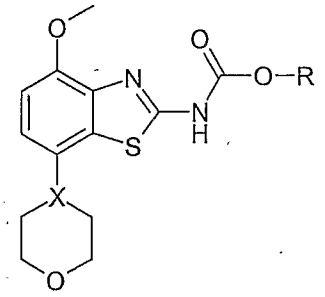
BENZOTHIAZOLE DERIVATIVES AND USE THEREOF IN THE TREATMENT OF DISEASES RELATED TO THE ADENOSINE A2A RECEPTOR

The present invention relates to compounds of the general formula



I

wherein

R is $C_{5,6}$-cycloalkyl, unsubstituted or substituted by hydroxy, or is ethyl, isobutyl or methoxyethyl, or is tetrahydropyran-4-yl or $-(CH_2)_n$-tetrahydrofuran-2 or 3-yl or is 5-hydroxy-bicyclo[2.2.1]hept-2-yl;

X is CH or N;

n is 0 or 1;

and to pharmaceutically acceptable acid addition salts thereof.

It has surprisingly been found that the compounds of general formula I are adenosine receptor ligands. Specifically, the compounds of the present invention have a good affinity to the A_{2A}-receptor and a high selectivity to the A_1- and A_3 receptors.

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 receptores 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: 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 a neuromodulator, able to modulate many aspects of physiological brain function. Endogenous adenosine, a central link between energy metabolism and neuronal activity, varies according to behavioural state and (patho)physiological conditions. Under conditions of increased demand and decreased availability of energy (such as hypoxia, hypoglycemia, and/or excessive neuronal activity), adenosine provides a powerful protective fedback mechanism. Interacting with adenosine receptors represents a promising target for therapeutic intervention in a number of neurological and psychiatric diseases such as epilepsy, sleep, movement disorders (Parkinson or Huntington's disease), Alzheimer's disease, depression, schizophrenia, or addiction 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 of neurodegenerative disorders, e.g. stroke. Adenosine A_{2a} receptor antagonists modulate the activity of striatal GABAergic neurons and regulate smooth and well-coordinated movements, thus offering a potential therapy for Parkinsonian symptoms. Adenosine is also implicated in a number of physiological processes involved in sedation, hypnosis, schizophrenia, anxiety, pain, respiration, depression, and drug addiction (amphetamine, cocaine, opioids, ethanol, nicotine, cannabinoids). Drugs acting at adenosine receptors therefore have therapeutic potential as sedatives, muscle relaxants, antipsychotics, anxiolytics, analgesics, respiratory stimulants, antidepressants, and to treat drug abuse. They may also be used in the treatment of ADHD (attention deficit hyper-activity disorder).

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). By acting at the A_1 receptor, adenosine A_1 agonists may protect against the injury caused by myocardial ischemia and reperfusion. The modulating influence of A_2a receptors on adrenergic function may have implications for a variety of disorders such as coronary artery disease and heart failure. A_{2a} antagonists may be of therapeutic benefit in situations

in which an enhanced antiadrenergic response is desirable, such as during acute myocardial ischemia. Selective antagonists at A_{2a} receptors may also enhance the effectiveness of adenosine in terminating supraventricula arrhytmias.

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 or and in the treament of diabetes mellitus and obesity.

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., 332, 39-41, (1999),
Am. J. Physiol., 276, H1113-1116, (1999) or
Naunyn Schmied, Arch. Pharmacol. 362, 375-381, (2000).

Objects of the present invention are the compounds of formula I per se, the use of compounds of formula I and their pharmaceutically acceptable salts for the manufacture of medicaments for the treatment of diseases, related to the adenosine A_2 receptor, 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, Huntington's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, drug addiction, such as amphetamine, cocaine, opioids, ethanol, nicotine, cannabinoids, or against 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 for disorders such as coronary artery disease and heart failure. 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 Alzheimer's disease, certain depressive disorders, drug addiction, neuroprotection and Parkinson's disease as well as ADHD.

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.

Preferred compounds of the present application are compounds of formula I, wherein R is $C_{5,6}$-cycloalkyl, optionally substituted by hydroxy, for example the following compounds:

(*trans*)-[4-methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-yl]-carbamic acid 4-hydroxy-cyclohexyl ester,
(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid cyclohexyl ester,
(trans)-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid 4-hydroxy-cyclohexyl ester,
(cis)-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid 4-hydroxy-cyclohexyl ester or
(*cis/trans*)-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid 3-hydroxy-cyclopentyl ester.

Preferred are further compounds of formula I, wherein R is ethyl, isobutyl, or methoxyethyl, for example the following compounds:

[4-methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-yl]-carbamic acid ethyl ester,
(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid 2-methoxy-ethyl ester or
(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid isobutyl ester.

Preferred compounds of the present application are compounds of formula I, wherein R is tetrahydropyran-4-yl or $-(CH_2)_n$-tetrahydrofuran-2 or 3-yl, for example the following compounds:

(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid tetrahydro-pyran-4-yl ester,
(*R*)-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid tetrahydro-furan-3-yl ester,

[4-methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-yl]-carbamic acid tetrahydro-furan-2-yl-methyl ester or

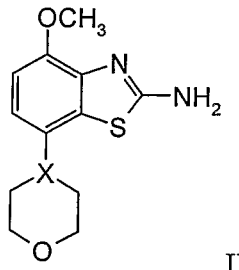
[4-Methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-yl]-carbamic acid (S)-(tetrahydro-furan-3-yl) ester.

Preferred are further compounds of formula I, wherein R is 5-hydroxy-bicyclo[2.2.1]hept-2-yl, for example the following compound:

(*rac*)-(*exo,exo*)-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid 5-hydroxy-bicyclo[2.2.1]hept-2-yl ester.

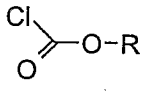
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

a) reacting a compound of formula



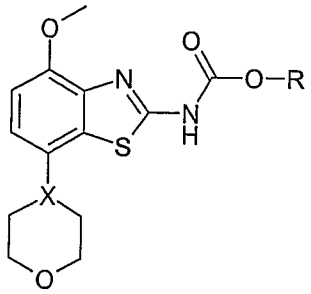
II

with a compound of formula



III

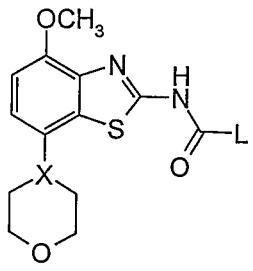
to a compound of formula



I

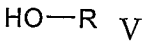
wherein R and X have the significances given above, or

b) reacting a compound of formula



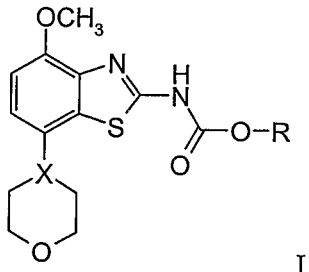
IV

with a compound of formula



V

to a compound of formula



I

wherein R and X are as defined above, L is a leaving group such as halogen, -O-phenyl or O-lower alkyl, and

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

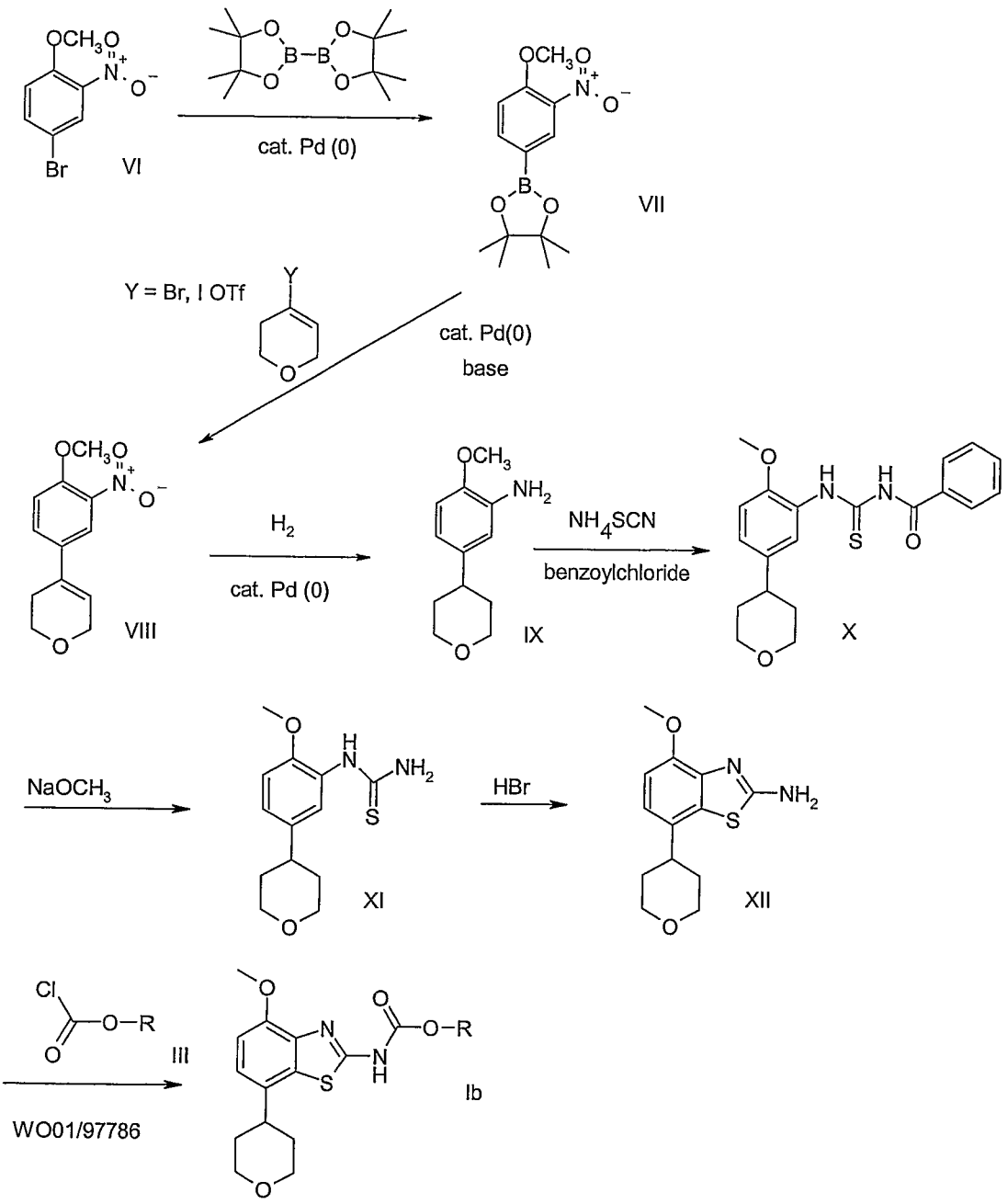
In Examples 1 – 13 and in the following schemes 1 and 2 the preparation of compounds of formula I are described in more detail.

The starting materials are known compounds or may be prepared according to methods known in the art.

Preparation of compounds of formula I

The intermediates 7-(morpholin-4-yl)-4-methoxy-benzothiazol-2-ylamine and 7-(tetrahydropyran-4-yl)-4-methoxy-benzothiazol-2-ylamine may be prepared according to methods disclosed in WO01/97786. The preparation of compounds of formula (I) using the intermediate of formula (II) is also described in WO01/97786.

Scheme 1



Preparation of compounds of formula (VII)

The aryl bromide compound of formula (VI) is reacted with a slight excess of bis(pinacolato)diboron in an organic solvent, preferably dimethyl sulfoxide, containing a palladium catalyst, preferably dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloromethane adduct, and an excess of potassium acetate. The reaction is carried out at elevated temperature, preferably about 80 °C, for about 2-24 hours, preferably about 2 hours. The product of formula

(VII) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

Preparation of compounds of formula (VIII)

One method of preparation of compounds of formula (VIII) is by treatment of a compound of formula (VII) with a vinyl bromide, vinyl iodide or vinyl triflate compound in the presence of a palladium catalyst, preferably dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloromethane adduct, and an inorganic base, preferably sodium carbonate. The reaction is carried out in a mixture of solvents, preferably a mixture of ethanol, toluene and water. The reaction is carried out at elevated temperature, preferably about 80 °C, for about 0.1-2 hours, preferably about 20 minutes. The product of formula (VIII) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation. The starting vinyl bromide, vinyl iodide or vinyl triflate compounds may be obtained commercially, for example from Fluka, or may be prepared according to methods well known in the art.

Preparation of compounds of formula (IX)

Compounds of formula (IX) may be prepared by hydrogenation of compounds of formula (VIII) in the presence of a hydrogenation catalyst, preferably 10 % palladium on charcoal. These reactions may be carried out in a variety of organic solvents, such as methanol, ethanol, or tetrahydrofuran, preferably methanol, at room temperature and at a pressure of one atmosphere or above, preferably at one atmosphere, for 16-72 hours, preferably about 72 hours. The product of formula (IX) is isolated by conventional means, and preferably purified by means of chromatography or recrystallisation.

Preparation of the compound of formula (X)

To a solution of ammonium rhodanide in acetone is added benzoyl chloride and a solution of 2-methoxy-5-(tetrahydro-pyran-4-yl)-phenylamine (IX). The reaction is carried out under reflux for about 20 minutes. The product 1-benzoyl-3-[2-methoxy-5-(tetrahydro-pyran-4-yl)-phenyl]-thiourea (X) is isolated by conventional means.

Preparation of the compound of formula (XI)

To a solution of 1-benzoyl-3-[2-methoxy-5-(tetrahydro-pyran-4-yl)-phenyl]-thiourea (X) in methanol is added sodium methylate solution and stirring continued for about 1 h at room temperature. The product (XI) [2-methoxy-5-(tetrahydro-pyran-4-yl)-phenyl]-thiourea is isolated by conventional means.

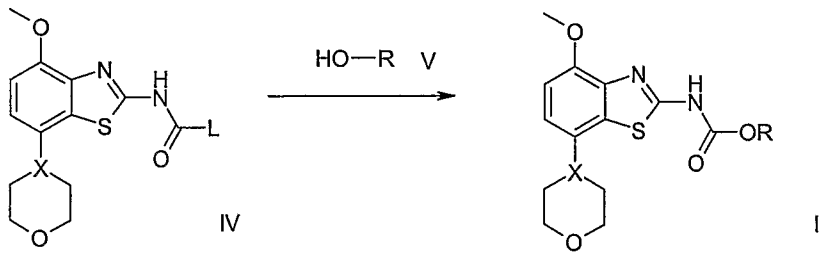
Preparation of the compound of formula (XII)

To a solution of 1 [2-methoxy-5-(tetrahydro-pyran-4-yl)-phenyl]-thiourea (XI) in acetic acid is added hydrobromic acid, and stirring continued for about 30 min at 80 °C. DMSO is then added dropwise and the reaction mixture stirred for a further 30 min at 80 °C. The product (XII) 4-methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-ylamine is isolated by conventional means.

Preparation of the compound of formula (Ib)

4-Methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-ylamine (XII) is first reacted with phenyl chloroformate as described for (4-methoxy-7-phenyl-benzothiazol-2-yl)-carbamic acid benzyl ester in WO01/97786 and then with N-ethyl-diisopropylamine and a corresponding alcohol of formula HO-R in dimethyl sulfoxide at about 50 °C for 2 h, as illustrated also in scheme 2.

Scheme 2



R and X are as described above, L is a leaving group such as halogen, -O-phenyl or O-lower alkyl.

Isolation and purification of the compounds

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

Salts of compounds of formula I

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

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

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

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 and possess a high affinity towards the adenosine A_{2A} receptor.

The compounds were investigated in accordance with the test 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; 1nM) 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.

The pKi value of compounds of the present application are in the range of 7.6 to 8.7. The most preferred compounds show a pKi > 8.0.

Example No.	hA_2 (pKi)	Example No.	hA_2 (pKi)
1	8.7	8	8.1
2	8.3	9	8.4
3	7.9	10	7.6
4	7.6	11	7.8
5	8.1	12	7.9
6	8.2	13	8.4
7	8.0		

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.

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.

The following preparation and examples illustrate the invention but are not intended to limit its scope.

Example 1

(*trans*)-[4-Methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-yl]-carbamic acid 4-hydroxy-cyclohexyl ester

4-Methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-ylamine (69 mg, 0.26 mmol) is first reacted with phenyl chloroformate as described for (4-methoxy-7-phenyl-benzothiazol-2-yl)-carbamic acid benzyl ester in WO01/97786 and then with N-ethyl-diisopropylamine (0.090 ml, 0.52 mmol) and (*trans*)-cyclohexane-1,4-diol (60 mg, 0.52 mmol) in dimethyl sulfoxide (10 ml) at 50 °C for 2 h. Then 100 ml dichloromethane are added, the mixture is extracted with saturated aqueous sodium carbonate and the organic phase is dryed and evaporated. Flash-chromatographic purification (silica, eluting with dichloromethane/methanol) yielded the title compound as white solid (7 % yield). MS: m/e= 407($M+H^+$), mp 282-284 °C.

Following the general method of example 1 the compounds of examples 2 to 11 were prepared.

Example 2

[4-Methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-yl]-carbamic acid ethyl ester

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and ethanol, the title compound was obtained as white solid (35 % yield). MS: m/e= 337($M+H^+$), mp 170-174 °C.

Example 3

(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid 2-methoxy-ethyl ester

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and 2-methoxy-ethanol, the title compound was obtained as off-white solid (52 % yield). MS: m/e= 368($M+H^+$), mp 149-152 °C.

Example 4

(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid isobutyl ester

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and isobutanol, the title compound was obtained as yellow crystals (12 % yield). MS: m/e= 366($M+H^+$), mp 164-168 °C.

Example 5

(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid cyclohexyl ester

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and cyclohexanol, the title compound was obtained as white solid (60 % yield). MS: m/e= 392($M+H^+$), mp 177-179 °C.

Example 6

(tran)s-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid 4-hydroxy-cyclohexyl ester

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and, the title compound was obtained as white foam (14 % yield). MS: m/e= 408($M+H^+$), mp 176-179 °C. MS: m/e= 407.49($M+H^+$).

Example 7

(cis)-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid 4-hydroxy-cyclohexyl ester

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and (*cis*)-cyclohexane-1,4-diol, the title compound was obtained as colorless crystals (40 % yield). MS: m/e= 408($M+H^+$), mp 204-206 °C.

Example 8

(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid tetrahydro-pyran-4-yl ester

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and tetrahydropyran-4-ol, the title compound was obtained as white solid (7 % yield). MS: m/e= 394($M+H^+$), mp 187-188 °C.

Example 9

(*rac*)-(*exo,exo*)-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid 5-hydroxy-bicyclo[2.2.1]hept-2-yl ester

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and (*rac*)-(*exo,exo*)-bicyclo[2.2.1]heptane-2,5-diol, the title compound was obtained as white solid (10 % yield). MS: m/e= 420($M+H^+$), mp 193-194 °C.

Example 10

(*R*)-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid tetrahydro-furan-3-yl ester

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and (*R*)-tetrahydro-furan-3-ol, the title compound was obtained as white crystals (33 % yield). MS: m/e= 380($M+H^+$), mp 198-200 °C.

Example 11

(*cis/trans*)-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid 3-hydroxy-cyclopentyl ester

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and (*cis/trans*)-cyclopentane-1,3-diol, the title compound was obtained as white solid (42 % yield). MS: m/e= 394($M+H^+$), mp 188-189 °C.

Example 12

[4-Methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-yl]-carbamic acid tetrahydro-furan-2-ylmethyl ester

Using 7-(tetrahydropyran-4-yl)-4-methoxy-benzothiazol-2-ylamine and (tetrahydro-furan-2-yl)-methanol, the title compound was obtained as white solid (8 % yield). MS: m/e= 393($M+H^+$), mp 175-180°C.

Example 13

[4-Methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-yl]-carbamic acid (S)-(tetrahydro-furan-3-yl) ester

Using 7-(tetrahydropyran-4-yl)-4-methoxy-benzothiazol-2-ylamine and (*S*)-etrahydro-furan-3-ol, the title compound was obtained as white solid (13 % yield). MS: m/e= 379($M+H^+$), mp 195-200°C.

Intermediates

Example 14

4-Methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-yl-amine (X)

a) 2-(4-Methoxy-3-nitro-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (VII)

To a stirred solution of 1.30 g (5.60 mmol) 4-bromo-2-nitroanisole (VI) in 25 ml DMSO were added 1.57 g (6.16 mmol) bis(pinacolato)diboron, 123 mg (0.17 mmol) dichloro(1,1′-bis(diphenylphosphino)ferrocene)palladium(II) dichloromethane adduct and 1.65 g (16.8 mmol) potassium acetate. The mixture was heated at 80 °C for 2 h and then cooled to room temperature, poured onto water, and extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (1/2 ethyl acetate/hexane then ethyl acetate) afforded 1.39 g 2-(4-methoxy-3-nitro-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (VII) as an off-white solid. ES-MS m/e (%): 280 ($M+H^+$, 100).

b) 4-(4-Methoxy-3-nitro-phenyl)-3,6-dihydro-2*H*-pyran (VIII)

To a stirred solution of 4.36 g (15.6 mmol) 2-(4-methoxy-3-nitro-phenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (VII) and 3.30 g (14.2 mmol) trifluoromethanesulfonic acid 3,6-dihydro-2*H*-pyran-4-yl ester in 33 ml ethanol and 82 ml toluene was added 580 mg (0.71 mmol) dichloro(1,1′-bis(diphenylphosphino)ferrocene)palladium(II) dichloromethane adduct. The mixture was heated at 80 °C and 16.5 ml (33.0 mmol) 2 M aqueous sodium carbonate solution was added dropwise. The reaction mixture was stirred for 20 minutes at 80 °C and then cooled to room temperature, poured onto water, and extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (1/4 ethyl acetate/hexane) afforded 2.00 g (60 %) 4-(4-methoxy-3-nitro-phenyl)-3,6-dihydro-2*H*-pyran (VIII) as a light yellow solid. ES-MS m/e (%): 253 ($M+NH_4^+$, 100), 236 ($M+H^+$, 24).

c) 2-Methoxy-5-(tetrahydro-pyran-4-yl)-phenylamine (IX)

To a stirred solution of 3.30 g (14.0 mmol) 4-(4-methoxy-3-nitro-phenyl)-3,6-dihydro-2*H*-pyran (VIII) in 70 ml methanol and 70 ml dichloromethane was added a spatula end of 10 % palladium on charcoal and the mixture was then stirred for 20 minutes at room temperature under an atmosphere of hydrogen. The mixture was then filtered, washing with dichloromethane, and the filtrate concentrated *in vacuo* to afford 2.75 g (95 %) 2-methoxy-5-(tetrahydro-pyran-4-yl)-phenylamine (IX) as an off-white crystalline solid. ES-MS m/e (%): 208 ($M+H^+$, 100).

d) 1-Benzoyl-3-[2-methoxy-5-(tetrahydro-pyran-4-yl)-phenyl]-thiourea (X)

To a stirred solution of 1.11 g (14.6 mmol) ammonium rhodanide in 60 ml acetone was added dropwise 1.54 ml (13.3 mmol) benzoyl chloride and the mixture heated at reflux for 10 minutes. A solution of 2.75 g (13.3 mmol) 2-methoxy-5-(tetrahydro-pyran-4-yl)-phenylamine in 30 ml acetone was then added dropwise and the reaction mixture heated at reflux for a further 10 minutes. The mixture was then cooled to room temperature, poured onto sodium bicarbonate solution, and extracted three times with dichloromethane. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (1/1 ethyl acetate/hexane) followed by trituration in ether afforded 3.25 g (66 %) 1-benzoyl-3-[2-methoxy-5-(tetrahydro-pyran-4-yl)-phenyl]-thiourea as a white solid. ES-MS m/e (%): 371 ($M+H^+$, 100).

e) [2-Methoxy-5-(tetrahydro-pyran-4-yl)-phenyl]-thiourea (XI)

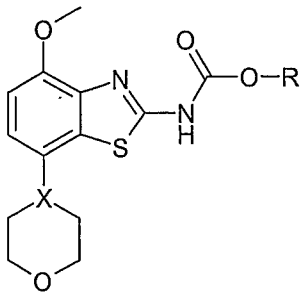
To a stirred solution of 3.25 g (8.77 mmol) 1-benzoyl-3-[2-methoxy-5-(tetrahydro-pyran-4-yl)-phenyl]-thiourea in 45 ml methanol was added dropwise 0.25 ml (1.32 mmol) 5.3 M sodium methylate solution and stirring continued for 1 h at room temperature. The mixture was then poured onto water and extracted three times with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (ethyl acetate) afforded 1.90 g (81 %) [2-methoxy-5-(tetrahydro-pyran-4-yl)-phenyl]-thiourea as a white foam. ES-MS m/e (%): 267 ($M+H^+$, 100).

f) 4-Methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-yl-amine (XII)

To a stirred solution of 1.90 g (7.13 mmol) [2-methoxy-5-(tetrahydro-pyran-4-yl)-phenyl]-thiourea in 20 ml acetic acid heated to 80 °C was added dropwise 1.45 ml (8.27 mmol) hydrobromic acid (5.7 M solution in acetic acid) and stirring continued for 30 min at 80 °C. 0.56 ml (7.85 mmol) DMSO was then added dropwise and the reaction mixture stirred for a further 30 min at 80 °C. The mixture was then cooled to room temperature, poured slowly onto sodium bicarbonate solution, and ethyl acetate added. The mixture was stirred for 10 minutes at room temperature and the resulting crystals collected by filtration, washing with ethyl acetate. The mother liquor phases were separated and the organic phase concentrated *in vacuo* to 5 ml. The resulting second crop of crystals was collected by filtration and combined with the first crop to afford 920 mg (49 %) 4-methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-ylamine as a white solid. ES-MS m/e (%): 265 ($M+H^+$, 100).

Claims

1. Compounds of the general formula



I

wherein

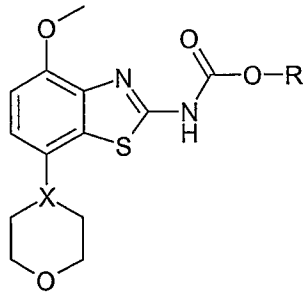
R is $C_{5,6}$-cycloalkyl, unsubstituted or substituted by hydroxy, or is ethyl, isobutyl or methoxyethyl, or is tetrahydropyran-4-yl or $-(CH_2)_n$-tetrahydrofuran-2 or 3-yl or is 5-hydroxy-bicyclo[2.2.1]hept-2-yl;

X is CH or N;

n is 0 or 1;

and pharmaceutically acceptable acid addition salts thereof.

2. Compounds of the general formula



I

wherein

R is $C_{5,6}$-cycloalkyl, unsubstituted or substituted by hydroxy, or is ethyl, isobutyl or methoxyethyl, or is tetrahydropyran-4-yl or tetrahydrofuran-3-yl or is 5-hydroxy-bicyclo[2.2.1]hept-2-yl;

X is CH or N;

and pharmaceutically acceptable acid addition salts thereof.

3. Compounds of formula I in accordance with claim 1, wherein R is $C_{5,6}$-cycloalkyl, optionally substituted by hydroxy.

4. Compounds of formula I in accordance with claim 3, which compounds are

(*trans*)-[4-methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-yl]-carbamic acid 4-hydroxy-cyclohexyl ester,
(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid cyclohexyl ester,
(*trans*)-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid 4-hydroxy-cyclohexyl ester,
(*cis*)-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid 4-hydroxy-cyclohexyl ester or
(*cis/trans*)-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid 3-hydroxy-cyclopentyl ester.

5. Compounds of formula I in accordance with claim 1, wherein R is ethyl, isobutyl or methoxyethyl.

6. Compounds of formula I in accordance with claim 4, which compounds are

[4-methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-yl]-carbamic acid ethyl ester,
(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid 2-methoxy-ethyl ester or
(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid isobutyl ester.

7. Compounds of formula I in accordance with claim 1, wherein R is tetrahydropyran-4-yl or $-(CH_2)_n$-tetrahydrofuran-2 or 3-yl.

8. Compounds of formula I in accordance with claim 7, which compounds are

(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid tetrahydro-pyran-4-yl ester,
(*R*)-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid tetrahydro-furan-3-yl ester,
[4-methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-yl]-carbamic acid tetrahydro-furan-2-yl-methyl ester or
[4-Methoxy-7-(tetrahydro-pyran-4-yl)-benzothiazol-2-yl]-carbamic acid (S)-(tetrahydro-furan-3-yl) ester.

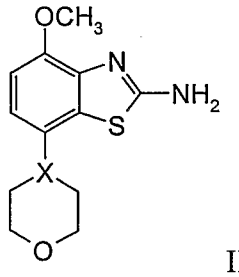
9. Compounds of formula I in accordance with claim 1, wherein R is 5-hydroxy-bicyclo[2.2.1]hept-2-yl.

10. Compounds of formula I in accordance with claim 9, which compound is

(*rac*)-(*exo,exo*)-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-carbamic acid 5-hydroxy-bicyclo[2.2.1]hept-2-yl ester.

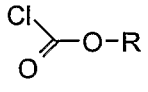
11. A process for preparing a compound of formula I as defined in claims 1 - 10, which process comprises

a) reacting a compound of formula



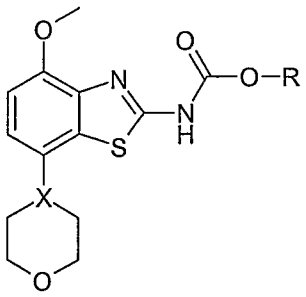
II

with a compound of formula



III

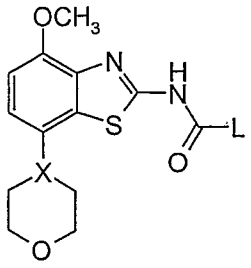
to a compound of formula



I

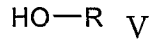
wherein R and X have the significances given above, or

b) reacting a compound of formula



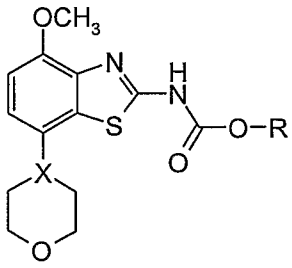
IV

with a compound of formula



V

to a compound of formula



I

wherein R and X are as defined above, L is a leaving group such as halogen, -O-phenyl or O-lower alkyl, and

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

12. A compound according to any one of claims 1 to 10, whenever prepared by a process as claimed in claim 10 or by an equivalent method.

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

14. A medicament according to claim 13 for the treatment of diseases related to the adenosine receptor.

15. The use of a compound in any one of claims 1 to 10 for the treatment of diseases.

16. The use of a compound in any one of claims 1 to 10 for the manufacture of corresponding medicaments for the treatment of diseases related to the adenosine A_{2A} receptor.

17. The invention as hereinbefore described.

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