

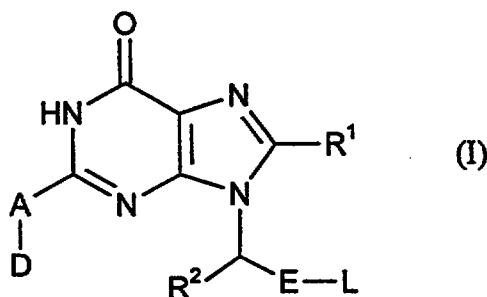
Purin-6-one derivatives

5 The present invention relates to purin-6-one derivatives, a process for their preparation and their use in medicaments, in particular for the treatment of cardiovascular and cerebrovascular disorders, peripheral vascular disorders and diseases of the urogenital system.

10 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 until now [nomenclature according to Beavo and Reifsnyder (cf. Beavo, J.A. and Reifsnyder, D.H.: Trends in Pharmacol. Sci 11, 150-155 (1990))], the Ca

15 calmodulin-activated PDE I, the cGMP-stimulable PDE II and the cGMP-specific PDE V are essentially responsible for the metabolism of cGMP. On account of the differing distribution of these cGMP-metabolizing PDEs in the tissue, selective inhibitors, according to the tissue distribution of the corresponding isoenzyme, should raise the cGMP level in the corresponding tissue. This can lead to a specific antiaggregatory, antispastic, vasodilating and/or antiarrhythmic action.

The present invention now relates to purin-6-one derivatives of the general formula (I)



This Sheet Has Been Replaced



in which

9611041-6

R¹ represents hydrogen or straight-chain or branched alkyl having up to 8 carbon atoms,

R² represents straight-chain or branched acyl having up to 4 carbon atoms, or
5 represents straight-chain or branched alkyl having up to 8 carbon atoms, which
is optionally substituted by hydroxyl, azido or by a group of the formula
-NR³R⁴ or -OSO₂R⁵,

in which

R³ and R⁴ are identical or different and
10 denote cycloalkyl having 3 to 6 carbon atoms, hydrogen, formyl or
straight-chain or branched alkyl having up to 6 carbon atoms, which is
optionally substituted by hydroxyl, carboxyl or by straight-chain or
branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms or
by a group of the formula -(CO)_a-NR⁶R⁷,

in which

15 a denotes a number 0 or 1,

R⁶ and R⁷ are identical or different and denote hydrogen, formyl,
hydroxyl, phenyl or straight-chain or branched alkyl having up to
6 carbon atoms, which is optionally substituted by hydroxyl or
by straight-chain or branched alkoxy having up to 5 carbon
20 atoms,

or

R³ and/or R⁴ denote straight-chain or branched alkoxycarbonyl having
up to 6 carbon atoms, carboxyl or straight-chain or branched acyl
having up to 6 carbon atoms, which is optionally substituted by



hydroxyl or straight-chain or branched alkoxy having up to 4 carbon atoms

or

5 R^3 and/or R^4 denote a radical of the formula $-(CO)_b-T-NR^8R^9$,
 $-CO-R^{10}$, $-SO_2R^{11}$ or $-SO_2NR^{12}R^{13}$, in which

b has the meaning of a indicated above and is identical to or different from this

10 T denotes straight-chain or branched alkyl having up to 5 carbon atoms
or if $b \neq 0$ can also denote a bond,

R^8 and R^9 have the meaning of R^6 and R^7 indicated above and are identical to or different from this

15

R^{10} denotes a saturated, partially unsaturated or unsaturated 5- to 7-membered heterocycle having up to 3 heteroatoms from the series S, N and/or O, which can optionally also be substituted via the N function, by straight-chain or branched alkyl, alkoxy or alkoxy carbonyl each having up to 4 carbon atoms, carboxyl, benzyloxycarbonyl or hydroxyl,

This Sheet Has Been Replaced



20

R^{11} denotes straight-chain or branched alkyl having up to 5 carbon atoms, benzyl or phenyl,

R^{12} and R^{13} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms,

or

R^3 and R^4 , together with the nitrogen atom, form a 5- or 6-membered

saturated, partially unsaturated or unsaturated heterocycle which can contain up to 3 heteroatoms from the series N, S and/or O or a radical $-NR^{14}$, and which is optionally substituted by carbonyl, by straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms or by straight-chain or branched alkyl having up to 5 carbon atoms, which for its part can be substituted by hydroxyl, carboxyl or by straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 6 carbon atoms,

in which

R^{14} denotes hydrogen, carbonyl or straight-chain or branched alkyl or alkoxycarbonyl each having up to 5 carbon atoms,

and

R^5 denotes phenyl or straight-chain or branched alkyl having up to 5 carbon atoms,

A represents a straight-chain or branched alkylene or alkenylene chain each having up to 6 carbon atoms,

D and L are identical or different and represent aryl having 6 to 10 carbon atoms or a 5- to 7-membered aromatic, optionally benzo-fused heterocycle having up to 3 heteroatoms from the series S, N and/or O, each of which is optionally substituted up to 3 times identically or differently by halogen, hydroxyl, nitro, trifluoromethyl, carboxyl, straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 6 carbon atoms or by a group of the formula $-(V_c)-NR^{15}R^{16}$ and/or $-OR^{17}$,

in which

This Sheet Has Been Replaced



c denotes a number 0 or 1,

V denotes a radical of the formula $-\text{CO}$ or $-\text{SO}_2$,

R^{15} and R^{16} are identical or different and have the meaning of R^3 and R^4 indicated above,

5 R^{17} denotes hydrogen, straight-chain or branched alkenyl having up to 8 carbon atoms or straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted up to 3 times identically or differently by hydroxyl, carboxyl or straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms,

10 and/or the cycles are optionally substituted by aryl having 6 to 10 carbon atoms or by a 5- to 7-membered aromatic, optionally benzo-fused heterocycle having up to 3 heteroatoms from the series S, N and/or O, each of which for its part is optionally substituted up to 2 times identically or differently by halogen, hydroxyl, nitro, carboxyl, trifluoromethyl or by straight-chain or branched alkyl,
15 alkoxy or alkoxycarbonyl each having up to 5 carbon atoms or by a group of the formula $(\text{V}')_d-\text{NR}^{18}\text{R}^{19}$,

in which

This Sheet Has Been Replaced



d has the meaning of a indicated above and is identical to or different from this,

20 R^{18} and R^{19} have the meaning of R^3 and R^4 indicated above and are identical to or different from this,

V' has the meaning of V indicated above and is identical or different from this,

and/or

the ring systems mentioned under D

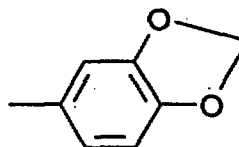
are optionally substituted by straight-chain or branched acyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl, straight-chain or branched alkoxy having up to 5 carbon atoms or by a group of the formula
5 $-NR^{20}R^{21}$,

in which

R^{20} and R^{21} are identical or different and have the meaning of R^3 and R^4 indicated above,

10 or

D represents a radical of the formula



and

This Sheet Has Been Replaced



E represents a radical of the formula $-CH_2-Y-Z-$,

in which

15 Y denotes a bond or an oxygen or sulphur atom or the $-NH$ group,

Z denotes a straight-chain or branched alkylene chain having up to 5 carbon atoms,

and their tautomers and salts.

The substances according to the invention can also exist as salts. In the context of the invention physiologically acceptable salts are preferred.

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,
10 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 image and mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the antipodes and to the racemic forms as well as the
15 diastereomer mixtures. Like the diastereomers, racemic forms can be separated into the stereoisomerically uniform constituents in a known manner.

Heterocycle in the content of the invention in general represents a partially unsaturated, saturated or unsaturated 5- to 7-membered, preferably 5- to 6-membered, heterocycle which can contain up to 3 heteroatoms from the series S, N and/or O. Examples which
20 may be mentioned are: pyridyl, pyrrolidiny, piperaziny, thienyl, indolyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, morpholiny or piperidyl. Pyridyl, thienyl, indolyl, furyl, piperaziny, morpholiny and pyrrolidiny are preferred.

Preferred compounds of the general formula (I) are those

in which

25 R^1 represents hydrogen or straight-chain or branched alkyl having up to 6 carbon

This Sheet Has Been Replaced



atoms,

5 R^2 represents straight-chain or branched acyl having up to 6 carbon atoms, or
represents straight-chain or branched alkyl having up to 6 carbon atoms, which
is optionally substituted by hydroxyl, azido or by a group of the formula
 $-NR^3R^4$ or $O-SO_2-R^5$,

in which

10 R^3 and R^4 are identical or different and
denote cyclopentyl, cyclohexyl, hydrogen, formyl or straight-chain or
branched alkyl having up to 5 carbon atoms, which is optionally
substituted by hydroxyl, carboxyl or by straight-chain or branched
alkoxy or alkoxy carbonyl each having up to 5 carbon atoms or by a
group of the formula $-(CO)_a-NR^6R^7$,

in which

This Sheet Has Been Replaced



a denotes a number 0 or 1,

15 R^6 and R^7 are identical or different and denote hydrogen, formyl,
hydroxyl, phenyl or straight-chain or branched alkyl having up to
5 carbon atoms, which is optionally substituted by hydroxyl or
by straight-chain or branched alkoxy having up to 4 carbon
atoms,

20 or

R^3 and/or R^4 denote straight-chain or branched alkoxy carbonyl having
up to 5 carbon atoms, carboxyl or straight-chain or branched acyl
having up to 5 carbon atoms, which is optionally substituted by
hydroxyl or straight-chain or branched alkoxy having up to 3

carbon atoms

or

R^3 and/or R^4 denote a radical of the formula $-(CO)_b-T-NR^8R^9$,
 $-CO-R^{10}$, $-SO_2R^{11}$ or $-SO_2NR^{12}R^{13}$, in which

5

b has the meaning of a indicated above and is identical to or different from this

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

or if $b \neq 0$ can also denote a bond,

10

R^8 and R^9 have the meaning of R^6 and R^7 indicated above and are identical to or different from this

15

R^{10} denotes morpholinyl, imidazolyl, pyridyl, piperazinyl, piperidinyl or pyrrolidinyl, each of which can optionally be substituted, also via the N function, by straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms, carboxyl, benzyloxycarbonyl or hydroxyl,

This Sheet Has Been Replaced



R^{11} denotes straight-chain or branched alkyl having up to 4 carbon atoms, benzyl or phenyl,

20

R^{12} and R^{13} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 5 carbon atoms,

or

R^3 and R^4 , together with the nitrogen atom, form a pyrrolidinyl, morpholinyl,

5 imidazolyl, piperidinyl or piperazinyl ring, each of which, optionally also via the nitrogen function, can be substituted by straight-chain or branched alkoxy carbonyl having up to 4 carbon atoms, carboxyl, or by straight-chain or branched alkyl having up to 4 carbon atoms, which for its part can be substituted by carboxyl, hydroxyl or by straight-chain or branched acyl, alkoxy or alkoxy carbonyl each having up to 4 carbon atoms,

and

This Sheet Has Been Replaced



10 R^5 denotes phenyl or straight-chain or branched alkyl having up to 4 carbon atoms,

A represents a straight-chain or branched alkylene or alkenylene chain each having up to 5 carbon atoms,

15 D and L are identical or different and represent phenyl, naphthyl, pyridyl, pyridinyl, thienyl, indolyl or furyl, each of which is optionally substituted up to 3 times identically or differently by fluorine, chlorine, bromine, trifluoromethyl, nitro, carboxyl, straight-chain or branched alkyl or alkoxy carbonyl each having up to 5 carbon atoms or by a group of the formula $-(V)_cNR^{15}R^{16}$ and/or $-OR^{17}$,

in which

c denotes a number 0 or 1,

20 V denotes a radical of the formula $-CO$ or $-SO_2$,

R^{15} and R^{16} are identical or different and have the meaning of R^3 and R^4 indicated above,

R^{17} denotes hydrogen, straight-chain or branched alkenyl having up to 6

carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted up to 2 times identically or differently by hydroxyl, carboxyl or by straight-chain or branched alkoxy carbonyl having up to 4 carbon atoms,

5 and/or the cycles are optionally substituted by naphthyl, phenyl, pyridyl, indolyl, thienyl, furyl, pyridazinyl, pyridyl, pyrrol or pyrimidyl, each of which for its part is optionally substituted by fluorine, chlorine, bromine, hydroxyl, nitro, carboxyl, trifluoromethyl or by straight-chain or branched alkyl, alkoxy or alkoxy carbonyl each having up to 3 carbon atoms or by a group of the formula
10 $-(V')_dNR^{18}R^{19}$,

in which



d has the meaning of a indicated above and is identical to or different from this,

15 V' has the meaning of V indicated above and is identical to or different from this,

R^{18} and R^{19} have the meaning of R^3 and R^4 indicated above,

and/or

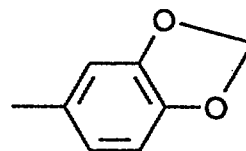
the ring systems mentioned under D

20 are optionally substituted by straight-chain or branched acyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl, straight-chain or branched alkoxy having up to 4 carbon atoms or by a group of the formula $-NR^{20}R^{21}$,

in which

R^{20} and R^{21} are identical or different and have the meaning of R^3 and R^4 indicated above,

or D represents a radical of the formula



This Sheet Has Been Replaced



E represents a radical of the formula $-CH_2-Y-Z-$,

5 in which

Y denotes a bond or an oxygen or sulphur atom or the $-NH$ group,

Z denotes a straight-chain or branched alkylene chain having up to 4 carbon atoms,

and their tautomers and salts.

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

in which

R^1 represents hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

15 R^2 represents straight-chain or branched acyl having up to 5 carbon atoms, or represents straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl, azido or by a group of the formula $-NR^3R^4$ or $O-SO_2R^5$,

in which

R^3 and R^4 are identical or different and

denote cyclopentyl, hydrogen, formyl or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or each alkoxycarbonyl having up to 3 carbon atoms or by a group of the formula $-(CO)_a-NR^6R^7$,

5

in which

This Sheet Has Been Replaced



a denotes a number 0 or 1,

R^6 and R^7 are identical or different and denote hydrogen, formyl, hydroxyl or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl, or by straight-chain or branched alkoxy having up to 3 carbon atoms,

10

or

R^3 and/or R^4 denote straight-chain or branched alkoxycarbonyl having up to 3 carbon atoms, carboxyl or straight-chain or branched acyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl, methoxy or ethoxy

15

or

R^3 and/or R^4 denote a radical of the formula $-(CO)_b-T-NR^8R^9$, $-CO-R^{10}$, $-SO_2R^{11}$ or $-SO_2NR^{12}R^{13}$, in which

20

b has the meaning of a indicated above and is identical to or different from this



T denotes straight-chain or branched alkyl having up to 3 carbon atoms

or if $b \neq 0$ can also denote a bond,

R^8 and R^9 have the meaning of R^6 and R^7 indicated above and are identical to or different from this

R^{10} denotes morpholinyl, piperidinyl, piperazinyl or pyrrolidinyl, each of which can optionally also be substituted via the N function, by straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms, benzyloxycarbonyl, carboxyl or hydroxyl,

R^{11} denotes straight-chain or branched alkyl having up to 3 carbon atoms, benzyl or phenyl,

R^{12} and R^{13} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

or

R^3 and R^4 , together with the nitrogen atom, form a pyrrolidinyl, morpholinyl, imidazolyl, piperidinyl or piperazinyl ring, each of which, optionally also via the nitrogen function, can be substituted by straight-chain or branched alkyl or alkoxycarbonyl each having up to 3 carbon atoms or carboxyl or by straight-chain or branched alkyl having up to 3 carbon atoms, which for its part can be substituted by carboxyl, hydroxyl or by straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms

and

R⁵ denotes phenyl or straight-chain or branched alkyl having up to 3 carbon atoms.

A represents an ethenyl (-vinyl) or an alkylene chain having up to 4 carbon atoms,

5 in which

This Sheet Has Been Replaced



D and L are identical or different and represent phenyl, naphthyl, furyl, thienyl, indolyl or pyridyl, each of which is optionally substituted up to 2 times identically or differently by fluorine, chlorine, bromine, nitro, carboxyl, trifluoromethyl, straight-chain or branched alkyl or alkoxycarbonyl each having up to 4 carbon atoms or by a group of the formula $-(V)_cNR^{15}R^{16}$ and/or $-OR^{17}$,

10 in which

c denotes a number 0 or 1,

V denotes a radical of the formula $-CO$ or $-SO_2$,

15 R¹⁵ and R¹⁶ are identical or different and have the meaning of R³ and R⁴ indicated above,

20 R¹⁷ denotes hydrogen, straight-chain or branched alkenyl having up to 4 carbon atoms or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted up to 2 times identically or differently by hydroxyl, carboxyl or by straight-chain or branched alkoxycarbonyl having up to 3 carbon atoms

and/or the cycles are optionally substituted by phenyl, pyrimidyl, pyridazinyl, pyridyl, thienyl or furyl, each of which for its part is optionally substituted by fluorine, chlorine, bromine, hydroxyl, nitro, carboxyl, trifluoromethyl or by straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms or by a group of the formula $-(V')_dNR^{18}R^{19}$,

This Sheet Has Been Replaced



5 in which

d has the meaning of a indicated above and is identical to or different from this,

V' has the meaning of V indicated above and is identical to or different from this,

10

R^{18} and R^{19} have the meaning of R^3 and R^4 indicated above,

and/or

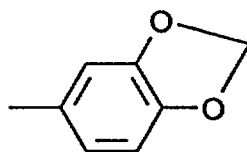
D is optionally substituted by straight-chain or branched acyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl, straight-chain or branched alkoxy having up to 3 carbon atoms or by a group of the formula $-NR^{20}R^{21}$,

in which

15

R^{20} and R^{21} are identical or different and have the meaning of R^3 and R^4 indicated above,

D represents a radical of the formula



This Sheet Has Been Replaced



E represents a radical of the formula $-\text{CH}_2-\text{Y}-\text{Z}-$,

in which

Y denotes a bond or an oxygen or sulphur atom or the $-\text{NH}$ group,

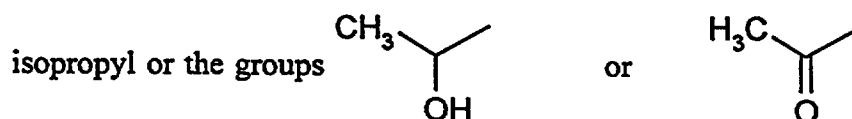
Z denotes an alkylene chain having up to 4 carbon atoms

and their tautomers and salts.

Very particularly preferred compounds of the general formula (I) are those

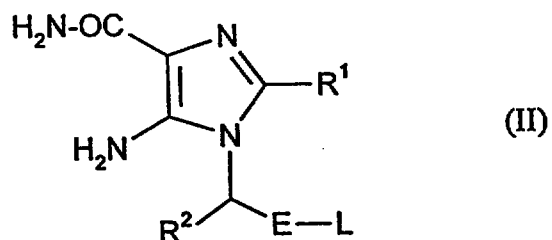
in which

L represents phenyl which is optionally substituted by fluorine, chlorine, methyl or methoxy, R^1 represents hydrogen, methyl or ethyl and R^2 represents CH_3 ,

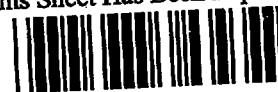


Processes for the preparation of the compounds of the general formula (I) according to the invention have additionally been found, characterized in that

[A] first compounds of the general formula (II)



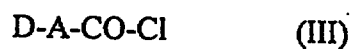
This Sheet Has Been Replaced



in which

R^1 , R^2 , E and L have the meaning indicated,

are converted by reaction with compounds of the general formula (III)

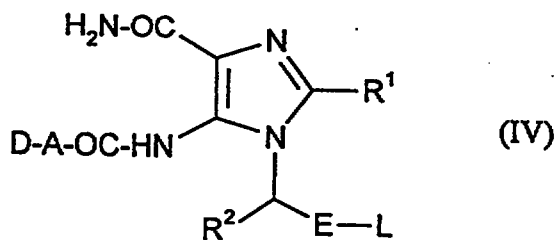


in which

A and D have the meaning indicated,

in inert solvents and in the presence of a base,

into the compounds of the general formula (IV)



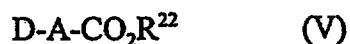
in which

A, D, E, L, R^1 and R^2 have the meaning indicated,

and in a second step these are cyclized in inert solvents and in the presence of a base,

or

[B] compounds of the general formula (II) are directly reacted with compounds of the general formula (V)



in which

D and A have the meaning indicated above and

R²² represents C₁-C₄-alkyl

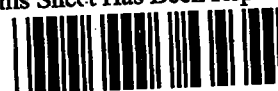
in alcohols and in the presence of a base,

and, if appropriate, the substituents mentioned under R² are introduced or derivatized by subsequent reactions such as acylation, oxidation, substitution and/or reduction,

and the substituents mentioned under D and L are likewise introduced and/or varied by customary methods.

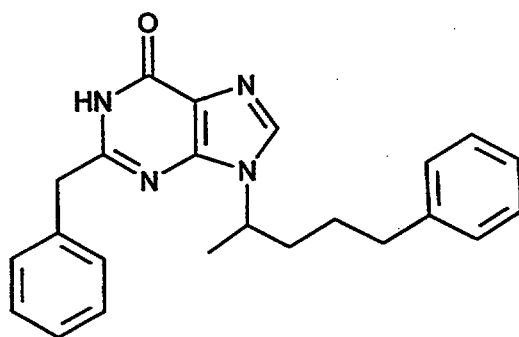
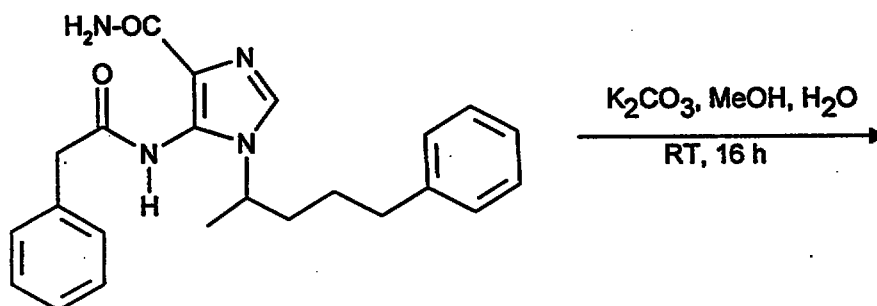
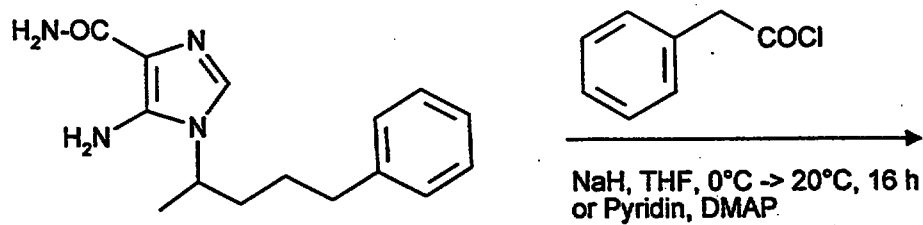
The process according to the invention can be illustrated by way of example by the following reaction scheme:

This Sheet Has Been Replaced

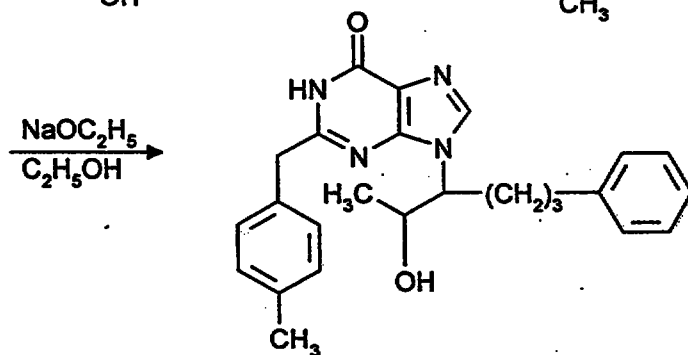
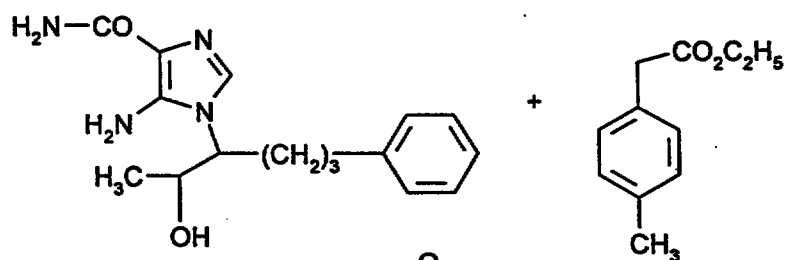




[A]



[B]





Suitable solvents for the first step of process [A] are inert organic solvents which do not change under the reaction conditions. These preferably include ethers such as, for example, diethyl ether, dioxane, tetrahydrofuran or glycol dimethyl ether or toluene, hexamethylphosphoramide and pyridine. Of course, it is possible to employ mixtures
5 of the solvents. Tetrahydrofuran, toluene and pyridine are particularly preferred.

Suitable bases are in general alkali metal hydrides or alkoxides, such as, for example, sodium hydride or potassium tert-butoxide, or cyclic amines, such as, for example, piperidine, pyridine, dimethylaminopyridine or C₁-C₄-alkylamines, such as, for example, triethylamine. Sodium hydride, pyridine, and/or dimethylaminopyridine are preferred.

10 The base is in general employed in an amount of from 1 mol to 4 mol, preferably from 1.2 mol to 3 mol, in each case relative to 1 mol of the compounds of the general formula (II).

The reaction temperature can in general be varied within a relatively wide range. In general, the reaction is carried out in a range from -20°C to 200°C, preferably from
15 0°C to 100°C.

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

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

Suitable bases for the cyclization are the customary inorganic bases. These preferably include alkali metal hydroxides or alkaline earth metal hydroxides such as, for example,
25 sodium hydroxide, potassium hydroxide or barium hydroxide, or alkali metal carbonates such as sodium or potassium carbonate or sodium hydrogen carbonate, or alkali metal

alkoxides such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide or potassium tert-butoxide. Potassium carbonate and sodium hydroxide are particularly preferred.

5 When carrying out the cyclization, the base is in general employed in an amount of from 2 to 6 mol, preferably from 3 to 5 mol, relative to 1 mol of the compounds of the formula (IV).

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

10 The cyclization is in general carried out at normal pressure. However, it is also possible to carry out the process at elevated pressure or at reduced pressure (e.g. in a range from 0.5 to 5 bar).

Suitable solvents for process [B] are the alcohols mentioned above, ethanol being preferred.

15 Suitable bases for process [B] are alkoxides, such as, for example, sodium methoxide, ethoxide or isopropoxide or potassium tert-butoxide. Sodium ethoxide is preferred.

The base is employed in an amount of from 2 mol to 8 mol, preferably from 3 mol to 6 mol, in each case relative to 1 mol of the compounds of the general formula (II).

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

20 The variations of the substituents on the aromatics are carried out according to known methods.

The enantiomerically pure compounds are accessible according to customary methods, for example by chromatography of the racemic compounds of the general formula (I)

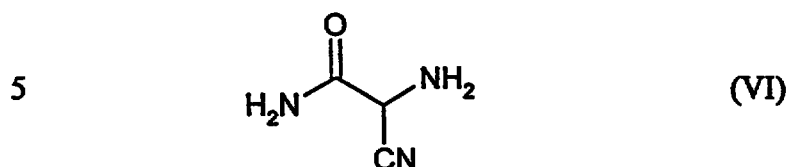




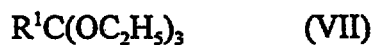
on chiral phases or by the use of chiral starting compounds.

The compounds of the general formula (II) are new and can be prepared, for example, by

reacting 2-amino-2-cyanoacetamide of the formula (VI)



with compounds of the general formula (VII)



in which

R^1 has the meaning indicated above,

10 and in a second step reacting with compounds of the general formula (VIII)



in which

R^2 , E and L have the meaning indicated,

in inert solvents.

15 Suitable solvents for the individual steps of the processes are the customary organic

solvents which do not change under the reaction conditions. These preferably include ethers such as diethyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether, or hydrocarbons such as benzene, toluene, xylene, hexane, cyclohexane or petroleum fractions, or halogenohydrocarbons such as dichloromethane, trichloromethane, 5 tetrachloromethane, dichloroethylene, trichloroethylene or chlorobenzene, or ethyl acetate, dimethylformamide, hexamethylphosphoramide, acetonitrile, acetone or dimethoxyethane. It is also possible to use mixtures of the solvents mentioned. Acetonitrile is particularly preferred.

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

The process steps according to the invention are in general carried out at normal pressure. However, it is also possible to work at elevated pressure or at reduced pressure (e.g. in a range from 0.5 to 5 bar).

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

The compounds of the general formulae (III) and (VII) are known per se or can be prepared according to customary methods.

The amines of the general formula (VIII) are known or can be prepared according to known methods [cf. L.R. Krepski et al., Synthesis, 1986, 301-303].

20 The compounds of the general formula (IV) are new and can be prepared as described above.

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

They inhibit either one or more of the c-GMP-metabolizing phosphodiesterases (PDE I,



PDE II and PDE V). This leads to a differentiated c-GMP-rise. An increase in the c-GMP level can lead to an antithrombotic, vasodilatory and/or antiarrhythmic action. The differentiating action is additionally determined by the distribution of the isoenzymes in the tissue.

- 5 The compounds according to the invention additionally potentiate the action of substances, such as, for example, EDRF (endothelium-derived relaxing factor) and ANP (atrial natriuretic peptide) which raise the c-GMP level.

They can therefore be employed in medicaments for the treatment of cardiovascular disorders, such as, for example, for the treatment of high blood pressure, neuronal
10 hypertension, stable and unstable angina, peripheral and cardiac vascular disorders, of arrhythmias, for the treatment of thromboembolic disorders and ischaemias such as myocardial infarct, cerebral infarct, transitory and ischaemic attacks, angina pectoris, peripheral circulatory disorders, prevention of restenoses after thrombolysis therapy, percutaneous transluminal angioplasty (PTA), percutaneous transluminal coronary
15 angioplasty (PTCA) and bypass. The relaxing action on the smooth musculature makes them suitable for the treatment of disorders of the urogenital system such as prostate hypertrophy, impotence and incontinence. They can furthermore also have significance for cerebrovascular disorders.

Activity of the phosphodiesterases (PDEs)

- 20 The c-GMP-stimulable PDE II, the c-GMP-inhibitable PDE III and the cAMP-specific PDE IV were isolated either from porcine or bovine myocardium. The Ca^{2+} calmodulin-stimulable PDE I was isolated from porcine aorta, porcine brain or preferably from bovine aorta. The c-GMP-specific PDE V was obtained from porcine small intestine, porcine aorta, human blood platelets and preferably from bovine aorta. Purification was
25 carried out by anion exchange chromatography on MonoQ® Pharmacia essentially according to the method of M. Hoey and Miles D. Houslay, Biochemical Pharmacology, Vol. 40, 193-202 (1990) and C. Lugman et al., Biochemical Pharmacology Vol. 35, 1743-1751 (1986).



The enzyme activity was determined in a test mixture of 100 μ l in 20 mM tris/HCl buffer pH 7.5 which contains 5 mM $MgCl_2$, 0.1 mg/ml of bovine serum albumin and either 800 Bq of 3H cAMP or 3H cGMP. The final concentration of the corresponding nucleotides is 10^{-6} mol/l. The reaction is started by addition of the enzyme; the amount of enzyme is proportioned such that during the incubation time of 30 min about 50% of the substrate is reacted. In order to test the cGMP-stimulable PDE II, 3H cAMP is used as a substrate and 10^{-6} mol/l of unlabelled cGMP is added to the mixture. In order to test the Ca calmodulin-dependent PDE I, additionally $CaCl_2$, 1 μ M and calmodulin, 0.1 μ M are added to the reaction mixture. The reaction is stopped by addition of 100 μ l of acetonitrile which contains 1 mM cAMP and 1 mM AMP. 100 μ l of the reaction mixture are separated on an HPLC and the cleavage products are quantitatively determined "on-line" using a flow scintillation counter. The substance concentration is measured at which the reaction rate is decreased by 50%. Additionally, the "phosphodiesterase [3H] cAMP-SPA enzyme assay" and the "phosphodiesterase [3H] cGMP-SPA enzyme assay" from Amersham Life Science were used for testing. The test was carried out according to the experimental protocol indicated by the manufacturer. For activity determination of the PDE2, the [3H] cAMP SPA assay was used, 10^{-6} M cGMP being added to the reaction mixture to activate the enzyme. For the measurement of PDE1, calmodulin, 10^{-7} M and $CaCl_2$, 1 μ M were added to the reaction mixture. The PDE5 was measured using the [3H] cGMP SPA assay.

This Sheet Has Been Replaced





Inhibition of the phosphodiesterases in vitro

Ex. No.	PDE I IC ₅₀ [nM]	PDE II IC ₅₀ [nM]	PDE V IC ₅₀ [nM]
1	500	200	300
33	3000	100	800
34	~500	20	500
69	3000	60	500
80	100	80	1000
82	100	20	500
83	300	20	500
84	100	20	1000
100	1000	4	1000
121	500	3	1000
122	500	4	1000
138	500	1	500

15 The compounds were examined for antihypertensive activity in the anaesthetized pig.

The erection-inducing action was measured in the anaesthetized rabbit. (C.G. Stief et al., World Journal Urology 1990, pp. 233-236).

The substances were administered intraduodenally, rectally, orally, transdermally or intravenously in doses of 0.03 to 10 mg/kg directly into the corpus cavernosum.

20 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 excipients or solvents. In this connection, the therapeutically active compound should in each case be present in a concentration of approximately 0.5 to 90% by weight of the total mixture, i.e. in amounts which are sufficient in order to achieve the dosage range indicated.

The formulations are prepared, for example, by extending the active compounds with solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, it being possible, for example, if water is used as a diluent optionally organic solvents to use as auxiliary solvents.

Administration is carried out in the customary manner, preferably orally, transdermally or parenterally, in particular perlingually or intravenously.

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

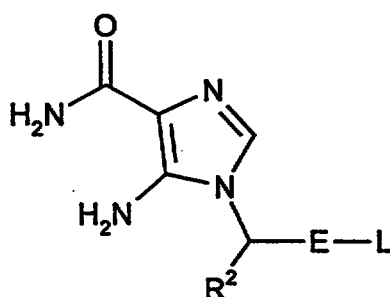
In spite of this, if appropriate it may sometimes be necessary to depart from the amounts mentioned, mainly depending on the body weight or the type of administration route, on individual behaviour towards the medicament, the manner of its formulation and the time or interval at which administration 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 has to be exceeded. In the case of the administration of relatively large amounts, it may be advisable to divide these into several individual doses over the course of the day.

This Sheet Has Been Replaced



Starting compounds

- 1.) The amines (formula VII / R^2 = alkyl) are prepared from the corresponding substituted phenethyl halides by addition to the appropriate β -keto esters, hydrolysis and decarboxylation and reductive amination of the corresponding ketones with sodium cyanoborohydride [cf. Lane, Synthesis, 1975, 135-146].
- 2.) The hydroxyamines (formula VII / R^2 = hydroxy-subst. alkyl) are prepared in a one-pot reaction from an aldehyde or ketone by addition of trimethylsilyl cyanide, reaction of the corresponding silylated cyanohydrins with Grignard reagents and reduction of the imines with sodium borohydride [cf. Krepski, Jensen, Heilmann, Rasmussen, Synthesis, 1986, 301-103].
- 3.) 1-Substituted 5-amino-imidazole-carboxamides (formula II)



Synthesis from 2-amino-2-cyano-acetamide (I.I. Logemann and G. Shaw, Chem. Ind. (London) 541, 1980) and the appropriate amine (see 1.) or hydroxyamine (see 2.) according to P.R. Birkett, C.B. Chapler and G. Mackenzie, Synthesis 1991, 157-159 or G. Shaw, R.W. Warrenner, N.D. Butler and R.K. Ralph, J. Chem. Soc., 1959, 1644-1655.

Preparation examples

This Sheet Has Been Replaced



Preparation of the purin-6-ones

Method A:

22 mmol of 1-substituted-5-amino-imidazole-4-carboxamide are refluxed with 1.76 g
5 (44 mmol) of sodium hydride (60% strength) in 300 ml of abs. THF for 30 minutes.
After cooling to 0°C, 40 mmol of the appropriate acid chloride are added dropwise in
50 ml of abs. THF. The mixture is stirred overnight at room temperature and
concentrated on a rotary evaporator after dropwise addition of 20 ml of methanol. The
residue is purified by flash chromatography on silica gel (eluent: CH₂Cl₂/MeOH
10 mixture) and the 5-acylamino-imidazole-4-carboxamides, which can be directly reacted
further, are obtained.

10 mmol of the 5-acylamino-imidazole-4-carboxamide and 5.52 g (40 mmol) of K₂CO₃
are refluxed overnight in 100 ml of methanol and 30 ml of water. The mixture is
acidified to pH 1 to 2 by addition of 2N hydrochloric acid. The methanol is stripped
15 off in vacuo, 100 ml of water are added and the mixture is extracted twice by shaking
with 100 ml of ethyl acetate each time. After drying the combined organic phases over
Na₂SO₄, the mixture is concentrated on a rotary evaporator and the residue is purified
by flash chromatography on silica gel (eluent: CH₂Cl₂/MeOH mixture). The fractions
containing the product are combined and evaporated. Solid residues are recrystallized
20 from ethyl acetate or ethyl acetate/diethyl ether.

Method B:

3.3 mmol of the corresponding acid chloride in a little abs. THF are added dropwise at
room temperature to a solution of 3 mmol of the 1-substituted-5-amino-imidazole-4-
carboxamide and 50 mg of DMAP in 20 ml of abs. pyridine. After 30 minutes at room
25 temperature, the mixture is stirred at 50°C for about 5 more hours (TLC checking).
The mixture is evaporated, the residue is taken up in 20 ml of CH₂Cl₂ and the solution

is washed with 20 ml of 2N HCl. After drying the organic phase over Na_2SO_4 , it is evaporated and the residue is purified by flash chromatography on silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ mixture). The 5-acylamino-imidazole-4-carboxamides are obtained, which are directly reacted further as described in Method A.

5 Method C:

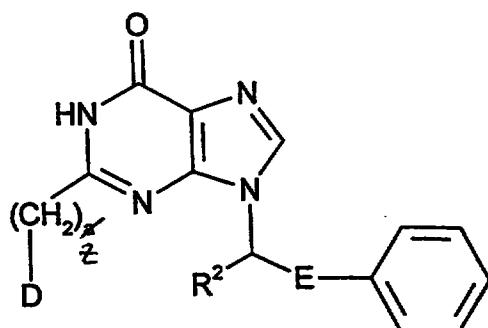
2 mmol of 1-substituted-5-amino-imidazole-4-carboxamide and 8 mmol of the appropriate ester are refluxed for 18 hours in 20 ml of a sodium ethoxide-ethanol solution (prepared from 0.23 g (10 mmol) of sodium and 20 ml of absolute ethanol). After cooling, the mixture is neutralized with glacial acetic acid and evaporated. The
10 residue is purified by flash chromatography and the fractions containing the product are combined and evaporated. Solid residues are recrystallized from ethyl acetate or ethyl acetate/ether.

The purin-6-ones prepared according to Method A, B or C are compiled in Tables 1 and 2.

This Sheet Has Been Replaced



Table 1:

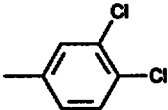
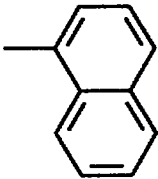
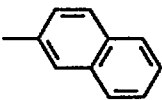
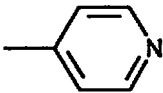
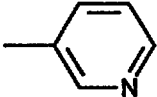
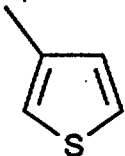
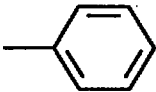


This Sheet Has Been Replaced



Ex. No.	z	D	R ²	E	Yield (% of theory)	Mp. ¹⁾ / R _f ²⁾
1	1		Me	(CH ₂) ₃	63.5	135
2	1		Me	(CH ₂) ₃	61	173
3	1		Me	(CH ₂) ₃	58	164
4	1		Me	(CH ₂) ₃	59	194
5	1		Me	(CH ₂) ₃	41	151
6	1		Me	(CH ₂) ₃	69	196
7	1		Me	(CH ₂) ₃	61	0.54
8	1		Me	(CH ₂) ₃	31	152

Table 1 - continued

Ex. No.	$\frac{n}{z}$	D	R ²	E	Yield (% of theory)	Mp. ¹⁾ / R _f ³⁾
9	1		Me	(CH ₂) ₃	19	107
10	1		Me	(CH ₂) ₃	44	150
11	1		Me	(CH ₂) ₃	51	125
12 ²⁾	1		Me	(CH ₂) ₃	50	156
13 ²⁾	1		Me	(CH ₂) ₃	27	130
14	1		Me	(CH ₂) ₃	81	171
15	2		Me	(CH ₂) ₃	68	187



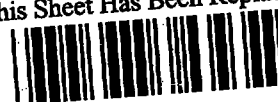


Table 1 - continued

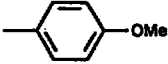
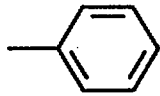
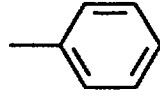
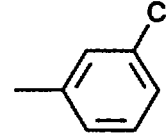
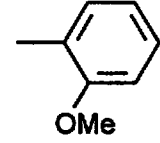
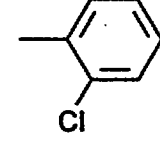
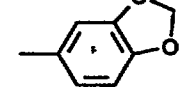
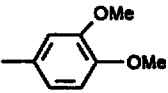
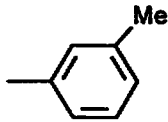
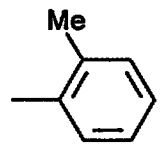
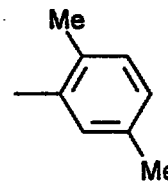
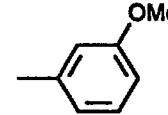
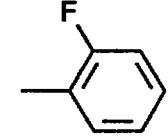
Ex. No.	a	D	R ²	E	Yield (% of theory)	Mp. ¹⁾ / R _f ³⁾
16	2		Me	(CH ₂) ₃	48	135
17	3		Me	(CH ₂) ₃	57	108
18	1		Iso-propyl	(CH ₂) ₃	56	154
19	1		Iso-propyl	(CH ₂) ₃	50	0.46
20	1		Me	(CH ₂) ₃	18.9	80
21	1		Me	(CH ₂) ₃	50	122
22	1		Me	(CH ₂) ₃	36	150
23	1		Me	(CH ₂) ₃	30.9	129

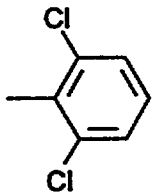
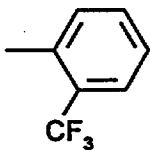
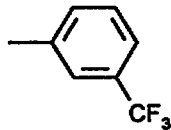
Table 1 - continued

Ex. No.	α Z	D	R ²	E	Yield (% of theory)	Mp. ¹⁾ / R _f ³⁾
24	1		Me	(CH ₂) ₃	43.2	127
25	1		Me	(CH ₂) ₃	29	0.55
26	1		Me	(CH ₂) ₃	41.5	160
27	1		Me	(CH ₂) ₃	43	160
28	1		Me	(CH ₂) ₃	77	0.52
29	1		Me	(CH ₂) ₃	22	0.45

This Sheet Has Been Replaced



Table 1 - continued

Ex. No.	α z	D	R ²	E	Yield (% of theory)	Mp. ¹⁾ / R _f ³⁾
30	1		Me	(CH ₂) ₃	36	157
31	1		Me	(CH ₂) ₃	60.7	200
32	1		Me	(CH ₂) ₃	31.4	126

1) Crystallizes from ethyl acetate or ethyl acetate/ether

2) Not acidified

3) Eluent CH₂Cl₂/ MeOH 10:1

This Sheet Has Been Replaced

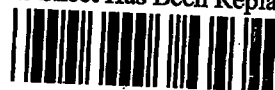
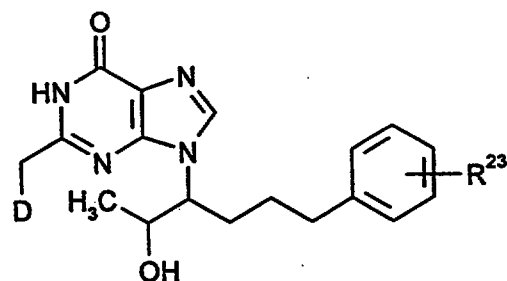
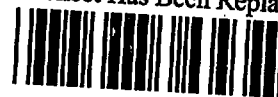


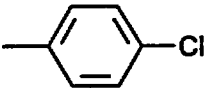
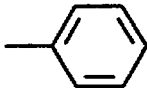
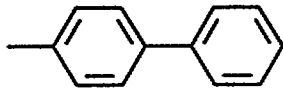
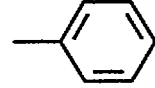
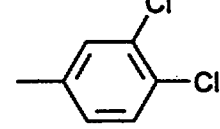
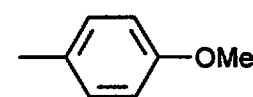
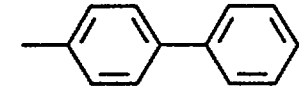
Table 2

This Sheet Has Been Replaced



Ex. No.	D	R ²³	Yield (% of theory)	Mp. ¹⁾ / R _f ²⁾
33		H	21	0.36
34		H	34	153
35		H	31	208
36		4-OMe	56.1	202
37		4-Me	32	191
38		4-Me	30	194

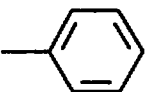
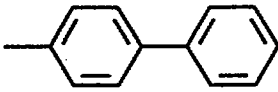
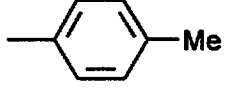
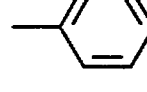
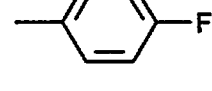
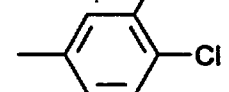
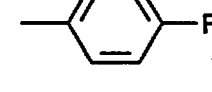
Table 2 - continued

Ex. No.	D	R ²³	Yield (% of theory)	Mp. ¹⁾ / R _f ²⁾
39		4-Me	31.6	213
40		4-Me	64.7	187
41		4-OMe	41.6	184
42		4-OMe	39.5	212
43		4-OMe	39.6	161
44		4-OMe	36.5	164
45		4-OMe	31	187
46		H	52.5	196

This Sheet Has Been Replaced



Table 2 - continued

Ex. No.	D	R ²³	Yield (% of theory)	Mp. ¹⁾ / R _f ²⁾
47		4-Cl	52.3	200
48		4-Cl	55.3	199
49		4-Cl	53.2	207
50		4-Cl	49.7	209
51		4-F	38	168
52		4-OMe	38.6	179
53		4-F	20.2	175
54		H	59.6	198

This Sheet Has Been Replaced



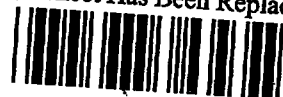


Table 2 - continued

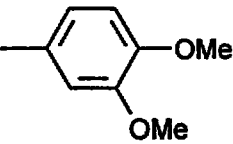
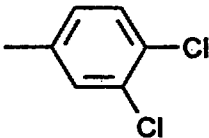
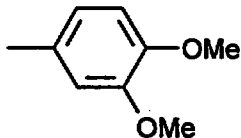
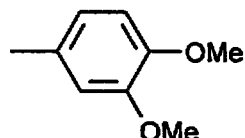
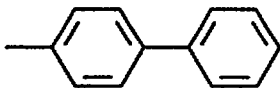
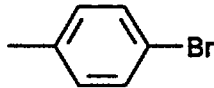
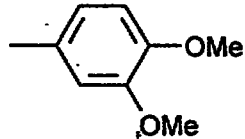
Ex. No.	D	R ²³	Yield (% of theory)	Mp. ¹⁾ / R _f ²⁾
55		H	47.7	160
56		4-Me	39.7	189
57		4-OMe	60	196
58		4-F	60	183
59		4-F	65.8	215
60		H	40	225
61		4-Cl	52.3	150



Table 2 - continued

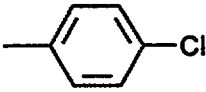
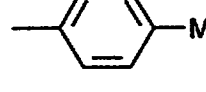
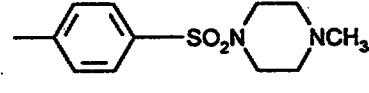
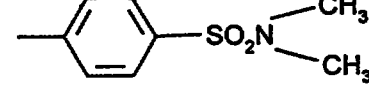
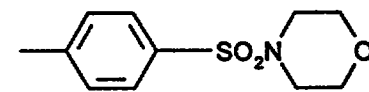
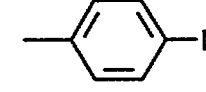
Ex. No.	D	R ²³	Yield (% of theory)	Mp. ¹⁾ / R _f ²⁾
62		4-F	93.4	210
63		4-Cl	33	188
64		4-F	47.4	165
65		4-F	24.4	191
66 ⁴⁾		H	9	0.25
67		H	28.2	0.38
68		H	25.4	0.42
69		H	44.1	191



Table 2 - continued

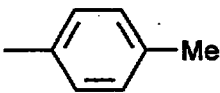
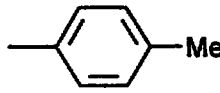
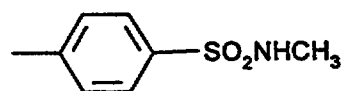
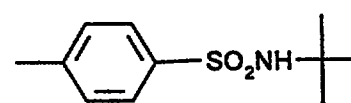
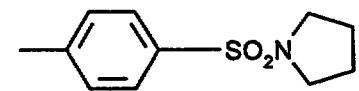
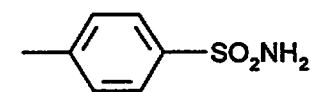
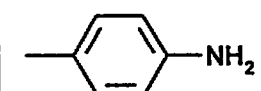
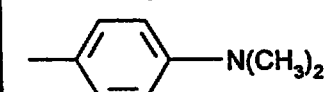
Ex. No.	D	R ²³	Yield (% of theory)	Mp. ¹⁾ / R _f ²⁾
70 ³⁾	 (+ Enantiomer)	H	27.5	[α] _D ²⁰ = + 14.0 (c=1. DMSO)
71 ³⁾	 (- Enantiomer)	H	26	[α] _D ²⁰ = -13.7 (c=1. DMSO)
72		H	23.9	0.29
73		H	41	0.46
74		H	63.6	0.58
75		H	34.3	0.26
76 ⁴⁾		H	55	0.51
77 ⁴⁾		H	52.6	250 (dec.)

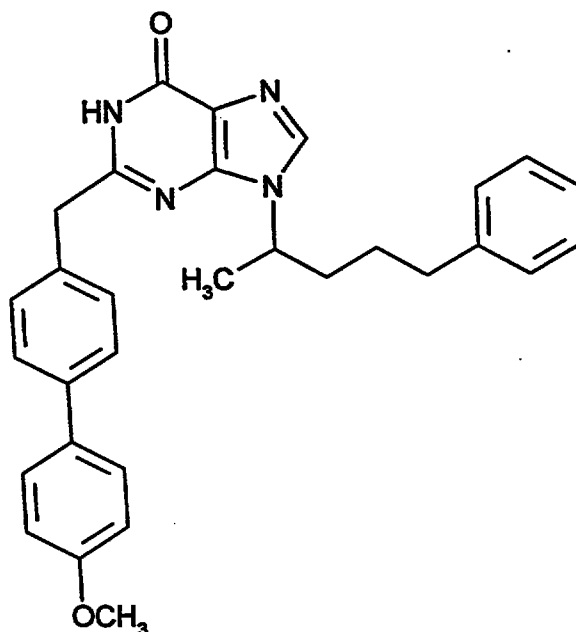


Table 2 - continued

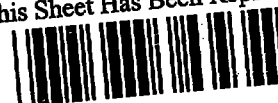
- 1) Crystallizes from ethyl acetate or ethyl acetate/ether
- 2) Eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1
- 3) Resolution of enantiomers by column chromatography using a chiral support
- 4) Mixture concentrated on a rotary evaporator and residue purified directly by flash chromatography without extraction by shaking. R_f determined using $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1 + 1% NH_3 as eluent

Example 78

9-(5-Phenyl-2-pentyl)-2-(4-p-methoxyphenylbenzyl)-purin-6-one



This Sheet Has Been Replaced



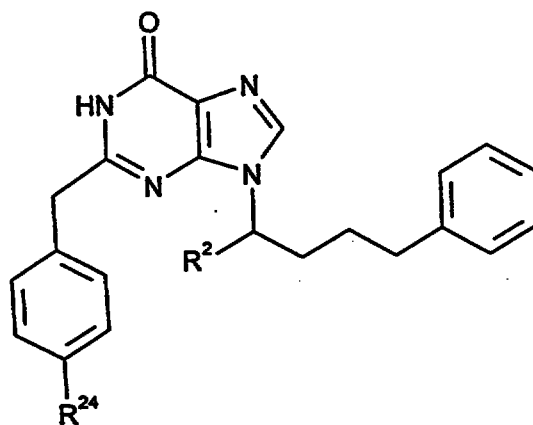
208 mg (0.46 mmol) of 9-(5-phenyl-2-pentyl)-2-(4-bromobenzyl)-purin-6-one
5 (Example 6), 90 mg (0.59 mmol) of p-methoxyphenylboronic acid and 210 mg of
bis(triphenylphosphine)-palladium(II) chloride are stirred at 70°C for 1 h in 10 ml of
abs. THF. 0.65 ml of 2N Na₂CO₃ solution are then added and the mixture is refluxed
for 5 h (TLC checking). The mixture is evaporated and the residue is purified by flash
chromatography (silica gel, eluent CH₂Cl₂/MeOH 30:1). The fractions containing the
10 product are combined and evaporated. The residue is recrystallized from ethyl
acetate/ether.

Yield: 161 mg (78.5%)

M.p.: 172°C

The examples shown in Table 3 were prepared in an analogous manner:

This Sheet Has Been Replaced

**Table 3:**

5

Ex.- No.	R ²⁴	R ²	Yield (% of theory)	Mp. / R _f
79		CH ₃	27	170 ¹⁾
80		CH ₃	69	193 ²⁾
81		CH ₃	68	128 ¹⁾

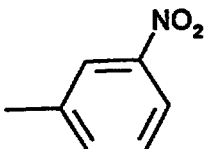
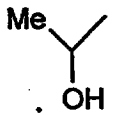
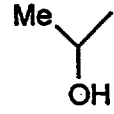
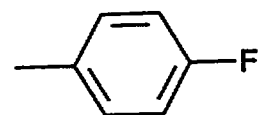
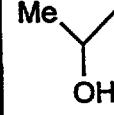
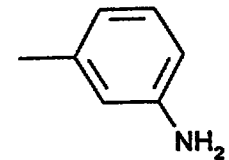
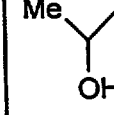
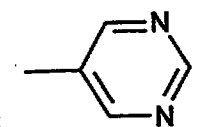
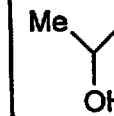


Table 3 - continued

Ex.- No.	R ²⁴	R ²	Yield (% of theory)	Mp. / R _f
82		CH ₃	54	178 ¹⁾
83		CH ₃	79	199 ¹⁾
84 ⁴⁾		CH ₃	67	0.33 ³⁾
85 ⁴⁾			41.8	191
86			49.6	209
87			76.8	200



Table 3 - continued

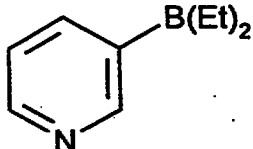
Ex.- No.	R ²⁴	R ²	Yield (% of theory)	Mp. / R _f
88			35.6	185
89			43	182
90			46	183
91			8	0.45 ³⁾
92			41.6	200

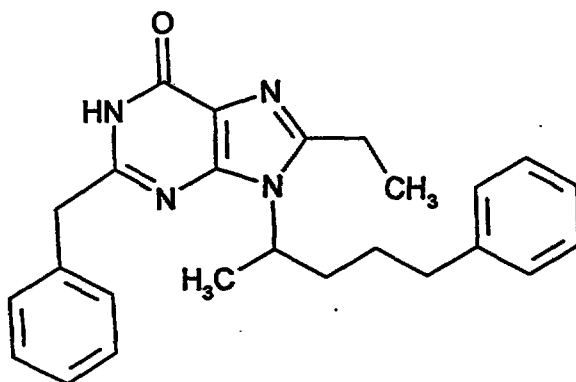
5

1) Crystallizes from ethyl acetate/ether

2) Crystallizes from ether

3) Eluent CH₂Cl₂/ MeOH 10:1

4) From  using Pd(PPh₃)₄ as catalyst

Example 93**9-(5-Phenyl-2-pentyl)-8-ethyl-2-benzyl-purin-6-one**

This Sheet Has Been Replaced



1.2 g (4 mmol) of 1-(5-phenyl-3-pentyl)-2-ethyl-5-aminoimidazole-4-carboxamide are
5 stirred at 50°C for 30 minutes with 240 mg (6 mmol) of sodium hydride (60%) in
30 ml of abs. THF and 10 ml of abs. DMF. After cooling to 20°C, 773 mg (5 mmol)
of phenylacetyl chloride in 10 ml of abs. THF are added dropwise and the mixture is
stirred overnight at 20°C. 10 ml of H₂O, then 10 ml of 2N HCl, then 100 ml of ethyl
acetate are slowly added. The organic phase is separated off, dried over Na₂SO₄ and
10 evaporated. The residue is purified by flash chromatography (silica gel, eluent
CH₂Cl₂/MeOH 50:1 > 20:1).

R_f = 0.32 (CH₂Cl₂/MeOH 10:1)

Yield: 441 mg (26.4%)

440 mg (1.05 mmol) of the acylated imidazole-carboxamide and 0.58 g (4.2 mmol) of
15 potassium carbonate are refluxed overnight in 20 ml of methanol and 5 ml of H₂O.
After cooling, 10 ml of 2N HCl are added, the mixture is extracted twice by shaking
with 20 ml of ethyl acetate each time and the combined ethyl acetate phases are
washed once with water and once with satd. NaCl solution. After drying over Na₂SO₄,
the organic phase is evaporated and the residue is purified by flash chromatography
20 (silica gel, eluent CH₂Cl₂/MeOH 30:1 > 20:1).

Yield: 161 mg (38.3%)

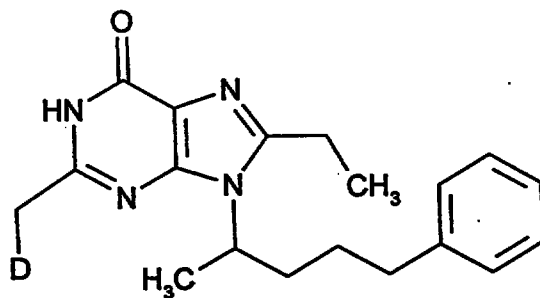
R_f = 0.33 (CH₂Cl₂/MeOH 10:1)

The examples shown in Table 4 are prepared in an analogous manner:



Table 4:

This Sheet Has Been Replaced



5

Ex.-No.	D	Yield (% of theory)	Mp. / R _f ¹⁾
94		59	0.35
95		39	0.32
96 ²⁾		64	0.26

10 ¹⁾ Eluent: CH₂Cl₂/ MeOH 10:1²⁾ Not extracted by shaking with HCl

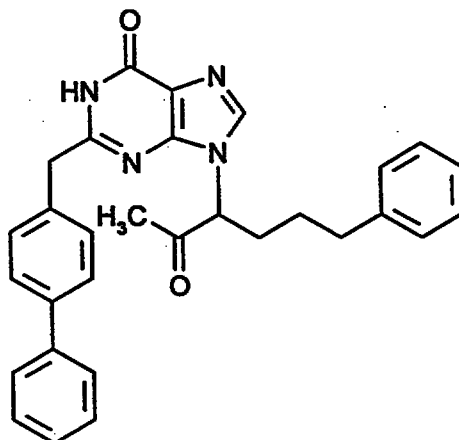
Example 97

9-(6-Phenyl-2-oxo-3-hexyl)-2-(4-phenyl-benzyl)-purin-6-one

This Sheet Has Been Replaced



5

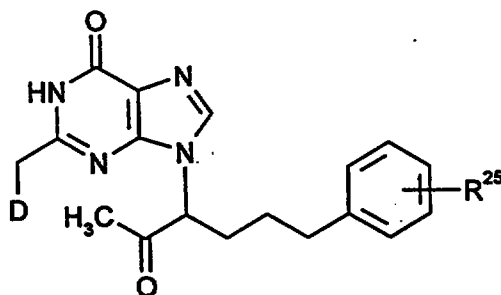


478 mg (1 mmol) of 9-(6-phenyl-2-hydroxy-3-hexyl)-2-(4-phenyl-benzyl)-purin-6-one (Ex. 46) and 1.3 ml of triethylamine are dissolved in 10 ml of CH_2Cl_2 and 3 ml of DMSO and 0.7 g of pyridine/ SO_3 complex is added at 0°C . The mixture is stirred at 20°C for 16 h and extracted by shaking with 10 ml of 2N HCl and 10 ml of saturated NaHCO_3 solution once each. After drying the organic phase over Na_2SO_4 , it is evaporated and the residue is purified by flash chromatography on silica gel (eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 40:1). Yield: 425 mg (89.3%), $R_f = 0.52$ ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 30:1)

15 The compounds shown in Table 5 are prepared in an analogous manner.

Table 5

This Sheet Has Been Replaced

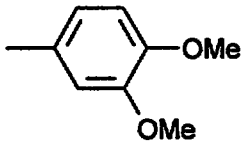
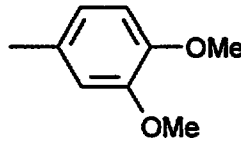
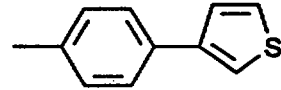
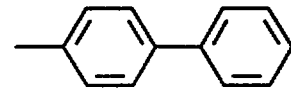


5

Ex. No.	D	R ²⁵	Yield	R _f ¹⁾
98		4-OMe	41.9	0.63
99		H	76.6	0.59
100		H	50	0.56
101		H	38.2	0.55
102		4-OMe	40	0.55

10

Table 5 - continued

Ex. No.	D	R ²⁵	Yield	R _f ¹⁾
103		4-F	35	0.54
104		4-Cl	11.5	0.49
105		H	62.8	0.54
106		4-F	25	0.48

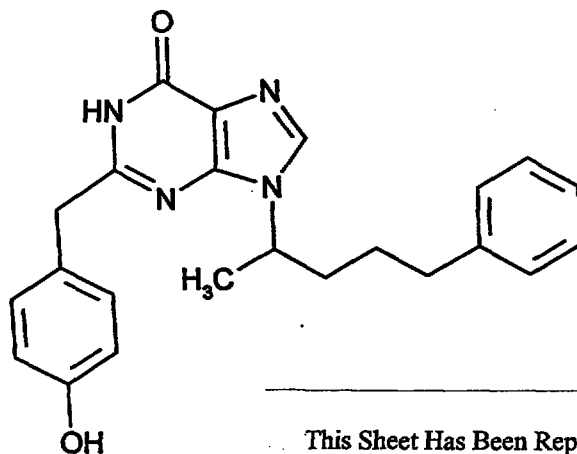
1) Eluent: CH₂Cl₂/MeOH 30:1

This Sheet Has Been Replaced



Example 107

9-(5-Phenyl-2-pentyl)-2-(4-hydroxybenzyl)-purin-6-one



This Sheet Has Been Replaced



- 2.2 ml of a 1 molar solution of boron tribromide in CH_2Cl_2 are added dropwise at
5 -78°C to 404 mg (1 mmol) of the compound from Example 7 in 5 ml of abs. CH_2Cl_2 .
After 30 minutes at -78°C , the mixture is stirred at 20°C for 2 hours. As starting
substance was still to be seen in the thin-layer chromatogram, a further 1.1 ml of the
1 molar BBr_3 solution were added dropwise at -78°C . After stirring overnight at room
temperature, the mixture is cooled to -78°C , and 5 ml of methanol are added dropwise.
10 The mixture is evaporated, the residue is taken up in 10 ml of CH_2Cl_2 and the solution
is extracted twice by shaking with 10 ml of 10% NaOH solution each time. The
combined NaOH phases are acidified to pH 1-2 by addition of conc. HCl solution and
extracted twice by shaking with 30 ml of ethyl acetate each time. The combined ethyl
acetate phases are evaporated and the residue is purified by flash chromatography (silica
15 gel, eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 50:1 $\rightarrow$ 30:1). Recrystallization from ethyl acetate/ether.

Yield: 250 mg (64.4%)

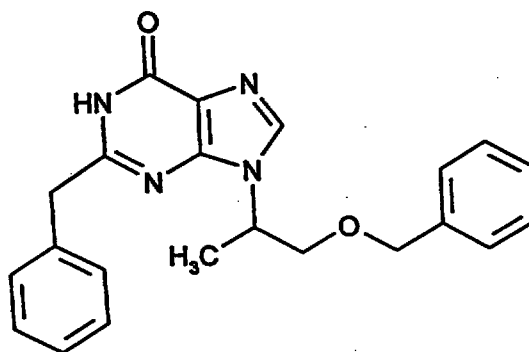
M.p.: 184°C

Example 108

5

9-(1-Benzoyloxy-2-propyl)-2-benzyl-purin-6-one

This Sheet Has Been Replaced



- 10 a) 22 g (0.22 mol) of 2-amino-2-cyano-acetamide and 37 ml of triethyl orthoformate are refluxed in 200 ml of acetonitrile for 1 hour. 17.5 ml of 2-amino-1-propanol are then added and the mixture is refluxed for a further 15 minutes. After cooling, it is concentrated, and the residue is dissolved in a little methanol and purified by flash chromatography on silica gel (eluent
- 15 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1). The yield of crystalline 5-amino-1-(1-hydroxy-2-propyl)-imidazole-4-carboxamide is 24.3 g (60%).
- b) 24 g (0.13 mol) of the compound from step a) are stirred at 50°C for 2 hours with 25 ml of acetic anhydride and 30 ml of pyridine in 100 ml of abs. CH_2Cl_2 .
- 20 After cooling, the mixture is extracted by shaking with std. NaCl, and the organic phase is dried over Na_2SO_4 and evaporated. The residue is crystallized from ethyl acetate/ether. The yield of 5-amino-1-(1-acetoxy-2-propyl)-imidazole-4-carboxamide is 23.4 g (84.2%).
- 25 c) 23 g (0.107 mol) of the compound from step b) and 1 g of DMAP (dimethylaminopyridine) are dissolved in 100 ml of pyridine. A solution of 12.1 ml of phenylacetyl chloride in 20 ml of abs. toluene is added dropwise to

this solution and it is stirred at 20°C for 30 minutes. It is then stirred at 60°C for 2 hours and evaporated, the residue is added to 100 ml of abs. toluene and the mixture is evaporated again. The residue is dissolved in methylene chloride and the organic phase is washed with water. The product crystallizes out of the methylene chloride phase, and is filtered off with suction, dried and directly reacted further without further purification. The yield of 5-phenylacetyl-amino-1-(1-acetoxy-2-propyl)-imidazole-4-carboxamide is 12.8 g (36%).

5
10
15
d) 12.8 g (38.5 mmol) of the compound from step c) and 6.2 g (155 mmol) of NaOH are refluxed for 3 hours in 100 ml of a methanol/water mixture (1:1). After cooling, the mixture is acidified with 10% HCl and extracted twice with ethyl acetate. The combined ethyl acetate phases are washed with saturated NaCl solution, dried over Na₂SO₄ and evaporated. The residue is recrystallized from ethyl acetate/ether. The yield of 9-(1-hydroxy-2-propyl)-2-benzylpurin-6-one is 6.2 g (55.2%), M.p.: 192°C.

20
25
e) 576 mg (2 mmol) of the purin-6-one from step d) and 200 mg of NaH (60% strength) are refluxed for 30 minutes in 30 ml of abs. THF. After cooling, 0.3 ml (2.4 mmol) of benzyl chloride are added dropwise in a little abs. THF at 20°C and the mixture is stirred for 16 hours. 5 ml of H₂O are added dropwise, then the mixture is evaporated and the residue is taken up in ethyl acetate. The organic phase is washed with 2N HCl and saturated NaCl solution, dried over Na₂SO₄ and evaporated. The residue is purified by flash chromatography on silica gel (eluent: CH₂Cl₂/MeOH 40:1). The fractions containing the product are combined and evaporated. The residue is crystallized using diethyl ether. Yield 510 mg (67.5%), M.p. 149°C.

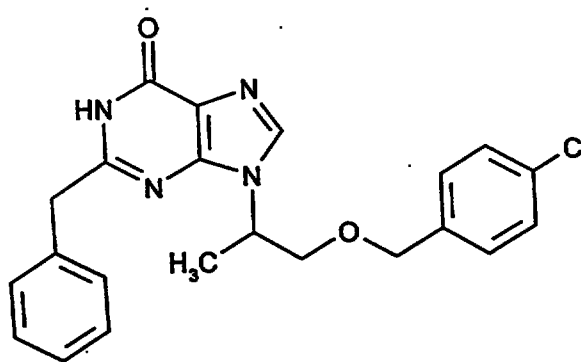
Example 109

This Sheet Has Been Replaced



30 9-(1-p-Chlorobenzyloxy-2-propyl)-2-benzyl-purin-6-one

This Sheet Has Been Replaced



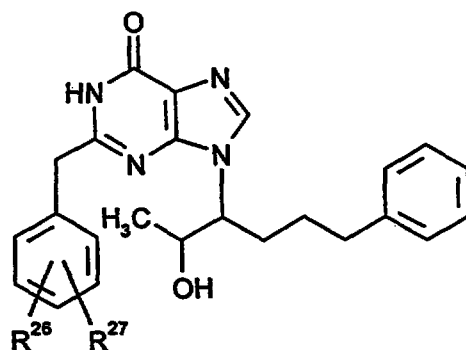
The title compound was prepared in an analogous manner to the procedure of Example 108. Yield: 59%, m.p. 166°C.

5

The examples shown in Table 6 were prepared according to the procedures mentioned above in analogy to the compounds from Table 2, as a rule according to method c).

Table 6:

This Sheet Has Been Replaced



5

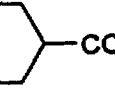
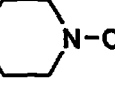
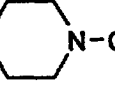
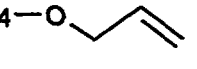
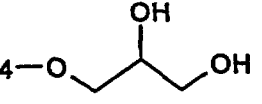
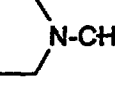
10

15

Ex.N o.	R ²⁶ / R ²⁷	Yield (% of theory)	Mp C / R _f
110	4-NH-COCH ₃ / H	44	236 ¹⁾
111	4-NHSO ₂ CH ₃ / H	60.6	0.28 ³⁾
112	4-NH-COCH ₂ OCH ₃ / H	34	201 ¹⁾
113	4-SO ₂ N ₂ CH ₂ CH ₂ CH ₂ CO ₂ C ₂ H ₅ / H	46.2	0.5 ³⁾
114	4-SO ₂ NHCH ₂ CH ₂ N(CH ₃) ₂ / H	31	0.16 ⁴⁾
115	4-NH-COCH ₂ CH ₂ N(CH ₃) ₂ / H	59	0.46 ⁵⁾
116	4-SO ₂ NHCH ₂ CH ₂ OH / H	15.2	0.29 ³⁾
117	4-SO ₂ NHCH ₂ CH ₂ OCH ₃ / H	19.8	0.48 ³⁾



Table 6 - continued

Ex.N o.	R ²⁶ / R ²⁷	Yield (% of theory)	Mp C / R _f
118	4—SO ₂ N—  —CO ₂ H ⁶⁾ / H	64.5	0.32 ⁴⁾
119	4-NH-CONH ₂ / H	89	0.27 ⁴⁾
120	4-NH-CHO / H	28	0.37 ⁵⁾
121	4-NH-CO—  —N-CO ₂ -CH ₂ -  / H	13.2	0.46 ⁵⁾
5 122	4-NH-CO—  —N-CO ₂ C ₂ H ₅ / H	36.5	0.4 ⁵⁾
123	4-NH-CO-NHCH ₃ / H	67.3	225 ¹⁾
124	4-SO ₂ NH-COCH ₃ / H	25.5	0.38 ⁴⁾
125	4-NH-CO-N(CH ₃) ₂	12.2	0.39 ⁵⁾
126	4-SO ₂ NH-CO ₂ CH ₃ / H	6.2	0.25 ⁴⁾
10 127	4-O—  / H	78.6	174 ¹⁾
128	4-O—  / H	55.5	0.25 ⁴⁾
129	3—SO ₂ —N—  —N-CH ₃ / 4-OCH ₃	25.2	0.3 ³⁾
130	4-SO ₂ NH-CONHCH ₃	17.4	0.39 ⁴⁾
131	4-O-CH ₂ -CO ₂ CH ₃	47.9	146 ¹⁾
15 132	4-O-CH ₂ -CO ₂ H ⁷⁾	93	0.37 ³⁾



Le A 31 383 - Foreign Countries

- 60 -

Table 6 - continued

Ex.N o.	R ²⁶ / R ²⁷	Yield (% of theory)	Mp C / R _f
133	$3\text{---SO}_2\text{NH---CH}_2\text{CH}_2\text{N(CH}_3)_2 \quad / \quad 4\text{---OCH}_3$	40.9	0.23 ¹⁾
134	$3\text{---SO}_2\text{NH---CH}_2\text{CH}_2\text{OCH}_3 \quad / \quad 4\text{---OCH}_3$	37.6	0.29 ³⁾
135	$3\text{---SO}_2\text{NH---CH}_2\text{CH}_2\text{OH} \quad / \quad 4\text{---OCH}_3$	44.9	0.14 ³⁾
136	3-SO ₂ NHCH ₃ / 4-OCH ₃	56.5	0.23 ³⁾
137	$3\text{---SO}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{C}_6\text{H}_{10} \end{array} \text{---CO}_2\text{C}_2\text{H}_5 \quad / \quad 4\text{---OCH}_3$	61	0.37 ³⁾
138	$3\text{---SO}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{C}_6\text{H}_{10} \end{array} \text{---CO}_2\text{H}^{3)} \quad / \quad 4\text{---OCH}_3$	54	0.16 ³⁾
139	3-NO ₂ / 4-OH	56.5	146°C ¹⁾
140	3-NO ₂ / 4-OC ₂ H ₅	57	180°C ¹⁾
141	3-NH ₂ / 4-OCH ₃	58	187°C ¹⁾ (dec.)
142	3-NH ₂ / 4-OH	31.5	152°C ¹⁾ (dec.)
143	3-NHSO ₂ CH ₃ / 4-OCH ₃	63	132°C ¹⁾
144	3-NH-COCH ₃ / 4-OCH ₃	54.5	0.42 ³⁾
145	3-NH-COCH ₃ / 4-OH	33.6	0.45 ³⁾

15 ¹⁾ Crystallizes from ethyl acetate/ether²⁾ Crystallizes from ether

This Sheet Has Been Replaced



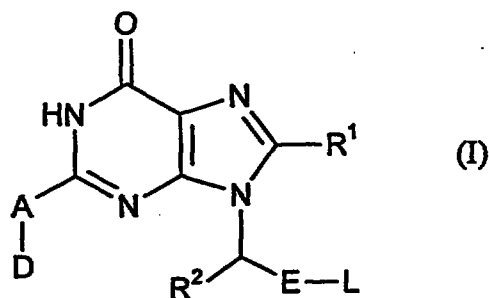
Table 6 - continued

- | | | |
|---|----|--|
| | 3) | Eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1 |
| | 4) | Eluent: $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 7:1 |
| | 5) | Eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1 + 1% NH_3 |
| | 6) | Prepared by hydrolysis of the corresponding ester Example 113 |
| 5 | 7) | Prepared by hydrolysis of the corresponding ester Example 131 |
| | 8) | Prepared by hydrolysis of the corresponding ester Example 137 |



Patent claims

1. Purin-6-one derivatives of the general formula (I)



This Sheet Has Been Replaced



in which

- 5 R^1 represents hydrogen or straight-chain or branched alkyl having up to 8 carbon atoms,
- R^2 represents straight-chain or branched acyl having up to 4 carbon atoms, or represents straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by hydroxyl, azido or by a group of the
- 10 formula $-NR^3R^4$ or $-OSO_2R^5$,

in which

R^3 and R^4 are identical or different and

denote cycloalkyl having 3 to 6 carbon atoms, hydrogen, formyl or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms or by a group of the formula $-(CO)_x-NR^6R^7$,

in which

15



a denotes a number 0 or 1,

5

R^6 and R^7 are identical or different and denote hydrogen, formyl, hydroxyl, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl or by straight-chain or branched alkoxy having up to 5 carbon atoms,

or

10

R^3 and/or R^4 denote straight-chain or branched alkoxycarbonyl having up to 6 carbon atoms, carboxyl or straight-chain or branched acyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl or straight-chain or branched alkoxy having up to 4 carbon atoms

or

15

R^3 and/or R^4 denote a radical of the formula $-(CO)_b-T-NR^8R^9$, $-CO-R^{10}$, $-SO_2R^{11}$ or $-SO_2NR^{12}R^{13}$, in which

b has the meaning of a indicated above and is identical to or different from this

20

T denotes straight-chain or branched alkyl having up to 5 carbon atoms
or if $b \neq 0$ can also denote a bond,

R^8 and R^9 have the meaning of R^6 and R^7 indicated above and are identical to or different from this

R^{10} denotes a saturated, partially unsaturated or unsaturated 5- to 7-



5

membered heterocycle having up to 3 heteroatoms from the series S, N and/or O, which can optionally also be substituted via the N function, by straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms, carboxyl, benzyloxycarbonyl or hydroxyl,

R¹¹ denotes straight-chain or branched alkyl having up to 5 carbon atoms, benzyl or phenyl,

R¹² and R¹³ are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms,

10

or

R³ and R⁴, together with the nitrogen atom, form a 5- or 6-membered saturated, partially unsaturated or unsaturated heterocycle which can contain up to 3 heteroatoms from the series N, S and/or O or a radical -NR¹⁴, and which is optionally substituted by carbonyl, by straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms or by straight-chain or branched alkyl having up to 5 carbon atoms, which for its part can be substituted by hydroxyl, carboxyl or by straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 6 carbon atoms,

15

20

in which

R¹⁴ denotes hydrogen, carbonyl or straight-chain or branched alkyl or alkoxycarbonyl each having up to 5 carbon atoms,

and

R⁵ denotes phenyl or straight-chain or branched alkyl having up to 5 carbon



atoms,

A represents a straight-chain or branched alkylene or alkenylene chain each having up to 6 carbon atoms,

5 D and L are identical or different and represent aryl having 6 to 10 carbon atoms or a 5- to 7-membered aromatic, optionally benzo-fused heterocycle having up to 3 heteroatoms from the series S, N and/or O, each of which is optionally substituted up to 3 times identically or differently by halogen, hydroxyl, nitro, trifluoromethyl, carboxyl, straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 6 carbon atoms or by a group
10 of the formula $-(V)_c-NR^{15}R^{16}$ and/or $-OR^{17}$,

in which

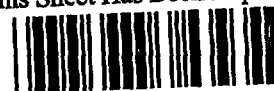
c denotes a number 0 or 1,

V denotes a radical of the formula $-CO$ or $-SO_2$,

15 R^{15} and R^{16} are identical or different and have the meaning of R^3 and R^4 indicated above,

20 R^{17} denotes hydrogen, straight-chain or branched alkenyl having up to 8 carbon atoms or straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted up to 3 times identically or differently by hydroxyl, carboxyl or straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms,

and/or the cycles are optionally substituted by aryl having 6 to 10 carbon atoms or by a 5- to 7-membered aromatic, optionally benzo-fused heterocycle having up to 3 heteroatoms from the series S, N and/or O, each of which for its part is optionally substituted up to 2 times identically or



differently by halogen, hydroxyl, nitro, carboxyl, trifluoromethyl or by straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 5 carbon atoms or by a group of the formula $(V')_d-NR^{18}R^{19}$,

in which

5 d has the meaning of a indicated above and is identical to or different from this,

R^{18} and R^{19} have the meaning of R^3 and R^4 indicated above and are identical to or different from this,

10 V' has the meaning of V indicated above and is identical or different from this,

and/or

the ring systems mentioned under D

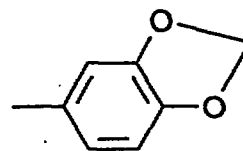
15 are optionally substituted by straight-chain or branched acyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl, straight-chain or branched alkoxy having up to 5 carbon atoms or by a group of the formula $-NR^{20}R^{21}$,

in which

R^{20} and R^{21} are identical or different and have the meaning of R^3 and R^4 indicated above,

20 or

D represents a radical of the formula



This Sheet Has Been Replaced



and

E represents a radical of the formula $-\text{CH}_2-\text{Y}-\text{Z}-$,

in which

5 Y denotes a bond or an oxygen or sulphur atom or the $-\text{NH}$ group,

Z denotes a straight-chain or branched alkylene chain having up to 5 carbon atoms,

and their tautomers and salts.

10 2. Purin-6-one derivatives of the formula according to Claim 1, in which

R^1 represents hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,

R^2 represents straight-chain or branched acyl having up to 6 carbon atoms, or represents straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by hydroxyl, azido or by a group of the formula $-\text{NR}^3\text{R}^4$ or $\text{O}-\text{SO}_2-\text{R}^5$,

15

in which



5

R^3 and R^4 are identical or different and

denote cyclopentyl, cyclohexyl, hydrogen, formyl or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or alkoxycarbonyl each having up to 5 carbon atoms or by a group of the formula $-(CO)_a-NR^6R^7$,

in which

This Sheet Has Been Replaced



a denotes a number 0 or 1,

10

R^6 and R^7 are identical or different and denote hydrogen, formyl, hydroxyl, phenyl or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl or by straight-chain or branched alkoxy having up to 4 carbon atoms,

or

15

R^3 and/or R^4 denote straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms, carboxyl or straight-chain or branched acyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl or straight-chain or branched alkoxy having up to 3 carbon atoms

20

or

R^3 and/or R^4 denote a radical of the formula $-(CO)_b-T-NR^8R^9$, $-CO-R^{10}$, $-SO_2R^{11}$ or $-SO_2NR^{12}R^{13}$, in which

b has the meaning of a indicated above and is identical to or different from this



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

or if $b \neq 0$ can also denote a bond,

5

R^8 and R^9 have the meaning of R^6 and R^7 indicated above and are identical to or different from this

10

R^{10} denotes morpholinyl, imidazolyl, pyridyl, piperazinyl, piperidinyl or pyrrolidinyl, each of which can optionally be substituted, also via the N function, by straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms, carboxyl, benzyloxycarbonyl or hydroxyl,

This Sheet Has Been Replaced



R^{11} denotes straight-chain or branched alkyl having up to 4 carbon atoms, benzyl or phenyl,

R^{12} and R^{13} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 5 carbon atoms,

15

or

20

R^3 and R^4 , together with the nitrogen atom, form a pyrrolidinyl, morpholinyl, imidazolyl, piperidinyl or piperazinyl ring, each of which, optionally also via the nitrogen function, can be substituted by straight-chain or branched alkoxycarbonyl having up to 4 carbon atoms, carboxyl, or by straight-chain or branched alkyl having up to 4 carbon atoms, which for its part can be substituted by carboxyl, hydroxyl or by straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms,

and



R^5 denotes phenyl or straight-chain or branched alkyl having up to 4 carbon atoms,

A represents a straight-chain or branched alkylene or alkenylene chain each having up to 5 carbon atoms,

5 D and L are identical or different and represent phenyl, naphthyl, pyridyl, pyrimidyl, thienyl, indolyl or furyl, each of which is optionally substituted up to 3 times identically or differently by fluorine, chlorine, bromine, trifluoromethyl, nitro, carboxyl, straight-chain or branched alkyl or alkoxycarbonyl each having up to 5 carbon atoms or by a group of the formula $-(V)_cNR^{15}R^{16}$ and/or $-OR^{17}$,

10 in which

c denotes a number 0 or 1,

V denotes a radical of the formula $-CO$ or $-SO_2$,

R^{15} and R^{16} are identical or different and have the meaning of R^3 and R^4 indicated above,

15 R^{17} denotes hydrogen, straight-chain or branched alkenyl having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted up to 2 times identically or differently by hydroxyl, carboxyl or by straight-chain or branched alkoxycarbonyl having up to 4 carbon atoms,

20 and/or the cycles are optionally substituted by naphthyl, phenyl, pyridyl, indolyl, thienyl, furyl, pyridazinyl, pyridyl, pyrrol or pyrimidyl, each of which for its part is optionally substituted by fluorine, chlorine, bromine, hydroxyl, nitro, carboxyl, trifluoromethyl or by straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms or by a

This Sheet Has Been Replaced





group of the formula $-(V')_dNR^{18}R^{19}$,

in which

d has the meaning of a indicated above and is identical to or different from this,

5 V' has the meaning of V indicated above and is identical to or different from this,

R^{18} and R^{19} have the meaning of R^3 and R^4 indicated above,

and/or

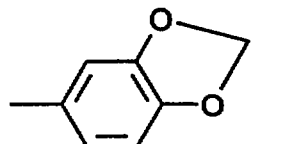
the ring systems mentioned under D

10 are optionally substituted by straight-chain or branched acyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl, straight-chain or branched alkoxy having up to 4 carbon atoms or by a group of the formula $-NR^{20}R^{21}$,

in which

15 R^{20} and R^{21} are identical or different and have the meaning of R^3 and R^4 indicated above,

or D represents a radical of the formula



This Sheet Has Been Replaced



E represents a radical of the formula $-\text{CH}_2-\text{Y}-\text{Z}-$,



in which

Y denotes a bond or an oxygen or sulphur atom or the $-\text{NH}$ group,

Z denotes a straight-chain or branched alkylene chain having up to 4 carbon atoms,

5

and their tautomers and salts.

3. Purin-6-one derivatives of the formula according to Claim 1, in which

This Sheet Has Been Replaced



R^1 represents hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

10

R^2 represents straight-chain or branched acyl having up to 5 carbon atoms, or represents straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by hydroxyl, azido or by a group of the formula $-\text{NR}^3\text{R}^4$ or $\text{O}-\text{SO}_2\text{R}^5$,

in which

15

R^3 and R^4 are identical or different and

denote cyclopentyl, hydrogen, formyl or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted by hydroxyl, carboxyl or by straight-chain or branched alkoxy or each alkoxycarbonyl having up to 3 carbon atoms or by a group of the formula $-(\text{CO})_a-\text{NR}^6\text{R}^7$,

20

in which



5

a denotes a number 0 or 1,

R^6 and R^7 are identical or different and denote hydrogen, formyl, hydroxyl or straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl, or by straight-chain or branched alkoxy having up to 3 carbon atoms,

or

This Sheet Has Been Replaced



10

R^3 and/or R^4 denote straight-chain or branched alkoxycarbonyl having up to 3 carbon atoms, carboxyl or straight-chain or branched acyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl, methoxy or ethoxy

or

R^3 and/or R^4 denote a radical of the formula $-(CO)_b-T-NR^8R^9$, $-CO-R^{10}$, $-SO_2R^{11}$ or $-SO_2NR^{12}R^{13}$, in which

15

b has the meaning of a indicated above and is identical to or different from this

T denotes straight-chain or branched alkyl having up to 3 carbon atoms
or if $b \neq 0$ can also denote a bond,

20

R^8 and R^9 have the meaning of R^6 and R^7 indicated above and are identical to or different from this

R^{10} denotes morpholinyl, piperidinyl, piperazinyl or pyrrolidinyl, each of which can optionally also be substituted via the N function, by straight-chain or branched alkyl, alkoxy or



alkoxycarbonyl each having up to 3 carbon atoms, benzyloxycarbonyl, carboxyl or hydroxyl,

R^{11} denotes straight-chain or branched alkyl having up to 3 carbon atoms, benzyl or phenyl,

5 R^{12} and R^{13} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

or

R^3 and R^4 , together with the nitrogen atom, form a pyrrolidinyl, morpholinyl, imidazolyl, piperidinyl or piperazinyl ring, each of which, optionally also via the nitrogen function, can be substituted by straight-chain or branched alkyl or alkoxycarbonyl each having up to 3 carbon atoms or carboxyl or by straight-chain or branched alkyl having up to 3 carbon atoms, which for its part can be substituted by carboxyl, hydroxyl or by straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms

10

This Sheet Has Been Replaced



15

and

R^5 denotes phenyl or straight-chain or branched alkyl having up to 3 carbon atoms.

A represents an ethenyl (-vinyl) or an alkylene chain having up to 4 carbon atoms,

20

in which

D and L are identical or different and represent phenyl, naphthyl, furyl, thienyl, indolyl or pyridyl, each of which is optionally substituted up to 2 times identically or differently by fluorine, chlorine, bromine, nitro, carboxyl,



trifluoromethyl, straight-chain or branched alkyl or alkoxy carbonyl each having up to 4 carbon atoms or by a group of the formula $-(V)_cNR^{15}R^{16}$ and/or $-OR^{17}$,

in which

This Sheet Has Been Replaced



5 c denotes a number 0 or 1,

V denotes a radical of the formula $-CO$ or $-SO_2$,

R^{15} and R^{16} are identical or different and have the meaning of R^3 and R^4 indicated above,

10 R^{17} denotes hydrogen, straight-chain or branched alkenyl having up to 4 carbon atoms or straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally substituted up to 2 times identically or differently by hydroxyl, carboxyl or by straight-chain or branched alkoxy carbonyl having up to 3 carbon atoms

15 and/or the cycles are optionally substituted by phenyl, pyrimidyl, pyridazinyl, pyridyl, thienyl or furyl, each of which for its part is optionally substituted by fluorine, chlorine, bromine, hydroxyl, nitro, carboxyl, trifluoromethyl or by straight-chain or branched alkyl, alkoxy or alkoxy carbonyl each having up to 3 carbon atoms or by a group of the formula $-(V')_dNR^{18}R^{19}$,

20 in which

d has the meaning of a indicated above and is identical to or different from this,

V' has the meaning of V indicated above and is identical to or



different from this,



R^{18} and R^{19} have the meaning of R^3 and R^4 indicated above,

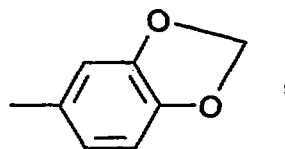
and/or

5 D is optionally substituted by straight-chain or branched acyl having up to 3 carbon atoms, which is optionally substituted by hydroxyl, straight-chain or branched alkoxy having up to 3 carbon atoms or by a group of the formula $-NR^{20}R^{21}$,

in which

10 R^{20} and R^{21} are identical or different and have the meaning of R^3 and R^4 indicated above,

D represents a radical of the formula



E represents a radical of the formula $-CH_2-Y-Z-$,

in which

Y denotes a bond or an oxygen or sulphur atom or the $-NH$ group,

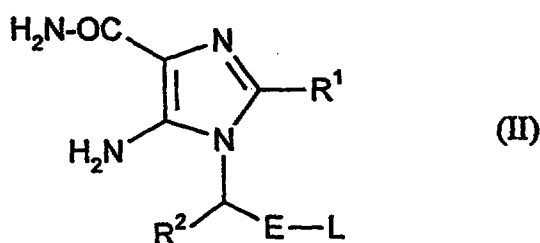
15 Z denotes an alkylene chain having up to 4 carbon atoms

and their tautomers and salts.

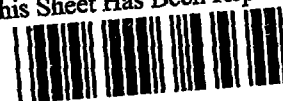


4. Purin-6-one derivatives according to Claims 1 to 3 for therapeutic use.
5. Process for the preparation of purin-6-one derivatives according to Claims 1 to 3, characterized in that

[A] first compounds of the general formula (II)



This Sheet Has Been Replaced



in which

R^1 , R^2 , E and L have the meaning indicated,

are converted by reaction with compounds of the general formula (III)



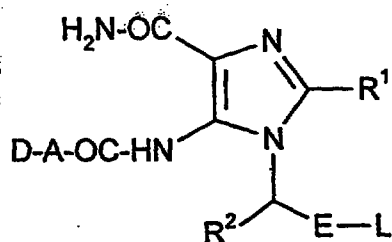
10

in which

A and D have the meaning indicated,

in inert solvents and in the presence of a base,

into the compounds of the general formula (IV)



(IV)

This Sheet Has Been Replaced



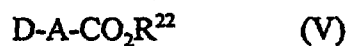
in which

A, D, E, L, R^1 and R^2 have the meaning indicated,

and in a second step these are cyclized in inert solvents and in the presence
5 of a base,

or

[B] compounds of the general formula (II) are directly reacted with
compounds of the general formula (V)



10

in which

D and A have the meaning indicated above and

R^{22} represents $\text{C}_1\text{-C}_4\text{-alkyl}$

in alcohols and in the presence of a base,

and, if appropriate, the substituents mentioned under R^2 are introduced or
15 derivatized by acylation, oxidation and/or azide exchange,



and the substituents mentioned under D and L are likewise introduced and/or varied by customary methods.

6. Medicaments containing purin-6-one derivatives according to Claims 1 to 3.
7. Medicaments according to Claim 6 for the treatment of cardiovascular disorders,
5 peripheral vascular disorders and disorders of the urogenital system.
8. Process for the production of medicaments according to Claims 6 and 7, characterized in that the purin-6-one derivatives are converted into a suitable administration form, if appropriate with the aid of customary auxiliaries and excipients.
- 10 9. Use of purin-6-one derivatives according to Claims 1 to 3 for the production of medicaments.
10. Use according to Claim 9 for the production of medicaments for the treatment of cardiovascular disorders, peripheral vascular disorders and disorders of the urogenital system.

This Sheet Has Been Replaced

