The invention relates to compounds of the formula and their use as pharmaceutical ingredients, in particular for the treatment of CNS related diseases (PDE 10A inhibitors).
Aryl- and heteroarylamid derivatives as PDE10A enzyme inhibitor

Field of the Invention
The invention provides compounds that are PDE10A enzyme inhibitors, and as such are useful to treat neurodegenerative and psychiatric disorders. The invention also provides pharmaceutical compositions comprising the compound of the invention and methods of treating disorders using the compound of the invention.

Background of the Invention
Throughout this application, various publications are referenced in full. The disclosures of these publications are hereby incorporated by reference into this application to describe more fully the state of the art to which this invention pertains.

The cyclic nucleotides cyclic-adenosine monophosphate (cAMP) and cyclic-guanosine monophosphate (cGMP) function as intracellular second messengers regulating a vast array of processes in neurons. Intracellular cAMP and cGMP are generated by adenyl and guanyl cyclases, and are degraded by cyclic nucleotide phosphodiesterases (PDEs). Intracellular levels of cAMP and cGMP are controlled by intracellular signaling, and stimulation/repression of adenyl and guanyl cyclases in response to GPCR activation is a well characterized way of controlling cyclic nucleotide concentrations (Antoni, F.A. Front. Neuroendocrinol. 2000, 21, 103-132). cAMP and cGMP levels in turn control activity of cAMP- and cGMP-dependent kinases as well as other proteins with cyclic nucleotide response elements, which through subsequent phosphorylation of proteins and other processes regulate key neuronal functions such as synaptic transmission, neuronal differentiation and survival.


PDE10A is primarily expressed in the neurons in the striatum, n. accumbens and in the olfactory tubercle.
PDE10A is expressed at high levels neurons in the striatum, by the medium spiny neurons (MSN) of the caudate nucleus, the accumbens nucleus and the corresponding neurons of the olfactory tubercle (Kotera, J. et al. Biochem. Biophys. Res. Comm. 1999, 261, 551-557 and Seeger, T.F. et al. Brain Research, 2003, 985, 113-126). Conversely, D receptor facilitation which functional classes of neurons: the D1 class expressing D1 dopamine receptors and the D2 class expressing D2 dopamine receptors. The D1 class of neurons is part of the 'direct' striatal output pathway, which broadly functions to facilitate behavioral responses. The D2 class of neurons is part of the 'indirect' striatal output pathway, which functions to suppress behavioral responses that compete with those being facilitated by the 'direct' pathway. These competing pathways act like the brake and accelerator in a car. In the simplest view, the poverty of movement in Parkinson's disease results from over-activity of the 'indirect' pathway, whereas excess movement in disorders such as Huntington's disease represent over-activity of the direct pathway. PDE10A regulation of cAMP and/or cGMP signaling in the dendritic compartment of these neurons may be involved in filtering the cortico/thalamic input into the MSN. Furthermore, PDE10A may be involved in the regulation of GABA release in the substantia nigra and globus pallidus (Seeger, T.F. et al. Brain Research, 2003, 985, 113-126).

Dopamine D2 receptor antagonism is well established in the treatment of schizophrenia. Since the 1950's, dopamine D2 receptor antagonism has been the mainstay in psychosis treatment and all effective antipsychotic drugs antagonise D2 receptors. The effects of D2 are likely to be mediated primarily through neurons in the striatum, n. accumbens and olfactory tubercle, since these areas receive the densest dopaminergic projections and have the strongest expression of D2 receptors (Konradi, C. and Heckers, S. Society of Biological Psychiatry, 2001, 50, 729-742). Dopamine D2 receptor agonism leads to decrease in cAMP levels in the cells where it is expressed through adenylate cyclase inhibition, and this is a component of D2 signalling (Stoof, J. C.; Kebabian J. W. Nature 1981, 294, 366-368 and Neve, K. A. et al. Journal of Receptors and Signal Transduction 2004, 24, 165-205). Conversely, D2 receptor
antagonism effectively increases cAMP levels, and this effect could be mimicked by inhibition of cAMP degrading phosphodiesterases.

Most of the 21 phosphodiesterase genes are widely expressed; therefore inhibition is likely to have side effects. Because PDE10A, in this context, has the desired expression profile with high and relatively specific expression in neurons in striatum, n. accumbens and olfactory tubercle, PDE10A inhibition is likely to have effects similar to D2 receptor antagonism and therefore have antipsychotic effects.

While PDE10A inhibition is expected to mimic D2 receptor antagonism in part, it might be expected to have a different profile. The D2 receptor has signalling components besides cAMP (Neve, K. A. et al. *Journal of Receptors and Signal Transduction* 2004, 24, 165-205), for which reason interference with cAMP through PDE10A inhibition may negatively modulate rather than directly antagonise dopamine signaling through D2 receptors. This may reduce the risk of the extrapyrimidal side effects that are seen with strong D2 antagonism. Conversely, PDE10A inhibition may have some effects not seen with D2 receptor antagonism. PDE10A is also expressed in D1 receptors expressing striatal neurons (Seeger, T. F. et al. *Brain Research*, 2003, 985, 113-126). Since D1 receptor agonism leads to stimulation of adenylate cyclase and resulting increase in cAMP levels, PDE10A inhibition is likely to also have effects that mimic D1 receptor agonism. Finally, PDE10A inhibition will not only increase cAMP in cells, but might also be expected to increase cGMP levels, since PDE10A is a dual specificity phosphodiesterase. cGMP activates a number of target protein in cells like cAMP and also interacts with the cAMP signalling pathways. In conclusion, PDE10A inhibition is likely to mimic D2 receptor antagonism in part and therefore has antipsychotic effect, but the profile might differ from that observed with classical D2 receptor antagonists.

The PDE10A inhibitor papaverine is shown to be active in several antipsychotic models. Papaverine potentiated the cataleptic effect of the D2 receptor antagonist haloperidol in rats, but did not cause catalepsy on its own (WO 03/093499). Papaverine reduced hyperactivity in rats induced by PCP, while reduction of amphetamine induced hyperactivity was insignificant (WO 03/093499). These models suggest that PDE10A inhibition has the classic antipsychotic potential that would be expected from theoretical

The tissue distribution of PDE10A indicates that PDE10A inhibitors can be used to raise levels of cAMP and/or cGMP within cells that express the PDE10 enzyme, especially neurons that comprise the basal ganglia, and the PDE10A inhibitors of the invention would therefore be useful in treating a variety of associated neuropsychiatric conditions involving the basal ganglia such as neurological and psychiatric disorders, schizophrenia, bipolar disorder, obsessive compulsive disorder, and the like, and may have the benefit of not possessing unwanted side effects, which are associated with the current therapies on the market.


With respect to inhibitors of PDE10A, EP 1250923 discloses the use of selective PDE10 inhibitors in general, and papaverine in particular, for the treatment of certain neurologic and psychiatric disorders.

WO09/152825 discloses phenylimidazole derivatives as PDE10A enzyme inhibitors useful for the treatment of various diseases, including CNS related diseases such as schizophrenia.

Pyrrrolodihydroisoquinolines and variants thereof are disclosed as inhibitors of PDE10 in WO 05/03129 and WO 05/02579. Piperidinyl-substituted quinazolines and isoquinolines that serve as PDE10 inhibitors are disclosed in WO 05/82883. WO 06/1 1040 discloses substituted quinazoline and isoquinoline compounds that serve as inhibitors of PDE10. US 20050182079 discloses substituted tetrahydroisoquinolinyl derivatives of quinazoline and isoquinoline that serve as effective phosphodiesterase
(PDE) inhibitors. In particular, US 20050182079 relates to said compounds, which are selective inhibitors of PDE10. Analogously, US 20060019975 discloses piperidine derivatives of quinazoline and isoquinoline that serve as effective phosphodiesterase (PDE) inhibitors. US 20060019975 also relates to compounds that are selective inhibitors of PDE10. WO 06/028957 discloses cinnoline derivatives as inhibitors of phosphodiesterase type 10 for the treatment of psychiatric and neurological syndromes. However, these disclosures do not pertain to the compound of the invention, which are structurally unrelated to any of the known PDE10 inhibitors (Kehler, J. et al. Expert Opin. Ther. Patents 2007, 17, 147-158).

The compound of the invention proves to be efficient PDE10A enzyme inhibitors and an in vivo active compound that reverses the PCP induced hyperactivity and may thus offer alternatives to current marketed treatments for neurodegenerative and/or psychiatric disorders, which are not efficacious in all patients. Hence, there remains a need for alternative methods of treatment.

**Summary of the Invention**

The objective of the invention is to provide compounds that are selective PDE10A enzyme inhibitors.

A further objective of the invention is to provide compounds that have such activity, and have good, preferably improved, solubility, metabolic stability and/or bioavailability compared to prior art compounds.

Another objective of the invention is to provide an effective treatment, in particular long-term treatment, of a human patient, without causing the side effects typically associated with current therapies for neurological and psychiatric disorders.

Further objectives of the invention will become apparent upon reading the specification.

Accordingly, in one aspect the invention relates to compounds of formula I:

![Formula I](image)

**Formula I - compound of the invention**
wherein heti (also denoted het-1) is selected from the group consisting of

![Chemical Structures](image1)

and wherein * denotes the attachment point,

5 and het₂ (also denoted het-2) is selected from the group consisting of

![Chemical Structures](image2)

and wherein * denotes the attachment point,

and wherein further L is a linker selected from the group consisting of

![Chemical Structures](image3)

and wherein R₁ is selected from the group consisting of H; C₁-C₆ alkyl such as methyl, ethyl, 1-propyl, 2-propyl, isobutyl n-butyl, sec-butyl or tert-butyl; C₁-C₆ alkyl(C₃-C₈)cycloalkyl such as cyclopropylmethyl, and wherein * denotes the attachment point,
as well as tautomers and pharmaceutically acceptable acid addition salts of the compound of the invention.

In an embodiment HET-2 in the compound of the invention is selected from the group consisting of

![Chemical structures]

In a further embodiment R1 is CH₃, in particular R1 is CH₃ if HET-2 is selected from the group consisting of

![Chemical structures]

In a still further embodiment the compound of the present invention is selected from the group consisting of N-Methyl-N-pyridin-4-yl-4-(quinolin-2-ylmethoxy)-benzamide, N-(benzo[d]thiazol-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide, N-(benzo[d]oxazol-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide, N-(imidazo[1,2-a]pyridin-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide, N-(imidazo[1,2-a]pyridin-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide, N-Methyl-4-(quinolin-2-ylmethoxy)-N-[1,2,4]triazolo[1,5-a]pyridin-6-yl-benzamide, N-[(1,2,4]triazolo[1,5-a]pyridin-7-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide, 2-Pyridin-3-yl-thiazole-4-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, 2-Pyridin-4-yl-thiazole-4-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, 2-Pyridin-3-yl-thiazole-4-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, 5-Pyridin-2-yl-1 H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, 5-Pyridin-3-yl-1 H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, 5-Pyridin-4-yl-1 H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, Benzothiazole-6-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, Benzothiazole-6-carboxylic acid methyl-[4-(1-methyl-1 H-benzoimidazol-2-
ylmethoxy)-phenyl]-amide, and N-Methyl-N-[4-(quinolin-2-ylmethoxy)-phenyl]-isonicotinamide.

In yet a further embodiment the compound of the invention is selected from the group consisting of N-(benzo[d]thiazol-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide, 5-Pyridin-3-yl-1 H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, 5-Pyridin-4-yl-1 H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, and benzothiazole-6-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide.

Where the linker is La the compound of the invention will for ease of reference be referred to as compound 1a

![La](image)

whereas when the linker is Lb the compound of the invention will for ease of reference be referred to as compound 1b

![Lb](image)

The invention further provides the compound of the invention, or a pharmaceutically acceptable acid addition salt thereof, for use as a medicament.

In another aspect, the invention provides a pharmaceutical composition comprising the compound of the invention and a pharmaceutically acceptable carrier, diluent or excipient.
The invention further provides the use of the compound of the invention for the preparation of a medicament for the treatment of a neurodegenerative or psychiatric disorder.

The invention further provides the compound of the invention for use as a medicament.

The invention further provides the compounds of the invention for the treatment of a psychiatric disorder selected from the group consisting of schizophrenia, for example of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophreniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; bipolar disorder, for example bipolar I disorder, bipolar II disorder, and cyclothymic disorder; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type.

Furthermore the invention provides a method of treating a patient suffering from a neurodegenerative disorder, comprising administering to the patient the compound of the invention. In a still further aspect, the invention provides a method of treating a patient suffering from a psychiatric disorder, comprising administering to the patient the compound of the invention. In another embodiment, the invention provides a method of treating a patient suffering from a drug addiction, such as an alcohol, amphetamine, cocaine, or opiate addiction comprising administering to the patient the compound of the invention.

**Detailed Description of the Invention**

Unless otherwise specified "compound of the invention" refers to one or more compounds covered by the compound of the invention, i.e. the compound of formula I.

Compounds of the invention have, when tested as described in the section PDE10A enzyme inhibition assay, an $IC_{50}$ value of between about 15 and 400 nM which make them useful compounds for inhibition of PDE 10A enzyme activity.
Further, the compounds have been tested for their ability to reverse phencyclidine (PCP) induced hyperactivity. The reversal of the PCP effect is measured as described in the section "Phencyclidine (PCP) induced hyperactivity". The experiment shows that the compounds of the invention are in vivo active compounds that reverse the PCP induced hyperactivity.

**Pharmaceutically Acceptable Salts**

The invention also comprises salts of the compounds the invention, typically, pharmaceutically acceptable salts. Such salts include pharmaceutically acceptable acid addition salts. Acid addition salts include salts of inorganic acids as well as organic acids.

Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, sulfamic, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, itaconic, lactic, methanesulfonic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methane sulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in Berge, S.M. et al., *J. Pharm. Sci.* 1977, 66, 2, the contents of which are hereby incorporated by reference.

Furthermore, the compound of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.
**Pharmaceutical compositions**

The invention further provides a pharmaceutical composition comprising the compound of the invention, alone or in combination with another active ingredient, and a pharmaceutically acceptable carrier or diluent. The invention also provides a pharmaceutical composition comprising the compound of the invention and a pharmaceutically acceptable carrier or diluent.

The compound of the invention may be administered alone or in combination with pharmaceutically acceptable carriers, diluents or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 21<sup>th</sup> Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 2005.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) routes. It will be appreciated that the route will depend on the general condition and age of the patient to be treated, the nature of the condition to be treated and the active ingredient.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, the compositions may be prepared with coatings such as enteric coatings or they may be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art. Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as
sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Other suitable administration forms include, but are not limited to, suppositories, sprays, ointments, creams, gels, inhalants, dermal patches and implants.

Typical oral dosages of the compound of the invention range from about 0.001 to about 100 mg/kg body weight per day. Typical oral dosages also range from about 0.01 to about 50 mg/kg body weight per day. Typical oral dosages of the compound of the invention further range from about 0.05 to about 10 mg/kg body weight per day. Oral dosages are usually administered in one or more dosages, typically, one to three dosages per day. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the patient treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The compositions may also be presented in a unit dosage form by methods known to those skilled in the art. For illustrative purposes, a typical unit dosage form for oral administration may contain from about 0.01 to about 1000 mg, from about 0.05 to about 500 mg, or from about 0.5 mg to about 200 mg of the compound of the invention.

For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typical doses are in the order of half the dose employed for oral administration.

The invention also provides a process for making a pharmaceutical composition comprising admixing the compound of the invention, alone or in combination with another active ingredient, and at least one pharmaceutically acceptable carrier or diluent.

The compound of this invention is generally utilized as the free substance or as a pharmaceutically acceptable salt thereof.

For parenteral administration, solutions of the compound of the invention in sterile aqueous solution, aqueous propylene glycol, aqueous vitamin E or sesame or peanut
oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The compound of the invention may be readily incorporated into known sterile aqueous media using standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. Examples of solid carriers include lactose, terra alba, sucrose, cyclodextrin, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and lower alkyl ethers of cellulose. Examples of liquid carriers include, but are not limited to, syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene and water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glycercyl monostearate or glycercyl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the compound of the invention and a pharmaceutically acceptable carrier are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The compositions may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Compositions of the invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and optionally a suitable excipient. Furthermore, the orally available compositions may be in the form of a powder or granules, a solution or suspension in an aqueous or non-aqueous liquid, or an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form or it may be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will range from about 25 mg to about 1 g per dosage unit. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.
The pharmaceutical compositions of the invention may be prepared by conventional methods in the art. For example, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine prepare tablets. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatin, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colorings, flavorings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Treatment of Disorders
As mentioned above, the compound of the invention is a PDE10A enzyme inhibitor and as such useful to treat associated neurological and psychiatric disorders.

The invention thus provides the compound of the invention as well as a pharmaceutical composition containing such a compound, for use in the treatment of a neurodegenerative disorder, psychiatric disorder or drug addiction in patients; wherein the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; and age-related cognitive decline; and wherein the psychiatric disorder is selected from the group consisting of schizophrenia, for example of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophreniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type; and wherein the drug addiction is an alcohol, amphetamine, cocaine, or opiate addiction.
The compound of the invention may be used in combination with one or more other drugs in the treatment of diseases or conditions for which the compound of the invention have utility, where the combination of the drugs together is safer or more effective than either drug alone. Additionally, the compound of the invention may be used in combination with one or more other drugs that treat, prevent, control, ameliorate, or reduce the risk of side effects or toxicity of the compound of the invention. Such other drugs may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with the compound of the invention. Accordingly, the pharmaceutical compositions of the invention include those that contain one or more other active ingredients, in addition to the compound of the invention. The combinations may be administered as part of a unit dosage form combination product, or as a kit or treatment protocol wherein one or more additional drugs are administered in separate dosage forms as part of a treatment regimen.

The invention provides a method of treating a patient suffering from a neurodegenerative disorder selected from a cognition disorder or movement disorder, which method comprises administering to the patient the compound of the invention.

This invention also provides a method of treating a patient suffering from a psychiatric disorder, which method comprises administering to the patient the compound of the invention. Examples of psychiatric disorders that can be treated according to the invention include, but are not limited to, schizophrenia, for example of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophréniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type; anxiety disorder is selected from panic disorder; agoraphobia; a specific phobia; social phobia; obsessive-compulsive disorder; post-traumatic stress disorder; acute stress disorder; and generalized anxiety disorder.

The compound of the invention may be administered in combination with at least one neuroleptic agent (which may be a typical or an atypical antipsychotic agent) to provide
improved treatment of psychiatric disorders such as schizophrenia. The combinations, uses and methods of treatment of the invention may also provide advantages in treatment of patients who fail to respond adequately or who are resistant to other known treatments.

The invention thus provides a method of treating a patient suffering from a psychiatric disorder, such as schizophrenia, which method comprises administering to the patient the compound of the invention, either alone or as combination therapy together with at least one neuroleptic agent.

The term "neuroleptic agent" as used herein refers to drugs, which have the effect on cognition and behaviour of antipsychotic agent drugs that reduce confusion, delusions, hallucinations, and psychomotor agitation in patients with psychoses. Also known as major tranquilizers and antipsychotic drugs, neuroleptic agents include, but are not limited to: typical antipsychotic drugs, including phenothiazines, further divided into the aliphatics, piperidines, and piperazines, thioxanthenes (e.g., cisordinol), butyrophenones (e.g., haloperidol), dibenzoxazepines (e.g., loxapine), dihydroindolones (e.g., molindone), diphenylbutylpiperidines (e.g., pimozide), and atypical antipsychotic drugs, including benzisoxazoles (e.g., risperidone), sertindole, olanzapine, quetiapine, osanetant and ziprasidone.

Particularly preferred neuroleptic agents for use in the invention are sertindole, olanzapine, risperidone, quetiapine, aripiprazole, haloperidol, clozapine, ziprasidone and osanetant.

The invention further provides a method of treating a patient suffering from a cognition disorder, which method comprises administering to the patient the compound of the invention. Examples of cognition disorders that can be treated according to the invention include, but are not limited to, Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading
disorder, mathematics disorder, or a disorder of written expression; attention-
deficit/hyperactivity disorder; and age-related cognitive decline.

This invention also provides a method of treating a movement disorder in a patient, which method comprises administering to the patient the compound of the invention. Examples of movement disorders that can be treated according to the invention include, but are not limited to, Huntington's disease and dyskinesia associated with dopamine agonist therapy. This invention further provides a method of treating a movement disorder selected from Parkinson's disease and restless leg syndrome, which comprises administering to the patient the compound of the invention.

This invention also provides a method of treating a mood disorder, which method comprises administering to the patient the compound of the invention. Examples of mood disorders and mood episodes that can be treated according to the invention include, but are not limited to, major depressive episode of the mild, moderate or severe type, a manic or mixed mood episode, a hypomanic mood episode; a depressive episode with a typical features; a depressive episode with melancholic features; a depressive episode with catatonic features; a mood episode with postpartum onset; post-stroke depression; major depressive disorder; dysthymic disorder; minor depressive disorder; premenstrual dysphoric disorder; post-psychotic depressive disorder of schizophrenia; a major depressive disorder superimposed on a psychotic disorder such as delusional disorder or schizophrenia; a bipolar disorder, for example bipolar I disorder, bipolar II disorder, and cyclothymic disorder. It is understood that a mood disorder is a psychiatric disorder.

This invention further provides a method of treating a drug addiction, for example an alcohol, amphetamine, cocaine, or opiate addiction, in a patient which method comprises administering to said patient an amount of the compound of the invention effective in treating drug addiction.

The term "drug addiction", as used herein, means an abnormal desire for a drug and is generally characterized by motivational disturbances such a compulsion to take the desired drug and episodes of intense drug craving.
Drug addiction is widely considered a pathological state. The disorder of addiction involves the progression of acute drug use to the development of drug-seeking behavior, the vulnerability to relapse, and the decreased, slowed ability to respond to naturally rewarding stimuli. For example, The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) has categorized three stages of addiction: preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect. These stages are characterized, respectively, everywhere by constant cravings and preoccupation with obtaining the substance; using more of the substance than necessary to experience the intoxicating effects; and experiencing tolerance, withdrawal symptoms, and decreased motivation for normal life activities.

This invention further provides a method of treating a disorder comprising as a symptom a deficiency in attention and/or cognition in a patient which method comprises administering to said patient an amount of the compound of the invention effective in treating said disorder.

Other disorders that can be treated according to the invention are obsessive/compulsive disorders, Tourette's syndrome and other tic disorders.

As used herein, and unless otherwise indicated, a "neurodegenerative disorder or condition" refers to a disorder or condition that is caused by the dysfunction and/or death of neurons in the central nervous system. The treatment of these disorders and conditions can be facilitated by administration of an agent which prevents the dysfunction or death of neurons at risk in these disorders or conditions and/or enhances the function of damaged or healthy neurons in such a way as to compensate for the loss of function caused by the dysfunction or death of at-risk neurons. The term "neurotrophic agent" as used herein refers to a substance or agent that has some or all of these properties.

Examples of neurodegenerative disorders and conditions that can be treated according to the invention include, but are not limited to, Parkinson's disease; Huntington's disease; dementia, for example Alzheimer's disease, multi-infarct dementia, AIDS-
related dementia, and Fronto temporal Dementia; neurodegeneration associated with cerebral trauma; neurodegeneration associated with stroke, neurodegeneration associated with cerebral infarct; hypoglycemia-induced neurodegeneration; neurodegeneration associated with epileptic seizure; neurodegeneration associated with neurotoxin poisoning; and multi-system atrophy.

In one embodiment of the invention, the neurodegenerative disorder or condition involves neurodegeneration of striatal medium spiny neurons in a patient.

In a further embodiment of the invention, the neurodegenerative disorder or condition is Huntington's disease.

In another embodiment, the invention provides a method of treating a patient to reduce body fat or body weight, or to treat non-insulin demanding diabetes mellitus (NIDDM), metabolic syndrome, or glucose intolerance, comprising administering to the patient in need thereof the compound of the invention. In some embodiments, the patient is overweight or obese and the compound of the invention is administered orally. In another preferred embodiment, the method further comprising administering a second therapeutic agent to the patient, preferably an anti-obesity agent, e.g., rimonabant, orlistat, sibutramine, bromocriptine, ephedrine, leptin, pseudoephedrine, or peptide YY3-36, or analogs thereof.

The term "metabolic syndrome" as used herein refers to a constellation of conditions that place people at high risk for coronary artery disease. These conditions include type 2 diabetes, obesity, high blood pressure, and a poor lipid profile with elevated LDL ("bad") cholesterol, low HDL ("good") cholesterol, and elevated triglycerides. All of these conditions are associated with high blood insulin levels. The fundamental defect in the metabolic syndrome is insulin resistance in both adipose tissue and muscle.

All references, including publications, patent applications and patents, cited herein are hereby incorporated by reference in their entirety and to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety (to the maximum extent permitted by law).
Headings and sub-headings are used herein for convenience only, and should not be construed as limiting the invention in any way.

The use of any and all examples, or exemplary language (including "for instance", "for example", "e.g.", and "as such") in the present specification is intended merely to better illuminate the invention, and does not pose a limitation on the scope of invention unless otherwise indicated.

The citation and incorporation of patent documents herein is done for convenience only, and does not reflect any view of the validity, patentability and/or enforceability of such patent documents.

The invention includes all modifications and equivalents of the patient-matter recited in the claims appended hereto, as permitted by applicable law.

**Experimental Section**

**Preparation of the compound of the invention**

Compounds of the general formula 1a and 1b of the invention may be prepared as described in the following reaction schemes. Unless otherwise indicated, in the reaction schemes and discussion that follow, R1-R5, are as defined above.

Scheme 1 below depicts a coupling reaction between an alkyl-[4-(heteroarylmethoxy)-phenyl]-amine of formula 2 and a derivative of heterocyclic carboxylic acid of formula 3, to generate the Heterocyclic 4-alkoxyAnilide compounds of formula 1a.
where X can be hydroxyl or a suitable leaving group like e.g. chloride. This reaction is typically carried out in a solvent such as, for example, dichloromethane, optionally in the presence of a carbonate base or an amine base, at a temperature range of from about 0°C to about 200°C. Other suitable solvents include toluene, benzene, chloroform, dioxane, acetonitrile, ethyl acetate, 2-propanol and xylene. Preferably the reactants are heated under reflux in a solvent mixture of toluene and 2-propanol for a period of from about 2 hours to about 24 hours, optionally using a microwave oven.

The reaction depicted in Scheme 1 can also conveniently be carried out by using a coupling reagent like e.g. Dicyclohexyl carbodiimide (DCC) when X is a hydroxyl group. Typically, a mixture of a compound of formula 2, a compound of formula 3 and a suitable coupling reagent is stirred at room temperature for 24 hours followed by purification of the product by preparative HPLC to obtain the desired product.

Starting materials of the formula 2 can be prepared by methods described in e.g. DE 3607382 and US 5157039. Starting materials of the formula 3 are either commercially available or can be prepared by methods known in the art.

Scheme 2 below depicts a coupling reaction between an alkyl-[4-(heteroarylmethoxy)-phenyl]-carboxylic acid of formula 4 and a derivative of heterocyclic amine of formula 5, to generate the heterocyclic 4-alkoxybenzamide compounds of formula 1b.
Scheme 2

Where X can be hydroxyl or a suitable leaving group like e.g. chloride. This reaction is typically carried out in a solvent such as, for example, dichloromethane, optionally in the presence of a carbonate base or an amine base, at a temperature range of from about 0°C to about 200°C. Other suitable solvents include toluene, benzene, chloroform, dioxane, acetonitrile, ethyl acetate, 2-propanol and xylene. Preferably the reactants are heated under reflux in a solvent mixture of toluene and 2-propanol for a period of from about 2 hours to about 24 hours, optionally using a microwave oven.

The reaction depicted in Scheme 2 can also conveniently be carried out by using a coupling reagent like e.g. Dicyclohexyl carbodiimide (DCC) when X is a hydroxyl group. Typically, a mixture of a compound of formula 4, a compound of formula 5 and a suitable coupling reagent is stirred at room temperature for 24 hours followed by purification of the product by preparative HPLC to obtain the desired product.

Starting materials of the formula 4 can be prepared by methods described in e.g. US 2007155779, Alexandria Journal of Pharmaceutical Sciences (1991), 5(1), 16-20; Journal of Medicinal Chemistry (2009), 52(16), 5188-5196; and Journal of Medicinal Chemistry (1991), 34(5), 1704-7. Starting materials of the formula 5 are either commercially available or can be prepared by methods known in the art.

The invention disclosed herein is further illustrated by the following non-limiting examples.
Preparation of intermediates

General Methods

Analytical LC-MS data were obtained using one of the following method.

A PE Sciex API 150EX instrument equipped with atmospheric pressure photo ionisation and a Shimadzu LC-8A/SLC-10A LC system was used. Column: 4.6 x 30 mm Waters Symmetry C18 column with 3.5 μm particle size; Column temperature: 60 °C; Solvent system: A = water/trifluoroacetic acid (100:0.05) and B = water/acetonitrile/trifluoroacetic acid (5:95:0.035); Method: Linear gradient elution with A:B = 90:10 to 0:100 in 2.4 minutes and with a flow rate of 3.3 mL/min.

Preparative LC-MS-purification was performed on a PE Sciex API 150EX instrument with atmospheric pressure chemical ionization. Column: 50 X 20 mm YMC ODS-A with 5 μm particle size; Method: Linear gradient elution with A:B = 80:20 to 0:100 in 7 minutes and with a flow rate of 22.7 mL/minute. Fraction collection was performed by split-flow MS detection.

¹H NMR spectra were recorded at 500.13 MHz on a Bruker Avance AV500 instrument or at 250.13 MHz on a Bruker Avance DPX250 instrument. TMS was used as internal reference standard. Chemical shift values are expressed in ppm. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, h = heptet, dd = double doublet, dt = double triplet, dq = double quartet, tt = triplet of triplets, m = multiplet, br s = broad singlet and br = broad signal.

Abbreviations are in accordance with the ACS Style Guide: "The ACS Styleguide - A manual for authors and editors" Janet S. Dodd, Ed. 1997, ISBN: 0841 234620

N-(4-Hydroxy-phenyl)-formamide

\[
\begin{align*}
\text{HO} & \quad \text{NH}_2 \\
\text{HO} & \quad \text{N} \quad \text{O}
\end{align*}
\]
To a mixture of HCOOH (72 g, 1.37 mol,) and ZnO (18.3 g, 0.229 mol) was added 4-aminophenol (50 g, 0.458 mol), and then the reaction mixture was stirred at 70°C with a magnetic stirrer. The progress of the reaction was monitored by TLC (Petroleum ether: EtOAc = 1:1). After the reaction was complete, 500 mL of EtOAc was added to the reaction mixture, and ZnO was removed by filtration. The organic layer was washed with H₂O (250 mL x 4), saturated NaHCO₃ (250 mL), dried over anhydrous Na₂SO₄, and concentrated under vacuum to give 2.1 g of N-(4-Hydroxy-phenyl)-formamide as a dark red solid.

N-[4-(Quinolin-2-ylmethoxy)-phenyl]-formamide

The mixture of N-(4-Hydroxy-phenyl)-formamide (1 g, 7.3 mmol), 2-Chloromethylquinoline (1.3 g, 7.3 mmol) and K₂CO₃ (4.0 g, 14.9 mmol) in anhydrous CH₃CN (10 mL) was stirred at reflux overnight. The reaction mixture was filtered and the filtrate was concentrated under vacuum to give 2.1 g crude N-[4-(Quinolin-2-ylmethoxy)-phenyl]-formamide, which was used for next step without further purification.

Methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amine

To a solution of crude N-[4-(Quinolin-2-ylmethoxy)-phenyl]-formamide (2.1 g, 7.5 mmol) in 150 mL of anhydrous THF with was added slowly LiAlH₄ (0.86 g, 22.5 mmol) in an ice bath. After 10 hours, the reaction was quenched by 15 mL of 10% NH₄Cl and 10 mL of 40% K₂CO₃. The organic layer was dried over Na₂SO₄ and concentrated under
vacuum. The residue was purified by column chromatography on silica gel (Petroleum ether: EtOAc = 5:1) to afford 0.6 g of Methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amine.

4-(Quinolin-2-ylmethoxy)-benzoic acid

A mixture of compound N-Methoxy-N-methyl-4-(quinolin-2-ylmethoxy)-benzamide (5.0 g, 0.015 mol) in 30 mL of 2 N NaOH was stirred at reflux until TLC (Petroleum ether: EtOAc = 1:1) showed compound 4 was completely consumed. The mixture was cooled to room temperature and acidified by concentration. HCl to pH = 3. The white solid was collected by filtration and dried under vacuum to give 2.2 g of 4-(Quinolin-2-ylmethoxy)-benzoic acid.

Example 1

/V-Methyl-/V-[4-(quinolin-2-ylmethoxy)-phenyl]-isonicotinamide

The mixture of Methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amine (0.3 g, 1.14 mmol), isonicotinoyl chloride (0.3 g, 2.13 mmol) and Et₃N (0.516 g, 5.1 mmol) in 20 mL of CH₂Cl₂ was stirred at room temperature for 6 hours until TLC (Petroleum ether: EtOAc = 1:1) indicated that the starting material was almost consumed. The reaction was quenched by 20 mL of saturated NaHCO₃, diluted with 20 mL of EtOAc. The resulting organic layer was separated, washed with brine (20 mL), the organic layer was dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated under vacuum to afford 1.0 g of a yellow residue. The residue was washed with ether to afford 0.25 g of N-Methyl-N-[4-(quinolin-2-ylmethoxy)-phenyl]-isonicotinamide.
The following compounds were prepared analogously:

- 2-Pyridin-4-yl-thiazole-4-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide
- 2-Pyridin-3-yl-thiazole-4-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide
- 5-Pyridin-2-yl-1H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide
- 5-Pyridin-3-yl-1H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide
- 5-Pyridin-4-yl-1H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide
- Benzothiazole-6-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide

Example 2

N-Methyl-N-pyridin-4-yl-4-(quinolin-2-ylmethoxy)-benzamide

A mixture of 4-(Quinolin-2-ylmethoxy)-benzoic acid (0.465 g, 1 mmol), Methyl-pyridin-4-yl-amine (0.108 g, 1 mmol), HBTU (0.76 g, 2 mmol), DIPEA (0.684 g, 5.3 mmol) in anhydrous DMF (5 mL) was stirred at room temperature overnight. The mixture was concentrated under vacuum and the residue was pre-purified by column chromatography on silica gel (Petroleum ether: EtOAc = 1:1) to give after combined another batch prepared from 1.5 g of 4-(Quinolin-2-ylmethoxy)-benzoic acid, a total of 1.2 g of N-Methyl-N-pyridin-4-yl-4-(quinolin-2-ylmethoxy)-benzamide.

The following compounds were prepared analogously:

- N-(benzo[d]thiazol-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide
- N-(benzo[d]oxazol-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide
- N-(imidazo[1,2-a]pyridin-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide
- N-Methyl-4-(quinolin-2-ylmethoxy)-N-[1,2,4]triazolo[1,5-a]pyridin-6-yl-benzamide
Example 3

N-methyl-N-(4-((1-methyl-1H-benzo[d]imidazol-2-yl)methoxy)phenyl)benzo[d]thiazole-6-carboxamide

N-(4-hydroxyphenyl)-N-methylbenzo[d]thiazole-6-carboxamide (200 mg, 0.7 mmol), 2-(chloromethyl)-1-methyl-1H-benzo[d]imidazole (160 mg, 0.77 mmol), cesium carbonate (460 mg, 1.4 mmol) and potassium iodide (230 mg, 1.4 mmol) were stirred in acetone (30 mL, 400 mmol) and heated at reflux for 21 hours. The cooled reaction was mixed with 100 mL H2O and extracted with 1 X 100 mL EtOAc, 2 X 50 mL EtOAc, and the combined organic phases were dried over MgSO4, filtered and the solvent removed in vacuum. The extract was purified by flash chromatography on a 24 g silica column (eluent: 100% n-heptane to 100% EtOAc) to yield the product (289 mg, 96%) as a white solid.

HRMS: (M+H+: C24H21N4O2S) Calculated: 429.1379, Found: 429.1380, deviation: 0.001 ppm.

1H NMR: (500 MHz, DMSO) δ 9.41 (s, 1H), 8.15 (s, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.29 (t, J = 7.6 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 5.33 (s, 2H), 3.79 (s, 3H), 3.36 (s, 3H).

<table>
<thead>
<tr>
<th>CHEMICAL NAME</th>
<th>RETENTION TIME</th>
<th>UV PURITY</th>
<th>ELSD PURITY</th>
<th>MS (M+H+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Methyl-N-pyridin-4-yl-4-(quinolin-2-ylmethoxy)benzamide</td>
<td>0.66</td>
<td>100</td>
<td>100</td>
<td>370.15</td>
</tr>
<tr>
<td>N-(benzo[d]thiazol-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide</td>
<td>2.77</td>
<td>99.48</td>
<td>100</td>
<td>426.12</td>
</tr>
<tr>
<td>N-(benzo[d]oxazol-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide</td>
<td>2.78</td>
<td>95.71</td>
<td>93.3</td>
<td>410.14</td>
</tr>
<tr>
<td>N-(imidazo[1,2-a]pyridin-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide</td>
<td>2.11</td>
<td>96.68</td>
<td>100</td>
<td>409.16</td>
</tr>
<tr>
<td>N-Methyl-4-(quinolin-2-ylmethoxy)-N-[1,2,4]triazolo[1,5-a]pyridin-6-yl-benzamide</td>
<td>1.03</td>
<td>99.3</td>
<td>100</td>
<td>410.15</td>
</tr>
</tbody>
</table>
Table 1. Analytical chemical characterization of exemplified compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Active PDE10A</th>
<th>PDE10A</th>
<th>% Inhibition</th>
<th>IC50 (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-(1,2,4)triazolo[1,5-a]pyridin-7-yl)-N-methyl-4-(quinolin-2-y lmethoxy)be nzamide</td>
<td>2.55</td>
<td>97.78</td>
<td>100</td>
<td>4.10.15</td>
</tr>
<tr>
<td>2-Pyridin-3-yl-thiazole-4-carboxylic acid methyl-[4-(quinolin-2-y lmethoxy)-phenyl]-amide</td>
<td>0.89</td>
<td>88.98</td>
<td>100</td>
<td>453.13</td>
</tr>
<tr>
<td>2-Pyridin-4-yl-thiazole-4-carboxylic acid methyl-[4-(quinolin-2-y lmethoxy)-phenyl]-amide</td>
<td>0.77</td>
<td>100</td>
<td>100</td>
<td>453.13</td>
</tr>
<tr>
<td>2-Pyridin-3-yl-thiazole-4-carboxylic acid methyl-[4-(quinolin-2-y lmethoxy)-phenyl]-amide</td>
<td>0.87</td>
<td>96</td>
<td>100</td>
<td>453.13</td>
</tr>
<tr>
<td>5-Pyridin-2-yl-1 H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-y lmethoxy)-phenyl]-amide</td>
<td>0.8</td>
<td>93.26</td>
<td>100</td>
<td>436.17</td>
</tr>
<tr>
<td>5-Pyridin-3-yl-1 H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-y lmethoxy)-phenyl]-amide</td>
<td>0.73</td>
<td>93.98</td>
<td>100</td>
<td>436.17</td>
</tr>
<tr>
<td>5-Pyridin-4-yl-1 H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-y lmethoxy)-phenyl]-amide</td>
<td>0.7</td>
<td>99.36</td>
<td>100</td>
<td>436.17</td>
</tr>
<tr>
<td>Benzothiazole-6-carboxylic acid methyl-[4-(quinolin-2-y lmethoxy)-phenyl]-amide</td>
<td>0.6</td>
<td>97.7</td>
<td>99.7</td>
<td>426.12</td>
</tr>
<tr>
<td>Benzothiazole-6-carboxylic acid methyl-[4-(1-methyl-1H-benzoimidazol-2-y lmethoxy)-phenyl]-amide</td>
<td>0.96</td>
<td>99.5</td>
<td>100</td>
<td>429.13</td>
</tr>
<tr>
<td>N-Methyl-N-[4-(quinolin-2-y lmethoxy)-phenyl]-isonicotinamide</td>
<td>0.69</td>
<td>96</td>
<td>100</td>
<td>370.15</td>
</tr>
</tbody>
</table>

Pharmacological Testing

5 PDE10A enzyme

Active PDE10A enzyme is prepared in a number of ways for use in PDE assays (Loughney, K. et al. Gene 1999, 234, 109-1 17; Fujishige, K. et al. Eur J Biochem. 1999, 266, 1118-1 127 and Soderling, S. et al. Proc. Natl. Acad. Sci. 1999, 96, 7071-7076). PDE10A can be expressed as full-length proteins or as truncated proteins, as long as they express the catalytic domain. PDE10A can be prepared in different cell types, for example insect cells or E. coli.

In the context of the present invention the catalytically active PDE10A enzymes were prepared the following way: The catalytic domain of human PDE10A (amino acids 440-779 from the sequence with accession number NP 006652) was amplified from total human brain total RNA by standard RT-PCR and cloned into the BamH1 and Xho1 sites of the pET28a vector (Novagen). Expression in coli was performed according to standard protocols. Briefly, the expression plasmids were transformed into the
BL21 (DE3) E. coli strain, and 50 ml cultures inoculated with the cells allowed to grow to an OD600 of 0.4-0.6 before protein expression was induced with 0.5 mM IPTG. Following induction, the cells were incubated overnight at room temperature, after which the cells were collected by centrifugation. Cells expressing PDE10A were resuspended in 12 mL (50 mM TRIS-HCl-pH 8.0, 1 mM MgCl2 and protease inhibitors). The cells were lysed by sonication, and after all cells are lysed, TritonX100 is added according to Novagen protocols. PDE10A was partially purified on Q sepharose and the most active fractions were pooled.

**PDE10A inhibition assay**

In the context of the invention the assay was performed in 60 uL assay buffer (50 mM HEPES pH 7.6; 10 mM MgCl2; 0.02% Tween20) containing enough PDE10A to convert 20-25% of 10 nM 3H-cAMP and varying amounts of inhibitors. Reactions were initiated by addition of the cyclic nucleotide substrate. Following 1 hour incubation at room temperature the reactions were terminated by addition of 15 uL 8 mg/mL yttrium silicate SPA beads (Amersham). The beads were allowed to settle for one hr in the dark before the plates were counted in a Wallac 1450 Microbeta counter. IC50 values were calculated by non linear regression using XLfit (IDBS).

Results of the experiments showed that the tested compounds of the invention inhibit the PDE10A enzyme with IC50 value between around 15 nM to 400nM, see Table 2:

<table>
<thead>
<tr>
<th>Compound</th>
<th>PDE10A IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Methyl-N-pyridin-4-yl-4-(quinolin-2-ylmethoxy)-benzamide</td>
<td>180</td>
</tr>
<tr>
<td>N-(benzo[d]thiazol-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide</td>
<td>15</td>
</tr>
<tr>
<td>N-(benzo[d]oxazol-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide</td>
<td>93</td>
</tr>
<tr>
<td>N-(imidazo[1,2-a]pyridin-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide</td>
<td>130</td>
</tr>
<tr>
<td>N-Methyl-4-(quinolin-2-ylmethoxy)-N-[1,2,4]triazolo[1,5-a]pyridin-6-yl-benzamide</td>
<td>240</td>
</tr>
<tr>
<td>N-[1,2,4]triazolo[1,5-a]pyridin-7-yl]-N-methyl-4-(quinolin-2-ylmethoxy)benzamide</td>
<td>400</td>
</tr>
<tr>
<td>2-Pyridin-3-yl-thiazole-4-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide</td>
<td>170</td>
</tr>
</tbody>
</table>
2-Pyridin-4-yl-thiazole-4-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide

2-Pyridin-3-yl-thiazole-4-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide

5-Pyridin-2-yl-1H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide

5-Pyridin-3-yl-1H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide

5-Pyridin-4-yl-1H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide

Benzothiazole-6-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide

Benzothiazole-6-carboxylic acid methyl-[4-(1-methyl-1H-benzoimidazol-2-ylmethoxy)-phenyl]-anriide

N-Methyl-N-[4-(quinolin-2-ylmethoxy)-phenyl]-isonicotinamide

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phencyclidine (PCP) induced hyperactivity</td>
<td></td>
</tr>
</tbody>
</table>

Male mice (NMRI, Charles River) weighing 20-25g were used. Eight mice were used in each group receiving the test compound (5 mg/kg) plus PCP (2.3 mg/kg) including the parallel control groups receiving the vehicle of the test compound plus PCP or vehicle injections only. The injection volume was 10 ml/kg. The experiment was made in normal light conditions in an undisturbed room. The test substance was injected per oss 60 min before injection of PCP, which is administered subcutaneous.

Immediately after injection of PCP the mice were placed individually in special designed test cage (20 cm x 32 cm). The activity was measured by 5X8 infrared light sources and photocells spaced by 4 cm. The light beams cross the cage 1.8 cm above the bottom of the cage. Recording of a motility count requires interruption of adjacent light beams, thus avoiding counts induced by stationary movements of the mice.

Motility was recorded in 5 min intervals for a period of 1 hour. The drug effect was calculated on the total counts during the 1 hour behavioral test period in the following manner:

The mean motility induced by vehicle treatment in the absence of PCP was used as baseline. The 100 per cent effect of PCP was accordingly calculated to be total motility...
counts minus baseline. The response in groups receiving test compound was thus
determined by the total motility counts minus baseline, expressed in per cent of the
similar result recorded in the parallel PCP control group. The per cent responses were
converted to per cent reversal of the PCP induced hyperactivity.

Results of the experiments showed that compounds of the invention are in vivo active
compounds that reverses the PCP induced hyperactivity for example N-Methyl-N-
pyridin-4-yl-4-(quinolin-2-ylmethoxy)-benzamide has an ED50 of 10 mg/kg and the
compound N-Methyl-N-[4-(quinolin-2-ylmethoxy)-phenyl]-isonicotinamide has an ED50
of 61 mg/kg.
What is claimed:

1. The compound

\[
het_1 - O - \text{Ph} - L - het_2
\]

wherein \( het_1 \) is selected from the group consisting of

and wherein \( \ast \) denotes the attachment point, and

\( het_2 \) is selected from the group consisting of

and wherein \( \ast \) denotes the attachment point, and

wherein further \( L \) is a linker selected from the group consisting of
and wherein \( R_1 \) is selected from the group consisting of \( \text{C}_1-\text{C}_6 \) alkyl such as methyl, ethyl, 1-propyl, 2-propyl, isobutyl, n-butyl, sec-butyl or tert-butyl; \( \text{C}_1-\text{C}_6 \) alkyl(\( \text{C}_3-\text{C}_8 \))cycloalkyl such as cyclopropylmethyl, and wherein * denotes the attachment point, as well as tautomers and pharmaceutically acceptable acid addition salts thereof.

2. The compound of claim 1 wherein HET-2 is selected from the group consisting of

3. The compound of any of claims 1 or 2 wherein \( R_1 \) in the linker \( L \) is \( \text{CH}_3 \).

4. The compound of claim 1 selected from the group consisting of N-Methyl-N-pyridin-4-yl-4-(quinolin-2-ylmethoxy)-benzamide, N-(benzo[d]thiazol-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)Benzamide, N-(benzo[d]oxazol-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)Benzamide, N-(imidazo[1,2-a]pyridin-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)Benzamide, N-Methyl-4-(quinolin-2-ylmethoxy)-N-[1,2,4]triazolo[1,5-a]pyridin-6-yl-benzamide, N-(([1,2,4]triazolo[1,5-a]pyridin-7-yl)-N-methyl-4-(quinolin-2-ylmethoxy)Benzamide, 2-Pyridin-3-yl-thiazole-4-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, 2-Pyridin-4-yl-thiazole-4-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, 2-Pyridin-3-yl-thiazole-4-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, 5-Pyridin-2-yl-1 H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, 5-Pyridin-3-yl-1 H-pyrazole-3-carboxylic acid methyl-
[4-(quinolin-2-ylmethoxy)-phenyl]-annide, 5-Pyridin-4-yl-1 H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, Benzothiazole-6-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, Benzothiazole-6-carboxylic acid methyl-[4-(1-methyl-1H-benzoimidazol-2-ylmethoxy)-phenyl]-amide, and N-Methyl-N-[4-(quinolin-2-ylmethoxy)-phenyl]-isonicotinamide.

5. The compound of claim 1 selected from the group consisting of N-(benzo[d]thiazol-6-yl)-N-methyl-4-(quinolin-2-ylmethoxy)benzamide, 5-Pyridin-3-yl-1 H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, 5-Pyridin-4-yl-1 H-pyrazole-3-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide, and benzothiazole-6-carboxylic acid methyl-[4-(quinolin-2-ylmethoxy)-phenyl]-amide.

6. The compound of any of claims 1 to 5 for use as a medicament.

7. The compound of any of claims 1 to 5 for use in the treatment of a neurodegenerative or psychiatric disorder, alone or in combination with one or more neuroleptic agents selected from the group consisting of sertindole, olanzapine, risperidone, quetiapine, aripiprazole, haloperidol, clozapine, ziprasidone and osanetant, wherein the neurodegenerative disorder is selected from the group consisting of Alzheimer’s disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington’s disease or Parkinson’s disease, or AIDS; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; and age-related cognitive decline, and the psychiatric disorder is selected from the group consisting of schizophrenia, for example the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophreniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; bipolar disorder, for example bipolar I disorder, bipolar II disorder, and cyclothymic disorder; substance-induced psychotic disorder, for example psychosis induced by...
alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type.

8. Use of the compound of any of claims 1 to 5 for the preparation of a medicament for the treatment of a neurodegenerative or psychiatric disorder, wherein the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; and age-related cognitive decline, and the psychiatric disorder is selected from the group consisting of schizophrenia, for example of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophreniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; bipolar disorder, for example bipolar I disorder, bipolar II disorder, and cyclothymic disorder; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type.

9. A method of treating a patient suffering from a neurodegenerative or psychiatric disorder, wherein the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; and age-related cognitive decline, and the
psychiatric disorder is selected from the group consisting of schizophrenia, for example of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophreniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; bipolar disorder, for example bipolar I disorder, bipolar II disorder, and cyclothymic disorder; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type; which method comprises administering an effective amount of a compound of any of claims 1 and 2 to a patient, alone or in combination with one or more neuroleptic agents selected from sertindole, olanzapine, risperidone, quetiapine, aripiprazole, haloperidol, clozapine, ziprasidone and osanetant.

10. A pharmaceutical composition comprising the compound of any of claims 1 to 5, and one or more pharmaceutically acceptable carriers, diluents and excipients.

11. Use of the compound of any of claims 1 and 2 and a further compound selected from the group consisting of sertindole, olanzapine, risperidone, quetiapine, aripiprazole, haloperidol, clozapine, ziprasidone and osanetant for the preparation of a medicament for the treatment of a neurodegenerative or psychiatric disorder, wherein the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; and age-related cognitive decline, and the psychiatric disorder is selected from the group consisting of schizophrenia, for example of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophreniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional
disorder; bipolar disorder, for example bipolar I disorder, bipolar II disorder, and cyclothymic disorder; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type.

12. The compound of any of claims 1-5 and a further compound selected from the group consisting of sertindole, olanzapine, risperidone, quetiapine, aripiprazole, haloperidol, clozapine, ziprasidone and osanetant as a combined preparation for simultaneous, separate or sequential use in the treatment of a neurodegenerative or psychiatric disorder, wherein the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; and age-related cognitive decline, and the psychiatric disorder is selected from the group consisting of schizophrenia, for example of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; bipolar disorder, for example bipolar I disorder, bipolar II disorder, and cyclothymic disorder; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type.

13. The compound of any of claims 1 to 5 for the treatment of a neurodegenerative or psychiatric disorder, wherein the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or
Parkinson’s disease, or AIDS-related dementia; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; and age-related cognitive decline, and the psychiatric disorder is selected from the group consisting of schizophrenia, for example of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophreniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; bipolar disorder, for example bipolar I disorder, bipolar II disorder, and cyclothymic disorder; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type.
**INTERNATIONAL SEARCH REPORT**

**International application No**

PCT/DK2011/05Q257

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D401/12 C07D401/14 C07D403/12 C07D413/12 C07D417/12 C07D417/14 C07D471/O4 A61K31/4427 A61K31/4178 A61P25/18

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

**Electronic data base consulted during the international search (name of data base and, where practical, search terms used)**

EPO-Internal , WPI Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

Further documents are listed in the continuation of Box C.

**See patent family annex.**

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "A" document member of the same patent family

**Date of the actual completion of the international search**

4 August 2011

**Date of mailing of the international search report**

12/08/2011

**Name and mailing address of the ISA/**

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Fax: (+31-70) 340-3016

**Authorized officer**

Gavi liu, Daniel a
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wo 2009152825 Al</td>
<td>23-12-2009</td>
<td>AR 072199 Al</td>
<td>11-08-20 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2009259209 Al</td>
<td>23-12-2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2728335 Al</td>
<td>23-12-2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 102124002 A</td>
<td>13-07-20 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2318394 Al</td>
<td>11-05-20 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20110020845 A</td>
<td>03-03-20 11</td>
</tr>
<tr>
<td>Wo 2009036766 Al</td>
<td>26-03-2009</td>
<td>AR 068466 Al</td>
<td>18-11-2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2691474 Al</td>
<td>26-03-2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 101743239 A</td>
<td>16-06-20 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2203438 Al</td>
<td>07-07-20 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2010539195 A</td>
<td>16-12-20 10</td>
</tr>
<tr>
<td>Wo 2006098912 Al</td>
<td>21-09-2006</td>
<td>AU 2006223508 Al</td>
<td>21-09-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2600860 Al</td>
<td>21-09-2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 101137376 A</td>
<td>05-03-2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2008537930 A</td>
<td>02-10-2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2009197883 Al</td>
<td>06-08-2009</td>
</tr>
</tbody>
</table>