IMIDAZOQUINOLINE DERIVATIVES

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) and (III) 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 has 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: e.g. inhibiting of adenylate cyclase, and 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 imidazoquinolin 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 imidazoquinolin 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 C_{3-6} cycloalkyl 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 a 5 membered heteroaromatic ring containing 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, R^5, R^6 and R^7 stand independently from each other for hydrogen atom, a straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom; or R^4 and R^7 stand for hydrogen atom and R^5 and R^6 form together a methylenedioxy group

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

R^9 and R^{10} stand independently from each other for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a C_{3-6} cycloalkyl group, or a phenyl group, phenyl-(C_{1-4})alkyl group, thienyl-(C_{1-4})alkyl group or furyl-(C_{1-4})alkyl 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 a 5 membered heteroaromatic ring, containing 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; or for a $-(CH_2)_m$-OH or $-(CH_2)_o$-$NR^{12}R^{13}$ group, or

R^9 and R^{10} form together with the nitrogen atom a 3-7 membered heterocyclic group, optionally substituted by a straight or branched C_{1-4} alkyl group;

R^{12} and R^{13} stand independently from each other for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a C_{3-6} cycloalkyl group, or a phenyl group, phenyl-(C_{1-4})alkyl group, thienyl-(C_{1-4})alkyl group or furyl-(C_{1-4})alkyl 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 a 5 membered heteroaromatic ring, containing 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, or for a $-(CH_2)_m$-OH or $-(CH_2)_o$-$NR^{12}R^{13}$ group, or

R^{12} and R^{13} form together with the nitrogen atom a 3-7 membered heterocyclic group, optionally substituted by a straight or branched C_{1-4} alkyl group

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

n stands for zero, 1 or 2 –

m stands for 1, 2, 3 or 4, and

o stands for zero, 1, 2, 3 or 4

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

fulfil 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 a 3-7 membered heterocyclic ring we mean dimethyleneimine (aziridine), trimethyleneimine, tetramethyleneimine (pyrrolidine), pentemethylenimine (pyperidine) or hexamethyleneimine group.

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 C_{3-6} cycloalkyl 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 a 5 membered heteroaromatic ring, containing 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, R^5, R^6, and R^7 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^4 and R^7 stand for hydrogen atom and R^5 and R^6 form together a methylenedioxy group;

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

R^9 and R^{10} stand independently from each other for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a C_{3-6} cycloalkyl group, or a phenyl group, phenyl-(C_{1-4}) alkyl group, thienyl-(C_{1-4}) alkyl group or furyl-(C_{1-4}) alkyl 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 $-(CH_2)_m$-OH or $-(CH_2)_o$-$NR^{12}R^{13}$ group, or

R^9 and R^{10} form together with the nitrogen atom a 3-7 membered heterocyclic group, optionally substituted by a straight or branched C_{1-4} alkyl group;

R^{12} and R^{13} stand independently from each other for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a C_{3-6} cycloalkyl group, or a phenyl group, phenyl-(C_{1-4})alkyl group, thienyl-(C_{1-4})alkyl group or furyl-(C_{1-4})alkyl 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 $-(CH_2)_m$-OH or $-(CH_2)_o$-$NR^{12}R^{13}$ group, or

R^{12} and R^{13} form together with the nitrogen atom a 3-7 membered heterocyclic group, optionally substituted by a straight or branched C_{1-4} alkyl group

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

n stands for zero, 1 or 2 –

m stands for 1, 2, 3 or 4, and

o stands for zero, 1, 2, 3 or 4

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

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

R^9 and R^{10} stand for methyl group, ethyl group or cyclopropyl group or R^9 and R^{10} together with the nitrogen atom form a 3-7 membered heterocyclic group, optionally substituted by a straight or branched C_{1-4} alkyl 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:

1-(9-benzylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carbonyl)pyrrolidine;

N,N-dimethyl-9-benzylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carboxamide-hemihydrate;

N-ethyl-9-benzylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carboxamide-hemihydrate;

1-(9-furfurylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carbonyl)-pyrrolidine-hemihydrate;

1-(9-thienylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carbonyl)-pyrrolidine-hemihydrate;

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 0,1-1000 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) and (III).

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

In the process according to our invention a compound of the formula (VIII) is acylated with an acid of the general Formula (II), or a reactive derivative thereof according to the acylation reactions known in the organic chemistry. As acylating agents acid halogenides or mixed anhydrides are used and the compound of the general formula (I)

thus obtained 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.

The preparation of the mixed anhydride used in the acylation reaction is carried out with pivaloyl-chloride, preferable in the presence of an organic base, preferably triethylamine in chloroform, although other methods know form the organic chemistry can also be used. The acylation can be carried out within a wide temperature range, preferably between 0°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., by selective hydrolysis of the compounds of the formula (III), by using selective hydrolysing processes known in the organic chemistry. For hydrolysing agent preferably alkali hydroxides can be applied, but other agents helping the hydrolysis of esters 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^7, R^8, X and n are as defined above and R^{14} stands for C_{1-4} alkyl group– can be prepared from the compounds of the formula (IV) - by using methods known per se (I. R. Ager and R. Westwood, J. Med. Chem. 31, 1098, (1988)).

The compounds of the general formula (IV) – wherein the meanings of R^1, R^2, R^3, R^4, R^5, R^6 , R^7, R^8 and X and n are as defined above – can be prepared from the compounds of the formula (V), by using methods known per se (Nan Zhang, Bioorg. and Med. Chem. Lett., 10, 2825, (2000)).

The compounds of the general formula (V) – wherein the meanings of R^4, R^5 , R^6, R^7 and R^8 are as defined above – can be prepared from the compounds of the formula (VI), by using methods known per se (D.L. Leysen, J. Heterocyclic Chem., 24, 1611, (1987)).

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

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

10

Fig. 1 shows compounds of formula (I),

Fig. 2 shows compounds of formula (II),

Fig. 3 shows compounds of formula (III),

Fig. 4 shows compounds of formula (IV),

Fig. 5 shows compounds of formula (V),

Fig. 6 shows compounds of formula (VI),

Fig. 7 shows compounds of formula (VII),

Fig. 8 shows compounds of formula (VIII).

Examples

Example 1

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

In general formula (I) R^1 and R^2 stand for hydrogen atoms, R^3 for phenyl group, R^4, R^5, R^6 and R^7 stand for hydrogen atom, R^9 and R^{10} form together a 1,3-butandiyl group, R^8 stands for cyano group, the meaning of X is –NH group, n is 1.

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

The mixture of 10 g of 2-amino-3-cyano-4-hydroxyquinolin 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-benzylaminoquinolin

5 g of 2-amino-3-cyano-4-chloroquinolin 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 IV can be obtained.

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

To the solution of 2,74 g of 2-amino-3-cyano-4-benzylaminoquinolin in 100 ml of abs. ethanol 2,14 ml of ethyl bromopiruvate are added, under stirring at 70°C. The reaction mixture is boiled for 2 hour, than the precipitate is filtered off. The resulting white crystalline material is recrystallized from 150 ml of acetonitrile to give 1.1 g of the title compound, mp.: 112-114 °C.

NMR, δ_H (400 MHz, DMSO-d_6): 1,32 ppm (t, 3H, $COOCH_2CH_3$), 4,30 ppm (q, 2H, $COOCH_2CH_3$), 5,09 ppm (d, 2H, $PhCH_2$), 7,25-7,38 ppm (m, 5H), 7,64-7,67 ppm (m, 1H), 7,85-7,88 ppm (m, 1H), 8,43-8,53 ppm (m, 3H), 9,04 ppm (s, 1H, 3-H).

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

The mixture of 2,71 g. ethyl 9-benzylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carboxylate monohydrate, 42 ml ethanol and 40 ml of 10% sodium hydroxide solution is stirred for 6 hours on 25°C. To the thick suspension 100 ml water are added and the pH of the suspension is acidified to value 3 with a 96% acetic acid solution.
The pale-yellow crystalline material is filtered off, washed with 3x25 ml water, and dried.Thus 2,3 g of the title compound are obtained. Mp.:178-182 °C.

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

e. 1-(9-Benzylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carbonyl)-pyrrolidine

To the mixture of 1,71 g. 9-benzylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carboxylic acid, 15 ml chloroform and 0,8 g triethylamin 0,6 g pivaloyl chloride in 10 ml chloroform are dropped, under stirring within 15 minutes at 5°C. The reaction mixture is stirred for 1 hour at 5°C, after that the mixture of 0,4 g pyrrolidine, 10 ml chloroform and 0,8 ml triethylamine is added to it. The mixture is stirred for 7 hours at 25°, diluted with 100 ml chloroform, extracted with 50 ml water, 50 ml of 5% sodium-hydrogen carbonate solution, and 50 ml water, dried on sodium-sulfate and evaporated in vacuo. The pale-yellow crystalline material is recrystallized from N,N-dimethylformamide to obtain 0,7 g of the title compound. Mp.: 206°C.

NMR, δ_H (400 MHz, DMSO-d_6): 1,79-1,92 ppm (m, 4H), 3,47-3,50 ppm (m, 2H), 3,95-3,98 ppm (m, 2H), 5,08 ppm (d, 2H, $PhCH_2$), 7,23-7,38 ppm (m, 5H), 7,62-7,65 ppm (m, 1H), 7,83-7,87 ppm (m, 1H), 8,36-8,42 ppm (m, 2H), 8,50-8,52 ppm (m, 1H), 8,80 ppm (s, 1H, 3-H).

Example 2

N,N-Dimethyl-9-benzylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carboxamide hemihydrate

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is phenyl group, R^4, R^5, R^6 and R^7 stand for hydrogen , R^8 means cyano group, R^9 and R^{10} mean independently from each other methyl group, X means -NH-group, n is 1.

To the mixture of 1,71 g. 9-benzylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carboxylic acid (prepared according to example 1), 15 ml chloroform and 0,8 g triethylamin 0,6 g pivaloyl chloride in 10 ml chloroform are dropped, under stirring within 15 minutes at 5°C. The reaction mixture is stirred for 1 hour at 9°C, than the mixture of 0,45 g dimethylammonium chloride, 10 ml chloroform and 1,6 ml triethylamine is added to it. The mixture is stirred for 3 hours at 25°, than. the pale-yellow crystalline material obtained according to the procedure described in example 1 is recrystallized from N,N-dimethylformamide to obtain 0,65 g of the title compound. Mp.: 262-264°C.

NMR, δ_H (400 MHz, DMSO-d_6): 2,98 ppm (s, 3H), 3,45 ppm (s, 3H), 5,08 ppm (d, 2H, $PhCH_2$), 7,23-7,38 ppm (m, 5H), 7,62-7,65 ppm (m, 1H), 7,84-7,87 ppm (m, 1H), 8,37-8,39 ppm (m, 2H), 8,50-8,53 ppm (m, 1H), 8,75 ppm (s, 1H, 3-H).

Example 3

N-Ethyl-9-benzylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carboxamide hemihydrate

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is phenyl group, R^4, R^5, R^6, and R^7 stand for hydrogen, R^8 means cyano group, R^9 means hydrogen, R^{10} means ethyl group, X means -NH-group, n is 1.

1,71 g 9-benzylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carboxylic acid, prepared as described in Example 1., is transformed with 0,45 g ethylamine hydrochloride, analogously as described in previous Example ., into the title compound. After recrystallization of the pale-yellow material from 80 ml ethanol 0,62 g of the title compound, are obtained. Mp.:275-277°C.

NMR, δ_H (200 MHz, DMSO-d_6): 1,11 ppm (t, 3H, $NHCH_2CH_3$), 3,30 ppm (q, 2H, $NHCH_2CH_3$), 5,09 ppm (d, 2H, $PhCH_2$), 7,22-7,40 ppm (m, 5H), 7,60-7,67 ppm (m, 1H), 7,82-7,94 ppm (m, 2H), 8,38-8,42 ppm (m, 2H), 8,50-8,54 ppm (m, 1H), 8,82 ppm (s, 1H, 3-H).

Example 4

1-(9-Furfurylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carbonyl)-pyrrolidine hemihydrate

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is 2-furyl group, R^4, R^5, R^6 and R^7 mean hydrogen, R^9 and R^{10} mean together a 1,4-butandiyl group, R^8 means cyano group, means X means -NH-group, n is 1.

a) 2-Amino-3-cyano-furfurylaminoquinolin

10 g of 2-amino-3-cyano-4-chloroquinolin and 19 ml of furfurylamine are heated under stirring at 120 °C,.for 3 hours. The reaction mixture is cooled to 25°C, and six times successively mixed with 50 ml of water, the resulting precipitate is filtered off and dried. The material thus obtained is recrystallized from 60 ml dimethylformamide to obtain 5.8 g of the title compound. Mp.: 206 °C.

NMR, δ_H (200 MHz, DMSO-d_6): 4,98 ppm (d, 2H, Furil-CH_2), 6,29 ppm (s, 2H), 6,35-6,42 ppm (m, 2H), 7,10-7,18 ppm (m, 1H), 7,31-7,35 ppm (m, 1H), 7,47-7,60 ppm (m, 2H), 8,13-8,20 ppm (m, 2H).

b) Ethyl 9-furfurylamino-10-cyano-imidazo[1,2-*a*]quinolin-carboxylate monohydrate

To the solution of 2,64 g of 2-amino-3-cyano-4-furfurylaminoquinolin in 100 ml of abs. ethanol 2,14 ml of ethyl bromopiruvate are added, under stirring at 70°C. The reaction

mixture is boiled for 2 hour, then the precipitate is filtered off. material is recrystallized 1.1 g of the title compound are obtained, mp.: 242-245 °C

NMR, δ_H (200 MHz, DMSO-d_6): 1,33 ppm (t, 3H, $COOCH_2CH_3$), 4,31 ppm (q, 2H, $COOCH_2CH_3$), 5,05 ppm (d, 2H, Furil-CH_2), 6,40-6,43 ppm (m, 2H), 7,58-7,66 ppm (m, 2H), 7,80-7,88 ppm (m, 1H), 8,31 ppm (t, 1H), 8,41-8,45 ppm (m, 2H), 9,04 ppm (s, 1H, 3-H).

c) 9-Furfurylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carboxylic acid

The mixture of 2,52 g. ethyl 9-furfurylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carboxylate monohydrate, 40 ml ethanol and 33 ml of 10% sodium hydroxide solution is stirred for 3 hours at 25°C. To the thick suspension 80 ml water are added and the pH of the suspension is acidified to value 3 with a 96% acetic acid solution.
The pale-yellow crystalline material is filtered off, washed with 3x25 ml water, and dried.Thus 2,32 g of the title compound are obtained. Mp.:180-185 °C, (decomposition).

NMR, δ_H (200 MHz, DMSO-d_6): 5,05 ppm (d, 2H, Furil-CH_2), 6,39-6,42 ppm (m, 2H), 7,56-7,64 ppm (m, 2H), 7,79-7,87 ppm (m, 1H), 8,27 ppm (t, 1H), 8,36-8,46 ppm (m, 2H), 8,93 ppm (s, 1H, 3-H).

d) 1-(9-Furfurylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carbonyl)-pyrrolidine hemihydrate

To the mixture of 1,79 g. 9-furfurylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carboxylic acid, 15 ml chloroform and 0,8 g triethylamin 0,6 g pivaloyl chloride in 10 ml chloroform are dropped, under stirring within 15 minutes at 5°C. The reaction mixture is stirred for 1 hour at 5°C, after that the mixture of 0,36 g pyrrolidine, 10 ml chloroform and 0,8 ml triethylamine is added to it. The mixture is stirred for 3 hours at 25°, diluted with 100 ml chloroform, extracted with 50 ml water, 50 ml of 5% sodium-hydrogen carbonate solution, and 50 ml water, dried on sodium-sulfate and evaporated in vacuo. The yellow crystalline material is recrystallized from 50 ml ethanol to obtain 0,15 g of the title compound. Mp.: 276-279°C.

NMR, δ_H (200 MHz, DMSO-d_6): 1,79-1,95 ppm (m, 4H), 3,47-3,54 ppm (m, 2H), 3,98-4,04 ppm (m, 2H), 5,05 ppm (d, 2H, Furil-CH_2), 6,40-6,44 ppm (m, 2H), 7,57-7,65 ppm (m, 2H), 7,80-7,88 ppm (m, 1H), 8,23 ppm (t, 1H), 8,39-8,46 ppm (m, 2H), 8,81 ppm (s, 1H, 3-H).

Example 5

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

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is 2-thienyl group, R^4, R^5, R^6 and R^7 mean hydrogen, R^9 and R^{10} mean together a 1,4-butandiyl group, R^8 means cyano group, means X means -NH-group, n is 1.

a. 2-Amino-3-cyano-thenylaminoquinolin

10 g of 2-amino-3-cyano-4-chloroquinolin and 19 ml of thienylamine are heated under stirring at 115 °C, for 4 hours. The reaction mixture is cooled to 25°C, and six times successively mixed with 50 ml of water, the resulting precipitate is filtered off, washed twice with 50 ml water and dried. The material thus obtained is recrystallized from 60 ml N,N-dimethylformamide to obtain 6.8 g pale-yellow title compound. Mp.: 208-209°C.

NMR, δ_H (200 MHz, DMSO-d_6): 5,18 ppm (d, 2H, Tienil-CH_2), 6,28 ppm (s, 2H), 6,96-7,00 ppm (m, 1H), 7,07-7,19 ppm (m, 2H), 7,31-7,42 ppm (m, 2H), 7,48-7,56 ppm (m, 1H), 8,09-8,13 ppm (m, 1H), 8,30 ppm (t, 1H).

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

To the solution of 5,61 g of 2-amino-3-cyano-4-thenylaminoquinolin in 200 ml of abs. ethanol 4,29 g of ethyl bromopiruvate are added, under stirring at 70°C. The reaction mixture is boiled for 2 hour, then the precipitate is filtered off. 2,54 g light beige title compound are obtained, mp.: 255-256 °C

NMR, δ_H (200 MHz, DMSO-d_6): 1,33 ppm (t, 3H, $COOCH_2CH_3$), 4,31 ppm (q, 2H, $COOCH_2CH_3$), 5,24 ppm (d, 2H, Tienil-CH_2), 6,96-7,00 ppm (m, 1H), 7,14 ppm (m, 1H), 7,40-7,43 ppm (m, 1H), 7,61-7,68 ppm (m, 1H), 7,82-7,90 ppm (m, 1H), 8,42-8,46 ppm (m, 3H), 9,05 ppm (s, 1H, 3-H).

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

The mixture of 2,54 g. ethyl 9-thenylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carboxylate, 40 ml ethanol and 33 ml of 10% sodium hydroxide solution is stirred for 6 hours at 25°C. To the thick suspension 80 ml water are added and the pH of the suspension is acidified to value 3 with a 96% acetic acid solution.

The pale-yellow crystalline material is filtered off, washed with 5x10 ml water, and dried.Thus 2,18 g of the title compound are obtained. Mp.:209-217 °C (decomposition).

NMR, δ_H (400 MHz, DMSO-d_6): 5,24 ppm (d, 2H, Tienil-CH_2), 8,88 ppm (s, 1H, 3-H).

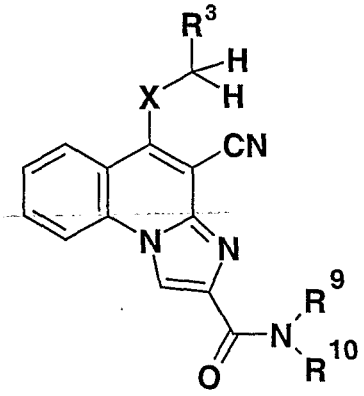
d. 1-(9-Thenylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carbonyl)-pyrrolidine hemihydrate

To the mixture of 1,80 g. 9-thenylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carboxylic acid, 10 ml chloroform and 1,1 ml triethylamin 0,87 g pivaloyl chloride in 10 ml chloroform are dropped, under stirring within 15 minutes at 5°C. The reaction mixture is stirred for 1 hour at 5°C, after that the mixture of 0,51 g pyrrolidine, 10 ml chloroform and 1,1 ml triethylamine is added to it. The mixture is stirred for 3 hours at 25°, diluted with 100 ml chloroform, extracted with 50 ml water, 50 ml of 5% sodium-hydrogen carbonate solution, and 50 ml water, dried on sodium-sulfate and evaporated in vacuo. The yellow crystalline material is recrystallized from 200 ml ethanol to obtain 0,29 g of the title compound. Mp.: 267-269°C.

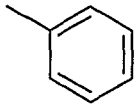
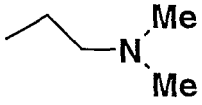
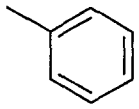
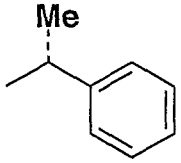
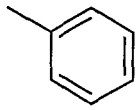
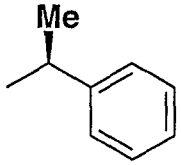
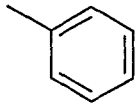
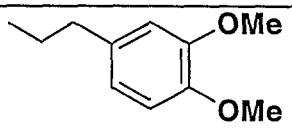
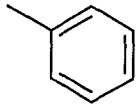
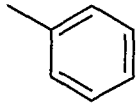
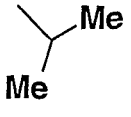
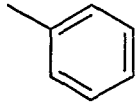
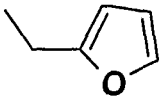
NMR, δ_H (400 MHz, DMSO-d_6): 1,79-1,94 ppm (m, 4H), 3,48-3,51 ppm (m, 2H), 3,98-4,01 ppm (m, 2H), 5,24 ppm (d, 2H, Tienil-CH_2), 6,97-7,00 ppm (m, 1H), 7,14 ppm (m, 1H), 7,41 ppm (m, 1H), 7,61-7,65 ppm (m, 1H), 7,83-7,87 ppm (m, 1H), 8,37-8,45 ppm (m, 3H), 8,82 ppm (s, 1H, 3-H).

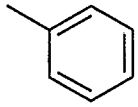
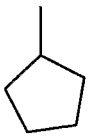
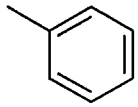
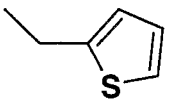
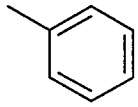
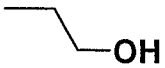
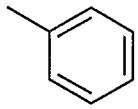
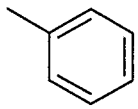
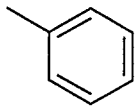
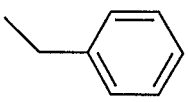
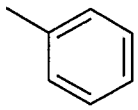
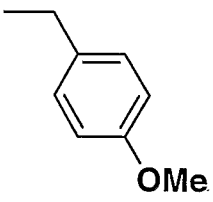
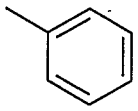
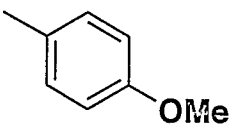
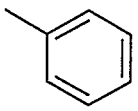
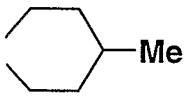
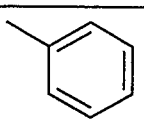
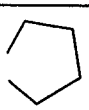
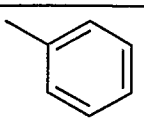
Structure and physical characteristics of further compounds of general formula (I) prepared by the method described in Example 1. are shown in Table I.

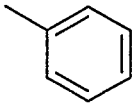
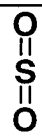
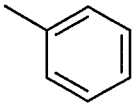
TABLE I.



(I)

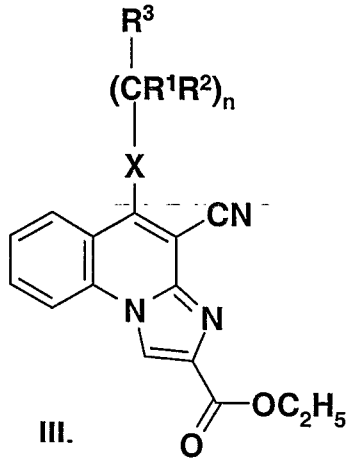
No.:	X	R^3	R^9	R^{10}	Mp [°C]
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7.	NH		H		122
8.	NH		H		104
9.	NH		H		185
10.	NH		H	H	265
11.	NH		H		269
12.	NH		H		248

13.	NH		H		275
14.	NH		H		239
15.	NH		H		149
16.	NH		H		235
17.	NH		H	Me	280
18.	NH		H		210
19.	NH		H		233
20.	NH		H		234
21.	NH				239
22.	O	Me			270
23.	O				233
24.	S				250

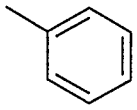
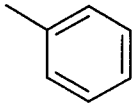
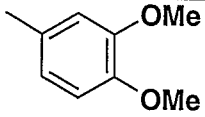
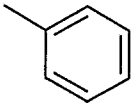
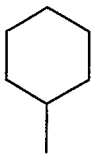
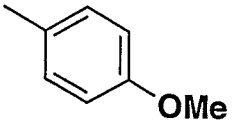
25.	S=O			333
26.				296

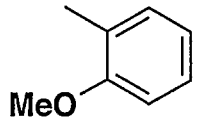
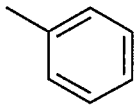
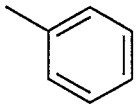
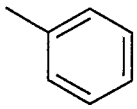
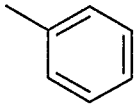
Structure and physical characteristics of the intermediates of the general formula (III) prepared by the method described in Example 1. are shown in Table (II)

TABLE II.



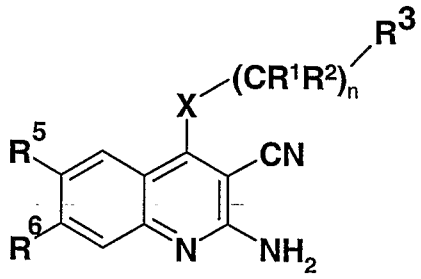
III.

	R^1	R^2	R^3	X	n	Mp [°C]
27.		H		NH	1	146
28.		H		NH	1	145
29.	H	H		NH	2	34
30.	H	H		NH	2	32
31.				NH	0	250
32.				NH	0	128
33.	H	H		NH	1	45

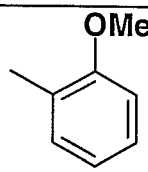
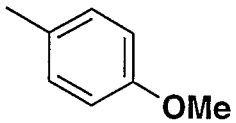
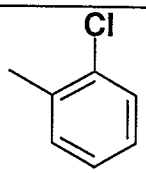
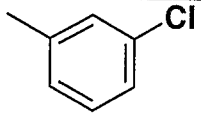
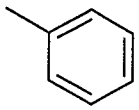
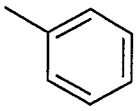
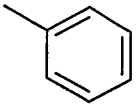
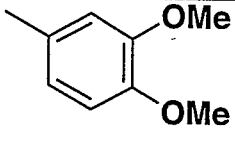
34.	H	H		NH	1	54
35.	H	H		O	1	185
36.	H	H		S	1	190
37.	H	H		S=O	1	230
38	H	H		O=S=O	1	255

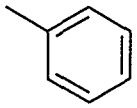
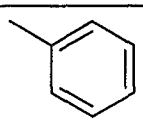
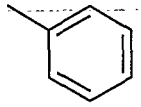
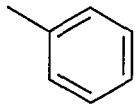
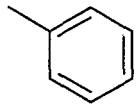
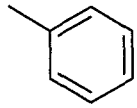
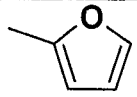
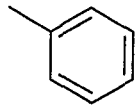
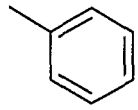
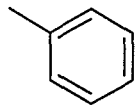
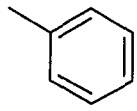
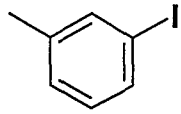
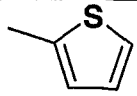
Structure and physical characteristics of the intermediates of the general formula (IV) prepared by the method described in Example l. are shown in Table (III)

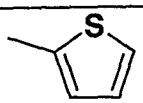
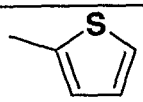
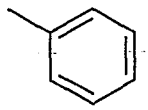
TABLE III.



(IV)

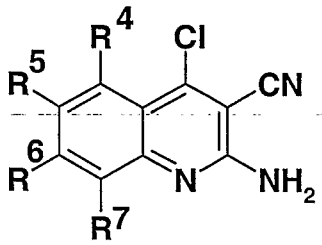
No.:	R^1	R^2	R^3	R^5	R^6	X	n	Mp [°C]
39.	H	H		H	H	NH	1	192
40.	H	H		H	H	NH	1	202
41.	H	H		H	H	NH	1	250
42.	H	H		H	H	NH	1	167
43.	H			H	H	NH	1	183
44.	H			H	H	NH	1	182
45.	H	H		H	H	NH	2	172
46.	H	H		H	H	NH	2	143

47.	H			H	H	NH	2	129
48.	H			H	H	NH	2	136
49.	H	H		H	H	N-Me	1	212
50.	H	H		H	H	S	1	168
51.	H	H		H	H	O	1	213
52.	H	H		Cl	H	NH	1	234
53.	H	H		Cl	H	NH	1	221
54.	H	H		Me	H	NH	1	198
55.	H	H		MeO	H	NH	1	201
56.	H	H		H	Cl	NH	1	191
57.	H	H		OH	H	NH	1	246
58.	H	H		H	H	NH	1	227
59.	H	H		MeO	H	NH	1	217

60	H	H		Me	H	NH	1	198
61.	H	H		Cl	H	NH	1	168
62.				H	H	NH	0	214

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

TABLE IV.



No:	R^4	R^5	R^6	R^7	Mp[°C]
63.	H	OH	H	H	360
64.	H	Cl	H	H	250
65.	H	H	Cl	H	278
66	H	Me	H	H	283
67.	H	OMe	H	H	360
68.	H	H	H	OMe	234
69	Me	H	H	H	246
70	H	H	H	Me	267
71	H	I	H	H	293

Example 72.

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 9 compounds, their K_i values are not higher than 150 nM. The compounds given as examples are especially advantageous. Their K_i values in human adenosine A_3 receptor binding studies are between 1.6 and 0.38 nM. The K_i values of the most advantageous compounds are 0.52 and 0.38 nM.

The compounds possess proper bioviabilities and exert at least 1,000-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 C_{3-6} cycloalkyl 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 a 5 membered heteroaromatic ring, containing 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 , R^5 , R^6 and R^7 stand independently from each other for hydrogen atom, a straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom; or R^4 and R^7 stand for hydrogen atom and R^5 and R^6 form together a methylenedioxy grou;

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

R^9 and R^{10} stand independently from each other for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a C_{3-6} cycloalkyl group, or a phenyl group, phenyl-(C_{1-4})alkyl group, thienyl-(C_{1-4})alkyl group or furyl-(C_{1-4})alkyl 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 a 5 membered heteroaromatic ring, containing 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; or for a $-(CH_2)_m$-OH or $-(CH_2)_o$-$NR^{12}R^{13}$ group, or

R^9 and R^{10} form together with the nitrogen atom a 3-7 membered heterocyclic group, optionally substituted by a straight or branched C_{1-4} alkyl group;

R^{12} and R^{13} stand independently from each other for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a C_{3-6} cycloalkyl group, or a phenyl group, phenyl-(C_{1-4})alkyl group, thienyl-(C_{1-4})alkyl group or furyl-(C_{1-4})alkyl 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 a 5 membered heteroaromatic ring, containing 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, or for a $-(CH_2)_m$-OH or $-(CH_2)_o$-$NR^{12}R^{13}$ group, or

R^{12} and R^{13} form together with the nitrogen atom a 3-7 membered heterocyclic group, optionally substituted by a straight or branched C_{1-4} alkyl group

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

n stands for zero, 1 or 2;

m stands for 1, 2, 3 or 4, and

o stands for zero, 1, 2, 3 or 4

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

2. Compounds of the general formula (I) according to claim l, 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 C_{3-6} cycloalkyl 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 a 5 membered heteroaromatic ring, containing 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, R^5, R^6, and R^7 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^4 and R^7 stand for hydrogen atom and R^5 and R^6 form together a methylenedioxy group;

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

R^9 and R^{10} stand independently from each other for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a C_{3-6} cycloalkyl group, or a phenyl group, phenyl-(C_{1-4}) alkyl group, thienyl-(C_{1-4}) alkyl group or furyl-(C_{1-4}) alkyl 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 $-(CH_2)_m$-OH or $-(CH_2)_o$-$NR^{12}R^{13}$ group, or

R^9 and R^{10} form together with the nitrogen atom a 3-7 membered heterocyclic group, optionally substituted by a straight or branched C_{1-4} alkyl group;

R^{12} and R^{13} stand independently from each other for hydrogen atom or a straight or branched C_{1-4} alkyl group, or a C_{3-6} cycloalkyl group, or a phenyl group, phenyl-(C_{1-4})alkyl group, thienyl-(C_{1-4})alkyl group or furyl-(C_{1-4})alkyl 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 $-(CH_2)_m$-OH or $-(CH_2)_o$-$NR^{12}R^{13}$ group, or

R^{12} and R^{13} form together with the nitrogen atom a 3-7 membered heterocyclic group, optionally substituted by a straight or branched C_{1-4} alkyl group

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

n stands for zero, 1 or 2;

m stands for 1, 2, 3 or 4, and

o stands for zero, 1, 2, 3 or 4

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

3. Compounds of the general formula (I) according to claims 1-2, wherein

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

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

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

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

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

R^9 and R^{10} stand for methyl group, ethyl group or cyclopropyl group or R^9 and R^{10} together with the nitrogen atom form a 3-7 membered heterocyclic group, optionally substituted by a straight or branched C_{1-4} alkyl group,

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

n stands for 1 –

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

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

1-(9-benzylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carbonyl)pyrrolidine;

N,N-dimethyl-9-benzylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carboxamide-hemihydrate;

N-ethyl-9-benzylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carboxamide-hemihydrate;

1-(9-furfurylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carbonyl)-pyrrolidine-hemihydrate;

1-(9-thienylamino-10-cyano-imidazo[1,2-*a*]quinolin-2-carbonyl)-pyrrolidine-hemihydrate;

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

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, R^9, R^{10}, R^{12}, R^{13}, X, n, m and o have the same meaning as defined in claim 1, characterized by acylating a compound of the general formula (VIII), wherein R^9 and R^{10} have the same meaning as defined in claim 1, with an acid 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, or a reactive derivative thereof 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 acylation in an organic solvent, in the presence of a base.

7. Process according to claims 5-6, characterized by using an acid halide or anhydride as the reactive derivative of the acid.

8. Process according to claims 5-6, characterized by using as organic solvent halogenated hydrocarbons, preferably chloroform.

9. Process according to claims 5-8, characterized by using as base an organic base, preferably triethylamine.

10. 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, R^9, R^{10}, 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.

11. Pharmaceutical compositions according to claim 10 containing as active ingredient one or more compounds of claim 3.

12 Pharmaceutical composition according to claim 10 containing as active ingredient one or more compound of claim 4.

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, R^9, R^{10}, 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.

14. 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, R^9, R^{10}, X and n have the same meaning as defined in claim 1 - 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 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.

15. 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 , R^9, R^{10}, X and n have the same meaning as defined in claim 1 - according to claims 13 and 14 as A_3 receptor antagonist in antiinflamatory, antiasthmatic, antiischemic, antidepressant, antiarrhytmic, renal protective, antitumor, antiparkinson and cognitive enchancing pharmaceutical compositions and in compositions for the treatment or prevention of miocardial referfusion 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 functions disorders, glaucoma and diabetes as active ingredient.

16. 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, R^9, R^{10}, X and n have the same meaning as defined in claim 1 – according to claims 13, 14 and 15 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.

17. 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.

18. Compounds of the general formula (III)-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 R^{14} stands for C_{1-4} alkyl group.