including disturbances of the Circadian rhythm), feeding disorders, such as anorexia and bulimia, certain gastrointestinal disorders such as Irritable Bowl Syndrome, diseases associated with neurodegeneration, such as stroke, spinal or head trauma and head injuries, such as hydrocephalus, drug addiction and obesity.

The addiction diseases include psychic disorders and behavioral disturbances which are caused by the abuse of psychotropic substances, such as pharmaceuticals or narcotics, and also other addiction diseases, such as addiction to gaming (impulse control disorders not elsewhere classified). Examples of addictive substances are: opioids (e.g. morphine, heroin and codeine), cocaine; nicotine; alcohol; substances which interact with the GABA chloride channel complex, sedatives, hypnotics and tranquilizers, for example benzodiazepines; LSD; cannabinoids; psychomotor stimulants, such as 3,4-methylenedioxy-N-methylamphetamine (ecstasy); amphetamine and amphetamine-like substances such as methylphenidate and other stimulants including caffeine. Addictive substances which come particularly into consideration are opioids, cocaine, amphetamine or amphetamine-like substances, nicotine and alcohol.

With regard to the treatment of addiction diseases, particular preference is given to those compounds according to the invention of the formula I which themselves do not possess any psychotropic effect. This can also be observed in a test using rats, which, after having been administered compounds which can be used in accordance with the invention, reduce their self administration of psychotropic substances, for example cocaine.

According to another aspect of the present invention, the compounds according to the invention are suitable for treating disorders whose causes can at least partially be attributed to an anomalous activity of 5-HT_6 receptors.

According to another aspect of the present invention, the treatment is directed, in particular, toward those disorders which can be influenced, within the sense of an expedient medicinal treatment, by the binding of preferably exogeneously administered binding partners (ligands) to 5-HT_6 receptors.

The diseases which can be treated with the compounds according to the invention are frequently characterized by progressive development, i.e. the above-described conditions change over the course of time; as a rule, the severity increases and conditions may possibly merge into each other or other conditions may appear in addition to those which already exist.

The compounds of formula I can be used to treat a large number of signs, symptoms and/or malfunctions which are connected with the disorders of the central nervous system and, in particular, the abovementioned conditions. These signs, symptoms and/or malfunctions include, for example, a disturbed relationship to reality, lack of insight and ability to meet customary social norms or the demands made by life, changes in temperament, changes in individual drives, such as hunger, sleep, thirst, etc., and in mood, disturbances in the ability to observe and combine, changes in personality, in particular emotional lability, hallucinations, ego-disturbances, distractedness, ambivalence, autism, depersonalization and false perceptions, delusional ideas, chanting speech, lack of synkinesia, short-step gait, flexed posture of trunk and limbs, tremor, poverty of facial expression, monotonous speech, depressions, apathy, impeded spontaneity and decisiveness, impoverished association ability, anxiety, nervous agitation, stammering, social phobia, panic disturbances, withdrawal symptoms in association with dependency, maniform syndromes, states of excitation and confusion, dysphoria, dyskinetic syndromes and tic disorders, e.g. Huntington's chorea and Gilles-de-la-Tourette's syndrome, vertigo syndromes, e.g. peripheral positional, rotational and oscillatory vertigo, melancholia, hysteria, hypochondria and the like.

Within the meaning of the invention, a treatment also includes a preventive treatment (prophylaxis), in particular as relapse prophylaxis or phase prophylaxis, as well as the treatment of acute or chronic signs, symptoms and/or malfunctions. The treatment can be orientated symptomatically, for example as the suppression of symptoms. It can be effected over a short period, be orientated over the medium term or can be a long-term treatment, for example within the context of a maintenance therapy.

The compounds according to the invention are preferentially suitable for treating diseases of the central nervous system, more preferably for treating cognitive dysfunctions and in particular, for treating cognitive dysfunctions associated with schizophrenia or with Alzheimer's disease.

According to another aspect of the invention the compounds of formula (I) are particularly suitable for treating addiction diseases caused for instance by the abuse of psychotropic substances, such as pharmaceuticals, narcotics, nicotine or alcohol, including psychic disorders and behavioral disturbances related thereto.

According to another aspect of the invention the compounds of formula (I) are particularly suitable for treating nutritional disorders, such as obesity, as well as diseases related thereto, such as cardiovascular diseases, digestive diseases, respiratory diseases, cancer or type 2 diabetes.

Within the context of the treatment, the use according to the invention of the described compounds involves a method. In this method, an effective quantity of one or more compounds, as a rule formulated in accordance with pharmaceutical and veterinary practice, is administered to the individual to be treated, preferably a mammal, in particular a human being, productive animal or domestic animal. Whether such a treatment is indicated, and in which form it is to take place, depends on the individual case and is subject to medical assessment (diagnosis) which takes into consideration signs, symptoms and/or malfunctions which are present, the risks of developing particular signs, symptoms and/or malfunctions, and other factors.

As a rule, the treatment is effected by means of single or repeated daily administration, where appropriate together, or alternating, with other active compounds or active compound-containing preparations such that a daily dose of preferably from about 0.1 to 1000 mg/kg of bodyweight, in the case of oral administration, or of from about 0.1 to 100 mg/kg of bodyweight, in the case of parenteral administration, is supplied to an individual to be treated.

The invention also relates to the production of pharmaceutical compositions for treating an individual, preferably a mammal, in particular a human being, productive animal or domestic animal. Thus, the compounds of formula I are customarily administered in the form of pharmaceutical compositions which comprise a pharmaceutically acceptable excipient together with at least one compound according to the invention and, where appropriate, other active compounds. These compositions can, for example, be administered orally, rectally, transdermally, subcutaneously, intravenously, intramuscularly or intranasally.

Examples of suitable pharmaceutical formulations are solid medicinal forms, such as powders, granules, tablets, in particular film tablets, lozenges, sachets, cachets, sugar-coated tablets, capsules, such as hard gelatin capsules and soft gelatin capsules, suppositories or vaginal medicinal forms, semisolid medicinal forms, such as ointments, creams, hydrogels, pastes or plasters, and also liquid medicinal forms, such as solutions, emulsions, in particular oil-in-water emulsions, suspensions, for example lotions, injection preparations and infusion preparations, and eyedrops and eardrops. Implanted release devices can also be used for administering inhibitors according to the invention. In addition, it is also possible to use liposomes or microspheres.

When producing the compositions, the compounds according to the invention are optionally mixed or diluted with one or more excipients. Excipients can be solid, semisolid or liquid materials which serve as vehicles, carriers or medium for the active compound.

Suitable excipients are listed in the specialist medicinal monographs. In addition, the formulations can comprise pharmaceutically acceptable carriers or customary auxiliary substances, such as glidants; wetting agents; emulsifying and suspending agents; preservatives; antioxidants; antiirritants; chelating agents; coating auxiliaries; emulsion stabilizers; film formers; gel formers; odor masking agents; taste corrigents; resin; hydrocolloids; solvents; solubilizers; neutralizing agents; diffusion accelerators; pigments; quaternary ammonium compounds; refatting and overfatting agents; raw materials for ointments, creams or oils; silicone derivatives; spreading auxiliaries; stabilizers; sterilants; suppository bases; tablet auxiliaries, such as binders, fillers, glidants, disintegrants or coatings; propellants; drying agents; opacifiers; thickeners; waxes; plasticizers and white mineral oils. A formulation in this regard is based on specialist knowledge as described, for example, in Fiedler, H.P., Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete [Encyclopedia of auxiliary substances for pharmacy, cosmetics and related fields], 4th edition, Aulendorf: ECV-Editio-Kantor-Verlag, 1996.

The following examples serve to explain the present invention without limiting its scope.

The compounds were either characterized via ^{1}H-NMR in d_6-dimethylsulfoxid or d-chloroform on a 400 MHz or 500 MHz NMR instrument (Bruker AVANCE), or by mass spectrometry, generally recorded via HPLC-MS in a fast gradient on C18-material (electrospray-ionisation (ESI) mode), or melting point.

The magnetic nuclear resonance spectral properties (NMR) refer to the chemical shifts (δ) expressed in parts per million (ppm). The relative area of the shifts in the ^{1}H-NMR spectrum corresponds to the number of hydrogen atoms for a particular functional type in the molecule. The nature of the shift, as regards multiplicity, is indicated as

singlet (s), broad singlet (s. br.), doublet (d), broad doublet (d br.), triplet (t), broad triplet (t br.), quartet (q), quintet (quint.) and multiplet (m).

Preparation Examples:

I. Preparation of the compounds

EXAMPLE 1

8-(Azetidin-3-yl)-3-(phenylsulfonyl)quinoline hydrochloride

1.1 3-Hydroxy-azetidine-1-carboxylic acid tert-butyl ester

To a degassed solution of 1-benzhydryl-azetidin-3-ol (4.75 g, 19.84 mmol) in methanol (MeOH) (150 ml) were added ammonium formate (8.76 g, 138.91 mmol), 10% Pd/C (450 mg) and Boc_2O (di-tert-butyl dicarbonate) (13 g, 59.56 mmol). The resulting suspension was heated to reflux under N_2 for 1h. It was then cooled down to room temperature, filtered through a short pad of celite and concentrated. The residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (heptane:ethyl acetate (EtOAc), 1:1) afforded the title compound (3.30 g, 96 %) as white crystals.

MS (ESI+) : m/z = 118.1 $[M\text{-}tBu+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ = 1.43 (s, 9H), 2.35 (d, J = 6.2 Hz, 1H), 3.80 (dd, J = 10.4, 4.4 Hz, 2H), 4.15 (dd, J = 9.6, 6.7 Hz, 2H), 4.58 ppm (m, 1H).

1.2 3-Iodo-azetidine-1-carboxylic acid tert-butyl ester

A solution of 3-hydroxy-azetidine-1-carboxylic acid tert-butyl ester (3.35 g, 19.34 mmol) in toluene (200 ml) was treated with imidazole (3.95 g, 58.01 mmol), triphenylphosphine (10.14 g, 38.65 mmol) and I_2 (7.36 g, 28.99 mmol). The mixture was heated at 100°C for 1 h, cooled down to room temperature and subsequently poured into a saturated aqueous solution of $NaHCO_3$ (30 ml). Excess triphenylphosphine was destroyed by addition of iodine until I_2 coloration persisted in organic layer. The latter was washed with an aqueous solution of $Na_2S_2O_3$ (5 % strength), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash column chromatography (heptane:EtOAc, 2:1) provides the title compound (5.19 g, 95 %) as a light yellow oil.

MS (ESI+) : m/z = 227.9 $[M\text{-}tBu+H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$) : δ = 1.44 (s, 9H), 4.29 (dd, J = 10.4, 5.4 Hz, 2H), 4.47 (m, 1H), 4.64 ppm (dd, J = 9.5, 8.0 Hz, 2H).

1.3 (1-(tert-Butoxycarbonyl)azetidin-3-yl)zinc(II) iodide

Zn dust (1.80 g, 27.5 mmol) was vigorously stirred in DMA (11 ml) under nitrogen and the suspension was heated at 65°C. Trimethylsilyl chloride (0.37 g, 3.39 mmol) and 1,2-dibromoethane (0.64 g, 3.39 mmol) was added and stirring continued for 40 min. A solution of 3-iodo-azetidine-1-carboxylic acid tert-butyl ester (6.00 g, 21.2 mmol) in dimethylacetamide (DMA, 10 ml) was then added dropwise to the solution over a period of 30 min and then the reaction mixture allowed to cool to room temperature over 16 h. The resulting solution was used without any purification in the next step.

1.4 tert-Butyl 3-(3-(phenylsulfonyl)quinolin-8-yl)azetidine-1-carboxylate

To a solution of 8-iodo-3-(phenylsulfonyl)quinoline (200 mg, 0.51 mmol, prepared according to WO2003080580) in DMA (1 ml) was added $PdCl_2$(dppf) (8.3 mg, 0.10 mmol; dppf = 1,1'-bis(diphenylphosphino)ferrocene) and CuI (11.6 mg, 0.06 mmol), followed by dropwise addition of (1-(tert-butoxycarbonyl)azetidin-3-yl)-zinc(II) iodide (317 mg, 0.91 mmol) in DMA (1 ml) over 10 min. The mixture was then heated at 80 °C for 6 h, then stirred at room temperature for 150 h and quenched with a saturated aqueous solution of NaCl. The reaction mixture was extracted with tert.-butyl-methyl-ether (MTBE). The organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography to give the title compound (54 mg, 25 %) as a light yellow oil.
MS (ESI+) : m/z = 425.1 $(M+H)^+$, 370.1 $(M-tBu+H)^+$.

1.5 8-(Azetidin-3-yl)-3-(phenylsulfonyl)quinoline hydrochloride

A solution of tert-butyl 3-(3-(phenylsulfonyl)quinolin-8-yl)azetidine-1-carboxylate (54 mg, 0.13 mmol) in CH_2Cl_2 (3 ml) was treated with hydrochloric acid (1M in ether, 0.3 ml) at 0°C and then stirred at room temperature for 16 h. After concentration, the product was washed with EtOAc and dried in vacuo to give the title compound (45 mg, 98 %) as a white solid.

MS (ESI+) : m/z = 325.1 $(M+H)^+$; ^{1}H-NMR (400 MHz, d_6-DMSO) : δ = 3.32 (m, 1H), 3.47 (m, 1H), 4.58 (m, 1H), 5.38 (m, 1H), 5.47 (m, 1H), 7.72 (m, 2H), 7.80 (m, 1H), 8.16 (m, 3H), 8.42 (m, 2H), 8.73 (s, 3H), 9.92 (s, 1H), 10.38 ppm (s, 1H).

EXAMPLE 2

3-(Phenylsulfonyl)-8-(piperidin-4-yl)quinoline hydrochloride

The title compound was prepared in an analogous manner to that described for preparation example 1.

2.1 tert-Butyl 4-(3-(phenylsulfonyl)quinolin-8-yl)piperidine-1-carboxylate

Yield : 45 %; MS (ESI+) : m/z = 453.1 $(M+H)^+$, 397.1 $(M-tBu+H)^+$.

2.2 3-(Phenylsulfonyl)-8-(piperidin-4-yl)quinoline hydrochloride

Yield : 62 %; MS (ESI+) : m/z = 353.1 $(M+H)^+$; ^{1}H-NMR (400 MHz, DMSO) : δ = 2.00 (m, 4H), 3.09 (m, 2H), 4.58 (m, 1H), 5.38 (m, 1H), 5.47 (m, 1H), 7.72 (m, 2H), 7.80 (m, 1H), 8.16 (m, 3H), 8.42 (m, 2H), 8.73 (s, 3H), 9.92 (s, 1H), 10.38 ppm (s, 1H).

EXAMPLE 3

8-(1-Benzylpyrrolidin-3-yl)-3-(phenylsulfonyl)quinoline

3-(Phenylsulfonyl)-8-vinylquinoline (210 mg, 0.71 mmol, prepared according to WO2007039219) was reacted with benzyl methoxymethyl trimethylsilylmethyl amine (253 mg, 1.07 mmol) in dichloromethane (2 ml) in the presence of trifluoroacetic acid for 20 minutes. The solution was washed with a saturated aqueous solution of $NaHCO_3$ solution, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by chromatography (100% dichloromethane) to give the title compound as a colourless oil (100 mg, 33 %).

MS (ESI+) : m/z = 429.1 $(M+H)^+$; ^{1}H-NMR (400 MHz, d_6-DMSO) : δ = 2.22 (m, 1H), 3.00 (m, 1H), 3.22 (m, 1H), 3.35 (m, 1H), 3.60 (m, 1H), 3.75 (m, 2H), 4.00 (m, 1H), 5.26 (d, 1H), 5.72 (d, 1H), 7.11 (m, 2H), 7.32 (m, 11H), 7.50 (m, 1H), 7.68 (d, 2H), 7.77 ppm (s, 1H).

EXAMPLE 4

8-(Piperidin-4-yl)-3-(3-(trifluoromethyl)phenylsulfonyl)quinoline

The title compound was prepared in an analogous manner to that described for preparation example 1.

4.1 tert-Butyl 4-(3-(3-(trifluoromethyl)phenylsulfonyl)quinolin-8-yl)piperidine-1-carboxylate

Yield: 26 %; ^{1}H-NMR (400 MHz, d_6-DMSO) : δ = 1.43 (s, 9H), 1.60 (m, 2H), 1.82 (m, 2H), 2.90 (m, 2H), 4.10 (m, 3H), 7.81 (m, 2H), 5.47 (m, 1H), 7.92 (m, 1H), 8.19 (m, 2H), 8.47 (m, 3H), 8.67 (br m, 1H), 9.30 (s, 1H), 9.43 ppm (s, 1H).

4.2 8-(Piperidin-4-yl)-3-(3-(trifluoromethyl)phenylsulfonyl)quinoline

Yield: 98 %; MS (ESI+): m/z = 421.1 $(M+H)^+$; ^{1}H-NMR (400 MHz, d_6-DMSO) : δ = 2.00 (m, 4H), 3.17 (m, 2H), 4.20 (m, 1H), 7.81 (m, 2H), 5.47 (m, 1H), 7.92 (m, 1H), 8.19 (m, 2H), 8.47 (m, 3H), 8.67 (br m, 1H), 9.30 (s, 1H), 9.43 ppm (s, 1H).

EXAMPLE 5

3-(4-Fluorophenylsulfonyl)-8-(piperidin-4-yl)quinoline

The title compound was prepared in an analogous manner to that described for preparation example 1.

5.1 tert-Butyl 4-(3-(4-fluorophenylsulfonyl)quinolin-8-yl)piperidine-1-carboxylate

Yield : 41 %; MS (ESI+) : m/z = 415.1 $(M+H-tBu)^+$; ^{1}H-NMR (400 MHz, d_6-DMSO) : δ = 1.42 (s, 9H), 1.67 (m, 2H), 1.82 (m, 2H), 2.90 (m, 2H), 4.10 (m, 3H), 7.49 (m, 2H), 7.73 (m, 1H), 7.86 (m, 1H), 8.15 (m, 3H), 9.15 (s, 1H), 9.36 ppm (s, 1H).

5.2 3-(4-Fluorophenylsulfonyl)-8-(piperidin-4-yl)quinoline

Yield : 96 %; MS (ESI+) : m/z = 371.1 $(M+H)^+$; ^{1}H-NMR (400 MHz, d_6-DMSO) : δ = 2.02 (m, 4H), 3.10 (m, 2H), 3.39 (m, 2H), 4.16 (m, 1H), 7.49 (m, 2H), 7.79 (m, 2H), 8.16 (m, 3H), 9.15 (s, 1H), 9.34 ppm (s, 1H).

EXAMPLE 6

3-(3-Bromophenylsulfonyl)-8-(piperidin-4-yl)quinoline

The title compound was prepared in an analogous manner to that described for preparation example 1.

6.1 3-(3-Bromophenylsulfonyl)-8-iodoquinoline

MS (ESI+) : m/z = 473.8, 475.8 $(M+H)^+$; ^{1}H-NMR (400 MHz, d_6-DMSO) : δ = 7.59 (m, 2H), 7.95 (d, 1H), 8.12 (d, 1H), 8.30 (d, 1H), 8.62 (d, 1H), 9.35 (s, 1H), 9.48 ppm (s, 1H).

6.2 tert-Butyl 4-(3-(3-bromophenylsulfonyl)quinolin-8-yl)piperidine-1-carboxylate

Yield : 54 %; MS (ESI+) : m/z = 475.0, 477.0 $(M+H - tBu)^+$; ^{1}H-NMR (400 MHz, d_6-DMSO) : δ = 1.48 (s, 9H), 1.67 (m, 2H), 1.82 (m, 2H), 2.90 (m, 2H), 4.10 (m, 3H), 7.62 (t, 2H), 7.73 (t, 1H), 7.86 (d, 1H), 7.89 (d, 1H), 8.13 (m, 3H), 8.30 (s, 1H), 9.18 (s, 1H), 9.38 ppm (s, 1H).

6.3 3-(3-Bromophenylsulfonyl)-8-(piperidin-4-yl)quinoline

Yield : 91 %; MS (ESI+) : m/z = 431.0, 433.0 $(M+H)^+$; ^{1}H-NMR (400 MHz, d_6-DMSO) : δ = 2.02 (m, 4H), 3.10 (m, 2H), 3.39 (m, 2H), 4.16 (m, 1H), 7.60 (t, 1H), 7.79 (m, 2H), 7.90 (m, 1H), 8.14 (m, 2H), 8.30 (s, 1H), 9.25 (s, 1H), 9.39 ppm (s, 1H).

EXAMPLE 7

8-(Piperidin-4-yl)-3-(3-(pyrrolidin-1-yl)phenylsulfonyl)quinoline

7.1 tert-Butyl-4-(3-(3-(pyrrolidin-1-yl)phenylsulfonyl)quinolin-8-yl)piperidine-1-carboxylate

A solution of tert-butyl 4-(3-(3-bromophenylsulfonyl)quinolin-8-yl)piperidine-1-carboxylate (100 mg, 0.19 mmol), pyrrolidine (40 mg, 0.564 mmol), Na tert.-butanolate (32 mg, 0.34 mmol), tris(dibenzylideneacetone)dipalladium (0) chloroform adduct (19 mg, 0.019 mmol) and [1,1'-binaphthalene]-2,2'-diylbis(diphenylphosphine) (BINAP, 23 mg, 0.038 mmol) in 10 mL tetrahydrofurane (THF) was heated at reflux for 2 hours. The cooled solution, after standard aqueous workup and chromatography, yielded 60 mg (61 %) of the BOC-protected product as a yellow solid.

MS (ESI+) : m/z = 422.3 $(M+H - tBu)^+$; ^{1}H-NMR (400 MHz, d_6-DMSO) : δ = 0.87 (d, 1H), 1.28 (m, 2H), 1.48 (s, 9H), 1.63 (m, 2H), 1.82 (m, 2H), 1.98 (m, 4H), 2.90 (m, 2H), 4.10 (m, 3H), 6.70 (m, 2H), 7.07 (s, 1H), 7.20 (d, 1H), 7.38 (m, !H), 7.73 (m, 1H), 7.84 (d, 1H), 8.13 (m, 1H), 9.18 (s, 1H), 9.38 ppm (s, 1H).

7.2 8-(Piperidin-4-yl)-3-(3-(pyrrolidin-1-yl)phenylsulfonyl)quinoline

The title compound was prepared in an analogous manner to that described for preparation example 1.

Yield : 88 %; MS (ESI+) : m/z = 431.0 $(M+H)^+$; ^{1}H-NMR (400 MHz, DMSO) : δ = 2.02 (m, 8H), 3.16 (m, 2H), 3.27 (m, 4H), 3.40 (m, 2H), 4.22 (m, 1H), 6.80 (d, 1H), 7.09 (s, 2H), 7.22 (d, 1H), 7.40 (m, 1H), 7.80 (m, 2H), 8.14 (m,12H), 8.30 (s, 1H), 9.15 (s, 1H), 9.35 ppm (s, 1H).

II. Biological investigations

Displacement of radioligands binding to the following cloned human receptors

1. Preparation of membranes by ultrasonic treatment and differential centrifugation

Cells from stable clonal cell lines expressing the corresponding receptor (5-HT_6, α_1-adrenergic, dopamine D_2 or histamine H_1 receptors) were washed with PBS (w/o Ca^{++}, Mg^{++}) and harvested in PBS with 0.02% EDTA. The cells were collected by centrifugation at 500 g for 10 min. at 4°C, washed with PBS and centrifuged (500 g, 10 min. 4°C). The pellets were stored at -80°C until use. For membrane preparation, the thawed cell pellet was resuspended in ice-cold sucrose buffer (0.25 M sucrose, 10 mM Hepes (pH 7.4), 1 mM Phenylmethylsulfonyl fluoride (PMSF) in DMSO, 5 µg/ml Pepstatin-A, 3 mM EDTA, 0.025 % Bacitracin) and homogenized with a Branson Sonifier W-250 (Settings: Timer 4; Output Control 3; Duty Cycle constant; 2 to 3 cycles). Cell disruption was checked with the aid of a microscope. Remaining unbroken cells were pelleted at 1.000 g for 10 min. at 4°C. The sucrose buffer supernatant was then centrifuged at 60.000 g for 1h at 4°C (Beckman Ultrazentrifuge XL 80). The pellet was resuspended in 30 ml ice-cold Tris buffer (20 mM TRIS (pH 7.4), 5 µg/ml Pepstatin A, 0.1 mM PMSF, 3 mM EDTA) by pipetting through a 10 ml serological pipet and centrifuged for 1h at 4°C at 60.000 g. A final resuspension was performed in a small volume of ice-cold Tris buffer (see above) by pressing through a serological pipet followed by ultrasonic treatment with a Branson Sonifier W-250 (Settings: Timer 1; Output Control 3; Duty Cycle constant; 1 cycle). Protein concentration was determined (BCA-Kit; Pierce) and aliquots stored at -80°C or in liquid nitrogen for long-term storage.

2. Receptor binding experiments

All receptor binding experiments were carried out in the corresponding assay buffer in a total volume of 200 µl in the presence of various concentrations of test compound (10^{-5} M to 10^{-9} M, tenfold serial dilution, duplicate determinations). The assays were terminated by filtration on polyethylenimine (PEI 0.1% or 0.3%) presoaked Packard Unifilter Plates (GF/C or GF/B) with a Tomtec MachIII U 96well-plate harvester. After the plates had been dried for 2 h at 55°C in a drying chamber scintillation cocktail (BetaPlate Scint; PerkinElmer) was added. Radioactivity was measured in a Microbeta

Trilux two hours after the addition of the scintillation mixture. Data derived from liquid scintillation counting were analysed by iterative non-linear regression analysis with the use of the Statistical Analysis System (SAS): a program similar to "LIGAND" as described by Munson and Rodbard (Analytical Biochemistry 107, 220-239 (1980).

a) 5-HT_6 receptor binding assay

HEK293 cells stably expressing the h-5-HT_6 receptor (NCBI Reference Sequence XM 001435) were cultured in RPMI1640 medium supplemented with 25 mM HEPES, 10 % fetal calf serum and 1-2 mM glutamine. The membrane preparation was performed as described in section 1. For these membranes a K_D of 1.95 nM for [^{3}H]-LSD (Lysergic Acid Diethylamide; Amersham, TRK1038) was determined by means of saturation binding experiments. On the day of the assay, the membranes were thawed, diluted in assay buffer (50 mM Tris-HCl, 5 mM $CaCl_2$, 0.1% ascorbic acid, 10 µM pargyline, pH 7.4) to a concentration of 8 µg protein/assay and homogenized by gentle vortexing For inhibition studies, 1nM [^{3}H]-Lysergic Acid Diethylamide was incubated in the presence of various concentrations of test compound in assay buffer. Non-specific binding was defined with 1 µM methiothepin. The binding reaction was carried out for 3.5 h at room temperature. During the incubation, the plates were shaken on a plate shaker at 100 rpm and terminated by filtration on Packard Unifilter GF/C (0.1% PEI) plates, followed by 2 wash cycles with ice-cold 50 mM Tris-HCl, 5 mM $CaCl_2$.

a) Dopamine D_2 receptor binding assay

HEK293 cells stably expressing the dopamine D_2 receptor (NCBI Reference Sequence NM_000795) were cultured in RPMI1640 medium supplemented with 25 mM HEPES, 10 % fetal calf serum and 1-2 mM glutamine. The membrane preparation was performed as described in section 1. For these membranes a K_D of 0.22 nM for [^{125}I]-iodospiperone (PerkinElmer Life Sciences, NEX284) was determined by means of saturation binding experiments. On the day of the assay, the membranes were thawed, diluted in assay buffer (50 mM Tris-HCl, 120 mM NaCl, 5 mM $MgCl_2$, 5 mM KCl, 1.5 mM $CaCl_2$, pH 7.4) to a concentration of 15 µg protein/assay and homogenized by gentle vortexing. For inhibition studies, 0.01 nM [^{125}I]-iodospiperone (PerkinElmer Life Sciences, NEX284) was incubated in the presence of various concentrations of test compound in assay buffer. Non-specific binding was defined with 1 µM haloperidol. The binding reaction was carried out for 1 h at room temperature and terminated by filtration on Packard Unifilter GF/B (0.1% PEI) plates, followed by 6 wash cycles with an ice-cold 7 % polyethylenglycol solution.

b) α_1-Adrenergic receptor binding assay

CHO-K_1 cells stably expressing the α_1-adrenergic receptor (NCBI Reference Sequence NM_033303) were cultured in RPMI1640 medium supplemented with 25 mM HEPES, 10 % fetal calf serum and 1-2 mM glutamine. The membrane preparation was performed as described in section 1. For these membranes a K_D of 0.12 nM for [^{3}H]-prazosine (PerkinElmer Life Sciences, NET823) was determined by means of saturation binding experiments. On the day of the assay, the membranes were thawed, diluted in assay buffer (50 mM Tris-HCl, pH 7.4) to a concentration of 4 µg protein/assay and homogenized by gentle vortexing. For inhibition studies, 0.1 nM [^{3}H]-prazosine (PerkinElmer Life Sciences, NET823) was incubated in the presence of various concentrations of test compound in assay buffer. Non-specific binding was defined with 1 µM phentolamine. The binding reaction was carried out for 1 h at room temperature and terminated by filtration on Packard Unifilter GF/C (0.1% PEI) plates, followed by 3 wash cycles with ice-cold assay buffer.

c) H_1 receptor binding assay

CHO-K_1 cells stably expressing the histamine H_1 receptor (Euroscreen-ES-390-C, NCBI Reference Sequence NM_000861) were cultured in RPMI1640 medium supplemented with 25 mM HEPES, 10 % fetal calf serum and 1-2 mM glutamine. The membrane preparation was performed as described in section 1. For these membranes a K_D of 0.83 nM for [^{3}H]-pyrilamine (PerkinElmer Life Sciences, NET594) was determined by means of saturation binding experiments. On the day of the assay, the membranes were thawed, diluted in assay buffer (50 mM Na_2HPO_4, 50 mM KH_2PO_4, pH 7.4) to a concentration of 6 µg protein/assay and homogenized by gentle vortexing. For inhibition studies, 1 nM [^{3}H]-pyrilamine (PerkinElmer Life Sciences, NET594) was incubated in the presence of various concentrations of test compound in assay buffer. Non-specific binding was defined with 1 µM pyrilamine. The binding reaction was carried out for 50 minutes at room temperature and terminated by filtration on Packard Unifilter GF/C (0.3% PEI) plates, followed by 2 wash cycles with ice-cold assay buffer.

3. Data Analysis

Data derived from liquid scintillation counting were analyzed by iterative non-linear regression analysis with the use of the Statistical Analysis System (SAS): a program similar to "LIGAND" as described by Munson and Rodbard (Anal. Biochem. 1980, 107, 220-239). Fitting was performed according to formulae described by Feldman (Anal. Biochem. 1972, 48, 317-338). IC_{50}, nH and K_i values were expressed as geometrical mean. For receptors with a low affinity for the test compound, where the highest tested compound concentration inhibited less than 30% of specific radioligand binding, K_i-values were determined according to the equation of Cheng and Prusoff (Biochem. Pharmacol. 1973, 22, 2099-2108) and expressed as greater than (>).

The results of the receptor binding studies are expressed as receptor binding constants K_i(5-HT_6), K_i(D_2), K_i(α_1-adrenergic) and K_i(H_1), respectively, as described herein before, and given in table I.

In these tests, the compounds according to the invention exhibit very good affinities for the 5-HT_6 receptor (K_i < 250 nM or< 50 nM or < 20 nM and frequently < 1 nM). Furthermore those compounds bind selectively to the 5-HT_6 receptor, as compared to the affinity for the D_2, the α_1-adrenergic or the H_1 receptors. These compounds exhibit little affinities for the D_2, α_1-adrenergic or H_1 receptors (K_i > 250 nM or > 1000 nM and frequently > 10000 nM).

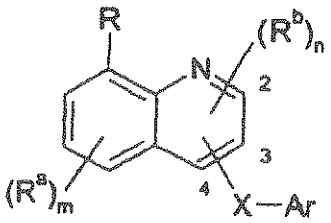
The results of the receptor binding studies on the human 5-HT6 receptor are compiled in table B. In table B (+) in each case indicates a K_i-value of > 1 µM, (++) in each case indicates a K_i-value of 100 nM - 1 µM and (+++) in each case indicates a K_i-value of < 100 nM.

Table B.

Example	Ki (human 5-HT6)
1	+++
2	+++
3	+
4	+++
5	+++
6	+++
7	+++

Claims

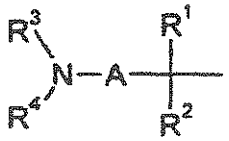
1. Quinoline compounds of formula (I)



(I)

wherein

R is a moiety of the formula



(R)

wherein

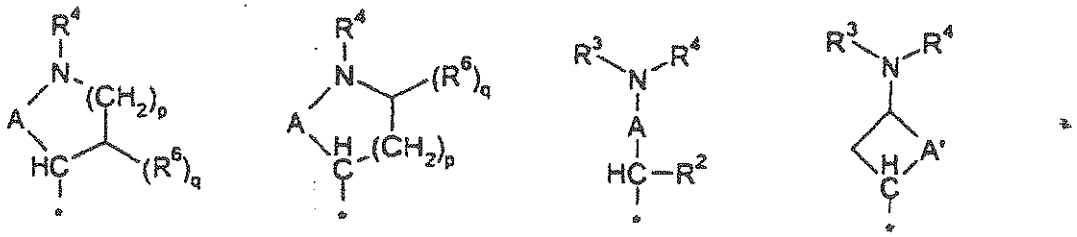
A is a chemical bond, CHR^5 or CH_2CHR^5;
R^1 is hydrogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C1- C4- haloalkoxy;
R^2 is hydrogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy;
R^3 is hydrogen or C_1-C_4-alkyl;
R^1 and R^3 together may also be linear C_1-C_4-alkylene, which may carry 1 or 2 radicals R^6;
R^4 is hydrogen, C_1-C_6-alkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-haloalkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, C_1-C_6-haloalkoxy-C_1-C_4-alkyl, C_3-C_6-cycloalkyl, C_3-C_6-halocycloalkyl, C_3-C_6-cycloalkyl-C_1-C_4-alkyl, aryl-C_1-C_4-alkyl, hetaryl-C_1-C_4-alkyl, C_3-C_6-alkenyl, C_3-C_6-haloalkenyl, formyl, C_1-C_4-alkylcarbonyl or C_1-C_4-alkoxycarbonyl;
R^5 is hydrogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy;
R^1 and R^5 together may also be a single bond, linear C_1-C_4-alkylene, which may carry 1 or 2 radicals R^7; or
R^3 and R^5 together may also be linear C_1-C_4-alkylene, which may carry 1 or 2 radicals R^8;
R^6 is C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy; or
R^5 and R^6 together may also be linear C_1-C_4-alkylene, which may carry 1 or 2 radical R^9;
R^7, R^8 and R^9 are independently selected from the group consisting of C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy and C_1-C_4-haloalkoxy;
n is 0, 1 or 2;
m is 0, 1, 2 or 3;
R^a, R^6 are independently selected from the group consisting of halogen, CN, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, $C(O)R^{aa}$, $C(O)NR^{cc}R^{bb}$ and $NR^{cc}R^{bb}$; wherein R^{aa} is hydrogen, C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-alkoxy or C_1-C_4-haloalkoxy, and R^{cc}, R^{bb} are independently selected from the group consisting of hydrogen and C_1-C_4-alkyl;
X is CH_2, C(O), S. S(O) or $S(O)_2$; which is located in the 3- or 4-position of the quinoline ring;

Ar is a radical Ar^1, Ar^2–Ar^3 or Ar^2–O- Ar^3, wherein Ar^1, Ar^2 and Ar^3 are each independently selected from the group consisting of aryl or hetaryl wherein aryl or hetaryl moieties may be unsubstituted or may canny 1, 2, 3 substituents R^x, wherein

R^x is halogen, CN, NO_2, C_1-C_6-alkyl, C_1-C_6-haloalkyl, C_1-C_6-hydroxyalkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, C_2-C_6-alkenyl, C_2-C_6-haloalkenyl, C_3-C_6-cycloalkyl, C_3-C_6-halocydoalkyl, C_1-C_6-alkoxy, C_1-C_6-hydroxy- alkoxy. C_1-C_6.alkoxy-C_1-C_4-alkoxy, C_1-C_6-haloalkoxy, C_1-C_6-alkylthio, C_1-C_6-haloalkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-haloalkylsulfinyl, C_1-C_6-alkylsutfonyl, C_1-C_6-haloalkytsulfonyl, C_1-C_6-alkylcarbonyl, C_1-C_6-haloalkylcarbonyl, C_1-C_6-alkylcarbonylamino, C_1-C_6-haloalkyl- carbonylamino, carboxy, NH-C(O)-$NR^{x1}R^{x2}$, $NR^{x1}R^{x2}$. $NR^{x1}R^{x2}$-C_1-C_6-alkylene, O-$NR^{x1}R^{x2}$, wherein R^{x1} and R^{x2} in the last 4 mentioned radicals are independently of each other hydrogen, C_1-C_6-alkyl, C_1-C_6-haloalkyl or C_1-C_6-alkoxy or R^{x1} and R^{x2} in the last 4 mentioned radicals together with the nitrogen atom form an N-bound 5-, 6- or 7-memhered, saturated heterocycle which is unsubstituted or which carries 1, 2, 3 or 4 radicals selected from C_1-C_4-alkyl, C_1-C_4-haloalkyl, C_1-C_4-hydroxyalkyl and C_1-C_4-alkoxy and wherein 2 radicals R^x, which are bound to adjacent carbon atoms of Ar may form a saturated or unsaturated 5- or 6-membered carbocyclic or heterocyclic ring, which itself may carry a radical R^x:

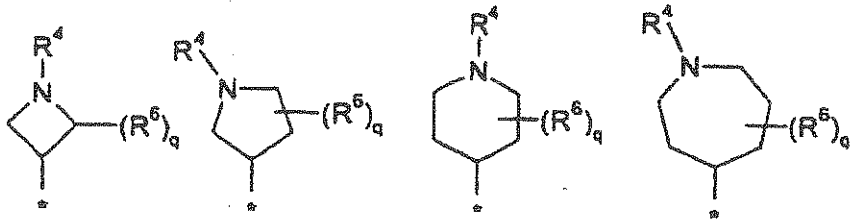
provided that for X being $S(O)_2$ at least one of the radicals R^1, R^2 and if present R^5 is different from hydrogen and C_1-C_4-alkyl;
and physiologically tolerated acid addition salts and the N-oxides thereof.

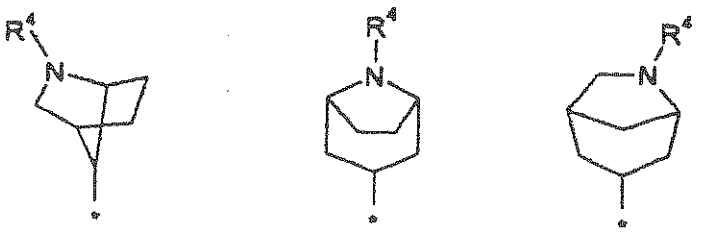
2. The compounds as claimed in claim 1, wherein the moiety R is a radical of the formulae:

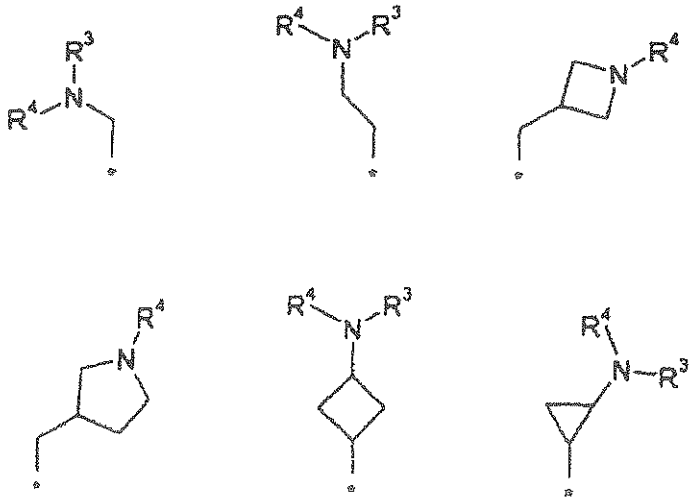


wherein A, R^2, R^3, R^4 and R^6 are as defined in claim 1, * indicates the binding site to the quinolinyl radical, p is 0, 1, 2 or 3, q is 0 or 1 and wherein A' is a single bond, CH_2, CH_2CH_2, CHR^7 or CH_2CHR^7, wherein R^7 is as defined in claim 1.

3. The compounds as claimed in claim 1, wherein the moiety R is a radical of the formulae:

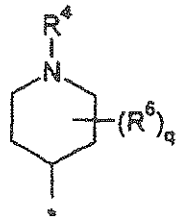






wherein R^3, R^4 and R^5 are as defined in claim 1, * indicates the binding site to the quinolinyl radical and wherein q is 0 or 1.

4. The compounds as claimed in claim 1, wherein the moiety R is a radical of the formulae :



wherein R^4 and R^6 are as defined in claim 1, * indicates the binding site to the quinolinyl radical and wherein q is 0 or 1.

5. The compounds as claimed in any of the preceding claims, wherein R^4 is hydrogen.

6. The compounds as claimed in any of the preceding claims, wherein X is SO_2.

7. The compounds as claimed in any of claims 1 to 5, wherein X is CH_2.

8. The compounds as claimed in any of claims 1 to 5, wherein X is C(O).

9. The compounds as claimed in any of the preceding claims, wherein X is located in the 3-position of the quinolinyl moiety.

10. The compounds as claimed in any of claims 1 to 8, wherein X is located in the 4-position of the quinolinyl moiety.

11. The compounds as claimed in any of the preceding claims, wherein Ar is phenyl, naphthyl, thienyl, pyridyl, pyrimidyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, triazolyl, thiadiazolyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, benzofuranyl, benzothienyl, benzoxazinyl, benzothiazolyl, benzoxadiazolyl, benzothiadiazolyl, benzomorpholinyl or indanyl, wherein the cyclic radical Ar is unsubstituted or may carry 1, 2 or 3 substituents R^x as defined in claim 1.

12. The compounds as claimed in claim 11, wherein Ar is phenyl, which is unsubstituted or may carry 1, 2 or 3 substituents R^x as defined in claim 1.

13. The compounds as claimed in any of the preceding claim, wherein R^x is selected from halogen, CN, C_1-C_4-alkyl,

C_1-C_4-haloalkyl, C_1-C_4-alkoxy, C_1-C_4-haloalkoxy, C_3-C_6-cycloalkyl and a group $NR^{x1}R^{x2}$.

14. The compounds as claimed in any of the preceding claims, wherein m is 0.

15. The compounds as claimed in any of the preceding claims, wherein n is 0.

16. The compounds as claimed in claim 1, which are selected from the group consisting of
8-(Azetidin-3-yl)-3-(phenylsulfonyl)quinoline,
3-(Phenylsudonyl)-8-(piperidin-4-yl)quinoline,
8-(1-Benzylpyrrolidin-3-yl)-3-(phenylsurfonyl)quinoline,
8-(Piperidin-4-yl)-3-(3-(trifluoromethyl)phenylsulfonyl)quinoline,
3-(4-Fluorophenylsulfonyl)-8-(piperidin-4-yl)quinoline,
3-(3-Bromophenylsulfonyl)-8-(piperidin-4-yl)quinoline,
8-(Piperidin-4-yl)-3-(3-(pyrrolidin-1-yl)phenylsulfonyl)quinoline,
and physiologically tolerated acid addition salts and the N-oxides thereof.

17. A pharmaceutical composition comprising at least one compound as claimed in any of the preceding claims, optionally together with at least one physiologically acceptable carrier or auxiliary substance.

18. The use of a compound as claimed in any of claims 1 to 16 for preparing a pharmaceutical composition.

19. The compound as claimed in any of claims 1 to 16 for the use as a medicament.

20. The use of the compound in any of claims 1 to 16 in the manufacture of a medicament for the treatment of a medical disorder which is selected from a disease of the central nervous system, in particular a cognitive dysfunction such as cognitive dysfunction associated with Alzheimer's disease and cognitive dysfunction associated with schizophrenia, addiction disease and obesity.