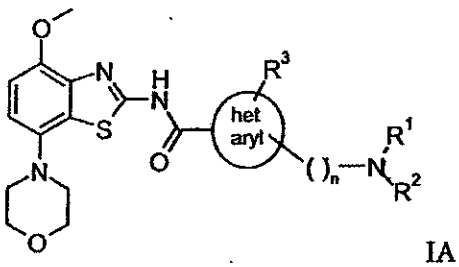
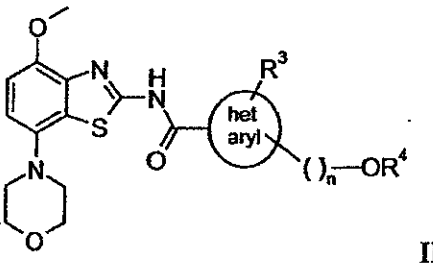
Case 22588

Benzothiazole derivatives

The present invention relates to compounds of the general formulas



IA or



IB

wherein

R^1, R^2 independently from each other are lower alkyl or $-(CH_2)_m$-O-lower alkyl, or form together with the N atom to which they are attach a heterocyclic ring;

R^3 is hydrogen or lower alkyl;

R^4 is lower alkyl;

hetaryl is 3*H*-imidazole-2,4-diyl or 1*H*-pyrazole-1,4-diyl;

n is 1 or 2 and

m is 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

It has surprisingly been found that the compounds of general formulas IA or IB 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.

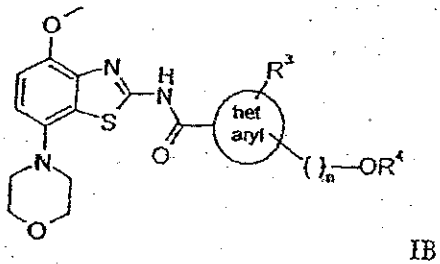
Numerous documents describe the current knowledge on adenosine receptors, for example the following publications:

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 embodiments disclosed herein are the compounds of formulas IA or IB per se, the use of compounds of formulas IA or IB 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 formulas IA or IB 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.

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



IB

wherein

R^3 is hydrogen or lower alkyl;

R^4 is lower alkyl;

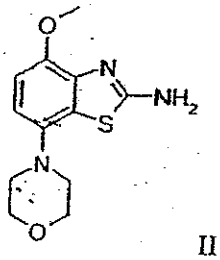
hetaryl is 3*H*-imidazole-2,4-diyl or 1*H*-pyrazole-1,4-diyl; and

n is 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

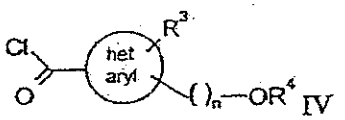
According to a second aspect, there is provided a process for preparing a compound of formula IB as defined above, which process comprises

a) reacting a compound of formula



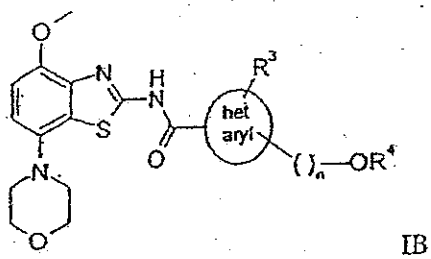
II

with a compound of formula



IV

to a compound of formula



IB

wherein R^3, R^4, hetaryl and n have the significances given as defined above, and

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

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

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

According to a fifth 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 against asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse, or is useful as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardiaprotective 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 "heterocyclic ring" denotes a saturated carbon ring system which may have in addition to the N atom one heteroatom, preferably O or N-atoms. Examples of such rings are morpholin or pyrrolidin.

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 IA. More specifically, preferred are compounds, wherein hetaryl is 3*H*-imidazole-2,4-diyl, for example the following compounds:

2-{[(2-methoxy-ethyl)-methyl-amino]-methyl}-3-methyl-3*H*-imidazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,
2-dimethylaminomethyl-3-methyl-3*H*-imidazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,
3-methyl-2-morpholin-4-ylmethyl-3*H*-imidazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide or
3-methyl-2-pyrrolidin-1-ylmethyl-3*H*-imidazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide.

Further preferred are compounds from formula IA, wherein hetaryl is 1*H*-pyrazole-1,4-diyl, for example the following compounds:

1-(2-pyrrolidin-1-yl-ethyl)-1*H*-pyrazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide,
1-(2-dimethylamino-ethyl)-1*H*-pyrazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide or
1-(2-morpholin-4-yl-ethyl)-1*H*-pyrazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide.

Preferred compounds of the present application are further compounds of formula IB. More specifically, preferred are compounds, wherein hetaryl is 3*H*-imidazole-2,4-diyl, for example the following compound:

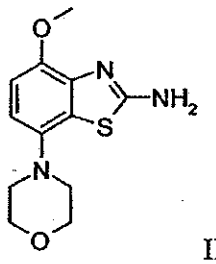
2-methoxymethyl-3-methyl-3*H*-imidazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide.

Further preferred are compounds from formula IB, wherein hetaryl is 1*H*-pyrazole-1,4-diyl, for example the following compound:

1-(2-methoxy-ethyl)-1*H*-pyrazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide.

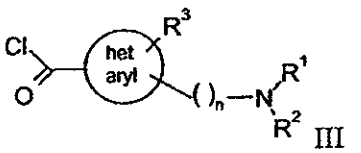
The present compounds of formulsa IA or IB and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

a) reacting a compound of formula



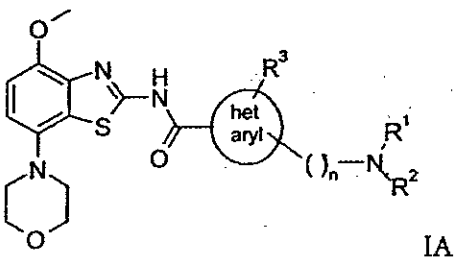
II

with a compound of formula



III

to a compound of formula

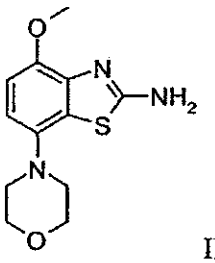


IA

wherein R^1, R^2, R^3, hetaryl and n have the significances given above,

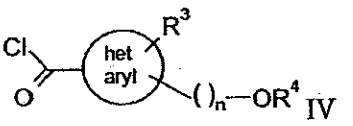
or

a) reacting a compound of formula



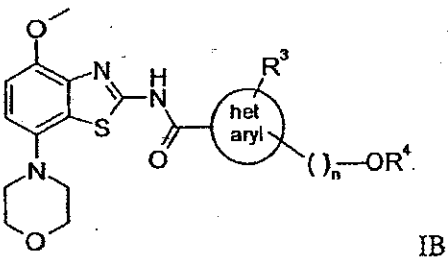
II

with a compound of formula



IV

to a compound of formula



IB

wherein R^1, R^2, R^3, hetaryl and n have the significances given above, and,

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

In Examples 1 – 9 the preparation of compounds of formulas IA and IB 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 formulas IA and IB

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 formulas IA and IB using the intermediate of formula II is generically described in WO01/97786.

Compounds of formula IA:

To a solution of 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine II in tetrahydrofurane at about -70°C is added a solution of tert.butyllithium solution in pentane and the suspension is warmed to about -30°C. At this time, a solution of a corresponding hetaryl-carboxylic acid phenyl ester (in analogy to formula III) in tetrahydrofurane is added and the mixture is stirred for about 1 h at room temperature. The reaction mixture is treated with saturated ammonium chloride solution, followed by ethyl acetate and the formed precipitate is collected, dried and purified in conventional manner.

Compounds of formula IB:

The compounds of formula IB may be prepared in analogy to the above mentioned method, using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine II and hetaryl-carboxylic acid phenyl ester (in analogy to formula IV).

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 formulas IA or IB

The compounds of formulas IA or IB 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 formulas IA or IB 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 formulas IA or IB 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 8.8 to 9.4. The preferred compounds show a pKi > 9.0.

Example No.	hA_2 (pKi)	Example No.	hA_2 (pKi)
1	9.3	6	9.1
2	9.2	7	9.0
3	9.2	8	9.4
4	8.8	9	9.3
5	9.1		

The compounds of formulas IA or IB and the pharmaceutically acceptable salts of the compounds of formulas IA or IB 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 formulas IA or IB 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 formulas IA or IB 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 formulas IA or IB 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 formulas IA or IB as well as their pharmaceutically acceptable salts are useful in the control or prevention of illnesses based on the adenosine receptor antagonistic activitysuch as 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 against asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse, or are useful as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardiaprotective agents for coronary artery disease and heart failure.

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)

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

2-{[(2-Methoxy-ethyl)-methyl-amino]-methyl}-3-methyl-3*H*-imidazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide

To a solution of 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine (220 mg, 0.83 mmol) in dry tetrahydrofurane (10 ml) at -70°C is slowly added a solution of tert.butyllithium (1.1 ml of a 1.5 M solution in pentane corresponding to 1.65 mmol) and the remaining suspension slowly warmed to about -30°C. At this time, a solution of 2-{[(2-methoxy-ethyl)-methyl-amino]-methyl}-3-methyl-3*H*-imidazole-4-carboxylic acid phenyl ester (252 mg, 0.83 mmol) in tetrahydrofurane (4 ml) was added and the mixture stirred for 1 h at room temperature. The reaction mixture was treated with saturated

aqueous ammonium chloride solution (10 ml) followed by ethyl acetate (20 ml) and the formed precipitate collected. The phases were separated and the aqueous phase extracted three times with ethyl acetate. The combined organic layers were extracted twice with water, dried with magnesium sulfate and evaporated to dryness to yiled anoher batch of raw product. Flash-chromatography on silica (eluent trichloromethane containing 30% of ethyl acetate) yielded the title compound as white solid (31% yield). MS: m/e= 475($M+H^+$), mp 176-178°C.

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

Example 2

2-Dimethylaminomethyl-3-methyl-3*H*-imidazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and 2-dimethylaminomethyl-3-methyl-3*H*-imidazole-4-carboxylic acid phenyl ester, the title compound was obtained as off-white solid (49% yield). MS: m/e= 431($M+H^+$), mp 229-231°C.

Example 3

3-Methyl-2-morpholin-4-ylmethyl-3*H*-imidazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and 3-methyl-2-morpholin-4-ylmethyl-3*H*-imidazole-4-carboxylic acid phenyl ester, the title compound was obtained as off-white solid (21% yield). MS: m/e= 473($M+H^+$), mp 244-246°C.

Example 4

3-Methyl-2-pyrrolidin-1-ylmethyl-3*H*-imidazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and 3-methyl-2-pyrrolidin-1-ylmethyl-3*H*-imidazole-4-carboxylic acid phenyl ester, the title compound was obtained as off-white solid (76% yield). MS: m/e= 457($M+H^+$), mp 255°C.

Example 5

1-(2-Pyrrolidin-1-yl-ethyl)-1*H*-pyrazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and 1-(2-pyrrolidin-1-yl-ethyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester, the title compound was obtained as white solid (13% yield). MS: m/e= 457($M+H^+$), mp 190-192°C.

Example 6

1-(2-Dimethylamino-ethyl)-1*H*-pyrazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and 1-(2-dimethylamino-ethyl)-1*H*-pyrazole-4-carboxylic acid phenyl ester, the title compound was obtained as white crystals 54% yield). MS: m/e= 431($M+H^+$), mp 203-205°C.

Example 7

1-(2-Morpholin-4-yl-ethyl)-1*H*-pyrazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and 1-(2-morpholin-4-yl-ethyl)-1*H*-pyrazole-4-carboxylic acid phenyl ester, the title compound was obtained as white crystals 42% yield). MS: m/e= 473($M+H^+$), mp 204-207°C.

Example 8

1-(2-Methoxy-ethyl)-1*H*-pyrazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and 1-(2-methoxy-ethyl)-1*H*-pyrazole-4-carboxylic acid phenyl ester, the title compound was obtained as light yellow crystals 43% yield). MS: m/e= 418($M+H^+$), mp 191-193°C.

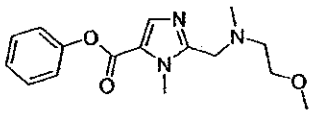
Example 9

2-Methoxymethyl-3-methyl-3*H*-imidazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide

Using 4-methoxy-7-morpholin-4-yl-benzothiazol-2-ylamine and 2-methoxymethyl-3-methyl-3*H*-imidazole-4-carboxylic acid phenyl ester, the title compound was obtained as white crystals 48% yield). MS: m/e= 418($M+H^+$), mp 242-245°C.

Intermediates:

Example 10

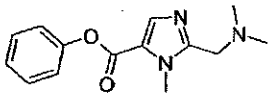


2-{[(2-Methoxy-ethyl)-methyl-amino]-methyl}-3-methyl-3*H*-imidazole-4-carboxylic acid phenyl ester

To a solution of 1-{2-[(2-methoxy-ethyl)-methyl-amino]-ethyl}-1H-pyrazole-4-carboxylic acid (467 mg, 1.54 mmol) and phenol (145 mg, 1.54 mmol) in dimethylformamide (8 ml) was added under argon at 0°C a solution of 4-dimethylaminopyridine (94 mg, 0.77 mmol) and brom-tripyrrolidinophosphonium-hexafluorophosphat (790 mg, .70 mmol) in dimethylformamide (8 ml) followed by triethylamine (0.65 ml, 4.6 mmol). After 48 h at ambient temperature, the reaction mixture is treated with saturated aqueous ammonium chloride (25 ml) and extracted three times with ethyl acetate (25 ml each). The combined organic layers are dryed with magnesium sulphate and evaporated to dryness. Flash chromatography (silice, eluent dichloromethane containing 4% methanol) afforded the title compound as colorless oil (55% yield). MS: m/e= 304($M+H^+$).

Following the general method of example 10 the compounds of examples 11 to 16 were prepared.

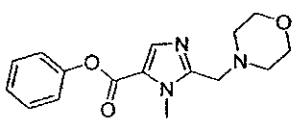
Example 11



2-Dimethylaminomethyl-3-methyl-3*H*-imidazole-4-carboxylic acid phenyl ester

Using 2-dimethylaminomethyl-3-methyl-3*H*-imidazole-4-carboxylic acid, the title compound was obtained as light brown wax (43% yield). MS: m/e= 260($M+H^+$).

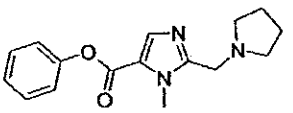
Example 12



3-Methyl-2-morpholin-4-ylmethyl-3*H*-imidazole-4-carboxylic acid phenyl ester

Using 3-methyl-2-morpholin-4-ylmethyl-3*H*-imidazole-4-carboxylic acid, the title compound was obtained as colorless wax (40% yield). MS: m/e= 302($M+H^+$).

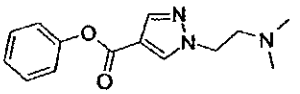
Example 13



3-Methyl-2-pyrrolidin-1-ylmethyl-3*H*-imidazole-4-carboxylic acid phenyl ester

Using 3-methyl-2-pyrrolidin-1-ylmethyl-3*H*-imidazole-4-carboxylic acid, the title compound was obtained as brown oil (22% yield). MS: m/e= 286($M+H^+$).

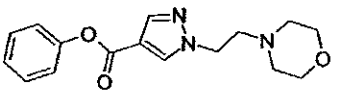
Example 14



1-(2-Dimethylamino-ethyl)-1*H*-pyrazole-4-carboxylic acid phenyl ester

Using 1-(2-dimethylamino-ethyl)-1*H*-pyrazole-4-carboxylic acid, the title compound was obtained as colorless liquid (56% yield). MS: m/e= 260($M+H^+$).

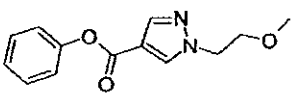
Example 15



1-(2-Morpholin-4-yl-ethyl)-1*H*-pyrazole-4-carboxylic acid phenyl ester

Using 1-(2-morpholin-4-yl-ethyl)-1*H*-pyrazole-4-carboxylic acid, the title compound was obtained as white solid (33% yield). MS: m/e= 302($M+H^+$), mp 73-76°C.

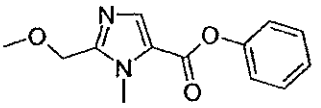
Example 16



1-(2-Methoxy-ethyl)-1*H*-pyrazole-4-carboxylic acid phenyl ester

Using, 1-(2-methoxy-ethyl)-*1H*-pyrazole-4-carboxylic acid, the title compound was obtained as colorless oil (55% yield). MS: m/e= 247($M-H^+$).

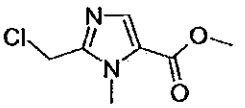
Example 17



2-Methoxymethyl-3-methyl-3*H*-imidazole-4-carboxylic acid phenyl ester

Using, 2-methoxymethyl-3-methyl-3*H*-imidazole-4-carboxylic acid, the title compound was obtained as light yellow solid (39 % yield). MS: m/e= 247($M-H^+$), mp 54-58°C.

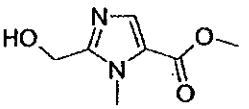
Example 18



2-Chloromethyl-3-methyl-3*H*-imidazole-4-carboxylic acid methyl ester hydrochloride

A solution of 2-hydroxymethyl-3-methyl-3*H*-imidazole-4-carboxylic acid methyl ester (250 mg, 1.5 mmol) in ethyl acetate/methanol 6 ml, 1:1) was converted to the hydrochloride by usage of an excess of an etheral solution of hydrogen chloride. After evaporation, the light brown residue was treated with thionyl chloride (1.1 ml, 15 mmol) and stirred for 0.5 h. After evaporation, the title compound was obtained as brown solid (100% yield). MS: m/e= 189($M+H^+$), mp 106-108°C.

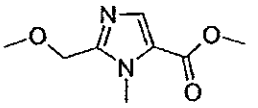
Example 19



2-Hydroxymethyl-3-methyl-3*H*-imidazole-4-carboxylic acid methyl ester

A suspension of 3-methyl-3*H*-imidazole-4-carboxylic acid methyl ester (4.0 g, 29 mmol) and paraformaldehyde (18 g, corresponding to 570 mmol) in methanol (40 ml) was heated in a sealed vessel to 135°C for 6 0 h. After cooling to ambient temperature, the solution was evaporated to dryness. Flash chromatography (silica, eluent dichloromethane containing 5% methanol) afforded the title compound as white crystals (56% yield). MS: m/e= 171($M+H^+$), mp 145-147°C.

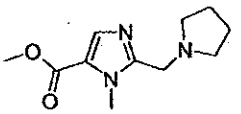
Example 20



2-Methoxymethyl-3-methyl-3*H*-imidazole-4-carboxylic acid methyl ester

A solution of 2-hydroxymethyl-3-methyl-3*H*-imidazole-4-carboxylic acid methyl ester (250 mg, 1.5 mmol) in dimethylformamide (10 ml) is subsequently treated with sodium hydride (71 mg 60% dispersion in mineral oil, 1.8 mmol) and after 0.5 h with dimethyl sulfate (0.17 ml, 1.8 mmol). After 1 h at ambient temperature, the volatile componantes are removed *in vacuo*, the residue taken up in ethyl accetate (20 ml) and water (20 ml) and the phases separated. The aqueous phase is extracted twice with ethyl acetate (20 ml each) and the combined organic layers are dryed with magnesium sulfate and evaporated to dryness. Flash chromatography (silica, eluent dichloromethane containing 4% methanol) afforded the title compound as white crystals (42% yield). MS: m/e= 185($M+H^+$), mp 74-77°C.

Example 21

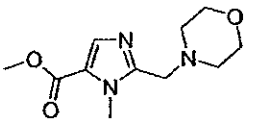


3-Methyl-2-pyrrolidin-1-ylmethyl-3*H*-imidazole-4-carboxylic acid methyl ester

2-Chloromethyl-3-methyl-3*H*-imidazole-4-carboxylic acid methyl ester hydrochloride (224 mg, 1 mmol) was dissolved in pyrrolidine (2.3 ml, 28 mmol) and stirred at ambient temperature for, the title compound was obtained as light yellow oil 45 min. After evaporation to dryness, the residue is taken up in ethyl acetate and saturated aqueous sodium carbonate (20 ml) and the phases separated. The aqueous phase is extracted twice with ethyl acetate (20 ml each) and the combined organic layers are dryed with magnesium sulfate and evaporated to dryness. Flash chromatography (silica, eluent dichloromethane7methanol 19:1) afforded the title compound aslight yellow oil (61% yield). MS: m/e= 224($M+H^+$).

Following the general method of example 21 the compounds of examples 22 to 24 were prepared.

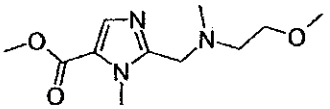
Example 22



3-Methyl-2-morpholin-4-ylmethyl-3*H*-imidazole-4-carboxylic acid methyl ester

Using 2-chloromethyl-3-methyl-3*H*-imidazole-4-carboxylic acid methyl ester hydrochloride and morpholine, the title compound was obtained as light brown solid (>98% yield). MS: m/e= 240($M+H^+$).

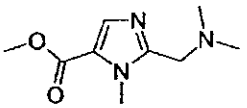
Example 2 3



2-{[(2-Methoxy-ethyl)-methyl-amino]-methyl}-3-methyl-*3H*-imidazole-4-carboxylic acid methyl ester

Using 2-chloromethyl-3-methyl-3*H*-imidazole-4-carboxylic acid methyl ester hydrochloride and (2-methoxy-ethyl)-methyl-amine, the title compound was obtained as light brown viscous oil (92% yield). MS: m/e= 242($M+H^+$).

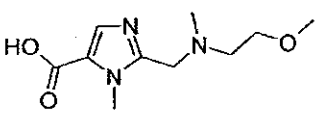
Example 24



2-Dimethylaminomethyl-3-methyl-3*H*-imidazole-4-carboxylic acid methyl ester

Using 2-chloromethyl-3-methyl-3*H*-imidazole-4-carboxylic acid methyl ester hydrochloride and dimethylamine (33% solution in ethanol), the title compound was obtained as brown viscous oil (85% yield). MS: m/e= 198($M+H^+$).

Example 25

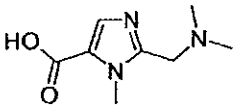


2-{[(2-Methoxy-ethyl)-methyl-amino]-methyl}-3-methyl-3*H*-imidazole-4-carboxylic acid

2-{[(2-Methoxy-ethyl)-methyl-amino]-methyl}-3-methyl-3*H*-imidazole-4-carboxylic acid methyl ester (380 mg, 1.58 mmol) were dissolved in methanol (4.5 ml) and treated with water (0.39 ml) and lithium hydroxide monohydrate (80 mg, 1.89 mmol) and stirred for 18 h at ambient temperature. The reaction mixture is the carefully acidified at 0°C with 1N hydrochloric acid and evaporated to dryness. The title compound was obtained as mixture with lithium chloride and used without further purification. Light brown solid (>98% yield by 1H-NMR). MS: m/e= 226($M-H^+$).

Following the general method of example 25 the compounds of examples 26 to 28 were prepared.

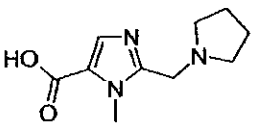
Example 26



2-Dimethylaminomethyl-3-methyl-3*H*-imidazole-4-carboxylic acid

Using 2-dimethylaminomethyl-3-methyl-3*H*-imidazole-4-carboxylic acid methyl ester, the title compound was obtained as light brown solid (>98% yield by 1H-NMR). MS: m/e= 182($M-H^+$).

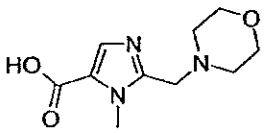
Example 27



3-Methyl-2-pyrrolidin-1-ylmethyl-3*H*-imidazole-4-carboxylic acid

Using 3-methyl-2-pyrrolidin-1-ylmethyl-3*H*-imidazole-4-carboxylic acid methyl ester, the title compound was obtained as brown wax (>98% yield by 1H-NMR). MS: m/e= 208($M-H^+$).

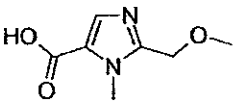
Example 28



3-Methyl-2-morpholin-4-ylmethyl-3*H*-imidazole-4-carboxylic acid

Using 3-methyl-2-morpholin-4-ylmethyl-3*H*-imidazole-4-carboxylic acid methyl ester, the title compound was obtained as light brown solid (>98% yield by 1H-NMR). MS: m/e= 224($M-H^+$).

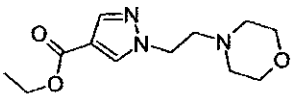
Example 29



2-Methoxymethyl-3-methyl-3*H*-imidazole-4-carboxylic acid

Using 2-methoxymethyl-3-methyl-3*H*-imidazole-4-carboxylic acid methyl ester, the title compound was obtained as brown solid and used withoud further characterization.

Example 30

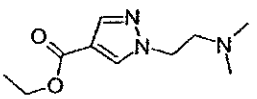


1-(2-Morpholin-4-yl-ethyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester

1*H*-Pyrazole-4-carboxylic acid (300 mg, 2.1 mmol), 4-(2-chloroethyl)morpholine (822 mg, 4.3 mmol) and potassium carbonate (1.2 g, 8.6 mmol) are dissolved in dimethylformamide (12 ml) and stirred for 6.5 h at 75 °C. Aftr stnding for another 18 h at ambient temperature, the reaction mixture was treated with water (25 ml) and extracted four times with ethyl acetate (25 ml each). The combined organic layers are extracted four times with water, dryed with magnesium sulphate and evaporated *in vacuo*. Flash chromatography (silice, eluent dichloromethane containing 4% methanol) afforded the title compound as colorles liquid (70% yield). MS: m/e= 254($M+H^+$).

Following the general method of example 30 the compounds of examples 31 to 32 were prepared.

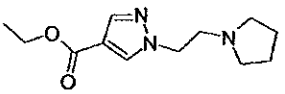
Example 31



1-(2-Dimethylamino-ethyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester

Using 1*H*-pyrazole-4-carboxylic acid and (2-chloro-ethyl)-dimethyl-amine, the title compound was obtained as colorless liquid(72% yield). MS: m/e= 212($M+H^+$).

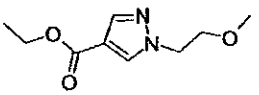
Example 32



1-(2-Pyrrolidin-1-yl-ethyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester

Using 1*H*-pyrazole-4-carboxylic acid and 1-(2-chloro-ethyl)-pyrrolidine, the title compound was obtained as light brown oil (65% yield). MS: m/e= 238($M+H^+$).

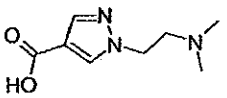
Example 33



1-(2-Methoxy-ethyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester

Using 1*H*-pyrazole-4-carboxylic acid and 2-bromoethyl methyl ether, the title compound was obtained as colorless oil (67% yield). MS: m/e= 199($M+H^+$).

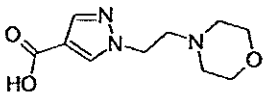
Example 34



1-(2-Dimethylamino-ethyl)-1*H*-pyrazole-4-carboxylic acid

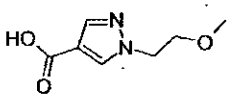
Using 1-(2-dimethylamino-ethyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester, the title compound was prepared in the same manner as described for 2-{[(2-methoxy-ethyl)-methyl-amino]-methyl}-3-methyl-3*H*-imidazole-4-carboxylic acid. White solid (>98% yield by ^{1}H-NMR). MS: m/e= 184($M+H^+$).

Example 35



Using 1-(2-morpholin-4-yl-ethyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester, the title compound was obtained as light yellow solid and used without further characterization. MS: m/e= 224($M-H^+$).

Example 36

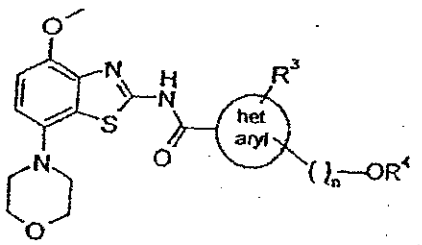


1-(2-Methoxy-ethyl)-*1H*-pyrazole-4-carboxylic acid

Using, 1-(2-methoxy-ethyl)-1*H*-pyrazole-4-carboxylic acid ethyl ester, the title compound was obtained as colorless oil and used without further characterization. MS: m/e= 169($M-H^+$).

Claims

1. Compounds of the general formula



IB

wherein

R^3 is hydrogen or lower alkyl;

R^4 is lower alkyl;

hetaryl is 3*H*-imidazole-2,4-diyl or 1*H*-pyrazole-1,4-diyl; and

n is 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

2. Compounds according to claim 1, wherein the hetaryl group is 3*H*-imidazole- 2,4-diyl.

3. Compounds according to claim 2, wherein the compound is

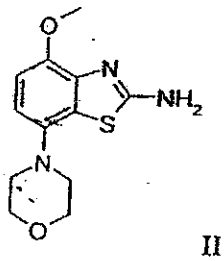
2-methoxymethyl-3-methyl-3*H*-imidazole-4-carboxylic acid (4-methoxy-7-morpholin- 4-yl-benzothiazol-2-yl)-amide.

4. Compounds according to claim 1, wherein the hetaryl group is 1*H*-pyrazole- 1,4-diyl.

5. Compounds according to claim 4, wherein the compound is 1-(2-methoxy-ethyl)-1*H*-pyrazole-4-carboxylic acid (4-methoxy-7-morpholin-4-yl-benzothiazol-2-yl)-amide.

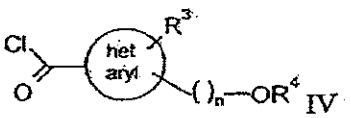
6. A process for preparing a compound of formula IB as defined in claim 1, which process comprises

a) reacting a compound of formula



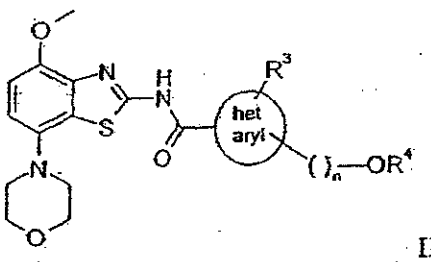
II

with a compound of formula



IV

to a compound of formula



IB

wherein R^3, R^4, hetaryl and n have the significances given in claim 1, and

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

7. A compound according to any one of claims 1 to 5, whenever prepared by a process as claimed in claim 6 or by an equivalent method.

8. A medicament containing one or more compounds as claimed in any one of claims 1 to 5 and pharmaceutically acceptable excipients.

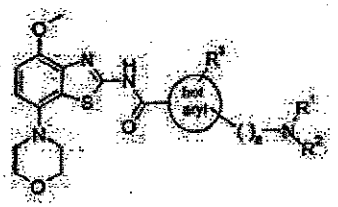
9. A medicament according to claim 8 for the treatment of Alzheimer's disease, Parkinson's disease, Huntington's disease, neuroprotection, schizophrenia, anxiety, pain, respiration deficits, depression, ADHD, drug addiction, such as amphetamine, cocaine, opioids, ethanol, nicotine, cannabinoids, or against asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse, or is useful as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardiaprotective agents for coronary artery disease and heart failure.

10. The use of a compound in any one of claims 1 to 5 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 against asthma, allergic responses, hypoxia, ischaemia, seizure and substance abuse, or is useful as sedatives, muscle relaxants, antipsychotics, antiepileptics, anticonvulsants and cardiaprotective agents for coronary artery disease and heart failure.

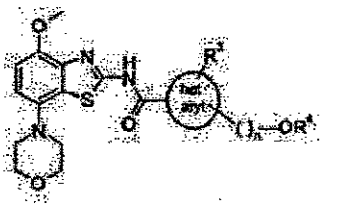
BENZOTHIAZOLE DERIVATIVES

ABSTRACT

The present invention relates to compounds of the general formula (IA) (IB) wherein R^1, R^2 independently from each other are lower alkyl or $-(CH_2)_m$-O-lower alkyl, or form together with the N atom to which they are attach a heterocyclic ring; R^3 is hydrogen or lower alkyl; R^4 is lower alkyl; hetaryl is 3*H*-imidazole-2,4-diyl or 1*H*-pyrazole-1,4-diyl; n is 1 or 2 and m is 1 or 2; and to pharmaceutically acceptable acid addition salts thereof. These compounds may be used 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 cardiaprotective agents for coronary artery disease and heart failure



(IA)



(IB)

(No suitable figure)