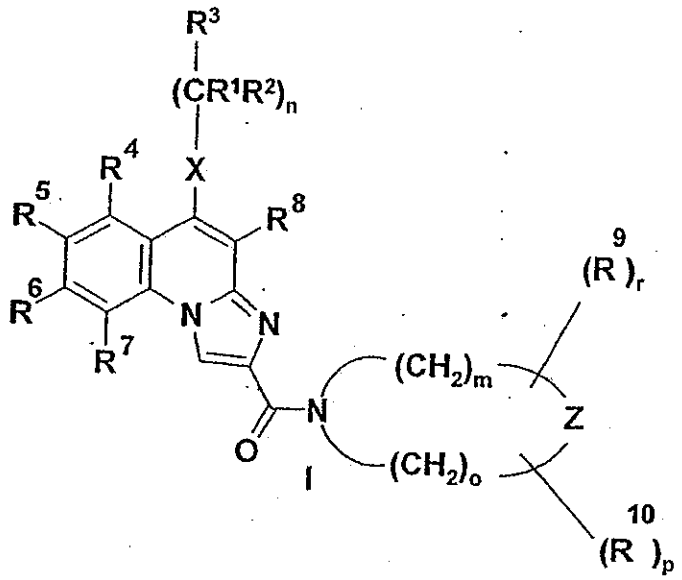
IMIDAZOQUINOLINE DERIVATIVES AS ADENOSINE A3 RECEPTOR LIGANDS

The present invention relates to the adenosine A_3 receptor ligands of the general formula (I),



within those preferably to the antagonists, as well as to their salts, solvates and isomers, to the pharmaceutical compositions containing them, to the use of the compounds of the general formula (I) and their salts, solvates and isomers, and to the preparation of the compounds of the general formula (I) and their salts, solvates and isomers.

Adenosine is a well-known component of several endogenous molecules (ATP, NAD^+, nucleic acids). Besides, it plays an important regulatory role in many physiological processes. The effect of adenosine on heart function was discovered already in 1929. (Drury and Szentgyörgyi, J Physiol 68:213, 1929). The identification of an increasing number of physiological functions mediated by adenosine and the discovery of new adenosine receptor subtypes give possibilities for therapeutic application of specific ligands (Poulse, S. A. and Quinn, R. J. Bioorganic and Medicinal Chemistry 6:619, 1998).

To date, the receptors for adenosine have been classified into three main classes: A_1, A_2 and A_3. The A_1 subtype is partly responsible for the inhibition of the adenylate cyclase by coupling to G_i membrane protein, partly influences other second messenger systems. The A_2 receptor subtype can be subdivided into two further subtypes – A_{2a} and A_{2b} -, which stimulate the adenylate cyclase activity. The sequence of adenosine A_3 receptors have been recently identified from rat testis cDNA library. Later it was proved that it corresponds to a novel, functional adenosine receptor. The activation of the A_3 receptors is connected also with several second-messenger systems: inhibiting of adenylate cyclase, stimulating phospholipase C and D.

The adenosine receptors are found in several organs and regulate their functions. Both A_1 and A_{2a} receptors play important role in the central nervous system and cardiovascular system. In the CNS, the adenosine inhibits the release of synaptic transmitters which effect is mediated by A_1 receptors. In the heart, also the A_1 receptors mediate the negative inotropic, chronotropic and dromotropic effects of adenosine. The adenosine A_{2a} receptors, which are located in a relatively high amount in the striatum, display functional interaction with the dopamine receptors in regulating the synaptic transmission. The A_{2a} adenosine receptors on endothelial and smooth muscle cells are responsible for adenosine-induced vasodilation.

On the basis of mRNA identification, the A_{2b} adenosine receptors are widely distributed in different tissues. They have been identified almost in every cell type, but its expression is the highest in the intestine and the bladder. This subtype probably also has important regulatory function in the regulation of the vascular tone and plays a role in the function of mast cells.

Contrary to A_1 and A_{2a} receptors, where the tissue distribution was detected on the protein level, the presence of A_{2b} and A_3 receptors was detected on the basis of their mRNA level. Expression levels for A_3 adenosine receptors are rather low compared to other subtypes and are highly species dependent. A_3 adenosine receptors are expressed primarily in the central nervous system, testis and immune

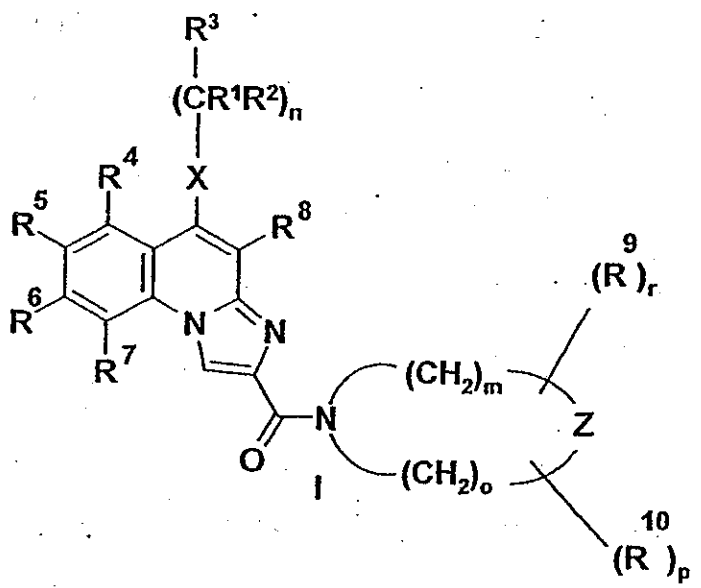
system, and appear to be involved in the modulation of mediator release from mast cells in immediate hypersensitivity reaction.

The A_3 antagonists published so far in the literature belong to the groups of flavonoides, 1,4-dihydropyridine derivatives, triazoloquinazolines, thiazolonaphthyridines and thiazolopyrimidines. The present invention relates to a novel type of effective A_3 antagonists, which have the aminoquinoline structure.

For therapeutic use it is essential to ensure that the molecule does not bind, or bind only in the case of very high concentration, to the A_1, A_{2a} and A_{2b} sub-types of the adenosine receptor. Our present invention relates to the compounds of the general formula (I) as well as their salts, solvates and isomers, which have great selectivity for the A_3 sub-type of the adenosine receptor.

Disclosed herein is the preparation of A_3 ligands, within them preferably antagonists, first of all with quinoline structure, which exert strong antagonistic effect and high selectivity for the A_3 receptor, i.e. they inhibit the A_3 receptor in much lower concentration than they inhibit the A_1, A_{2a} and A_{2b} receptors. Further disclosed herein are compounds that may have stability, bioavailability, therapeutic index and toxicity data, enabling the compounds to develop into drug substances, and that the new compounds possess favourable enteric absorption to be applied orally.

In the first aspect, there is provided the compounds of the general formula (I),



I

- wherein

R^1 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^2 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^3 stands for hydrogen atom, or a straight or branched C_{1-4} alkyl group, C_{3-6} cycloalkyl group, a phenyl-, thienyl-, or furyl group, optionally substituted with one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom; a six- or five-membered heteroaromatic ring containing one, two or three nitrogen atoms, or a five-membered heteroaromatic ring containing one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom, optionally substituted with one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group or halogen atom;

R^4, R^5, R^6 and R^7 independently stand for hydrogen atom, straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom, or R^4 and R^7 stand for hydrogen atom and R^5 and R^6 form together a methylenedioxy group;

R^8 stands for hydrogen atom or a cyano group, aminocarbonyl group, C_{1-4} alkoxycarbonyl group, or carboxy group;

R^9 and R^{10} independently stand for hydrogen atom, straight or branched C_{1-4} alkyl group, C_{3-6} cycloalkyl group.

X stands for $-CH_2-$ group, –NH- group, $-NR^{11}-$ group, or sulphur atom, oxygen atom, sulpho group or sulphoxy group -wherein R^{11} stands for straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group;

Z means oxygen atom, sulphur atom, -NH- group or $-NR^{12}-$ group, - wherein R^{12} stands for straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group;

m stands for zero, 1, 2 or 3;

n stands for zero, 1 or 2;

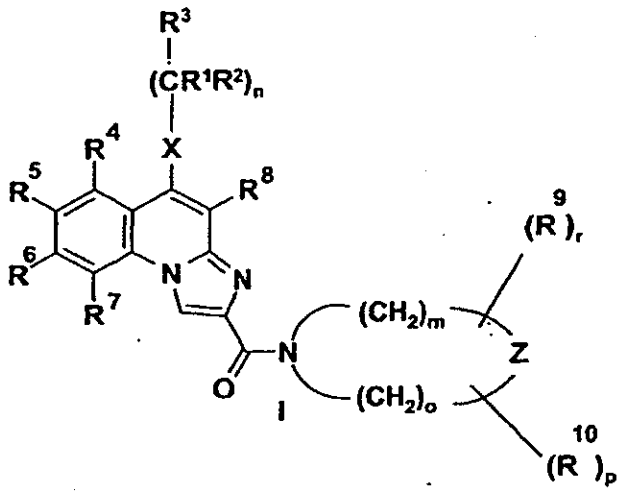
o stands for zero, 1, 2 or 3;

p stands for zero or 1,

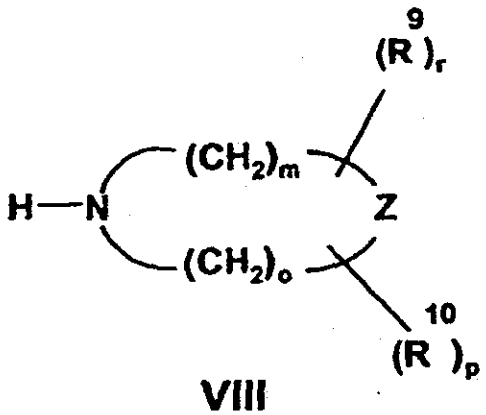
r stands for zero or 1, with the proviso that at least one of m and o is different from zero ,

and their salts, solvates, and isomers, as well as the salts and solvates thereof fulfil the above criteria.

In a second aspect, there is provided process for the preparation of the compounds of the general formula (I)

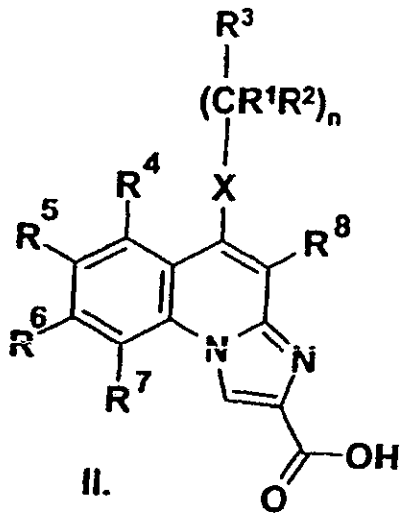


and their salts, solvates and isomers, wherein in the formula R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, X, Z, n, m, o, p and r have the meaning as defined in Claim 1, **characterized in that** a compound of the general formula (VIII)



VIII

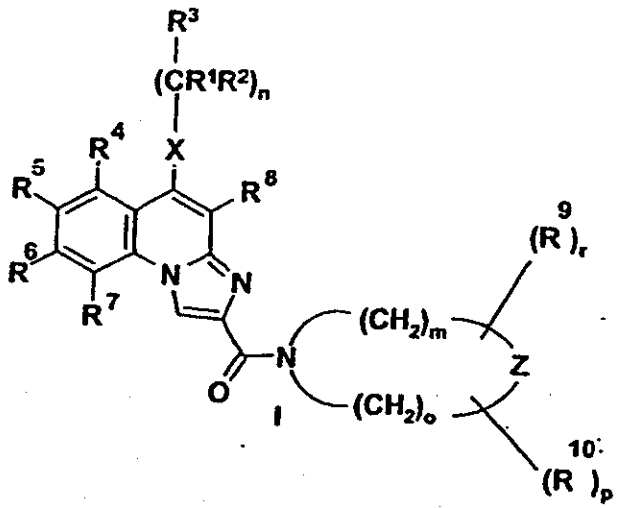
- wherein R^9, R^{10}, Z, m, o, p and r have the meaning as defined in Claim 1- is acylated with an acid or reactive acid derivative of the general formula (II)



II.

- wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the meaning as defined in Claim 1 and, if desired, the substituents of the resulting compound of the general formula (I) are transformed into each other by known methods, and/or the compound of the general formula (I) is transformed into its salt or solvate, or liberated from its salt or solvate, and/or it is resolved into its optically active isomers, or the optically active isomer is transformed into the racemic compound.

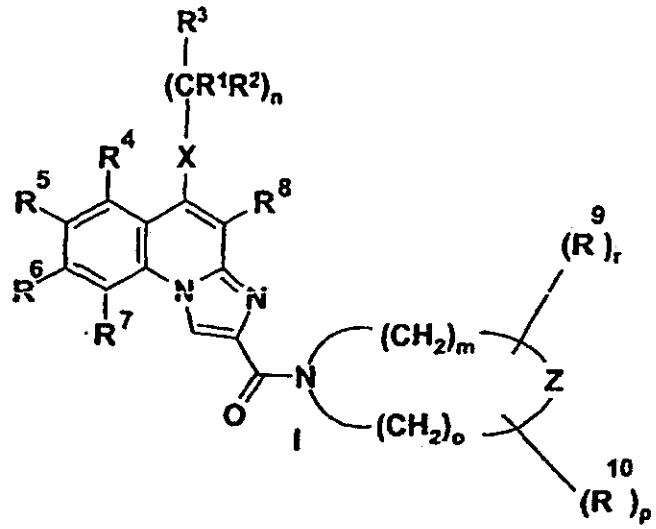
In a third aspect, there is provided pharmaceutical composition, characterized in that it contains one or more compounds of the general formula (I)



I

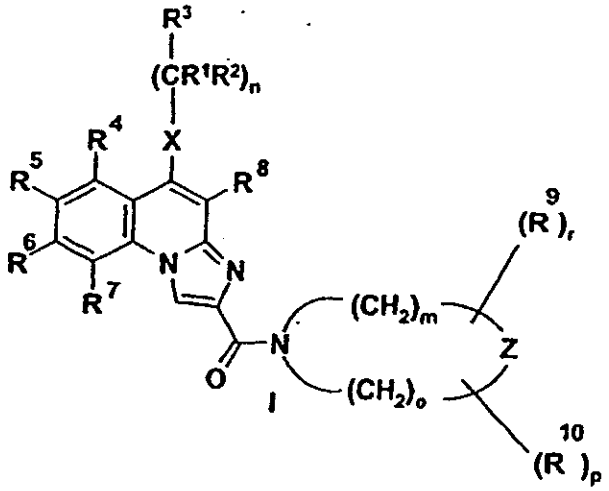
- wherein in the formula R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, X, Z, n, m, o, p and r have the meaning as defined in Claim 1.,- and/or their salts, solvates, isomers, the salts, solvates thereof, and one or more auxiliary materials, commonly used in the pharmaceutical industry.

In a fourth aspect, there is provided use of the compounds of the general formula (I)



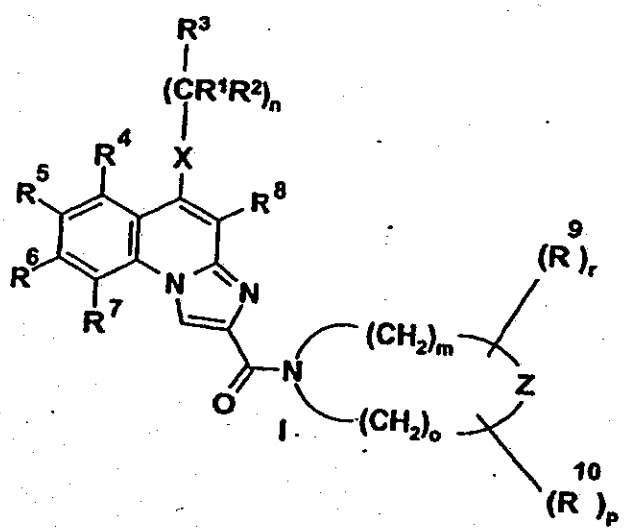
- wherein in the formula R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, X, Z, n, m, o, p, and r have the meaning as defined in claim 1.- for the preparation of a medicament for the treatment of pathologies where A_3 receptor plays a role in the development of the disease.

In a fifth aspect, there is provided use of the compounds of the general formula (I)



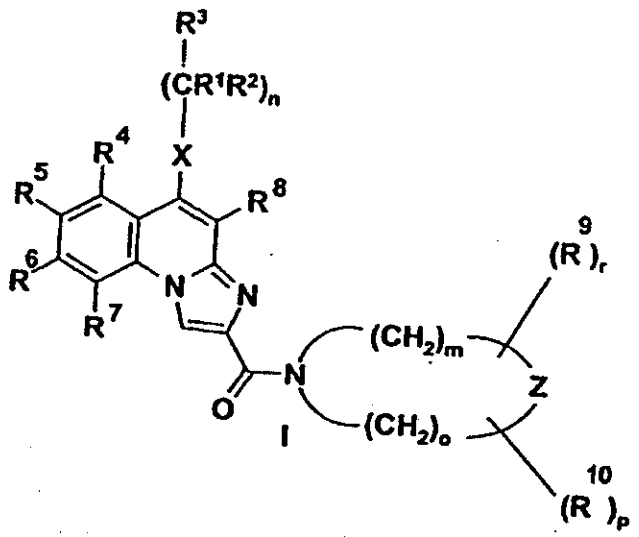
- where in the formula R^1, R^2 R^3 R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, X, Z, n, m, o, p, and r have the meaning as defined in claim 1.- as As receptor ligands, for the preparation of a medicament in the therapeutic and/or protective treatment of disfunctions of the heart, kidney, respiratory system and central nervous system, for blocking of the protective effect of the adenosine on the growing tumoric cells, for prevention of the degranulation of the mast cells, for hindering of the formation of the cytokines, for decreasing the inner pressure of the eye, for prevention of the TNFa liberation, for hindering the migration of the eozinofil and neutrofil granulocytes and other inflammation cells, for prevention of the constriction of the trachea, and for prevention of infiltration of the blood plasma through the blood-vessel.

In a sixth aspect, there is provided use of the compounds of the general formula (I)



- where in the formula R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, X, Z, n, m, o, p, and r have the meaning as defined in claim 1.- as A_3 receptor antagonists, as active compounds for the preparation of antiinflammatory, antiasthmatic, antiischemic, antidepressant, antiarrhythmic, kidney function protective, tumor preventing, antiparkinson or cognitive function stimulating medicaments and as active compounds for the preparation of a medicament which can be used in the treatment or prevention of the following diseases: injury of the heart muscle during reperfusion, chronic obstructive pulmonary disease (COPD), adult respiratory insufficiency (ARDS) - including chronic bronchitis, pulmonary emphysema or difficult breathing-, allergic reactions (e.g. rhinitis, poison ivy-induced responses, nettle-rush, scleroderma, arthritis), other autoimmune diseases, inflammatory bowel diseases, Addison disease, Crohn disease, psoriasis, diseases of the joints, hypertonia, abnormal neurological functions, glaucoma and diabetes.

In a seventh aspect, there is provided use of the compounds of the general formula (I)



- where in the formula R^1, R^2, R^3, R^4 R^5, R^6, R^7, R^8, R^9 R^{10}, X, Z, n, m, o, p, and r have the meaning as defined in claim 1.- as active components for the preparation of a medicament for the treatment of disfunctions like asthma,COPDand ARDS, glaucoma, tumor, allergic and inflammatory diseases, ischemia, hypoxia, arrhythmia of the heart and diseases of the kidney.

Detailed meanings of the above listed substituents are as follows:

By a straight or branched C_{1-4} alkyl group we mean methyl-, ethyl-, propyl-, isopropyl-, butyl-, isobutyl-, secondary-butyl-, terciary-butyl-, preferably ethyl- or methyl group.

By a straight or branched C_{1-4} alkoxy group we mean methoxy-, ethoxy-, propoxy-, isopropoxy-, butoxy-, isobutoxy-, secondary-butoxy-, terciary-butoxy-, preferably ethoxy- or methoxy group.

By a C_{3-6} cycloalkyl group we mean cyclopropyl-, cyclobutyl-, cyclopentyl- or cyclohexyl group.

The heteroaromatic ring containing one or two or three nitrogen atoms means pyrrole, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, pyridine, pyrimidine, pyridazine, pyrazine and 1,3,4-triazine ring. The ring is optionally substituted by a C_{1-4} alkyl, or alkoxy group or by a halogen atom.

The heteroaromatic ring containing one nitrogen atom and one oxygen or sulphur atom means oxazole, isoxazole, thiazole, isothiazole ring. The ring is optionally substituted by a C_{1-4} alkyl, or alkoxy group or by a halogen atom.

The $-(CH_2)_m-Z-(CH_2)_o-$ group forms together with the nitrogen atom an oxaziridino-, diaziridino-, 1,2-diazetidino-, 1,3-diazetidino-, isoxazolidino-, oxazolidino-, imidazolidino-, pirazolidino-, thiazolidino-, morpholino, piperazino-, or 4-methyl-piperazino-group, optionally substituted with a C_{1-4} alkyl group or C_{3-6} cycloalkyl group.

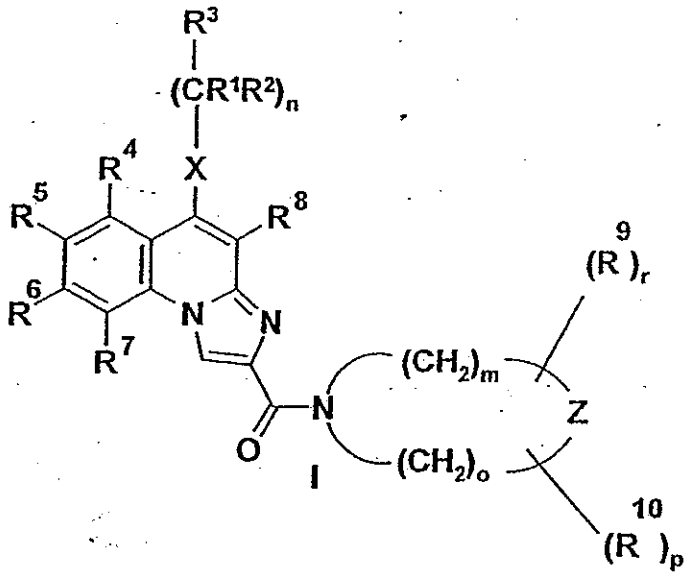
By salts of the compounds of the general formula (I) we mean salts given with inorganic and organic acids and bases. Preferred salts are those given with pharmaceutically accepted acids, as for instance hydrochloric acid, sulphuric acid, ethanesulphonic acid, tartaric acid, succinic acid, malic acid, citric acid, and with

pharmaceutically accepted bases, as for instance sodium hydroxide, potassium hydroxide, ethanolamine.

By solvates we mean solvates given with various solvents, as for instance with water or ethanol.

The compounds of the general formula (I) show geometric and optical isomerism, therefore the invention also relates to mixtures of the geometric isomers, to racemic or optically active geometric isomers, as well as to their salts and solvates.

A favoured group of the compounds of the general formula (I)



I

is that, wherein

R^1 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^2 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;

R^3 stands for hydrogen atom, or a straight or branched C_{1-4} alkyl group, C_{3-6} cycloalkyl group, a phenyl-, thienyl-, or furyl group, optionally substituted with one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

R^4, R^5, R^6 and R^7 independently stand for hydrogen atom, straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or

halogen atom, or R^4 and R^7 stand for hydrogen atom and R^5 and R^6 form together a methylenedioxy group;

R^8 stands for hydrogen atom or a cyano group, aminocarbonyl group, C_{1-4} alkoxycarbonyl group, or carboxy group;

R^9 and R^{10} independently stand for hydrogen atom, straight or branched C_{1-4} alkyl group, or C_{3-6} cycloalkyl group.

X stands for $-CH_2-$ group, –NH- group, $-NR^{11}-$ group, or sulphur atom, oxygen atom, sulpho group or sulphoxy group -wherein R^{11} stands for straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group;

Z means oxygen atom, sulphur atom, -NH- group or $-NR^{12}-$ group, - wherein R^{12} stands for straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group;

m stands for zero, 1, 2 or 3;

n stands for zero, 1 or 2;

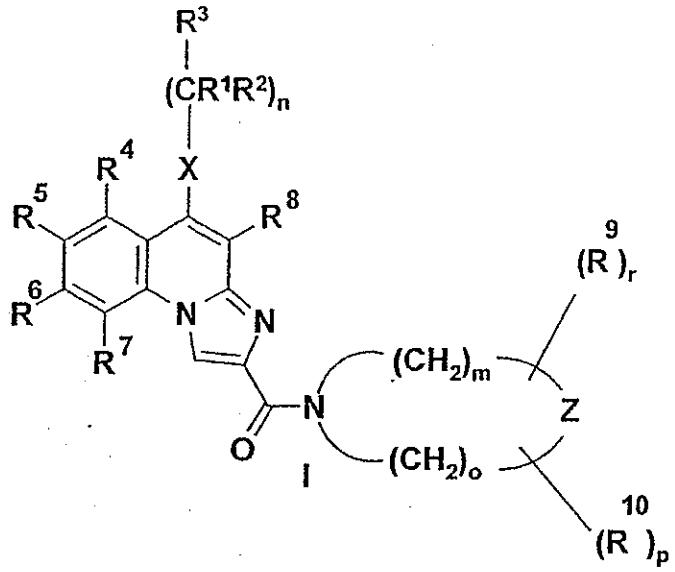
o stands for zero, 1, 2 or 3;

p stands for zero or 1,

r stands for zero or 1, with the proviso that at least one of m and o is different from zero ,

and their salts, solvates, and optically active isomers, as well as the salts and solvates thereof.

A more favoured group of the compounds of the general formula (I)



are those wherein

R^1 stands for hydrogen atom or methyl group;

R^2 stands for hydrogen atom or methyl group;

R^3 stands for phenyl-, thienyl-, or furyl group;

R^4, R^5, R^6 and R^7 independently stand for hydrogen atom, straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom, or

R^4 and R^7 stand for hydrogen atom and R^5 and R^6 form together a methylenedioxy group;

R^8 stands for hydrogen atom or a cyano group;

R^9 and R^{10} stand for hydrogen atom, methyl- ethyl-, or cyclopropyl group.

X stands for –NH- group or oxygen atom;

Z means oxygen atom, sulphur atom, -NH- group or $-NR^{12}$- group, - wherein R^{12} stands for straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group; and

m stands for 2;

n stands for 1;

o stands for 2;

p stands for zero;

r stands for zero,

and their salts, solvates, and isomers, as well as the salts and solvates thereof.

Especially favoured are the following compounds which fulfil the above criteria:

1-(9-Benzylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)-4-methylpiperazine

1-(9-Benzylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)morpholine

1-(9-Furfurylamino-10-cyano-imidazo[1,2-a]quinoline-2-carbonyl)-4-methylpiperazine

1-(9-Furfurylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)piperazine:

1-(9-Furfurylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)morpholine

1- (9-Thenylamino- 10-cyano-imidazo[1,2-*a*]quinolin-2-carbonyl)morpholine

1- (9-Thenylamino- 10-cyano-imidazo[1,2-*a*]quinoline-2- carbonyl)piperazine

and their salts, solvates and isomers, as well as the salts and solvates thereof.

The present invention also relates to pharmaceutical compositions containing as active principles the compounds of the general formula (I) or their isomers, salts and solvates, which are preferably oral compositions, but inhalable, parenteral and transdermal formulations are also subjects of the invention. The above pharmaceutical compositions may be solids or liquids, such as tablets, pellets, capsules, patches, solutions, suspensions or emulsions. The solid compositions, first of all tablets and capsules are preferred.

The above pharmaceutical compositions are prepared by applying usual pharmaceutical auxiliary materials and by using standard methods.

The compounds of the general formula (I) can be used for the treatment of pathologies, where A_3 receptor plays a role in the development of the disease.

The compounds having selective activity on the A_3 receptor can be used in the therapeutic and/or preventive treatment of disfunctions of the heart, kidney, respiratory system, central nervous system. They block the protective effect of adenosine on the growing tumoric cells, prevent degranulation of the mast cells, hinder the formation of cytokines, decrease the inner pressure in the eye, prevent the TNFα liberation, hinder the migration of the eozinofil and neutrofil granulocytes and of other inflammation cells, prevent the constriction of the trachea and prevent the blood plasm to pass through the wall of the blood-vessel.

Based on the above effects, adenosine A_3 receptor antagonists may be therapeutically useful as antiinflammatory, antiasthmatic, antiischemic, antidepressive, antiarrhythmic, kidney function protective, tumor preventing, antiparkinson and cognitive function stimulating drugs. They may also be useful in the treatment or prevention of the following diseases: injury of the heart muscle during reperfusion, chronic obstructive pulmonary disease (COPD), adult respiratory insufficiency (ARDS) – including chronic bronchitis, pulmonary emphysema or difficult breathing -, allergic reactions (e.g. rhinitis, poison ivy-induced responses, nettle-rush, scleroderma, arthritis), other autoimmune diseases, inflammatory bowel diseases, Addison disease, Crohn disease, psoriasis, diseases of the joints, hypertonia, abnormal neurological functions, glaucoma and diabetes (K. N. Klotz, Naunyn-Schmiedberg`s Arch. Pharmacol. 362:382, 2000; P. G. Baraldi és P. A. Borea, TiPS 21:456, 2000).

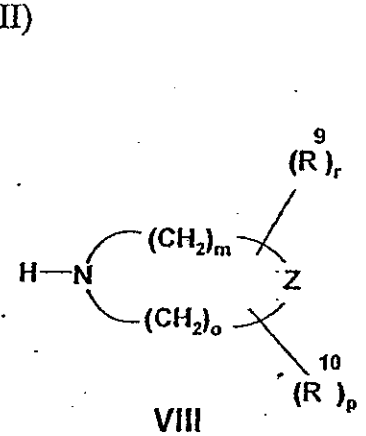
The compounds of the present invention can favourably be used in the treatment of disfunctions like asthma, COPD and ARDS, glaucoma, tumor, allergic and inflammatory diseases, ischemia, , hypoxia, arrhythmia of the heart, and diseases of the kidney.

The present invention relates furthermore to the use of the compounds of the general formula (I) in the treatment of the above pathologies. The suggested daily dose is 0.1 - 1000 mg active ingredient, depending on the nature and severeness of the disease and on the sex, weight etc. of the patient.

A further subject of the invention is the preparation of the compounds of the general formula (I).

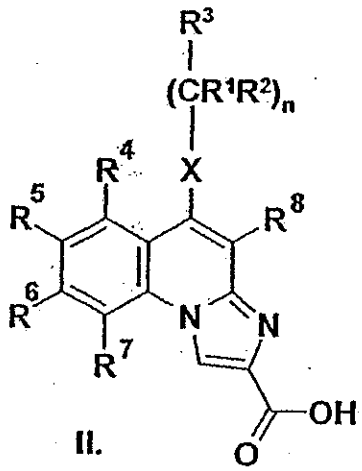
The substituents in the formulae of the intermediates of the general formulae (II), (III), (IV), (V), (VI), (VII) and (VIII) have the meanings as defined above.

In the process according to our invention the compounds of the general formula (VIII)



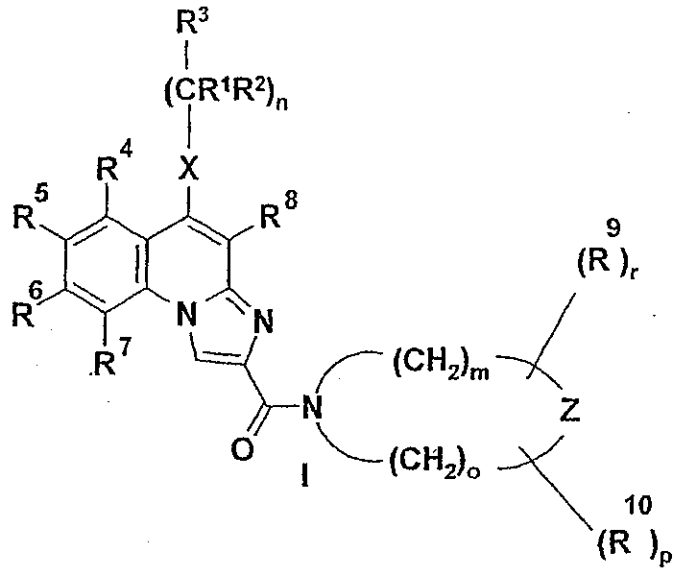
VIII

are acylated with the acids or their reactive derivatives of the general formula (II),



II.

by applying an acylation method known in the organic chemistry. As for acylating agent, acid halogenides or mixed anhydrides are preferably used. The resulting compound of the general formula (I)



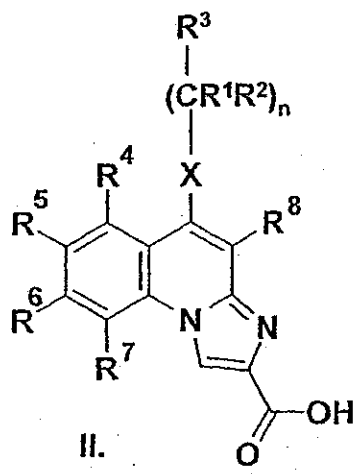
I

is -if desired- transformed into one of its salts or solvates, or liberated from its salt or solvate and separated into its geometric or optical isomers.

The substituents of the compounds of the general formula (I) may be transformed into each other, by known methods.

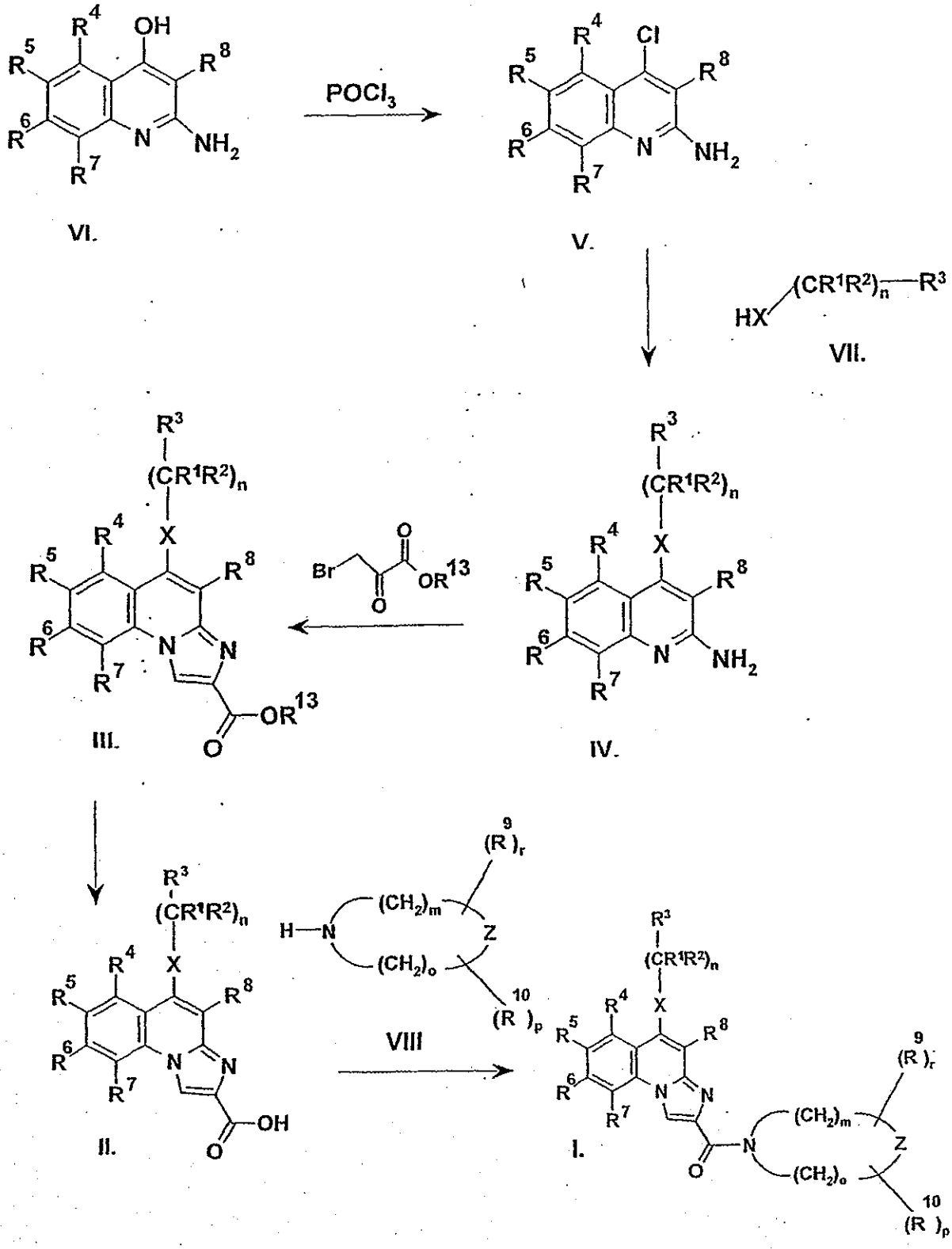
The mixed anhydride used for the acylation reaction can be prepared with pivaloyl chloride, favourably by using organic bases dissolved in chloroform, preferably by using triethylamine, but other methods known in the organic chemistry can also be applied. Acylation can be performed in a broad temperature range, preferably between 0 °C and 100 °C.

The intermediates of the general formula (II)

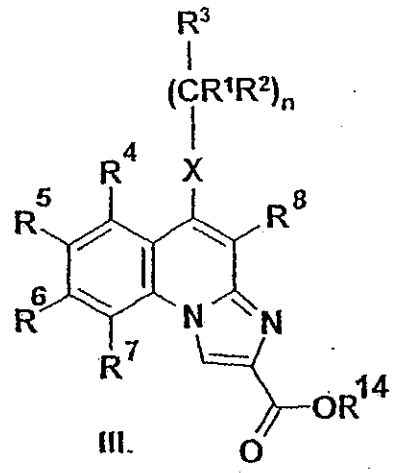


II.

–wherein the meanings of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n are as defined above – can be obtained by several known methods, for example by the method demonstrated in Scheme 1.



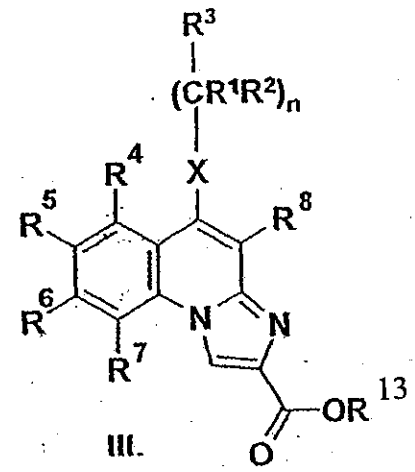
starting from the compounds of the general formula (III)



III.

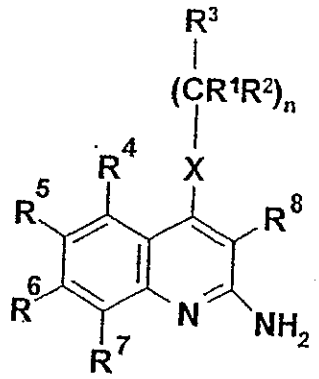
and applying a hydrolysis method known in the organic chemistry. As for hydrolysing agent alkali hydroxides can be used, but other compounds promoting the hydrolysis of esters can also be applied.

The compounds of the general formula (III)



III.

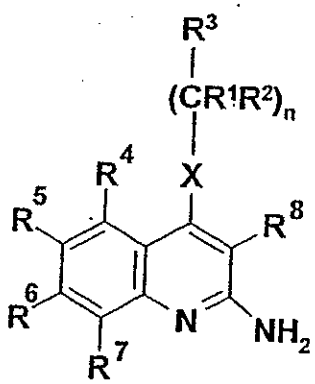
- wherein the meanings of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n are as defined above, and R^{13} means a C_{1-4} alkyl group, can be prepared from the compounds of the formula (IV)



IV.

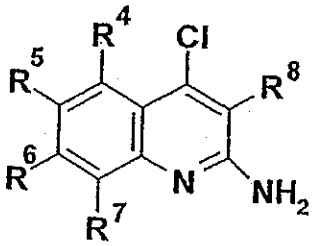
- by using methods known per se. (I. R. Ager and R. Westwood, J. Med. Chem. 31, 1098, 1988).

The compounds of the general formula (IV)



IV.

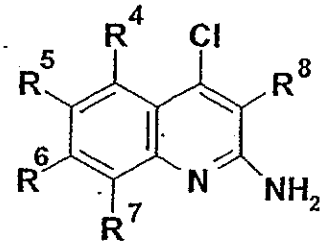
- wherein the meanings of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n are as defined above, can be prepared from the compounds of the formula (V)



V.

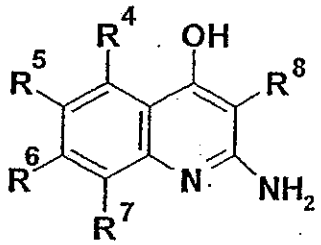
- by using methods known per se (Nan Zhang, Bioorg. and Med. Chem. Lett., 10, 2825, 2000).

The compounds of the general formula (V)



V.

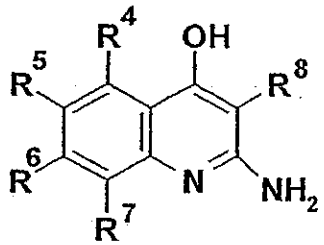
- wherein the meanings of R^4, R^5, R^6, R^7 and R^8 are as defined above, can be prepared from the compounds of the formula (VI)



VI.

- by using methods known per se (D. L. Leysen, J. Heterocyclic Chem., 24, 1611, 1987).

The compounds of the general formula (VI)



VI.

– wherein the meanings of R^4, R^5, R^6, R^7 and R^8 are as defined above, can be prepared by using methods known per se (Pfizer (Inc) USP 4,175,193).

The compounds of the invention, of the general formulae (I), (II), (III), (IV) and (V), their preparation and biological activity are demonstrated by the following Examples, without limiting the claims to the Examples.

Examples

Example 1

1-(9-Benzylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)-4-methyl-piperazine:

In the general formula (I) R^1 and R^2 stand for hydrogen atom, R^3 for phenyl group, R^4, R^5, R^6 and R^7 for hydrogen atom, R^8 for cyano group, R^{12} for methyl group, X means -NH-group, Z means nitrogen atom, the value of n is 1, the value of m and o is 2, and the value of r and p is 0.

a.) 2-Amino-3-cyano-4-chloroquinoline:

The mixture of 10 g of 2-amino-3-cyano-4-hydroxyquinoline and 15 ml of phosphoryl chloride is heated under stirring at 110 °C. The reaction mixture is cooled down, poured onto 100 ml of ice-water and neutralized with 60 ml of 10 % sodium hydroxide solution. The resulting yellow precipitate is filtered off, washed with 50 ml of water. After drying 7.5 g of the title compound is obtained, mp.: 210 °C.

NMR, δH (400 MHz, DMSO-d6): 7.21 ppm, (s, 2H, NH2), 7.35-7.40 ppm, (dd, 1H, 6-H), 7.53-7.57 ppm, (d, 1H, 5-H), 7.70-7.75 ppm, (dd, 1H, 7-H), 7.93-7.98 ppm, (d, 1H, 8-H)

b.) 2-Amino-3-cyano-4-benzylaminoquinoline

5 g of 2-amino-3-cyano-4-chloroquinoline and 11 ml of benzylamine are heated under stirring at 130 °C. The reaction mixture is poured onto 50 ml of water, the resulting precipitate is filtered off, washed with 50 ml of water. The pale-yellow precipitate is recrystallized from 25 ml of dimethylformamide to obtain 5.2 g of the title compound. Mp.: 206 °C.

NMR, δ_H (400 MHz, DMSO-d_6): 5.02-5.03 ppm, (d, 2H, N-CH_2), 6.22 ppm, (s, 2H, NH_2), 7.14-7.16 ppm, (dd, 1H, 6-H), 7.24-7.26 ppm,(dd,1H, 5-H), 7.30 ppm, (s, 5H, Ph), 7.50-7.52 ppm, (dd, 1H, 7-H), 8.16-8.19 ppm, (d, 1H, 8-H), 8.30-8.33 ppm, (t, 1H, NH).

Using 2-aminomethylpyridine or 3-aminomethylpyridine or 4-aminomethylpyridine instead of benzylamine, the appropriate compounds of the general formula IV can be obtained.

c. Ethyl 9-benzylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carboxylate monohydrate:

To the solution of 2.74 g of 2-amino-3-cyano-4-benzylaminoquinoline in 100 ml of abs. ethanol, 2.14 g of ethyl bromopyruvate is added under stirring at 70 °C. The reaction mixture is heated under reflux for 2 hours, the resulting precipitate is filtered off. The white crystals are recrystallized from 120 ml of acetonitrile. 1.1 g of the title compound is obtained, m.p.: 112-114 °C.

NMR, δ_H (400 MHz, DMSO-d_6): 1.32 ppm (t, 3H, $COOCH_2CH_3$), 4.30 ppm (q, 2H, $COOCH_2CH_3$), 5.09 ppm (d, 2H, $PhCH_2$), 7.25-7.38 ppm (m, 5H), 7.64-7.67 ppm (m, 1H), 7.85-7.88 ppm (m, 1H), 8.43-8.53 ppm (m, 3H), 9.04 ppm (s, 1H, 3-H).

d. 9-Benzylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carboxylic acid:

The mixture of 2.71 g of ethyl 9-benzylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carboxylate monohydrate, 42 ml of ethanol and 40 ml of 10 % sodium hydroxide is stirred at 25 °C for 6 hours. To the thick suspension 100 ml of water is added and the pH of the mixture is adjusted to pH = 3 with 96 % acetic acid. The pale yellow crystals are filtered off, washed 3 times with 25 ml of water, and dried. 2.3 g title compound is obtained, m.p.: 178-182 °C.

NMR, δ_H (200 MHz, DMSO-d_6): 5,09 ppm (d, 2H, $PhCH_2$), 7,22-7,40 ppm (m, 5H), 7,59-7,67 ppm (m, 1H), 7,81-7,89 ppm (m, 1H), 8,37-8,54 ppm (m, 3H), 8,90 ppm (s, 1H, 3-H).

e.1-(9-Benzylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)-4-methylpiperazine:

To the solution of 1.71 g of 9-benzylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carboxilic acid and 0.8 ml of triethylamine in 15 ml of chloroform, the solution of 0.6 g of pyvaloyl chloride in 10 ml of choroform is added dropwise, under stirring, at 5 °C, in a period of 15 minutes. The reaction mixture is stirred at 5 °C for 1 hour, then the mixture of 0.5 g of *N*-methylpiperazine, 10 ml of chloroform and 0.8 ml of triethylamine is added to it. The mixture is stirred at 25 °C for 7 hours, diluted with 100 ml of chloroform, extracted consecutively with 50 ml of water, 50 ml of 5 % sodium hydrogen carbonate solution and 50 ml of water, dried on sodium sulfate and concentrated in vacuo. The pale yellow crystalline material is recrystallized from 6 ml of *N,N*-dimethylformamide. 0.6 g of the title compound is obtained, m.p.: 217 °C.

NMR, δ_H (400 MHz, DMSO-d_6): 2.17 ppm (s, 3H), 2.24 ppm (m, 4H), 3.57 ppm (m, 2H), 4.11 ppm (m,2H), 5.08 ppm (d, 2H, $PhCH_2$), 7.23-7.38 ppm (m, 5H), 7.62-7.65 ppm (m, 1H), 7.83-7.87 ppm (m, 1H), 8.36-8.42 ppm (m, 2H), 8.50-8.52 ppm (m, 1H), 8.80 ppm (s, 1H, 3-H).

Example 2

1-(9-Benzylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)morpholine:

In the general formula (I) R^1 and R^2 stand for hydrogen atom, R^3 for phenyl group, R^4, R^5, R^6 and R^7 for hydrogen atom, R^8 for cyano group, X means -NH-group, Z means oxygen atom, the value of n is 1, the value of m and o is 2, and the value of r and p is 0.

To the mixture of 1.71 g of 9-benzylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carboxilic acid and 0.8 ml of triethylamine in 15 ml of chloroform, the solution of 0.6 g of pyvaloyl chloride in 10 ml of choroform is added under stirring at 5 °C, in a period of 15 minutes. The reaction mixture is stirred at 5 °C for 1 hour, then the mixture of 0.45 g of morpholine, 10 ml of chloroform and 1.6 ml of triethylamine is added to it. The mixture is stirred at 25 °C for 3 hours, then treated as described in the previous example. The resulting pale yellow crystals are

recrystallised from 10 ml of *N,N*-dimethylformamide, to obtain 0.55 g of the title compound, m.p.: 279 °C.

NMR, δ_H (400 MHz, DMSO-d_6): 3.6 ppm (m, 6H), 4.2 ppm (m, 2H), 5.08 ppm (d, 2H, $PhCH_2$), 7.23-7.38 ppm (m, 5H), 7.62-7.65 ppm (m, 1H), 7.84-7.87 ppm (m, 1H), 8.37-8.39 ppm (m, 2H), 8.50-8.53 ppm (m, 1H), 8.75 ppm (s, 1H, 3-H).

Example 3

1-(9-Furfurylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)-4-methylpiperazine:

In the general formula (I) R^1 and R^2 stand for hydrogen atom, R^3 for 2-furyl group, R^4, R^5, R^6 and R^7 for hydrogen atom, R^8 for cyano group, R^{12} for methyl group, X means -NH-group, Z means nitrogen atom, the value of n is 1, the value of m and o is 2, and the value of r and p is 0.

a. 2-Amino-3-cyano-4-furfurylaminoquinoline:

10 g of 2-amino-3-cyano-4-chloroquinoline is heated with 19 g of furfurylamine at 120 °C for 3 hours. The reaction mixture is cooled to 25 °C and mixed 6 times with 50 ml of water. The crystals are filtered off and dried. The resulting product is recrystallized from 60 ml of *N,N*-dimethylformamide, to obtain 5.8 g of the title compound, m.p.: 206 °C.

NMR, δ_H (200 MHz, DMSO-d_6): 4.98 ppm (d, 2H, Furyl-CH_2), 6.29 ppm (s, 2H), 6.35-6.42 ppm (m, 2H), 7.10-7.18 ppm (m, 1H), 7.31-7.35 ppm (m, 1H), 7.47-7.60 ppm (m, 2H), 8.13-8.20 ppm (m, 2H).

b. Ethyl 9-furfurylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carboxylate monohydrate:

To the solution of 2.64 g of 2-amino-3-cyano-4-furfurylaminoquinoline in 100 ml of abs. ethanol, 2.14 g of ethyl bromopyruvate is added at 70 °C under

stirring. The reaction mixture is heated under reflux for 2 hours and the precipitated crystals are filtered off, to obtain 1.15 g of the title compound. M.p.: 242-245 °C.

NMR, δ_H (200 MHz, DMSO-d_6): 1.33 ppm (t, 3H, $COOCH_2CH_3$), 4.31 ppm (q, 2H, $COOCH_2CH_3$), 5.05 ppm (d, 2H, Furyl-CH_2), 6.40-6.43 ppm (m, 2H), 7.58-7.66 ppm (m, 2H), 7.80-7.88 ppm (m, 1H), 8.31 ppm (t, 1H), 8.41-8.45 ppm (m, 2H), 9.04 ppm (s, 1H, 3-H).

c. 9-Furfurylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carboxylic acid:

The mixture of 2.52 g of ethyl 9-furfurylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carboxylate monohydrate, 40 ml of ethanol and 33 ml of 10 % sodium hydroxide is stirred at 25 °C for 3 hours. To the thick suspension 80 ml of water is added and with 96 % acetic acid the mixture acidified to pH = 3. The pale yellow crystals are filtered off, washed 3 times with 25 ml of water and dried. 2.32 g of the title compound is obtained, m.p.: 180-185 °C.

NMR, δ_H (200 MHz, DMSO-d_6): 5.05 ppm (d, 2H, Furyl-CH_2), 6.39-6.42 ppm (m, 2H), 7.56-7.64 ppm (m, 2H), 7.79-7.87 ppm (m, 1H), 8.27 ppm (t, 1H), 8.36-8.46 ppm (m, 2H), 8.93 ppm (s, 1H, 3-H).

d.1-(9-Furfurylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)-4-methylpiperazine:

To the mixture of 1.79 g of 9-furfurylamino-10-cyanoimidazo[1,2-*a*]quinoline-2-carboxylic acid and 0.8 ml of triethylamine in 15 ml of chloroform, the solution of 0.6 g of pyvaloyl chloride in 10 ml of chloroform is added dropwise, under stirring at 5 °C, in a period of 15 minutes. The reaction mixture is stirred at 5°C for 1 hour, then the mixture of 0.46 g of *N*-methylpiperazine, 10 ml of chloroform and 0.8 ml of triethylamine is added to it. The mixture is stirred at 25°C for 3 hours, diluted with 100 ml of chloroform, extracted consecutively with 50 ml of water, 50 ml of 5 % sodium hydrogen carbonate solution and 50 ml of water, dried over sodium sulfate and concentrated in vacuum. The pale yellow crystalline

material is recrystallized from 50 ml of ethanol. 0.18 g of the title compound is obtained, m.p.: 237 °C.

NMR, δ_H (200 MHz, DMSO-d_6): 2.17 ppm (s, 3H), 2.24 ppm (m, 4H), 3.57 ppm (m, 2H), 4.11 ppm (m, 2H), 5.05 ppm (d, 2H, Furyl-CH_2), 6.40-6.44 ppm (m, 2H), 7.57-7.65 ppm (m, 2H), 7.80-7.88 ppm (m, 1H), 8.23 ppm (t, 1H), 8.39-8.46 ppm (m, 2H), 8.81 ppm (s, 1H, 3-H).

Example 4

1-(9-Furfurylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)piperazine:

In the general formula (I) R^1 and R^2 stand for hydrogen atom, R^3 for 2-furyl group, R^4, R^5, R^6 and R^7 for hydrogen atom, R^8 for cyano group, X means –NH- group, Z means –NH- group, the value of n is 1, the value of m and o is 2, and the value of r and p is 0.

To the mixture of 1.79 g of 9-furfurylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carboxylic acid -obtained as described in Example 3.- and 0.8 ml of triethylamine in 15 ml of chloroform, the solution of 0.6 g of pyvaloyl chloride in 10 ml of chloroform is added dropwise, under stirring at 5 °C, in a period of 15 minutes. The reaction mixture is stirred at 5°C for 1 hour, then the mixture of 0.46 g of piperazine, 10 ml of chloroform and 0.8 ml of triethylamine is added to it. The mixture is stirred at 25°C for 3 hours, diluted with 100 ml of chloroform, extracted consecutively with 50 ml of water, 50 ml of 5 % sodium hydrogen carbonate solution and 50 ml of water, dried over sodium sulfate and concentrated in vacuum. The pale yellow crystalline material is recrystallized from 50 ml of ethanol. 0.14 g of the title compound is obtained, m.p.: 239 °C

NMR, δ_H (200 MHz, DMSO-d_6): 2.7 ppm (m, 4H), 3.5 ppm (m, 2H), 4.05 ppm (m, 2H), 5.05 ppm (d, 2H, Furyl-CH_2), 6.40-6.44 ppm (m, 2H), 7.57-7.65 ppm (m, 2H), 7.80-7.88 ppm (m, 1H), 8.23 ppm (t, 1H), 8.39-8.46 ppm (m, 2H), 8.81 ppm (s, 1H, 3-H).

Example 5

1-(9-Furfurylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)morpholine:

In the general formula (I) R^1 and R^2 stand for hydrogen atom, R^3 for 2-furyl group, R^4, R^5, R^6 and R^7 for hydrogen atom, R^8 for cyano group, X means –NH- group, Z means oxygen atom, the value of n is 1, the value of m and o is 2, and the value of r and p is 0.

To the mixture of 1.79 g of 9-furfurylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carboxylic acid -obtained as described in Example 3.- and 0.8 ml of triethylamine in 15 ml of chloroform, the solution of 0.6 g of pyvaloyl chloride in 10 ml of chloroform is added dropwise, under stirring at 5 °C, in a period of 15 minutes. The reaction mixture is stirred at 5°C for 1 hour, then the mixture of 0.66 g of morpholine, 10 ml of chloroform and 0.8 ml of triethylamine is added to it. The mixture is stirred at 25°C for 3 hours, diluted with 100 ml of chloroform, extracted consecutively with 50 ml of water, 50 ml of 5 % sodium hydrogen carbonate solution and 50 ml of water, dried over sodium sulfate and concentrated in vacuum. The pale yellow crystalline material is recrystallized from 50 ml of ethanol. 0.18 g of the title compound is obtained, m.p.: 267 °C

NMR, δ_H (200 MHz, DMSO-d_6): 3.6 ppm (m, 6H), 4.2 ppm (m, 2H), 5.05 ppm (d, 2H, Furyl-CH_2), 6.40-6.44 ppm (m, 2H), 7.57-7.65 ppm (m, 2H), 7.80-7.88 ppm (m, 1H), 8.23 ppm (t, 1H), 8.39-8.46 ppm (m, 2H), 8.81 ppm (s, 1H, 3-H).

Example 6

1-(9-Thenylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)morpholine:

In the general formula (I) R^1 and R^2 stand for hydrogen atom, R^3 for 2-thienyl group, R^4, R^5, R^6 and R^7 for hydrogen atom, R^8 for cyano group, X means –NH- group, Z means oxygen atom, the value of n is 1, the value of m and o is 2, and the value of r and p is 0.

a. 2-Amino-3-cyano-4-thenylaminoquinoline:

10 g of 2-amino-3-cyano-4-chloroquinoline is heated with 19 g of thienylmethylamine at 115 °C for 4 hours. The reaction mixture is cooled to 25 °C and mixed 6 times with 50 ml of water. The crystals are filtered off, washed 2 times with 50 ml of water and dried. The resulting product is recrystallized from 60 ml of *N,N*-dimethylformamide, to obtain 6.8 g pale yellow title compound, m.p.: 208-209 °C.

NMR, δ_H (200 MHz, DMSO-d_6): 5.18 ppm (d, 2H, Thienyl-CH_2), 6.28 ppm (s, 2H), 6.96-7.00 ppm (m, 1H), 7.07-.19 ppm (m, 2H), 7.31-7.42 ppm (m, 2H), 7.48-7.56 ppm (m, 1H), 8.09-8.13 ppm (m, 1H), 8.30 ppm (t, 1H).

b. Ethyl 9-thenylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carboxylate:

To the solution of 5.61 g of 2-amino-3-cyano-4-thenylaminoquinoline in 200 ml of abs. ethanol, 4.29 g of ethyl bromopyruvate is added at 70 °C under stirring. The reaction mixture is heated under reflux for 2 hours and the precipitated crystals are filtered off to obtain 2.54 g of the title compound. M.p.: 255-256 °C.

NMR, δ_H (200 MHz, DMSO-d_6): 1.33 ppm (t, 3H, $COOCH_2CH_3$), 4.31 ppm (q, 2H, $COOCH_2CH_3$), 5.24 ppm (d, 2H, Thienyl-CH_2), 6.96-7.00 ppm (m, 1H), 7.14 ppm (m, 1H), 7.40-7.43 ppm (m, 1H), 7.61-7.68 ppm (m, 1H), 7.82-7.90 ppm (m, 1H), 8.42-8.46 ppm (m, 3H), 9.05 ppm (s, 1H, 3-H).

c. 9-Thenylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carboxylic acid:

The mixture of 2.54 g of ethyl 9-thenylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carboxylate, 40 ml of ethanol and 33 ml of 10 % sodium hydroxide is stirred at 25 °C for 6 hours. To the thick suspension 80 ml of water is added and with 96 % acetic acid the mixture acidified to pH = 3. The pale yellow crystals are filtered off, washed 5 times with 10 ml of water and dried. 2.18 g of the title compound is obtained, m.p.: 209-217 °C under decomposition.

NMR, δ_H (400 MHz, DMSO-d_6): 5.24 ppm (d, 2H, Thienyl-CH_2), 8,88 ppm (s, 1H, 3-H).

d. 1-(9-Thenylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)morpholine:

To the mixture of 1.80 g of 9-thenylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carboxylic acid and 1.1 ml of triethylamine in 10 ml of chloroform, the solution of 0.87 g of pyvaloyl chloride in 10 ml of chloroform is added dropwise, under stirring at 5 °C, in a period of 15 minutes. The reaction mixture is stirred at 5°C for 1 hour, then the mixture of 0.61 g of morpholine, 10 ml of chloroform and 1.1 ml of triethylamine is added to it. The mixture is stirred at 25°C for 3 hours, diluted with 100 ml of chloroform, extracted consecutively with 50 ml of water, 50 ml of 5 % sodium hydrogen carbonate solution and 50 ml of water, dried over sodium sulfate and concentrated in vacuum. The yellow crystalline material is recrystallized from 200 ml of ethanol. 0.19 g of the title compound is obtained, m.p.: 315°C

NMR, δ_H (400 MHz, DMSO-d_6): 3.6 ppm (m, 6H), 4.2 ppm (m, 2H), 5.24 ppm (d, 2H, Thienyl-CH_2), 6.97-7.00 ppm (m, 1H), 7.14 ppm (m, 1H), 7.41 ppm (m, 1H), 7.61-7.65 ppm (m, 1H), 7.83-7.87 ppm (m, 1H), 8.37-8.45 ppm (m, 3H), 8.82 ppm (s, 1H, 3-H).

Example 7

1-(9-Thenylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)piperazine

In the general formula (I) R^1 and R^2 stand for hydrogen atom, R^3 for 2-thienyl group, R^4, R^5, R^6 and R^7 for hydrogen atom, R^8 for cyano group, X means –NH- group, Z means –NH- group, the value of n is 1, the value of m and o is 2, and the value of r and p is 0.

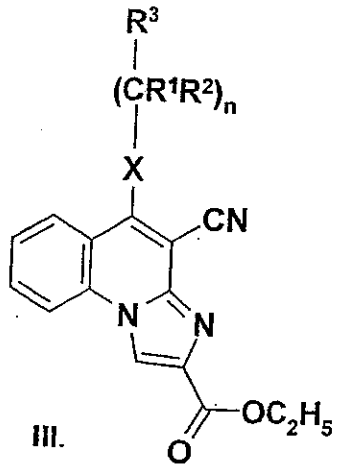
To the mixture of 1.80 g of 9-thenylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carboxylic acid -obtained as described in Example 6.- and 1.1 ml of triethylamine in 10 ml of chloroform, the solution of 0.87 g of pyvaloyl chloride in 10 ml of chloroform is added dropwise, under stirring at 5 °C, in a period of 15 minutes. The reaction mixture is stirred at 5°C for 1 hour, then the mixture of 0.61 g of piperazine, 10 ml of chloroform and 1.1 ml of triethylamine is added to it. The

mixture is stirred at 25°C for 3 hours, diluted with 100 ml of chloroform, extracted consecutively with 50 ml of water, 50 ml of 5 % sodium hydrogen carbonate solution and 50 ml of water, dried over sodium sulfate and concentrated in vacuum. The pale yellow crystalline material is recrystallized from 50 ml of ethanol. 0.19 g of the title compound is obtained, m.p.: 269 °C

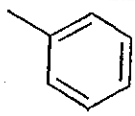
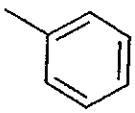
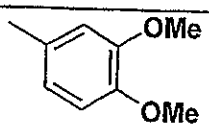
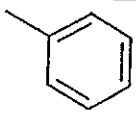
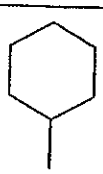
NMR, δ_H (400 MHz, DMSO-d_6): 2.7 ppm (m, 4H), 3.5 ppm (m, 2H), 4.05 ppm (m, 2H), 5.24 ppm (d, 2H, Thienyl-CH_2), 6.97-7.00 ppm (m, 1H), 7.14 ppm (m, 1H), 7.41 ppm (m, 1H), 7.61-7.65 ppm (m, 1H), 7.83-7.87 ppm (m, 1H), 8.37-8.45 ppm (m, 3H), 8.82 ppm (s, 1H, 3-H).

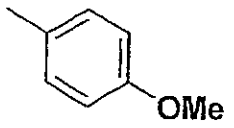
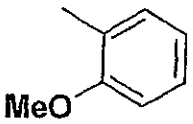
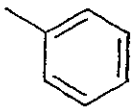
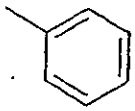
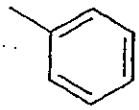
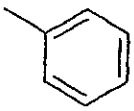
Structure and physical parameters of the compounds of the formula (III) prepared according to Example 1. is demonstrated in Table I.

TABLE I.



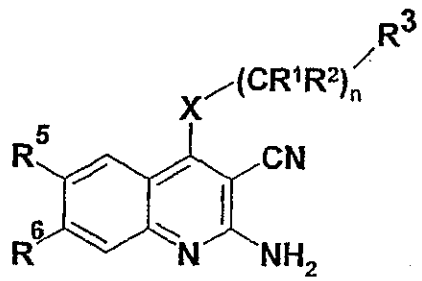
III.

	R^1	R^2	R^3	X	n	Mp [°C]
8.	Me	H		NH	1	146
9.	Me	H		NH	1	145
10.	H	H		NH	2	34
11.	H	H		NH	2	32
12.				NH	0	250
13.				NH	0	128

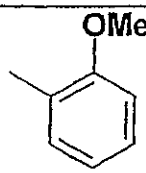
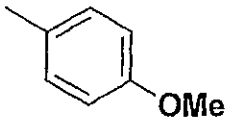
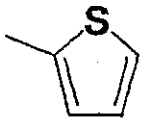
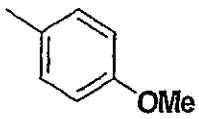
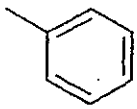
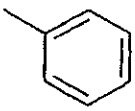
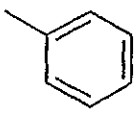
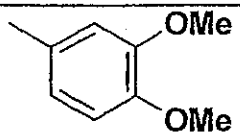
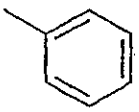
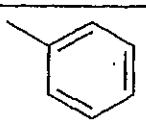
	R^1	R^2	R^3	X	n	Mp [°C]
14.	H	H		NH	1	45
15.	H	H		NH	1	54
16.	H	H		O	1	185
17.	H	H		S	1	190
18.	H	H		S=O	1	230
19.	H	H		O=S=O	1	255

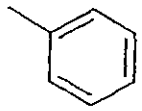
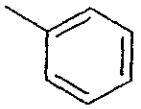
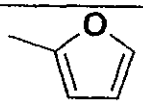
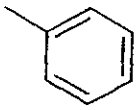
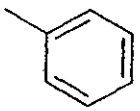
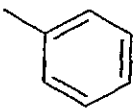
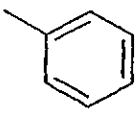
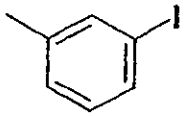
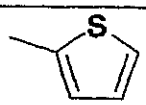
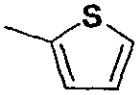
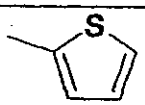
Structure and physical parameters of the compounds of the formula (IV) prepared according to Example 1. is demonstrated in Table II.

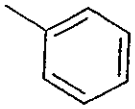
TABLE II.



(IV)

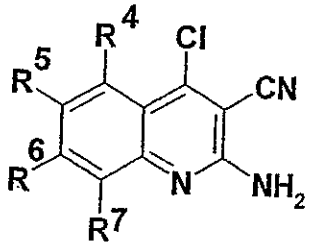
No.:	R^1	R^2	R^3	R^5	R^6	X	n	Mp [°C]
20.	H	H		H	H	NH	1	192
21.	H	H		H	H	NH	1	202
22.	H	H		I	H	NH	1	198
23.	H	H		H	H	NH	1	167
24.	H			H	H	NH	1	182
25.	H			H	H	NH	1	183
26.	H	H		H	H	NH	2	172
27.	H	H		H	H	NH	2	143
28.	H	H		H	H	N-Me	1	212
29.	H	H		H	H	S	1	168

No.:	R^1	R^2	R^3	R^5	R^6	X	n	Mp [°C]
30.	H	H		H	H	O	1	213
31.	H	H		Cl	H	NH	1	234
32.	H	H		Cl	H	NH	1	221
33.	H	H		Me	H	NH	1	198
34.	H	H		MeO	H	NH	1	201
35.	H	H		H	Cl	NH	1	191
36.	H	H		OH	H	NH	1	246
37.	H	H		H	H	NH	1	227
38.	H	H		MeO	H	NH	1	217
39.	H	H		Me	H	NH	1	198
40.	H	H		Cl	H	NH	1	168

No.:	R^1	R^2	R^3	R^5	R^6	X	n	Mp [°C]
41.				H	H	NH	0	214

Structure and physical parameters of the compounds of the formula (V) prepared according to Example 1. is demonstrated in Table III.

TABLE III.



No:	R^4	R^5	R^6	R^7	Mp[°C]
42.	H	OH	H	H	360
43.	H	Cl	H	H	250
44.	H	H	Cl	H	278
45.	H	Me	H	H	283
46.	H	OMe	H	H	360
47.	H	H	H	OMe	234
48.	Me	H	H	H	246
49.	H	H	H	Me	267
50.	H	I	H	H	293

Example 51

The tablet of the following composition is prepared by known methods:

Active ingredient:	25 mg
Lactose	50 mg
Avicel	21 mg
Crospovidone	3 mg
Magnesium stearate	1 mg

Biology

Methods

Human adenosine A_3 receptor binding

Preparing membrane suspension: ovarium cells of cloned golden hamster expressing human A_3 receptor (further: CHO-hA_3) are appropriately cultured and propagated. Achieving confluent cell layer, the culturating liquide is removed from the cells by washing them with 37 °C PBS, then the cell are suspended in ice cold PBS, centrifuged (1000 x g 10 perc) (Sigma 3K30) and homogenated using teflon homogenizer (B.Braun Potter S) at 1500/min rotation speed, for 15 sec. in the following buffer: 50 mM Tris, 10 mM $MgCl_2$, 1 mM EDTA, pH 8.0. The homogenatum is centrifuged (43.000 g, 10 min). The precipitate is suspended in the above buffer, protein concentration 0.1 mg/ml (Bradford method). Aliquots of the membrane preparatum are stored at -80 °C.

Binding protocol: incubate CHO-hA_3 membrane preparation (2 µg protein content) in incubation buffer (50 mM Tris, 10 mM $MgCl_2$, 1 mM EDTA, 3 U/mL adenosine deaminase, pH 8.0), in the presence of 0.5 nM [^{125}I]AB-MECA (p-amino--3-iodo-benzyl-5′-N-methylcarboxamido-adenosine) (100.000 cpm) and 100 µM R-PIA (N^6-[L-2-phenylisopropyl]adenosine) to define non-specific binding of test compound in a total volume of 50 µL for 1 hr at room temperature. Filter over Whatman GF/B glass fibre filters (presoaked in 0.5% polyethylenimine for 3 hours), wash 4x with 1 mL ice-cold 50 mM Tris, 10 mM $MgCl_2$, 1 mM EDTA (pH 8.0) on 96-well Brandel Cell Harvester. Detection of activity: in gamma-counter (1470 Wizard, Wallac). Inhibition [%] = 100-((activity in the presence of test compound - non-specific activity)/(total activity - non-specific activity))*100

Human adenosine A_1 receptor binding

Preparing membrane suspension: ovarium cells of cloned golden hamster expressing human A_1 receptor (further: CHO-hA_1) are appropriately cultured and propagated. Achieving confluent cell layer the culturating liquide is removed from the cells by washing them with 37 °C PBS, then the cell are suspended in ice cold PBS, washed 3 times with ice cold PBS, centrifuged (1000 x g 10 perc) (Sigma 3K30) and homogenated using teflon homogenizer (B.Braun Potter S) at 1500/min rotation speed, for 15 sec. in the following buffer: 50 mM Tris, 10 mM HCl, pH 7.4. The homogenatum is centrifuged (43.000 g, 10 min). The precipitate is suspended in the above buffer, protein concentration 5 mg/mL (Bradford method). Aliquots of the membrane preparatum are stored at -80 °C.

Binding protocol: incubate CHO-hA_1 membrane preparation (50 µg protein content) in incubation buffer (50 mM Tris, 3 U/mL adenosine deaminase, pH 7.4), 10 nM [^{3}H]CCPA (2-chloro-N^6-cyclopenthyl-adenosine) (80.000 dpm) and 10 µM R-PIA (N^6-[L-2-phenylisopropyl]adenosine) to define the non-specific binding or test compound in a total volume of 100 µL for 3 hr at room temperature. Filter over Whatman GF/B glass fibre filters (presoaked in 0.5% polyethylenimine for 3 hours), wash 4x with 1 mL ice-cold 50 mM Tris (pH 7.4) on 96-well Brandel Cell Harvester. Detection of activity: in the presence of 200 µL of HiSafe-3 coctail in beta-counter (1450 Microbeta, Wallac). Inhibition [%] = 100-((activity in the presence of test compound - non-specific activity)/(total activity - non-specific activity))*100

Human adenosine A_{2a} receptor binding

Binding protocoll: Incubate 7 µg of membranes (human A_{2a} adenosine receptors transfected into HEK-293 cells, source: Receptor Biology, Inc.), buffer (50 mM Tris-HCl, 10 mM $MgCl_2$, 1 mM EDTA, 2 U/mL adenosine deaminase, pH 7.4), 20 nM [^{3}H]CGS-21680 (2-[p-(2-carbonylethyl)phenylethylamino]-5`-N-ethylcarboxamido-adenosine) (200.000 dpm) and 50 µM NECA (5`-N-ethylcarboxamido-adenosine) to define the non-specific binding of test compound, in a total volume of 100 µl for 90 min at room temperature. Filter in vacuum over

Whatman GF/B glass fibre filters (presoaked for 3 hours in 0.5% polyethylenimine), wash 4x with 1 mL ice-cold 50 mM Tris, 10 mM $MgCl_2$, 1 mM EDTA, 0.9 % NaCl, pH 7.4) on 96-well Brandel Cell Harvester. Detection of activity: in beta-counter (1450 Microbeta, Wallac) in the presence of 200 µL of HiSafe-3 coctail. Inhibition [%] = 100-((activity in the presence of test compound - non-specific activity)/(total activity - non-specific activity))*100.

Human adenosine A_{2b} receptor binding

Binding protocol: incubate 20.8 µg of membranes (human A_{2b} adenosine receptors transfected into HEK-293 cells, source: Receptor Biology, Inc.), buffer (50 mM Tris-HCl, 10 mM $MgCl_2$, 1 mM EDTA, 0.1 mM benzamidine, 2 U/mL adenosine deaminase, pH 6.5), 32.4 nM [^{3}H]DPCPX (8-cyclopenthyl-1,3-dipropylxanthine) (800.000 dpm) and 100 µM NECA (5`-N-ethylcarboxamido-adenosine) to define non-specific binding or test compound in a total volume of 100 µL for 30 min at room temperature. Filter under 25 Hgmm vacuum over Whatman GF/C glass fibre filters (presoaked in 0.5% polyethylenimine for 3 hours), wash 4x with 1 mL ice-cold 50 mM Tris-HCl (pH 6.5) on 96-well Brandel Cell Harvester. Detection of activity: in the presence of 200 µL of HiSafe-3 coctail in beta-counter (1450 Microbeta, Wallac). Inhibition [%] = 100-((activity in the presence of test compound - non-specific activity)/(total activity - non-specific activity))*100

Results

We consider the compounds as biologically actives ones if they inhibit the binding of the radioligand on human adenosine A_3 receptors with an activity above 80 % at 1 µM in our experimental conditions.

The dissociation constant (K_d) of [^{125}I]AB-MECA on CHO-hA_3 membrane preparation is determined by isotope saturation studies with the help of Scatchard analysis (G. Scatchard, Ann. N. Y. Acad. Sci. 51:660, 1949). The IC_{50} is converted to an affinity constant (K_i) by application of the Cheng-Prusoff equation (Y. J. Cheng and W. H. Prusoff, Biochem. Pharmacol. 22:3099, 1973).

Several compounds of the general formula (I), (II), (III), (IV) and (V) display remarkable biological effects. Most important activities are exhibited by the compounds of the general formula (I) defined in claims 1-3. Especially advantageous are the compounds given in the Examples, their K_i values are in the range of 0.8 nM and 700 nM. K_i values of the most advantageous compounds are 0.8 and 15 nM.

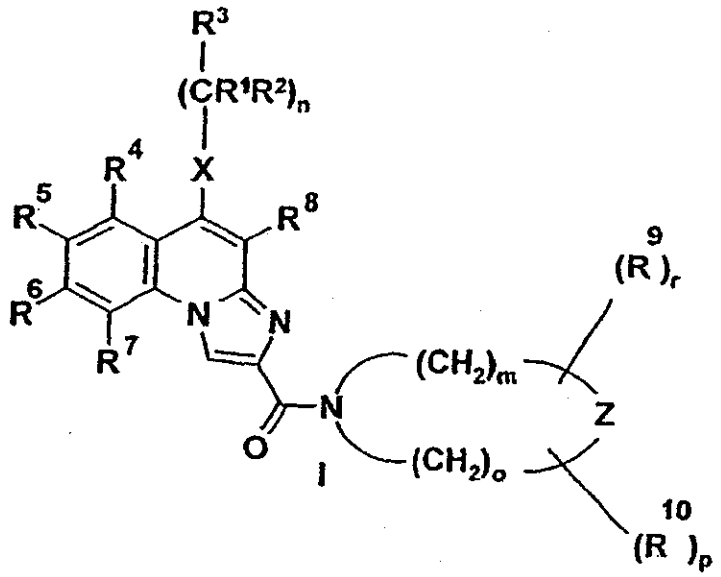
The compounds possess proper bioavailability and a selectivity of at least 3 order of magnitude, in respect of the human adenosine A_1, A_{2a} and A_{2b} receptor subtypes.

Further, the duration of their action at intravenous and oral administration is long, their ED_{50} values are low, their toxicological and side-effect profiles are advantageous.

These above data favour the therapeutic application of the compounds of the general formula (I).

Claims

1. Compounds of the general formula (I)

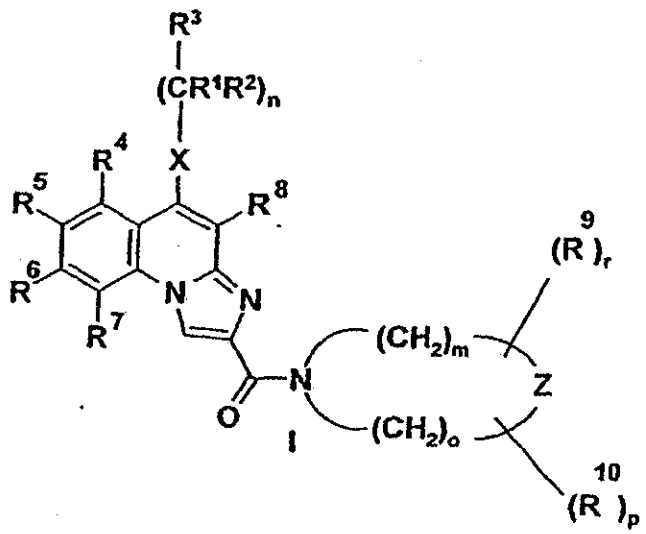


wherein

R^1 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;
R^2 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;
R^3 stands for hydrogen atom, or a straight or branchedC_{1-4} alkyl group,C_{3-6} cycloalkyl group, a phenyl-, thienyl-, or furyl group, optionally substituted with one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom; a six- or five-membered heteroaromatic ring containing one, two or three nitrogen atoms, or a five-membered heteroaromatic ring containing one nitrogen atom and one oxygen atom, or one nitrogen atom and one sulphur atom, optionally substituted with one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;
R^4, R^5, R^6 and R^7 independently stand for hydrogen atom, straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom, or R^4 and R^7 stand for hydrogen atom and R^5 and R^6 form together a methylenedioxy group;
R^8 stands for hydrogen atom or for cyano group, aminocarbonyl group, C_{1-4} alkoxycarbonyl group, carboxy group;
R^9 and R^{10} independently stand for hydrogen atom, straight or branched C_{1-4} alkyl group, C_{3-6} cycloalkyl group.
X stands for $-CH_2-$ group, -NH- group, $-NR^{11}-$ group, or sulphur atom, oxygen atom, sulpho group or sulphoxy group -wherein R^{11} means straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group;
Z means oxygen atom, sulphur atom, -NH- group or $-NR^{12}-$ group,-wherein R^{12} stands for straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-;
n has the value of zero, 1 or 2;
m has the value of zero, 1, 2 or 3
o has the value of zero, 1, 2 or 3
p has the value of zero or 1
r has the value of zero or 1, with the proviso that at least one of m and

o is different from zero ,
and their salts, solvates, and isomers, as well as the salts and solvates thereof.

2. Compounds of the general formula (I)

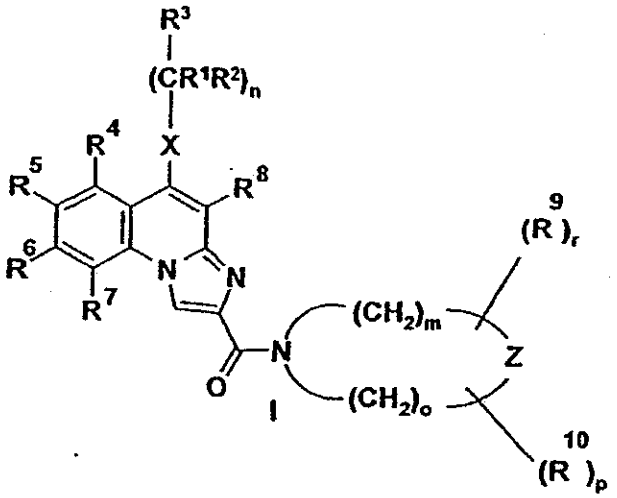


as defined in Claim 1, wherein

R^1 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;
R^2 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group;
R^3 stands for hydrogen atom, or a straight or branchedC_{1-4} alkyl group,C_{3-6} cycloalkyl group, a phenyl-, thienyl-, or furyl group, optionally substituted with one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;
R^4, R^5, R^6 and R^7 independently stand for hydrogen atom, straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom, or R^4 and R^7 stand for hydrogen atom and R^5 and R^6 form together a methylenedioxy group;
R^8 stands for hydrogen atom or for cyano group, aminocarbonyl group, C_{1-4} alkoxycarbonyl group, carboxy group;
R^9 and R^{10} independently stand for hydrogen atom, straight or branched C_{1-4} alkyl group, C_{3-6} cycloalkyl group,
X stands for -CH_2- group, -NH- group, -NR^{11}- group, or sulphur atom, oxygen atom, sulpho group or sulphoxy group -wherein R^{11} means straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-;
Z means oxygen atom, sulphur atom, -NH- group or -NR^{12}- group,-wherein R^{12} stands for straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-;
n has the value of zero, 1 or 2;
m has the value of zero, 1, 2 or 3
o has the value of zero, 1, 2 or 3
p has the value of zero or 1
r has the value of zero or 1, with the proviso that at least one of m and

o is different from zero,
and their salts, solvates, and isomers, as well as the salts and solvates thereof.

3. Compounds of the general formula (I)



as defined in Claims 1.-2., wherein

R^1 stands for hydrogen atom or methyl group;
R^2 stands for hydrogen atom or methyl group;
R^3 stands for phenyl- or thienyl- or furyl group;
R^4, R^5, R^6 and R^7 independently stand for hydrogen atom, straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom, or R^4 and R^7 stand for hydrogen atom and R^5 and R^6 form together a methylenedioxy group;
R^8 stands for hydrogen atom or cyano group;
R^9 and R^{10} stand for hydrogen atom, methyl-, ethyl- or cyclopropyl group,
X means -NH- group or oxygen atom;
Z means oxygen atom, sulphur atom, -NH- group or $-NR^{12}$- group, - wherein R^{12} stands for straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-; and
n has the value of 1;
m has the value of 2,
o has the value 2,
p has the value of zero,
r has the value of zero

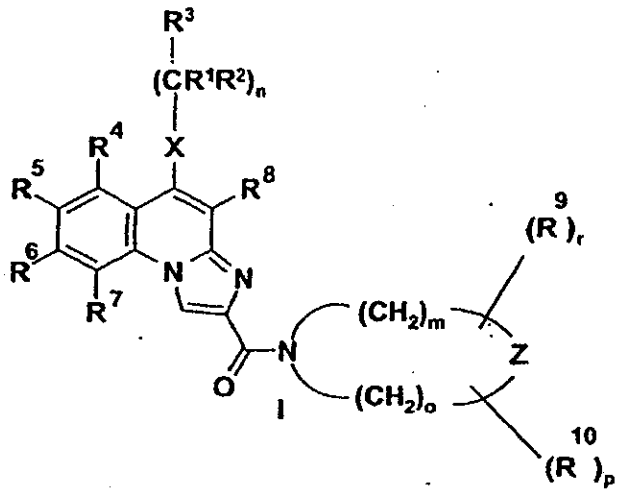
and their salts, solvates, and isomers, as well as the salts and solvates thereof.

4. Compounds according to Claims 1.-3., as follows:

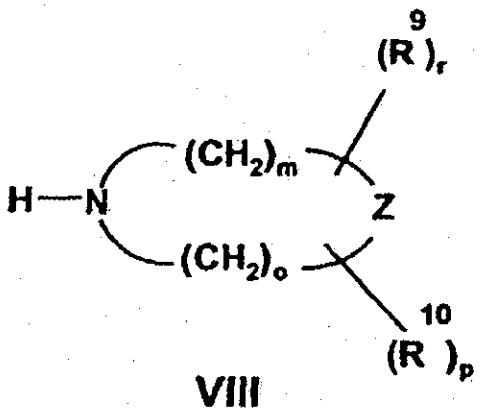
1-(9-Benzylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)-4-methylpiperazine
1-(9- Benzylamino-l10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)morpholine
1-(9-Furfurylamino- 10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)-4-methylpiperazine
1-(9-Furfurylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)piperazine:
1-(9-Furfurylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)morpholine
1-(9-Thenylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carbonyl)morpholine
1-(9-Thenylamino-10-cyano-imidazo[1,2-*a*]quinoline-2-carbonyl)piperazine

and their salts, solvates and isomers, as well as the salts and solvates thereof.

5. Process for the preparation of the compounds of the general formula (I)

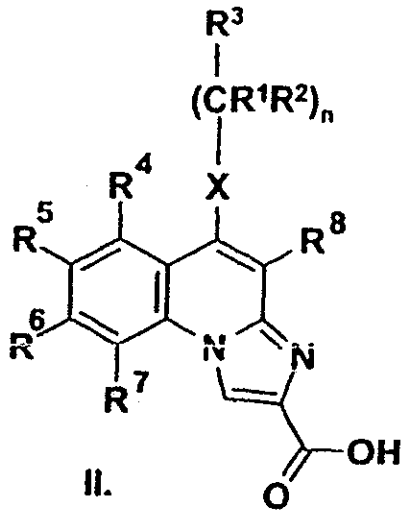


and their salts, solvates and isomers, wherein in the formula R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, X, Z, n, m, o, p and r have the meaning as defined in Claim 1., **characterized in that** a compound of the general formula (VIII)



VIII

- wherein R^9, R^{10}, Z, m, o, p and r have the meaning as defined in Claim 1- is acylated with an acid or reactive acid derivative of the general formula (II)



II.

- wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the meaning as defined in Claim 1 and, if desired, the substituents of the resulting compound of the general formula (I) are transformed into each other by known methods, and/or the compound of the general formula (I) is transformed into its salt or solvate, or liberated from its salt or solvate, and/or it is resolved into its optically active isomers, or the optically active isomer is transformed into the racemic compound.

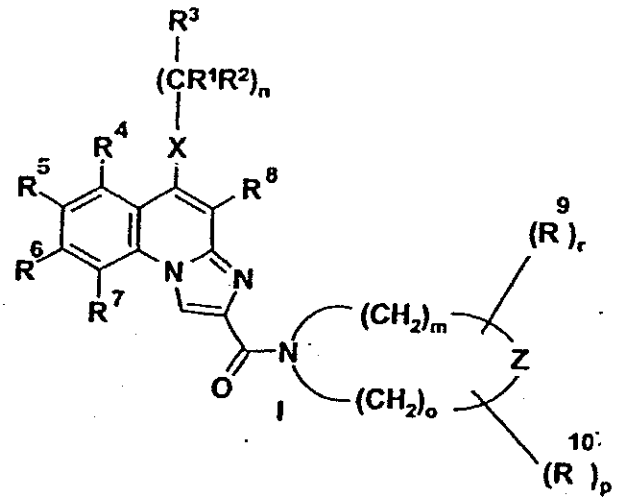
6. Process, as defined in claim 5., **characterized in that** the acylation is carried out in the presence of a base, in an organic solvent.

7. Process, as defined in claims 5.-6., **characterized in that** the reactive derivative of the acid of the general formula (II) is the appropriate acid halogenide or mixed anhydride.

8. Process, as defined in claims 5.-7., **characterized in that** the organic solvent is a halogenated hydrocarbon, preferably chloroform.

9. Process, as defined in claims 5.-8., **characterized in that** the base is an organic base, preferably triethylamine.

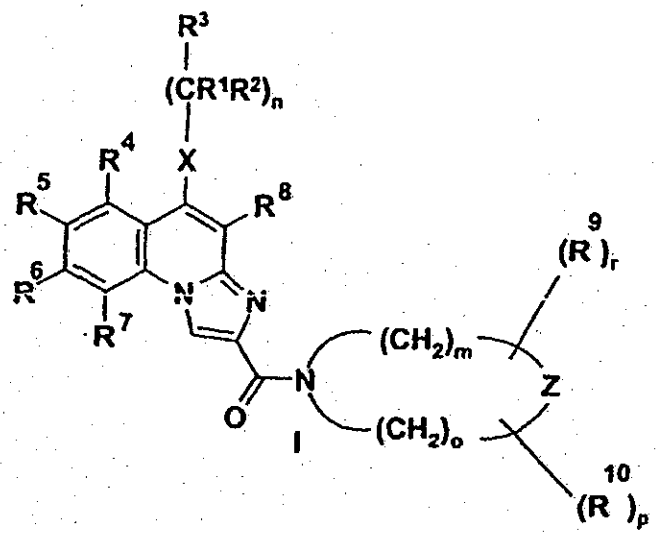
10. Pharmaceutical composition, **characterized in that** it contains one or more compounds of the general formula (I)



- wherein in the formula R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, X, Z, n, m, o, p and r have the meaning as defined in Claim 1.,- and/or their salts, solvates, isomers, the salts, solvates thereof, and one or more auxiliary materials, commonly used in the pharmaceutical industry.

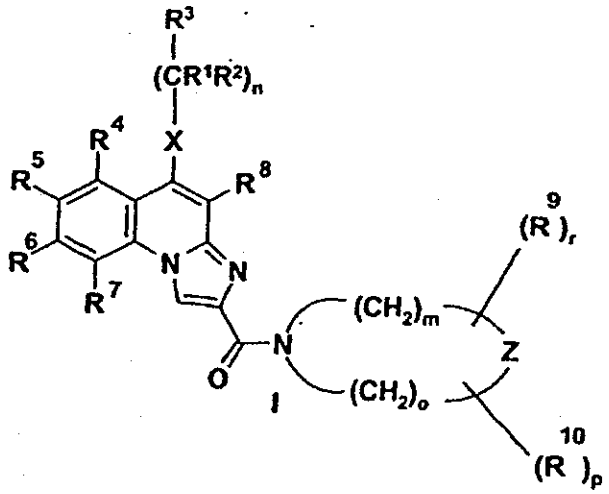
11. Pharmaceutical composition as defined in claim 10., **characterized in that** it contains as active substance one or more of the compounds defined in claim 3.

12. Use of the compounds of the general formula (I)



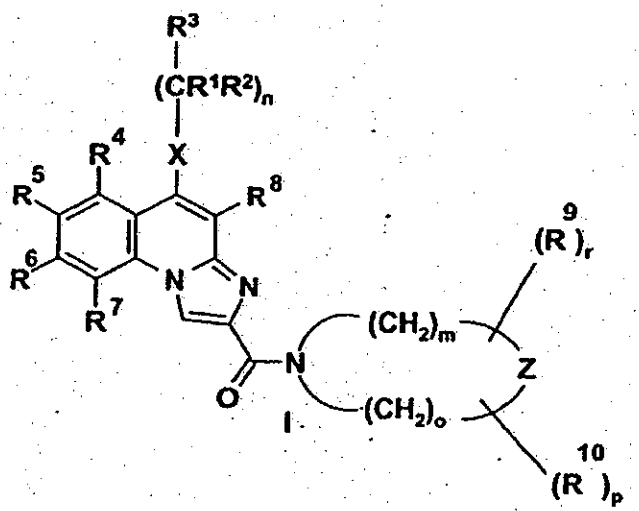
- wherein in the formula R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, X, Z, n, m, o, p, and r have the meaning as defined in claim 1.- for the preparation of a medicament for the treatment of pathologies where A_3 receptor plays a role in the development of the disease.

13. Use of the compounds of the general formula (I)



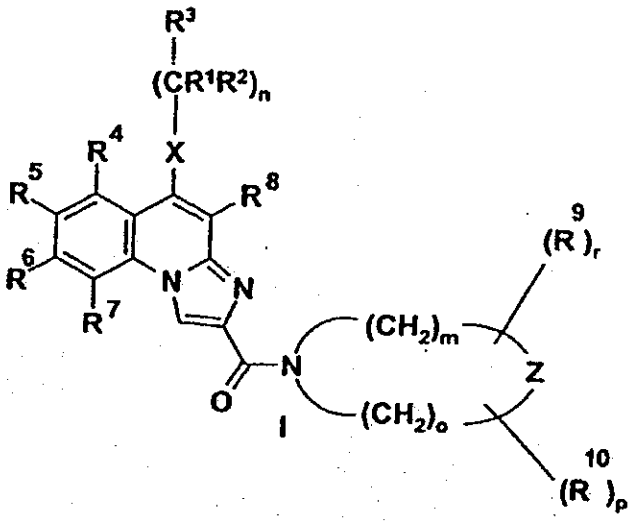
- where in the formula R^1, R^2 R^3 R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, X, Z, n, m, o, p, and r have the meaning as defined in claim 1.- as A_3 receptor ligands, for the preparation of a medicament in the therapeutic and/or protective treatment of disfunctions of the heart, kidney, respiratory system and central nervous system, for blocking of the protective effect of the adenosine on the growing tumoric cells, for prevention of the degranulation of the mast cells, for hindering of the formation of the cytokines, for decreasing the inner pressure of the eye, for prevention of the TNFα liberation, for hindering the migration of the eozinofil and neutrofil granulocytes and other inflammation cells, for prevention of the constriction of the trachea, and for prevention of infiltration of the blood plasma through the blood-vessel.

14. Use of the compounds of the general formula (I)



- where in the formula R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, X, Z, n, m, o, p, and r have the meaning as defined in claim 1.- as A_3 receptor antagonists, as active compounds for the preparation of antiinflammatory, antiasthmatic, antiischemic, antidepressant, antiarrhythmic, kidney function protective, tumor preventing, antiparkinson or cognitive function stimulating medicaments and as active compounds for the preparation of a medicament which can be used in the treatment or prevention of the following diseases: injury of the heart muscle during reperfusion, chronic obstructive pulmonary disease (COPD), adult respiratory insufficiency (ARDS) – including chronic bronchitis, pulmonary emphysema or difficult breathing-, allergic reactions (e.g. rhinitis, poison ivy-induced responses, nettle-rush, scleroderma, arthritis), other autoimmune diseases, inflammatory bowel diseases, Addison disease, Crohn disease, psoriasis, diseases of the joints, hypertonia, abnormal neurological functions, glaucoma and diabetes.

15. Use of the compounds of the general formula (I)



I

- where in the formula R^1, R^2, R^3, R^4 R^5, R^6, R^7, R^8, R^9 R^{10}, X, Z, n, m, o, p, and r have the meaning as defined in claim 1.- as active components for the preparation of a medicament for the treatment of disfunctions like asthma,COPDand ARDS, glaucoma, tumor, allergic and inflammatory diseases, ischemia, hypoxia, arrhythmia of the heart and diseases of the kidney.