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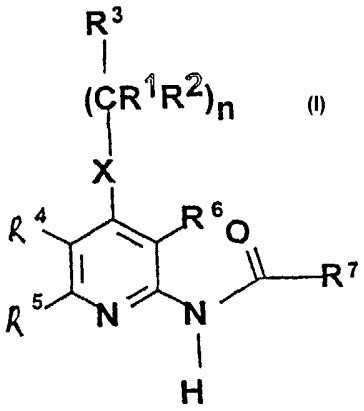

(57) Abstract: Compounds of general formula (I), wherein R^4 and R^5 stand for hydrogen atom or form together an 1,3-butadienyl group, optionally substituted by a methylenedioxy group or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom; are strong adenosine A_3 receptor ligands preferably antagonists.

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AMINOQUINOLINE AND AMINOPYRIDINE DERIVATIVES AND THEIR USE AS ADENOSINE A3 LIGANDS

The present invention relates to adenosine A_3 receptor ligands of the general formula (I), within those preferably antagonists, as well as their salts, solvates and isomers, and the pharmaceutical compositions containing them, to the use of the compounds of the general formula (I), as well as their salts, solvates and isomers, to the preparation of the compounds of the general formula (I) and their salts, solvates and isomers, furthermore to the new intermediates of the general formulae (II) (III) and (IV) and to the preparation thereof.

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 inhibiting 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 receptors 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 of 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 roles 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 located relatively in a higher amount in the striatum, display a

functional interaction with 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 comparing to other subtypes and highly species dependent. A_3 adenosine receptors are expressed primarily in the central nervous system, testis, 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.

Our aim was to prepare A_3 ligands first of all with quinoline structure, and within those preferably antagonists, which have strong antagonistic effect and show high selectivity for the A_3 receptor, ie. they inhibit the A_3 receptor in much lower concentration than they inhibit the A_1, A_{2a} and A_{2b} receptors. Further aims were to have stability, bioavailability, therapeutic index and toxicity data which make possible to develope the new compounds into drug substances and that due to their favourable enteral absorbtion the compounds can be applied orally.

We have found that the 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 branched C_{1-4} alkyl group, or a phenyl group, thienyl group, or furyl group, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom, or for a 5- or 6 membered heteroaromatic ring -containing one, two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom-

optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

R^4 and R^5 stand for hydrogen atom or form together an 1,3-butadienyl group, optionally substituted by a methylenedioxy group or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom;

R^6 stands for hydrogen atom or a cyano group, aminocarbonyl group, C_{1-4} alkoxycarbonyl group, or carboxy group;

R^7 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a phenyl group, benzyl group, thienyl group or furyl group, optionally substituted by a methylenedioxy group, or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group, trifluoromethyl group, cyano group or halogen atom, or for a 5 or 6 membered heteroaromatic ring -containing one, two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom- optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom,

X stands for a $-CH_2-$ group, –NH- group, $-NR^8-$ group, or a sulphur atom or an oxygen atom or a sulpho group or a sulphoxy group -wherein R^8 stands for a straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-;

n stands for zero, 1 or 2 – and their salts, solvates, and isomers and the salts, solvates of the latter, fulfill the above criteria.

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.

By 1,3-butadienyl-group we mean (-CH=CH-CH=CH-)-group, ie. the pyridine ring substituted by R^4 and R^5 substituents means a benzopyridine ring or by its trivial name a quinoline ring.

The heteroaromatic ring containing one or two or three nitrogen atoms means pyrrol, 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.

Salts of the compounds of the general formula (I) 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, fumaric acid, malic acid, citric acid, and bases, as for instance sodium hydroxide, potassium hydroxide, ethanolamine.

Solvates 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 favourable group of the compounds of the general formula (I) is formed by the compounds of the general formula (IA), 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, or a phenyl group, thienyl group, or furyl group, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom, or for a 5- or 6 membered heteroaromatic ring -containing one, two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom- optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

R^9, R^{10}, R^{11}, and R^{12} independently mean hydrogen atom or straight or branched C_{1-4} alkyl group, or straight or branched C_{1-4} alkoxy group, or hydroxy group or halogen atom, or

R^9 and R^{12} stand for hydrogen atom and R^{10} and R^{11} form together a methylenedioxy group;

R^6 stands for hydrogen atom or a cyano group, aminocarbonyl group, C_{1-4} alkoxycarbonyl group, or carboxy group;

R^7 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a phenyl group, benzyl group, thienyl group or furyl group, optionally substituted by a methylenedioxy group, or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group, trifluoromethyl group, cyano group or halogen atom, or for a 5 or 6 membered heteroaromatic ring -containing one, two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom- optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom,

X stands for a $-CH_2-$ group, –NH- group, $-NR^8-$ group, or a sulphur atom or an oxygen atom or a sulpho group or a sulphoxy group -wherein R^8 stands for a straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-;

n stands for zero, 1 or 2 –

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

A favourable group of the compounds of the general formula (IA) is formed by the compounds 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^9, R^{10}, R^{11}, and R^{12} mean independently hydrogen atom or straight or branched C_{1-4} alkyl group, or straight or branched C_{1-4} alkoxy group, or hydroxy group or halogen atom, or

R^9 and R^{12} stand for hydrogen atom and R^{10} and R^{11} form together a methylenedioxy group;

R^6 stands for hydrogen atom, or cyano group;

R^7 stands for 4-methoxyphenyl-, 3-methylphenyl-, 3-methoxyphenyl-, 3-thienyl-, or 3-furyl-group,

X stands for -NH-group or for oxygen atom and

n stands for 1 –

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

Especially favourable are the following compounds complying with the above criteria:

3-methyl-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide;

4-methoxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide;

3-methoxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide;

3,4-methylenedioxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide;

N-(4-benzylamino-3-cyanoquinolin-2-yl)thiophene-2-carboxamide;

N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)thiophene-3-carboxamide;

4-methoxy-N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)benzamide;

3,4-methylenedioxy-N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)-benzamide;

N-(4-[2-furylmethylamino]-3-cyanoquinolin-2-yl)furan-2-carboxamide;

N-(4-[2-furylmethylamino]-3-cyanoquinolin-2-yl)thiophene-3-carboxamide,

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

According to another of its aspects, 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 liquides, such as tablets, pellets, capsules, patches, solutions, suspensions or emulsions. The solid compositions, first of all tablets and capsules are the preferred pharmaceutical forms.

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

The compounds of the general formula (I) can be used in treating pathologies, in the development of which A_3 receptor plays a role.

The compounds of the present invention 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 inhibit the protective effect of adenosine in growing tumor cells, prevent mast cell degranulation, inhibit the cytokine production, reduce the inraocular pressure, inhibit the TNFα release, inhibit the migration of eosinophils, neutrophils and other immune cells, inhibit the bronchoconstriction and plasma extravasation.

Based on these effects, adenosine A_3 receptor antagonists of the present invention may be therapeutically useful as antiinflammatory, antiasthmatic, antiischemic, antidepressant, antiarrhytmic, renal protective, antitumor, antiparkinson and cognitive enhancing drugs. They also may be useful in the treatment or prevention of miocardial reperfusion injury, chronic obstructive pulmonary disease (COPD) and adult respiratory distress syndrome (ARDS) including chronic bronchitis, pulmonary emphysema or dyspnea, allergic reactions (e.g. rhinitis, poison ivy induced responses, urticaria, scleroderma, arthritis) other autoimmune diseases, inflammatory bowel disease, Addison`s disease, Crohn`s disease, psoriasis, rheumatism, hypertension, neurogical function disorders, 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 may be preferable used for the treatment of diseases such as asthma, COPD and ARDS, glaucoma, tumor, allergic and inflammatory diseases, ischemia, hypoxia, arrythmia and renal diseases.

According to another of its aspects, the present invention relates to the use of the compounds of the general formula (I) in the treatment of the above pathologies. Suggested

daily dose is 1-100 mg active ingredient depending on the nature and severeness of the disease and on sex, weight etc. of the patient.

Further subject of the invention is the preparation of the compounds of the general formula (I) and of the intermediates of the general formulae (II) (III) and (IV).

The intermediates of the general formulae (II) (III) and (IV) which are used in the preparation process according to the invention, are novel. Substituents of the general formulae (II), (III) and (IV) have the meanings as defined above.

In the process according to our invention the bis-carboxamide of the general formula (II) is selectively hydrolysed and the resulting compound of the general formula (I) is, if desired, transformed into its salts, solvates or, liberated from its salt, solvate and separated into its geometric or optical isomers.

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

Selective hydrolysis is performed by using alcoholic, preferably methanolic alkali hydroxide solution, preferably potassium and/or sodium hydroxide solutions, but other agents helping the hydrolysis of amides can also be used.

The selective hydrolysis can be carried out in a wide temperature range, favourably between 20 °C- 100 °C.

The compounds of the general formula (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, among them the one demonstrated in Scheme 1 (Figure 6), by acylation of the compounds of the formula (III), by using an acylation method known in the organic chemistry. For acylating agent preferably acyl chloride, for acid binding agent triethylamine and/or pyiridine can be applied, but other acid binding agents can also be used.

The compounds of the general formula (III) – wherein the meanings of R^1, R^2, R^3, R^4, R^5, R^6, R^8, X and n are as defined above – can be prepared from the compounds of the formula (IV) - by using methods known per se (Nan Zhang, Bioorg. and Med. Chem. Lett., 10, 2825, 2000).

The compounds of the general formula (IV) – wherein the meanings of R^4, R^5 and R^6 are as defined above – can be prepared from the compounds of the formula (V), by using methods known per se (D.L. Leysen, J. Heterocyclic Chem., 24, 1611, 1987).

The compounds of the general formula (V) – wherein the meanings of R^4, R^5 and R^6 are as defined above – can be prepared from the compounds of the formula (VI), by using methods known per se (Pfizer (Inc) USP 4,175,193) .

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

Figure 1 shows general formula (I), Figure 2 shows general formula (IA), Figure 3 shows general formula (II), Figure 4 shows general formula (III) and Figure 5 shows general formula (IV). Figure 6 shows Scheme 1 the reaction route for the preparation of compounds of the general formula (I).

Examples

Example 1

3-Methyl-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide:

In general formula (I) R^1 and R^2 stand for hydrogen atoms, R^3 for phenyl group, R^4 and R^5 form together a 1,3-butadienyl group, R^6 stands for cyano group, R^7 for 3-methylphenyl group, the meaning of X is –NH group, n is 1.

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, δ_H (400 MHz, DMSO-d_6): 7.21 ppm, (s, 2H, NH_2), 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 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 general formula III can be obtained.

c.) 3-Methyl-N-(3-methylbenzoyl)-N-(4-benzylamino-3-cyanoquinoline-2-yl)benzamide:
To the solution of 5 g of 2-amino-3-cyano-4-benzylaminoquinoline in 30 ml of pyridine 6 ml of 3-methylbenzoyl chloride are dropped, under stirring at 0°C. The reaction mixture is stirred at 80 °C for 8 hour, then it is poured onto 150 ml of ice-water. The precipitate is filtered off, washed twice with 40 ml of water. The resulting white crystalline material is recrystallized from 200 ml of ethanol to give 9.2 g of the title compound, mp.: 234 °C

By using pyridine-3-carbonyl chloride as acylating agent, the appropriate compound of general formula II can be obtained.

d.) 3-Methyl-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide
To the solution of 5 g of 3-methyl-N-(3-methylbenzoyl)-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide in 80 ml of acetonitrile 20 ml of 1N methanolic potassium hydroxide solution are added. The reaction mixture is refluxed for 3 minutes, then 3 ml of glacial acetic acid is added to it, then it is neutralized with 50 ml of 1M sodium hydrogen carbonate solution and the resulting crystals are filtered off. The white crystalline material is recrystallized from 130 ml of acetonitrile to give 3.1 g of the title compound of general formula (I). Mp.: 230 °C.

Example 2
4-Methoxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide
In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is phenyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 4-methoxyphenyl group, X means -NH-group, n is 1.

2-amino-3-cyano-4-benzylaminoquinoline, prepared as described in Example 1., is transformed with 4-methoxybenzoyl chloride, analogously as described in Example 1., into 4-methoxy-N-(4-methoxybenzoyl)-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide, which after selective hydrolysis, by the method described in Example 1., results the title compound of general formula (I). Melting point of the title compound: 188 °C.

Sodium salt of the title compound is prepared by the following method:

4-methoxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide is dissolved in methanol and equivalent amount of sodium hydroxide in methanol is added to it. The precipitated white crystalline material is filtered off. Mp.: 255 °C.

Ethanesulfonate salt of the title compound is prepared by the following method:
4-methoxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide is dissolved in methanol and equivalent amount of ethanesulfonic acid is added to it. The precipitated white crystalline material is filtered off. Mp.: 223 °C.

Example 3

3-Methoxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is phenyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 3-methoxyphenyl group, X means -NH-group, n is 1.

2-amino-3-cyano-4-benzylaminoquinoline, prepared as described in Example 1., is transformed with 3-methoxybenzoyl chloride, analogously as described in Example 1., into 3-methoxy-N-(3-methoxybenzoyl)-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide, which after selective hydrolysis by the method described in Example 1., results the title compound of general formula (I). Melting point of the title compound: 186 °C.

Example 4

3,4-Methylenedioxy-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is phenyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 3,4-methylenedioxyphenyl group, X means -NH-group, n is 1.

2-amino-3-cyano-4-benzylaminoquinoline prepared as described in Example 1., is transformed with 4-methoxybenzoyl chloride analogously as described in Example 1., into 3,4-methylenedioxy-N-(3,4-methylenedioxybenzoyl)-N-(4-benzylamino-3-cyanoquinolin-2-yl)benzamide which after selective hydrolysis by the method described in Example 1.,

results the title compound of general formula (I).

Melting point of the title compound: 231 °C.

Example 5

N-(4-benzylamino-3-cyanoquinolin-2-yl)thiophene-2-carboxamide

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is phenyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 2-thienyl group, X means -NH-group, n is 1.

2-amino-3-cyano-4-benzylaminoquinoline prepared as described in Example 1. is transfomed with thiophene-2-carbonyl chloride, analogously as described in Example 1., into N-(2-thiophenecarbonyl)-N-(4-benzylamino-3-cyanoquinolin-2-yl)thiophene-2-carboxamide, which after selective hydrolysis, by the method described in Example 1., results the title compound of general formula (I).

Melting point of the title compound: 197°C.

Example 6

N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)thiophene-3-carboxamide

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is 2-thienyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 3-thienyl group, X means -NH-group, n is 1.

a.) 2-amino-3-cyano-4-(2-thienylmethylamino)quinoline

5 g of 2-amino-3-cyano-4-chloroquinoline, prepared as described in Example 1, is stirred with 11 ml of 2-thienylmethylamine at 130 °C for 3 hours. 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 material is recrystallized from 25 ml of ethanol to obtain 5.2 g of title compound, mp.: 208 °C.

The 2-amino-3-cyano-4-(2-thienylmethylamino)quinoline prepared as described above is transformed with thiophene-3-carbonyl chloride, analogously as described in Example 1, into N-(3-thiophenecarbonyl)-N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)-

thiophene-3-carboxamide which after selective hydrolysis, by the method described in Example 1, gives the title compound of general formula (I). Melting point of the title compound: 223 °C.

Example 7

4-methoxy-N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)benzamide

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is 2-thienyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 4-methoxyphenyl group, X means -NH-group, n is 1.

The 2-amino-3-cyano-4-(2-thienylmethylamino)quinoline prepared as described in Example 6. is transformed with 4-methoxybenzoyl chloride into 4-methoxy-N-(4-methoxybenzoyl)-N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)benzamide by the method described in Example 1, which after selective hydrolysis gives the title compound of general formula (I). Melting point of the title compound: 173 °C.

Example 8

3,4-methylenedioxy-N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)-benzamide

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is 2-thienyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 3,4-methylenedioxyphenyl group, X means -NH-group, n is 1.

2-amino-3-cyano-4-(2-thienylmethylamino)quinoline prepared as described in Example 6. is transformed with 3,4-methylenedioxybenzoyl chloride into 3,4-methylenedioxy-N-(3,4-methylenedioxybenzoyl)-N-(4-[2-thienylmethylamino]-3-cyanoquinolin-2-yl)benzamide by the method described in Example 1, which after selective hydrolysis gives the title compound of general formula (I). Melting point of the title compound: 241°C.

Example 9

N-(4-[2-furylmethylamino]-3-cyanoquinolin-2-yl)furan-2-carboxamide

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is 2-furyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 2-furyl group, X means -NH-group, n is 1.

a.) 2-Amino-3-cyano-4-(2-furylmethylamino)quinoline

5 g of 2-amino-3-cyano-4-chloroquinoline, prepared as described in Example 1 are stirred with 1 ml of 2-furylmethylamine (furfurylamine) at 130 °C for 3 hours. 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 material is recrystallized from 20 ml of ethanol to obtain 4.8 g of the title compound, mp.: 208 °C.

The 2-amino-3-cyano-4-(2-furylmethylamino)quinoline prepared as described above is transformed with furan-2-carbonyl chloride by the method described in Example 1. into N-(2-furancarbonyl)-N-(4-[2-furylmethylamino]-3-cyanoquinolin-2-yl)furan-2-carboxamide which after selective hydrolysis gives the title compound of general formula (I). Melting point of the title compound: 196 °C.

Example 10

N-(4-[2-furylmethylamino]-3-cyanoquinolin-2yl)thiophene-3-carboxamide

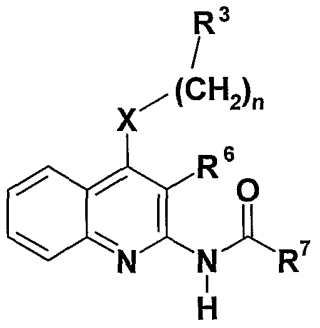
In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is 2-furyl group, R^4 and R^5 mean together a 1,3-butadienyl group, R^6 means cyano group, R^7 means 3-thienyl group, X means -NH-group, n is 1.

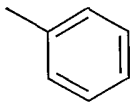
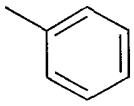
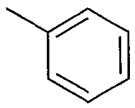
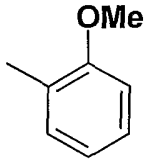
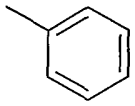
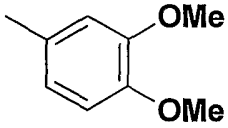
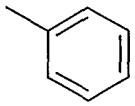
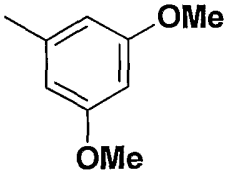
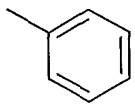
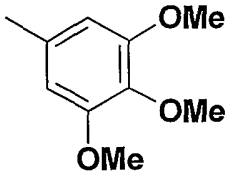
1.

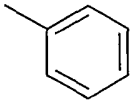
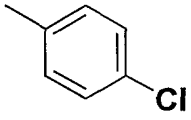
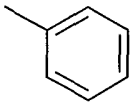
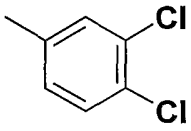
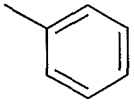
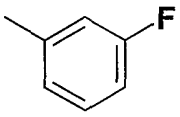
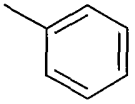
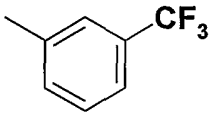
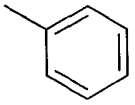
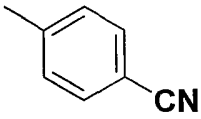
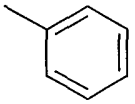
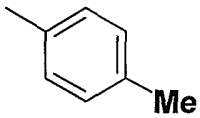
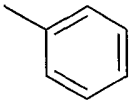
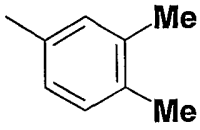
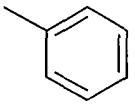
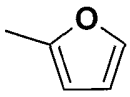
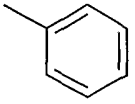
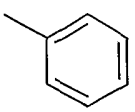
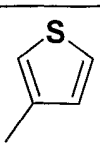
The 2-amino-3-cyano-4-(2-furylmethylamino)quinoline prepared analogously as described in Example 6. is transformed with thiophene-3-carbonyl chloride by the method described in Example 1. into N-(3-thiophene carbonyl)-N-(4-[2-furylmethylamino]-3-cyanoquinolin-2-yl)thiophene-3-carboxamide which after selective hydrolysis, performed analogously as described in Example 1. gives the title compound of general formula (I). Melting point of the title compound: 118 °C.

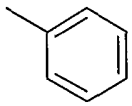
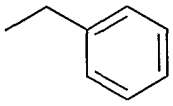
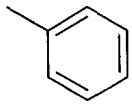
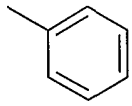
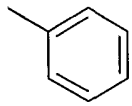
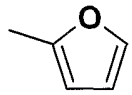
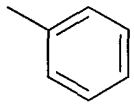
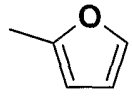
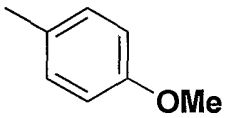
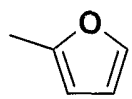
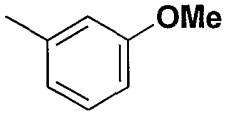
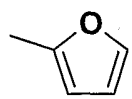
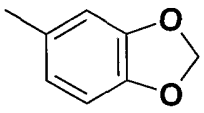
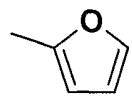
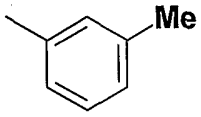
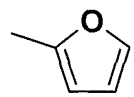
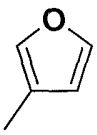
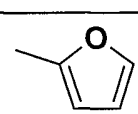
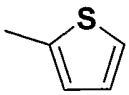
Structure and physical characteristics of further compounds of general formula (I) prepared by the method described in Example 1. are shown in Tables I. and II.

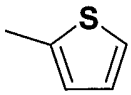
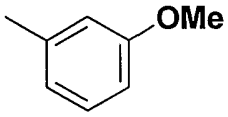
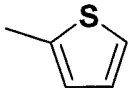
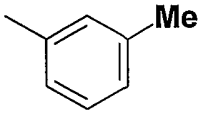
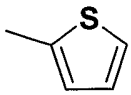
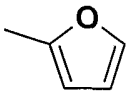
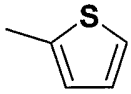
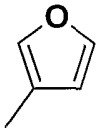
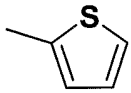
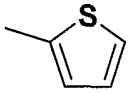
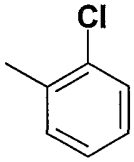
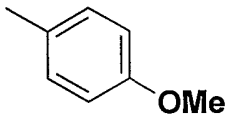
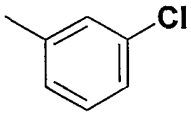
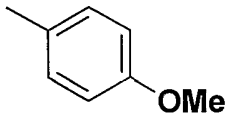
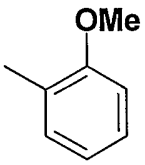
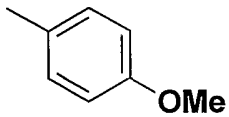
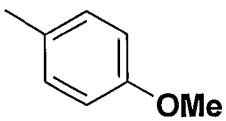
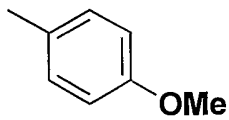
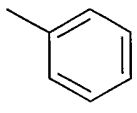
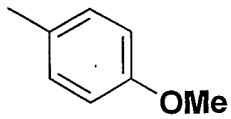
TABLE I.

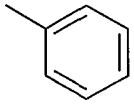
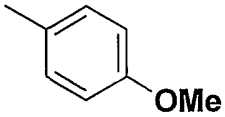
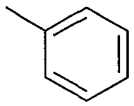
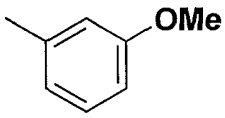
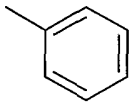
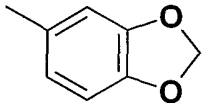
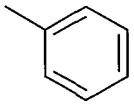
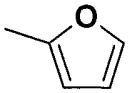
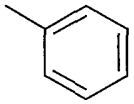
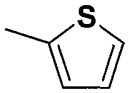
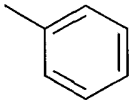
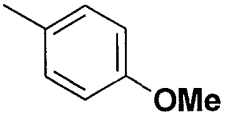
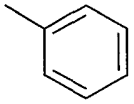
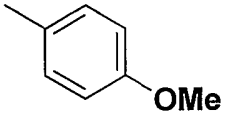
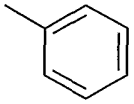
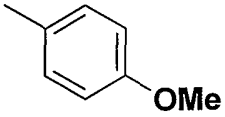
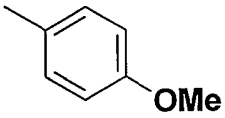
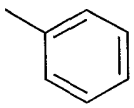
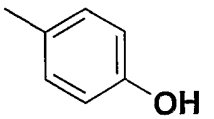


No.:	X	R^3	R^6	R^7	n	Mp [°C]
11.	NH		CN		1	237
12.	NH		CN		1	128
13.	NH		CN		1	116
14.	NH		CN		1	100,5
15.	NH		CN		1	223

16.	NH		CN		1	193,5
17.	NH		CN		1	193
18.	NH		CN		1	208
19.	NH		CN		1	215
20.	NH		CN		1	250
21.	NH		CN		1	205
22.	NH		CN		1	238
23.	NH		CN		1	212
24.	NH		CN		1	215
25.	NH		CN		1	234

26.	NH		CN		1	160,5
27.	NH		CN	—Me	1	184
28.	NH		CN		1	141,5
29.	NH		CN		1	194
30.	NH		CN		1	203
31.	NH		CN		1	152
32.	NH		CN		1	190
33.	NH		CN		1	202
34.	NH		CN		1	207
35.	NH		CN		1	159
36.	NH		CN		1	200

37.	NH		CN		1	206
38.	NH		CN		1	221
39.	NH		CN		1	198
40	NH		CN		1	158
41.	NH		CN		1	178
42.	NH		CN		1	198,5
43.	NH		CN		1	197,5
44.	NH		CN		1	191
45.	NH		CN		1	168,5
46.	N-Me		CN		1	155

47.	NH		H		1	172
48.	NH		H		1	250
49.	NH		H		1	264
50.	NH		H		1	265
51.	NH		H		1	163
52.	O		CN		1	157
53.	S		CN		1	196
54.	S=O		CN		1	205
55.	NH	H	CN		0	266
56.	NH		CN		1	154

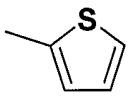
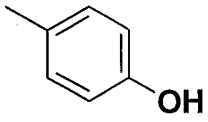
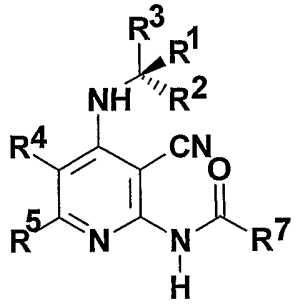
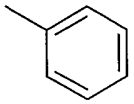
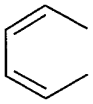
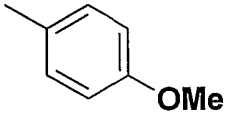
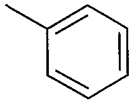
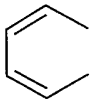
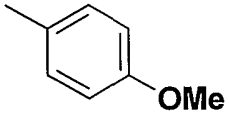
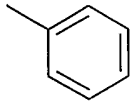
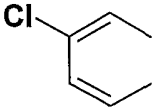
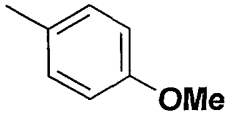
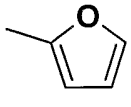
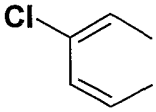
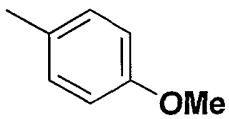
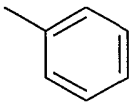
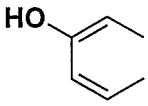
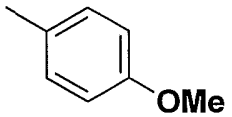
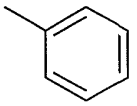
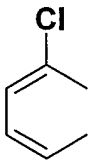
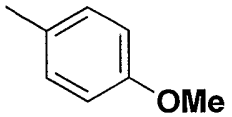
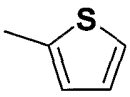
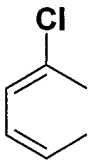
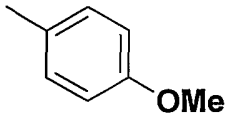
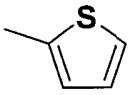
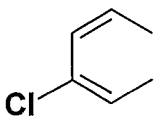
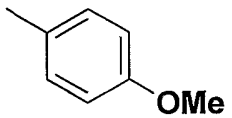
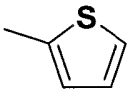
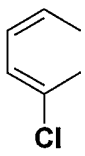
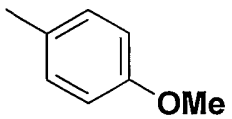
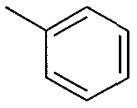
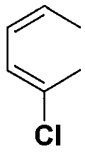
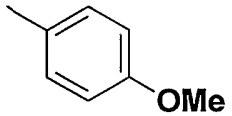
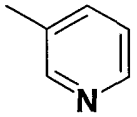
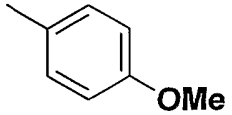
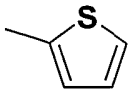
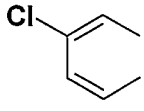
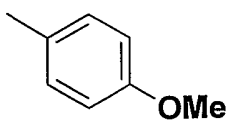
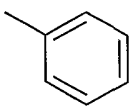
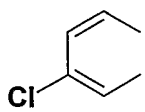
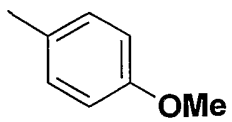
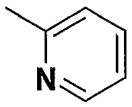
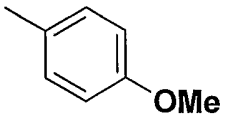
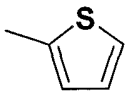
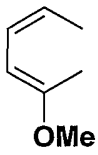
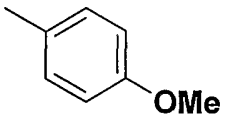
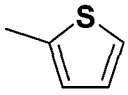
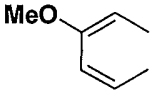
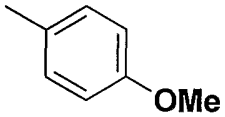
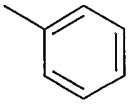
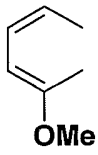
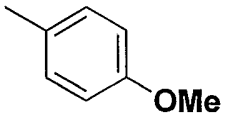
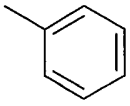
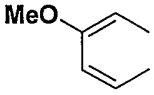
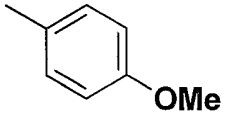
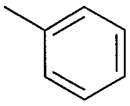
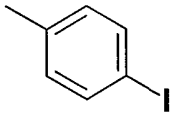
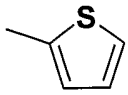
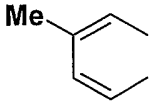
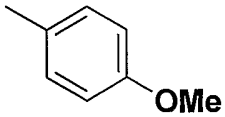
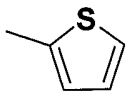
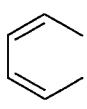
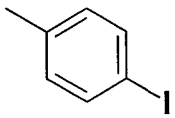
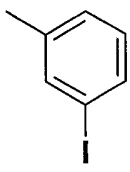
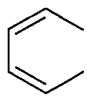
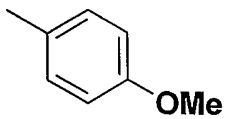
57	NH		CN		1	145

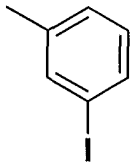
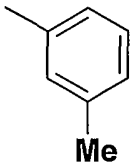
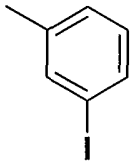
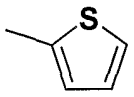
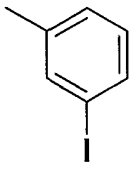
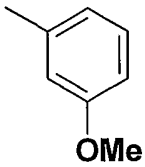
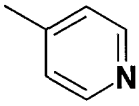
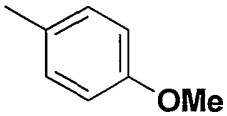
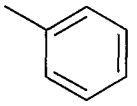
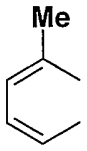
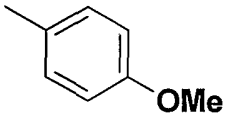
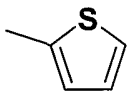
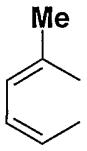
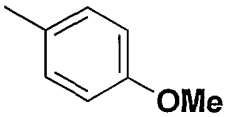
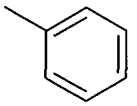
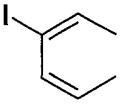
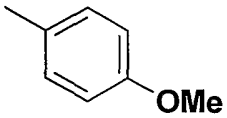
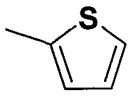
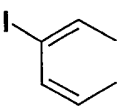
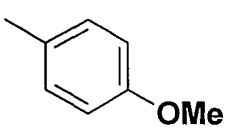
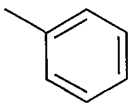
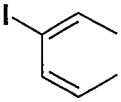
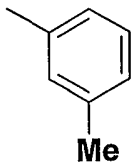
TABLE II.

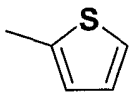
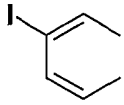
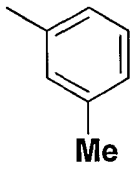
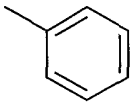
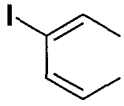
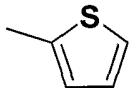
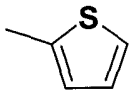
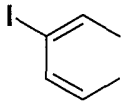
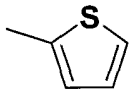
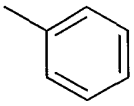
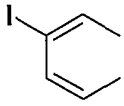
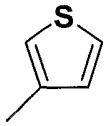
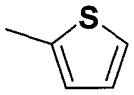
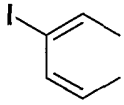
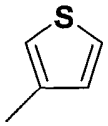
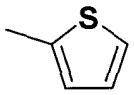
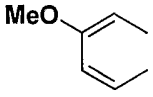
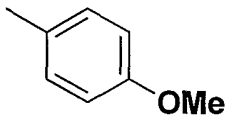
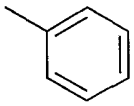
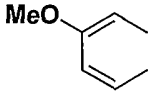
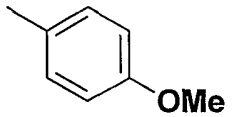
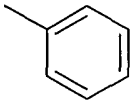
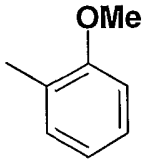
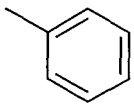
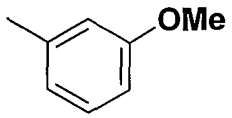
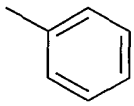
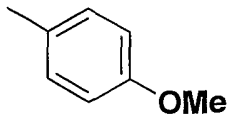


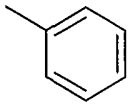
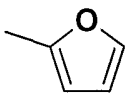
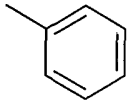
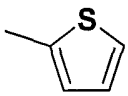
	R^1	R^2	R^3	R^4	R^5	R^7	Mp [°C]
58.	Me	H					165
59.	H	Me					145
60.	H	H					119
61.	H	H					119

62.	H	H				243
63.	H	H				176
64.	H	H				171
65.	H	H				199
66.	H	H				203
67.	H	H				180
68.	H	H				117
70.	H	H				153
71.	H	H				215

72.	H	H				237
73.	H	H				275
74.	H	H				245
75.	H	H				247
76.	H	H				222
77.	H	H				218
78.	H	H				214
79.	H	H				252
80.	H	H				178

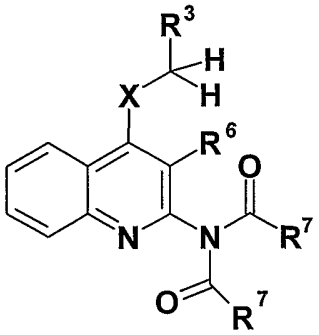
81.	H	H				173
82.	H	H				212
83.	H	H				184
84.	H	H				150
85.	H	H				195
86.	H	H				171
87.	H	H				217
88.	H	H				149
89.	H	H				135

90.	H	H				127
91.	H	H				257
92.	H	H				260
93.	H	H				153
94.	H	H				145
95.	H	H				214
96.	H	H				183
97.	H	H		H	H		167
98.	H	H		H	H		162
99.	H	H		H	H		183

100	H	H		H	H		216
101	H	H		H	H		206

Structure and physical characteristics of intermediates of general formula (II) prepared by the method described in Example 1. are shown in Table III.

TABLE III.



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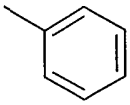
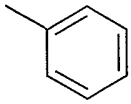
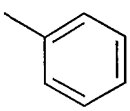
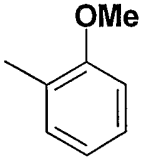
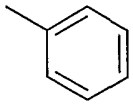
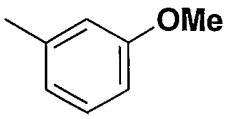
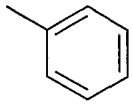
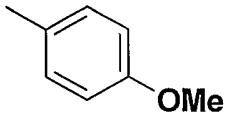
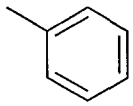
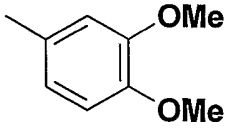
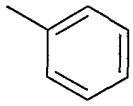
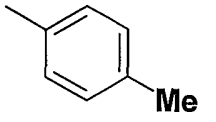
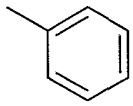
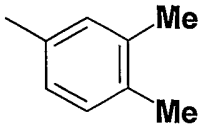
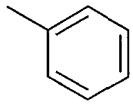
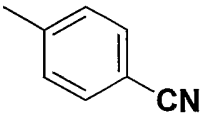
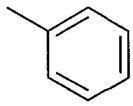
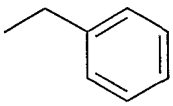
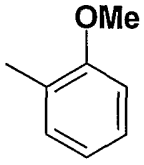
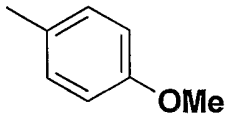
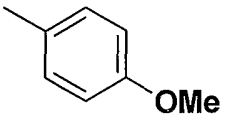
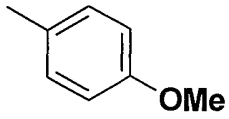
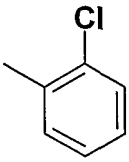
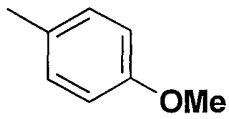
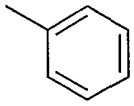
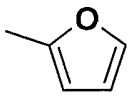
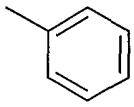
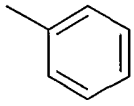
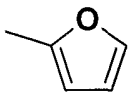
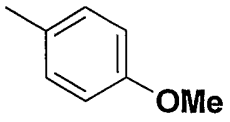
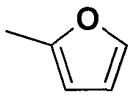
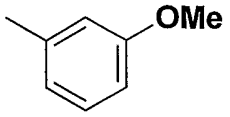
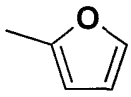
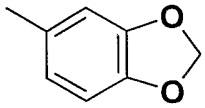
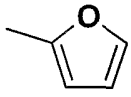
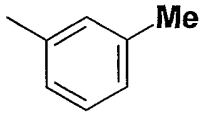
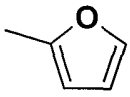
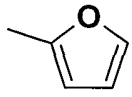
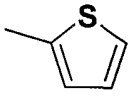
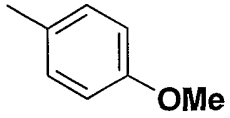
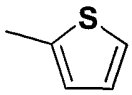
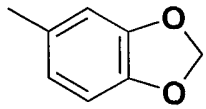
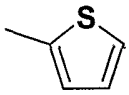
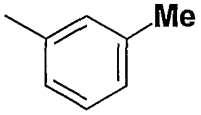
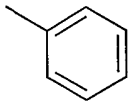
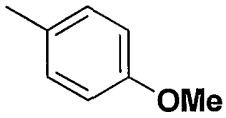
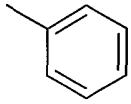
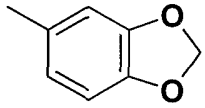
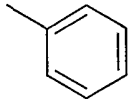
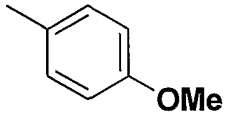
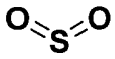
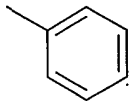
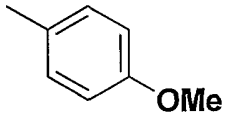
102	NH		CN		213
103.	NH		CN		208

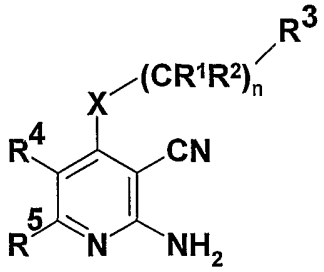
104	NH		CN		178s
105	NH		CN		158
106	NH		CN		210
107	NH		CN		223
108	NH		CN		224
109	NH		CN		212
110	NH		CN		198
111	NH		CN		208
112	NH		CN		168
113	NH		CN		168

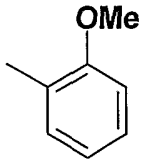
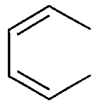
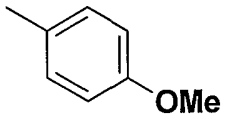
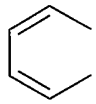
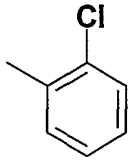
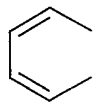
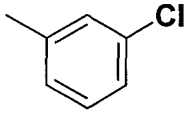
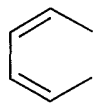
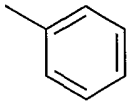
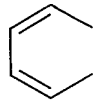
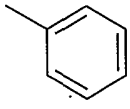
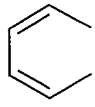
114	NH		CN		225
115	NH		CN	Me	152
116	NH		CN	Et	192
117	NH		CN		177
118	NH		CN		169
119	NH		CN		151
120	NH		CN		218
121	NH		CN		194
122	NH		CN		188
123	NH		CN		179

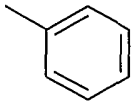
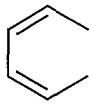
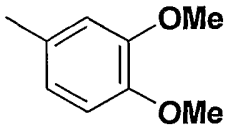
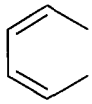
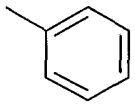
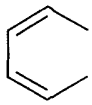
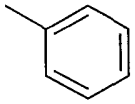
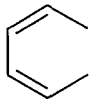
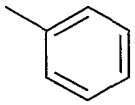
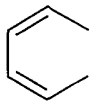
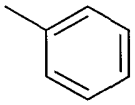
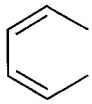
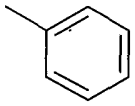
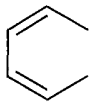
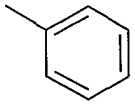
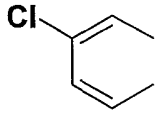
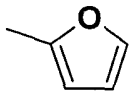
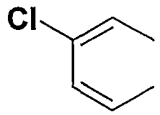
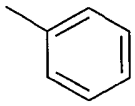
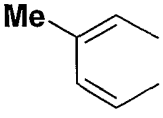
124	NH		CN		239
125	NH		H		162
126	NH		H		262
127	S		CN		170
128			CN		228

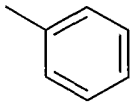
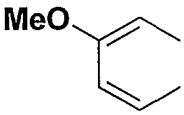
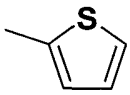
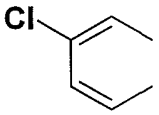
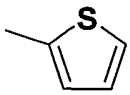
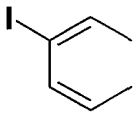
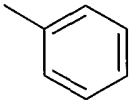
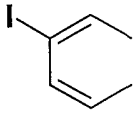
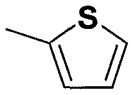
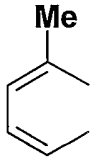
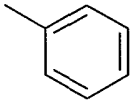
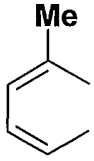
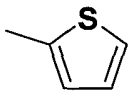
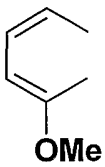
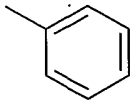
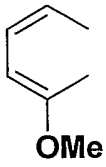
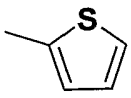
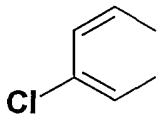
Structure and physical characteristics of intermediates of general formula (III) and (IIIa) prepared by the method described in Example 1. are shown in Table IV.

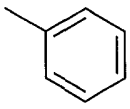
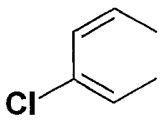
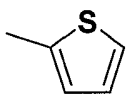
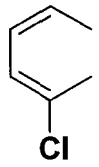
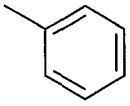
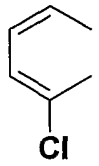
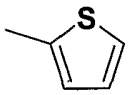
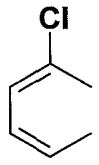
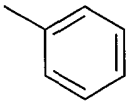
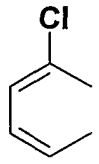
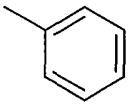
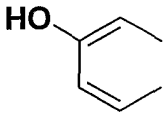
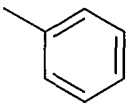
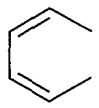
TABLE IV.



No.:	R^1	R^2	R^3	R^4	R^5	X	n	Mp [°C]
129	H	H				NH	1	192
130	H	H				NH	1	202
131	H	H				NH	1	250
132	H	H				NH	1	167
133	H					NH	1	183
134	H					NH	1	182

135	H	H			NH	2	172
136	H	H			NH	2	143
137	H				NH	2	129
138	H				NH	2	136
139	H	H			N-Me	1	212
140	H	H			S	1	168
141	H	H			O	1	213
142	H	H			NH	1	234
143	H	H			NH	1	221
144	H	H			NH	1	198

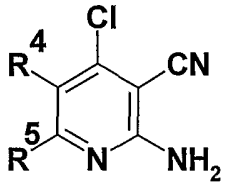
145	H	H			NH	1	201
146	H	H			NH	1	213
147	H	H			NH	1	198
147	H	H			NH	1	201
148	H	H			NH	1	167
149	H	H			NH	1	156
150	H	H			NH	1	187
151	H	H			NH	1	178
152	H	H			NH	1	207

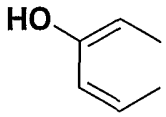
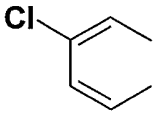
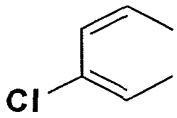
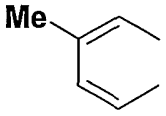
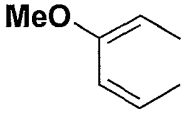
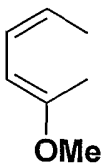
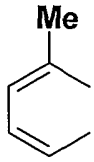
153	H	H			NH	1	217
154	H	H			NH	1	204
155	H	H			NH	1	216
156	H	H			NH	1	205
158	H	H			NH	1	213
159	H	H			NH	1	200
160					NH	0	214

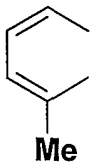
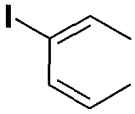
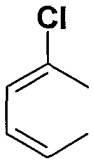
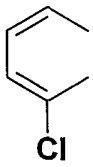
Structure and physical characteristics of intermediates of general formula (V) prepared by the method described in Example 1. are shown in Table V.

5

TABLE V.



No:	R^4 R^5	Mp [°C]
161.		360
162.		250
163.		278
164		283
165.		360
166.		234
167		246

168		267
169		293
170		289
171		307

Example 172.

Tablets of the following composition are made by known methods used in the pharmaceutical industry

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: collect CHO cells expressing hA3 receptors by washing three times with ice cold PBS, centrifugate at 1000 x g 10 min, homogenize for 15 sec in buffer (50 mM Tris, 10 mM $MgCl_2$, 1 mM EDTA, pH 8.0), centrifugate at 43.000 x g for 10 min (Sigma 3K30), suspense the membrane preparation in the buffer mentioned above, store the aliquots 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-benzyl-methylcarboxamido-adenosine) (100.000 cpm) and 100 μM R-PIA (N^6-[L-2-phenylisopropyl]adenosine) to define non-specific binding or 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: collect CHO cells expressing hA_1 receptors by washing three times with ice cold PBS, centrifugate at 1000 x g 10 min, homogenize for 15 sec in buffer (50 mM Tris, pH 7.4), centrifugate at 43.000 x g for 10 min (Sigma 3K30), suspense the membrane preparation in the buffer mentioned above, store the aliquots 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 96-well plate in the presence 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 protocol: 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 or test compound in a total volume of 100 µl for 90 min at room temperature. Filter over Whatman GF/B glass fibre filters (presoaked 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 96-well plate in the presence 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_{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 over Whatman GF/C glass fibre filters (presoaked in 0.5% polyethylenimine), wash 4x with 1 mL ice-50 mM Tris-HCl (pH 6.5) on 96-well Brandel Cell Harvester. Detection of activity: in 96-well plate in the presence 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 active 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) and (IV) display remarkable biological effects. The compounds of the general formula (IA), defined in claim 2, as a subgroup of the general formula (I), defined in claim 1, exert the most important activities. Except of 5 compounds, their K_i values are not higher than 20 nM. The compounds given as examples are especially advantageous. Their K_i values in human adenosine A_3 receptor binding studies are between 0.19 and 0.69 nM. The K_i values of the most advantageous compounds are 0.14 and 0.15 nM.

The compounds possess proper bioviabilities and exert at least 10,000-fold selectivity in respect of human adenosine A_1, A_{2a} and A_{2b} receptor subtypes.

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

Data above make the compounds of the general formula (I) probable for therapeutic applications.

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 branched C_{1-4} alkyl group, or a phenyl group, thienyl group, or furyl group, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom, or for one , two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom containing 5- or 6 membered heteroaromatic ring, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

R^4 and R^5 stand for hydrogen atom or form together an 1,3-butadienyl group, optionally substituted by a methylenedioxy group or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom;

R^6 stands for hydrogen atom or a cyano group, aminocarbonyl group, C_{1-4} alkoxycarbonyl group, or carboxy group;

R^7 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, a phenyl group, benzyl group, thienyl group or furyl group, optionally substituted by a methylenedioxy group, or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group, trifluoromethyl group, cyano group or halogen atom , or for one , two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom containing 5 or 6 membered heteroaromatic ring, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

X stands for a $-CH_2-$ group, –NH- group, $-NR^8-$ group, or a sulphur atom or an oxygen atom or a sulpho group or a sulphoxy group -wherein R^8 stands for a straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-;

n stands for zero, 1 or 2 –

and their salts and solvates, optically active isomers and their salts and solvates.

2) Compounds of the general formula (IA) according to 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 branched C_{1-4} alkyl group, or a phenyl group, thienyl group, or furyl group, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom, or for one , two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom containing 5- or 6 membered heteroaromatic ring, optionally substituted by one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, or halogen atom;

R^9, R^{10}, R^{11} or R^{12} stand independently from each other for hydrogen atom, or straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom; or

R^9 and R^{12} stand for hydrogen atom and R^{10} and R^{11} form together a methylendioxy group;

R^6 stands for hydrogen atom or a cyano group, aminocarbonyl group, C_{1-4} alkoxycarbonyl group, or carboxy group;

R^7 stands for hydrogen atom or a straight or branched C_{1-4} alkyl group, a phenyl group, benzyl group, thienyl group or furyl group, optionally substituted with a methylenedioxy group, or one or more straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group, trifluoromethyl group, cyano group or halogen atom , or for one , two or three nitrogen atoms or one nitrogen atom and one oxygen atom or one nitrogen atom and one sulphur atom containing 5 or 6 membered heteroaromatic ring, 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;

X stands for a $-CH_2-$ group, –NH- group, $-NR^8-$ group, or a sulphur atom or an oxygen atom or a sulpho group or a sulphoxy group -wherein R^8 stands for a straight or branched C_{1-4} alkyl group or C_{3-6} cycloalkyl group-;

n stands for zero, 1 or 2 –

and their salts and solvates, optically active isomers and their salts and solvates.

3) Compounds of the formula (IA) according to claim 2, -wherein

R^1 stands for hydrogen atom or a methyl group;

R^2 stands for hydrogen atom or a methyl group;

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

R^9, R^{10}, R^{11} or R^{12} stand independently from each other for hydrogen atom, or straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom; or

R^9 and R^{12} stand for hydrogen atom and R^{10} and R^{11} form together a methylendioxy group;

R^6 stands for hydrogen atom or cyano group;

R^7 stands for 4-methoxyphenyl group, 3-methylphenyl group, 3-thienyl group or 3-furyl group;

X stands for –NH- group or oxygen atom and

n stands for 1-

and their salts, solvates and optically active isomers and their salts and solvates.

4) Compounds according to claims 1-3 as follows:

3-Methyl-N-(4-benzylamino-3-cyano-quinolin-2-yl)benzamide;

4-Methoxy-N-(4-benzylamino-3-cyano-quinolin-2-yl)benzamide;

3-Methoxy- N-(4-benzylamino-3-cyano-quinolin-2-yl)benzamide;

3,4-Methylenedioxy-N-(4-benzylamino-3-cyano-quinolin-2-yl)benzamide;

N-(4-benzylamino-3-cyano-quinolin-2-yl)thiophene-3-carboxamide;

N-(4-[2-thienylmethylamino]-3-cyano-quinolin-2-yl)thiophene-3-carboxamide;

4-Methoxy-N-(4-[2-thienylmethylamino]-3-cyano-quinolin-2-yl)benzamide;

3,4-Methylenedioxy-N-(4-[2-thienylmethylamino]-3-cyano-quinolin-2-yl)benzamide;

N-(4-[2-furylmethylamino]-3-cyano-quinolin-2-yl)furan-2-carboxamide;

N-(4-[2-furylmethylamino]-3-cyano-quinolin-2-yl)thiophene-2-carboxamide

and their salts, solvates, optically active isomers and their salts and solvates.

5) Process for the preparation of a compound of the general formula (I), its salts, solvates, optically active isomers and their salts and solvates-wherein in the formula R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1, characterized

by selective hydrolysis of a bis acid amide of the general formula (II) -wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1- and if desired transforming the substituens of the compound of the general formula (I) thus obtained in each other by methods known per se and/or transforming the compound of the general formula (I) thus obtained into its salts, or solvates, or liberating it from its salts or solvates and/or separating it into its optically active isomeric forms or transforming the optically active forms into the racemic form

6) Process according to claim 5, characterized by carrying out the selective hydrolysis in an alcoholic medium in the presence of an alkali hydroxide, preferable potassium or sodium hydroxide

7) Pharmaceutical compositions containing as active ingredient one or more compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 – or their salts, solvates, or optically active isomers and the salts, solvates thereof, in admixture with one or more excipients used in the pharmaceutical industry.

8) Pharmaceutical compositions according to claim 7 containing as active ingredient one or more compounds of the general formula (IA) – wherein R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X and n have the same meaning as defined in claim 2 – or their salts, solvates, or optically active isomers and the salts, solvates thereof, in admixture with one or more excipients used in the pharmaceutical industry

9) Pharmaceutical composition according to claim 8 containing as active ingredient one or more compound of claim 4.

10)Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 - in the treatment of diseases in development of which the receptor A_3 plays a role.

11)Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 - according to claim 10 as A_3 ligand in the case of diseases of the heart, kidney, respiratory organs and central nervous system, for the inhibition of the protection of adenosine in growing tumor cells, prevention of mast cell degranulation, inhibition of the cytokine production, reduction of intraocular pressure, inhibition of the TNFα release, inhibition of eosinophil, neutrophil and other immune cell migration., inhibition of bronchoconstriction and plasma extravasation.

12) Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 - according to claims 10 and 11 as A_3 receptor antagonist in antiinflamatory, antiasthmatic, antiischemic, antidepressant, antiarrhytmic, renal protective, antitumor, antiparkinson and cognitive enhancing pharmaceutical compositions and in compositions for the treatment or prevention of miocardial reperfusion injury, chronic obstructive pulmonary disease (COPD) and adult respiratory distress syndrome (ARDS) including chronic bronchitis, pulmonary emphysema or dyspnea, allergic reactions (e.g. rhinitis, poison ivy induced responses, urticaria, scleroderma, arthritis) other autoimmune diseases, inflammatory bowel disease, Addison`s disease, Crohn`s disease, psoriasis, rheumatism, hypertension, neurogical function disorders, glaucoma and diabetes as active ingredient.

13) Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 – according to claims 10, 11 and 12 as A_3 receptor antagonist for the treatment of diseases such as asthma, COPD and ARDS, glaucoma, tumor, allergic and inflammatory diseases, ischemia, hypoxia, arrhytmia and renal diseases as active ingredient.

14) Use of the compounds of the general formula (IA) – wherein R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X and n have the same meaning as defined in claim 2 - in the treatment of diseases in development of which the receptor A_3 plays a role.

15) Use of the compounds of the general formula (IA) – wherein R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11},R^{12}, X and n have the same meaning as defined in claim 2 - according to claim 13 as A_3 ligand in the case of diseases of the heart, kidney, respiratory organs and central nervous system, for the inhibition or protection of adenosine in growing tumor cells, prevention of mast cell degranulation, inhibition of the cytokine production, reduction of the inraocular pressure, inhibition of the TNFα release, inhibition of eosinophil, neutrophil and other immune cell migration., inhibition of bronchoconstriction and plasma extravasation.

16) Use of the compounds of the general formula (IA) – wherein R^1, R^2, R^3, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, X and n have the same meaning as defined in claim 2 - according to claims 13 and 14 as A_3 receptor antagonist in antiinflamatory, antiasthmatic, antiischemic, antidepressant, antiarrhytmic, renal protective, antitumor, antiparkinson and cognitive enhancing pharmaceutical compositions and in compositions for the treatment or prevention of miocardial reperfusion injury, chronic obstructive pulmonary disease (COPD) and adult respiratory distress syndrome (ARDS) including chronic bronchitis, pulmonary emphysema or dyspnea, allergic reactions (e.g. rhinitis, poison ivy induced responses, urticaria, scleroderma, arthritis) other autoimmune diseases, inflammatory bowel disease, Addison`s disease, Crohn`s disease, psoriasis, rheumatism, hypertension, neurogical function disorders, glaucoma and diabetes as active ingredient.

17) Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1 – according to claims 14, 15 and 16 as A_3 receptor antagonist for the treatment of diseases such as asthma, COPD and ARDS, glaucoma, tumor, allergic reactions, inflammatory diseases, ischemia, hypoxia, arrhytmia and renal diseases.

18) Compounds of the general formula (II)- wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and n have the same meaning as defined in claim 1.

19) Compounds of the general formula (III)-wherein R^1, R^2, R^3, R^4, R^5, R^6, R^8, X and n have the same meaning as defined in claim 1, with the proviso that R^3 cannot stand for phenyl group, if R^1 and R^2 stand for hydrogenatom, n=1, X stands for a –NH– group, R^4 and R^5 form together an 1,3-butadienyl group and R^6 stands for a cyano group.

20) Compounds of the general formula (IV)- wherein R^4, R^5, and R^6 have the same meaning as defined in claim 1.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/HU 02/00048

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/48 A61K31/4706 A61P43/00 C07D405/12 C07D409/12
C07D409/14 C07D405/14 C07D215/46 C07D401/12 C07D213/85

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 116, no. 25, 22 June 1992 (1992-06-22) Columbus, Ohio, US; abstract no. 255453f, GEWALD K. ET AL.: "Simple synthesis of 2,3-diaminoquinoline-3-carbonitriles." XP002214323 abstract & J. PRAKT. CHEM/CHEM.-ZTG., vol. 334, no. 1, - 1992 pages 89-91, -& DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 1992:255453 XP002214325 compound with RN 141648-22-8 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 September 2002	07/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Van Bijlen, H

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/HU 02/00048

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 11244 A (ZENECA LTD.) 27 April 1995 (1995-04-27) * page 110-111: example 82a) and 82b) *	1
P,X	CHEMICAL ABSTRACTS, vol. 136, Columbus, Ohio, US; abstract no. 69693x, SARHAN, ABD EL-WARETH A. O. ET AL.: "Synthesis, characterization and reactions of 2-deoxo-5-deazaalloxazines." XP002214324 abstract & BIOORGANIC & MEDICINAL CHEMISTRY, vol. 9, no. 11, - 2001 pages 2993-2998, -& DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; Database accession no. 2001:845787 XP002214326 compounds with RN 383866-39-5 and -61-3	1
A	EP 1 180 518 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 20 February 2002 (2002-02-20) page 5	1,7

INTERNATIONAL SEARCH REPORT

ıational application No.
PCT/HU 02/00048

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10-17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/HU 02/00048

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