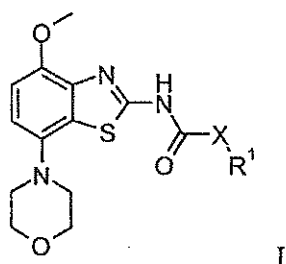


Case 22587

Substituted benzothiazoles

The present invention relates to compounds of the general formula



wherein

- R¹ is cycloalkyl, substituted by OR or is 2-(7-oxa-bicyclo[2.2.1]hept-1-yl)-ethyl;
 5 R is hydrogen, lower alkyl or C(O)-lower alkyl;
 X is -CHR'-; and
 R' is hydrogen or lower alkyl;

and to pharmaceutically acceptable acid addition salts, optically pure enantiomers, racemates or diastereomeric mixtures thereof.

- 10 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 A₁- and A₃ 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
 15 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
 20 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 A₁, A_{2A}, A_{2B} and A₃ receptors, belonging to the family of G protein-coupled receptors. Activation of adenosine receptors
 Pop/26.04.2005

by adenosine initiates signal transduction mechanism. These mechanisms are dependent on the receptor associated G protein. Each of the adenosine receptor subtypes has been classically characterised by the adenylate cyclase effector system, which utilises cAMP as a second messenger. The A₁ and A₃ 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 A₁ receptor system include the activation of phospholipase C and modulation of both potassium and calcium ion channels. The A₃ subtype, in addition to its association with adenylate cyclase, also stimulates phospholipase C and so activates calcium ion channels.

The A₁ 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 A₁ and A_{2A} receptors. The A₃ receptor (317-320 amino acids) was cloned from human, rat, dog, rabbit and sheep.

The A₁ 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 (A₁) or increase the oxygen supply (A_{2A}) and so reinstate the balance of energy supply: demand within the tissue. The actions of both subtypes 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 A₃ receptor resulted in increased inositol triphosphate and intracellular calcium concentrations, which potentiated antigen induced secretion of inflammatory mediators. Therefore, the A₃ 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 feedback 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 excitatory 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 supraventricular arrhythmias.

Adenosine modulates many aspects of renal function, including renin release, glomerular filtration rate and renal blood flow. Compounds which antagonise the renal effects 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 treatment of diabetes mellitus and obesity.

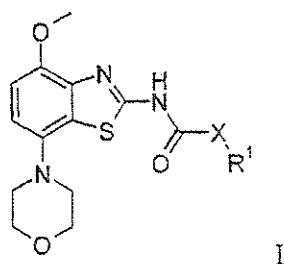
Numerous documents describe the current knowledge on adenosine receptors, for example the following publications:

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 disclosure 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 A₂ 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 for the treatment of 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 cardioprotective 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.

4a

In a first aspect, there is provided compounds of the general formula



wherein

R^1 is cycloalkyl, substituted by OR or is 2-(7-oxa-bicyclo[2.2.1]hept-1-yl)-ethyl;

R is hydrogen, lower alkyl or C(O)-lower alkyl;

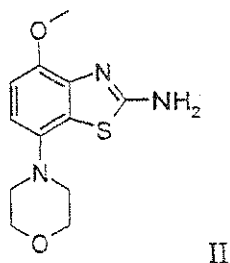
X is $-CHR'$ - ; and

R' is hydrogen or lower alkyl;

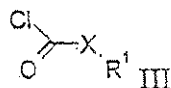
and pharmaceutically acceptable acid addition salts, optically pure enantiomers, racemates or diastereomeric mixtures thereof.

In a second aspect, there is provided a process for preparing a compound of formula I as defined above, which process comprises

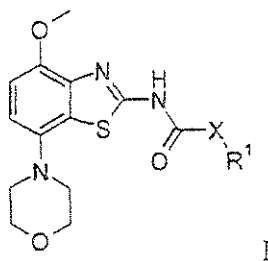
reacting a compound of formula



with a compound of formula



to a compound of formula



wherein R^1 and X have the significances given above,

and

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

In a third aspect, there is provided a compound as defined above, whenever prepared by a process as defined above or by an equivalent method.

In a fourth aspect, there is provided a medicament containing one or more compounds as defined above and pharmaceutically acceptable excipients.

In a fifth aspect, there is provided a medicament as defined above for the treatment of Alzheimer's disease, Parkinson's disease, Huntington's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, ADHD, drug addiction, such as amphetamine, cocaine, opioids, ethanol, nicotine, cannabinoids, or for the treatment of asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse, or for use as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardioprotective agents for coronary artery disease and heart failure.

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

In a seventh aspect, there is provided the use of a compound as defined above for the manufacture of corresponding medicaments for the treatment of Alzheimer's disease, Parkinson's disease, Huntington's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, ADHD, drug addiction, such as amphetamine, cocaine, opioids, ethanol, nicotine, cannabinoids, or for the treatment of asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse, or for use as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardioprotective agents for coronary artery disease and heart failure.

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 "cycloalkyl" denotes a saturated carbocyclic group, containing 3 – 7 carbon atoms.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, 5 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 R¹ is substituted cyclopentyl and X is –CH₂–, for example

- (*cis*)-2-(3-acetoxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-
10 acetamide,
(*cis*)-2-(3-acetoxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-
acetamide,
(-)-(*cis*)-2-(3-hydroxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-
yl)-acetamide or
15 (+)-(*cis*)-2-(3-hydroxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-
yl)-acetamide.

Further preferred are compounds, wherein R¹ is substituted cyclohexyl and X is –CH₂–, for example

- (*cis*)-2-(4-hydroxy-cyclohexyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-
20 acetamide or
(*trans*)-2-(4-hydroxy-cyclohexyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-
acetamide.

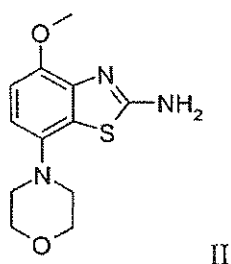
A further preferred embodiment of the invention are those compounds, wherein R¹ is 2-(7-oxa-bicyclo[2.2.1]hept-1-yl)- ethyl, for example

- 25 (*rac*)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-2-(7-oxa-bicyclo[2.2.1]hept-
1-yl)-propionamide.

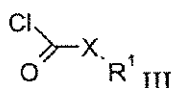
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

- 30 reacting a compound of formula

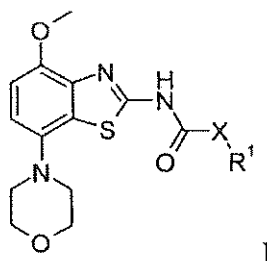
- 6 -



with a compound of formula



to a compound of formula



5

wherein R¹ and X have the significances given above,

and

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

10 In Examples 1 – 7 the preparation of compounds of formula I is 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

15 The intermediate 7-(morpholin-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.

For example a compound of formula I may be prepared as follows:

To a solution of a substituted cycloalkaneacetic acid and *N,N*-dimethylformamide in dichloromethane is added oxalyl chloride and the resulting solution is stirred for about 18 h at ambient temperature. After evaporation of the volatile components *in vacuo*, the residue is taken up in toluene and again evaporated to dryness. The obtained acid chloride of formula (III) is then dissolved in dichloromethane and subsequently treated with *N*-ethyl-diisopropyl amine and 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine (II). After stirring for about 2 h at ambient temperature the mixture is cooled to room temperature and treated with saturated aqueous sodium hydrogen carbonate, extracted and dried. Separation by preparative chiral HPLC affords the desired compound of formula I.

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 such as 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.

5 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.

10 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 CaCl₂ and 10 mM MgCl₂ (pH 7.4) (buffer A). The [³H]-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 1 hour at room temperature before centrifugation and then bound ligand determined using a Packard Topcount scintillation counter. IC₅₀ values were calculated using a non-linear curve fitting program and Ki values calculated using the Cheng-Prusoff equation.

The pK_i value of compounds of the present application are in the range of 7.7 to 8.5. The preferred compounds show a pK_i > 8.0.

Example No.	hA ₂ (pKi)	Example No.	hA ₂ (pKi)
1	8.0	5	8.2
2	8.2	6	8.5
3	8.2	7	7.7
4	8.2		

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, 5 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, 10 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, 15 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 20 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 25 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 cardioprotective 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 Parkinson's disease, neuroprotection or certain depressive disorders.

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)

	<u>Item</u>	<u>Ingredients</u>	<u>mg/tablet</u>			
			5 mg	25 mg	100 mg	500 mg
20	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
25	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.
- 30 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
5	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

10 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
 15 limit its scope.

Example 1

(*cis*)-2-(3-Acetoxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-acetamide

To a solution of (*rac*)-(*cis*)-3-(acetyloxy)-cyclopentaneacetic acid (770 mg, 4.1 mmol)
 20 and *N,N*-dimethylformamide (0.01 ml, 0.13 mmol) in dichloromethane (10 ml) were added oxalyl chloride (1.4 ml, 17 mmol) and the resulting solution stirred for 18 h at ambient temperature. After evaporation of the volatile components *in vacuo*, the residue was taken up in toluene (10 ml) and again evaporated to dryness. The obtained acid chloride was then dissolved in dichloromethane (20 ml) and subsequently treated with *N*-ethyl-diisopropyl amine (2.5 ml, 15 mmol) and 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine (960 mg, 3.6 mmol). After stirring for 2 h at ambient temperature and another hour at 50°C, the mixture was cooled to room temperature and treated with saturated aqueous sodium hydrogen carbonate (15 ml) and extracted twice with dichloromethane (20 ml each). After drying over magnesium sulphate and
 25 evaporatuion of the solvents, flash chromatography (silica, eluent dichloromethane/ethyl acetate 85:15) afforded (*rac*)-(*cis*)-2-(3-acetoxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-acetamide as off-white solid. Separation by:
 30

preparative chiral HPLC (Chiralpack AD, eluent heptane/isopropanol 85:15) afforded the title compound as first eluting isomer. Light yellow solid (4% yield). MS: $m/e=434(M+H^+)$, mp 171-172°C.

Following the general method of example 1 the compounds of examples 2 to 7 were
5 prepared.

Example 2

(*cis*)-2-(3-Acetoxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-acetamide

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and and (*rac*)-(*cis*)-acetic acid 3-chlorocarbonylmethyl-cyclopentyl ester, (*rac*)-(*cis*)-2-(3-acetoxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-acetamide was obtained. Separation by preparative chiral HPLC (Chiralpack AD, eluent heptane/isopropanol 85:15) afforded the title compound as later eluting isomer. Light yellow crystals (4% yield). MS: $m/e=434(M+H^+)$, mp 172-173°C.

15

Example 3

(-)-(*cis*)-2-(3-Hydroxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-acetamide

(*cis*)-2-(3-Acetoxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-acetamide (first eluting isomer, 64 mg, 0.15 mmol), potassium carbonate (82 mg, 0.59
20 mmol) and sodium methoxide (5.4M in methanol, 1.37 ul, 0.0074 mmol) are stirred together in methanol (6 ml) for 4 h at ambient temperature. Evaporation of the solvent, dissolution in methylene chloride and extraction with saturated sodium carbonate afforded, after drying and evaporation of the methylene chloride, a crude material. After crystallization from diethyl ether, the title compound was obtained as light yellow crystals
25 (91% yield). MS: $m/e=392(M+H^+)$, mp 168-171°C, $\alpha_{589}=-4.87$ (CH₂Cl₂, c= 1.1%).

Example 4

(+)-(*cis*)-2-(3-Hydroxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-acetamide

(*cis*)-2-(3-Acetoxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-acetamide (later eluting isomer, 64 mg, 0.15 mmol), potassium carbonate (82 mg, 0.59
30 mmol) and sodium methoxide (5.4M in methanol, 1.37 ul, 0.0074 mmol) are stirred together in methanol (6 ml) for 4 h at ambient temperature. Evaporation of the solvent,

dissolution in methylene chloride and extraction with saturated sodium carbonate afforded, after drying and evaporation of the methylene chloride, a crude material. After crystallization from diethyl ether, the title compound was obtained as light yellow crystals (90% yield). MS: $m/e = 392(M+H^+)$, mp 167-170°C, $\alpha_{D20}^{25} = +4.32$ (CH₂Cl₂, $c = 1.1\%$).

5

Example 5

(*cis*)-2-(4-Hydroxy-cyclohexyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-acetamide

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and (*cis*)-acetic acid 4-chlorocarbonylmethyl-cyclohexyl ester, the title compound was synthesized in exact the
10 same manner as (*cis*)-2-(3-acetoxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-acetamide and obtained as light yellow crystals (33% yield). MS: $m/e = 406(M+H^+)$, mp 212-216°C.

Example 6

(*trans*)-2-(4-Hydroxy-cyclohexyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-
15 acetamide

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and (*trans*)-acetic acid 4-chlorocarbonylmethyl-cyclohexyl ester, the title compound was synthesized in exact the same manner as described for (*cis*)-2-(4-Hydroxy-cyclohexyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-acetamide and obtained as light yellow crystals (51%
20 yield). MS: $m/e = 406(M+H^+)$, mp 190-192°C.

Example 7

(*rac*)-N-(4-Methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-2-(7-oxa-bicyclo[2.2.1]hept-1-yl)-propionamide

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and 2-(7-oxa-bicyclo[2.2.1]hept-1-yl)-propionyl chloride, the title compound was obtained as white
25 solid (67% yield). MS: $m/e = 418(M+H^+)$, mp 195-197°C.

Example 8 (intermediate)

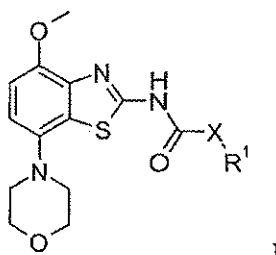
(*rac*)-2-(7-Oxa-bicyclo[2.2.1]hept-1-yl)-propionic acid

The title compound was prepared by standard Wittig-Horner reaction from 4-hydroxy-cyclohexanone, 2-(diethoxy-phosphoryl)-propionic acid ethyl ester and sodium hydride
30 (J. Boutagy, R. Thomas, *Chem. Rev.* 1974, 74, 87-99) and subsequent saponification with

potassium hydroxide in ethanol. After recrystallization from n-heptane, the title compound was obtained as white solid. EI-MS: $m/e = 170(M^+)$, 1H -NMR (90 MHz, $CDCl_3$, TMS): δ 1.3 (d, $J=8$ Hz, 3H, Me), 1.7 (m, 8H, CH₂), 3.0 (q, $J=8$ Hz, 1H, CH-Me), 4.6 (t, $J=4.5$ Hz, 1H, CH-O), 7.2 (s, 1H, COOH), mp 61-62°C, bp 120°C (0.008 mbar).

Claims

1. Compounds of the general formula



wherein

- 5 R^1 is cycloalkyl, substituted by OR or is 2-(7-oxa-bicyclo[2.2.1]hept-1-yl)-ethyl;
 R is hydrogen, lower alkyl or C(O)-lower alkyl;
 X is $-CHR'$; and
 R' is hydrogen or lower alkyl;

and pharmaceutically acceptable acid addition salts, optically pure enantiomers,
 10 racemates or diastereomeric mixtures thereof.

2. Compounds of formula I according to claim 1, wherein R^1 is substituted cyclopentyl and X is $-CH_2-$.

3. Compounds of formula I according to claim 2, wherein the compounds are

- (*cis*)-2-(3-acetoxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-
 15 acetamide,
 (*cis*)-2-(3-acetoxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-
 acetamide,
 (-)-(*cis*)-2-(3-hydroxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-
 yl)-acetamide or
 20 (+)-(*cis*)-2-(3-hydroxy-cyclopentyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-
 yl)-acetamide.

4. Compounds of formula I according to claim 1, wherein R^1 is substituted cyclohexyl and X is $-CH_2-$.

5. Compounds of formula I according to claim 4, wherein the compounds are

(*cis*)-2-(4-hydroxy-cyclohexyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-acetamide or

(*trans*)-2-(4-hydroxy-cyclohexyl)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-acetamide.

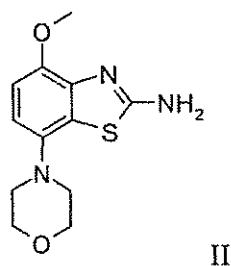
- 5 6. Compounds of formula I according to claim 1, wherein R¹ is 2-(7-oxa-bicyclo[2.2.1]hept-1-yl)-ethyl.

7. Compounds of formula I according to claim 6, wherein the compound is

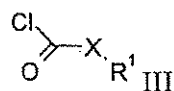
(*rac*)-N-(4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-2-(7-oxa-bicyclo[2.2.1]hept-1-yl)-propionamide.

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

reacting a compound of formula

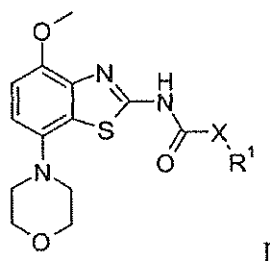


with a compound of formula



15

to a compound of formula



wherein R¹ and X have the significances given above,
and

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

5

9. A compound according to any one of claims 1 to 7, whenever prepared by a process as claimed in claim 10 or by an equivalent method.

10

10. A medicament containing one or more compounds as claimed in any one of claims 1 to 7 and pharmaceutically acceptable excipients.

15

11. A medicament according to claim 10 for the treatment of Alzheimer's disease, Parkinson's disease, Huntington's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, ADHD, drug addiction, such as amphetamine, cocaine, opioids, ethanol, nicotine, cannabinoids, or for the treatment of asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse, or for use as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardioprotective agents for coronary artery disease and heart failure.

20

12. A compound according to any one of claims 1 to 7 for use as a medicament.

25

13. The use of a compound in any one of claims 1 to 9 for the manufacture of corresponding medicaments for the treatment of Alzheimer's disease, Parkinson's disease, Huntington's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, ADHD, drug addiction, such as amphetamine, cocaine, opioids, ethanol, nicotine, cannabinoids, or for the treatment of asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse, or for use as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardioprotective agents for coronary artery disease and heart failure.

30