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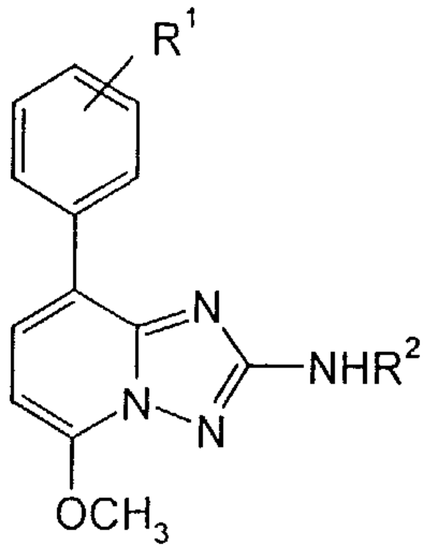
(54) Titre : DERIVES DE 5-METHOXY-8-ARYL-[1,2,4] TRIAZOLO [1,5-A] PYRIDINE EN TANT QU'ANTAGONISTES DU RECEPTEUR D'ADENOSINE

(54) Title: 5-METHOXY-8-ARYL-[1,2,4] TRIAZOLO [1,5-A] PYRIDINE DERIVATIVES AS ADENOSINE RECEPTOR ANTAGONISTS



(I)

(57) Abrégé/Abstract:
The present application relates to compounds of the formula (I) wherein R^1 is hydrogen, halogen or lower alkoxy; R^2 is hydrogen or is C(O)- lower alkyl or -C(0)-phenyl, wherein the phenyl ring is unsubstituted or substituted by one or two substituents, selected from the group, consisting of halogen, lower alkoxy or trifluoromethyl, or is -C(O)-furanyl or -C(O)- thiophenyl, wherein the rings are unsubstituted or substituted by halogen; and to their pharmaceutically acceptable salts. The compounds may be used in the treatment of diseases associated with the adenosine A2 receptor.

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(54) Title: 5-METHOXY-8-ARYL-[1,2,4] TRIAZOLO [1,5-A] PYRIDINE DERIVATIVES AS ADENOSINE RECEPTOR ANTAGONISTS

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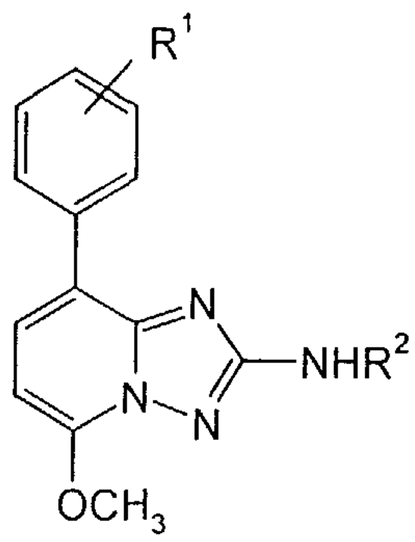
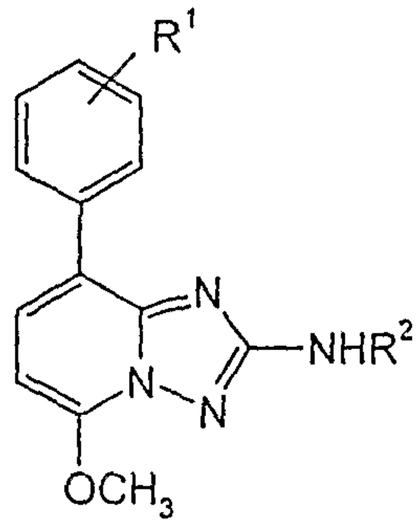


(I)

(57) Abstract: The present application relates to compounds of the formula (I) wherein R^1 is hydrogen, halogen or lower alkoxy; R^2 is hydrogen or is C(O)- lower alkyl or -C(0)-phenyl, wherein the phenyl ring is unsubstituted or substituted by one or two substituents, selected from the group, consisting of halogen, lower alkoxy or trifluoromethyl, or is -C(O)-furanyl or -C(O)- thiophenyl, wherein the rings are unsubstituted or substituted by halogen; and to their pharmaceutically acceptable salts. The compounds may be used in the treatment of diseases associated with the adenosine A2 receptor.

5-Methoxy-8-aryl-[1,2,4]triazolo[1,5-a]pyridine derivatives

The present invention relates to compounds of the general formula



I

wherein

R^1 is hydrogen, halogen or lower alkoxy;

R^2 is hydrogen or is –C(O)-lower alkyl or –C(O)-phenyl, wherein the phenyl ring is unsubstituted or substituted by one or two substituents, selected from the group, consisting of halogen, lower alkyl, lower alkoxy or trifluoromethyl,
or is –C(O)-furanyl or –C(O)-thiophenyl, wherein the rings are unsubstituted or substituted by halogen;

and to their pharmaceutically acceptable salts.

It has surprisingly been found that the compounds of general formula I are adenosine receptor ligands.

Adenosine modulates a wide range of physiological functions by interacting with specific cell surface receptors. The potential of adenosine receptors as drug targets was first reviewed in 1982. Adenosine is related both structurally and metabolically to the bioactive nucleotides adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP) and cyclic adenosine monophosphate (cAMP); to the biochemical methylating agent S-adenosyl-L-methione (SAM); and structurally to the coenzymes NAD, FAD and coenzym A; and to RNA. Together adenosine and these related compounds are important in the regulation of many aspects of cellular metabolism and in the modulation of different central nervous system activities.

The receptors for adenosine have been classified as A_1, A_{2A}, A_{2B} and A_3 receptors, belonging to the family of G protein-coupled receptors. Activation of adenosine receptors by adenosine initiates signal transduction mechanism. These mechanisms are dependent on the receptor associated G protein. Each of the adenosine receptor subtyps has been classically characterised by the adenylate cyclase effector system, which utilises cAMP as a second messenger. The A_1 and A_3 receptors, coupled with G_i proteins inhibit adenylate cyclase, leading to a decrease in cellular cAMP levels, while A_{2A} and A_{2B} receptors couple to G_s proteins and activate adenylate cyclase, leading to an increase in cellular cAMP levels. It is known that the A_1 receptor system include the activation of phospholipase C and modulation of both potassium and calcium ion channels. The A_3 subtype, in addition to its association with adenylate cyclase, also stimulates phospholipase C and so activates calcium ion channels.

The A_1 receptor (326-328 amino acids) was cloned from various species (canine, human, rat, dog, chick, bovine, guinea-pig) with 90–95% sequence identify among the mammalian species. The A_{2A} receptor (409-412 amino acids) was cloned from canine, rat, human, guinea pig and mouse. The A_{2B} receptor (332 amino acids) was cloned from human and mouse with 45% homology of human A_{2B} with human A_1 and A_{2A} receptors. The A_3 receptor (317-320 amino acids) was cloned from human, rat, dog, rabbit and sheep.

The A_1 and A_{2A} receptor subtypes are proposed to play complementary roles in adenosine's regulation of the energy supply. Adenosine, which is a metabolic product of ATP, diffuses from the cell and acts locally to activate adenosine receptors to decrease the oxygen demand (A_1) or increase the oxygen supply (A_{2A}) and so reinstate the balance of energy supply versus demand within the tissue. The actions of both subtyps is to increase the amount of available oxygen to tissue and to protect cells against damage caused by a short term imbalance of oxygen. One of the important functions of endogenous adenosine is preventing damage during traumas such as hypoxia, ischaemia, hypotension and seizure activity.

Furthermore, it is known that the binding of the adenosine receptor agonist to mast cells expressing the rat A_3 receptor resulted in increased inositol triphosphate and intracellular calcium concentrations, which potentiated antigen induced secretion of inflammatory mediators. Therefore, the A_3 receptor plays a role in mediating asthmatic attacks and other allergic responses.

Adenosine is also a neuromodulator, possessing global importance in the modulation of molecular mechanisms underlying many aspects of physiological brain function by mediating central inhibitory effects. An increase in neurotransmitter release follows traumas such as hypoxia, ischaemia and seizures. These neurotransmitters are ultimately

responsible for neural degeneration and neural death, which causes brain damage or death of the individual. The adenosine A_1 agonists which mimic the central inhibitory effects of adenosine may therefore be useful as neuroprotective agents. Adenosine has been proposed as an endogenous anticonvulsant agent, inhibiting glutamate release from excitory neurons and inhibiting neuronal firing. Adenosine agonists therefore may be used as antiepileptic agents. Adenosine antagonists stimulate the activity of the CNS and have proven to be effective as cognition enhancers. Selective A_{2a}-antagonists have therapeutic potential in the treatment of various forms of dementia, for example in Alzheimer's disease and are useful as neuroprotective agents. Adenosine A_2- receptor antagonists inhibit the release of dopamine from central synaptic terminals and reduce locomotor activity and consequently improve Parkinsonian symptoms. The central activities of adenosine are also implicated in the molecular mechanism underlying sedation, hypnosis, schizophrenia, anxiety, pain, respiration, depression and substance abuse. Drugs acting at adenosine receptors therefore have also therapeutic potential as sedatives, muscle relaxants, antipsychotics, anxiolytics, analgesics, respiratory stimulants and antidepressants.

An important role for adenosine in the cardiovascular system is as a cardioprotective agent. Levels of endogenous adenosine increase in response to ischaemia and hypoxia, and protect cardiac tissue during and after trauma (preconditioning). Adenosine agonists thus have potential as cardioprotective agents.

Adenosine modulates many aspects of renal function, including renin release, glomerular filtration rate and renal blood flow. Compounds, which antagonise the renal affects of adenosine, have potential as renal protective agents. Furthermore, adenosine A_3 and/or A_{2B} antagonists may be useful in the treatment of asthma and other allergic responses.

Numerous documents describe the current knowledge on adenosine receptors, for example the following publications:

Bioorganic & Medicinal Chemistry, 6, (1998), 619-641,
Bioorganic & Medicinal Chemistry, 6, (1998), 707-719,
J. Med. Chem., (1998), 41, 2835-2845,
J. Med. Chem., (1998), 41, 3186-3201,
J. Med. Chem., (1998), 41, 2126-2133,
J. Med. Chem., (1999), 42, 706-721,
J. Med. Chem., (1996), 39, 1164-1171,
Arch. Pharm. Med. Chem., (1999), 332, 39-41.

Objects of the present invention are compounds of formula I and their pharmaceutically acceptable salts per se and as pharmaceutically active substances, their

manufacture, medicaments based on a compound in accordance with the invention and their production as well as the use of compounds of formula I in the control or prevention of illnesses based on the modulation of the adenosine system, such as Alzheimer's disease, Parkinson's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse. Furthermore, compounds of the present invention may be useful as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardiaprotective agents.The most preferred indications in accordance with the present invention are those, which base on the A_{2A} receptor antagonistic activity and which include disorders of the central nervous system, for example the treatment or prevention of certain depressive disorders, neuroprotection and Parkinson's disease.

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

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "lower alkoxy" denotes a group wherein the alkyl residues is as defined above, and which is attached via an oxygen atom.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

Compounds of formula I of the present invention, wherein R^2 is –C(O)-phenyl, substituted by halogen, are preferred. For example the following compounds:

4-Fluoro-N-(5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-benzamide,
4-bromo-N-(5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-benzamide,
4-bromo-N-[5-methoxy-8-(3-methoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-benzamide,
4-fluoro-N-[8-(4-fluoro-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-benzamide or
4-fluoro-N-[5-methoxy-8-(3-methoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-benzamide.

Further preferred are compounds, wherein R^2 is –C(O)-furanyl, substituted by halogen. Examples of this group are the following compounds:

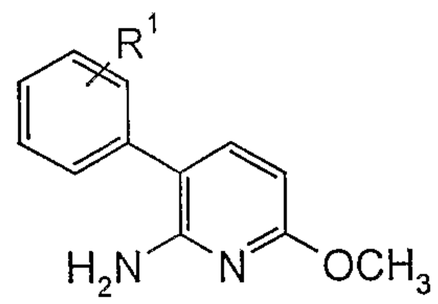
5-Bromo-furan-2-carboxylic acid [8-(3-fluoro-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide or
5-bromo-furan-2-carboxylic acid [5-methoxy-8-(3-methoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide.

Compounds of formula I of the present invention, wherein R^2 is –C(O)-thiophenyl, are also preferred. For example the following compound:

Thiophene-2-carboxylic acid [5-methoxy-8-(3-methoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide

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

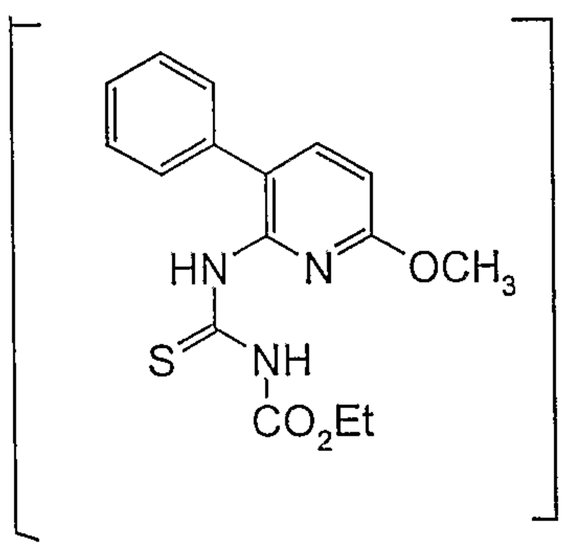
a) reacting a compound of formula



II

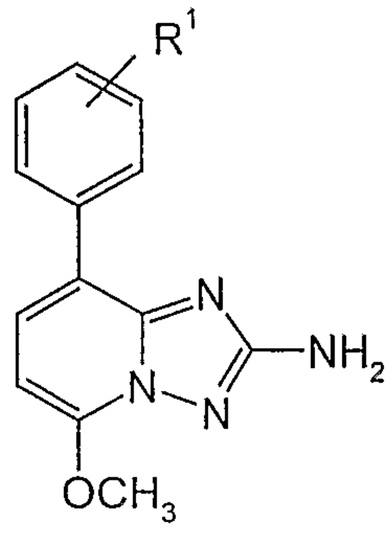
with ethoxycarbonyl isothiocyanate

to a compound of formula



III

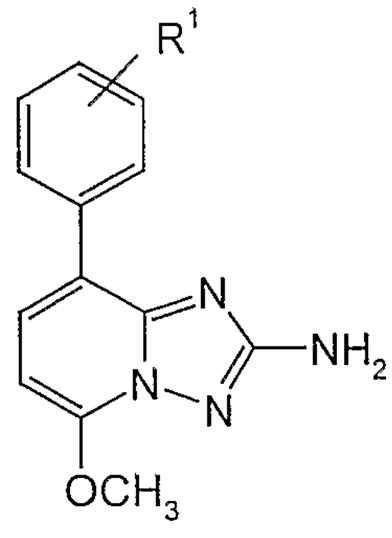
and cyclizing the compound of formula III in the presence of hydroxylamine to a compound of formula



Ia

wherein R^1 has the significance given above, or

b) reacting a compound of formula

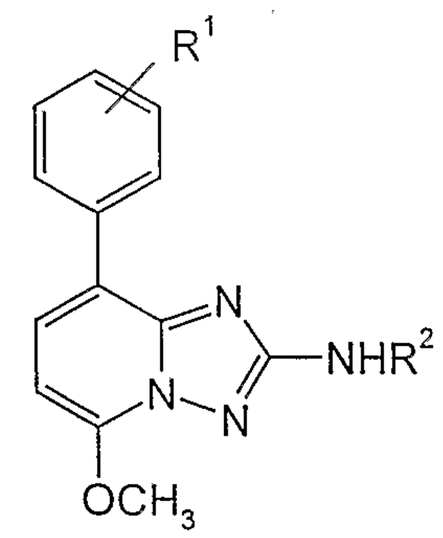


Ia

with a compound of formula

R^2Cl

to give a compound of formula



I

wherein R^1 and R^2 are as defined above.

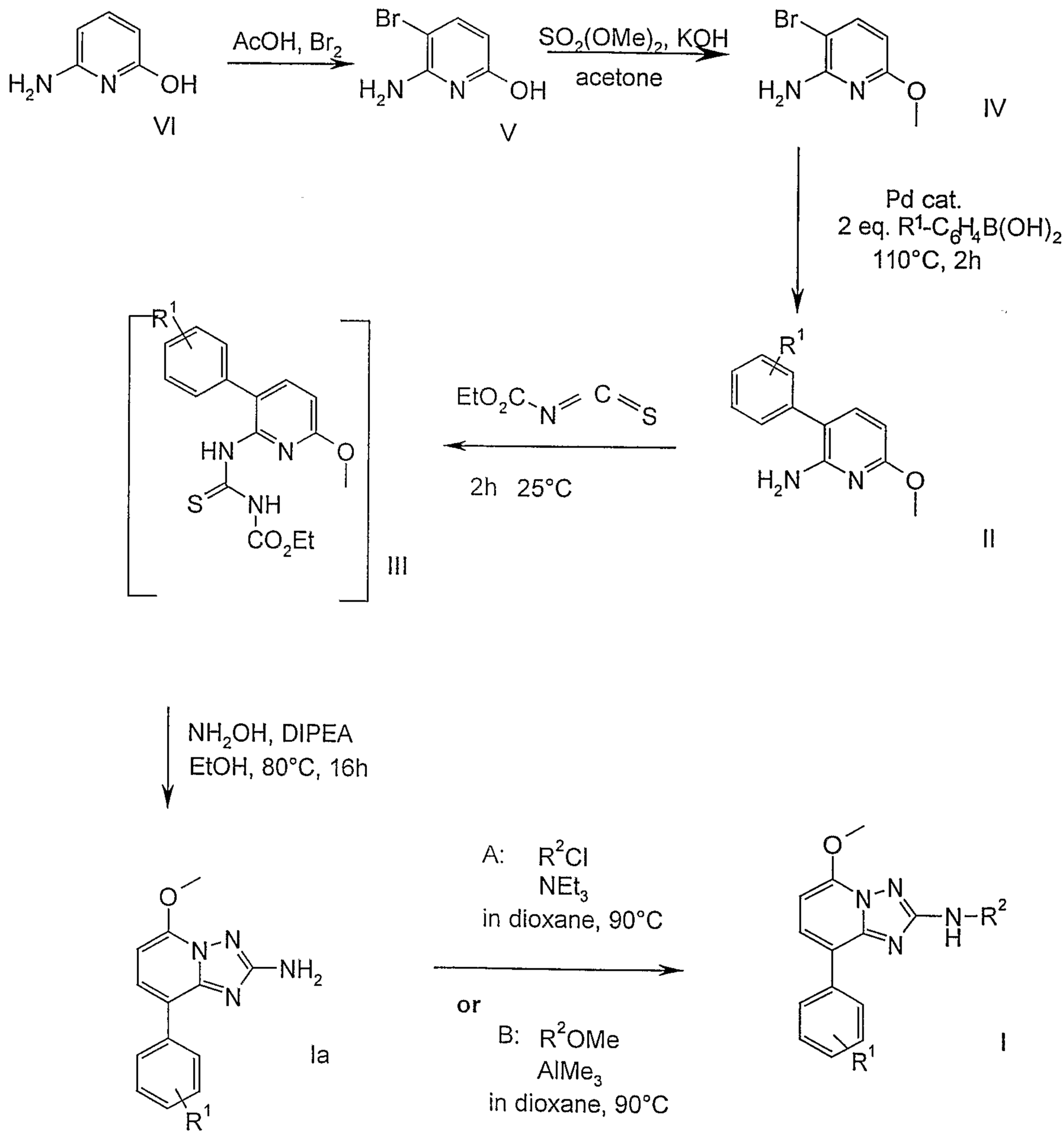
and

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

In Examples 1 - 42 and in the following scheme 1 the preparation of compounds of formula I is described in more detail.

DIPEA in scheme 1 means N-ethyldiisopropyl-amine.

Scheme 1



In accordance with scheme 1, the compound of formula V (6-amino-5-bromo-pyridin-2-ol) may be prepared as described in *Kelly, T. R.; Jagoe, C. T.; Gu, Z. Tetrahedron Letters 1991, 32, 4263-4266)* as follows: To a solution of 6-amino-pyridin-2-ol in acetic acid at room temperature is added bromine and stirred for 15 min. The mixture is diluted with

water and the precipitate is filtered off. The filtrate is extracted and the combined organic layers are dried and evaporated to dryness. Then a suspension of 6-amino-5-bromo-pyridin-2-ol is treated with KOH pellets and dimethylsulfate. The mixture is stirred for 4 h at room temperature and evaporated to dryness. The residue is purified and 3-bromo-6-methoxy-pyridin-2-yl-amine (IV) is obtained. Furthermore, a mixture of 3-bromo-6-methoxy-pyridin-2-yl-amine, phenylboronic acid (wherein the phenyl ring may be substituted by R^1), Na_2CO_3 and dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium II)dichloromethane adduct in dioxane is heated to 110 °C for 2 h. The mixture is concentrated, diluted Na_2CO_3 aq. is added and extracted. The combined organic phases are dried and evaporated. The residue is purified to yield the corresponding compound of formula II, for example 6-methoxy-3-phenyl-pyridin-2-yl-amine. A mixture 6-methoxy-3-phenyl-pyridin-2-yl-amine (II) and ethoxycarbonyl isothiocyanate is stirred at room temperature for 2 h and afterwards evaporated to dryness. The obtained compound of formula III is then treated with a mixture of hydroxylamine hydrochloride and N-ethyldiisopropylamine (DIPEA). The mixture is heated to 80 °C for 16 h, concentrated to dryness, taken up in water and extracted with diethyl ether. The combined organic phases are dried and evaporated to yield, for example, 5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl-amine (Ia). A mixture of 5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl-amine and a compound of formula R^2Cl, for example 3-fluorophenyl carboxylic acid chloride, and NEt_3 in dioxane is heated to 90 °C for 16 h. The mixture is purified to give a compound of formula I, for example 3-fluoro-N-(5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-benzamide.

The salt formation is effected at room temperatures in accordance with methods which are known per se and which are familiar to any person skilled in the art. Not only salts with inorganic acids, but also salts with organic acids came into consideration. Hydrochlorides, hydrobromides, sulphates, nitrates, citrate, acetates, maleates, succinates, methan-sulphonates, p-toluenesulphonates and the like are examples of such salts.

The compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. Specifically, it has been found that the compounds of the present invention are adenosine receptor ligands.

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

Human adenosine A_{2A} receptor

The human adenosine A_{2A} receptor was recombinantly expressed in chinese hamster ovary (CHO) cells using the semliki forest virus expression system. Cells were harvested, washed twice by centrifugation, homogenised and again washed by centrifugation. The

final washed membrane pellet was suspended in a Tris (50 mM) buffer containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$ and 10 mM $MgCl_2$ (pH 7.4) (buffer A). The [^{3}H]-SCH-58261 (Dionisotti et al., 1997, Br. J. Pharmacol. 121, 353) binding assay was carried out in 96-well plates in the presence of 2.5 µg of membrane protein, 0.5 mg of Ysi-poly-l-lysine SPA beads and 0.1 U adenosine deaminase in a final volume of 200 µl of buffer A. Non-specific binding was defined using xanthine amine congener (XAC; 2 µM). Compounds were tested at 10 concentrations from 10 µM - 0.3 nM. All assays were conducted in duplicate and repeated at least two times. Assay plates were incubated for 1hour at room temperature before centrifugation and then bound ligand determined using a Packard Topcount scintillation counter. IC_{50} values were calculated using a non-linear curve fitting program and Ki values calculated using the Cheng-Prussoff equation.

In accordance with the invention, it has been shown that compounds of formula I have a high affinity toward the A_{2A} receptor. In the table below are described specific values of prepared compounds.

The compounds of formula I and the pharmaceutically acceptable salts of the compounds of formula I can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions.

The compounds of formula I can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

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

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention, as is a process for their production, which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

In accordance with the invention compounds of formula I as well as their pharmaceutically acceptable salts are useful in the control or prevention of illnesses based on the adenosine receptor antagonistic activity, such as Alzheimer's disease, Parkinson's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse. Furthermore, compounds of the present invention may be useful as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardiaprotective agents and for the production of corresponding medicaments.

The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of certain depressive disorders, neuroprotection and Parkinson's disease.

The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

Example 1

5-Methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl-amine

a) 6-Amino-5-bromo-pyridin-2-ol

(Lit.: Kelly, T. R.; Jagoe, C. T.; Gu, Z. *Tetrahedron Letters* 1991, *32*, 4263-4266)

To a solution of 11 g (100 mmol) 6-amino-pyridin-2-ol in 220 ml acetic acid at room temperature was added 5.12 ml (100 mmol) bromine and stirred for 15 min. The mixture was diluted with water and the precipitate was filtered off. The filtrate was extracted four times with 400 ml ethyl acetate. The combined organic layers were dried with $MgSO_4$ and evaporated to dryness to yield 12.2 g (65 %) of the title compound as light brown solid.

1-H-NMR (400MHz, DMSO-d6): δ= 10.0 (s, br, 1H, OH), 7.37 (d, J = 3 Hz, 1H, H-4), 6.10 (s, br, 2H, NH_2), 5.58 (d, J = 3 Hz, 1H, H-3).

MS m/e (%): 190 ($M+H^+$, 100).

b) 3-Bromo-6-methoxy-pyridin-2-yl-amine

A suspension of 11.58 g (61 mmol) 6-amino-5-bromo-pyridin-2-ol in 200 ml acetone was treated with 10.3 g (184 mmol) KOH pellets and 10 g (80 mmol) dimethylsulfate. The mixture was stirred for 4 h at room temperature and evaporated to dryness. 400 ml water was added and the mixture was extracted four times with 300 ml ethyl acetate. The combined organic phases were dried with $MgSO_4$ and evaporated. The residue was purified by flash column chromatography on silica eluting with hexane/ ethyl acetate 1:1 to yield 3.455 g (28 %) of the title compound as orange oil.

1-H-NMR (400MHz, DMSO-d6): δ= 7.54 (d, J = 2 Hz, 1H, H-4), 6.10 (s, br, 2H, NH_2), 5.90 (d, J = 2 Hz, 1H, H-3), 3.75 (s, 3H, OCH_3).

MS m/e (%): 204 ($M+H^+$, 100).

c) 6-Methoxy-3-phenyl-pyridin-2-yl-amine

A mixture of 330 mg (1.625 mmol) 3-bromo-6-methoxy-pyridin-2-yl-amine, 396 mg (3.25 mmol) phenylboronic acid, 1 ml 2N Na_2CO_3 and 59 mg (0.08 mmol) dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium (II) dichloromethane adduct in 10 ml dioxane was heated to 110 °C for 2 h. The mixture was concentrated, diluted Na_2CO_3 aq. was added and extracted 2 x with 100 ml diethyl ether. The combined organic phases were dried with $MgSO_4$ and evaporated. The residue was purified by flash column chromatography on silica eluting with a gradient of hexane/ ethyl acetate to yield 230 mg (71 %) of the title compound.

1-H-NMR (400MHz, DMSO-d6): δ= 7.54 (d, J = 2 Hz, 1H, H-4), 7.43 (m, 5H, Ph), 6.12 (s, br, 2H, NH_2), 5.92 (d, J = 2 Hz, 1H, H-3), 3.73 (s, 3H, OCH_3).

MS m/e (%): 204 ($M+H^+$, 100).

d) 3-(3-Fluoro-phenyl)-6-methoxy-pyridin-2-ylamine

According to step c) the title compound was synthesised from 3-bromo-6-methoxy-pyridin-2-y-lamine and 3-fluorophenylboronic acid.

MS m/e (%): 248.7 ($M+H^+$, 100).

e) 3-(4-Fluoro-phenyl)-6-methoxy-pyridin-2-yl-amine

According to step c) the title compound was synthesised from 3-bromo-6-methoxy-pyridin-2-yl-amine and 4-fluorophenylboronic acid.

MS m/e (%): 218.6 ($M+H^+$, 100).

f) 3-(4-Chloro-phenyl)-6-methoxy-pyridin-2-yl-amine

According to step c) the title compound was synthesised from 3-bromo-6-methoxy-pyridin-2-ylamine and 4-chlorophenylboronic acid.

MS m/e (%): 234.7 ($M+H^+$, 100).

g) 6-Methoxy-3-(3-methoxy-phenyl)-pyridin-2-yl-amine

According to step c) the title compound was synthesised from 3-bromo-6-methoxy-pyridin-2-yl-amine and 3-methoxyphenylboronic acid.

MS m/e (%): 230.7 ($M+H^+$, 100).

h) 5-Methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl-amine

A mixture of 230 mg (1.15 mmol) 6-methoxy-3-phenyl-pyridin-2-yl-amine and 142.8 µl ethoxycarbonyl isothiocyanate was stirred at room temperature for 2 h and afterwards evaporated to dryness. The residue was taken up in 20 ml MeOH / EtOH 1:1 and treated with a mixture of 399 mg (5.74 mmol) hydroxylamine hydrochloride and 590 µl N-ethyldiisopropylamine. The mixture was heated to 80 °C for 16 h, concentrated to dryness, taken up in 100 ml water and extracted with 3x150 ml diethyl ether. The combined organic phases were dried with $MgSO_4$ and evaporated to yield 379 mg (80 %) of the title compound.

1-H-NMR (300MHz, DMSO-d6): δ= 8.05 (d, J = 8.49 Hz, 2H, phenyl), 7.73 (d, J = 8.31 Hz, 1H, H-7), 7.45 (t, J = 7.26 Hz, 2H, phenyl), 7.33 (d, t = 7.26 Hz, 1H, phenyl), 6.52 (d, J = 8.31 Hz, 1H, H-6), 6.08 (s, br, 2H, NH_2), 4.09 (s, 3H, OCH_3).

MS m/e (%): 241.3 ($M+H^+$, 100).

Example 2

8-(3-Fluoro-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl-amine

According to example 1h) 8-(3-fluoro-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl-amine was synthesised from 3-(3-fluoro-phenyl)-6-methoxy-pyridin-2-ylamine,

ethoxycarbonyl isothiocyanate and subsequently reaction of the respective intermediate with hydroxylamine hydrochloride and N-ethyldiisopropylamine.

1-H-NMR (300MHz, DMSO-d6): δ= 8.05 (d, J = 10.7 Hz, 1H, phenyl), 7.92 (d, J = 10.7 Hz, 1H, phenyl), 6.88 (d, J = 8.37 Hz, 1H, 7-H), 7.49 (m, 1H, phenyl), 7.15 (m, 1H, phenyl), 6.53 (d, J = 8.37 Hz, 1H, 6-H), 6.14 (s, br, 2H, NH_2), 4.1 (s, 3H, OCH3).

MS m/e (%): 259.1 ($M+H^+$, 100).

Example 3

8-(4-Fluoro-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl-amine

According to example 1h) 8-(4-fluoro-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl-amine was synthesised from 3-(4-fluoro-phenyl)-6-methoxy-pyridin-2-ylamine, ethoxycarbonyl isothiocyanate and subsequently reaction of the respective intermediate with hydroxylamine hydrochloride and N-ethyldiisopropylamine.

1-H-NMR (300MHz, DMSO-d6): μ= 8.16 (t, J = 5.67 Hz, 2H, phenyl), 7.79 (d, J = 8.22 Hz, 1H, H-7), 7.34 (t, J = 5.67 Hz, 2H, phenyl), 6.57 (d, J = 8.22 Hz, 1H, H-6), 6.19 (s, br, 2H, NH_2), 4.15 (s, 3H, OCH_3).

MS m/e (%): 259.1 ($M+H^+$, 100).

Example 4

8-(4-Chloro-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl-amine

According to example 1h) 8-(4-cloro-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl-amine was synthesised from 3-(4-chloro-phenyl)-6-methoxy-pyridin-2-ylamine, ethoxycarbonyl isothiocyanate and subsequently reaction of the respective intermediate with hydroxylamine hydrochloride and N-ethyldiisopropylamine.

1-H-NMR (300MHz, DMSO-d6): μ= 8.13 (d, J = 8.67 Hz, 2H, phenyl), 7.79 (d, J = 8.37 Hz, 1H, H-7), 7.51 (d, J = 8.67 Hz, 2H, phenyl), 6.53 (d, J = 8.37 Hz, 1H, H-6), 6.11 (s, br, 2H, NH_2), 4.09 (s, 3H, OCH_3).

MS m/e (%): 275.2 ($M+H^+$, 100).

Example 5

5-Methoxy-8-(3-methoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl-amine

According to example 1h) 8-(3-methoxy-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-

a]pyridin-2-y-lamine was synthesised from 3-(3-methoxy-phenyl)-6-methoxy-pyridin-2-yl-amine, ethoxycarbonyl isothiocyanate and subsequently reaction of the respective intermediate with hydroxylamine hydrochloride and N-ethyldiisopropylamine.

1-H-NMR (300MHz, DMSO-d6): μ= 7.76 (d, J = 8.25 Hz, 1H, H-7), 7.68 (s, 1H, phenyl), 7.62 (d, J = 7.89 Hz, 1H, phenyl), 7.36 (t, J = 7.89 Hz, 1H, phenyl), 6.91 (d, J = 7.89 Hz, 1H, phenyl), 6.51 (d, J = 8.25 Hz, 1H, H-6), 6.07 (s, br, 2H, NH_2), 4.09 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3).

MS m/e (%): 271.2 ($M+H^+$, 100).

Example 6

3-Fluoro-N-(5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-benzamide

A mixture of 15 mg (0.062 mmol) 5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl-amine, 11 mg (0.068 mmol) 3-fluorophenyl carboxylic acid chloride, and 31.5 μl (0.312 mmol) NEt_3 in 1 ml dioxane was heated to 90 °C for 16 h. The mixture was purified by preparative HPLC on reversed phase eluting with an acetonitrile / water gradient. Evapotation yielded the title compound.

MS m/e (%): 281.7 ($(M+CH_3CN)^+$, 100).

Example 7

3-Bromo-N-(5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-benzamide

According to example 6 the title compound was synthesised from 5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-y-lamine and 3-bromo-phenyl carboxylic acid chloride (MS m/e (%): 423.3 ($M+H^+$, 100).

Example 8

4-Fluoro-N-(5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-benzamide

According to example 6 the title compound was synthesised from 5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl-amine and 4-fluoro-phenyl carboxylic acid chloride. (MS m/e (%): 362.4 ($M+H^+$, 100).

Example 9

3-Methoxy-N-(5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-benzamide

According to example 6 the title compound was synthesised from 5-methoxy-8-phenyl-

[1,2,4]triazolo[1,5-a]pyridin-2-yl-amine and 3-methoxy-phenyl carboxylic acid chloride. (MS m/e (%): 374.4 ($M+H^+$, 100).

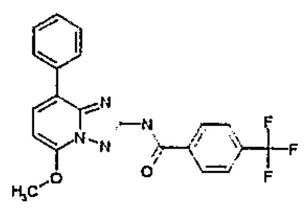
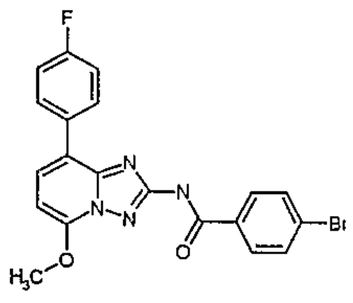
Example 10

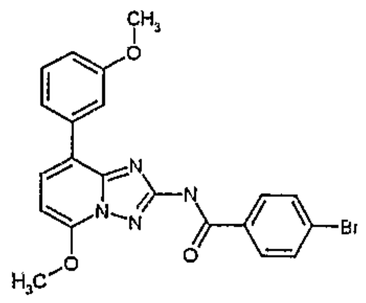
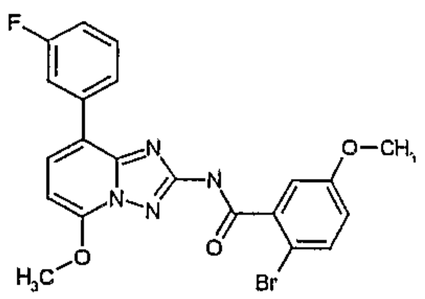
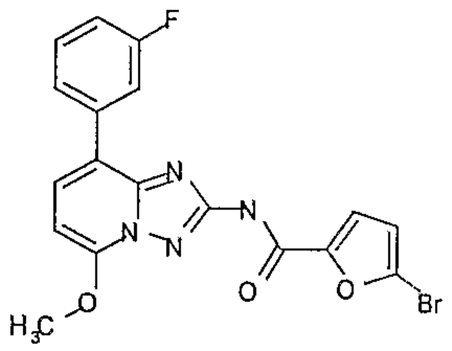
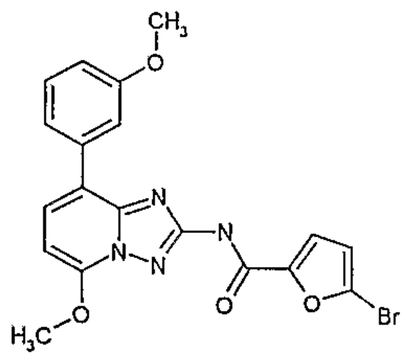
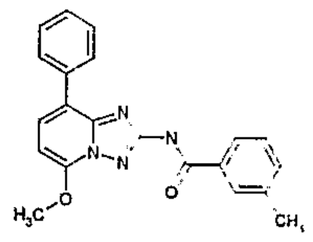
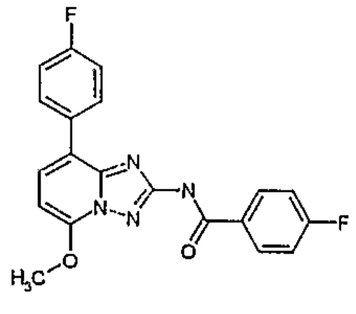
4-Bromo-N-(5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-benzamide

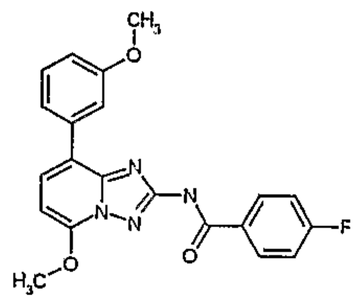
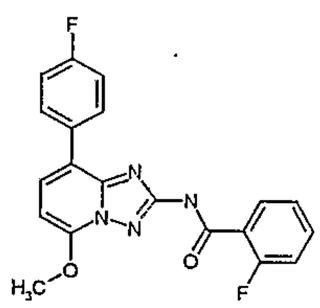
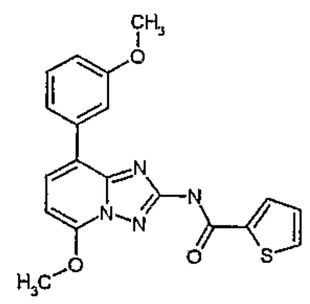
To a solution of 24 mg (0.1 mmol) 5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl-amine in 1 ml dioxane was added 0.4 ml (0.4 mmol) of a 1 M solution of $AlMe_3$ in toluene and allowed to stirr for 1 h at room temperature. 86 mg (0.4 mmol) 4-bromo-phenyl carboxylic acid methyl ester in 1 ml dioxane was added and the mixture was stirred for 48 h at 90 °C. 0.5 ml 1N HCl aq. was added and the mixture was evaporated to dryness. The residue was taken up in 1.5 ml formic acid and 0.5 ml methanol and subjected to reversed phase HPLC chromatography eluting with a water / acetonitrile gradient. Evaporation of the eluents yielded 6 mg (15 %) of the title compound.

MS m/e (%): 423.3 ($M+H^+$, 100).

According to example 10 further [1,2,4]triazolo[1,5-a]pyridin-derivatives have been synthesised. The results are compiled in the following list comprising example 11 to example 42.

No	HA2a KI(nM)	Structure	Name	MW	MS MH^+ (%)
11	884		N-(5-Methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-4-trifluoromethyl-benzamide	412.4	413 (100)
12	776		4-Bromo-N-[8-(4-fluoro-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-benzamide	441.3	442 (100)

No	HA2a KI(nM)	Structure	Name	MW	MS MH^+ (%)
13	480		4-Bromo-N-[5-methoxy-8-(3-methoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-benzamide	453.3	454 (100)
14	908		2-Bromo-N-[8-(3-fluoro-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-5-methoxy-benzamide	471.3	472 (100)
15	572		5-Bromo-furan-2-carboxylic acid [8-(3-fluoro-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide	431.2	432 (100)
16	560		5-Bromo-furan-2-carboxylic acid [5-methoxy-8-(3-methoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide	443.3	444 (100)
17	984		N-(5-Methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-3-methyl-benzamide	358.4	359 (100)
18	664		4-Fluoro-N-[8-(4-fluoro-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-benzamide	380.4	381 (100)

No	HA2a KI(nM)	Structure	Name	MW	MS MH^+ (%)
19	748		4-Fluoro-N-[5-methoxy-8-(3-methoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-benzamide	392.4	393 (100)
20	784		2-Fluoro-N-[8-(4-fluoro-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-benzamide	380.4	381 (100)
21	516		Thiophene-2-carboxylic acid [5-methoxy-8-(3-methoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide	380.4	381 (100)

Tablet Formulation (Wet Granulation)

Item	Ingredients	mg/tablet			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

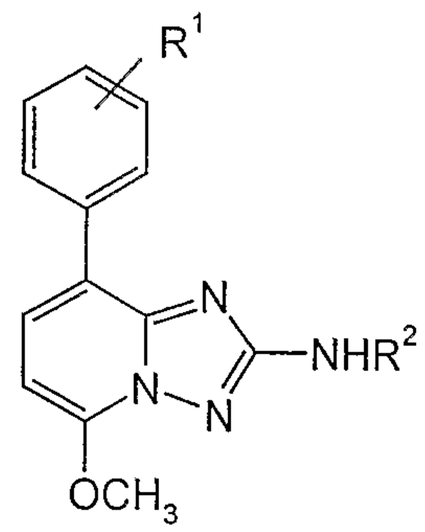
Item	Ingredients	mg/capsule			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure

1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Claims

1. A compound of the general formula



I

wherein

R^1 is hydrogen, halogen or lower alkoxy;

R^2 is hydrogen or is –C(O)-lower alkyl or –C(O)-phenyl, wherein the phenyl ring is unsubstituted or substituted by one or two substituents, selected from the group, consisting of halogen, lower alkyl, lower alkoxy or trifluoromethyl,

or is –C(O)-furanyl or –C(O)-thiophenyl, wherein the rings are unsubstituted or substituted by halogen;

and its pharmaceutically acceptable salts.

2. A compound of formula I in accordance with claim 1, wherein R^2 is –C(O)-phenyl, substituted by halogen.

3. A compound of formula I in accordance with claim 2, wherein the compound is

4-fluoro-N-(5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-benzamide,
4-bromo-N-(5-methoxy-8-phenyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)-benzamide,
4-bromo-N-[5-methoxy-8-(3-methoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-benzamide,
4-fluoro-N-[8-(4-fluoro-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-benzamide or
4-fluoro-N-[5-methoxy-8-(3-methoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-benzamide.

4. A compound of formula I in accordance with claim 1, wherein R^2 is –C(O)-furanyl, substituted by halogen.

5. A compound of formula I in accordance with claim 4, wherein the compound is 5-bromo-furan-2-carboxylic acid [8-(3-fluoro-phenyl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide or
5-bromo-furan-2-carboxylic acid [5-methoxy-8-(3-methoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide.

6. A compound of formula I in accordance with claim 1, wherein R^2 is –C(O)-thiophenyl.

7. A compound of formula I in accordance with claim 6, wherein the compound is thiophene-2-carboxylic acid [5-methoxy-8-(3-methoxy-phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl]-amide.

8. A compound of formula I in accordance with claim 1, wherein R^2 is hydrogen.

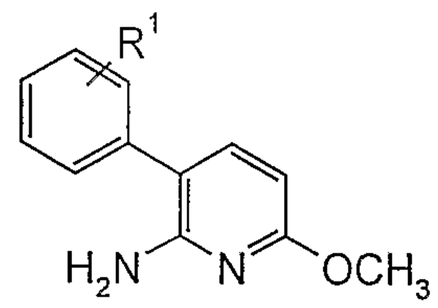
9. A compound of formula I in accordance with claim 1, wherein R^2 is –C(O)-lower alkyl.

10. A medicament containing one or more compounds of formula I as claimed in any one of claims 1 – 9 and pharmaceutically acceptable excipients.

11. A medicament according to claim 10 for the treatment of diseases related to the adenosine receptor.

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

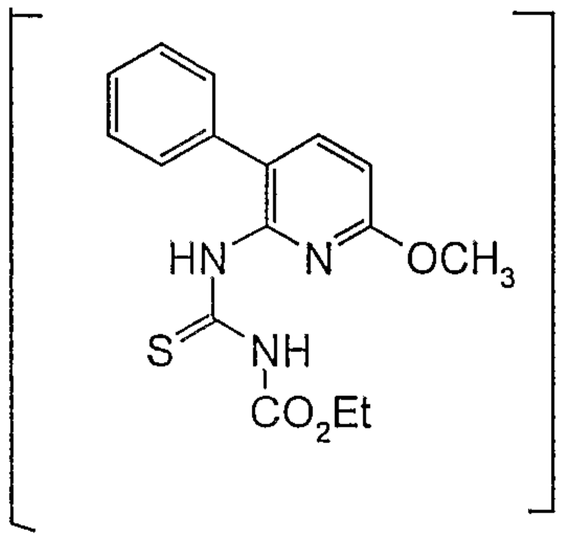
a) reacting a compound of formula



II

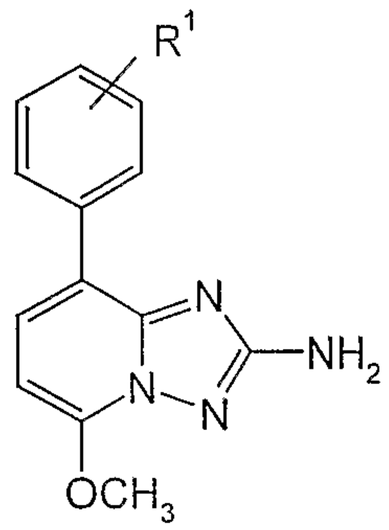
with ethoxycarbonyl isothiocyanate

to a compound of formula



III

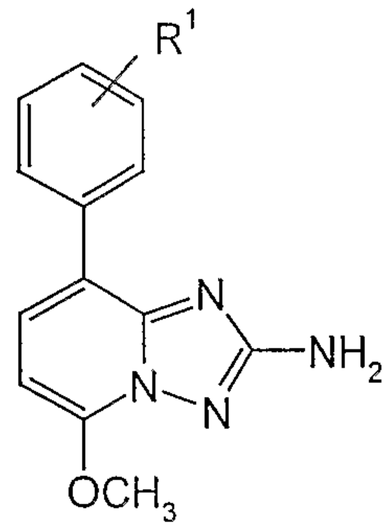
and cyclizing the compound of formula III in the presence of hydroxylamine to a compound of formula



Ia

wherein R^1 has the significance given above, or

b) reacting a compound of formula

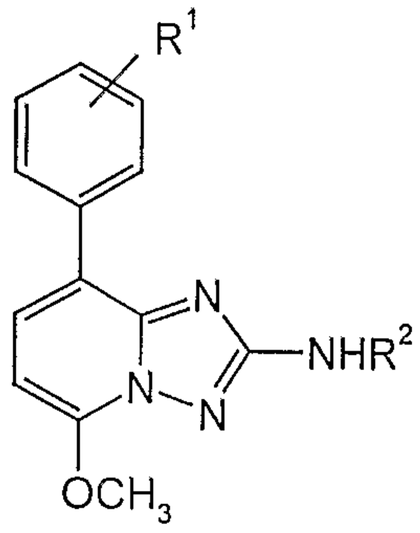


Ia

with a compound of formula

R^2Cl

to give a compound of formula



I

wherein R^1 and R^2 are as defined above.

and

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

13. A compound according to any one of claims 1 – 9, whenever prepared by a process as claimed in claim 12 or by an equivalent method.

14. The use of a compound in any one of claims 1 – 9 for the treatment of diseases.

15. The use of a compound in any one of claims 1 – 9 for the manufacture of corresponding medicaments for the treatment of diseases related to the adenosine A_{2A} receptor.

16. The invention as hereinbefore described.

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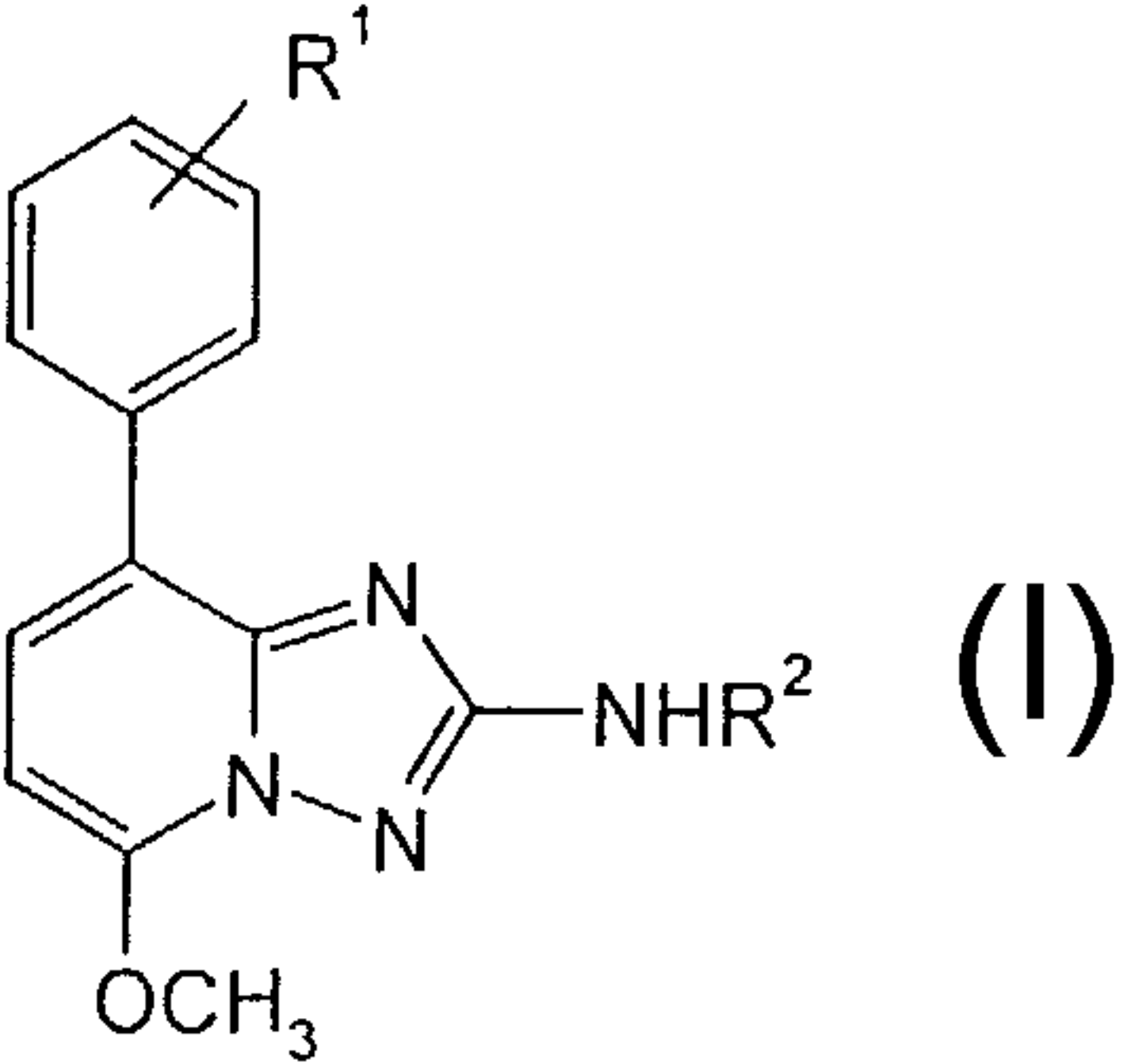

(I)