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9-substituted 2-(2-n-alkoxyphenyl)-purin-6-ones

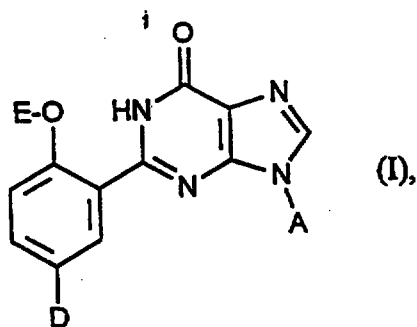
5 The present invention relates to 9-substituted 2-(2-n-alkoxyphenyl)-purin-6-ones, processes for their preparation and their use in medicaments, in particular for treatment of inflammations, thromboembolic and cardiovascular diseases and diseases of the urogenital system.

10 Purinones and quinazolinones having a selective cGMP PDE-inhibiting action are known from the publications WO 94/00453 and WO 93/12095.

Phosphodiesterases (PDEs) play an essential role in the regulation of the intracellular cGMP and cAMP level. Of the phosphodiesterase isoenzyme groups PDE I to PDE V described to date [nomenclature according to Beavo and Reifsnyder (cf. Beavo, J.A. and Reifsnyder, D.H., Trends in Pharmacol. Sci. 11, 150-155 (1990))], the
15 Ca-calmodulin-activated PDE I, the cGMP-stimulatable PDE II and the cGMP-specific PDE V are essentially responsible for the metabolism of cGMP. Because of the differing distribution of these cGMP-metabolizing PDEs in tissue, selective inhibitors should raise the cGMP level in the corresponding tissue according to the tissue distribution of the corresponding isoenzyme. This can lead to a specific,
20 antiaggregatory, antispastic, vasodilating, antiarrhythmic and/or antiinflammatory action.

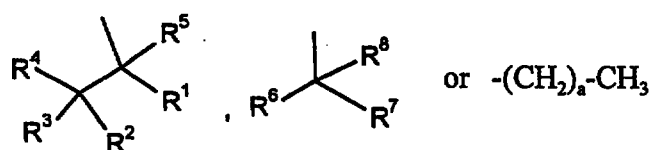
The present invention thus relates to 9-substituted 2-(2-n-alkoxyphenyl)-purin-6-ones of the general formula (I),





in which

A represents a radical of the formula



wherein,

a denotes a number 9, 10, 11, 12, 13, 14 or 15,

R^1 denotes straight-chain or branched alkyl having 2 to 10 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by halogen, nitro, cyano, by straight-chain or branched alkyl having up to 6 carbon atoms or by a group of the formula $-SO_2-NR^9R^{10}$,

wherein

R^9 and R^{10} are identical or different and

denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, or together with the nitrogen atom form a 5- to 6-membered, saturated heterocyclic radical which has up to 2



further heteroatoms from the series consisting of S, N and/or O and is optionally substituted, including via a free N function, by straight-chain or branched alkyl having up to 6 carbon atoms, which in turn can be substituted by hydroxyl,

5 and/or

alkyl is optionally substituted by a group of the formula $-NR^{11}R^{12}$,

wherein

R^{11} and R^{12} have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these,

10 R^2 denotes hydrogen, azido, straight-chain or branched alkyl having up to 6 carbon atoms or a group of the formula $-OR^{13}$, $O-SO_2R^{14}$ or $-NR^{15}R^{16}$,

wherein

15 R^{13} is hydrogen, a hydroxyl-protecting group, straight-chain or branched acyl having up to 6 carbon atoms, benzoyl or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxy carbonyl having up to 6 carbon atoms or by a group of the formula $-CO-NR^{17}R^{18}$,

wherein

20 R^{17} and R^{18} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,



R^{14} denotes straight-chain or branched alkyl having up to 4 carbon atoms or phenyl,

5 R^{15} and R^{16} are identical or different and denote hydrogen, an amino-protecting group, straight-chain or branched alkyl or acyl having in each case up to 6 carbon atoms, formyl, benzoyl or a group of the formula $-SO_2R^{19}$,

wherein

R^{19} has the abovementioned meaning of R^{14} and is identical to or different from this,

10 R^3 denotes hydrogen,

or

R^2 and R^3 together form a radical of the formula $=O$ or $=N-OR^{20}$,

wherein

15 R^{20} denotes hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by phenyl or by a group of the formula $-NR^{21}R^{22}$,

wherein

20 R^{21} and R^{22} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms,

R^4 denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,



R^5 and R^8 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

R^6 denotes hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl,

5 R^7 denotes straight-chain or branched alkyl having 2 to 8 carbon atoms, which is substituted by a group of the formula $-NR^{23}R^{24}$,

wherein

10 R^{23} and R^{24} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl,

or is substituted by phenyl, which in turn is substituted by the group of the formula $-SO_2-NR^{25}R^{26}$,

wherein

R^{25} and R^{26} have the abovementioned meaning of R^9 and R^{10} ,

15 D represents hydrogen or represents a group of the formula $-SO_2-NR^{27}R^{28}$,

wherein

R^{27} and R^{28} are identical or different and have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these, and

E represents straight-chain or branched alkyl having up to 8 carbon atoms,

20 and tautomers and salts thereof.



The substances according to the invention can also be in the form of salts. Physiologically acceptable salts are preferred in the context of the invention.

5 Physiologically acceptable salts can be salts of the compounds according to the invention with inorganic or organic acids. Preferred salts are those with inorganic acids, such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or salts with organic carboxylic or sulphonic acids, such as, for example, acetic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, lactic acid, benzoic acid or methanesulphonic acid, ethanesulphonic acid, phenylsulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid.

10 The compounds of the general formula (I) according to the invention can occur in various stereochemical forms which either behave as mirror images (enantiomers) or do not behave as mirror images (diastereomers). The invention relates both to the antipodes and to the racemic forms as well as the diastereomer mixtures. The racemic forms, like the diastereomers, can be separated into the stereoisomerically uniform
15 constituents in a known manner.

A 5- to 6-membered saturated heterocyclic radical which is bonded via the nitrogen atom and can also contain, as heteroatom, up to 2 oxygen, sulphur and/or nitrogen atoms in general represents piperidyl, morpholinyl, piperazinyl or pyrrolidinyl. Piperidyl and morpholinyl are particularly preferred.

20 Hydroxyl-protecting group in the context of the abovementioned definition in general represents a protecting group from the series consisting of: trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyl-dimethylsilyl, triphenylsilyl or benzyl. Trimethylsilyl, tert-butyl-dimethylsilyl or benzyl are preferred.

Amino-protecting groups in the context of the invention are the customary amino-
25 protecting groups used in peptide chemistry.

These include, preferably: benzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl,

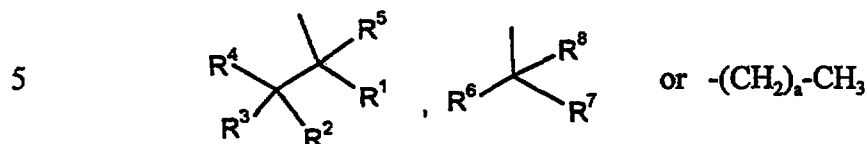


tert-butoxycarbonyl, formyl or acetyl.

Preferred compounds are those of the general formula (I),

in which

A represents a radical of the formula



wherein,

a denotes a number 9, 10, 11, 12 or 13,

10 R^1 denotes straight-chain or branched alkyl having 2 to 8 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by fluorine, chlorine, bromine, nitro, cyano, by straight-chain or branched alkyl having up to 4 carbon atoms or by a group of the formula $-\text{SO}_2-\text{NR}^9\text{R}^{10}$,

wherein

15 R^9 and R^{10} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl,
or, together with the nitrogen atom, form a morpholinyl, pyrrolidinyl or piperidinyl ring or a piperazinyl ring, which is optionally substituted, including via a free NH function, by
20 straight-chain or branched alkyl having up to 3 carbon atoms, which in turn can be substituted by hydroxyl,



and/or

alkyl is optionally substituted by a group of the formula $-NR^{11}R^{12}$,

wherein

5 R^{11} and R^{12} have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these,

R^2 denotes hydrogen, azido, straight-chain or branched alkyl having up to 4 carbon atoms or a group of the formula $-OR^{13}$, $-O-SO_2-R^{14}$ or $-NR^{15}R^{16}$,

wherein

10 R^{13} denotes hydrogen, benzyl, straight-chain or branched acyl having up to 4 carbon atoms, benzoyl or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxy carbonyl having up to 4 carbon atoms or by a group of the formula $-CO-NR^{17}R^{18}$,

wherein

15 R^{17} and R^{18} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

R^{14} denotes straight-chain or branched alkyl having up to 3 carbon atoms or phenyl,

20 R^{15} and R^{16} are identical or different and denote hydrogen, tert-butoxycarbonyl, benzyloxycarbonyl or straight-chain or branched alkyl or acyl having in each case up to 4 carbon atoms, formyl, benzoyl or a group of the formula $-SO_2R^{19}$,



wherein

R^{19} has the abovementioned meaning of R^{14} and is identical to or different from this,

R^3 denotes hydrogen,

5 or

R^2 and R^3 together form a radical of the formula $=O$ or $=N-OR^{20}$,

wherein

10 R^{20} denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by phenyl or by a group of the formula $-NR^{21}R^{22}$,

wherein

R^{21} and R^{22} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms,

15 R^4 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

R^5 and R^8 are identical or different and denote hydrogen or methyl,

R^6 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl,

20 R^7 denotes straight-chain or branched alkyl having 2 to 6 carbon atoms, which is substituted by a group of the formula $-NR^{23}R^{24}$,



wherein

R^{23} and R^{24} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl,

5 or is substituted by phenyl, which in turn is substituted by a group of the formula $-\text{SO}_2-\text{NR}^{25}\text{R}^{26}$,

wherein

R^{25} and R^{26} are identical or different and have the abovementioned meaning of R^9 and R^{10} ,

10 D represents hydrogen, or represents a group of the formula $-\text{SO}_2-\text{NR}^{27}\text{R}^{28}$,

wherein

R^{27} and R^{28} are identical or different and have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these, and

E represents straight-chain or branched alkyl having up to 6 carbon atoms,

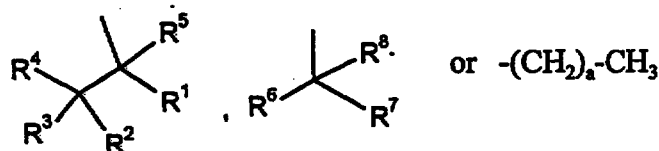
15 and tautomers and salts thereof.

Particularly preferred compounds are those of the general formula (I),

in which

A represents a radical of the formula





wherein,

a denotes a number 9, 10, 11 or 12,

5 R^1 denotes straight-chain or branched alkyl having 2 to 7 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by fluorine, chlorine, bromine, nitro, cyano, by straight-chain or branched alkyl having up to 3 carbon atoms or by a group of the formula $-\text{SO}_2-\text{NR}^9\text{R}^{10}$,

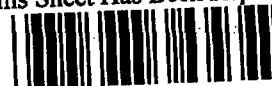
wherein

10 R^9 and R^{10} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl,
 or, together with the nitrogen atom, form a morpholinyl, pyrrolidinyl or piperidinyl ring or a piperazinyl ring, which is
 15 optionally substituted, including via free NH function, by straight-chain or branched alkyl having up to 3 carbon atoms, which in turn can be substituted by hydroxyl,

and/or

alkyl is optionally substituted by a group of the formula $-\text{NR}^{11}\text{R}^{12}$,

20 wherein



R^{11} and R^{12} have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these,

R^2 denotes hydrogen, azido, straight-chain or branched alkyl having up to 3 carbon atoms or a group of the formula $-OR^{13}$, $-OSO_2R^{14}$ or $-NR^{15}R^{16}$,

5 wherein

R^{13} denotes hydrogen, straight-chain or branched acyl having up to 3 carbon atoms, benzoyl or straight-chain or branched alkyl having up to 3 carbon atoms; which is optionally substituted by carboxyl or straight-chain or branched alkoxy carbonyl having up to 3 carbon atoms or by a group of the formula $-CO-NR^{17}R^{18}$,

10

wherein

R^{17} and R^{18} are identical or different and denote hydrogen, methyl or ethyl,

R^{14} denotes straight-chain or branched alkyl having up to 3 carbon atoms or phenyl,

15

R^{15} and R^{16} are identical or different and denote hydrogen, tert-butoxycarbonyl, straight-chain or branched alkyl or acyl having in each case up to 3 carbon atoms, formyl, benzoyl or a group of the formula $-SO_2R^{19}$,

20 wherein

R^{19} has the abovementioned meaning of R^{14} and is identical to or different from this,

R^3 denotes hydrogen,



or

R^2 and R^3 together form a radical of the formula $=O$ or $=N-OR^{20}$,

wherein

5 R^{20} denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by phenyl or by a group of the formula $-NR^{21}R^{22}$,

wherein

10 R^{21} and R^{22} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 3 carbon atoms,

R^4 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

R^5 and R^8 are identical or different and denote hydrogen or methyl,

15 R^6 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl,

R^7 denotes straight-chain or branched alkyl having 2 to 6 carbon atoms, which is substituted by a group of the formula $-NR^{23}R^{24}$,

wherein

20 R^{23} and R^{24} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl,



or is substituted by phenyl, which in turn is substituted by the group of the formula $-\text{SO}_2-\text{R}^{25}\text{R}^{26}$,

wherein

R^{25} and R^{26} have the abovementioned meaning of R^9 and R^{10} ,

5 D represents hydrogen, or represents a group of the formula $-\text{SO}_2-\text{NR}^{27}\text{R}^{28}$,

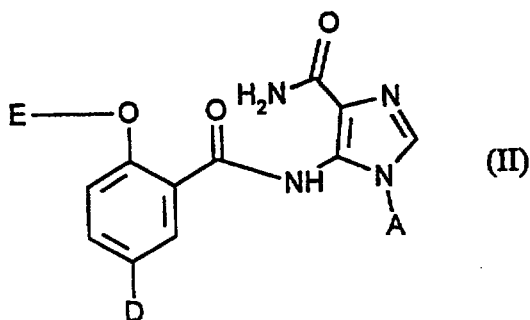
wherein

R^{27} and R^{28} are identical or different and have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these, and

E represents straight-chain or branched alkyl having up to 5 carbon atoms,

10 and tautomers and salts thereof.

A process has furthermore been found for the preparation of the compounds of the general formula (I) according to the invention, characterized in that compounds of the general formula (II)



in which

15 D, E and A have the abovementioned meaning,

are first cyclized in inert solvents and in the presence of a base,



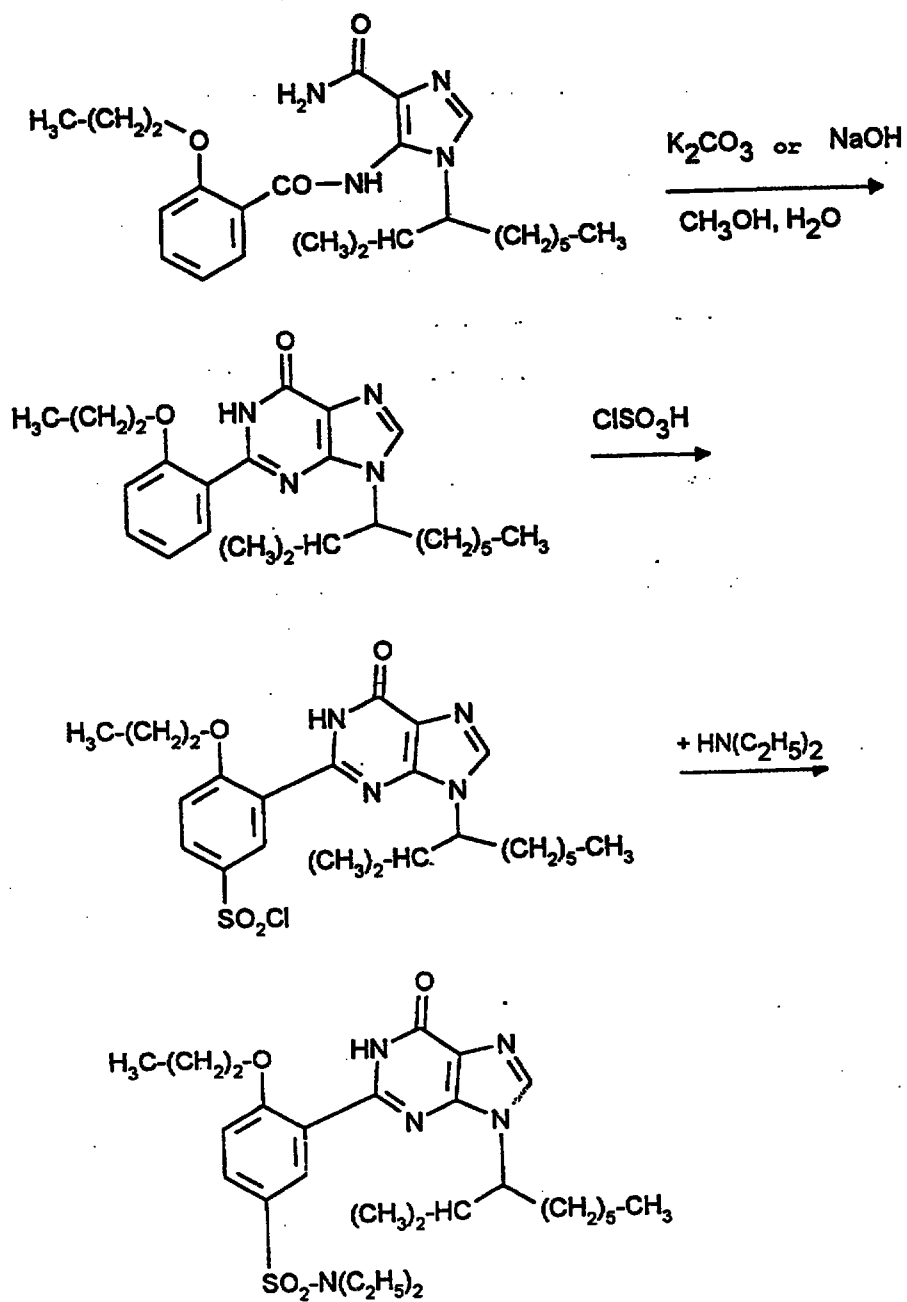
and in the case where $D = H$, the corresponding sulphonic acid chlorides are first prepared by reaction with chlorosulphonic acid and the corresponding sulphonamides are then prepared with amines ($NR^{25}R^{26}$),

5 and the substituents R^1-R^8 are introduced or derivatized by customary methods, such as, for example alkylation, acylation, amination, oxidation or azide exchange.

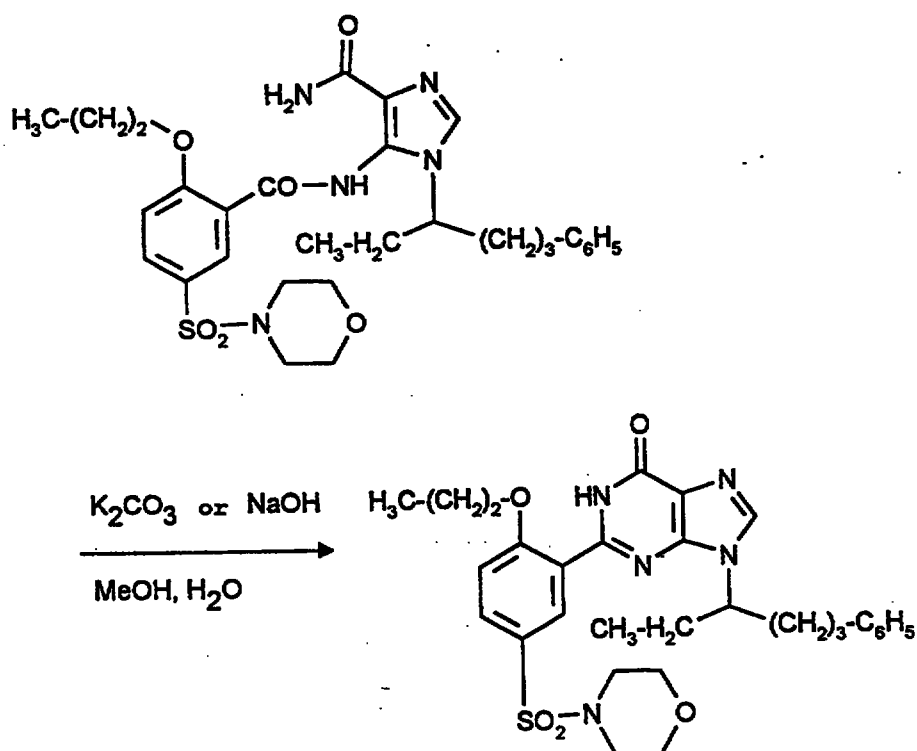
The process according to the invention can be illustrated by way of example by the following equations:



Equation A:



Equation B:



Inert organic solvents which do not change under the reaction conditions are suitable for the process. These include, preferably, ethers, such as, for example, diethyl ether, dioxane, tetrahydrofuran or glycol mono- or dimethyl ether, ethyl acetate, toluene, acetonitrile, hexamethylphosphoric acid triamide, pyridine and acetone. It is of course possible to employ mixtures of the solvents. Tetrahydrofuran, toluene or pyridine are particularly preferred.

Suitable solvents for the cyclization are the customary organic solvents. These include, preferably, alcohols, such as methanol, ethanol, propanol, isopropanol or butanol, or ethers, such as tetrahydrofuran or dioxane, or dimethylformamide or dimethyl sulphoxide. Alcohols, such as methanol, ethanol, propanol or isopropanol, are particularly preferably used. It is also possible to employ mixtures of the solvents mentioned.

Suitable bases for the cyclization are the customary inorganic bases. These include,



preferably, alkali metal hydroxides or alkaline earth metal hydroxides, such as, for example, sodium hydroxide, potassium hydroxide or barium hydroxide, or alkali metal carbonates, such as sodium carbonate or potassium carbonate or sodium bicarbonate, or alkali metal alcoholates, such as sodium methanolate, sodium ethanolate, potassium methanolate, potassium ethanolate or potassium tert-butanolate. Potassium carbonate and sodium hydroxide are particularly preferred.

In carrying out the cyclization, the base is in general employed in an amount of 2 to 6 mol, preferably 3 to 5 mol, per mole of the compounds of the formula (II).

The cyclization is in general carried out in a temperature range from 0°C to 160°C, preferably at the boiling point of the particular solvent.

The cyclization is in general carried out under normal pressure. However, it is also possible to carry out the process under increased pressure or under reduced pressure (for example in a range from 0.5 to 5 bar).

The chlorosulphonation is carried out either without a solvent or in the presence of one of the abovementioned inert solvents.

The preparation of the sulphonamides is in general carried out in one of the abovementioned solvents, preferably in tetrahydrofuran or methylene chloride.

The chlorosulphonation and the amidation are in general carried out in a temperature range from -20°C to +80°C, preferably -10°C to +30°C, under normal pressure.

Suitable bases for this are, in addition to the abovementioned bases, preferably in some cases triethylamine and/or dimethylaminopyridine, DBU or DABCO. It is also possible for the amine employed to be used in excess.

The base is employed in an amount of 0.5 mol to 10 mol, preferably 1 mol to 3 mol per mole of the corresponding chlorosulphonic acid.



The alkylation is in general carried out with alkylating agents, such as, for example, (C₁-C₁₀)-alkyl halides, sulphonic acid esters or substituted or unsubstituted (C₁-C₁₀)-dialkyl- or (C₁-C₁₀)-diarylsulphonates, preferably methyl iodide or dimethyl sulphate.

5 Suitable solvents for the alkylation are likewise the customary organic solvents which do not change under the reaction conditions. These include, preferably, ethers, such as diethyl ether, dioxane, tetrahydrofuran or glycol dimethyl ether, or hydrocarbons, such as benzene, toluene, xylene, hexane, cyclohexane or petroleum fractions, or halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethylene, trichloroethylene or chlorobenzene, or ethyl acetate, 10 dimethylformamide, hexamethylphosphoric acid triamide, acetonitrile or acetone. It is also possible to use mixtures of the solvents mentioned. Methylene chloride is preferred.

The alkylation is carried out in the abovementioned solvents at temperatures from 0°C to +150°C, preferably at room temperature to +100°C, under normal pressure.

15 The amino-protecting groups are split off in a manner known per se under acid or basic conditions, or reductively by catalytic hydrogenation, for example with Pd/C in organic solvents, such as ethers, for example tetrahydrofuran or dioxane, or alcohols, for example methanol, ethanol or isopropanol.

20 The hydroxyl-protecting group is split off from the corresponding esters by customary hydrolytic methods.

The reaction with alkyl sulphonic acid chlorides is carried out, starting from the corresponding free hydroxy compounds, in one of the abovementioned solvents and one of the bases, preferably with methylene chloride and triethylamine in a temperature range from -20°C to +20°C, preferably 0°C, under normal pressure.

25 The introduction of the azide radical is in general carried out by reaction of the corresponding alkylsulphonyloxy-substituted compounds with sodium azide in one of the abovementioned solvents, preferably dimethylformamide, in a temperature range



from 50°C to +120°C, preferably 100°C, under normal pressure.

The reduction of azido-substituted compounds to give the corresponding free amines is in general carried out by hydrogenation in one of the abovementioned alcohols, preferably methanol, with hydrogen in the presence of a palladium catalyst, preferably Pd/C, in a temperature range from 0°C to +50°C, preferably 25°C.

The hydrogenation is in general carried out under normal pressure.

The acylations are carried out, starting from the corresponding free amino or hydroxy compounds, in one of the abovementioned solvents, preferably methylene chloride, and in the presence of one of the abovementioned bases, preferably triethylamine, with addition of dimethylaminopyridine (DMAP), in a temperature range from 0°C to +80°C, preferably at +20°C to +40°C, under normal pressure.

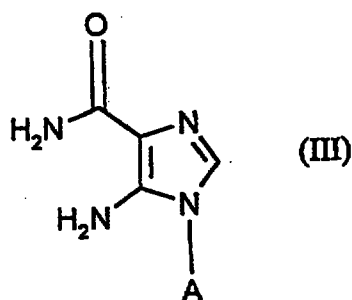
The ketones are prepared by known methods (Swern oxidation) starting from the corresponding hydroxy compounds.

The oxime formation is in general carried out by reaction of the corresponding ketone with hydroxylamines in one of the abovementioned alcohols, preferably methanol, at the reflux temperature under normal pressure.

The enantiomerically pure compounds are accessible by customary methods, for example by chromatography or the racemic compounds of the general formula (I) on chiral phases.

The compounds of the general formula (II) are known in some cases or are new and can be prepared by a procedure in which compounds of the general formula (III)

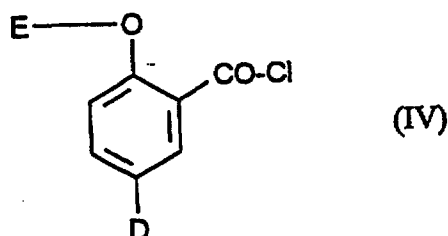




in which

A has the abovementioned meaning,

are reacted with 2-n-alkoxybenzoic acid chlorides of the general formula (IV)



in which

5 D and E have the abovementioned meaning,

in inert solvents and in the presence of a base.

Suitable solvents are the abovementioned solvents, toluene and tetrahydrofuran being preferred.

10 Suitable bases are in general alkali metal hydrides or alcoholates, such as, for example, sodium hydride or potassium tert-butyrate, or cyclic amines, such as, for example, piperidine, pyridine, dimethylaminopyridine or C₁-C₄-alkylamine, such as, for example, triethylamine. Sodium hydride, pyridine and dimethylaminopyridine are preferred.



The base is in general employed in an amount of 1 mol to 4 mol, preferably 1.2 mol to 3 mol, in each case per mole of the compounds of the general formula (III).

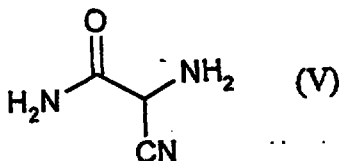
5 The reaction temperature can in general be varied within a relatively wide range. The reaction is in general carried out in a range from -20°C to 200°C, preferably 0°C to 25°C.

In one variant, the reaction is carried out in pyridine, to which a catalytic amount of DMAP is added. If appropriate, toluene can also be added.

The compounds of the general formula (IV) are known per se.

10 The compounds of the general formula (III) are new in most cases and can be prepared, for example, by a procedure in which

2-amino-2-cyanoacetamide of the formula (V)



is reacted with compounds of the general formula (VI)



in which

A has the abovementioned meaning,

15 in inert solvents in the presence of triethyl orthoformate.

Suitable solvents for the individual steps of the processes are the customary organic solvents which do not change under the reaction conditions. These include, preferably,



ethers, such as diethyl ether, dioxane, tetrahydrofuran or glycol dimethyl ether, or hydrocarbons, such as benzene, toluene, xylene, hexane, cyclohexane or petroleum fractions, or halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethylene, trichloroethylene or chlorobenzene, or ethyl acetate, dimethylformamide, hexamethylphosphoric acid triamide, acetonitrile, acetone or dimethoxyethane. It is also possible to use mixtures of the solvents mentioned. Acetonitrile is particularly preferred.

The process according to the invention is in general carried out in a temperature range from 0°C to +180°C, preferably +30°C to +150°C.

10 The process steps according to the invention are in general carried out under normal pressure. However, it is also possible to carry out the process steps under increased pressure or under reduced pressure (for example in a range from 0.5 to 5 bar).

The compound of the formula (V) is known [cf. Logemann, G. Shaw, Chemistry and Industry, 1980 (13), 541-542].

15 The amines of the general formula (VI) are known in some cases or are new and they can then be prepared by known methods [cf. L.R. Krepski et al., Synthesis, 1986, 301-303].

The compounds of the general formula (I) according to the invention display an unforeseeable, valuable pharmacological action spectrum.

20 They inhibit either one or more of the cGMP-metabolizing phosphodiesterases (PDE I, PDE II and PDE V). This leads to a different increase in cGMP. An increase in the cGMP level can lead to an antithrombotic, vasodilatory, antiarrhythmic and/or anti-inflammatory action. The selectivity is also determined by the distribution of the isoenzymes in the tissue.

25 The compounds according to the invention furthermore intensify the action of substances, such as, for example, EDRF (endothelium-derived relaxing factor) and ANP



(atrial natriuretic peptide), which increase the cGMP level.

They can therefore be employed in medicaments for treatment of inflammatory diseases, such as, for example, asthma, inflammatory dermatoses, for treatment of high blood pressure, stable and unstable angina, peripheral and cardiac vascular diseases and
5 of arrhythmias, for treatment of thromboembolic diseases and ischaemias, such as myocardial infarction, cerebral stroke, transitory and ischaemic attacks, angina pectoris, peripheral circulatory disturbances, prevention of restenoses, such as after thrombolysis treatment, percutaneous transluminal angioplasties (PTA) and bypass, percutaneous
10 transluminal coronary angioplasties (PTCA), bypass, septic shock and diseases of the urogenital system, such as, for example prostate hypertrophy, impotence and incontinence.

Activity of the phosphodiesterases (PDE's)

The cGMP-stimulatable PDE II, the cGMP-inhibitable PDE III and the cAMP-specific PDE IV were isolated from either the porcine or the bovine myocardium. The
15 Ca-calmodulin-stimulatable PDE I was isolated from porcine aorta or porcine brain. The cGMP-specific PDE V was obtained from porcine small intestine, porcine aorta and/or human blood platelets. Purification was carried out by anion exchange chromatography on MonoQ^R Pharmacia essentially by the method of M. Hoey and Miles D. Houslay, Biochemical Pharmacology, Volume 40, 193-202 (1990).

20 The enzyme activity is determined in a test batch of 100 µl in 20 mM Tris/HCl buffer of pH 7.5 which contains 5 mM MgCl₂, 0.1 mg/ml of bovine serum albumin and either 800 Bq of ³HcAMP or ³HcGMP. The final concentration of the corresponding nucleotides is 10⁻⁶ mol/l. The reaction is started by addition of the enzyme and the
25 amount of enzyme is chosen such that about 50% of the substrate is reacted during the incubation time of 30 minutes. In order to test the cGMP-stimulatable PDE II, ³HcAMP is used as the substrate and 10⁻⁶ mol/l of non-labelled cGMP is added to the batch. In order to test the Ca-calmodulin-dependent PDE I, 1 µM CaCl₂ and 0.1 µM calmodulin are also added to the reaction batch. The reaction is stopped by addition of 100 µl of acetonitrile which contains 1 mM cAMP and 1 mM AMP. 100 µl of the reaction batch



are separated on the HPLC and the cleavage products are determined quantitatively "on line" with a flow-through scintillation counter. The substance concentration at which the rate of reaction is reduced by 50% is measured.

Inhibition of the phosphodiesterases in vitro

5	Example No.	PDE I IC ₅₀ [μM]	PDE II IC ₅₀ [μM]	PDE V IC ₅₀ [μM]
	3	50	6	0.1
	4	2	1	5
	5	1	0.5	2
	11	0.5	0.3	0.5
10	37	2	2	1
	57	0.3	0.3	0.1

The antihypertensive activity was measured after intravenous administration to SHR rats.

15 To determine the cyclic nucleotides, heart and aorta tissue was removed and deep-frozen immediately. The samples were powdered under liquid N₂ and extracted with 70% ethanol and the content of cGMP and cAMP was determined using commercial radioimmunoassays (Amersham).

The erection-inducing action was measured on anaesthetized rabbits (C.G. Stief et al., World Journal Urology 1990, pages 233-236).

20 The substances were administered in dosages of 0.1 to 10 mg/kg either directly into the corpus cavernosum or intraduodenally, rectally, orally, transdermally or intravenously.

The new active compounds can be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions,



suspensions and solutions, using inert, non-toxic, pharmaceutically suitable carriers or solvents. The therapeutically active compound should in each case be present here in a concentration of about 0.5 to 90% by weight of the total mixture, i.e. in amounts which are sufficient to achieve the stated dosage range.

- 5 The formulations are prepared, for example, by extending the active compounds with solvents and/or carriers, if appropriate using emulsifying agents and/or dispersing agents, and in the case where water is used as the diluent, for example, organic solvents can be used as auxiliary solvents if appropriate.

10 The formulations are administered in the customary manner, preferably orally, parenterally, transdermally, perlingually or intravenously.

In general, it has proved advantageous in the case of intravenous administration to administer amounts of about 0.01 to 10 mg/kg, preferably about 0.1 to 10 mg/kg of body weight to achieve effective results.

15 Nevertheless, it may be necessary, if appropriate, to deviate from the amounts mentioned, and in particular as a function of the body weight or the nature of the administration route, of the behaviour of the individual towards the medicament, of the nature of the formulation thereof and of the time or interval at which administration takes place. Thus, in some cases it may be sufficient to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must
20 be exceeded. In the case of administration of relatively large amounts, it may be advisable to divide these into several individual doses over the course of the day.

Starting compounds

General working instructions for the preparation of 1-substituted 5-(2-n-alkoxy-benzoylamino)-imidazole-4-carboxamides of the formula (IV)



Method A:

10 mmol of 1-substituted 5-amino-imidazole-4-carboxamide and 15 mmol of NaH (if one of the abovementioned radicals R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 or R^8 contains a hydroxyl group, 30 mmol of NaH are employed) are stirred in 50 ml of absolute tetrahydrofuran at 20°C for 3 hours (in the case of sparingly soluble imidazoles, the mixture is refluxed for up to 12 hours). 10 mmol of 2-n-alkoxybenzoic acid chloride (or 20 mmol if a hydroxyl group is present) in 25 ml of absolute tetrahydrofuran are added dropwise at 20°C and the mixture is stirred at room temperature overnight. It is evaporated, the residue is taken up in ethyl acetate and the mixture is extracted by shaking with water. The organic phase is dried over Na_2SO_4 and evaporated and the residue is purified by recrystallization or flash chromatography.

If the 5-amino-imidazole-4-carboxamide contains a free hydroxyl group in the radicals R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 or R^8 , this is in the form of the 2-n-alkoxybenzoic acid ester, which can be hydrolysed by the known method (1 N NaOH, CH_3OH). However, it is also possible for the ester to be cyclized directly with NaOH as the base to give the purinones, the ester likewise being hydrolysed.

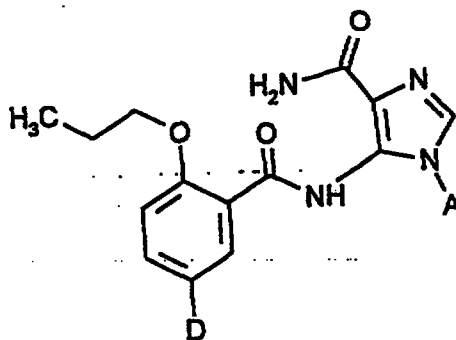
Method B:

10 mmol of 1-substituted 5-amino-imidazole-4-carboxamide and 50 mg of DMAP are initially introduced into 20 ml of dry pyridine at room temperature. A solution of 10 mmol of n-alkoxybenzoic acid chloride in 10 ml of absolute toluene is added dropwise and the mixture is stirred at room temperature until, in the thin-layer chromatogram, the reaction has ended (30 minutes to 16 hours). The precipitate is filtered off and the solvent is removed in a rotary evaporator in vacuo. The residue is taken up in 30 ml of methylene chloride and the mixture is washed with 30 ml of 1 N HCl and 30 ml of H_2O . After drying over Na_2SO_4 , the mixture is evaporated in vacuo and the residue is purified by flash chromatography or recrystallization.

The 1-substituted 5-(2-n-alkoxybenzoylamino)-imidazole-5-carboxamides listed in Table 1 are prepared in accordance with these instructions:



Table 1:

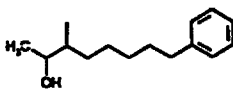
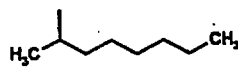
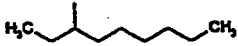
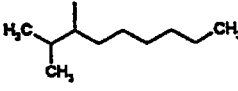
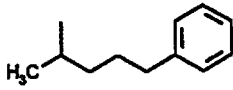
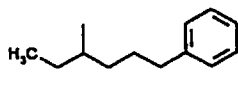
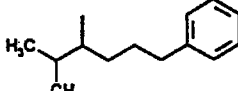
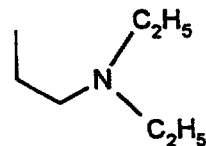
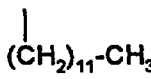
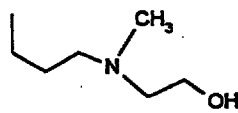


5

Example No.	A	D	Yield (% of theory)	Melting point (°C)/R _f
I		H	41	
II		H	38	
III		H	52	
IV		H	57	
V		H	11	104 (ether)
VI		H	12	



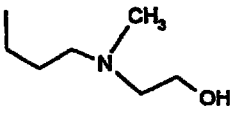
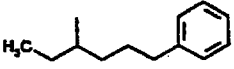
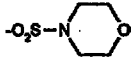
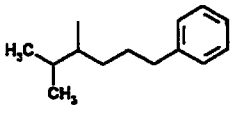
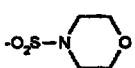
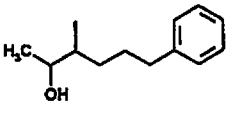
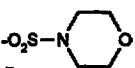
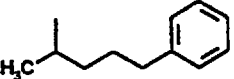
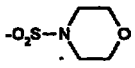
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Example No.	A	D	Yield (% of theory)	Melting point (°C)/R _f
VII		H	41	
VIII		H	30	
IX		H	26.6	
X		H	46	
XI		H	30	
XII		H	50	
XIII		H	26	
XIV		H	27	
XV		H	41	
XVI		H	8	

10



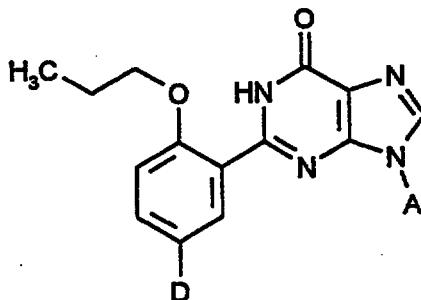
5

Example No.	A	D	Yield (% of theory)	Melting point (°C)/R _f
XVI		H	8	
XVII			27	
XVIII			33	
XIX			53	
XX			38	



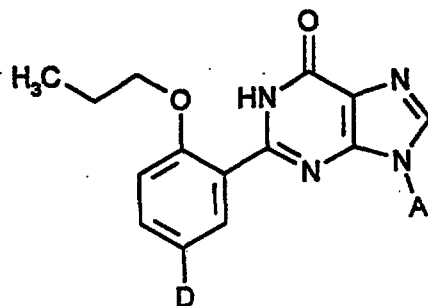
Preparation examples

General working instructions for 9-substituted 2-(2-n-alkoxyphenyl)purin-6-ones of the general formula (I)



- 10 mmol of the 1-substituted 5-(2-n-alkoxybenzoylamino)-imidazole-4-carboxamide
5 (IV) and 40 mmol of K_2CO_3 are refluxed overnight in a mixture of 100 ml of ethanol and 50 ml of water. The solvent is distilled off in vacuo, the residue is taken up in ethyl acetate and the mixture is extracted twice by shaking with water. After the organic phase has been dried with sodium sulphate, it is evaporated and the residue is purified by recrystallization or flash chromatography.
- 10 The compounds listed in Table II are prepared in accordance with these instructions:



Table II:

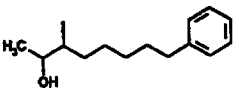
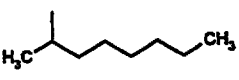
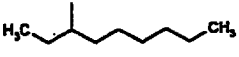
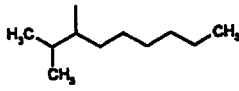
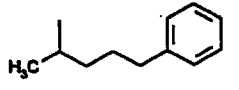
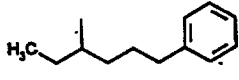
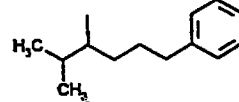
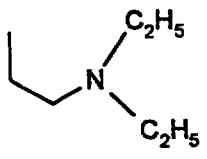
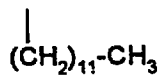
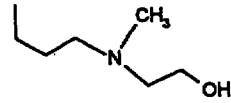
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Example No.	A	D	Yield (% of theory)	Melting point (°C)/R _f
1		H	63	186
2		H	87	0.33 a)
3		H	67	113
4		H	39	82
5		H	51	104
6		H	27	68



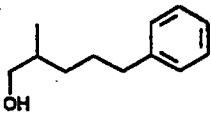
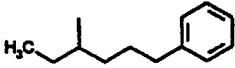
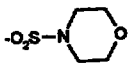
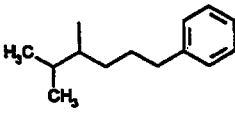
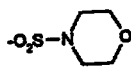
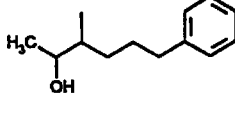
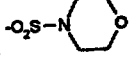
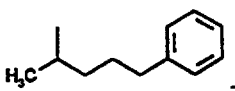
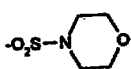
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10

Example No.	A	D	Yield (% of theory)	Melting point (°C)/R _f
7		H	31	91
8		H	75	0.58 a)
9		H	54	0.6 a)
10		H	58	0.44 a)
11		- H	95	0.54 a)
12		H	71	0.58 a)
13		H	63	0.59 a)
14		H	50	143
15		H	42	80
16		H	56	188



5

Example No.	A	D	Yield (% of theory)	Melting point (°C)/R _f
17		H	23	0.33 a)
18			80	165
19			33	0.44 b)
20			25	172
21			57	170

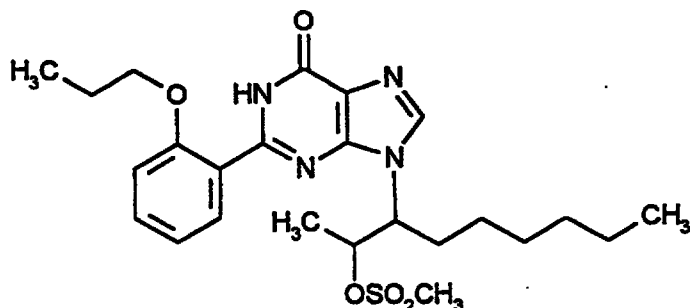
a) Mobile phase: CH₂Cl₂/MeOH 10:1

b) Mobile phase: toluene/acetone 1:1



Example 22

9-(2-Methanesulphonyloxy-3-nonyl)-2-(2-n-propoxy-phenyl)-purin-6-one



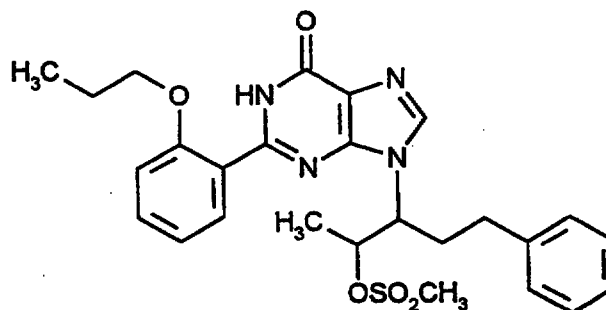
412 mg (1 mmol) of 9-(2-hydroxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 3) are cooled to 0°C in 10 ml of CH₂Cl₂. After addition of 0.5 ml of triethylamine, 138 mg (1.2 mmol) of methanesulphonyl chloride in 2 ml of CH₂Cl₂ are added dropwise and the mixture is subsequently stirred for 30 minutes. It is poured onto 20 ml of ice-water, the organic phase is separated off and the aqueous phase is extracted once more with 20 ml of CH₂Cl₂. The combined CH₂Cl₂ phases are dried over Na₂SO₄ and evaporated in vacuo and the oily residue is crystallized by trituration with ether.

Melting point: 158°C

Yield: 380 mg (81%)

Example 23

9-(2-Methanesulphonyloxy-5-phenyl-3-pentyl)-2-(2-n-propoxyphenyl)-purin-6-one



The title compound is prepared analogously to the instructions of Example 22, starting

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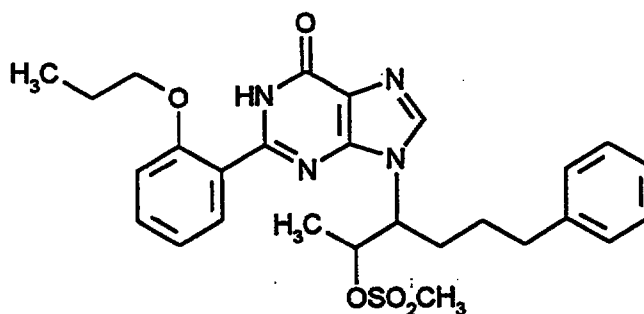
from 9-(2-hydroxy-5-phenyl-3-methyl)-2-(2-n-propoxyphenyl)purin-6-one (Example 4).

$R_f = 0.52$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 95.3%

Example 24

5 9-(2-Methanesulphonyloxy-6-phenyl-3-hexyl)-2-(2-n-propoxyphenyl)-purin-6-one



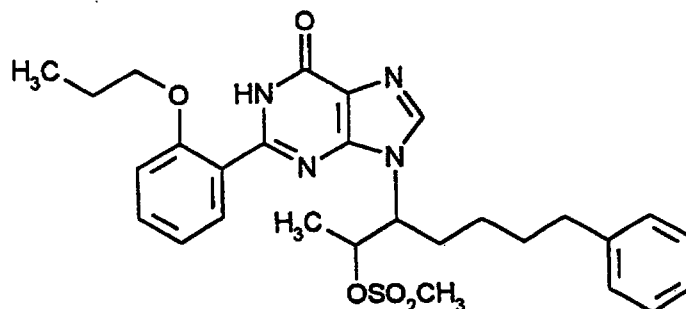
The title compound is prepared analogously to the instructions of Example 22, starting from 9-(2-hydroxy-6-phenyl-3-hexyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 5).

$R_f = 0.52$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 82.7%

10 **Example 25**

9-(2-Methanesulphonyloxy-7-phenyl-3-heptyl)-2-(2-n-propoxyphenyl)-purin-6-one



The title compound is prepared analogously to the instructions of Example 22, starting from 9-(2-hydroxy-7-phenyl-3-heptyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 6).

$R_f = 0.55$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

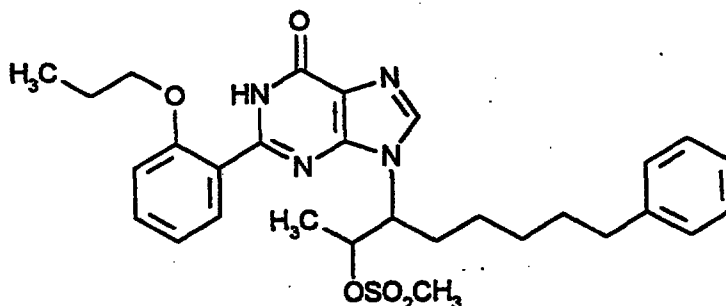
Le A 30 701



Yield: 90.3%

Example 26

9-(2-Methanesulphonyloxy-8-phenyl-3-octyl)-2-(2-n-propoxyphenyl)-purin-6-one



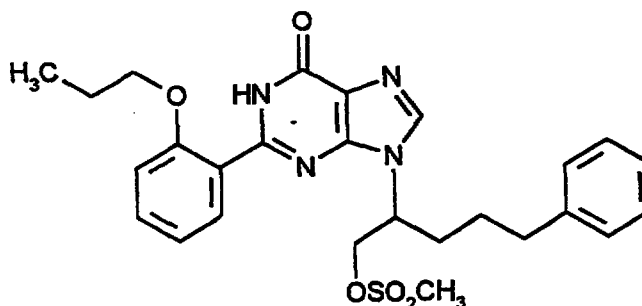
5 The title compound is prepared analogously to the instructions of Example 22, starting from 9-(2-hydroxy-8-phenyl-3-octyl)-2-(2-n-propoxyphenyl)-purin-7-one (Example 7).

$R_f = 0.58$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 89%

Example 27

9-(1-Methanesulphonyloxy-5-phenyl-2-pentyl)-2-(2-n-propoxyphenyl)-purin-6-one



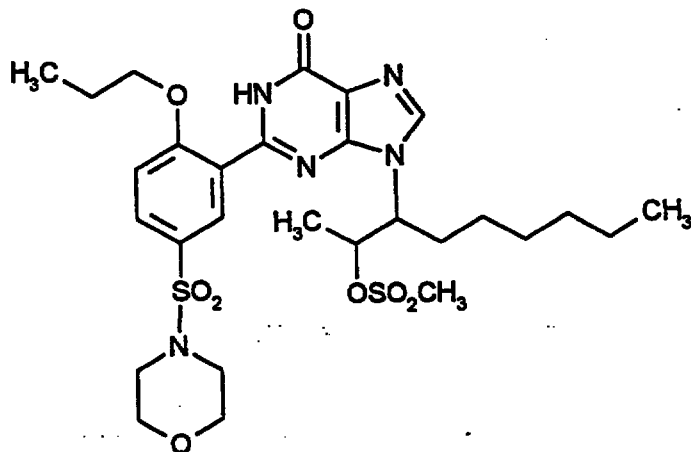
10 The title compound is prepared analogously to the instructions of Example 22, starting from 9-(1-hydroxy-5-phenyl-3-pentyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 17).

$R_f = 0.49$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 28.5%

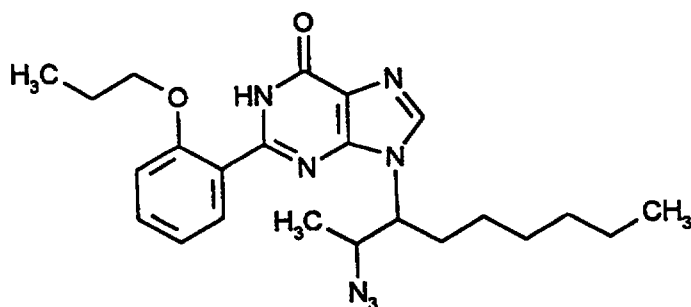
Le A 30 701

**9-(2-Methanesulphonyloxy-3-nonyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-
purin-6-one**


$$R_f = 0.48 \text{ (CH}_2\text{Cl}_2/\text{CH}_3\text{OH 10:1)}$$

Yield: 51.4%

10 9-(2-Azido-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one

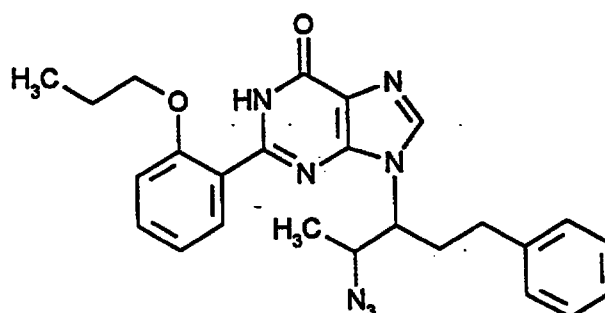


474 mg (1 mmol) of 9-(2-methanesulphonyloxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 22) and 78 mg (1.2 mmol) of sodium azide are stirred in 5 ml of dimethylformamide at 100°C for 6 hours (monitoring by thin-layer chromatography).

Yield: 369 mg (88.4%)

Example 30

9-(2-Azido-5-phenyl-3-pentyl)-2-(2-n-propoxy-phenyl)-purin-6-one



10 The title compound is prepared analogously to the instructions of Example 29, starting from 9-(2-methanesulphonyloxy-5-phenyl-3-pentyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 23).

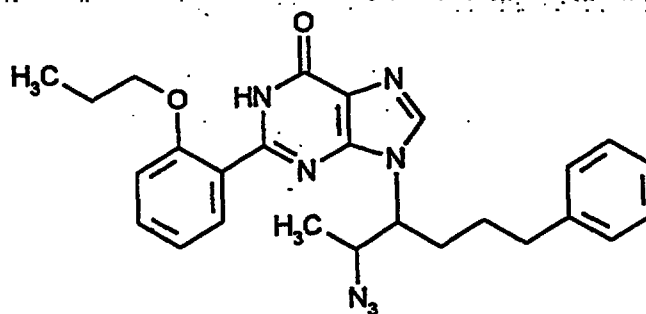
$$R_f = 0.54 \text{ (CH}_2\text{Cl}_2/\text{CH}_3\text{OH 10:1)}$$

Yield: 87.4%

Example 31

15 9-(2-Azido-6-phenyl-3-hexyl)-2-(2-n-propoxyphenyl)-purin-6-one





The title compound is prepared analogously to the instructions of Example 29, starting from 9-(2-methanesulphonyloxy-6-phenyl-3-hexyl)-2-(2-n-propoxyphenyl)-purin-6-one

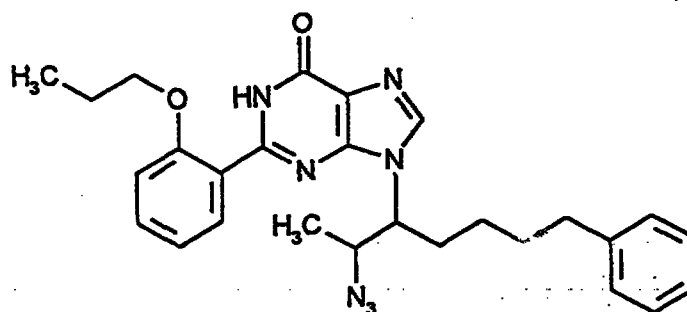
(Example 24).

5 $R_f = 0.55$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 74.9%

Example 32

9-(2-Azido-7-phenyl-3-heptyl)-2-(2-n-propoxyphenyl)-purin-6-one



10 The title compound is prepared analogously to the instructions of Example 29, starting from 9-(2-methanesulphonyloxy-7-phenyl-3-heptyl)-2-(2-n-propoxyphenyl)-purin-6-one

(Example 25).

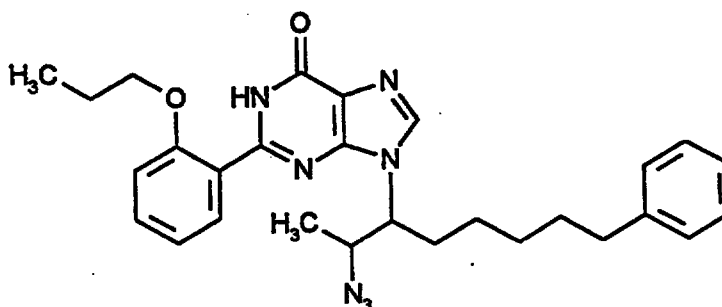
$R_f = 0.6$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 67%



Example 33

9-(2-Azido-8-phenyl-3-octyl)-2-(2-n-propoxyphenyl)-purin-6-one



5 The title compound is prepared analogously to the instructions of Example 29, starting from 9-(2-methanesulphonyloxy-8-phenyl-3-octyl)-2-(2-n-propoxyphenyl)-purin-6-one

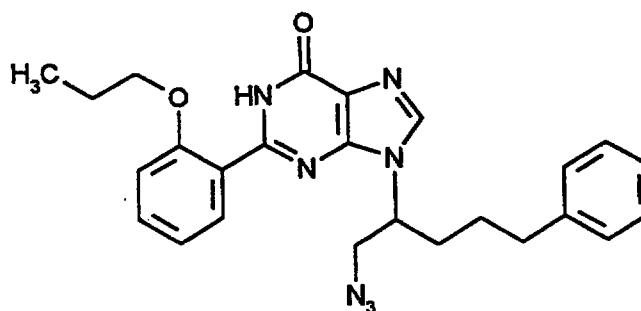
(Example 26).

$R_f = 0.61$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 88%

Example 34

10 9-(1-Azido-5-phenyl-2-pentyl)-2-(2-n-propoxyphenyl)-purin-6-one



The title compound is prepared analogously to the instructions of Example 29, starting from 9-(1-methanesulphonyloxy-5-phenyl-2-pentyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 27).

$R_f = 0.56$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1)

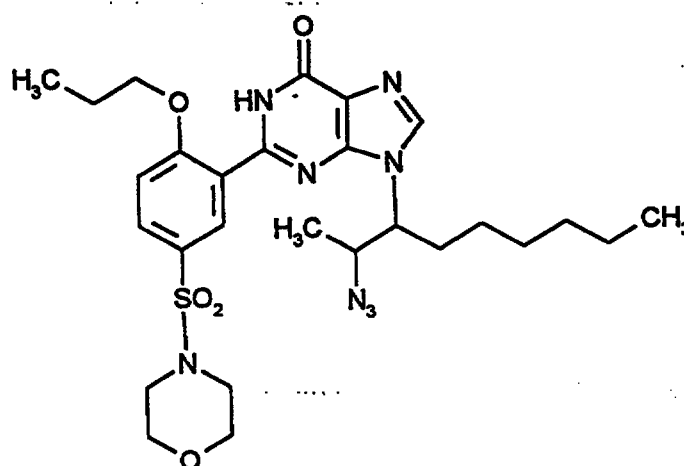
15 Yield: 98%

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Example 35

9-(2-Azido-3-nonyl)-2-(2-n-propoxy-5-morpholinesulphonyl-phenyl)-purin-6-one



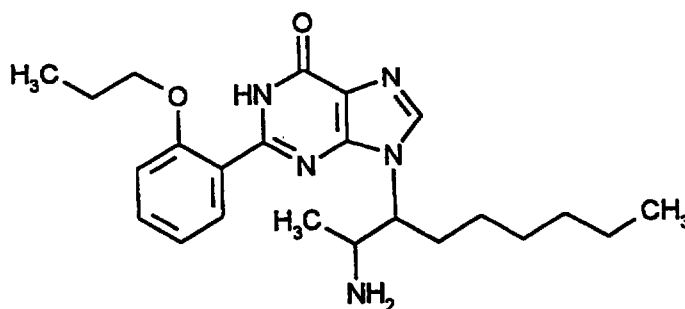
The title compound is prepared analogously to the instructions of Example 29, starting from 9-(2-methanesulphonyloxy-3-nonyl)-2-(2-n-propoxy-5-morpholinesulphonyl-phenyl)-purin-6-one (Example 28).

$R_f = 0.55$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 38%

Example 36

9-(2-Amino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



10 5.3 g (12.13 mmol) of 9-(2-azido-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 29) are hydrogenated in 70 ml of absolute methanol in the presence of 0.1 g of Pd/C (10%) with hydrogen under normal pressure at room temperature. After 4



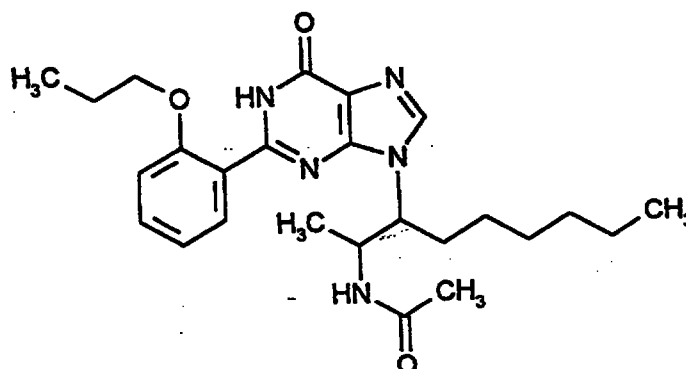
hours, the catalyst is filtered off, the solvent is distilled off in vacuo and the residue is purified by flash chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 20:1).

$R_f = 0.28$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 4.1 g (82.3%)

5 **Example 37**

9-(2-Acetamido-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



210 mg (0.5 mmol) of 9-(2-amino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 36) are dissolved in 20 ml of absolute CH_2Cl_2 . 101 mg (1 mmol) of triethylamine are added at room temperature, and 78 mg (1 mmol) of acetyl chloride in 2 ml of absolute CH_2Cl_2 are then added dropwise. After 1 hour at room temperature, the organic phase is extracted by shaking with 10 ml of 2 N HCl and with 10 ml of saturated NaHCO_3 solution. After the organic phase has been dried over Na_2SO_4 , the solvent is evaporated in vacuo and the residue is purified by flash chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 40:1).

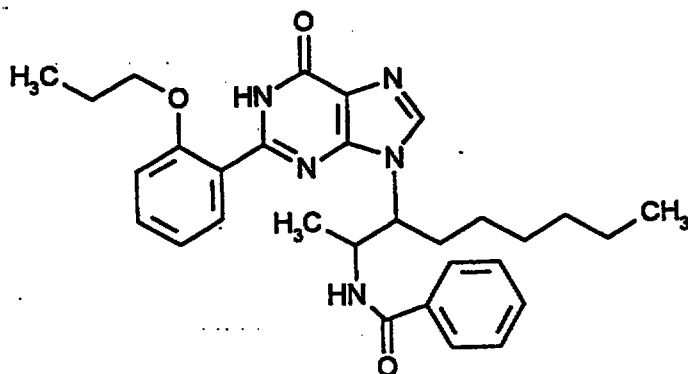
15 $R_f = 0.37$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 174 mg (77%)

Example 38

9-(2-Benzoylamino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one





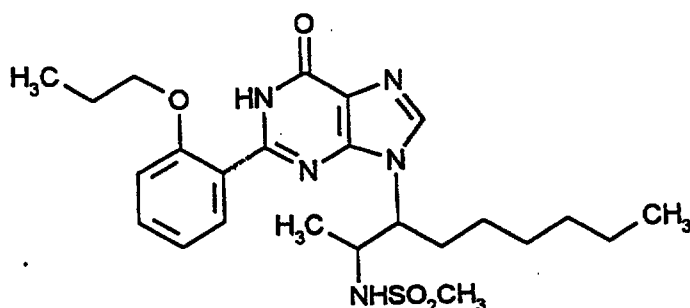
The title compound is prepared analogously to the instructions of Example 37 starting from 9-(2-amino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 36) and benzoyl chloride.

Melting point: 184°C (toluene)

5 Yield: 59%

Example 39

9-(2-Methylsulphonylamino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



10 The title compound is prepared analogously to the instructions of Example 37, starting from 9-(2-amino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 36) and methylsulphonyl chloride.

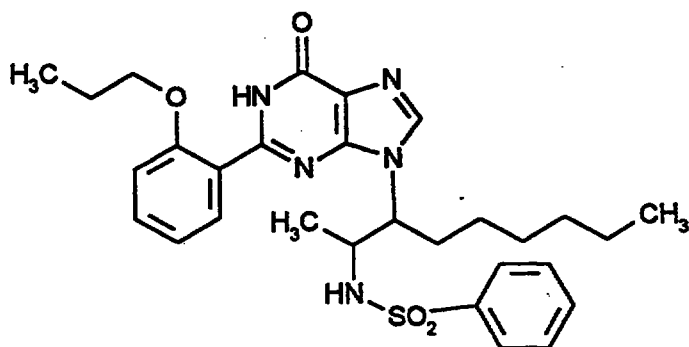
$R_f = 0.46$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 78.2%



Example 40

9-(2-Phenylsulphonylamino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



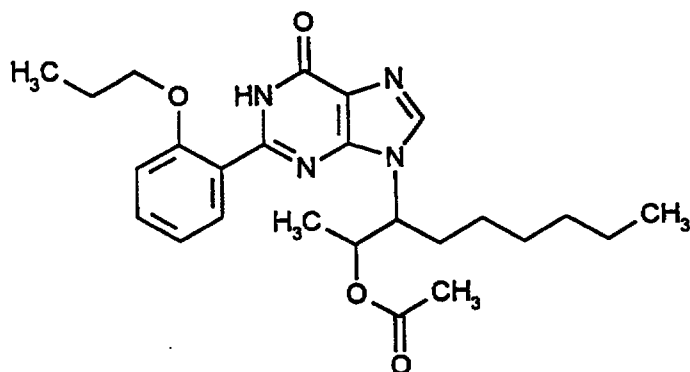
The title compound is prepared analogously to the instructions of Example 37, starting from 9-(2-amino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 36) and phenylsulphonyl chloride.

Melting point: 112°C (toluene/ether)

Yield: 62.9%

Example 41

9-(2-Acetoxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



206 mg (0.5 mmol) of 9-(2-hydroxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 3), 47 mg (0.6 mmol) of acetyl chloride, 47 mg (0.6 mmol) of pyridine and 5 mg of DMAP are stirred in 10 ml of absolute CH₂Cl₂ at 25°C for 1 hour and then



at 40°C for 1 hour. The mixture is extracted by shaking twice with 10 ml of 2 N HCl solution each time and twice with 10 ml of saturated NaHCO₃ solution each time and washed once with saturated NaCl solution. After the organic phase has been dried over Na₂SO₄, the solvent is evaporated in vacuo and the residue is dried under a high vacuum.

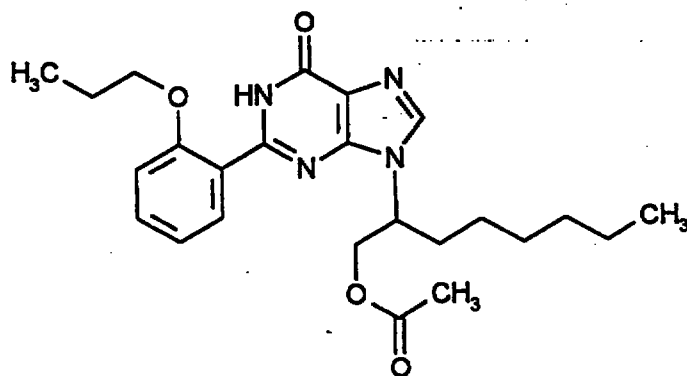
5

$R_f = 0.53$ (CH₂Cl₂/CH₃OH 100:1)

Yield: 90.5%

Example 42

9-(1-Acetoxy-2-octyl)-2-(2-n-propoxyphenyl)-purin-6-one



- 10 The title compound is prepared analogously to the instructions of Example 41, starting from 9-(1-hydroxy-2-octyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 2).

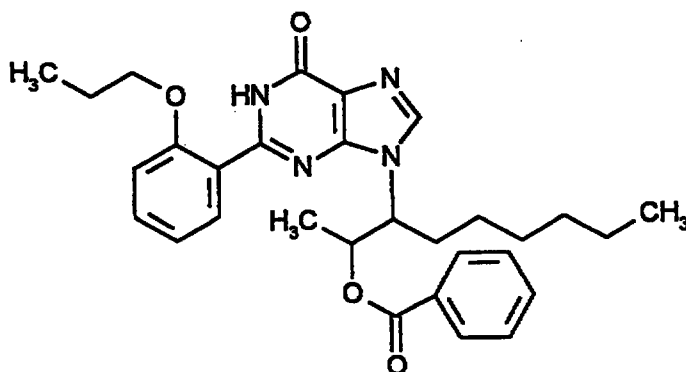
$R_f = 0.52$ (CH₂Cl₂/CH₃OH 100:1)

Yield: 88.5%



Example 43

9-(2-Benzoyloxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



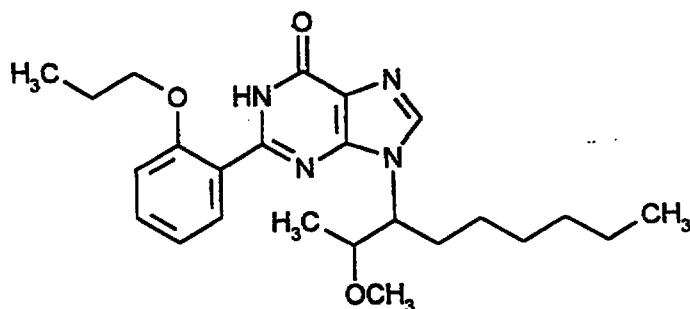
The title compound is prepared analogously to the instructions of Example 41, starting from 9-(2-hydroxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 3) and benzoyl chloride.

$R_f = 0.57$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 100:1)

Yield: 89%

Example 44

9-(2-Methoxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



- 10 48 mg of 60% strength NaH (1.2 mmol) are suspended in 2 ml of absolute tetrahydrofuran at 20°C. 206 mg (0.5 mmol) of 9-(2-hydroxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 3) in 3 ml of absolute tetrahydrofuran are added dropwise. After 15 minutes at 20°C, 85 mg (0.6 mmol) of methyl iodide in 3 ml of



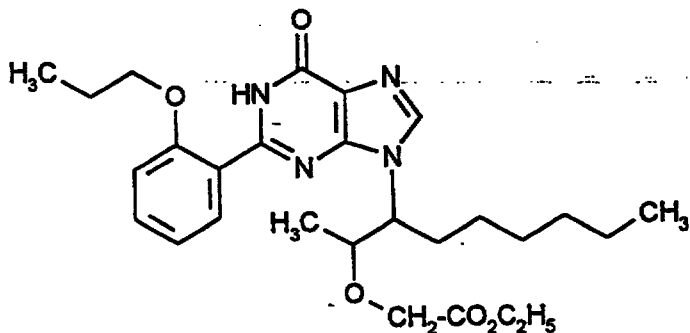
5

R_f = 0.58 (CH₂Cl₂/CH₃OH 100:1)

Yield: 74.2%

Example 45

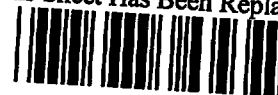
9-(2-Ethoxycarbonylmethyleneoxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



- 10

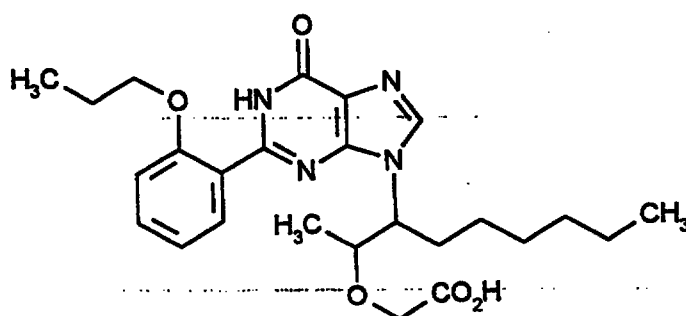
$$R_f = 0.55 \text{ (CH}_2\text{Cl}_2/\text{CH}_3\text{OH 100:1)}$$

Yield: 85.8%



Example 46

9-(2-Carboxymethyleneoxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



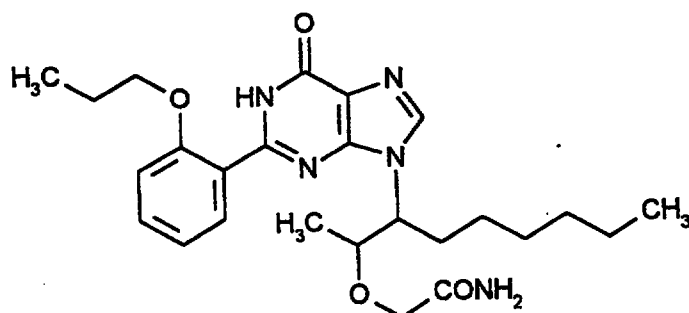
498 mg (1 mmol) of the ester from Example 45 are stirred in 4 ml of 1 N NaOH and 5 ml of MeOH at 20°C for 1 hour. The methanol is distilled off in vacuo. After
5 addition of 5 ml of H₂O, the mixture is extracted by shaking with ethyl acetate. The aqueous phase is acidified with 4 ml of 2 N HCl and extracted by shaking twice with 10 ml of ethyl acetate each time. The combined ethyl acetate phases are dried over Na₂SO₄ and evaporated.

R_f = 0.27 (CH₂Cl₂/CH₃OH 10:1)

10 Yield: 88.5%

Example 47

9-(2-Amidocarbonylmethyleneoxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



The title compound is prepared analogously to the instructions of Example 45, starting from 9-(2-hydroxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 3) and



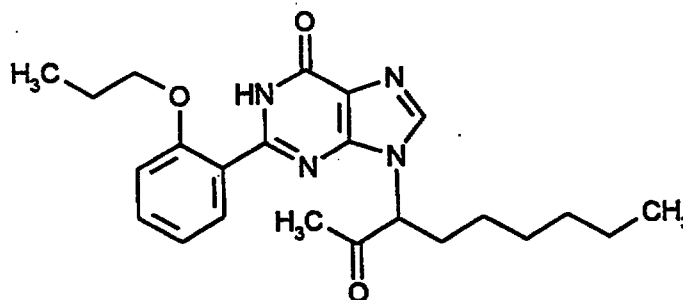
bromoacetamide.

$R_f = 0.26$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 31.6%

Example 48

5 **9-(2-Oxo-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one**



0.31 ml of absolute dimethyl sulphoxide (4.4 mmol) in 3 ml of absolute CH_2Cl_2 is added dropwise to 0.19 ml (2.2 mmol) of oxalyl chloride in 5 ml of CH_2Cl_2 at -60°C in the course of 10 minutes and the mixture is subsequently stirred for 20 minutes. 824 mg (2 mmol) of 9-(2-hydroxy-3-methyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 3) in 5 ml of absolute CH_2Cl_2 are then added dropwise in the course of 45 minutes and the mixture is subsequently stirred at -60°C for 1 hour. 1.39 ml (10 mmol) of triethylamine in 5 ml of absolute CH_2Cl_2 are added dropwise to this solution in the course of 30 minutes and the mixture is subsequently stirred at -60°C for 15 minutes. It is allowed to come to 20°C , 10 ml of H_2O are added, the phases are separated and the organic phase is washed with 20 ml of saturated NaCl solution. After the mixture has been dried over Na_2SO_4 , it is evaporated and the residue is purified by flash chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 40:1).

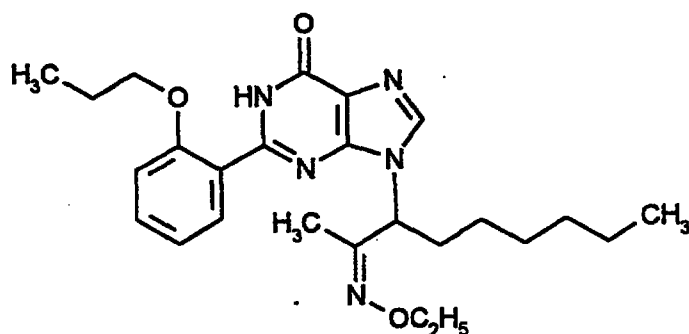
Melting point: 83°C (ether/cyclohexane)

Yield: 535 mg (65.2%)



Example 49

9-(2-Ethyloximino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one

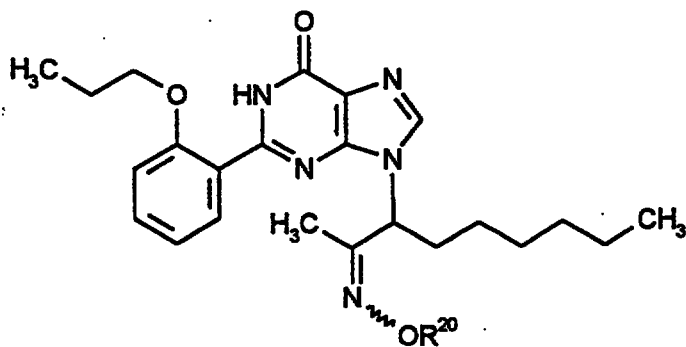


- 412 mg (1 mmol) of 9-(2-oxo-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 48) are dissolved in 10 ml of methanol, and 117 mg (1.2 mmol) of ethylhydroxylamine hydrochloride, dissolved in 1.5 ml of water, are added. The mixture is boiled under reflux for 2 hours, cooled and evaporated in vacuo. The residue is taken up in 10 ml of ethyl acetate and washed with 10 ml of saturated NaHCO₃ solution. After the organic phase has been dried with Na₂SO₄, the solvent is distilled off in vacuo and the residue is purified by flash chromatography (eluent: toluene/acetone 4:1).
- $R_f = 0.53$ (toluene/acetone 1:1)
- Yield: 366 mg (80.8%)

The oximes listed in Table III are prepared in accordance with these instructions using the corresponding hydroxylamine hydrochlorides (all the oximes are in the form of cis/trans mixtures).



Table III:



Example No.	R^{20}	Yield (% of theory)	Melting point ($^{\circ}\text{C}$)/ R_f
50	H	69.4	111
51	$\text{C}(\text{CH}_3)_3$	79.4	0.56 a)
52	$-\text{CH}_2-\text{C}_6\text{H}_5$	98.4	0.55 a)
53	$-\text{CH}_2\text{CH}_2-\text{N}(\text{C}_2\text{H}_5)_2$	70.2	0.29 b)

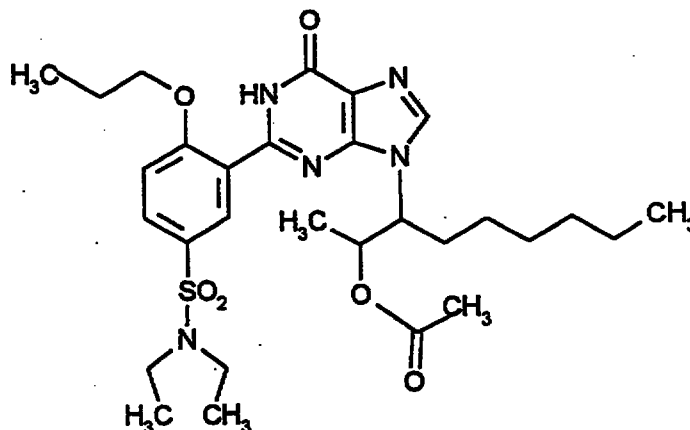
a) Mobile phase: toluene/acetone 1:1

b) Mobile phase: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1



Example 54

9-(2-Acetoxy-3-nonyl)-2-(2-n-propoxy-5-diethylaminosulphonyl-phenyl)-purin-6-one



1.28 g (2.82 mmol) of 9-(2-acetoxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 41) are added in portions to 4 ml of chlorosulphonic acid at 0°C and the mixture is stirred overnight at 20°C. The batch is added dropwise to 30 ml of ice-water and the aqueous phase is extracted twice with 20 ml of ethyl acetate each time. The combined organic phases are dried over Na₂SO₄ and the solvent is distilled off in vacuo.

Yield: 0.9 g (57.8%)

10 $R_f = 0.52$ (CH₂Cl₂/CH₃OH 10:1)

The residue is taken up in 30 ml of absolute ethanol without further purification, 5.1 ml of diethylamine are added and the mixture is stirred at 25°C for 6 hours (monitoring by thin-layer chromatography). The ethanol is distilled off in vacuo, the residue is taken up in 50 ml of ethyl acetate and the mixture is washed twice with 50 ml of H₂O each time. After drying over Na₂SO₄, the organic phase is evaporated in vacuo and the residue is purified by flash chromatography (eluent: toluene/acetone 3:1).

15

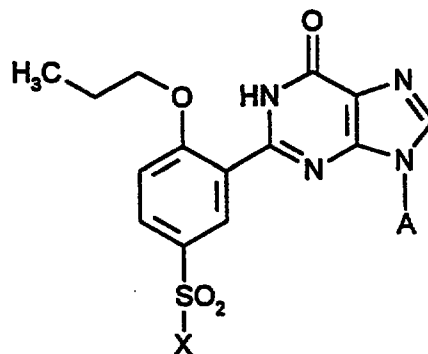
$R_f = 0.52$ (CH₂Cl₂/CH₃OH 10:1)

Yield: 549 mg (57.2%)



The compounds listed in Table IV are prepared analogously to the instructions of Example 54 from the corresponding purinone and the corresponding amine:

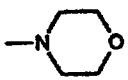
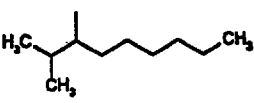
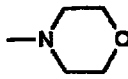
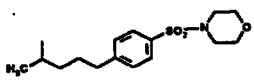
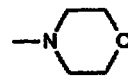
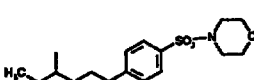
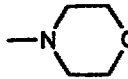
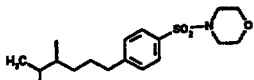
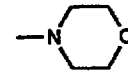
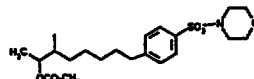
Table IV:



Example No.	X	A	Yield (% of theory)	Melting point (°C)/R _f
55			37.4	0.53 a)
56			72.3	0.58 a)
57			80.9	0.51 a)
58			78.4	0.39 a)
59			35.9	0.3 b)



5

Example No.	X	A	Yield (% of theory)	Melting point (°C)/R _f
60			58	0.52 a)
61			41	0.27 b)
62			26.5	0.33 b)
63			76.3	0.35 b)
64			37	0.39 b)

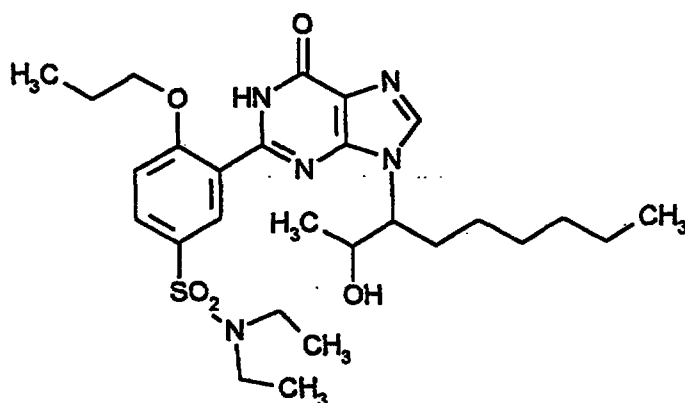
a) Mobile phase: CH₂Cl₂/CH₃OH 10:1

b) Mobile phase: toluene/acetone 1:1



Example 65

9-(2-Hydroxy-3-nonyl)-2-(2-n-propoxy-5-diethylaminosulphonyl-phenyl)-purin-6-one

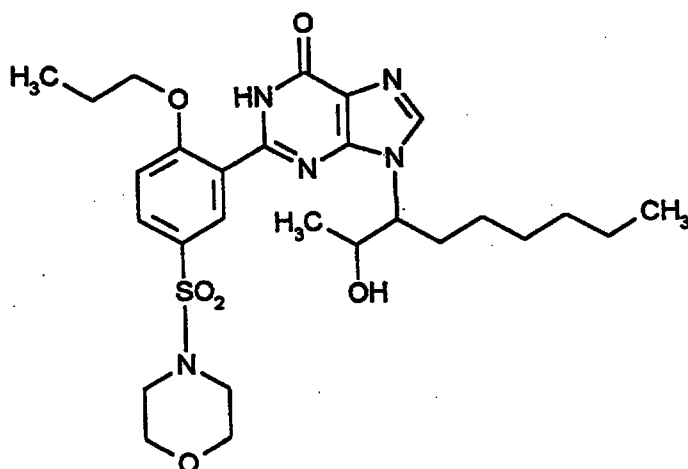


- 140 mg(0.24 mmol) of 5-(2-acetoxy-3-nonyl)-2-(2-n-propoxy-5-diethylaminosulphonyl-phenyl)-purin-6-one (Example 54) are dissolved in 5 ml of methanol. After addition of
- 5 0.5 ml of aqueous 1 N NaOH solution, the mixture is stirred at 25°C for 2 hours. 0.25 ml of aqueous 2 N HCl solution is added, the methanol is distilled off in vacuo and 10 ml of ethyl acetate and 10 ml of water are added. The organic phase is separated off, dried over Na₂SO₄ and evaporated. The residue is purified by flash chromatography (eluent: CH₂Cl₂/CH₃OH 40:1).
- 10 R_f = 0.47 (CH₂Cl₂/CH₃OH 10:1)
Yield: 112 mg (85%)



Example 66

9-(2-Hydroxy-3-nonyl)-2-(2-n-propoxy-5-morpholinosulphonylphenyl)-purin-6-one



The title compound is prepared analogously to the instructions of Example 65, starting from 2-(2-acetoxy-3-nonyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one

5 (Example 55).

$R_f = 0.45$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

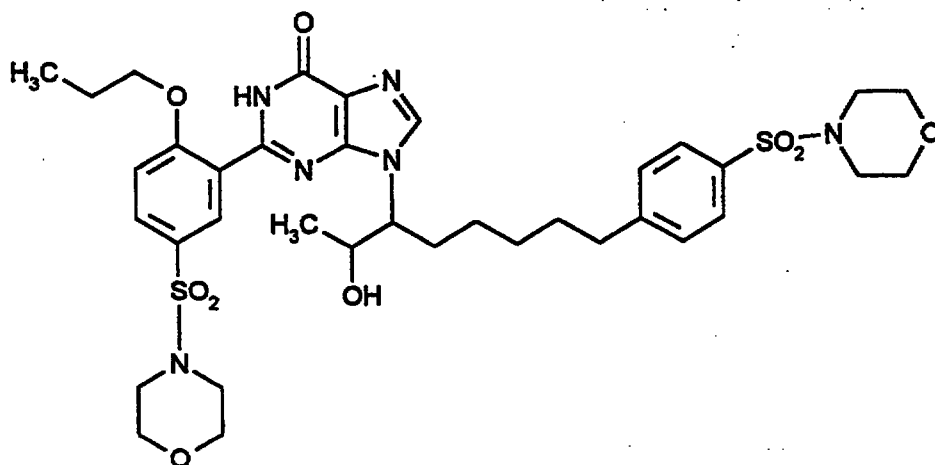
Yield: 80.6%

Example 67

9-(2-Hydroxy-8-(4-morpholinosulphonyl-phenyl)-3-octyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one

10





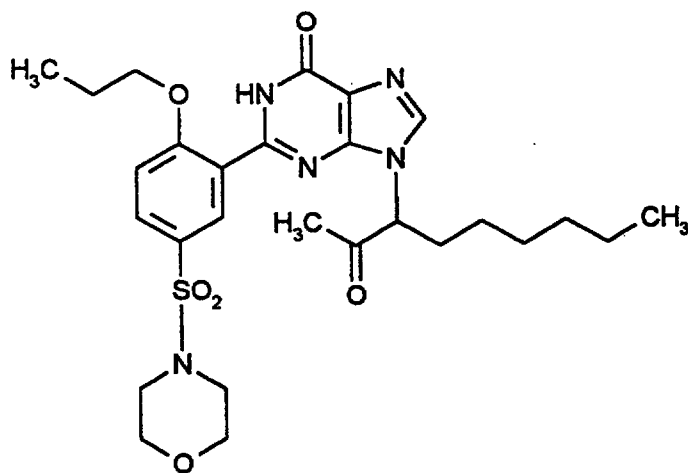
The title compound is prepared analogously to the instructions of Example 65, starting from 9-(2-acetoxy-8-(4-morpholinosulphonyl-phenyl)-3-octyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one (Example 64).

5 $R_f = 0.35$ (toluene/acetone 1:1)

Yield: 79.6%

Example 68

9-(2-Oxo-3-nonyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one



$R_f = 0.52$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:19)

Example 69

CCOC1=CC=C(C(=C1)S(=O)(=O)N2CCOCC2)C3=C(NC(=O)N3)c4nc5c(ncn45)C(=O)C(C)CCCCCc6ccc(cc6)S(=O)(=O)N7CCOCC7

$R_f = 0.41$ (toluene/acetone 1:1)

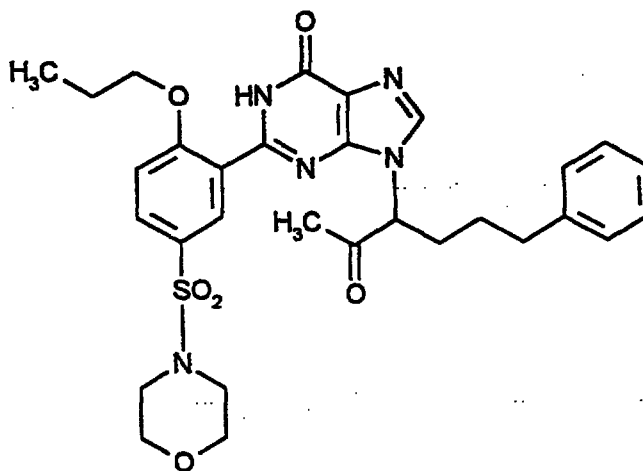
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Example 70

9-(2-Oxo-6-phenyl-3-hexyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one



The title compound is prepared analogously to the instructions of Example 48, starting from 9-(2-hydroxy-6-phenyl-3-hexyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one (Example 20).

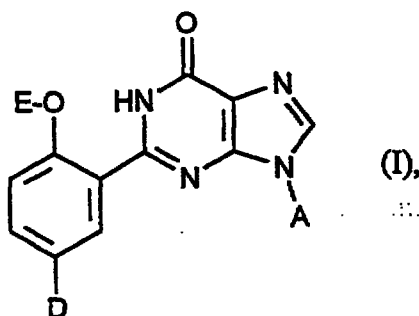
$R_f = 0.6$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 51%.



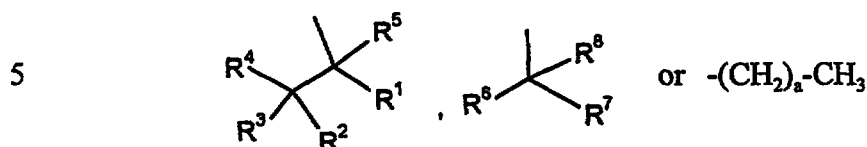


1. 9-Substituted 2-(2-n-alkoxyphenyl)purin-6-ones of the general formula (I)



in which

A represents a radical of the formula



wherein,

a denotes a number 9, 10, 11, 12, 13, 14 or 15,

10 R^1 denotes straight-chain or branched alkyl having 2 to 10 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by halogen, nitro, cyano, by straight-chain or branched alkyl having up to 6 carbon atoms or by a group of the formula $-SO_2-NR^9R^{10}$,

wherein

R^9 and R^{10} are identical or different and denote hydrogen, phenyl or





5

straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, or together with the nitrogen atom form a 5- to 6-membered, saturated heterocyclic radical which has up to 2 further heteroatoms from the series consisting of S, N and/or O and is optionally substituted, including via a free N function, by straight-chain or branched alkyl having up to 6 carbon atoms, which in turn can be substituted by hydroxyl,

and/or

10

alkyl is optionally substituted by a group of the formula $-NR^{11}R^{12}$,

wherein

R^{11} and R^{12} have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these,

15

R^2 denotes hydrogen, azido, straight-chain or branched alkyl having up to 6 carbon atoms or a group of the formula $-OR^{13}$, $O-SO_2R^{14}$ or $-NR^{15}R^{16}$,

wherein

20

R^{13} is hydrogen, a hydroxyl-protecting group, straight-chain or branched acyl having up to 6 carbon atoms, benzoyl or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxy carbonyl having up to 6 carbon atoms or by a group of the formula $-CO-NR^{17}R^{18}$,

wherein

R^{17} and R^{18} are identical or different and denote hydrogen or





straight-chain or branched alkyl having up to 4 carbon atoms,

R^{14} denotes straight-chain or branched alkyl having up to 4 carbon atoms or phenyl,

5 R^{15} and R^{16} are identical or different and denote hydrogen, an amino-protecting group, straight-chain or branched alkyl or acyl having in each case up to 6 carbon atoms, formyl, benzoyl or a group of the formula $-SO_2R^{19}$,

wherein

10 R^{19} has the abovementioned meaning of R^{14} and is identical to or different from this,

R^3 denotes hydrogen,

or

R^2 and R^3 together form a radical of the formula $=O$ or $=N-OR^{20}$,

15 wherein

R^{20} denotes hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by phenyl or by a group of the formula $-NR^{21}R^{22}$,

wherein

20 R^{21} and R^{22} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms,



R^4 denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

R^5 and R^8 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

5 R^6 denotes hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl,

R^7 denotes straight-chain or branched alkyl having 2 to 8 carbon atoms, which is substituted by a group of the formula $-NR^{23}R^{24}$,

wherein

10 R^{23} and R^{24} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl,

or is substituted by phenyl, which in turn is substituted by the group of the formula $-SO_2-NR^{25}R^{26}$,

15 wherein

R^{25} and R^{26} have the abovementioned meaning of R^9 and R^{10} ,

D represents hydrogen or represents a group of the formula $-SO_2-NR^{27}R^{28}$,

wherein

20 R^{27} and R^{28} are identical or different and have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these, and

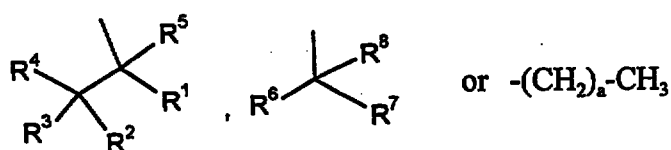


E represents straight-chain or branched alkyl having up to 8 carbon atoms,
and tautomers and salts thereof.

2. 9-Substituted 2-(2-n-alkoxyphenyl)purin-6-ones of the formula (I) according to Claim 1,

5 in which

A represents a radical of the formula



wherein,

a denotes a number 9, 10, 11, 12 or 13,

10 R¹ denotes straight-chain or branched alkyl having 2 to 8 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by fluorine, chlorine, bromine, nitro, cyano, by straight-chain or branched alkyl having up to 4 carbon atoms or by a group of the formula -SO₂-NR⁹R¹⁰,

15 wherein

R⁹ and R¹⁰ are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl,
or, together with the hydrogen atom, form a morpholinyl,
pyrrolidinyl or piperidinyl ring or a piperazinyl ring, which is

20



optionally substituted, including via a free NH function, by straight-chain or branched alkyl having up to 3 carbon atoms, which in turn can be substituted by hydroxyl,

and/or

5 alkyl is optionally substituted by a group of the formula $-NR^{11}R^{12}$,

wherein

R^{11} and R^{12} have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these,

10 R^2 denotes hydrogen, azido, straight-chain or branched alkyl having up to 4 carbon atoms or a group of the formula $-OR^{13}$, $-O-SO_2-R^{14}$ or $-NR^{15}R^{16}$,

wherein

15 R^{13} denotes hydrogen, benzyl, straight-chain or branched acyl having up to 4 carbon atoms, benzoyl or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxy carbonyl having up to 4 carbon atoms or by a group of the formula $-CO-NR^{17}R^{18}$,

wherein

20 R^{17} and R^{18} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

R^{14} denotes straight-chain or branched alkyl having up to 3 carbon atoms or phenyl,



R⁶ denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl,

R⁷ denotes straight-chain or branched alkyl having 2 to 6 carbon atoms, which is substituted by a group of the formula -NR²³R²⁴,

5 wherein

R²³ and R²⁴ are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl,

10 or is substituted by phenyl, which in turn is substituted by a group of the formula -SO₂-NR²⁵R²⁶,

 wherein

R²⁵ and R²⁶ are identical or different and have the abovementioned meaning of R⁹ and R¹⁰,

D represents hydrogen, or represents a group of the formula -SO₂-NR²⁷R²⁸,

15 wherein

R²⁷ and R²⁸ are identical or different and have the abovementioned meaning of R⁹ and R¹⁰ and are identical to or different from these, and

E represents straight-chain or branched alkyl having up to 6 carbon atoms,
and tautomers and salts thereof.

20 3. 9-Substituted 2-(2-n-alkoxyphenyl)purin-6-ones of the formula according to Claim 1,

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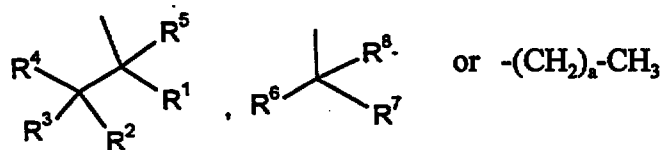
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wherein

A represents a radical of the formula



wherein,

5 a denotes a number 9, 10, 11 or 12,

R¹ denotes straight-chain or branched alkyl having 2 to 7 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by fluorine, chlorine, bromine, nitro, cyano, by straight-chain or branched alkyl having up to 3 carbon atoms or by a group of the formula
10 -SO₂-NR⁹R¹⁰,

wherein

R⁹ and R¹⁰ are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl,
15 or, together with the nitrogen atom, form a morpholinyl, pyrrolidinyl or piperidinyl ring or a piperazinyl ring, which is optionally substituted, including via free NH function, by straight-chain or branched alkyl having up to 3 carbon atoms, which in turn can be substituted by hydroxyl,

20 and/or

alkyl is optionally substituted by a group of the formula -NR¹¹R¹²,

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wherein

R^{11} and R^{12} have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these,

5 R^2 denotes hydrogen, azido, straight-chain or branched alkyl having up to 3 carbon atoms or a group of the formula $-OR^{13}$, $-OSO_2R^{14}$ or $-NR^{15}R^{16}$,

wherein

10 R^{13} denotes hydrogen, straight-chain or branched acyl having up to 3 carbon atoms, benzoyl or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxy carbonyl having up to 3 carbon atoms or by a group of the formula $-CO-NR^{17}R^{18}$,

wherein

R^{17} and R^{18} are identical or different and denote hydrogen, methyl or ethyl,

15 R^{14} denotes straight-chain or branched alkyl having up to 3 carbon atoms or phenyl,

20 R^{15} and R^{16} are identical or different and denote hydrogen, tert-butoxycarbonyl, straight-chain or branched alkyl or acyl having in each case up to 3 carbon atoms, formyl, benzoyl or a group of the formula $-SO_2R^{19}$,

wherein

R^{19} has the abovementioned meaning of R^{14} and is identical to or different from this,





R^3 denotes hydrogen,

or

R^2 and R^3 together form a radical of the formula $=O$ or $=N-OR^{20}$,

wherein

5 R^{20} denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by phenyl or by a group of the formula $-NR^{21}R^{22}$,

wherein

10 R^{21} and R^{22} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 3 carbon atoms,

R^4 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

15 R^5 and R^8 are identical or different and denote hydrogen or methyl,

R^6 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl,

R^7 denotes straight-chain or branched alkyl having 2 to 6 carbon atoms, which is substituted by a group of the formula $-NR^{23}R^{24}$,

20 wherein

R^{23} and R^{24} are identical or different and denote hydrogen or straight-



chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl,

or is substituted by phenyl, which in turn is substituted by the group of the formula $-\text{SO}_2-\text{R}^{25}\text{R}^{26}$,

5 wherein

R^{25} and R^{26} have the abovementioned meaning of R^9 and R^{10} ,

D represents hydrogen, or represents a group of the formula $-\text{SO}_2-\text{NR}^{27}\text{R}^{28}$,

wherein

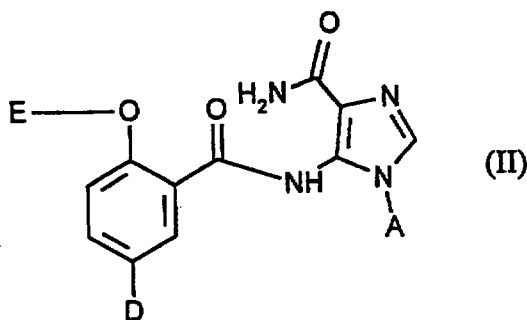
10 R^{27} and R^{28} are identical or different and have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these, and

E represents straight-chain or branched alkyl having up to 5 carbon atoms,

and tautomers and salts thereof.

4. 9-Substituted 2-(2-n-alkoxyphenyl)purin-6-ones according to Claim 1 to 3 for therapeutic use.

15 5. Process for the preparation of 9-substituted 2-(2-n-alkoxyphenyl)purin-6-ones according to Claim 1 to 3, characterized in that compounds of the general formula (II)



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in which

D, E and A have the abovementioned meaning,

are first cyclized in inert solvents and in the presence of a base,

5 and in the case where $D = H$, the corresponding sulphonic acid chlorides are first prepared by reaction with chlorosulphonic acid and the corresponding sulphonamides are then prepared with amines ($NR^{25}R^{26}$),

and the substituents R^1-R^8 are introduced or derivatized by customary methods, such as, for example alkylation, acylation, amination, oxidation or azide exchange.

10 6. Medicaments comprising 9-substituted 2-(2-n-alkoxyphenyl)purin-6-ones according to Claim 1 to 3.

7. Medicaments according to Claim 6 for treatment of inflammations, thromboembolic diseases and cardiovascular diseases.

8. Medicaments according to Claims 6 and 7 for treatment of impotence.

15 9. Use of 9-substituted 2-(2-n-alkoxyphenyl)purin-6-ones according to Claim 1 to 3 for the preparation of medicaments.

10. Use according to Claim 8, characterized in that the medicaments are for treatment of inflammations, thromboembolic diseases and cardiovascular diseases.

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9-Substituted 2-(2-n-alkoxyphenyl)purin-6-ones

Abstract

9-Substituted 2-(2-n-alkoxyphenyl)purin-6-ones are prepared by cyclizing correspondingly substituted imidazoles and derivatizing the purines thus obtained. The
5 9-substituted 2-(2-n-alkoxyphenyl)purin-6-ones can be employed as active compounds in medicaments, in particular in medicaments for treatment of inflammations, thromboembolic diseases and cardiovascular diseases.

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9-substituted 2-(2-n-alkoxyphenyl)-purin-6-ones

5 The present invention relates to 9-substituted 2-(2-n-alkoxyphenyl)-purin-6-ones, processes for their preparation and their use in medicaments, in particular for treatment of inflammations, thromboembolic and cardiovascular diseases and diseases of the urogenital system.

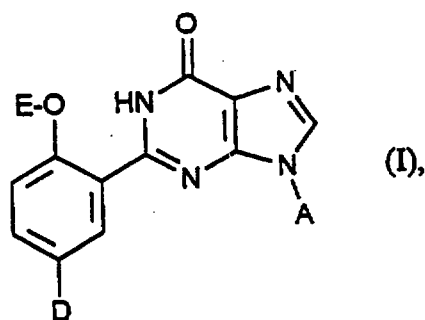
10 Purinones and quinazolinones having a selective cGMP PDE-inhibiting action are known from the publications WO 94/00453 and WO 93/12095.

Phosphodiesterases (PDEs) play an essential role in the regulation of the intracellular cGMP and cAMP level. Of the phosphodiesterase isoenzyme groups PDE I to PDE V described to date [nomenclature according to Beavo and Reifsnnyder (cf. Beavo, J.A. and Reifsnnyder, D.H., Trends in Pharmacol. Sci. 11, 150-155 (1990))], the
15 Ca-calmodulin-activated PDE I, the cGMP-stimulatable PDE II and the cGMP-specific PDE V are essentially responsible for the metabolism of cGMP. Because of the differing distribution of these cGMP-metabolizing PDEs in tissue, selective inhibitors should raise the cGMP level in the corresponding tissue according to the tissue
20 distribution of the corresponding isoenzyme. This can lead to a specific, antiaggregatory, antispastic, vasodilating, antiarrhythmic and/or antiinflammatory action.

The present invention thus relates to 9-substituted 2-(2-n-alkoxyphenyl)-purin-6-ones of the general formula (I),

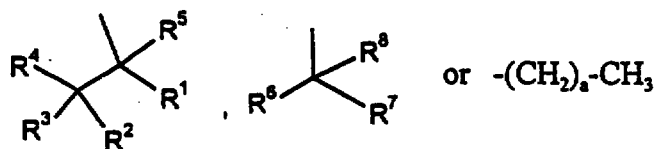
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in which

A represents a radical of the formula



wherein,

a denotes a number 9, 10, 11, 12, 13, 14 or 15,

R^1 denotes straight-chain or branched alkyl having 2 to 10 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by halogen, nitro, cyano, by straight-chain or branched alkyl having up to 6 carbon atoms or by a group of the formula $-SO_2-NR^9R^{10}$,

wherein

R^9 and R^{10} are identical or different and

denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, or together with the nitrogen atom form a 5- to 6-membered, saturated heterocyclic radical which has up to 2

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further heteroatoms from the series consisting of S, N and/or O and is optionally substituted, including via a free N function, by straight-chain or branched alkyl having up to 6 carbon atoms, which in turn can be substituted by hydroxyl,

5 and/or

alkyl is optionally substituted by a group of the formula $-NR^{11}R^{12}$,

wherein

R^{11} and R^{12} have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these,

10 R^2 denotes hydrogen, azido, straight-chain or branched alkyl having up to 6 carbon atoms or a group of the formula $-OR^{13}$, $O-SO_2R^{14}$ or $-NR^{15}R^{16}$,

wherein

15 R^{13} is hydrogen, a hydroxyl-protecting group, straight-chain or branched acyl having up to 6 carbon atoms, benzoyl or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxy carbonyl having up to 6 carbon atoms or by a group of the formula $-CO-NR^{17}R^{18}$,

wherein

20 R^{17} and R^{18} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

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R^{14} denotes straight-chain or branched alkyl having up to 4 carbon atoms or phenyl,

R^{15} and R^{16} are identical or different and denote hydrogen, an amino-protecting group, straight-chain or branched alkyl or acyl having in each case up to 6 carbon atoms, formyl, benzoyl or a group of the formula $-SO_2R^{19}$,

wherein

R^{19} has the abovementioned meaning of R^{14} and is identical to or different from this,

R^3 denotes hydrogen,

or

R^2 and R^3 together form a radical of the formula $=O$ or $=N-OR^{20}$,

wherein

R^{20} denotes hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by phenyl or by a group of the formula $-NR^{21}R^{22}$,

wherein

R^{21} and R^{22} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms,

R^4 denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

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R^5 and R^8 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

R^6 denotes hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl,

5 R^7 denotes straight-chain or branched alkyl having 2 to 8 carbon atoms, which is substituted by a group of the formula $-NR^{23}R^{24}$,

wherein

10 R^{23} and R^{24} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl,

or is substituted by phenyl, which in turn is substituted by the group of the formula $-SO_2-NR^{25}R^{26}$,

wherein

R^{25} and R^{26} have the abovementioned meaning of R^9 and R^{10} ,

15 D represents hydrogen or represents a group of the formula $-SO_2-NR^{27}R^{28}$,

wherein

R^{27} and R^{28} are identical or different and have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these, and

E represents straight-chain or branched alkyl having up to 8 carbon atoms,

20 and tautomers and salts thereof.

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The substances according to the invention can also be in the form of salts. Physiologically acceptable salts are preferred in the context of the invention.

Physiologically acceptable salts can be salts of the compounds according to the invention with inorganic or organic acids. Preferred salts are those with inorganic acids, such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or salts with organic carboxylic or sulphonc acids, such as, for example, acetic acid, maleic acid, fumaric acid, malic acid, citric acid, tartaric acid, lactic acid, benzoic acid or methanesulphonic acid, ethanesulphonic acid, phenylsulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid.

The compounds of the general formula (I) according to the invention can occur in various stereochemical forms which either behave as mirror images (enantiomers) or do not behave as mirror images (diastereomers). The invention relates both to the antipodes and to the racemic forms as well as the diastereomer mixtures. The racemic forms, like the diastereomers, can be separated into the stereoisomerically uniform constituents in a known manner.

A 5- to 6-membered saturated heterocyclic radical which is bonded via the nitrogen atom and can also contain, as heteroatom, up to 2 oxygen, sulphur and/or nitrogen atoms in general represents piperidyl, morpholinyl, piperazinyl or pyrrolidinyl. Piperidyl and morpholinyl are particularly preferred.

Hydroxyl-protecting group in the context of the abovementioned definition in general represents a protecting group from the series consisting of: trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyl-dimethylsilyl, triphenylsilyl or benzyl. Trimethylsilyl, tert-butyl-dimethylsilyl or benzyl are preferred.

Amino-protecting groups in the context of the invention are the customary amino-protecting groups used in peptide chemistry.

These include, preferably: benzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl,

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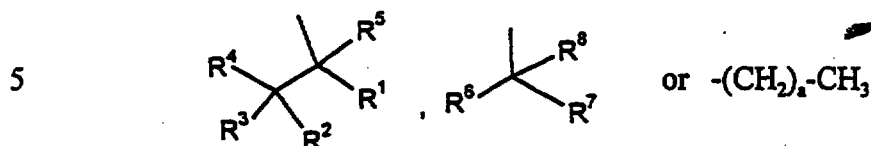
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tert-butoxycarbonyl, formyl or acetyl.

Preferred compounds are those of the general formula (I),

in which

A represents a radical of the formula



wherein,

a denotes a number 9, 10, 11, 12 or 13,

10 R^1 denotes straight-chain or branched alkyl having 2 to 8 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by fluorine, chlorine, bromine, nitro, cyano, by straight-chain or branched alkyl having up to 4 carbon atoms or by a group of the formula $-\text{SO}_2-\text{NR}^9\text{R}^{10}$,

wherein

15 R^9 and R^{10} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl,
or, together with the nitrogen atom, form a morpholinyl, pyrrolidinyl or piperidinyl ring or a piperazinyl ring, which is optionally substituted, including via a free NH function, by
20 straight-chain or branched alkyl having up to 3 carbon atoms, which in turn can be substituted by hydroxyl,

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and/or

alkyl is optionally substituted by a group of the formula $-NR^{11}R^{12}$,

wherein

5. R^{11} and R^{12} have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these.

R^2 denotes hydrogen, azido, straight-chain or branched alkyl having up to 4 carbon atoms or a group of the formula $-OR^{13}$, $-O-SO_2-R^{14}$ or $-NR^{15}R^{16}$,

wherein

10 R^{13} denotes hydrogen, benzyl, straight-chain or branched acyl having up to 4 carbon atoms, benzoyl or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxy carbonyl having up to 4 carbon atoms or by a group of the formula $-CO-NR^{17}R^{18}$,

wherein

15 R^{17} and R^{18} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

R^{14} denotes straight-chain or branched alkyl having up to 3 carbon atoms or phenyl,

20 R^{15} and R^{16} are identical or different and denote hydrogen, tert-butoxycarbonyl, benzyloxycarbonyl or straight-chain or branched alkyl or acyl having in each case up to 4 carbon atoms, formyl, benzoyl or a group of the formula $-SO_2R^{19}$,

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wherein

R^{19} has the abovementioned meaning of R^{14} and is identical to or different from this,

R^3 denotes hydrogen,

5 or

R^2 and R^3 together form a radical of the formula $=O$ or $=N-OR^{20}$,

wherein

10 R^{20} denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by phenyl or by a group of the formula $-NR^{21}R^{22}$,

wherein

R^{21} and R^{22} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms,

15 R^4 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

R^5 and R^8 are identical or different and denote hydrogen or methyl,

R^6 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl,

20 R^7 denotes straight-chain or branched alkyl having 2 to 6 carbon atoms, which is substituted by a group of the formula $-NR^{23}R^{24}$,

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wherein

R^{23} and R^{24} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl,

5 or is substituted by phenyl, which in turn is substituted by a group of the formula $-SO_2-NR^{25}R^{26}$,

wherein

R^{25} and R^{26} are identical or different and have the abovementioned meaning of R^9 and R^{10} ,

10 D represents hydrogen, or represents a group of the formula $-SO_2-NR^{27}R^{28}$,

wherein

R^{27} and R^{28} are identical or different and have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these, and

E represents straight-chain or branched alkyl having up to 6 carbon atoms,

15 and tautomers and salts thereof.

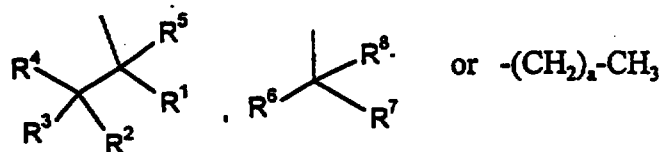
Particularly preferred compounds are those of the general formula (I),

in which

A represents a radical of the formula

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wherein,

a denotes a number 9, 10, 11 or 12,

5 R^1 denotes straight-chain or branched alkyl having 2 to 7 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by fluorine, chlorine, bromine, nitro, cyano, by straight-chain or branched alkyl having up to 3 carbon atoms or by a group of the formula $-\text{SO}_2 - \text{NR}^9 \text{R}^{10}$,

wherein

10 R^9 and R^{10} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl,
 15 or, together with the nitrogen atom, form a morpholinyl, pyrrolidinyl or piperidinyl ring or a piperazinyl ring, which is optionally substituted, including via free NH function, by straight-chain or branched alkyl having up to 3 carbon atoms, which in turn can be substituted by hydroxyl,

and/or

alkyl is optionally substituted by a group of the formula $-\text{NR}^{11} \text{R}^{12}$,

20 wherein

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R^{11} and R^{12} have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these,

R^2 denotes hydrogen, azido, straight-chain or branched alkyl having up to 3 carbon atoms or a group of the formula $-OR^{13}$, $-OSO_2R^{14}$ or $-NR^{15}R^{16}$,

5 wherein

R^{13} denotes hydrogen, straight-chain or branched acyl having up to 3 carbon atoms, benzoyl or straight-chain or branched alkyl having up to 3 carbon atoms; which is optionally substituted by carboxyl or straight-chain or branched alkoxy carbonyl having up to 3 carbon atoms or by a group of the formula $-CO-NR^{17}R^{18}$,

10

wherein

R^{17} and R^{18} are identical or different and denote hydrogen, methyl or ethyl,

R^{14} denotes straight-chain or branched alkyl having up to 3 carbon atoms or phenyl,

15

R^{15} and R^{16} are identical or different and denote hydrogen, tert-butoxycarbonyl, straight-chain or branched alkyl or acyl having in each case up to 3 carbon atoms, formyl, benzoyl or a group of the formula $-SO_2R^{19}$,

20 wherein

R^{19} has the abovementioned meaning of R^{14} and is identical to or different from this,

R^3 denotes hydrogen,

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or

R^2 and R^3 together form a radical of the formula $=O$ or $=N-OR^{20}$,

wherein

5 R^{20} denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by phenyl or by a group of the formula $-NR^{21}R^{22}$,

wherein

10 R^{21} and R^{22} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 3 carbon atoms,

R^4 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

R^5 and R^8 are identical or different and denote hydrogen or methyl,

15 R^6 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl,

R^7 denotes straight-chain or branched alkyl having 2 to 6 carbon atoms, which is substituted by a group of the formula $-NR^{23}R^{24}$,

wherein

20 R^{23} and R^{24} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl,

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or is substituted by phenyl, which in turn is substituted by the group of the formula $-\text{SO}_2-\text{R}^{25}\text{R}^{26}$,

wherein

R^{25} and R^{26} have the abovementioned meaning of R^9 and R^{10} ,

5 D represents hydrogen, or represents a group of the formula $-\text{SO}_2-\text{NR}^{27}\text{R}^{28}$,

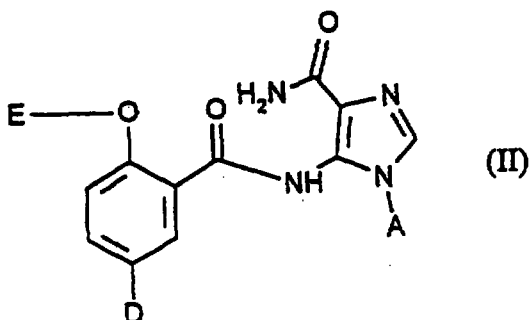
wherein

R^{27} and R^{28} are identical or different and have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these, and

E represents straight-chain or branched alkyl having up to 5 carbon atoms,

10 and tautomers and salts thereof.

A process has furthermore been found for the preparation of the compounds of the general formula (I) according to the invention, characterized in that compounds of the general formula (II)



in which

15 D, E and A have the abovementioned meaning,

are first cyclized in inert solvents and in the presence of a base,

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and in the case where $D = H$, the corresponding sulphonic acid chlorides are first prepared by reaction with chlorosulphonic acid and the corresponding sulphonamides are then prepared with amines ($NR^{25}R^{26}$),

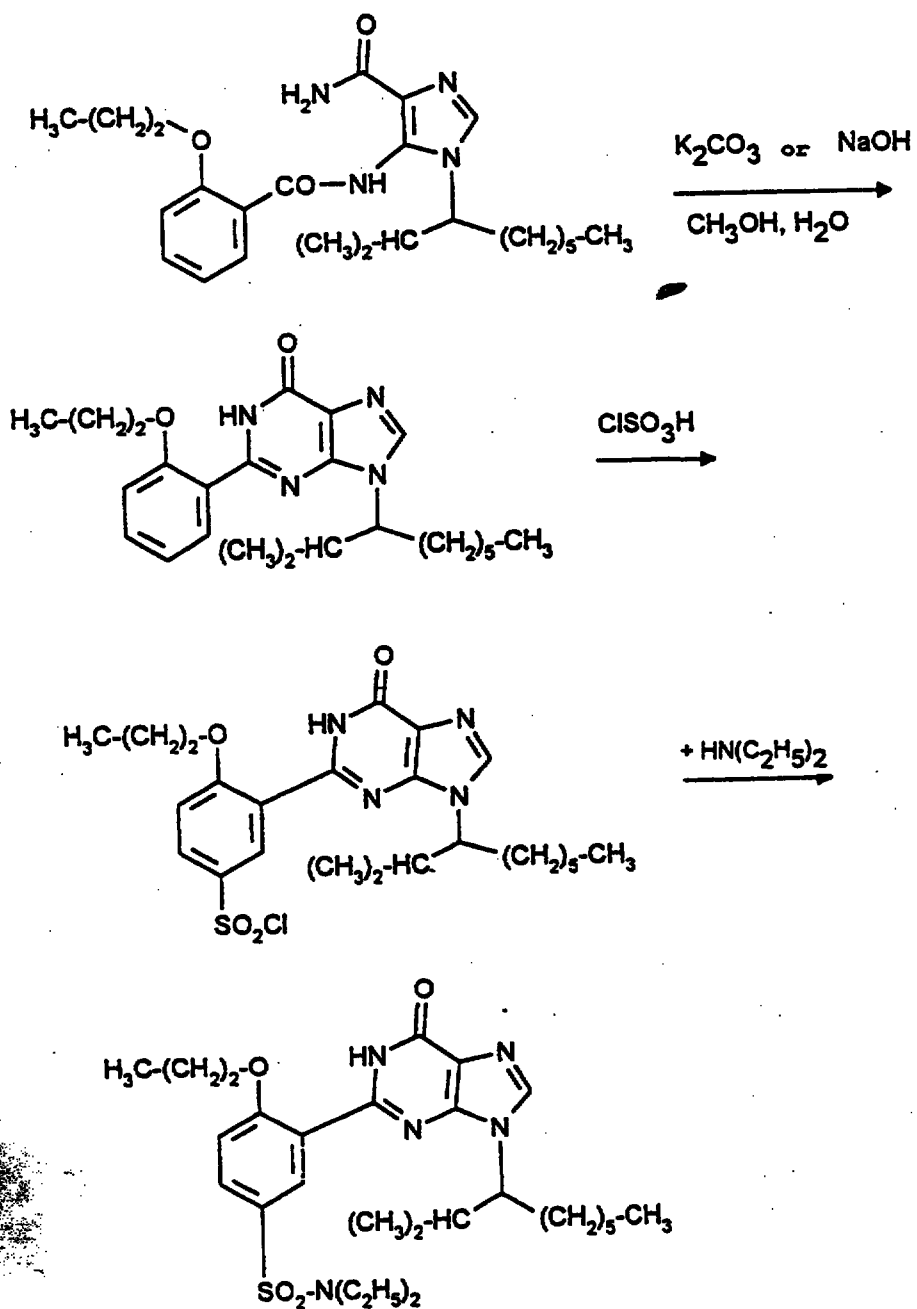
5 and the substituents R^1-R^8 are introduced or derivatized by customary methods, such as, for example alkylation, acylation, amination, oxidation or azide exchange.

The process according to the invention can be illustrated by way of example by the following equations:

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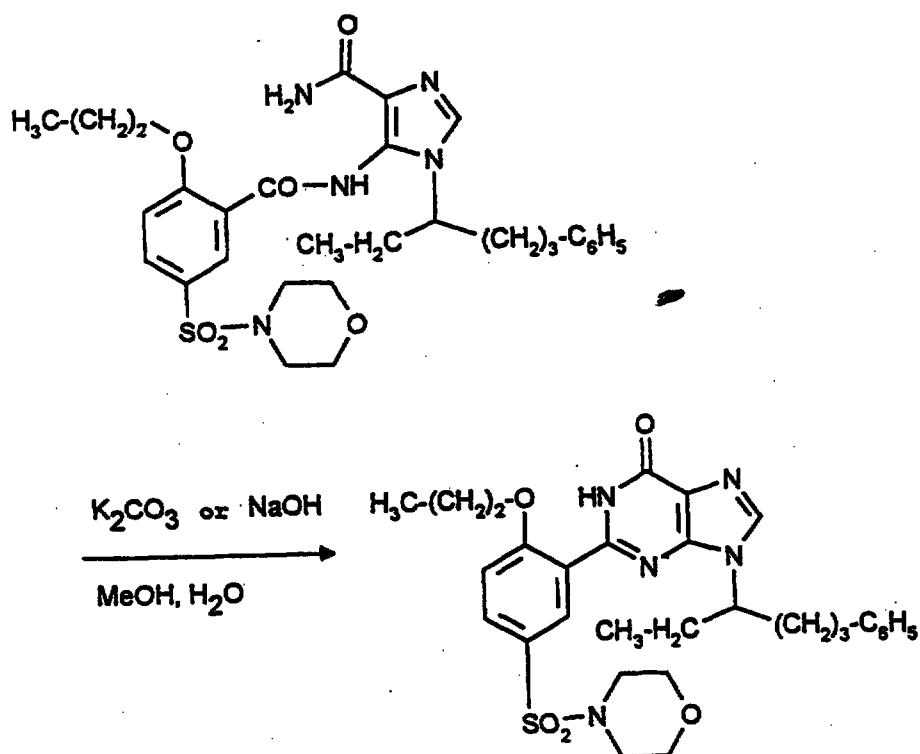
Equation A:



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Equation B:



Inert organic solvents which do not change under the reaction conditions are suitable for the process. These include, preferably, ethers, such as, for example, diethyl ether, dioxane, tetrahydrofuran or glycol mono- or dimethyl ether, ethyl acetate, toluene, acetonitrile, hexamethylphosphoric acid triamide, pyridine and acetone. It is of course possible to employ mixtures of the solvents. Tetrahydrofuran, toluene or pyridine are particularly preferred.

Suitable solvents for the cyclization are the customary organic solvents. These include, preferably, alcohols, such as methanol, ethanol, propanol, isopropanol or butanol, or ethers, such as tetrahydrofuran or dioxane, or dimethylformamide or dimethyl sulphoxide. Alcohols, such as methanol, ethanol, propanol or isopropanol, are particularly preferably used. It is also possible to employ mixtures of the solvents mentioned.

Suitable bases for the cyclization are the customary inorganic bases. These include,

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preferably, alkali metal hydroxides or alkaline earth metal hydroxides, such as, for example, sodium hydroxide, potassium hydroxide or barium hydroxide, or alkali metal carbonates, such as sodium carbonate or potassium carbonate or sodium bicarbonate, or alkali metal alcoholates, such as sodium methanolate, sodium ethanolate, potassium methanolate, potassium ethanolate or potassium tert-butanolate. Potassium carbonate and sodium hydroxide are particularly preferred.

In carrying out the cyclization, the base is in general employed in an amount of 2 to 6 mol, preferably 3 to 5 mol, per mole of the compounds of the formula (II).

The cyclization is in general carried out in a temperature range from 0°C to 160°C, preferably at the boiling point of the particular solvent.

The cyclization is in general carried out under normal pressure. However, it is also possible to carry out the process under increased pressure or under reduced pressure (for example in a range from 0.5 to 5 bar).

The chlorosulphonation is carried out either without a solvent or in the presence of one of the abovementioned inert solvents.

The preparation of the sulphonamides is in general carried out in one of the abovementioned solvents, preferably in tetrahydrofuran or methylene chloride.

The chlorosulphonation and the amidation are in general carried out in a temperature range from -20°C to +80°C, preferably -10°C to +30°C, under normal pressure.

Suitable bases for this are, in addition to the abovementioned bases, preferably in some cases triethylamine and/or dimethylaminopyridine, DBU or DABCO. It is also possible for the amine employed to be used in excess.

The base is employed in an amount of 0.5 mol to 10 mol, preferably 1 mol to 3 mol per mole of the corresponding chlorosulphonic acid.

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The alkylation is in general carried out with alkylating agents, such as, for example, (C₁-C₁₀)-alkyl halides, sulphonic acid esters or substituted or unsubstituted (C₁-C₁₀)-dialkyl- or (C₁-C₁₀)-diarylsulphonates, preferably methyl iodide or dimethyl sulphate.

5 Suitable solvents for the alkylation are likewise the customary organic solvents which do not change under the reaction conditions. These include, preferably, ethers, such as diethyl ether, dioxane, tetrahydrofuran or glycol dimethyl ether, or hydrocarbons, such as benzene, toluene, xylene, hexane, cyclohexane or petroleum fractions, or halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethylene, trichloroethylene or chlorobenzene, or ethyl acetate, 10 dimethylformamide, hexamethylphosphoric acid triamide, acetonitrile or acetone. It is also possible to use mixtures of the solvents mentioned. Methylene chloride is preferred.

The alkylation is carried out in the abovementioned solvents at temperatures from 0°C to +150°C, preferably at room temperature to +100°C, under normal pressure.

15 The amino-protecting groups are split off in a manner known per se under acid or basic conditions, or reductively by catalytic hydrogenation, for example with Pd/C in organic solvents, such as ethers, for example tetrahydrofuran or dioxane, or alcohols, for example methanol, ethanol or isopropanol.

20 The hydroxyl-protecting group is split off from the corresponding esters by customary hydrolytic methods.

The reaction with alkyl sulphonic acid chlorides is carried out, starting from the corresponding free hydroxy compounds, in one of the abovementioned solvents and one of the bases, preferably with methylene chloride and triethylamine in a temperature range from -20°C to +20°C, preferably 0°C, under normal pressure.

25 The introduction of the azide radical is in general carried out by reaction of the corresponding alkylsulphonyloxy-substituted compounds with sodium azide in one of the abovementioned solvents, preferably dimethylformamide, in a temperature range

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from 50°C to +120°C, preferably 100°C, under normal pressure.

The reduction of azido-substituted compounds to give the corresponding free amines is in general carried out by hydrogenation in one of the abovementioned alcohols, preferably methanol, with hydrogen in the presence of a palladium catalyst, preferably Pd/C, in a temperature range from 0°C to +50°C, preferably 25°C.

The hydrogenation is in general carried out under normal pressure.

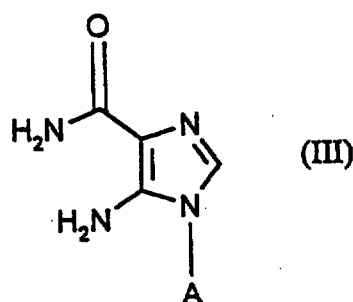
The acylations are carried out, starting from the corresponding free amino or hydroxy compounds, in one of the abovementioned solvents, preferably methylene chloride, and in the presence of one of the abovementioned bases, preferably triethylamine, with addition of dimethylaminopyridine (DMAP), in a temperature range from 0°C to +80°C, preferably at +20°C to +40°C, under normal pressure.

The ketones are prepared by known methods (Swern oxidation) starting from the corresponding hydroxy compounds.

The oxime formation is in general carried out by reaction of the corresponding ketone with hydroxylamines in one of the abovementioned alcohols, preferably methanol, at the reflux temperature under normal pressure.

The enantiomerically pure compounds are accessible by customary methods, for example by chromatography or the racemic compounds of the general formula (I) on chiral phases.

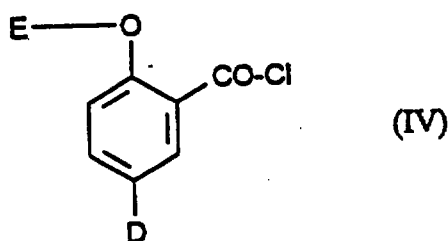
The compounds of the general formula (II) are known in some cases or are new and can be prepared by a procedure in which compounds of the general formula (III)



in which

A has the abovementioned meaning,

are reacted with 2-n-alkoxybenzoic acid chlorides of the general formula (IV)



in which

5 D and E have the abovementioned meaning,

in inert solvents and in the presence of a base.

Suitable solvents are the abovementioned solvents, toluene and tetrahydrofuran being preferred.

10 Suitable bases are in general alkali metal hydrides or alcoholates, such as, for example, sodium hydride or potassium tert-butyrate, or cyclic amines, such as, for example, piperidine, pyridine, dimethylaminopyridine or C₁-C₄-alkylamine, such as, for example, triethylamine. Sodium hydride, pyridine and dimethylaminopyridine are preferred.

The base is in general employed in an amount of 1 mol to 4 mol, preferably 1.2 mol to 3 mol, in each case per mole of the compounds of the general formula (III).

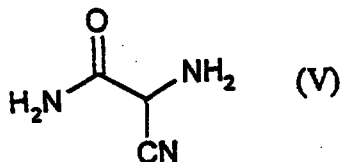
5 The reaction temperature can in general be varied within a relatively wide range. The reaction is in general carried out in a range from -20°C to 200°C , preferably 0°C to 25°C .

In one variant, the reaction is carried out in pyridine, to which a catalytic amount of DMAP is added. If appropriate, toluene can also be added.

The compounds of the general formula (IV) are known per se.

10 The compounds of the general formula (III) are new in most cases and can be prepared, for example, by a procedure in which

2-amino-2-cyanoacetamide of the formula (V)



is reacted with compounds of the general formula (VI)



in which

A has the abovementioned meaning,

15 in inert solvents in the presence of triethyl orthoformate.

Suitable solvents for the individual steps of the processes are the customary organic solvents which do not change under the reaction conditions. These include, preferably,

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ethers, such as diethyl ether, dioxane, tetrahydrofuran or glycol dimethyl ether, or hydrocarbons, such as benzene, toluene, xylene, hexane, cyclohexane or petroleum fractions, or halogenated hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethylene, trichloroethylene or chlorobenzene, or ethyl acetate, dimethylformamide, hexamethylphosphoric acid triamide, acetonitrile, acetone or dimethoxyethane. It is also possible to use mixtures of the solvents mentioned. Acetonitrile is particularly preferred.

The process according to the invention is in general carried out in a temperature range from 0°C to +180°C, preferably +30°C to +150°C.

10 The process steps according to the invention are in general carried out under normal pressure. However, it is also possible to carry out the process steps under increased pressure or under reduced pressure (for example in a range from 0.5 to 5 bar).

The compound of the formula (V) is known [cf. Logemann, G. Shaw, Chemistry and Industry, 1980 (13), 541-542].

15 The amines of the general formula (VI) are known in some cases or are new and they can then be prepared by known methods [cf. L.R. Krepski et al., Synthesis, 1986, 301-303].

The compounds of the general formula (I) according to the invention display an unfetterable, valuable pharmacological action spectrum.

20 They inhibit either one or more of the cGMP-metabolizing phosphodiesterases (PDE I, PDE II and PDE V). This leads to a different increase in cGMP. An increase in the cGMP level can lead to an antithrombotic, vasodilatory, antiarrhythmic and/or anti-inflammatory action. The selectivity is also determined by the distribution of the isoenzymes in the tissue.

25 The compounds according to the invention furthermore intensify the action of substances, such as, for example, EDRF (endothelium-derived relaxing factor) and ANP

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(atrial natriuretic peptide), which increase the cGMP level.

They can therefore be employed in medicaments for treatment of inflammatory diseases, such as, for example, asthma, inflammatory dermatoses, for treatment of high blood pressure, stable and unstable angina, peripheral and cardiac vascular diseases and of arrhythmias, for treatment of thromboembolic diseases and ischaemias, such as myocardial infarction, cerebral stroke, transitory and ischaemic attacks, angina pectoris, peripheral circulatory disturbances, prevention of restenoses, such as after thrombolysis treatment, percutaneous transluminal angioplasties (PTA) and bypass, percutaneous transluminal coronary angioplasties (PTCA), bypass, septic shock and diseases of the urogenital system, such as, for example prostate hypertrophy, impotence and incontinence.

Activity of the phosphodiesterases (PDE's)

The cGMP-stimulatable PDE II, the cGMP-inhibitable PDE III and the cAMP-specific PDE IV were isolated from either the porcine or the bovine myocardium. The Ca-calmodulin-stimulatable PDE I was isolated from porcine aorta or porcine brain. The cGMP-specific PDE V was obtained from porcine small intestine, porcine aorta and/or human blood platelets. Purification was carried out by anion exchange chromatography on MonoQ^R Pharmacia essentially by the method of M. Hoey and Miles D. Houslay, Biochemical Pharmacology, Volume 40, 193-202 (1990).

The enzyme activity is determined in a test batch of 100 µl in 20 mM Tris/HCl buffer of pH 7.5 which contains 5 mM MgCl₂, 0.1 mg/ml of bovine serum albumin and either 800 Bq of ³HcAMP or ³HcGMP. The final concentration of the corresponding nucleotides is 10⁻⁶ mol/l. The reaction is started by addition of the enzyme and the amount of enzyme is chosen such that about 50% of the substrate is reacted during the incubation time of 30 minutes. In order to test the cGMP-stimulatable PDE II, ³HcAMP is used as the substrate and 10⁻⁶ mol/l of non-labelled cGMP is added to the batch. In order to test the Ca-calmodulin-dependent PDE I, 1 µM CaCl₂ and 0.1 µM calmodulin are also added to the reaction batch. The reaction is stopped by addition of 100 µl of acetonitrile which contains 1 mM cAMP and 1 mM AMP. 100 µl of the reaction batch

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are separated on the HPLC and the cleavage products are determined quantitatively "on line" with a flow-through scintillation counter. The substance concentration at which the rate of reaction is reduced by 50% is measured.

Inhibition of the phosphodiesterases in vitro

Example No.	PDE I IC ₅₀ [μM]	PDE II IC ₅₀ [μM]	PDE V IC ₅₀ [μM]
3	50	6	0.1
4	2	1	5
5	1	0.5	2
11	0.5	0.3	0.5
37	2	2	1
57	0.3	0.3	0.1

The antihypertensive activity was measured after intravenous administration to SHR rats.

To determine the cyclic nucleotides, heart and aorta tissue was removed and deep-frozen immediately. The samples were powdered under liquid N₂ and extracted with 70% ethanol and the content of cGMP and cAMP was determined using commercial radioimmunoassays (Amersham).

The erection-inducing action was measured on anaesthetized rabbits (C.G. Stief et al., World Journal Urology 1990, pages 233-236).

The substances were administered in dosages of 0.1 to 10 mg/kg either directly into the corpus cavernosum or intraduodenally, rectally, orally, transdermally or intravenously.

The new active compounds can be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions,

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suspensions and solutions, using inert, non-toxic, pharmaceutically suitable carriers or solvents. The therapeutically active compound should in each case be present here in a concentration of about 0.5 to 90% by weight of the total mixture, i.e. in amounts which are sufficient to achieve the stated dosage range.

- 5 The formulations are prepared, for example, by extending the active compounds with solvents and/or carriers, if appropriate using emulsifying agents and/or dispersing agents, and in the case where water is used as the diluent, for example, organic solvents can be used as auxiliary solvents if appropriate.

10 The formulations are administered in the customary manner, preferably orally, parenterally, transdermally, perlingually or intravenously.

In general, it has proved advantageous in the case of intravenous administration to administer amounts of about 0.01 to 10 mg/kg, preferably about 0.1 to 10 mg/kg of body weight to achieve effective results.

- 15 Nevertheless, it may be necessary, if appropriate, to deviate from the amounts mentioned, and in particular as a function of the body weight or the nature of the administration route, of the behaviour of the individual towards the medicament, of the nature of the formulation thereof and of the time or interval at which administration takes place. Thus, in some cases it may be sufficient to manage with less than the above-mentioned minimum amount, while in other cases the upper limit mentioned must
20 be exceeded. In the case of administration of relatively large amounts, it may be advisable to divide these into several individual doses over the course of the day.

Starting compounds

General working instructions for the preparation of 1-substituted 5-(2-n-alkoxy-benzoylamino)-imidazole-4-carboxamides of the formula (IV)

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Method A:

10 mmol of 1-substituted 5-amino-imidazole-4-carboxamide and 15 mmol of NaH (if one of the abovementioned radicals R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 or R^8 contains a hydroxyl group, 30 mmol of NaH are employed) are stirred in 50 ml of absolute tetrahydrofuran at 20°C for 3 hours (in the case of sparingly soluble imidazoles, the mixture is refluxed for up to 12 hours). 10 mmol of 2-n-alkoxybenzoic acid chloride (or 20 mmol if a hydroxyl group is present) in 25 ml of absolute tetrahydrofuran are added dropwise at 20°C and the mixture is stirred at room temperature overnight. It is evaporated, the residue is taken up in ethyl acetate and the mixture is extracted by shaking with water. The organic phase is dried over Na_2SO_4 and evaporated and the residue is purified by recrystallization or flash chromatography.

If the 5-amino-imidazole-4-carboxamide contains a free hydroxyl group in the radicals R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 or R^8 , this is in the form of the 2-n-alkoxybenzoic acid ester, which can be hydrolysed by the known method (1 N NaOH, CH_3OH). However, it is also possible for the ester to be cyclized directly with NaOH as the base to give the purinones, the ester likewise being hydrolysed.

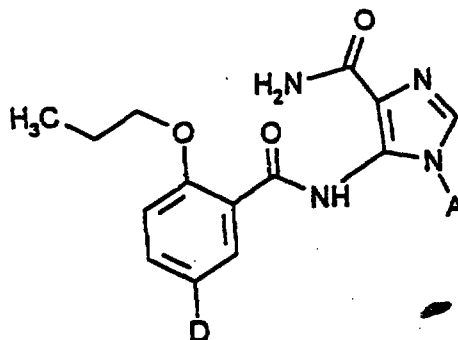
Method B:

10 mmol of 1-substituted 5-amino-imidazole-4-carboxamide and 50 mg of DMAP are initially introduced into 20 ml of dry pyridine at room temperature. A solution of 10 mmol of n-alkoxybenzoic acid chloride in 10 ml of absolute toluene is added dropwise and the mixture is stirred at room temperature until, in the thin-layer chromatogram, the reaction has ended (30 minutes to 16 hours). The precipitate is filtered off and the solvent is removed in a rotary evaporator in vacuo. The residue is taken up in 30 ml of methylene chloride and the mixture is washed with 30 ml of 1 N HCl and 30 ml of H_2O . After drying over Na_2SO_4 , the mixture is evaporated in vacuo and the residue is purified by flash chromatography or recrystallization.

The 1-substituted 5-(2-n-alkoxybenzoylamino)-imidazole-5-carboxamides listed in Table 1 are prepared in accordance with these instructions:

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Table 1:

Example No.	A	D	Yield (% of theory)	Melting point (°C)/R _f
I		H	41	
II		H	38	
III		H	52	
IV		H	57	
V		H	11	104 (ether)
VI		H	12	

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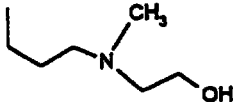
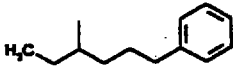
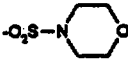
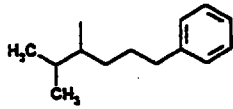
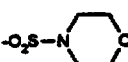
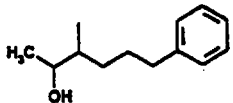
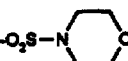
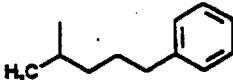
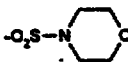
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Example No.	A	D	Yield (% of theory)	Melting point (°C)/R _f
VII		H	41	
VIII		H	30	
IX		H	26.6	
X		H	46	
XI		H	30	
XII		H	50	
XIII		H	26	
XIV		H	27	
XV		H	41	
XVI		H	8	

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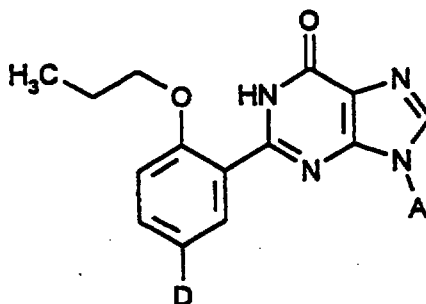
Example No.	A	D	Yield (% of theory)	Melting point (°C)/R _f
XVI		H	8	
XVII			27	
XVIII			33	
XIX			53	
XX			38	

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Preparation examples

General working instructions for 9-substituted 2-(2-n-alkoxyphenyl)purin-6-ones of the general formula (I)



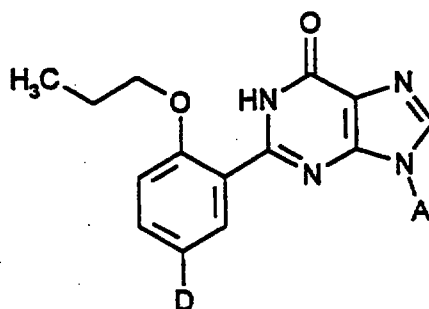
- 10 mmol of the 1-substituted 5-(2-n-alkoxybenzoylamino)-imidazole-4-carboxamide (IV) and 40 mmol of K_2CO_3 are refluxed overnight in a mixture of 100 ml of ethanol and 50 ml of water. The solvent is distilled off in vacuo, the residue is taken up in ethyl acetate and the mixture is extracted twice by shaking with water. After the organic phase has been dried with sodium sulphate, it is evaporated and the residue is purified by recrystallization or flash chromatography.
- 10 The compounds listed in Table II are prepared in accordance with these instructions:

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Table II:

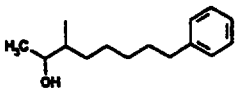
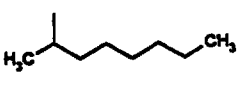
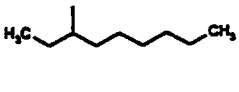
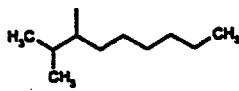
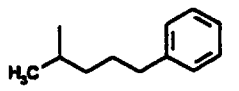
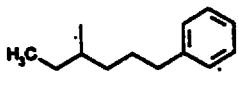
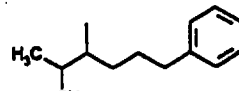
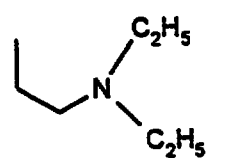
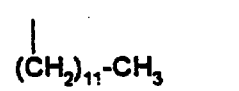
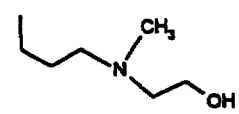
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Example No.	A	D	Yield (% of theory)	Melting point (°C)/R _f
1		H	63	186
2		H	87	0.33 a)
3		H	67	113
4		H	39	82
5		H	51	104
6		H	27	68

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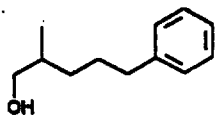
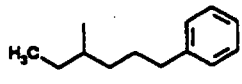
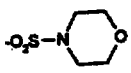
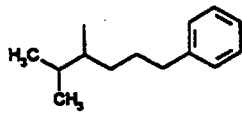
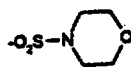
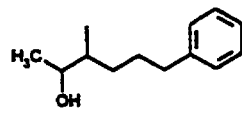
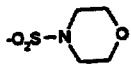
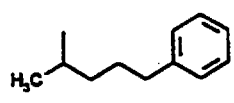
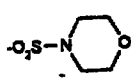
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Example No.	A	D	Yield (% of theory)	Melting point (°C)/R _f
7		H	31	91
8		H	75	0.58 a)
9		H	54	0.6 a)
10		H	58	0.44 a)
11		H	95	0.54 a)
12		H	71	0.58 a)
13		H	63	0.59 a)
14		H	50	143
15		H	42	80
16		H	56	188

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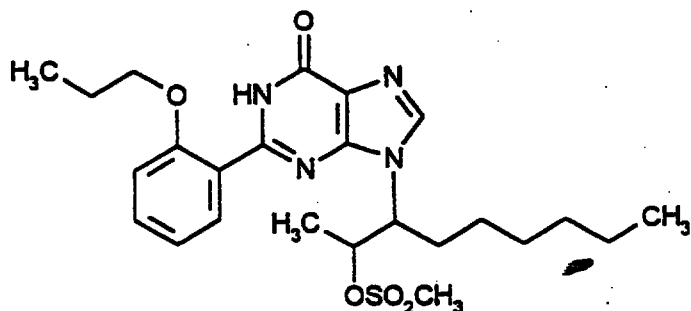
Example No.	A	D	Yield (% of theory)	Melting point (°C)/R _f
17		H	23	0.33 a)
18			80	165
19			33	0.44 b)
20			25	172
21			57	170

a) Mobile phase: CH₂Cl₂/MeOH 10:1

b) Mobile phase: toluene/acetone 1:1

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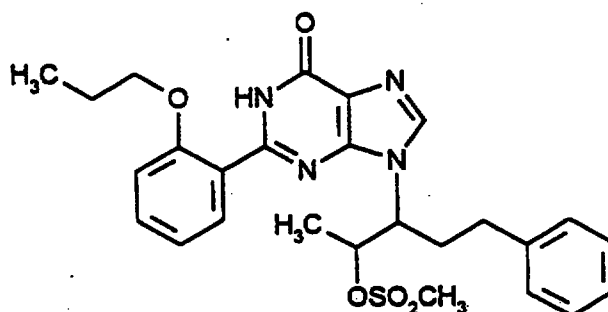
Date: 1 8 MAY 1996

Example 22**9-(2-Methanesulphonyloxy-3-nonyl)-2-(2-n-propoxy-phenyl)-purin-6-one**

412 mg (1 mmol) of 9-(2-hydroxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 3) are cooled to 0°C in 10 ml of CH₂Cl₂. After addition of 0.5 ml of triethylamine, 138 mg (1.2 mmol) of methanesulphonyl chloride in 2 ml of CH₂Cl₂ are added dropwise and the mixture is subsequently stirred for 30 minutes. It is poured onto 20 ml of ice-water, the organic phase is separated off and the aqueous phase is extracted once more with 20 ml of CH₂Cl₂. The combined CH₂Cl₂ phases are dried over Na₂SO₄ and evaporated in vacuo and the oily residue is crystallized by trituration with ether.

Melting point: 158°C

Yield: 380 mg (81%)

Example 23**9-(2-Methanesulphonyloxy-5-phenyl-3-pentyl)-2-(2-n-propoxyphenyl)-purin-6-one**

The title compound is prepared analogously to the instructions of Example 22, starting

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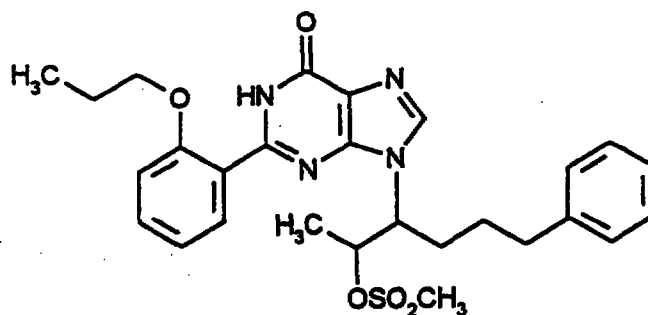
from 9-(2-hydroxy-5-phenyl-3-methyl)-2-(2-n-propoxyphenyl)purin-6-one (Example 4).

$R_f = 0.52$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 95.3%

Example 24

5 9-(2-Methanesulphonyloxy-6-phenyl-3-hexyl)-2-(2-n-propoxyphenyl)-purin-6-one



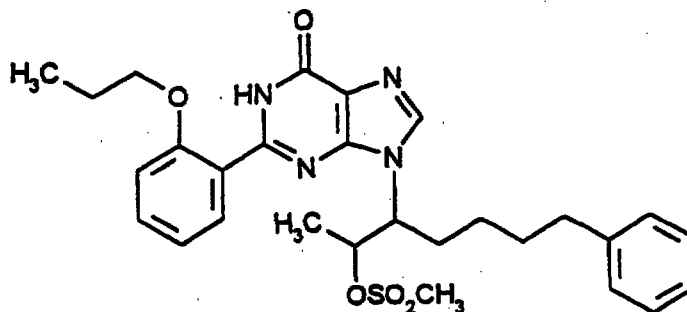
The title compound is prepared analogously to the instructions of Example 22, starting from 9-(2-hydroxy-6-phenyl-3-hexyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 5).

$R_f = 0.52$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 82.7%

10 Example 25

9-(2-Methanesulphonyloxy-7-phenyl-3-heptyl)-2-(2-n-propoxyphenyl)-purin-6-one



The title compound is prepared analogously to the instructions of Example 22, starting from 9-(2-hydroxy-7-phenyl-3-heptyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 6).

$R_f = 0.55$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

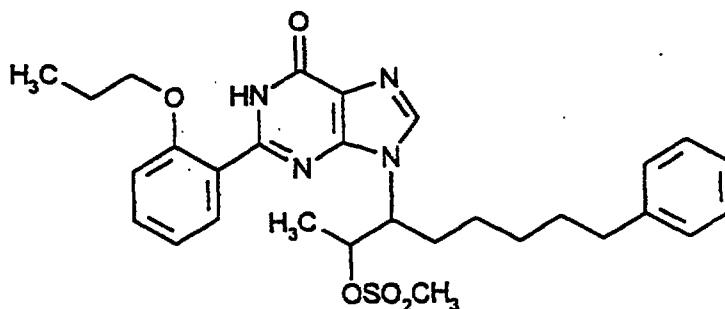
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Yield: 90.3%

Example 26

9-(2-Methanesulphonyloxy-8-phenyl-3-octyl)-2-(2-n-propoxyphenyl)-purin-6-one



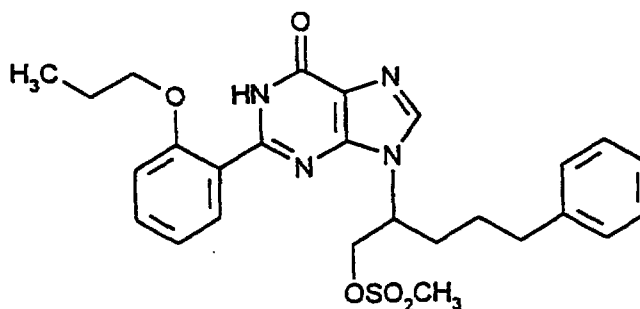
The title compound is prepared analogously to the instructions of Example 22, starting from 9-(2-hydroxy-8-phenyl-3-octyl)-2-(2-n-propoxyphenyl)-purin-7-one (Example 7).

$R_f = 0.58$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 89%

Example 27

9-(1-Methanesulphonyloxy-5-phenyl-2-pentyl)-2-(2-n-propoxyphenyl)-purin-6-one



The title compound is prepared analogously to the instructions of Example 22, starting from 9-(1-hydroxy-5-phenyl-3-pentyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 17).

$R_f = 0.49$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

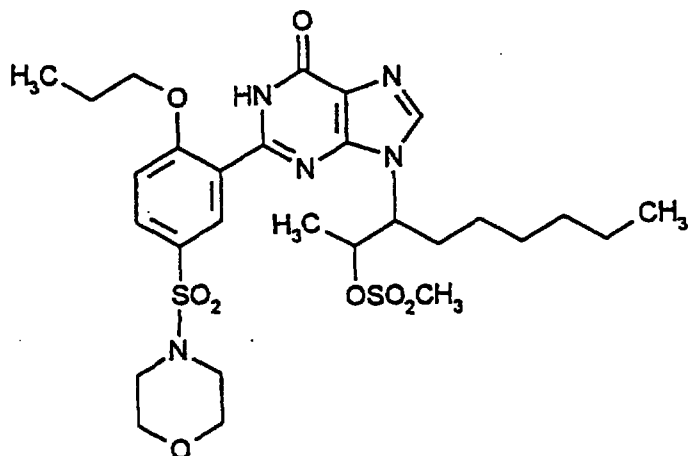
Yield: 28.5%

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Example 28

9-(2-Methanesulphonyloxy-3-nonyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one



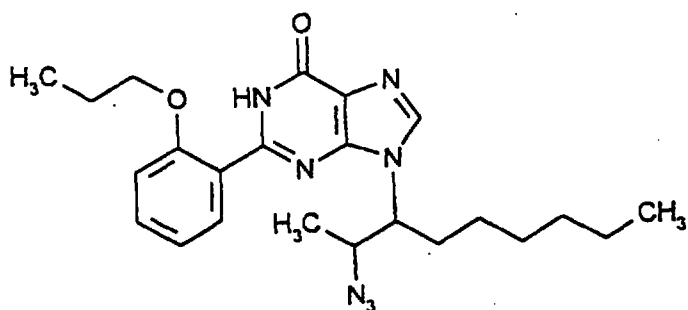
The title compound is prepared analogously to the instructions of Example 22, starting from 9-(2-hydroxy-3-nonyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one (Example 20).

$R_f = 0.48$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 51.4%

Example 29

9-(2-Azido-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



474 mg (1. mmol) of 9-(2-methanesulphonyloxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 22) and 78 mg (1.2 mmol) of sodium azide are stirred in 5 ml of dimethylformamide at 100°C for 6 hours (monitoring by thin-layer chromatography).

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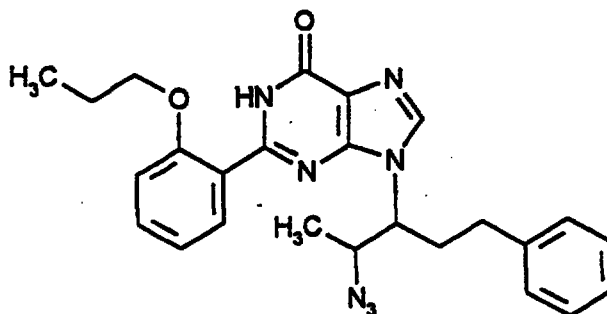
After cooling, 20 ml of ethyl acetate are added and the mixture is extracted by shaking 3 times with 50 ml of water each time and once with 50 ml of saturated NaCl solution. After drying over Na_2SO_4 , the organic phase is evaporated in vacuo and the residue is purified by flash chromatography (eluent: toluene/acetone 4:1).

5 $R_f = 0.64$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 369 mg (88.4%)

Example 30

9-(2-Azido-5-phenyl-3-pentyl)-2-(2-n-propoxy-phenyl)-purin-6-one



10 The title compound is prepared analogously to the instructions of Example 29, starting from 9-(2-methanesulphonyloxy-5-phenyl-3-pentyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 23).

$R_f = 0.54$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

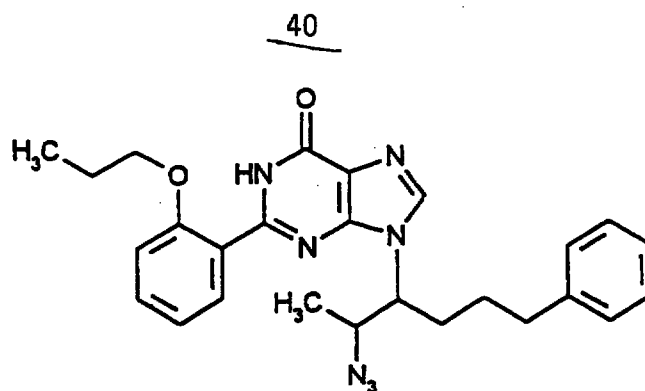
Yield: 87.4%

Example 31

15 9-(2-Azido-6-phenyl-3-hexyl)-2-(2-n-propoxyphenyl)-purin-6-one

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The title compound is prepared analogously to the instructions of Example 29, starting from 9-(2-methanesulphonyloxy-6-phenyl-3-hexyl)-2-(2-n-propoxyphenyl)-purin-6-one

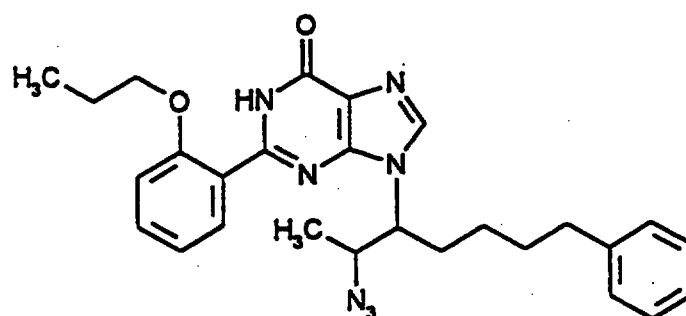
(Example 24).

5 $R_f = 0.55$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 74.9%

Example 32

9-(2-Azido-7-phenyl-3-heptyl)-2-(2-n-propoxyphenyl)-purin-6-one



10 The title compound is prepared analogously to the instructions of Example 29, starting from 9-(2-methanesulphonyloxy-7-phenyl-3-heptyl)-2-(2-n-propoxyphenyl)-purin-6-one

(Example 25).

$R_f = 0.6$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

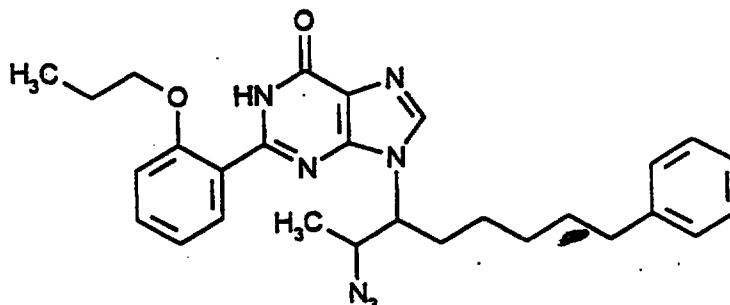
Yield: 67%

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Example 33

9-(2-Azido-8-phenyl-3-octyl)-2-(2-n-propoxyphenyl)-purin-6-one



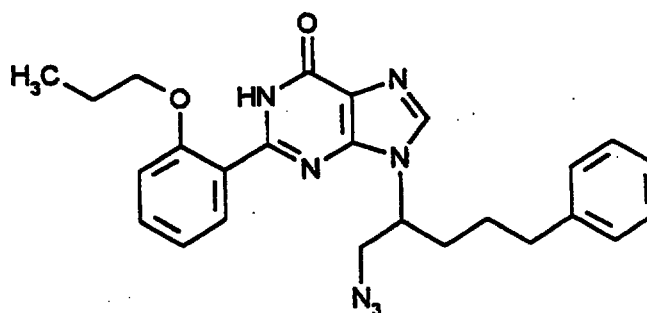
The title compound is prepared analogously to the instructions of Example 29, starting from 9-(2-methanesulphonyloxy-8-phenyl-3-octyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 26).

$R_f = 0.61$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 88%

Example 34

9-(1-Azido-5-phenyl-2-pentyl)-2-(2-n-propoxyphenyl)-purin-6-one



The title compound is prepared analogously to the instructions of Example 29, starting from 9-(1-methanesulphonyloxy-5-phenyl-2-pentyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 27).

$R_f = 0.56$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1).

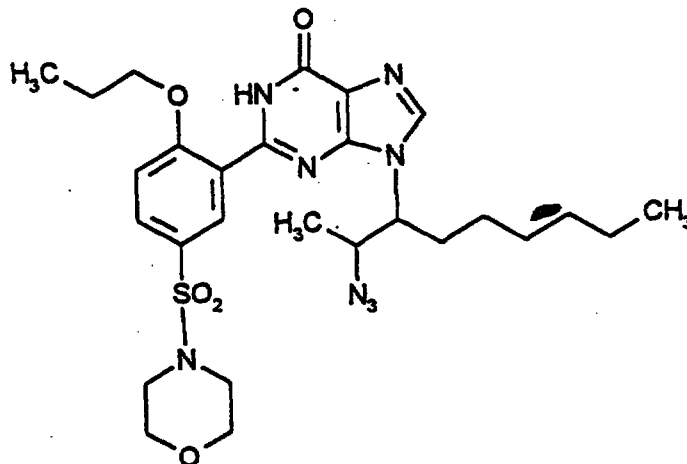
Yield: 98%

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Example 35

9-(2-Azido-3-nonyl)-2-(2-n-propoxy-5-morpholinesulphonyl-phenyl)-purin-6-one



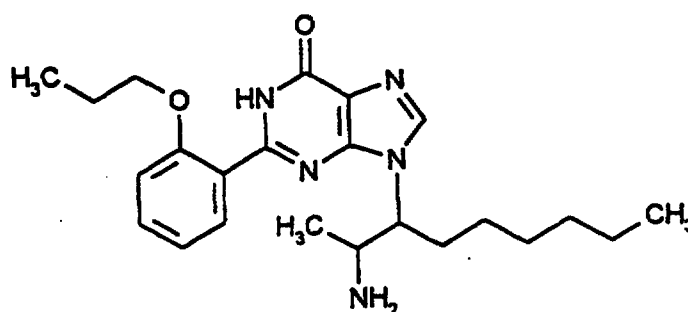
The title compound is prepared analogously to the instructions of Example 29, starting from 9-(2-methanesulphonyloxy-3-nonyl)-2-(2-n-propoxy-5-morpholinesulphonyl-phenyl)-purin-6-one (Example 28).

$R_f = 0.55$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 38%

Example 36

9-(2-Amino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



10 5.3 g (12.13 mmol) of 9-(2-azido-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 29) are hydrogenated in 70 ml of absolute methanol in the presence of 0.1 g of Pd/C (10%) with hydrogen under normal pressure at room temperature. After 4

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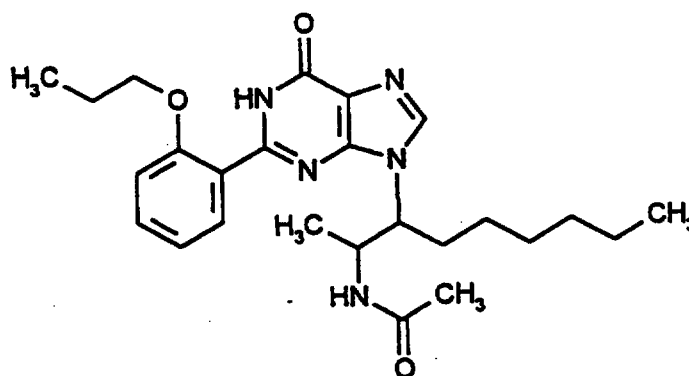
hours, the catalyst is filtered off, the solvent is distilled off in vacuo and the residue is purified by flash chromatography over silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 20:1).

$R_f = 0.28$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 4.1 g (82.3%)

5 Example 37

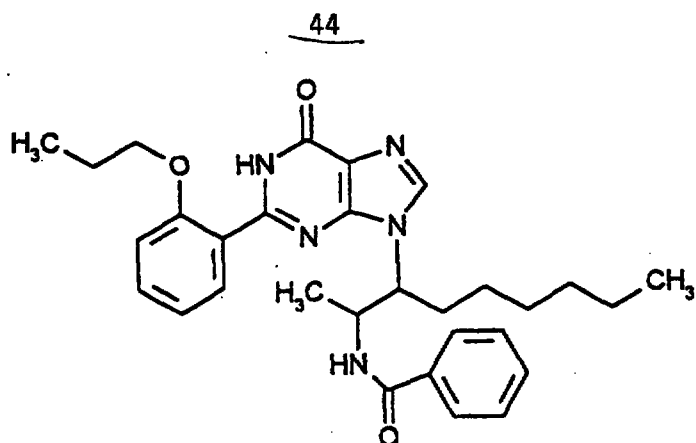
9-(2-Acetamido-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



- 210 mg (0.5 mmol) of 9-(2-amino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 36) are dissolved in 20 ml of absolute CH_2Cl_2 . 101 mg (1 mmol) of triethylamine are added at room temperature, and 78 mg (1 mmol) of acetyl chloride in 2 ml of absolute CH_2Cl_2 are then added dropwise. After 1 hour at room temperature, the organic phase is extracted by shaking with 10 ml of 2 N HCl and with 10 ml of saturated NaHCO_3 solution. After the organic phase has been dried over Na_2SO_4 , the solvent is evaporated in vacuo and the residue is purified by flash chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 40:1).
- 15 $R_f = 0.37$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)
Yield: 174 mg (77%)

Example 38

9-(2-Benzoylamino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



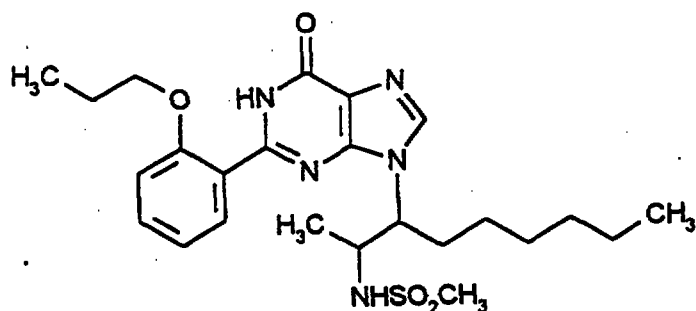
The title compound is prepared analogously to the instructions of Example 37 starting from 9-(2-amino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 36) and benzoyl chloride.

Melting point: 184°C (toluene)

5 Yield: 59%

Example 39

9-(2-Methylsulphonylamino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



The title compound is prepared analogously to the instructions of Example 37, starting from 9-(2-amino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 36) and methylsulphonyl chloride.

$R_f = 0.46$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 78.2%

10

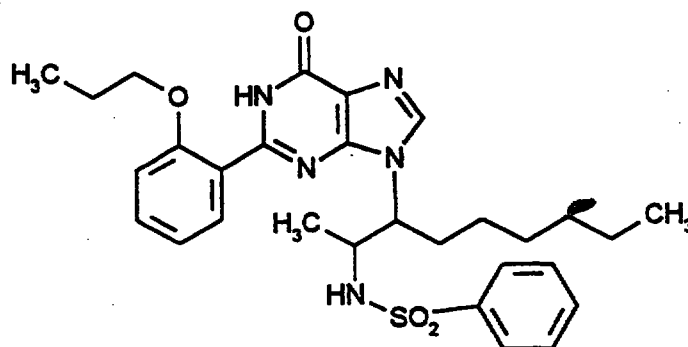
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Example 40

9-(2-Phenylsulphonylamino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



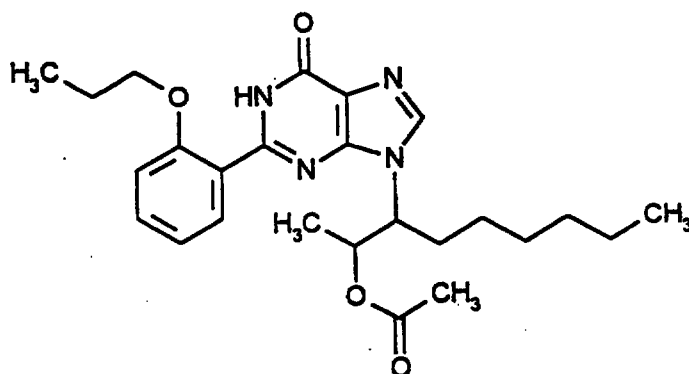
The title compound is prepared analogously to the instructions of Example 37, starting from 9-(2-amino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 36) and phenylsulphonyl chloride.

Melting point: 112°C (toluene/ether)

Yield: 62.9%

Example 41

9-(2-Acetoxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



206 mg (0.5 mmol) of 9-(2-hydroxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 3), 47 mg (0.6 mmol) of acetyl chloride, 47 mg (0.6 mmol) of pyridine and 5 mg of DMAP are stirred in 10 ml of absolute CH_2Cl_2 at 25°C for 1 hour and then

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at 40°C for 1 hour. The mixture is extracted by shaking twice with 10 ml of 2 N HCl solution each time and twice with 10 ml of saturated NaHCO₃ solution each time and washed once with saturated NaCl solution. After the organic phase has been dried over Na₂SO₄, the solvent is evaporated in vacuo and the residue is dried under a high vacuum.

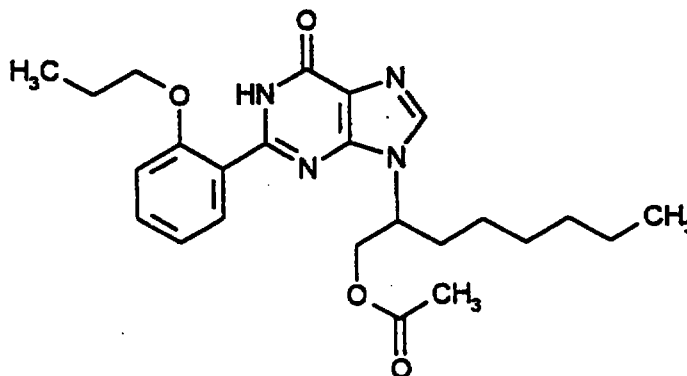
5

$R_f = 0.53$ (CH₂Cl₂/CH₃OH 100:1)

Yield: 90.5%

Example 42

9-(1-Acetoxy-2-octyl)-2-(2-n-propoxyphenyl)-purin-6-one



- 10 The title compound is prepared analogously to the instructions of Example 41, starting from 9-(1-hydroxy-2-octyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 2).

$R_f = 0.52$ (CH₂Cl₂/CH₃OH 100:1)

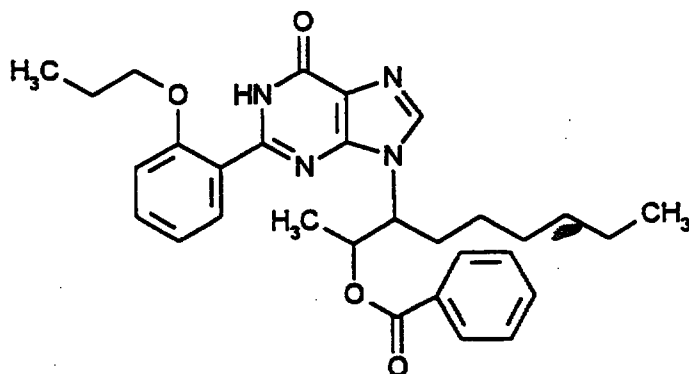
Yield: 88.5%

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Example 43

9-(2-Benzoyloxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



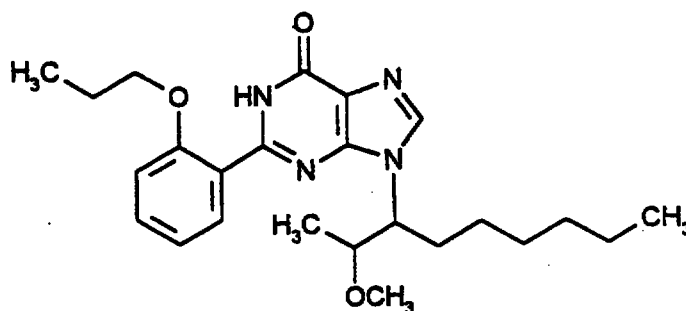
The title compound is prepared analogously to the instructions of Example 41, starting from 9-(2-hydroxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 3) and benzoyl chloride.

$R_f = 0.57$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 100:1)

Yield: 89%

Example 44

9-(2-Methoxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



48 mg of 60% strength NaH (1.2 mmol) are suspended in 2 ml of absolute tetrahydrofuran at 20°C. 206 mg (0.5 mmol) of 9-(2-hydroxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 3) in 3 ml of absolute tetrahydrofuran are added dropwise. After 15 minutes at 20°C, 85 mg (0.6 mmol) of methyl iodide in 3 ml of

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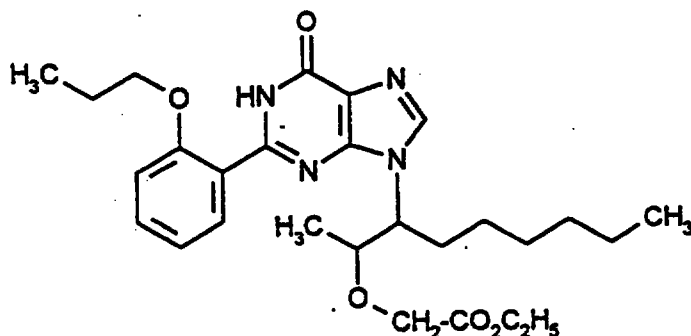
absolute tetrahydrofuran are added dropwise and the mixture is stirred overnight at 20°C. The solvent is removed on a rotary evaporator in vacuo, the residue is taken up in 10 ml of ethyl acetate and the mixture is washed with 20 ml of water. After the organic phase has been dried with Na₂SO₄, it is evaporated on a rotary evaporator and the product is purified by column chromatography (eluent: toluene/acetone 5:1).

$R_f = 0.58$ (CH₂Cl₂/CH₃OH 100:1)

Yield: 74.2%

Example 45

9-(2-Ethoxycarbonylmethyleneoxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



10 The title compound is prepared analogously to the instructions of Example 44 starting from 9-(2-hydroxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 3) and ethyl bromoacetate.

$R_f = 0.55$ (CH₂Cl₂/CH₃OH 100:1)

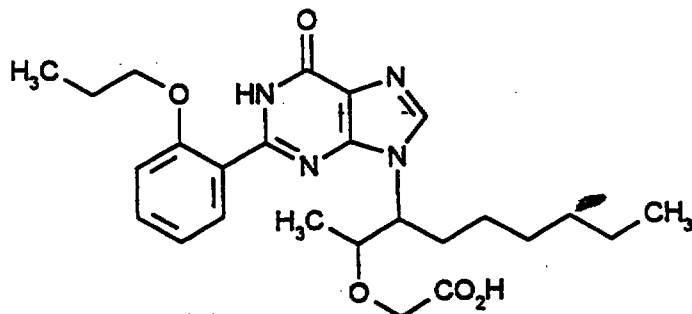
Yield: 85.8%

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Example 46

9-(2-Carboxymethyleneoxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



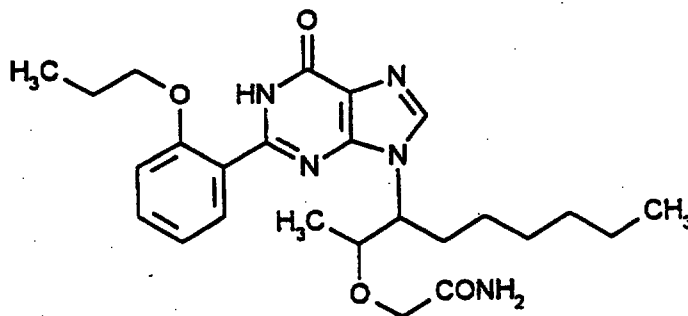
- 498 mg (1 mmol) of the ester from Example 45 are stirred in 4 ml of 1 N NaOH and 5 ml of MeOH at 20°C for 1 hour. The methanol is distilled off in vacuo. After addition of 5 ml of H₂O, the mixture is extracted by shaking with ethyl acetate. The aqueous phase is acidified with 4 ml of 2 N HCl and extracted by shaking twice with 10 ml of ethyl acetate each time. The combined ethyl acetate phases are dried over Na₂SO₄ and evaporated.

$R_f = 0.27$ (CH₂Cl₂/CH₃OH 10:1)

- 10 Yield: 88.5%

Example 47

9-(2-Amidocarbonylmethyleneoxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



The title compound is prepared analogously to the instructions of Example 45, starting from 9-(2-hydroxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 3) and

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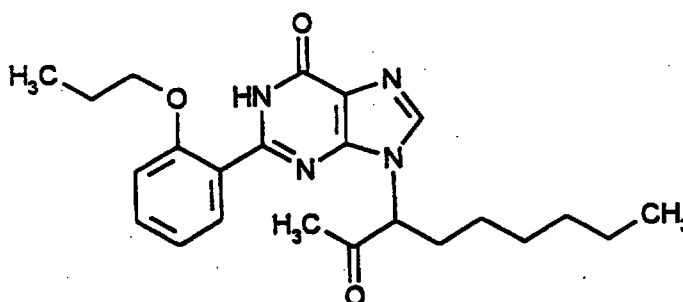
bromoacetamide.

$R_f = 0.26$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

Yield: 31.6%

Example 48

5 9-(2-Oxo-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



0.31 ml of absolute dimethyl sulphoxide (4.4 mmol) in 3 ml of absolute CH_2Cl_2 is added dropwise to 0.19 ml (2.2 mmol) of oxalyl chloride in 5 ml of CH_2Cl_2 at -60°C in the course of 10 minutes and the mixture is subsequently stirred for 20 minutes. 824 mg (2 mmol) of 9-(2-hydroxy-3-methyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 3) in 5 ml of absolute CH_2Cl_2 are then added dropwise in the course of 45 minutes and the mixture is subsequently stirred at -60°C for 1 hour. 1.39 ml (10 mmol) of triethylamine in 5 ml of absolute CH_2Cl_2 are added dropwise to this solution in the course of 30 minutes and the mixture is subsequently stirred at -60°C for 15 minutes. It is allowed to come to 20°C , 10 ml of H_2O are added, the phases are separated and the organic phase is washed with 20 ml of saturated NaCl solution. After the mixture has been dried over Na_2SO_4 , it is evaporated and the residue is purified by flash chromatography (eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 40:1).

Melting point: 83°C (ether/cyclohexane)

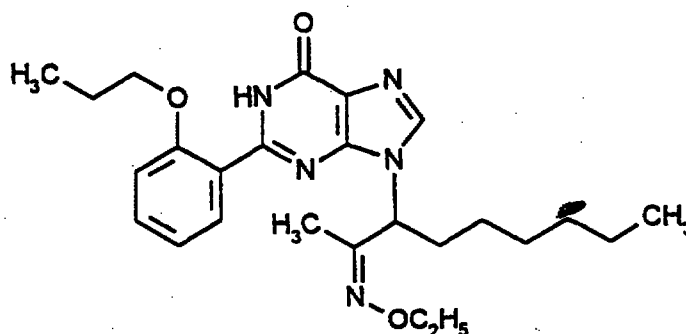
Yield: 535 mg (65.2%)

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Example 49

9-(2-Ethyloximino-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one



412 mg (1 mmol) of 9-(2-oxo-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 48) are dissolved in 10 ml of methanol, and 117 mg (1.2 mmol) of ethylhydroxylamine hydrochloride, dissolved in 1.5 ml of water, are added. The mixture is boiled under reflux for 2 hours, cooled and evaporated in vacuo. The residue is taken up in 10 ml of ethyl acetate and washed with 10 ml of saturated NaHCO_3 solution. After the organic phase has been dried with Na_2SO_4 , the solvent is distilled off in vacuo and the residue is purified by flash chromatography (eluent: toluene/acetone 4:1).

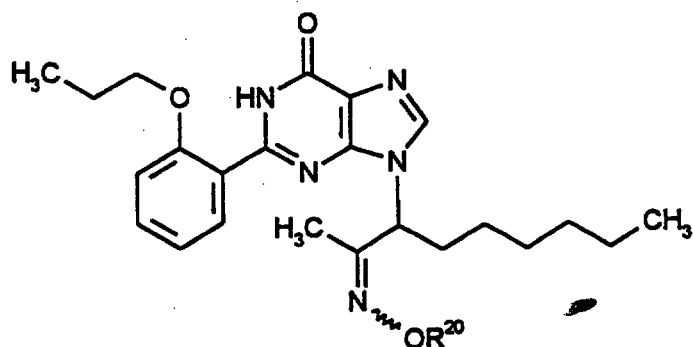
$R_f = 0.53$ (toluene/acetone 1:1)

Yield: 366 mg (80.8%)

The oximes listed in Table III are prepared in accordance with these instructions using the corresponding hydroxylamine hydrochlorides (all the oximes are in the form of cis/trans mixtures).

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Table III:

Example No.	R ²⁰	Yield (% of theory)	Melting point (°C)/R _f
50	H	69.4	111
51	C(CH ₃) ₃	79.4	0.56 a)
52	-CH ₂ -C ₆ H ₅	98.4	0.55 a)
53	$ \begin{array}{c} \text{C}_2\text{H}_5 \\ \diagup \\ \text{-CH}_2\text{CH}_2\text{-N} \\ \diagdown \\ \text{C}_2\text{H}_5 \end{array} $	70.2	0.29 b)

a) Mobile phase: toluene/acetone 1:1

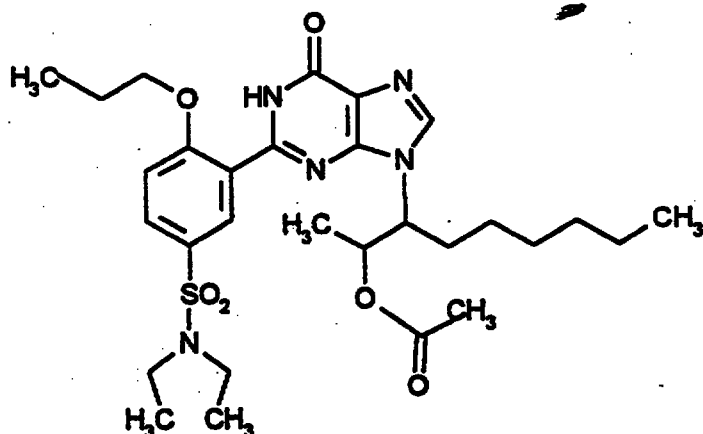
b) Mobile phase: CH₂Cl₂/MeOH 10:1

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Example 54

9-(2-Acetoxy-3-nonyl)-2-(2-n-propoxy-5-diethylaminosulphonyl-phenyl)-purin-6-one



1.28 g (2.82 mmol) of 9-(2-acetoxy-3-nonyl)-2-(2-n-propoxyphenyl)-purin-6-one (Example 41) are added in portions to 4 ml of chlorosulphonic acid at 0°C and the mixture is stirred overnight at 20°C. The batch is added dropwise to 30 ml of ice-water and the aqueous phase is extracted twice with 20 ml of ethyl acetate each time. The combined organic phases are dried over Na₂SO₄ and the solvent is distilled off in vacuo.

Yield: 0.9 g (57.8%)

10 $R_f = 0.52$ (CH₂Cl₂/CH₃OH 10:1)

The residue is taken up in 30 ml of absolute ethanol without further purification, 5.1 ml of diethylamine are added and the mixture is stirred at 25°C for 6 hours (monitoring by thin-layer chromatography). The ethanol is distilled off in vacuo, the residue is taken up in 50 ml of ethyl acetate and the mixture is washed twice with 50 ml of H₂O each time. After drying over Na₂SO₄, the organic phase is evaporated in vacuo and the residue is purified by flash chromatography (eluent: toluene/acetone 3:1).

$R_f = 0.52$ (CH₂Cl₂/CH₃OH 10:1)

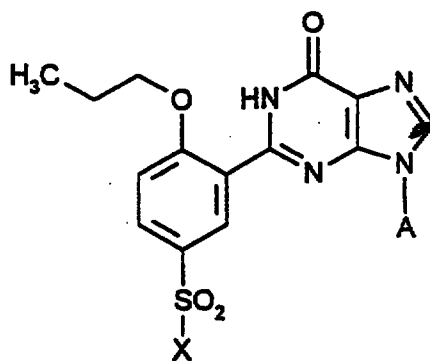
Yield: 549 mg (57.2%)

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The compounds listed in Table IV are prepared analogously to the instructions of Example 54 from the corresponding purinone and the corresponding amine:

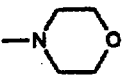
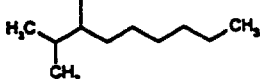
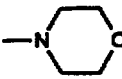
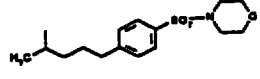
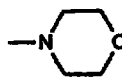
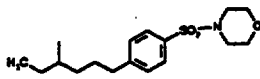
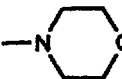
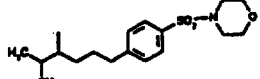
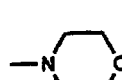
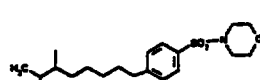
Table IV:



Example No.	X	A	Yield (% of theory)	Melting point (°C)/R _f
55			37.4	0.53 a)
56			72.3	0.58 a)
57			80.9	0.51 a)
58			78.4	0.39 a)
59			35.9	0.3 b)

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Example No.	X	A	Yield (% of theory)	Melting point (°C)/R _f
60			58	0.52 a)
61			41	0.27 b)
62			26.5	0.33 b)
63			76.3	0.35 b)
64			37	0.39 b)

a) Mobile phase: CH₂Cl₂/CH₃OH 10:1

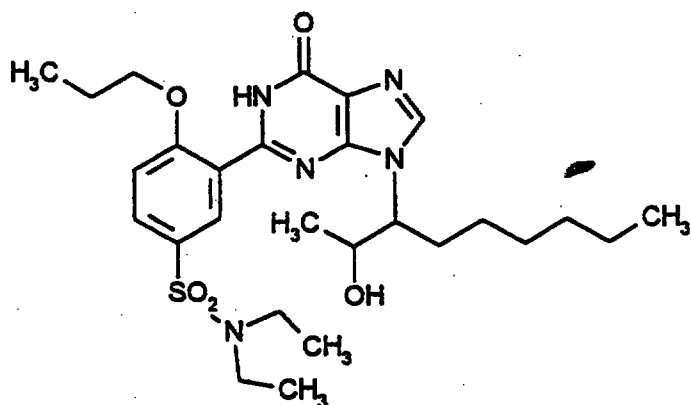
b) Mobile phase: toluene/acetone 1:1

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Example 65

9-(2-Hydroxy-3-nonyl)-2-(2-n-propoxy-5-diethylaminosulphonyl-phenyl)-purin-6-one



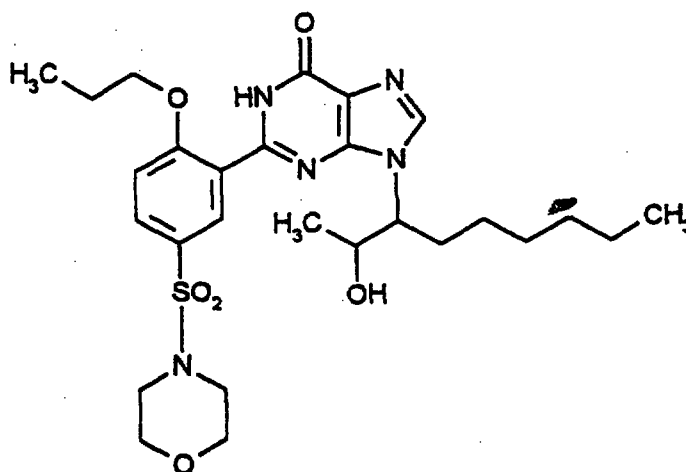
- 140 mg (0.24 mmol) of 5-(2-acetoxy-3-nonyl)-2-(2-n-propoxy-5-diethylaminosulphonyl-phenyl)-purin-6-one (Example 54) are dissolved in 5 ml of methanol. After addition of 0.5 ml of aqueous 1 N NaOH solution, the mixture is stirred at 25°C for 2 hours. 0.25 ml of aqueous 2 N HCl solution is added, the methanol is distilled off in vacuo and 10 ml of ethyl acetate and 10 ml of water are added. The organic phase is separated off, dried over Na₂SO₄ and evaporated. The residue is purified by flash chromatography (eluent: CH₂Cl₂/CH₃OH 40:1).
- $R_f = 0.47$ (CH₂Cl₂/CH₃OH 10:1)
- Yield: 112 mg (85%)

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Example 66

9-(2-Hydroxy-3-nonyl)-2-(2-n-propoxy-5-morpholinosulphonylphenyl)-purin-6-one



The title compound is prepared analogously to the instructions of Example 65, starting from (2-acetoxy-3-nonyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one (Example 55).

$R_f = 0.45$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

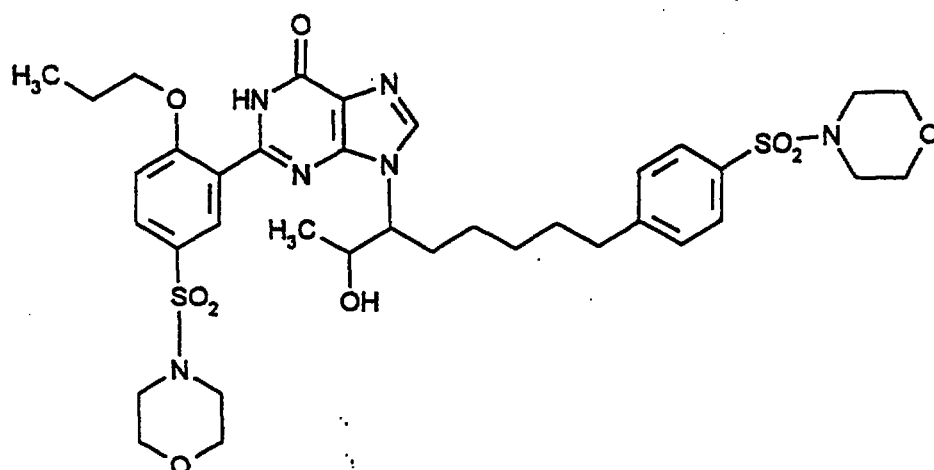
Yield: 80.6%

Example 67

9-(2-Hydroxy-8-(4-morpholinosulphonyl-phenyl)-3-octyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one

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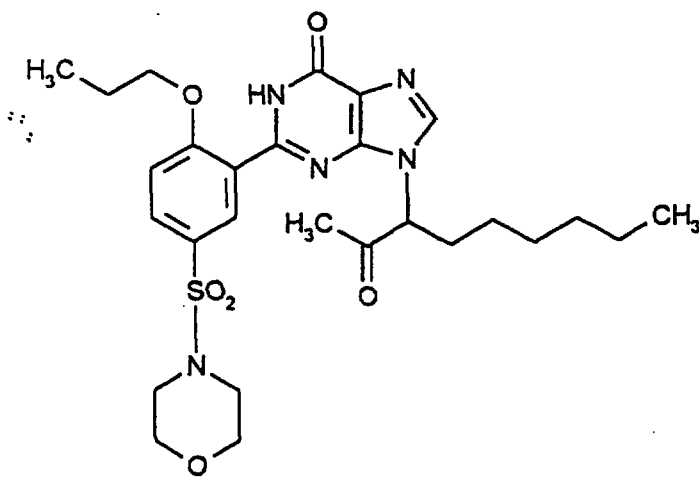
The title compound is prepared analogously to the instructions of Example 65, starting from 9-(2-acetoxy-8-(4-morpholinosulphonyl-phenyl)-3-octyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one (Example 64).

5 $R_f = 0.35$ (toluene/acetone 1:1)

Yield: 79.6%

Example 68

9-(2-Oxo-3-nonyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one



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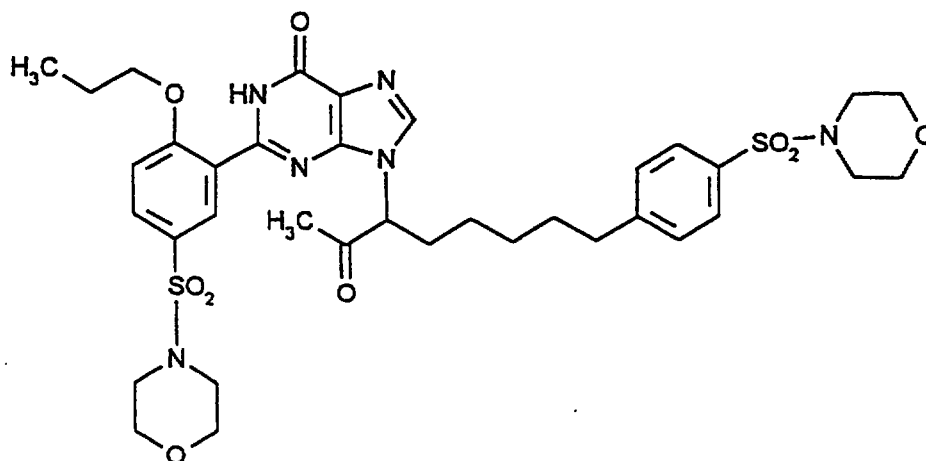
The title compound is prepared analogously to the instructions of Example 48 starting from 9-(2-hydroxy-3-nonyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one (Example 66).

$R_f = 0.52$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:19)

5 Yield: 63.2%

Example 69

9-(2-Oxo-8-(4-morpholinosulphonyl-phenyl)-3-octyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one



10 The title compound is prepared analogously to the instructions of Example 48, starting from 9-(2-hydroxy-8-(4-morpholinosulphonyl-phenyl)-3-octyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one (Example 67).

$R_f = 0.41$ (toluene/acetone 1:1)

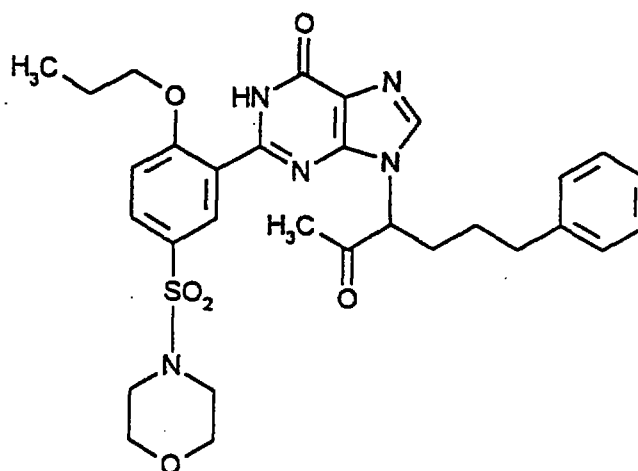
Yield: 51.1%

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Example 70

9-(2-Oxo-6-phenyl-3-hexyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one



The title compound is prepared analogously to the instructions of Example 48, starting from 9-(2-hydroxy-6-phenyl-3-hexyl)-2-(2-n-propoxy-5-morpholinosulphonyl-phenyl)-purin-6-one (Example 20).

$R_f = 0.6$ ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1)

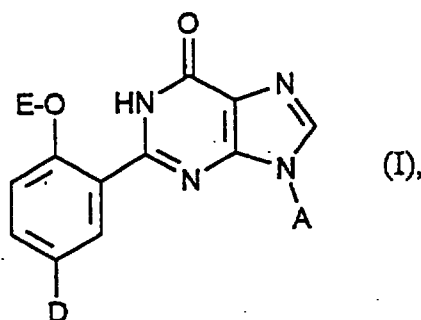
Yield: 51%.

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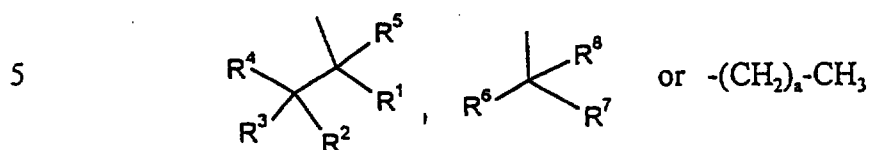
Patent claims

1. 9-Substituted 2-(2-n-alkoxyphenyl)purin-6-ones of the general formula (I)



in which

A represents a radical of the formula



wherein,

a denotes a number 9, 10, 11, 12, 13, 14 or 15,

R^1 denotes straight-chain or branched alkyl having 2 to 10 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by halogen, nitro, cyano, by straight-chain or branched alkyl having up to 6 carbon atoms or by a group of the formula $-SO_2-NR^9R^{10}$,

wherein

R^9 and R^{10} are identical or different and denote hydrogen, phenyl or

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straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, or together with the nitrogen atom form a 5- to 6-membered, saturated heterocyclic radical which has up to 2 further heteroatoms from the series consisting of S, N and/or O and is optionally substituted, including via a free N function, by straight-chain or branched alkyl having up to 6 carbon atoms, which in turn can be substituted by hydroxyl,

and/or

10

alkyl is optionally substituted by a group of the formula $-NR^{11}R^{12}$,

wherein

R^{11} and R^{12} have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these,

15

R^2 denotes hydrogen, azido, straight-chain or branched alkyl having up to 6 carbon atoms or a group of the formula $-OR^{13}$, $O-SO_2R^{14}$ or $-NR^{15}R^{16}$,

wherein

20

R^{13} is hydrogen, a hydroxyl-protecting group, straight-chain or branched acyl having up to 6 carbon atoms, benzoyl or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxy carbonyl having up to 6 carbon atoms or by a group of the formula $-CO-NR^{17}R^{18}$,

wherein

R^{17} and R^{18} are identical or different and denote hydrogen or



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straight-chain or branched alkyl having up to 4 carbon atoms,

R^{14} denotes straight-chain or branched alkyl having up to 4 carbon atoms or phenyl,

5 R^{15} and R^{16} are identical or different and denote hydrogen, an amino-protecting group, straight-chain or branched alkyl or acyl having in each case up to 6 carbon atoms, formyl, benzoyl or a group of the formula $-SO_2R^{19}$,

wherein

10 R^{19} has the abovementioned meaning of R^{14} and is identical to or different from this,

R^3 denotes hydrogen,

or

R^2 and R^3 together form a radical of the formula $=O$ or $=N-OR^{20}$,

15 wherein

R^{20} denotes hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by phenyl or by a group of the formula $-NR^{21}R^{22}$,

wherein

20 R^{21} and R^{22} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms,

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R^4 denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

R^5 and R^8 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

5 R^6 denotes hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl,

R^7 denotes straight-chain or branched alkyl having 2 to 8 carbon atoms, which is substituted by a group of the formula $-NR^{23}R^{24}$,

wherein

10 R^{23} and R^{24} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl,

or is substituted by phenyl, which in turn is substituted by the group of the formula $-SO_2-NR^{25}R^{26}$,

15 wherein

R^{25} and R^{26} have the abovementioned meaning of R^9 and R^{10} ,

D represents hydrogen or represents a group of the formula $-SO_2-NR^{27}R^{28}$,

wherein

20 R^{27} and R^{28} are identical or different and have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these, and

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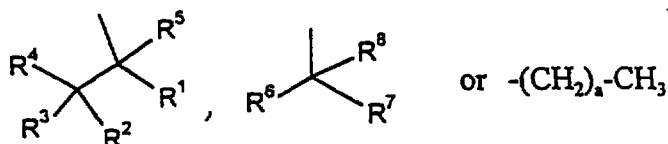
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E represents straight-chain or branched alkyl having up to 8 carbon atoms, and tautomers and salts thereof.

2. 9-Substituted 2-(2-n-alkoxyphenyl)purin-6-ones of the formula (I) according to Claim 1,

5 in which

A represents a radical of the formula



wherein,

a denotes a number 9, 10, 11, 12 or 13,

10 R¹ denotes straight-chain or branched alkyl having 2 to 8 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by fluorine, chlorine, bromine, nitro, cyano, by straight-chain or branched alkyl having up to 4 carbon atoms or by a group of the formula -SO₂-NR⁹R¹⁰,

15 wherein

R⁹ and R¹⁰ are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl, or, together with the hydrogen atom, form a morpholinyl, pyrrolidinyl or piperidinyl ring or a piperazinyl ring, which is

20



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optionally substituted, including via a free NH function, by straight-chain or branched alkyl having up to 3 carbon atoms, which in turn can be substituted by hydroxyl,

and/or

5 alkyl is optionally substituted by a group of the formula $-NR^{11}R^{12}$,

wherein

R^{11} and R^{12} have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these,

10 R^2 denotes hydrogen, azido, straight-chain or branched alkyl having up to 4 carbon atoms or a group of the formula $-OR^{13}$, $-O-SO_2-R^{14}$ or $-NR^{15}R^{16}$,

wherein

15 R^{13} denotes hydrogen, benzyl, straight-chain or branched acyl having up to 4 carbon atoms, benzoyl or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxy carbonyl having up to 4 carbon atoms or by a group of the formula $-CO-NR^{17}R^{18}$,

wherein

20 R^{17} and R^{18} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

R^{14} denotes straight-chain or branched alkyl having up to 3 carbon atoms or phenyl,

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R^{15} and R^{16} are identical or different and denote hydrogen, tert-butoxycarbonyl, benzyloxycarbonyl or straight-chain or branched alkyl or acyl having in each case up to 4 carbon atoms, formyl, benzoyl or a group of the formula $-SO_2R^{19}$,

5

wherein

R^{19} has the abovementioned meaning of R^{14} and is identical to or different from this,

R^3 denotes hydrogen,

or

10

R^2 and R^3 together form a radical of the formula $=O$ or $=N-OR^{20}$,

wherein

R^{20} denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by phenyl or by a group of the formula $-NR^{21}R^{22}$,

15

wherein

R^{21} and R^{22} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms,

20

R^4 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

R^5 and R^8 are identical or different and denote hydrogen or methyl,



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R⁶ denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl,

R⁷ denotes straight-chain or branched alkyl having 2 to 6 carbon atoms, which is substituted by a group of the formula -NR²³R²⁴,

5 wherein

R²³ and R²⁴ are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl,

10 or is substituted by phenyl, which in turn is substituted by a group of the formula -SO₂-NR²⁵R²⁶,

wherein

R²⁵ and R²⁶ are identical or different and have the abovementioned meaning of R⁹ and R¹⁰,

D represents hydrogen, or represents a group of the formula -SO₂-NR²⁷R²⁸,

15 wherein

R²⁷ and R²⁸ are identical or different and have the abovementioned meaning of R⁹ and R¹⁰ and are identical to or different from these, and

E represents straight-chain or branched alkyl having up to 6 carbon atoms,

and tautomers and salts thereof.

20 3. 9-Substituted 2-(2-n-alkoxyphenyl)purin-6-ones of the formula according to Claim 1,

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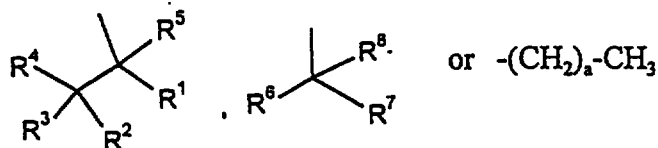


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wherein

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A represents a radical of the formula



wherein,

5 a denotes a number 9, 10, 11 or 12,

10 R¹ denotes straight-chain or branched alkyl having 2 to 7 carbon atoms, which is optionally substituted by phenyl, which in turn can be substituted by fluorine, chlorine, bromine, nitro, cyano, by straight-chain or branched alkyl having up to 3 carbon atoms or by a group of the formula -SO₂-NR⁹R¹⁰,

wherein

15 R⁹ and R¹⁰ are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl, or, together with the nitrogen atom, form a morpholinyl, pyrrolidinyl or piperidinyl ring or a piperazinyl ring, which is optionally substituted, including via free NH function, by straight-chain or branched alkyl having up to 3 carbon atoms, which in turn can be substituted by hydroxyl,

20 and/or

alkyl is optionally substituted by a group of the formula -NR¹¹R¹²,

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* C L N S *

wherein

R^{11} and R^{12} have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these,

5 R^2 denotes hydrogen, azido, straight-chain or branched alkyl having up to 3 carbon atoms or a group of the formula $-OR^{13}$, $-OSO_2R^{14}$ or $-NR^{15}R^{16}$,

wherein

10 R^{13} denotes hydrogen, straight-chain or branched acyl having up to 3 carbon atoms, benzoyl or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxycarbonyl having up to 3 carbon atoms or by a group of the formula $-CO-NR^{17}R^{18}$,

wherein

R^{17} and R^{18} are identical or different and denote hydrogen, methyl or ethyl,

15 R^{14} denotes straight-chain or branched alkyl having up to 3 carbon atoms or phenyl,

20 R^{15} and R^{16} are identical or different and denote hydrogen, tert-butoxycarbonyl, straight-chain or branched alkyl or acyl having in each case up to 3 carbon atoms, formyl, benzoyl or a group of the formula $-SO_2R^{19}$,

wherein

R^{19} has the abovementioned meaning of R^{14} and is identical to or different from this,

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R^3 denotes hydrogen, ⁷¹

or

R^2 and R^3 together form a radical of the formula $=O$ or $=N-OR^{20}$,

wherein

5 R^{20} denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by phenyl or by a group of the formula $-NR^{21}R^{22}$,

wherein

10 R^{21} and R^{22} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 3 carbon atoms,

R^4 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

15 R^5 and R^8 are identical or different and denote hydrogen or methyl,

R^6 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl,

R^7 denotes straight-chain or branched alkyl having 2 to 6 carbon atoms, which is substituted by a group of the formula $-NR^{23}R^{24}$,

20 wherein

R^{23} and R^{24} are identical or different and denote hydrogen or straight-



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chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl,

or is substituted by phenyl, which in turn is substituted by the group of the formula $-\text{SO}_2-\text{R}^{25}\text{R}^{26}$,

5 wherein

R^{25} and R^{26} have the abovementioned meaning of R^9 and R^{10} ,

D represents hydrogen, or represents a group of the formula $-\text{SO}_2-\text{NR}^{27}\text{R}^{28}$,

wherein

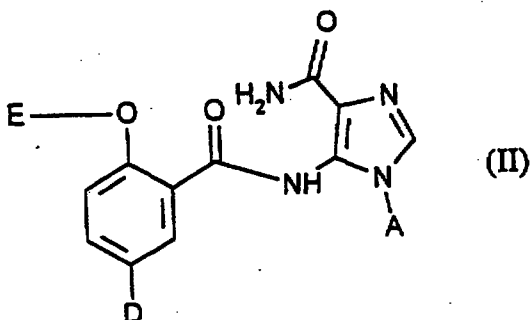
10 R^{27} and R^{28} are identical or different and have the abovementioned meaning of R^9 and R^{10} and are identical to or different from these, and

E represents straight-chain or branched alkyl having up to 5 carbon atoms,

and tautomers and salts thereof.

4. 9-Substituted 2-(2-n-alkoxyphenyl)purin-6-ones according to Claim 1 to 3 for therapeutic use.

15 5. Process for the preparation of 9-substituted 2-(2-n-alkoxyphenyl)purin-6-ones according to Claim 1 to 3, characterized in that compounds of the general formula (II)



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in which

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D, E and A have the abovementioned meaning,

are first cyclized in inert solvents and in the presence of a base,

and in the case where $D = H$, the corresponding sulphonic acid chlorides are first
5 prepared by reaction with chlorosulphonic acid and the corresponding sulphonamides
are then prepared with amines ($NR^{25}R^{26}$),

and the substituents R^1-R^8 are introduced or derivatized by customary methods, such as,
for example alkylation, acylation, amination, oxidation or azide exchange.

6. Medicaments comprising 9-substituted 2-(2-n-alkoxyphenyl)purin-6-ones
10 according to Claim 1 to 3.

7. Medicaments according to Claim 6 for treatment of inflammations,
thromboembolic diseases and cardiovascular diseases.

8. Medicaments according to Claims 6 and 7 for treatment of impotence.

9. Use of 9-substituted 2-(2-n-alkoxyphenyl)purin-6-ones according to Claim 1 to
15 3 for the preparation of medicaments.

10. Use according to Claim 8, characterized in that the medicaments are for
treatment of inflammations, thromboembolic diseases and cardiovascular diseases.

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Date: 1 8 MAY 1996

9-Substituted 2-(2-n-alkoxyphenyl)purin-6-ones**Abstract**

9-Substituted 2-(2-n-alkoxyphenyl)purin-6-ones are prepared by cyclizing correspondingly substituted imidazoles and derivatizing the purines thus obtained. The
5 9-substituted 2-(2-n-alkoxyphenyl)purin-6-ones can be employed as active compounds in medicaments, in particular in medicaments for treatment of inflammations, thromboembolic diseases and cardiovascular diseases.

This is the replacement sheet

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