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(54) Title: TRIAZOLO-QUINOLIN DERIVATIVES USEFUL AS ADENOSINE RECEPTOR LIGANDS

(57) Abstract: 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 theirs salts, solvates and isomers, furthermore to the new intermediates of the general formulae (II) and to the preparation thereof.

TRIAZOLO-QUINOLIN DERIVATIVES USEFUL AS ADENOSINE RECEPTOR 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) 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 triazolo-quinolin 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 triazolo-quinolin structure, and within those preferably antagonists, which have strong antagonistic effect and show high selectivity for the A_3 receptor, i.e. they inhibit the A_3 receptor in much lower concentration than they inhibit the A_1, A_{2a} and A_{2b} receptors. Further 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 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 and R^5 stand independently from each other for hydrogen atom, or form together an 1,3-butadienyl 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 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 C_{1-4} alkylene group, optionally substituted by a phenyl group,or for 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, amino, mono- or dialkylamino group, 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;

X stands for a $-CH_2-$ group, –NH- group, $-NR^{12}-$ group, or a sulphur atom or an oxygen atom or a sulpho group or a sulphoxy group -wherein R^{12} 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 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.

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 group.

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 group.

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.

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 methyl group;

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

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

R^8, R^9, R^{10} and R^{11} independently from each other stand for hydrogen atom, straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom,or

R^8 and R^{11} stand for hydrogen atom and R^9 and R^{10} form together a methylenedioxy group,

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

R^7 stands for 4-methoxyphenyl group, 3-methylphenyl group, 3-methoxyphenyl group, 3-thienyl group, 3-pyridyl group, 3-hydroxyphenyl group 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:

2-(4-Methoxyphenyl)-9-benzylamino-10-cyano-*s*-triazolo[1,5-*a*]quinolin,

2-(2-Furyl)-9-(2-furylmethylamino)-10-cyano-*s*-triazolo[1,5-*a*]quinolin,

2-(3,4-Methylenedioxyphenyl)-9-(2-furylmethylamino)-10-cyano-*s*-triazolo[1,5-*a*] quinolin,

2-(3-Pyridyl)-9-(2-thienylmethylamino)-10-cyano-*s*-triazolo[1,5-*a*]quinolin,

2-(3-hydroxyphenyl)-9-(2-thienylmethylamino)-10-cyano-*s*-triazolo[1,5-*a*]quinolin, 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), (III), and (IV).

The intermediates of the general formula (II) are novel. Substituents of the general formulae (II), (III), and (IV) have the meanings as defined above.

In the process according to our invention an 1,2-diamino-azinium salt of the general formula (II) is reacted with a compound of the general Formula (VII), wherein R^7 is defined above and Y stands for hydrogen atom, halogen atom or a C_{1-4} alkoxy group, preferable with the suitable acid halogenide or ester (D.W. Robertson, J. Med. Chem., 28, 717, (1985)) 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.

The ring closure can be carried out in the presence of triethylamine in dimethylformamide or of other compounds known as catalysts for ring closures similar type.

The ring closure can be carried out within wide temperature range, preferable within 20°C and 150°C.

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

The compounds of the general formula (II) –wherein the meanings of R^1, R^2, R^3, R^4, R^5, R^6, X and n are as defined above – can be obtained by several known methods, among them the one demonstrated in Scheme 1., by *N*-amination of the compounds of the formula (III), using *N*-amination processes known in the organic chemistry (E.E. Glover, R.T. Rowbotton, J. Chem. Soc. Perkin. Trans I., 376, (1976), G. Timári, Gy. Hajós, S. Bátori és A. Messmer, Chem. Ber., 125, 929 (1992)). For *N*-amination agent preferably *O*-tosyl-hydroxylamine can be applied, but other agents known for N-amination 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, 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 , 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 , R^6 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) and (IV)), their preparation and biological activity are demonstrated in the following Examples, without limiting the scope of claims to the Examples.

Fig. 1 shows compounds of the formula (I),
Fig. 2 shows compounds of the formula (Ia),
Fig. 3 shows compounds of the formula (II),
Fig. 4 shows compounds of the formula (III),
Fig. 5 shows compounds of the formula (IV),
Fig. 6 shows compounds of the formula (V),
Fig. 7 shows compounds of the formula (VI),
Fig.8 shows compunds of the formula (VII).

Examples

Example 1

2-(4-Methoxyphenyl)-9-benzylamino-10-cyano-*s*-triazolo[1,5-*a*]quinolin

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 stands for 4-methoxyphenyl 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)

c.) 1,2-Diamino-3-cyano-4-benzylamino-quinolinium-tozylate

To the solution of 2,0 g of 2-amino-3-cyano-4-benzylaminoquinolin in 30 ml of dimethylformamide 1,78 g *O*-tozyl-hydroxylamine in 20 ml dichloromethane are dropped at 20°C within 15 minutes.. The reaction mixture is stirred for 5 hour, than the precipitate is

filtered off. The resulting white crystalline material is recrystallized from acetonitrile to give 3,1 g of the title compound, mp.: 207 °C

d. 2-(4-Methoxyphenyl)-9-benzylamino-10-cyano-*s*-triazolo[1,5-*a*]quinolin-

To the mixture of 2,0 g. 1,2-diamino-3-cyano-4-benzylamino-quinolinium-tozylate and 15 ml pyridine 2 g of aniseacid-chloride are added. The reaction mixture is stirred for 8 hour at 100°C. The mixture is poured onto 50 ml of water, the cristalls precipitated are filtered off and recrystallised from acetonitrile to give 1,1 g of the title compound. Mp.: 237C.

NMR, δ_H (400 MHz, DMSO-d_6): 8.78 ppm (t,1H), 8.58 (d,1H), 8,38 (d,1H), 8.10 (d,2H), 7.98 (t,1H), 7.39 (m, 5H), 7.07 (d,2H), 5.14(d,2H), 3.82 (s,3H).

Example 2

2-(2-Furyl)-9-(2-furylmethylamino)-10-cyano-*s*-triazolo[1,5-*a*]quinolin

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^5form together an 1,3-butadienyl group, R^6 stands for cyano group, R^7 stands for 2-furyl group , X means -NH-group, n is 1.

a.)2-Amino-3-cyano-4-(2-Furylmethylamino)-quinolin

5 g of 2-amino-3-cyano-4-chloroquinolin and 1 ml of furylmethylamine (furfurylamine) 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 20 ml ethanol to obtain 4.8 g of the title compound. Mp.: 208 °C.

b.) 1,2-Diamino-3-cyano-4-(2-furylmethylamino)-quinolinium-tozylate

To the solution of 2,0 g of 2-amino-3-cyano-4-(2-furylmethylamino)-quinolin in 30 ml dimethylformamide 1,78 g O-tozyl-hydroxylamine in 20 ml dichloromethane are dropped at 20°C within 15 minutes. The reaction mixture is stirred for 5 hour, than the precipitated white cristalline material is filtered off and recrystallized from acetonitrile to give 2.1 g of the title compound, mp.: 211 °C

c.). 2-(2-Furyl)-9-(2-furylmethylamino)-10-cyano-*s*-triazolo[1,5-*a*]quinolin-

To the mixture of 2,0 g. 1,2-diamino-3-cyano-4-(2-furylmethylamino)-quinolinium-tozylate and 15 ml pyridine 2 g of furan-2-carboxylic-acid-chloride are added. The reaction mixture is stirred for 8 hour at 100°C. The mixture is poured onto 50 ml of water, the cristalls precipitated are filtered off and recrystallised from acetonitrile to give 1,1 g of the title compound. Mp.: 203C.

NMR, δ_H (400 MHz, DMSO-d_6): 8.74 ppm (t,1H), 8.52 (d,1H), 8,32 (d,1H), 7.90 (m,3H), 7.63 (m,2H), 7.14 (m,1H), 6.68 (m,1H), 6.44(m,2H), 5.11 (d,2H).

Example 3

2-(3,4-Methylendioxyphenyl)-9-(2-furylmethylamino)-10-ciano-*s*-triazolo[1,5-*a*]quinolin

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

a.).2-(3,4-Methylendioxyphenyl)-9-(2-furylmethylamino)-10-cyano-*s*-triazolo[1,5-*a*] quinolin-

To the mixture of 2,0 g. 1,2-diamino-3-cyano-4-(2-furylmethylamino)-quinolinium-tozylate and 15 ml pyridine 2 g of 3,4-methylendioxy-benzoic-acid-chloride are added. The reaction mixture is stirred for 8 hour at 100°C. The mixture is poured onto 50 ml of water, the cristalls precipitated are filtered off and recrystallised from acetonitrile to give 1,4 g of the title compound. Mp.: 185C.

NMR, δ_H (400 MHz, DMSO-d_6): 8.55 ppm (m,1H), 8.51(d,1H), 8,31 (d,1H), 7.93 (t,1H), 7.57-7.70 (m,3H), 7.05 (d,1H), 6.44 (m,2H), 6.11(s,2H), 5.08 (d,2H).

Example 4

2-(3-Pyridyl)-9-(2-tienylmethylamino)-10-cyano-*s*-triazolo[1,5-*a*]quinolin

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is 2-tienyl group, R^4 and R^5 form together an 1,3-butadienyl group, R^6 stands for cyano group, R^7 stands for 3-pyridyl group , X means -NH-group, n is 1.

a.)2-amino-3-cyano-4-(2-tienylmethylamino)-quinolin

5 g of 2-amino-3-cyano-4-chloroquinolin and 11 ml of tienylmethylamine are heated under stirring at 130 °C. The reaction mixture is poured onto 50 ml of water, the resulting precipitate is filtered off, washed with 50 ml of water. The pale-yellow precipitate is recrystallized from 25 ml ethanol to obtain 5.2 g of the title compound. Mp.: 208 °C.

b.) 1,2-Diamino-3-cyano-4-(2-tienylmethylamino)-quinolinium-tozylate

To the solution of 2,0 g of 2-amino-3-cyano-4-(2-tienylmethylamino)-quinolin in 30 ml dimethylformamide 1,78 g *O*-tozyl-hydroxylamine in 20 ml dichloromethane are dropped at 20°C within 15 minutes.. The reaction mixture is stirred for 5 hour, than the precipitated white cristalline material is filtered off and recrystallized from acetonitrile to give 2.1 g of the title compound, mp.: 198°C

c.). 2-(3-Pyridyl)-9-(2-tienylmethylamino)-10-cyano-*s*-triazolo[1,5-*a*]quinolin-

To the mixture of 2,0 g. 1,2-diamino-3-cyano-4-(2-tienylmethylamino)-quinolinium-tozylate and 20 ml dimethylformamide 4 ml of triethylamine and 4 g of pyridine-3-carboxaldehyde are added. The reaction mixture is stirred for 8 hour at 100°C. The mixture is poured onto 50 ml of water, the cristalls precipitated are filtered and recrystallised from acetonitrile to give 0.8 g of the title compound. Mp.: 249C.

NMR, δ_H (400 MHz, DMSO-d_6): 9.25 ppm (s,1H), 8.71 (m,2H), 8,35 (m,3H), 7.86(m,1H), 7.51 (m,3H), 7.17(m,1H), 6.98 (m,1H), 5.25 (d,2H).

Example 5

2-(3-Hydroxyphenyl)-9-(2-tienylmethylamino)-10-cyano-*s*-triazolo[1,5-*a*]quinolin

In the general formula (I) the meaning of R^1 and R^2 is hydrogen atom, R^3 is 2-tienyl group, R^4 and R^5 form together an 1,3-butadienyl group, R^6 stands for cyano group, R^7 stands for 3-hydroxyphenyl group , X means -NH-group, n is 1.

a.). 2-(3-Hydroxyphenyl)-9-(2-tienylmethylamino)-10-cyano-*s*-triazolo[1,5-*a*]quinolin-

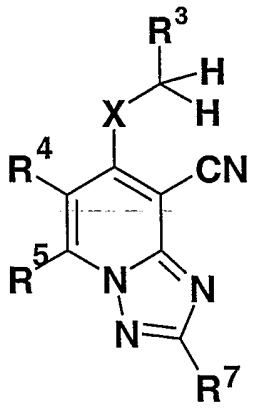
To the mixture of 2,0 g. 1,2-diamino-3-cyano-4-(2-tienylmethylamino)-quinolinium-tozylate and 20 ml dimethylformamide 4 ml of triethylamine and 4 g of 3-hydroxy-benzaldehyde are added. The reaction mixture is stirred for 8 hour at 100°C. The mixture is

poured onto 50 ml of water, the cristalls precipitated are filtered off and recrystallised from acetonitrile to give 0.9 g of the title compound. Mp.: 248C.

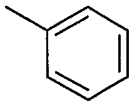
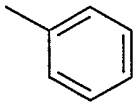
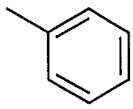
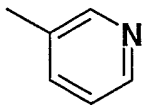
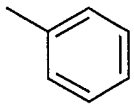
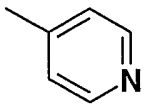
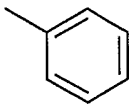
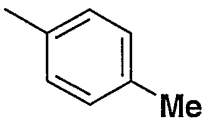
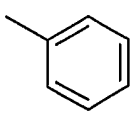
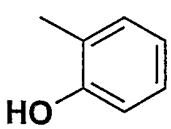
NMR, δ_H (400 MHz, DMSO-d_6): 9.66 ppm (s,1H), 8.81 (m,1H), 8,52 (m,1H), 8.35(m,1H), 796(m,1H), 7.62 (m,3H), 7.44(m,1H), 7.32(m,1H), 7.18 (m,1H), 7.01(m,1H), 6.88 (m,1H), 5.29 (d,2H).

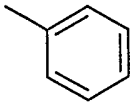
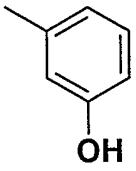
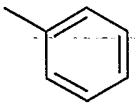
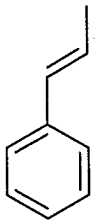
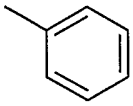
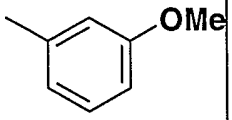
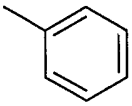
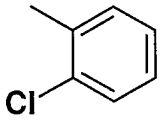
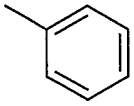
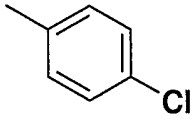
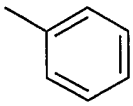
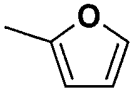
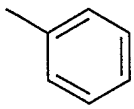
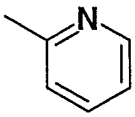
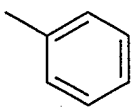
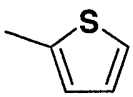
Structure and physical characteristics of further compounds of general formula (I) prepared by the method described in Example 1. are shown in Table I.

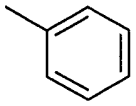
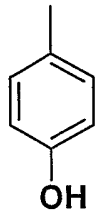
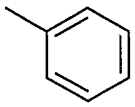
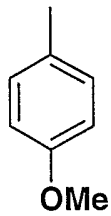
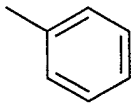
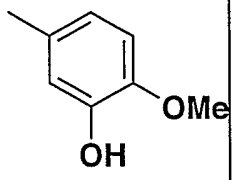
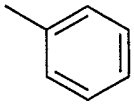
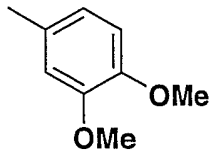
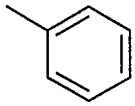
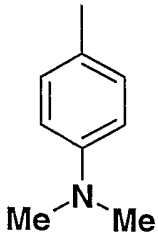
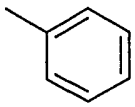
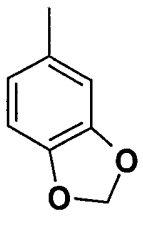
Table I.

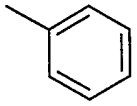
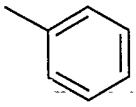
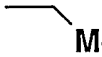
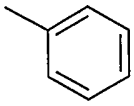
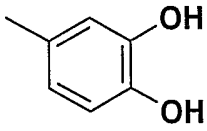
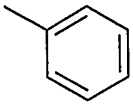
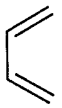
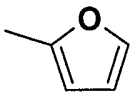
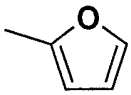
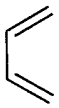
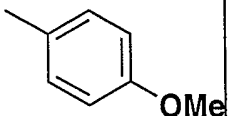
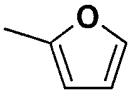
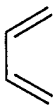
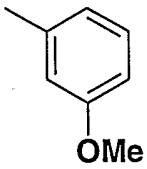
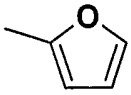
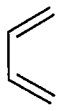
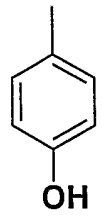
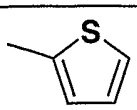
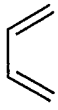
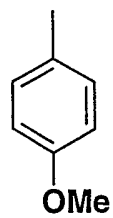


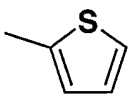
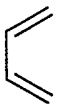
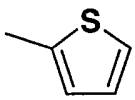
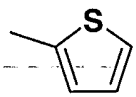
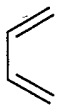
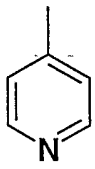
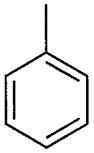
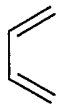
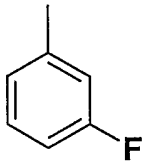
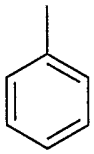
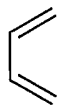
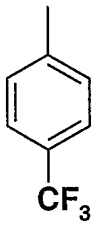
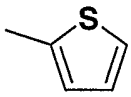
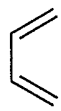
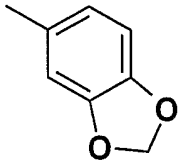
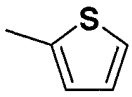
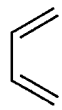
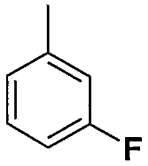
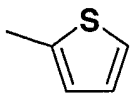
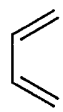
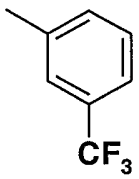
(I)

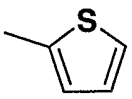
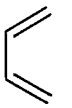
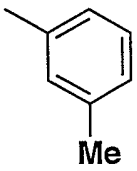
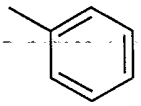
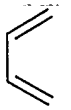
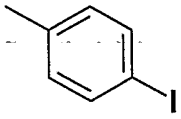
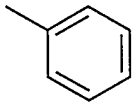
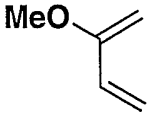
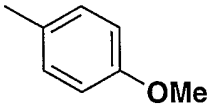
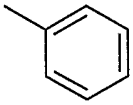
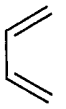
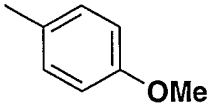
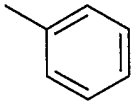
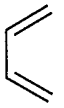
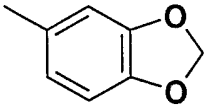
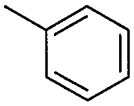
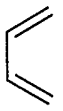
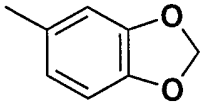
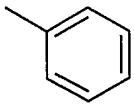
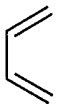
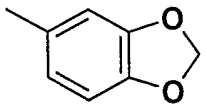
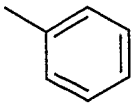
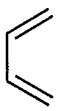
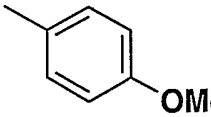
No.:	X	R^3	R^4	R^5	R^7	Mp: [°C]
6.	NH		H	H		271
7.	NH		H	H		259
8.	NH		H	H		246
9.	NH		H	H		266
10.	NH		H	H		209

11.	NH		H	H		260
12.	NH		H	H		214
13.	NH		H	H		264
14.	NH		H	H		245
15.	NH		H	H		285
16.	NH		H	H		274
17.	NH		H	H		295
18.	NH		H	H		280

19.	NH		H	H		273
20.	NH		H	H		253
21.	NH		H	H		280
22.	NH		H	H		230
23.	NH		H	H		243
24.	NH		H	H		286

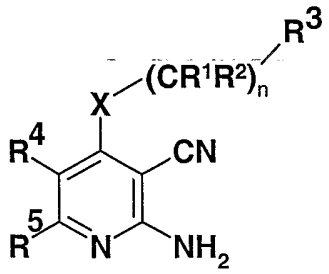
25.	NH		H	H		218
26.	NH		H	H		198
27.	NH		H	H		317
28.	NH					160
29.	NH					231
30.	NH					179
31.	NH					250
32.	NH					219

33.	NH				220
34.	NH				250
35	NH				158
36.	NH				195
37.	NH				298
38.	NH				239
39.	NH				216

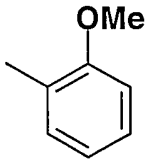
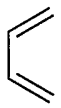
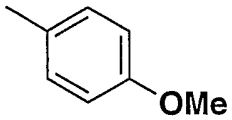
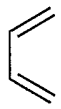
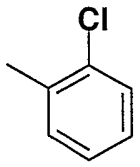
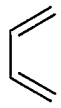
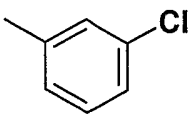
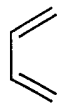
40.	NH				217
41.	NH				260
42.	NH				254
43.	O				232
44.	S				207
45.	S=O				248
46.	SO_2				301
47.	S				160

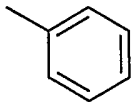
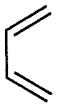
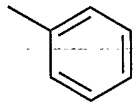
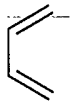
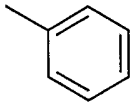
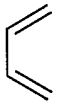
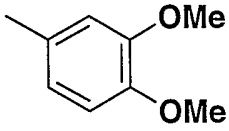
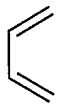
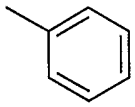
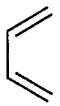
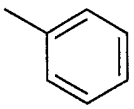
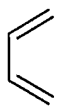
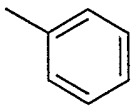
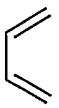
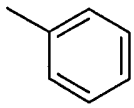
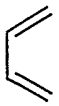
Structure and physical characteristics of the intermediates of the general formula (III) prepared by the method described in Example 1. are shown in Table (II)

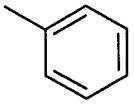
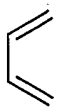
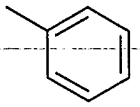
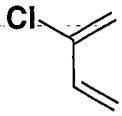
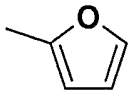
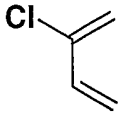
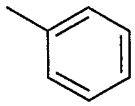
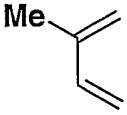
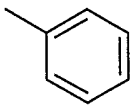
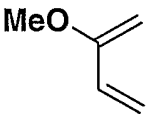
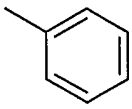
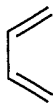
Table II.



(III)

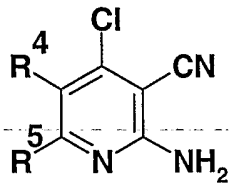
No.:	R^1	R^2	R^3	R^4 R^5	X	n	Mp: [°C]
48	H	H			NH	1	192
49	H	H			NH	1	202
49	H	H			NH	1	250
50.	H	H			NH	1	167

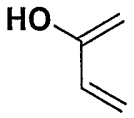
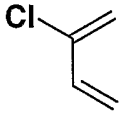
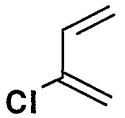
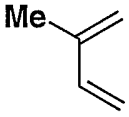
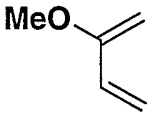
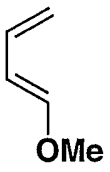
51.	H				NH	1	183
52.	H				NH	1	182
53.	H	H			NH	2	172
54.	H	H			NH	2	143
55.	H				NH	2	129
56.	H				NH	2	136
57	H	H			N-Me	1	212
58	H	H			S	1	168

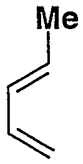
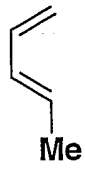
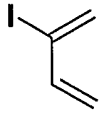
59.	H	H			O	1	213
60	H	H			NH	1	234
61	H	H			NH	1	221
62.	H	H			NH	1	198
63.	H	H			NH	1	201
64.					NH	0	214

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

Table III.



No:	R^4 + R^5	Mp [°C]
65.		360
66.		250
67.		278
68.		283
69.		360
70.		234

71.		246
72.		267
73.		293

Example 74.

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 20 nM. The compounds given as examples are especially advantageous. Their K_i values in human adenosine A_3 receptor binding studies are between 3.5 and 0.78 nM. The K_i values of the most advantageous compounds are 0.82 and 0.78 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 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 and R^5 stand independently from each other for hydrogen atom, or form together an 1,3-butadienyl 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 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 C_{1-4} alkylene group, optionally substituted by a phenyl group,or for 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, amino, mono- or dialkylamino group, 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;

X stands for a $-CH_2-$ group, –NH- group, $-NR^{12}-$ group, or a sulphur atom or an oxygen atom or a sulpho group or a sulphoxy group -wherein R^{12} 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 optically active isomers and the salts, solvates thereof.

2) Compounds of the general formula (Ia) 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 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^8, R^9, R^{10} and R^{11} independently from each other stand for hydrogen atom, straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom,or

R^8 and R^{11} stand for hydrogen atom and R^9 and R^{10} 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 C_{1-4} alkylene group, optionally substituted by a phenyl group,or for 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, amino, mono- or dialkylamino group, 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;

X stands for a $-CH_2-$ group, –NH- group, $-NR^{12}-$ group, or a sulphur atom or an oxygen atom or a sulpho group or a sulphoxy group -wherein R^{12} 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 optically active isomers and the salts, solvates thereof.

3) Compounds of the general formula (IA) according to claim2, 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^8 , R^9, R^{10} and R^{11} independently from each other stand for hydrogen atom, straight or branched C_{1-4} alkyl group, straight or branched C_{1-4} alkoxy group, hydroxy group or halogen atom,or

R^8 and R^{11} stand for hydrogen atom and R^9 and R^{10} form together a methylenedioxy group,

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

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

2-(4-Methoxyphenyl)-9-benzylamino-10-cyano-*s*-triazolo[1,5-*a*]quinolin,

2-(2-Furyl)-9-(2-furylmethylamino)-10-cyano-*s*-triazolo[1,5-*a*]quinolin,

2-(3,4-Methylenedioxyphenyl)-9-(2-furylmethylamino)-10-cyano-*s*-triazolo[1,5-*a*] quinolin,

2-(3-Pyridyl)-9-(2-thienylmethylamino)-10-cyano-*s*-triazolo[1,5-*a*]quinolin,

2-(3-hydroxyphenyl)-9-(2-thienylmethylamino)-10-cyano-*s*-triazolo[1,5-*a*]quinolin, 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, X and n have he same meaning as defined in claim 1, characterized by ring closure of an 1,2-diamino-pyridinium salt of the general formula (II), wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and n have the same meaning as defined in claim 1, with a compound of the general Formula (VII), wherein R^7 is 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 ring closure in dimethylformamide in the presence of triethylamine in the case of compounds of the formula (VII), where Y stands for hydrogen atom.

7.) Process according to claims 5, characterized by carrying out the ring closure in pyridine in the case of compounds of the formula (VII), where Y stands for halogen atom.

8) 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, 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.

9.) Pharmaceutical compositions according to claim 8, containing as active ingredient one or more compounds of the general formula (Ia) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, 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.

10) Pharmaceutical compositions according to claim 9 containing as active ingredient one or more compounds of claim 4.

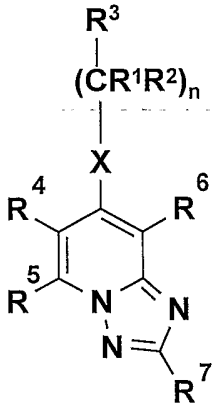
11) Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and n have the same meaning as defined in claim 1 - in the treatment of diseases in development of which the receptor A_3 plays a role.

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, X and n have the same meaning as defined in claim 1 - according to claim 11as 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.

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, X and n have the same meaning as defined in claim 1 - according to claims 11 and 12 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.

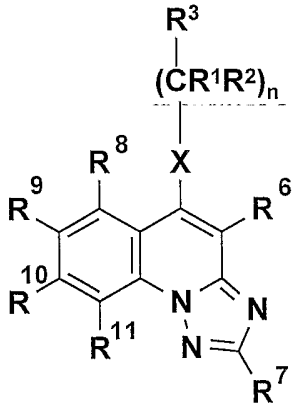
14) Use of the compounds of the general formula (I) – wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, X and n have the same meaning as defined in claim 1 – according to claims 11, 12 and 13 as A_3 receptor antagonist for the treatment of diseases such as asthma, COPD and ARDS, glaucoma, tumor, allergic and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

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



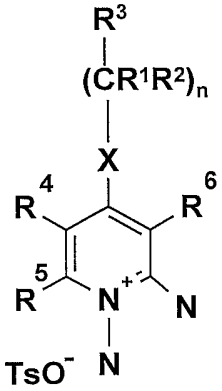
I

Fig. 1



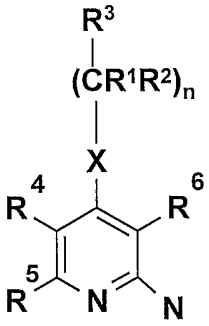
Ia

Fig. 2



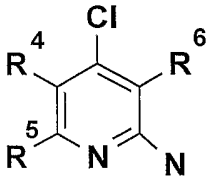
II.

Fig. 3



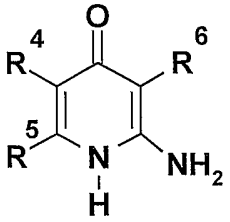
III.

Fig. 4



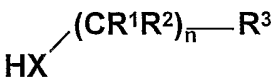
IV.

Fig. 5



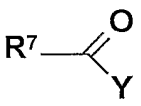
V.

Fig. 6



VI.

Fig. 7



VII.

Fig. 8

Reaction scheme 1

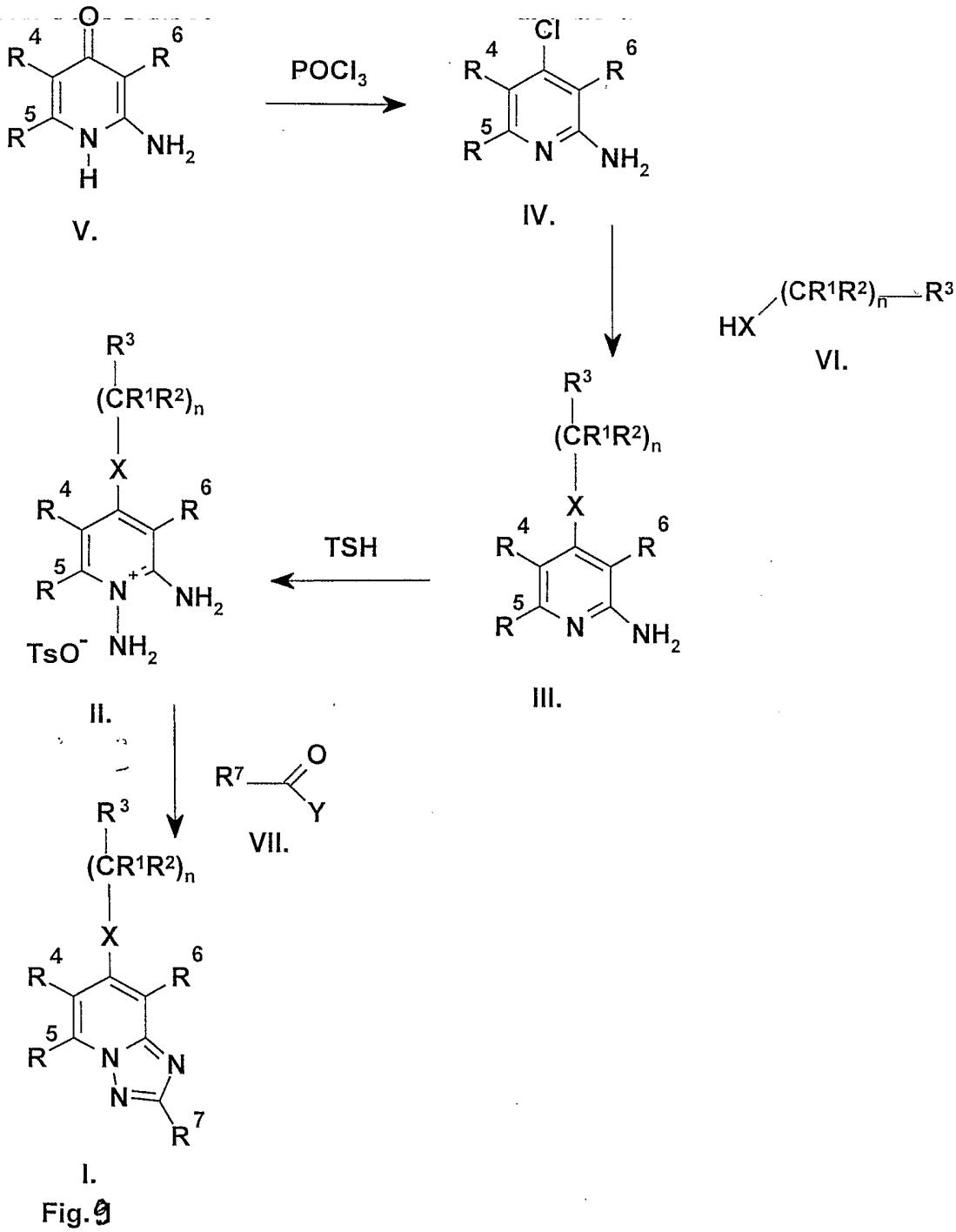


Fig. 9

INTERNATIONAL SEARCH REPORT

Internatic ›plication No
PCT/HU 02/00143

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 C07D213/89 C07D405/12 A61K31/505 A61N25/00

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

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, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	DD 280 110 A (HUMBOLDT-UNIVERSITAET ZU BERLIN, GER. DEM. REP.) 27 June 1990 (1990-06-27) Table 1	1

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
28 April 2003	19/05/2003

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	Wolf, C

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PCT/HU 02/00143

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BROWN, ROGER F. C. ET AL: "N-Alkylation and electrophilic substitution reactions of 2-methylpyrazolo'1,5-a!pyridin-5-ol and related compounds" retrieved from STN Database accession no. 121:134019 XP002239505 rn 156969-56-1 abstract & AUSTRALIAN JOURNAL OF CHEMISTRY (1994), 47(6), 1009-21 , ---	1
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BROWN, ROGER F. C. ET AL: "The pyrolytic rearrangement of 1-alkynoyl-3-methylpyrazoles: synthesis of pyrazolo'1,5-a!pyridin-5-ols and related compounds" retrieved from STN Database accession no. 121:108613 XP002239506 general formula II, rn 156969-57-2 abstract & AUSTRALIAN JOURNAL OF CHEMISTRY (1994), 47(6), 991-1007 , --- -/--	1

INTERNATIONAL SEARCH REPORT

Internatio pplication No
PCT/HU 02/00143

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SELBY, THOMAS P. ET AL: "7-Phenyl-1,2,4-triazolo'1,5-a!pyrimidines and related heterocycles. A ne family of bleaching herbicides" retrieved from STN Database accession no. 118:2390 XP002239507 general formula I, rn 144730-28-9, rn 145707-04-6 abstract & ACS SYMPOSIUM SERIES (1992), 504(SYNTH. CHEM. AGROCHEM. III), 91-102 , -----	1

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Information on patent family members

Internatio pplication No
PCT/HU 02/00143

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