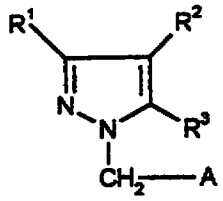
NEW SUBSTITUTED PYRAZOLE DERIVATIVES FOR THE TREATMENT OF CARDIOVASCULAR DISORDERS

The present invention relates to new substituted pyrazole derivatives, processes for their preparation and their use as medicaments, in particular as medicaments for the treatment of cardiovascular disorders.

It has already been disclosed that 1-benzyl-3-(substituted heteroaryl)-fused pyrazole derivatives inhibit platelet aggregation (cf. EP 667 345 A1).

The present invention relates to new substituted pyrazole derivatives of the general formula (I)



(I)

in which

R^1 represents a saturated or aromatic 5- or 6-membered heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, which can be bonded via a nitrogen atom and which is optionally substituted up to 3 times identically or differently by amino, azido, formyl, mercaptyl, carboxyl, hydroxyl, straight-chain or branched acyl, alkoxy, alkylthio or alkoxycarbonyl each having up to 6 carbon atoms, nitro, cyano, halogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl, amino, azido, carboxyl, straight-chain or branched acyl, alkoxy, alkoxycarbonyl or acylamino each having up to 5 carbon atoms or by a radical of the formula $-OR^4$,

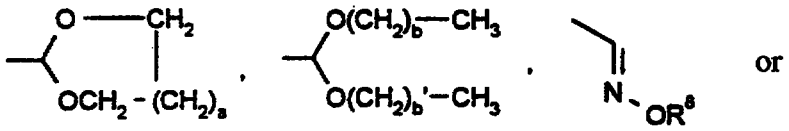
in which

R^4 denotes straight-chain or branched acyl having up to 5 carbon atoms or a group of the formula $-SiR^5R^6R^7$,

in which

R^5, R^6 and R^7 are identical or different and denote aryl having 6 to 10 carbon atoms or alkyl having up to 6 carbon atoms,

and/or is substituted by a radical of the formula



or

$-S(O)_c-NR^9R^{10}$,

in which

a, b and b' are identical or different and denote a number 0, 1, 2 or 3,

R^8 denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

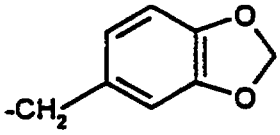
c denotes a number 1 or 2 and

R^9 and R^{10} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 10 carbon atoms, which can optionally be substituted by cycloalkyl having 3 to 8 carbon atoms or by aryl having 6 to 10 carbon atoms, which for its part can be substituted by halogen, or

denote aryl having 6 to 10 carbon atoms, which is optionally substituted by halogen, or
denote cycloalkyl having 3 to 7 carbon atoms, or

R^9 and R^{10}, together with the nitrogen atom, form a 5- to 7-membered saturated heterocycle which can optionally contain a further oxygen atom or a radical $-NR^{11}$, in which

R^{11} denotes hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms or a radical of the formula



or denotes benzyl or phenyl,

where the ring systems are optionally substituted by halogen,

R^2 and R^3, including the double bond, form a 6-membered saturated or aromatic heterocycle having up to 3 heteroatoms from the group consisting of N, S and/or O, which is optionally substituted up to 3 times identically or differently by formyl, carboxyl, hydroxyl, mercaptyl, straight-chain or branched acyl, alkylthio or alkoxycarbonyl each having up to 6 carbon atoms, nitro, cyano, halogen or straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms, which for its part can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 5 carbon atoms,

and/or the heterocycle is optionally substituted by a group of the formula $-NR^{12}R^{13}$ or $-S(O)_cNR^{9'}R^{10'}$, in which

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

R^{12} denotes hydrogen and

R^{13} denotes formyl

c', $R^{9'}$ and $R^{10'}$ have the meaning of c, R^9 and R^{10} indicated above and are identical to or different from these

and/or the heterocycle is optionally substituted by phenyl which for its part can be substituted up to 2 times identically or differently by halogen or by straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms

and/or the heterocycle is optionally substituted by a group of the formula $-N=CH-NR^{14}R^{15}$, in which

R^{14} and R^{15} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms,

A represents a 5- or 6-membered aromatic or saturated heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O or phenyl, each of which is optionally substituted up to 3 times identically or differently by amino, mercaptyl, hydroxyl, formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkyloxyacyl, alkoxy or alkoxycarbonyl each having up to 6 carbon atoms, nitro, cyano, trifluoromethyl, azido, halogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 5 carbon atoms,

and/or is substituted by a group of the formula $-(CO)_d-NR^{16}R^{17}$,

in which

d denotes a number 0 or 1,

R^{16} and R^{17} are identical or different and

denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl or acyl each having up to 5 carbon atoms,

and their isomeric forms and salts.

The compounds of the general formula (I) according to the invention can also be present in the form of their salts. In general, salts with organic or inorganic bases or acids may be mentioned here.

In the context of the present invention, physiologically acceptable salts are preferred. Physiologically acceptable salts of the compounds according to the invention can be salts of the substances according to the invention with mineral acids, carboxylic acids or sulphonic acids. Particularly preferred salts are, for example, those with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid.

Physiologically acceptable salts can also be metal or ammonium salts of the compounds according to the invention which have a free carboxyl group. Those particularly preferred are, for example, sodium, potassium, magnesium or calcium salts, and also ammonium salts which are derived from ammonia, or organic amines such as, for example, ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine or ethylenediamine.

The compounds according to the invention can exist in stereoisomeric 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 enantiomers or diastereomers and their respective mixtures. Like the diastereomers, the racemic forms can also be separated into the stereoisomerically uniform constituents in a known manner.

Heterocycle in the context of the invention, depending on the abovementioned substituents, in general represents a saturated or aromatic 5- or 6-membered heterocycle which can contain up to 3 heteroatoms from the group consisting of S, N and/or O and which in the case of a nitrogen atom can also be bonded via this. Examples which may be mentioned are: oxadiazolyl, thiadiazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, thienyl, furyl, pyrrolyl, tetrahydropyranyl, tetrahydrofuranyl, 1,2,3-triazolyl, thiazolyl, oxazolyl, imidazolyl, morpholinyl or piperidyl. Thiazolyl, furyl, oxazolyl, pyrazolyl, triazolyl, pyridyl, pyrimidinyl, pyridazinyl and tetrahydropyranyl are preferred.

Preferred compounds of the general formula (I) according to the invention are those

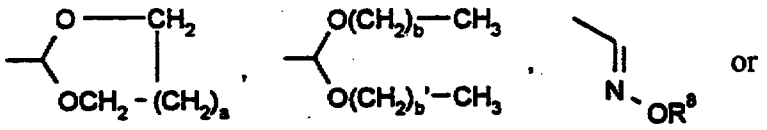
in which

R^1 represents pyrimidinyl, pyridazinyl, pyridyl, pyrazinyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, thiazolyl, 1,2,3-triazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, isothiazolyl, pyranyl or morpholinyl, each of which is optionally substituted up to 3 times identically or differently by amino, formyl, mercaptyl, carboxyl, hydroxyl, straight-chain or branched acyl, alkoxy, alkylthio or alkoxycarbonyl each having up to 5 carbon atoms, nitro, cyano, azido, fluorine, chlorine, bromine, phenyl or straight-chain or branched alkyl having up to 5 carbon atoms, which for its part can be substituted by hydroxyl, amino, azido, carboxyl, straight-chain or branched acyl, alkoxy, alkoxycarbonyl or acylamino each having up to 4 carbon atoms or by a radical of the formula $-OR^4$,

in which

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

and/or by a radical of the formula



-$S(O)_c$-NR^9R^{10},

in which

a, b and b' are identical or different and denote a number 0, 1, 2 or 3,

R^8 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

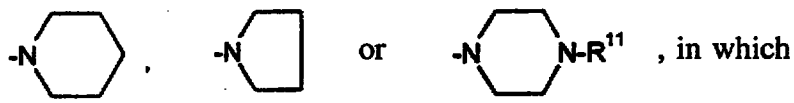
c denotes a number 1 or 2 and

R^9 and R^{10} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 9 carbon atoms, which can optionally be substituted by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or naphthyl or phenyl, which for their part can be substituted by fluorine or chlorine, or

denote phenyl or naphthyl, each of which is optionally substituted by fluorine or chlorine, or

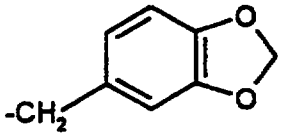
denote cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, or

R^9 and R^{10}, together with the nitrogen atom, form a morpholine ring or a radical of the formula



, in which

R^{11} denotes hydrogen, methyl or a radical of the formula



or denotes benzyl or phenyl, where the

ring systems are optionally substituted by fluorine or chlorine,

R^2 and R^3, including the double bond, form a pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl ring, each of which is optionally substituted up to 3 times identically or differently by formyl, carboxyl, hydroxyl, mercaptyl, straight-chain or branched acyl, alkylthio or alkoxycarbonyl each having up to 5 carbon atoms, nitro, cyano, azido, fluorine, chlorine, bromine or straight-chain or branched alkyl or alkoxy each having up to 5 carbon atoms, which for its part can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms,

and/or the abovementioned heterocyclic rings are optionally substituted by a group of the formula $-NR^{12}R^{13}$ or $-S(O)_cNR^{9'}R^{10'}$, in which

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^{12} denotes hydrogen and

R^{13} denotes formyl

c', $R^{9'}$ and $R^{10'}$ have the meaning of c, R^9 and R^{10} indicated above and are identical to or different from these

and/or the abovementioned heterocyclic rings are optionally substituted by phenyl, which for its part can be substituted by fluorine, chlorine, bromine or by straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms

and/or the abovementioned heterocyclic rings are optionally substituted by a group of the formula , in which

R^{14} and R^{15} denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

A represents thienyl, tetrahydropyranyl, tetrahydrofuranyl, phenyl, morpholinyl, pyrimidyl, pyrazinyl, pyridazinyl or pyridyl, each of which is optionally substituted up to 2 times identically or differently by hydroxyl, formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkoxyacyl, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl or straight-chain or branched alkyl having up to 4 carbon atoms, which for its part can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms,

and/or by a group of the formula $-(CO)_d-NR^{16}R^{17}$,

in which

d denotes a number 0 or 1,

R^{16} and R^{17} are identical or different and

denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl or acyl each having up to 4 carbon atoms,

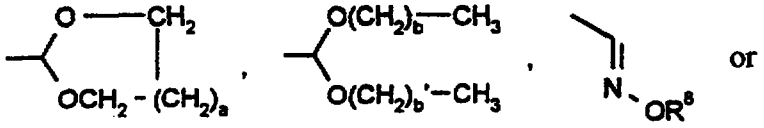
and their isomeric forms and salts.

Particularly preferred compounds of the general formula (I) according to the invention are those

in which

R^1 represents imidazolyl, furyl, pyridyl, pyrrolyl, pyrazinyl, pyrimidyl, isoxazolyl, oxazolyl or thiazolyl, each of which is optionally substituted up to 3 times identically or differently by formyl, fluorine, chlorine, amino, mercaptyl, cyano, straight-chain or branched acyl, alkylthio, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms or straight-chain or branched alkyl having up to 4 carbon atoms, which for its part can be substituted by hydroxyl, carboxyl, amino, azido, straight-chain or branched acyl, alkoxy, alkoxycarbonyl or acylamino each having up to 3 carbon atoms,

and/or by a radical of the formula



or

$-S(O)_c-NR^9R^{10}$,

in which

a, b and b' are identical or different and denote a number 0, 1 or 2,

R^8 denotes hydrogen or methyl,

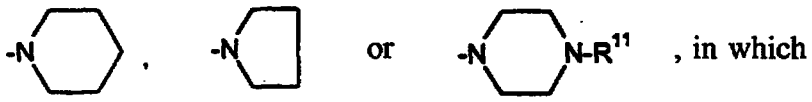
c denotes a number 1 or 2 and

R^9 and R^{10} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 9 carbon atoms, which can optionally be substituted by phenyl or naphthyl, or

denote phenyl or naphthyl, each of which is optionally substituted by fluorine or chlorine, or

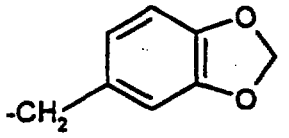
denote cyclopropyl or cycloheptyl, or

R^9 and R^{10}, together with the nitrogen atom, form a morpholine ring or a radical of the formula



, in which

R^{11} denotes hydrogen, methyl or a radical of the formula



or denotes benzyl or phenyl, where the ring

systems are optionally substituted by chlorine,

R^2 and R^3, including the double bond, form a pyridyl, pyrazinyl, pyrimidinyl or pyridazinyl ring, each of which is optionally substituted up to 3 times identically or differently by formyl, mercaptyl, carboxyl, hydroxyl, straight-chain or branched acyl, alkoxy, alkylthio or alkoxycarbonyl each having up to 4 carbon atoms, nitro, cyano, fluorine, chlorine or straight-chain or branched alkyl or alkoxy each having up to 3 carbon atoms, which for its part can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms,

and/or the heterocyclic rings are optionally substituted by amino, N,N-dimethyl-amino or by a radical of the formula -NH-CHO or $-N=CH-N(CH_3)_2$ and/or by phenyl,

which for its part can be substituted by a radical of the formula $-O(CH_2)_2-CH_3$,

A represents tetrahydropyranyl, phenyl, pyrimidyl, thienyl or pyridyl, each of which is optionally substituted up to 2 times identically or differently by formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkyloxyacyl,

alkoxy or alkoxycarbonyl each having up to 3 carbon atoms, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl or straight-chain or branched alkyl having up to 3 carbon atoms, which for its part can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms,

and their isomeric forms and salts.

Very particularly preferred compounds of the general formula (I) according to the invention are those in which

A represents phenyl, pyrimidyl or fluorine-substituted phenyl or pyrimidyl

and their isomeric forms and salts.

Processes for the preparation of the compounds of the general formula (I) according to the invention have additionally been found, characterized in that, depending on the various meanings of the heterocycles mentioned under R^2 and R^3 above,

[A] compounds of the general formula (II)

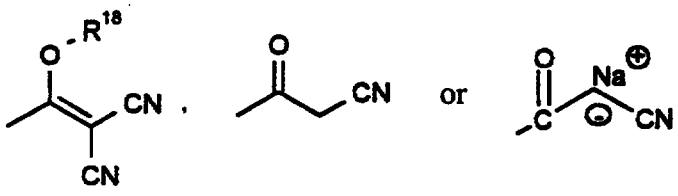
$$R^1\text{-}D \quad (II)$$

in which

R^1 has the meaning indicated above,

and

D represents radicals of the formula



in which

R^{18} represents C_1-C_4-alkyl,

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

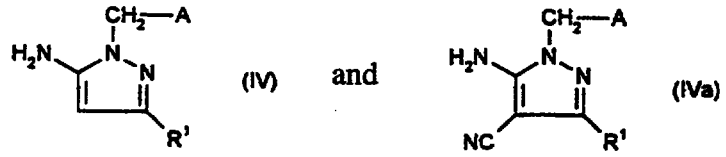


(III)

in which

A has the meaning indicated above

in inert solvents, if appropriate in the presence of a base, into the compounds of the general formula (IV) or (IVa)



in which

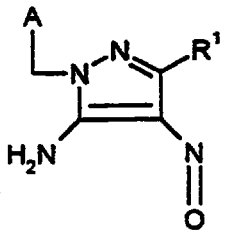
A and R^1 have the meaning indicated above,

and, in the case of the compounds of the general formula (IVa), then cyclized with carboxylic acids, nitriles, formamides or guanidinium salts,

and, in the case of the compounds of the general formula (IV), then cyclized with 1,3-dicarbonyl derivatives, their salts, tautomers, enol ethers or enamines, in the presence of acids and, if appropriate, under microwaves,

or

[B] in the case where R^2 and R^3 together form a pyrazine ring, compounds of the general formula (IV) are first converted by nitrosation into the compounds of the general formula (V)

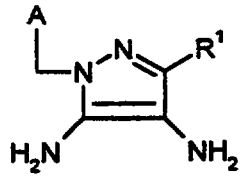


(V),

in which

A and R^1 have the meaning indicated above,

in a second step, by means of a reduction, the compounds of the general formula (VI)



(VI),

in which

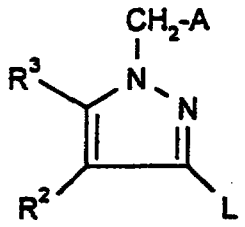
A and R^1 have the meaning indicated above,

are prepared

and finally cyclized with 1,2-dicarbonyl compounds, preferably aqueous glyoxal solution,

or

[C] compounds of the general formula (VII)



(VII)

in which

A^1, R^2 and R^3 have the meaning indicated above,

and

L represents a radical of the formula $-SnR^{19}R^{20}R^{21}$, ZnR^{22}, iodine, bromine or triflate,

in which

R^{19}, R^{20} and R^{21} are identical or different and denote straight-chain or branched alkyl having up to 4 carbon atoms,

and

R^{22} denotes halogen,

are reacted with compounds of the general formula (VIII)

$$R^1\text{-}T \qquad \text{(VIII)}$$

in which

R^1 has the meaning indicated above

and

if L = $SnR^{19}R^{20}R^{21}$ or ZnR^{22},

T represents triflate or halogen, preferably bromine,

and

if L = iodine, bromine or triflate,

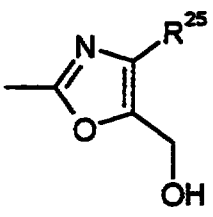
T represents a radical of the formula $SnR^{19'}R^{20'}R^{21'}$, $ZnR^{22'}$ or $BR^{23'}R^{24'}$,

in which

$R^{19'}$, $R^{20'}$, $R^{21'}$ and $R^{22'}$ have the meaning of R^{19}, R^{20}, R^{21} and R^{22} indicated above and are identical to or different from these,

$R^{23'}$ and $R^{24'}$ are identical or different and denote hydroxyl, aryloxy having 6 to 10 carbon atoms or straight-chain or branched alkyl or alkoxy each having up to 5 carbon atoms, or together form a 5- or 6-membered carbocyclic ring,

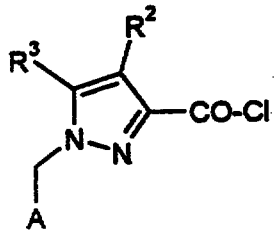
in a palladium-catalysed reaction in inert solvents, if appropriate in the presence of a base,

[D] if R^1 = 

in which

R^{25} denotes (C_1-C_6)-alkyl which is optionally substituted by halogen,

compounds of the general formula (IX)

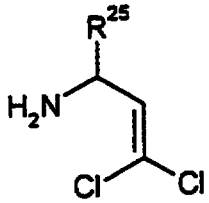


(IX),

in which

A, R^2 and R^3 have the meaning indicated above,

are converted either directly by reaction with the compound of the formula (X)



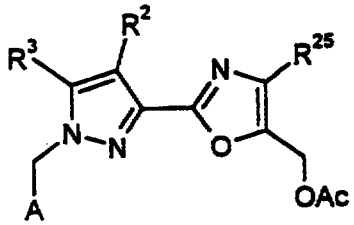
(X)

in which

R^{25} has the meaning indicated above,

in the system $NaOCO-CH_3$/N-methylpyrrolidine

into the compounds of the general formula (Ia)



(Ia),

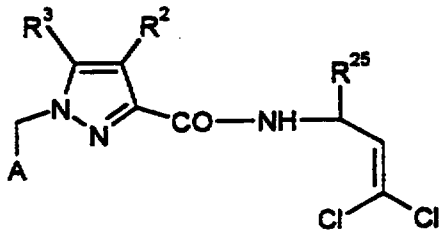
in which

R^2, R^3 and A and R^{25} have the meaning indicated above,

and then, by action of potassium hydroxide in methanol, the acetyl group is removed,

or

first by reaction of the compounds of the general formula (IX) with the compound of the formula (X) the compounds of the general formula (XI)



(XI),

in which

R^2, R^3, A and R^{25} have the meaning indicated above,

are prepared,

and in a further step by action of potassium hydroxide the hydroxymethyl compounds are prepared,

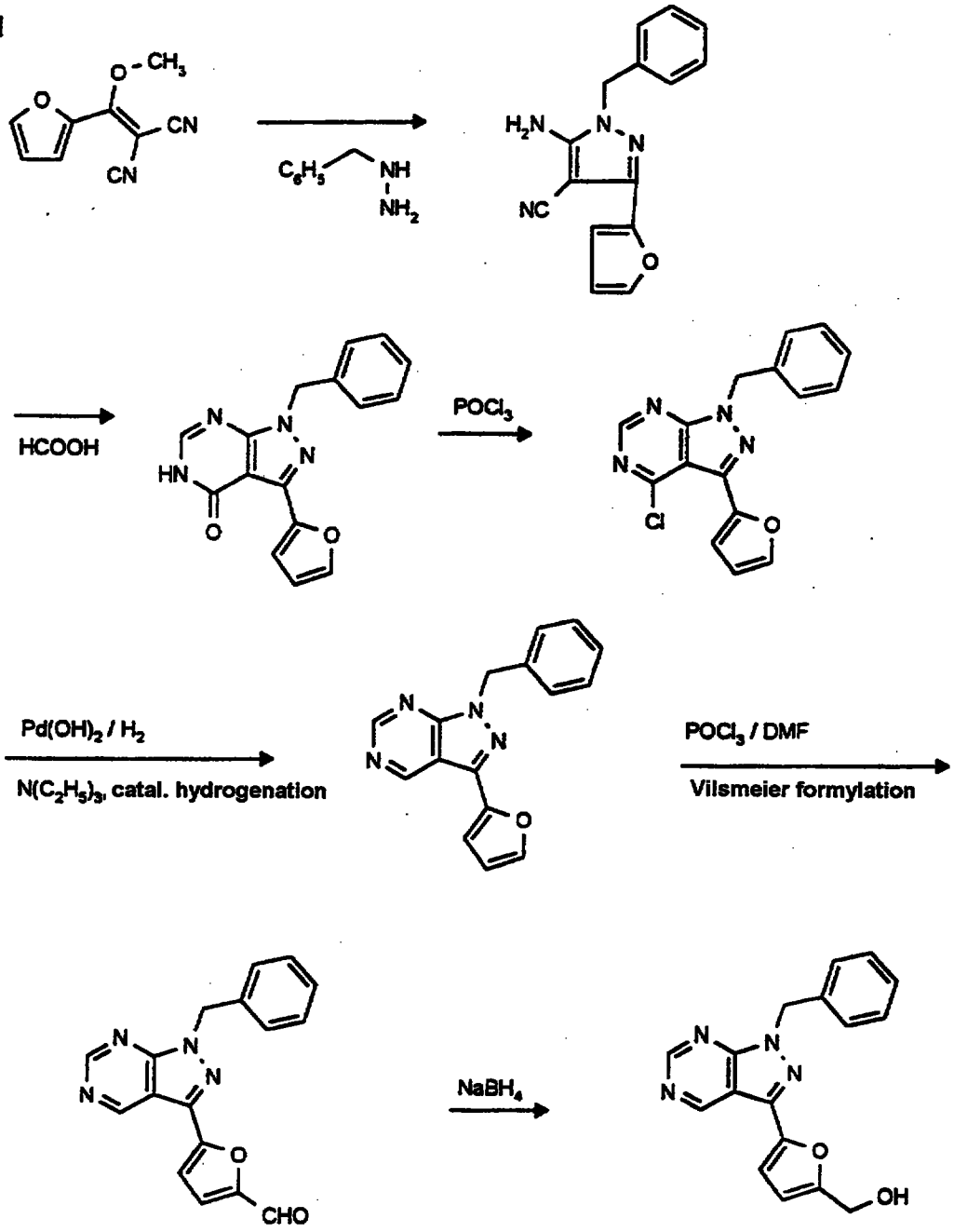
and in the case of the groups $-S(O)_cNR^9R^{10}$ and $-S(O)_cNR^{9'}R^{10'}$, starting from the unsubstituted compounds of the general formula (I), first reacted with thionyl chloride and in a second step with the appropriate amines

and, if appropriate, the substituents mentioned under R^1, R^2, R^3 and/or A are varied or introduced according to customary methods, preferably by chlorination, catalytic hydrogenation, reduction, oxidation, removal of protective groups and/or nucleophilic substitution.

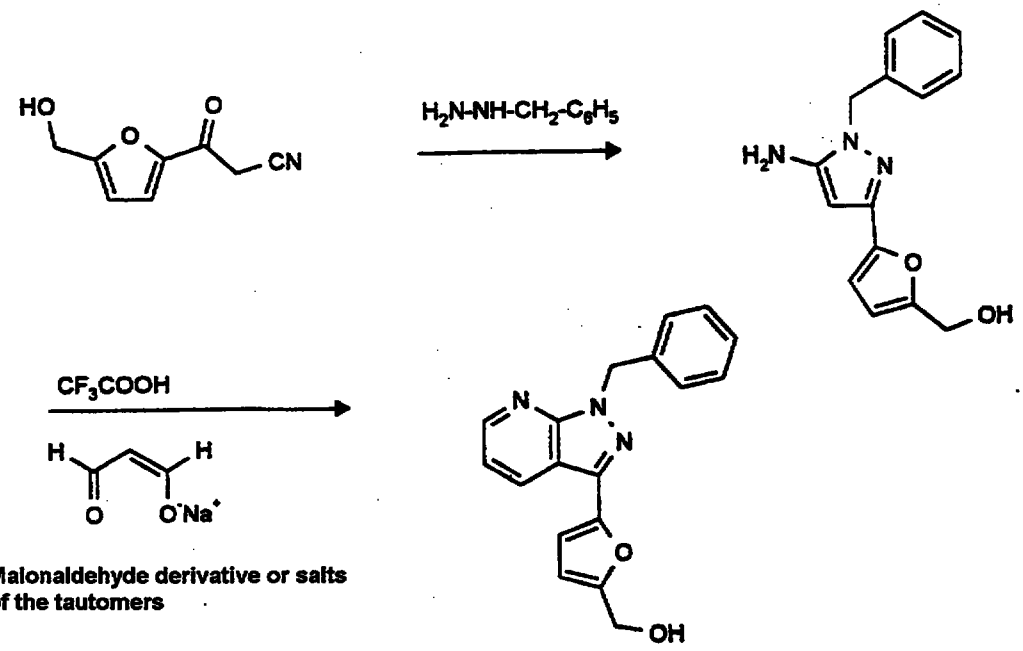
The heterocycles mentioned under R^2 and R^3 can also be introduced by reaction of the appropriately substituted compounds of the general formula (II) according to other known heterocyclic syntheses.

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

[A]

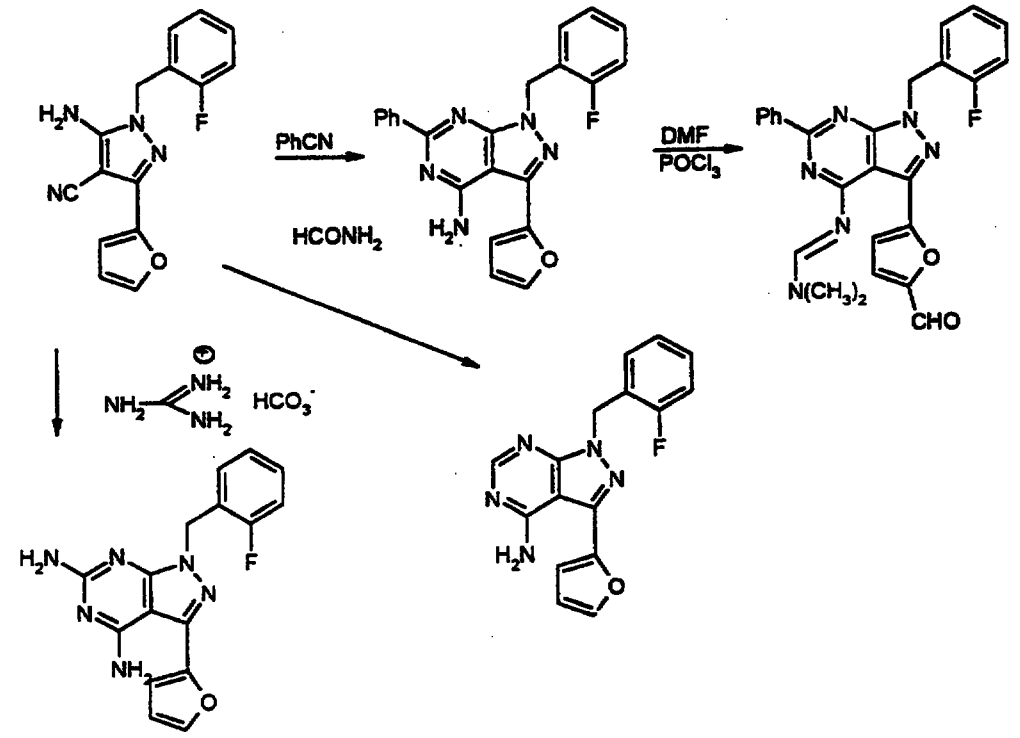

O-CH3
CN
CN
C6H5
NH
NH2
H2N
N
N
NC
O
HCOOH
HN
O
POCl3
Cl
Pd(OH)2 / H2
N(C2H5)3, catal. hydrogenation
POCl3 / DMF
Vilsmeier formylation
NaBH4
CHO
OH

[A]

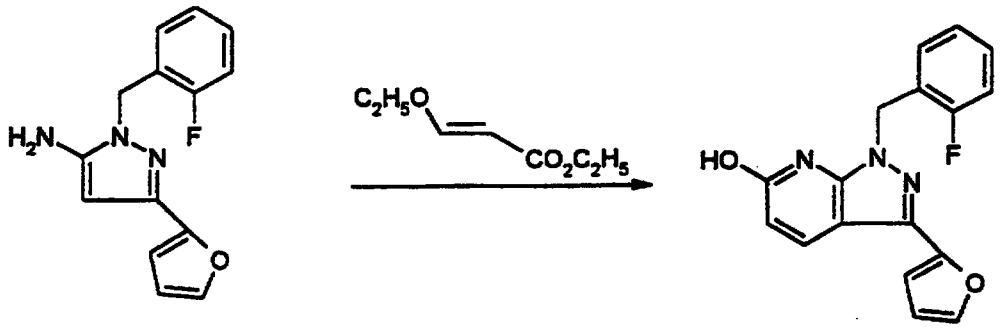


Malonaldehyde derivative or salts of the tautomers

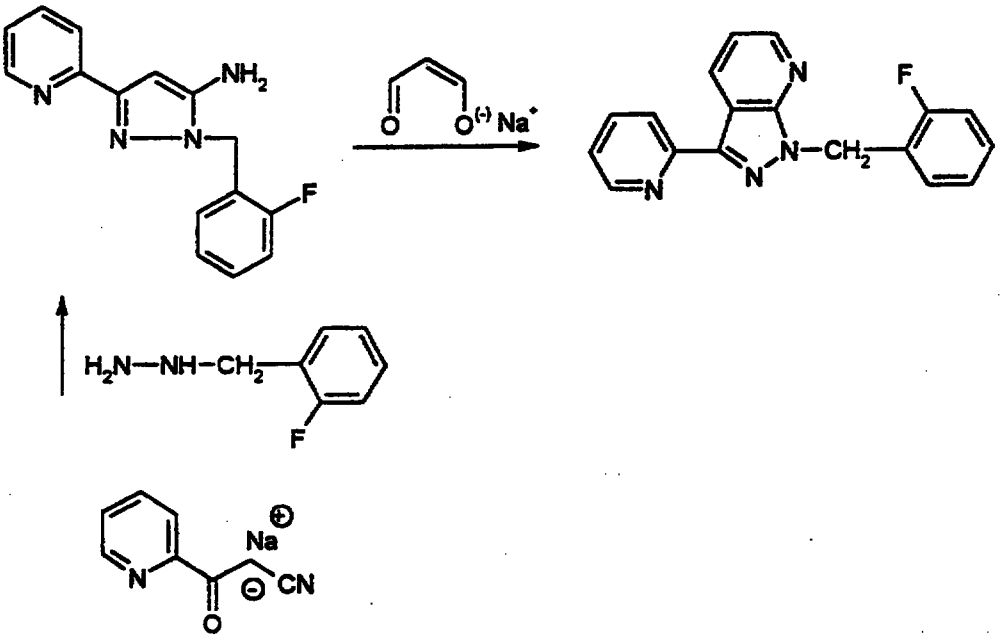
[A] and derivatization



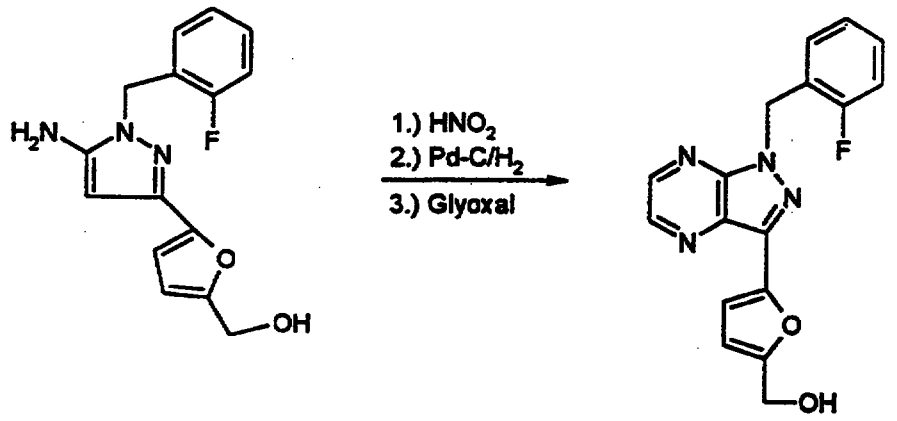
[A]



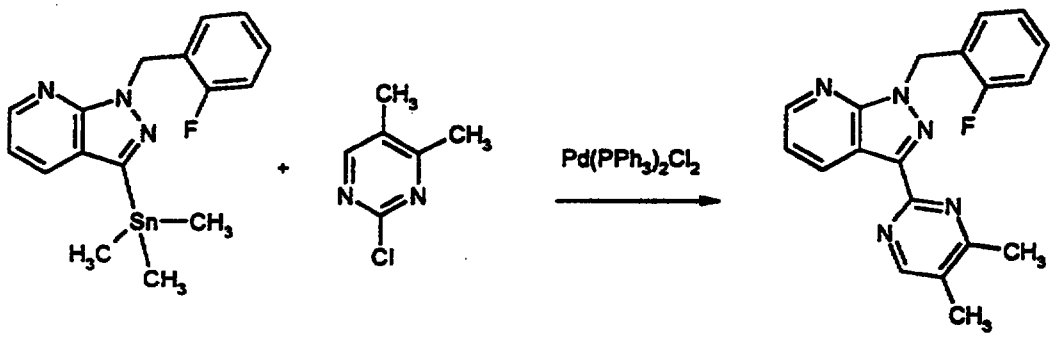
[A]



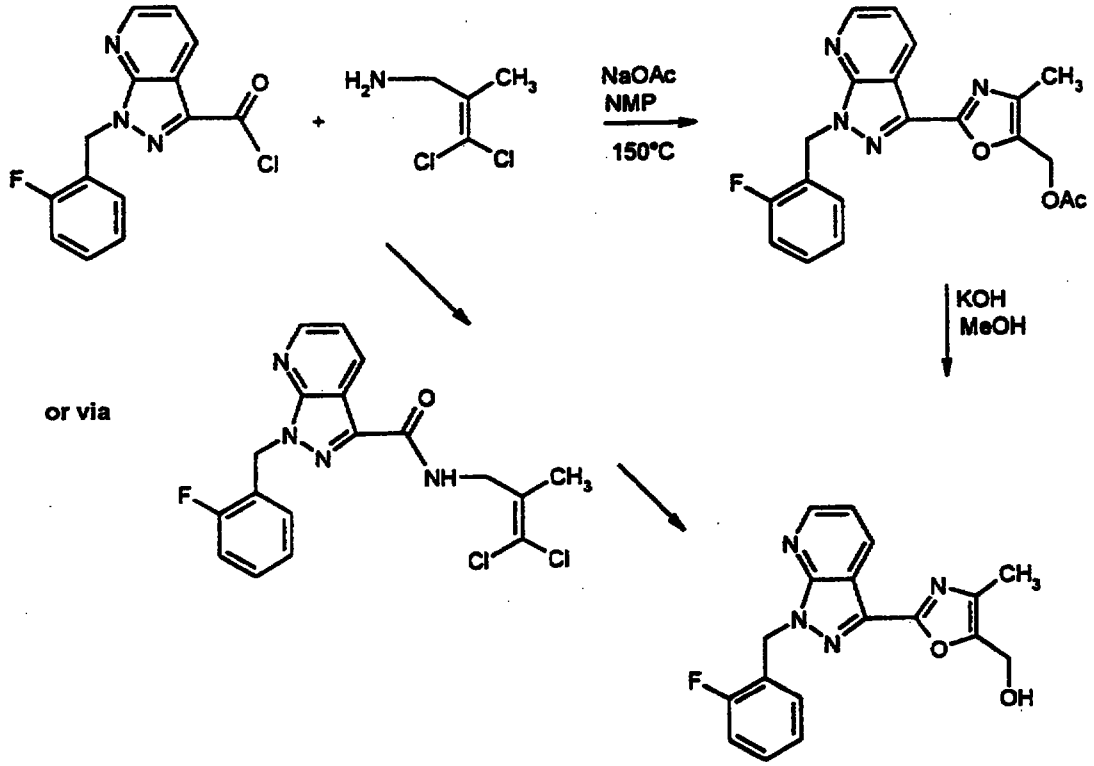
[B]



[C]



[D]



Suitable solvents here for the individual steps of the processes are inert organic solvents which do not change under the reaction conditions.

These include ethers, such as diethyl ether or tetrahydrofuran, DME, dioxane, alcohols such as methanol and ethanol, halogenohydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, nitromethane, dimethylformamide, acetone, acetonitrile or hexamethylphosphoramide. It is also possible to employ mixtures of the solvents. Tetrahydrofuran, dimethylformamide, toluene, dioxane or dimethoxyethane is particularly preferred.

Bases employed for the processes according to the invention can in general be inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, sodium hydroxide or potassium hydroxide, alkaline earth metal hydroxides

such as, for example, barium hydroxide, alkali metal carbonates such as sodium carbonate or potassium carbonate, alkaline earth metal carbonates such as calcium carbonate, or alkali metal or alkaline earth metal alkoxides such as sodium or potassium methoxide, sodium or potassium ethoxide or potassium tert-butoxide, or organic amines (trialkyl(C_1-C_6)-amines) such as triethylamine, or heterocycles such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, diaminopyridine, methylpiperidine or morpholine. It is also possible to employ as bases alkali metals such as sodium and their hydrides such as sodium hydride. Sodium and potassium carbonate, triethylamine and sodium hydride are preferred.

The base is employed in an amount from 1 mol to 5 mol, preferably from 1 mol to 3 mol, relative to 1 mol of the compound of the general formula (II).

The reaction is in general carried out in a temperature range from 0°C to 150°C, preferably from +20°C to +110°C.

The reaction can be carried out at normal, elevated or at reduced pressure (e.g. 0.5 to 5 bar). In general, it is carried out at normal pressure.

Suitable acids for the cyclization are in general protonic acids. These preferably include inorganic acids such as, for example, hydrochloric acid or sulphuric acid, or organic carboxylic acids having 1 - 6 C atoms, optionally substituted by fluorine, chlorine and/or bromine, such as, for example, acetic acid, trifluoroacetic acid, trichloroacetic acid or propionic acid, or sulphonic acids having C_1-C_4-alkyl radicals or aryl radicals such as, for example, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid or toluenesulphonic acid.

The catalytic hydrogenation can in general be carried out by means of hydrogen in water or in inert organic solvents such as alcohols, ethers or halogenohydrocarbons, or mixtures thereof with catalysts such as Raney nickel, palladium, palladium on animal charcoal or platinum, or with hydrides or boranes in inert solvents, if appropriate in the

presence of a catalyst.

Chlorination is in general carried out using the customary chlorinating agents such as, for example, PCl_3, PCl_5, $POCl_3$ or elemental chlorine. $POCl_3$ is preferred in the context of the invention.

If the radicals of the formulae $-S(O)_cNR^9R^{10}$ and $-S(O)_cNR^{9'}R^{10'}$ are present, the corresponding unsubstituted compounds are first reacted with thionyl chloride. In a further step, the reaction with the amines is carried out in one of the abovementioned ethers, preferably dioxane. If c = 2, an oxidation is then carried out according to customary methods. The reactions are carried out in a temperature range from 0°C to 70°C and normal pressure.

The nucleophilic substitutions and Vilsmeier reactions are carried out according to customary, published methods.

The reductions are in general carried out using reducing agents, preferably using those which are suitable for the reduction of carbonyl to hydroxyl compounds. Reduction using metal hydrides or complex metal hydrides in inert solvents is particularly suitable here, if appropriate in the presence of a trialkylborane. Preferably, the reduction is carried out using complex metal hydrides such as, for example, lithium borohydride, sodium borohydride, potassium borohydride, zinc borohydride, lithium trialkylborohydride, diisobutylaluminium hydride or lithium aluminium hydride. Reduction with diisobutylaluminium hydride and sodium borohydride is very particularly preferred.

The reducing agent is in general employed in an amount from 1 mol to 6 mol, preferably from 1 mol to 4 mol relative to 1 mol of the compounds to be reduced.

The reduction in general proceeds in a temperature range from -78°C to +50°C, preferably from -78°C to 0°C in the case of DIBAH, 0°C to room temperature in the case of $NaBH_4$.

The reduction in general proceeds at normal pressure, but it is also possible to work at elevated or reduced pressure.

The compounds of the general formulae (II) and (III) are known per se or can be prepared by customary methods [cf. for this: J. Hromatha et al., Monatsh. Chem. 1976, 107, 233).

The compounds of the general formulae (IV), (IVa), (V) and (VI) are known in some cases and can be prepared as described above.

Suitable solvents here for process [C] are inert organic solvents which do not change under the reaction conditions. These include ethers, such as diethyl ether or tetrahydrofuran, DME, dioxane, halogenohydrocarbons such as dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, trichloroethane, tetrachloroethane, 1,2-dichloroethylene or trichloroethylene, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, nitromethane, dimethylformamide, acetone, acetonitrile or hexamethylphosphoramide. It is also possible to employ mixtures of the solvents. Tetrahydrofuran, dimethylformamide, toluene, dioxane or dimethoxyethane is particularly preferred.

The reaction is in general carried out in a temperature range from 0°C to 150°C, preferably from +20°C to +110°C.

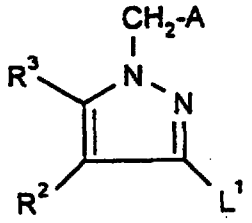
The reaction can be carried out at normal, elevated or at reduced pressure (e.g. 0.5 to 5 bar). In general, it is carried out at normal pressure.

Suitable palladium compounds in the context of the present invention are in general $PdCl_2(P(C_6H_5)_3)_2$, palladium bis-dibenzylideneacetone ($Pd(dba)_2$), [1,1'-bis-(diphenylphosphino)ferrocene]-palladium(II) chloride ($Pd(dppf)Cl_2$) or $Pd(P(C_6H_5)_3)_4$. $Pd(P(C_6H_5)_3)_4$ is preferred.

The compounds of the general formula (VIII) are known per se or can be prepared by

customary methods.

The compounds of the general formula (VII) are known in some cases or, in the case of the stannyls, are new and can then be prepared, for example, by reacting the compounds of the general formula (XII)



(XII)

in which

R^2, R^3 and A have the meaning indicated above,

L^1 represents triflate or halogen, preferably iodine,

with compounds of the general formula (XIII)

$$(SnR^{19}R^{20}R^{21})_2 \qquad \text{(XIII)}$$

in which

R^{19}, R^{20}, R^{21} have the meaning indicated above

as described above with palladium catalysis.

The compounds of the general formulae (XII) and (XIII) are known per se or can be prepared by customary methods.

Process [D] according to the invention is carried out using one of the abovementioned bases, preferably in N-methylpyrrolidone, in a temperature range from 100°C to 200°C, preferably at 150°C.

The compounds of the general formulae (IX) and (X) are known or can be prepared by customary methods.

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

In the case in which typical protective groups are employed in the course of derivatization reactions, their removal is in general carried out in one of the abovementioned alcohols and/or THF or acetone, preferably methanol/THF in the presence of hydrochloric acid or trifluoroacetic acid or toluenesulphonic acid in a temperature range from 0°C to 70°C, preferably at room temperature and normal pressure.

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

The compounds according to the invention of the general formula (I) lead to a vasorelaxation/inhibition of platelet aggregation and to a blood pressure fall and also to an increase in the coronary blood flow. These actions are mediated via a direct stimulation of soluble guanylate cyclase and an intracellular cGMP increase. Additionally, the compounds according to the invention increase the action of substances which raise the cGMP level, such as, for example, EDRF (endothelium-derived relaxing factor), NO donors, protoporphyrin IX, arachidonic acid or phenylhydrazine derivatives.

They can therefore be employed in medicaments for the treatment of cardiovascular disorders such as, for example, for the treatment of high blood pressure and cardiac insufficiency, stable and unstable angina pectoris, peripheral and cardiac vascular disorders, arrhythmias, for the treatment of thromboembolic disorders and ischaemias such as myocardial infarct, stroke, transitory and ischaemic attacks, peripheral circulatory disorders, prevention of restenoses such as after thrombolysis therapy, percutaneous transluminal angioplasty (PTA), percutaneous transluminal coronary angioplasty (PTCA), bypass and also for the treatment of arteriosclerosis and disorders

of the urogenital system such as, for example, prostate hypertrophy, erectile dysfunction and incontinence.

The invention moreover includes the combination of the compounds of the general formula (I) according to the invention with organic nitrates and NO donors.

Organic nitrates and NO donors in the context of the invention are in general substances which display their therapeutic action via the release of NO or NO species. Sodium nitroprusside, nitroglycerine, isosorbide dinitrate, isosorbide mononitrate, molsidomine and SIN-1 are preferred.

The invention additionally includes combination with compounds which inhibit the degradation of cyclic guanosine monophosphate (cGMP). These are, in particular, inhibitors of phosphodiesterases 1, 2 and 5; nomenclature according to Beavo and Reifsnyder (1990) TiPS 11 p. 150 to 155. The action of the compounds according to the invention is potentiated and the desired pharmacological effect is increased by these inhibitors.

To determine the cardiovascular actions, the following investigations were carried out: in in vitro investigations on cells of vascular origin, the influx on guanylate cyclase-dependent cGMP formation was tested with and without NO donor. The anti-aggregatory properties were shown on human platelets stimulated with collagen. The vasorelaxant action was determined in rabbit aortal rings precontracted with phenylephrine. The hypotentive action was investigated in anaesthetized rats.

Stimulation of soluble guanylate cyclase in primary endothelial cells

Primary endothelial cells were isolated from rabbit aortas by treatment with collagenase soln. The cells were then cultured in culture medium at 37°C/5% CO_2 until confluence was reached. For the investigations, the cells were passaged, inoculated into 24-hole cell culture plates and subcultured until reaching confluence (~ 2×10^5 cells/hollow). For the stimulation of endothelial guanylate cyclase, the culture medium was aspirated and

the cells were washed once with Ringer solution. After removing the Ringer solution, the cells were incubated for 10 minutes at 37°C/5% CO_2 in stimulation buffer with or without NO donor (sodium nitroprusside, SNP, 1 µM). Following this, the test substances (final concentration 1 µM) were added to the cells by pipette and they were incubated for a further 10 minutes. After the end of the incubation time, the buffer solution was aspirated and cold stop buffer at 4°C was added to the cells. The cells were then lysed at -20°C for 16 hours. The supernatants containing the intracellular cGMP were then removed and the cGMP concentration was determined by means of the cGMP-SPA system (Amersham Buchler, Brunswick).

Table A

Ex. No.	cGMP increase (%)
14	> 1000
15	504
16	652
17	> 1000
32	135

Vasorelaxant action in vitro

Rabbits are anaesthetized by a blow to the neck and exsanguinated. The aorta is removed, freed from adhering tissue, divided into 1.5 mm wide rings and individually transferred under a pretension into 5 ml organ baths containing warm, carbogen aerated Krebs-Henseleit solution at 37°C of the following composition (mM): NaCl: 119; KCl: 4.8; $CaCl_2 \times 2\ H_2O$: 1; $MgSO_4 \times 7\ H_2O$: 1.4; KH_2PO_4: 1.2; $NaHCO_3$: 25; glucose: 10.

The contractility is detected using Statham UC2 cells, amplified and digitalized by

means of A/D converters (DAS-1802 HC, Keithley Instruments Munich), and recorded in parallel on linear recorders. To produce a contraction, phenylephrine is added to the bath cumulatively in increasing concentration.

After several control cycles, the substance to be investigated is investigated in each further passage in increasing dosage in each case and the height of the contraction is compared with the height of the contraction achieved in the last preliminary passage. From this, the concentration is calculated which is necessary in order to reduce the height of the control value by 50% (IC_{50}). The standard administration volume is 5 µl and the proportion of DMSO in the bath solution corresponds to 0.1%.

Table B

Ex. No.	Aorta (IC_{50}) µM
14	1.8
15	13.0
16	1.7

Blood pressure measurements in anaesthetized rats

Male Wistar rats having a body weight of 300 - 350 g are anaesthetized with thiopental (100 mg/kg i.p.). After tracheotomy, a catheter is inserted in the femoral artery for blood pressure measurement. The substances to be tested are administered orally in various doses by means of stomach tube as a suspension in Tylose solution.

Table C

Ex. No.	Dose (mg/kg)	Max. blood pressure fall (mm Hg)	Time (min)
13	10	-13	60
	30	-23	60
14	10	-18	40
	30	-21	50
16	10	-9	50
	30	-16	50

Inhibition of platelet aggregation in vitro

For determination of the platelet aggregation-inhibiting action, blood from healthy subjects of both sexes was used. As an anticoagulant, 9 parts of blood were admixed to one part of 3.8% strength aqueous sodium citrate solution. By means of centrifugation, platelet-rich citrate plasma (PRP) was obtained from this blood (Jürgens/ Beller, Klinische Methoden der Blutgerinnungsanalyse [Clinical Methods of Blood Coagulation Analysis]; Thieme Verlag, Stuttgart, 1959).

For these investigations, 445 µl of PRP and 5 µl of the active compound solution were preincubated at 37°C in a water bath. The platelet aggregation was then determined at 37°C in an aggregometer by the turbidometric method (Born, G.V.R., J. Physiol. (London), 168, 178-195, 1963). For this purpose, the preincubated sample was treated with 50 µl of collagen, an aggregation-inducing agent, and the change in the optical density was determined. For quantitative evaluation, the maximum aggregation response was determined and from this the percentage inhibition compared to the control was calculated.

The compounds described in the present invention are also active compounds for the control of illnesses in the central nervous system which are characterized by disorders of the NO/cGMP system. In particular, they are suitable for the elimination of cognitive deficits, for the improvement of learning and memory power and for the treatment of Alzheimer's disease. They are also suitable for the treatment of disorders of the central nervous system such as anxiety, tension and depressive states, central nervous system-related sexual dysfunctions and sleep disorders, and also for the regulation of pathological disorders of foodstuff, tea, coffee, alcohl, tobacco and addictive drug intake.

Furthermore, these active compounds are also suitable for the regulation of the cerebral blood circulation and are thus effective agents for the control of migrane.

They are also suitable for the prophylaxis and control of the sequelae of cerebral infarcts (cerebral apoplexy) such as stroke, cerebral ischaemias and craniocerebral trauma. The compounds according to the invention can also be employed for the control of states of pain.

The present invention includes pharmaceutical preparations which, in addition to non-toxic, inert pharmaceutically acceptable excipients, contain one or more compounds according to the invention or which consist of one or more active compounds according to the invention, as well as processes for the production of these preparations.

The active compound(s) can optionally be present in one or more of the excipients indicated above and also in microencapsulated form.

The therapeutically active compounds should be present in the abovementioned pharmaceutical preparations in a concentration from approximately 0.1 to 99.5, preferably from approximately 0.5 to 95, % by weight of the total mixture.

In addition to the compounds according to the invention, the abovementioned pharmaceutical preparations can also contain further pharmaceutical active compounds.

In general, it has proved advantageous both in human and in veterinary medicine to administer the active compound(s) in total amounts from approximately 0.5 to approximately 500, preferably 5 to 100, mg/kg of body weight every 24 hours, if appropriate in the form of several individual doses, to achieve the desired results. An individual dose contains the active compound(s) preferably in amounts from approximately 1 to approximately 80, in particular 3 to 30, mg/kg of body weight.

Abbreviations

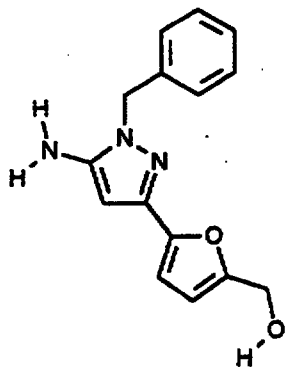
MeOH	=	methanol
E	=	ethanol
EA	=	ethyl acetate
T	=	toluene
Ph	=	phenyl

The numbers after the solvent abbreviations in the following tables under the column R_f denote parts by weight.

Starting compounds

Example I A

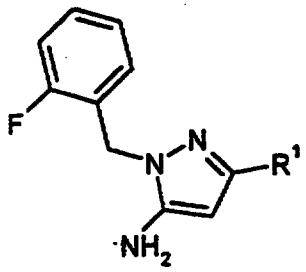
5-Amino-1-benzyl-3-(5-hydroxymethyl-2-furyl)-pyrazole



44.1 g (817 mmol) of sodium methoxide is added with stirring to a solution of 79.5 g (408 mmol) of benzylhydrazine dihydrochloride in 1.3 l of ethanol. After 15 min, 67.4 g (408 mmol) of 2-cyanomethylcarbonyl-5-hydroxymethylfuran are added and the mixture is stirred under reflux for 3 hours. After cooling, 1 l of water is added, the ethanol part is evaporated in vacuo and the precipitated crystals are filtered off with suction. After washing with water and then with ether, the precipitate is dried over P_2O_5. 91 g (83% of theory) of product having an m.p. of 163°C are obtained.

The compounds shown in Table 1A were prepared analogously:

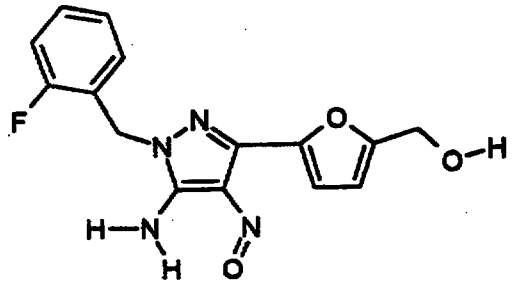
Table 1A:



Ex. No.	R^1	m.p. [°C]	R_f	Yield [% of theory]
2A	2-furyl	124	0.63 (T1E1)	49
3A	2-pyrimidinyl	178	0.49 (MeOH1E4)	66.5
4A	2-pyridyl	130	0.08 (T1E1)	30

Example 5A

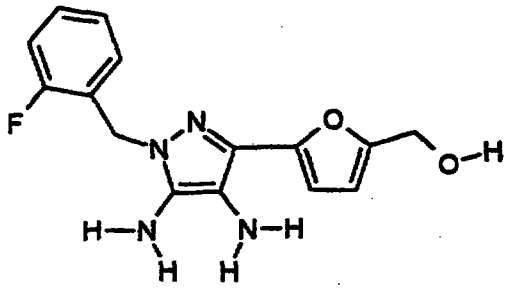
5-Amino-1-(2-fluorobenzyl)-3-(5-hydroxymethyl-2-furyl)-4-nitroso-pyrazole



10 g (34.8 mmol) of 5-amino-1-(2-fluorobenzyl)-3-(5-hydroxymethyl-2-furyl)-pyrazole are initially introduced in a mixture of 66 ml of ethanol and 26.7 ml of 5% strength aqueous hydrochloric acid, treated in the course of 5 minutes with 26.4 ml of a 15% strength ethanolic solution of ethyl nitrite and stirred at room temperature for 1 h. The deep violet reaction solution is added to aqueous potassium carbonate solution and extracted with ethyl acetate. After evaporating the organic phase in vacuo, 8 g of the residue are obtained, which can be immediately reacted further. (R_f = 0.17, T1E1, SiO_2).

Example 6A

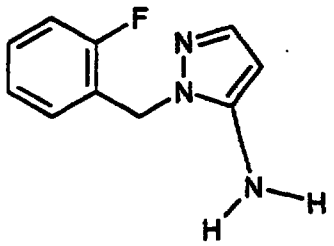
4,5-Diamino-1-(2-fluorobenzyl)-3-(5-hydroxymethyl-2-furyl)-pyrazole



The compound from Example 5A (8 g) is dissolved in ethanol, treated with 0.5 g of 5% strength palladium on carbon and hydrogenated for 15 minutes in a Parr apparatus at a hydrogen pressure of 2 bar. The solution is filtered off with suction through kieselguhr and used for the next batch (R_f = 0.21, T1E1, SiO_2).

Example 7A

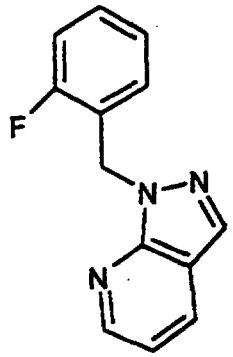
3-Amino-2-(2-fluorobenzyl)-pyrazole



Was obtained analogously to the process described in the patent Fr. 1403372 (Chem. Abstr. 1965, 63, 14871a).

Example 8A

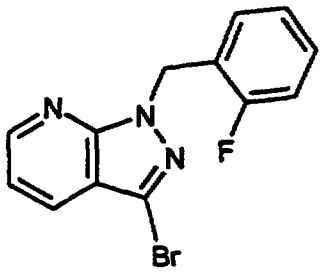
1-(2-Fluorobenzyl)-pyrazolo[3,4-b]pyrimidine



32 g of 3-amino-2-(2-fluorobenzyl)-pyrazole are dissolved in 1.5 l of dioxane and treated with 31.45 g of dimethylaminoacrolein. The mixture is warmed to 50°C and 16.65 g of trifluoroacetic acid are then added. The mixture is boiled for 60 hours, the solvent is then evaporated in vacuo, the residue is treated with water and the mixture is extracted with ethyl acetate. The organic phase is dried using Na_2SO_4 and evaporated in vacuo, and the residue is chromatographed on silica gel. After elution with toluene → toluene/ethyl acetate 9:1, 17.3 g (46.3% of theory) of the title compound having an R_f of 0.69 (SiO_2, T_1E_1) are obtained.

Example 9A

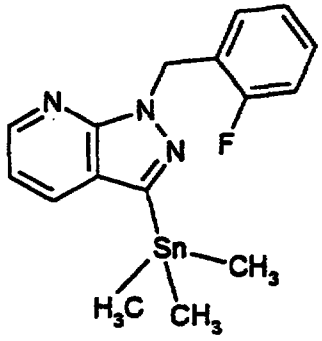
3-Bromo-1-(2-fluorobenzyl)-pyrazolo[3,4-b]pyrimidine



8 g (35.2 mmol) of 1-(2-fluorobenzyl)pyrazolo[3,4-b]pyrimidine are dissolved in 284 ml of chloroform and treated slowly at room temperature with 14 g (87.3 mmol) of bromine. The mixture is stirred overnight and a further 1.2 ml of bromine are then added dropwise. After 2 h, the reaction is terminated and evaporated in vacuo. The residue is treated with 20 ml of ethyl acetate and induced to crystallize. After washing the crystals with ether, 7.5 g (70% of theory) of the title compound having an R_f of 0.2 (SiO_2, toluene) are obtained.

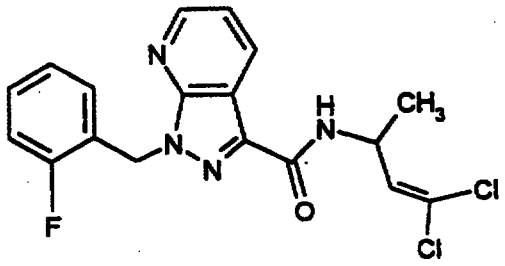
Example 10A

1-(2-Fluorobenzyl)-3-trimethylstannylpyrazolo[3,4-b]pyrimidine



1.22 g (4 mmol) of 3-bromo-1-(2-fluorobenzyl)pyrazolo[3,4-b]pyrimidine are dissolved in 200 ml of dioxane under argon and treated with 4.5 g (13.74 mmol) of hexamethyldistannane and 1.2 g of tetrakis(triphenylphosphine)palladium. The mixture is stirred overnight at 100°C, added to water and extracted with ethyl acetate. The organic phase is dried using Na_2SO_4, evaporated in vacuo and chromatographed on silica gel. After elution with toluene, 1.4 g (89.7% of theory) of the title compound having an R_f of 0.074 (SiO_2, toluene) are obtained.

Example 11A



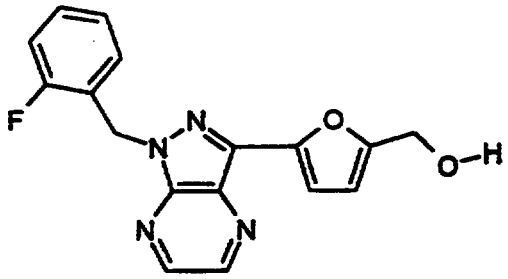
500 mg of 1-(2-fluorobenzyl)pyrazolo[3,4-b]pyridine-3-carboxylic acid (1.84 mmol) are partly dissolved in 10 ml of methylene chloride. 400 mg of N-(3-dimethylamino-propyl)-N'-ethylcarbodiimide hydrochloride (2.3 mmol) are added. The mixture is stirred at RT for 10 min (complete solution), then a solution of 260 mg of 1,1-dichloro-3-amino-but-1-ene (1.84 mmol) in 5 ml of methylene chloride is added dropwise.

After approximately 3 h, the mixture is concentrated and purified on silica gel (solvent: cyclohexane/EA 1:1). 340 mg (47%) of 1-(2-fluorobenzyl)-3-(1,1-dichlorobut-1-en-3-yl-amido)pyrazolo[3,4]pyridine are obtained, R_f 0.35 (cyclohexane:EA 2:1). MS (ESI-POSITIVE): 417 (27, $[M+Na]^+$); 415 (42, $[M+Na]^+$); 395 (60, $[M+H]^+$); 393 (100, $[M+H]^+$).

Preparation examples

Example 1

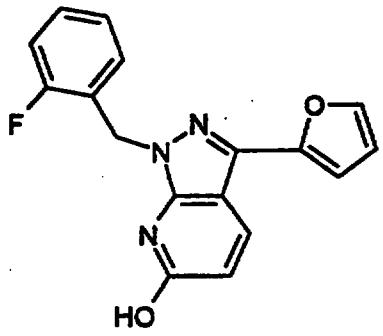
1-(2-Fluorobenzyl)-3-(2-hydroxymethyl-2-furyl)pyrazolo[3,4-b]pyrazine



The crude batch (8 g in 200 ml of ethanol) from Example 6A is treated with 4.61 g of a 40% strength aqueous glyoxal solution and stirred at room temperature for 10 h. The mixture is evaporated in vacuo and chromatographed on SiO_2 using toluene/ethyl acetate mixtures. After crystallization with ether, 0.57 g (7.6% of theory) of the title compound having an m.p. of 194°C is obtained.

Example 2

1-(2-Fluorobenzyl)-3-(2-furyl)-6-hydroxypyrazolo[3,4-b]pyridine

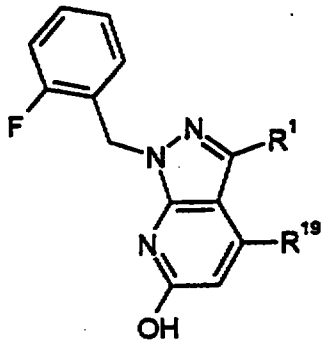


7 g (27.2 mmol) of 5-amino-1-(2-fluorobenzyl)-3-(2-furyl)pyrazole, 3.94 g (27.3 mmol) of ethyl 3-ethoxyacrylate and 1.96 ml (27.3 mmol) of trifluoroacetic acid are intimately mixed and made to react for 2 minutes in a microwave oven. The mixture is added to

a solution of 10 g of K_2HPO_4 in 500 ml of water and extracted with 500 ml of ethyl acetate. After drying of the organic phase with $MgSO_4$, 30 g of silica gel are added and the mixture is evaporated in vacuo. The residue is chromatographed on a silica gel column using a toluene-ethyl acetate gradient. The first fraction is crystallized using ether and affords 1.8 g (21.4% of theory) of the title compound having an m.p. of 250°C.

The compounds listed in Table 1 were prepared in analogy to the procedure of Example 2:

Table 1

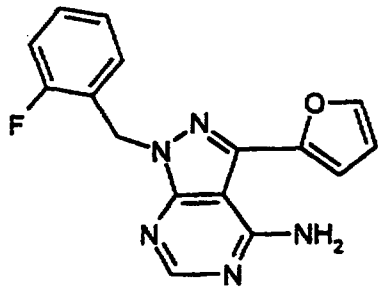


Ex. No.	R^1	R^{19}	Yield (% of theory)	R_f/m.p.°C
3 *	2-furyl	$-CH_3$	24	226
4	2-pyridyl	H		0.8 (EA)

* from ethyl acetoacetate

Example 5

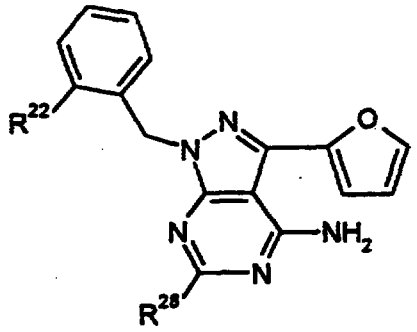
4-Amino-1-(2-fluorobenzyl)-3-(2-furyl)pyrazolo[3,4-d]pyrimidine



2 g (7.1 mmol) of 5-amino-4-cyano-1-(2-fluorobenzyl)-3-(2-furyl)pyrazole and 30 ml of formamide are stirred first at 100°C and then at 195°C for 3 h. The material crystallizing on cooling is filtered off with suction and washed with cold formamide, the residue is taken up in ethyl acetate and the solution is washed with water. After drying and evaporating the organic phase, 2.13 g (97% of theory) of the title compound having an m.p. of 190°C are obtained. R_f = 0.07 (T1E1).

The compounds listed in Table 2 are obtained in an analogous manner, for example, from 2-propyloxyphenylnitrile, benzonitrile or guanidinium hydrogencarbonate:

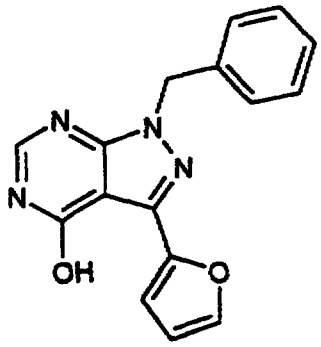
Table 2



Ex. No.	R^{27}	R^{28}	m.p. [°C]	R_f	Yield [% of theory]
6	F	2-propyloxyphenyl	187	0.6 (T1E1)	42.7
7	F	Ph	205	0.69 (T1E1)	100
8	F	NH_2	205	0.22 (EA)	71
9	H	H	174	0.15 (T1E1)	90

Example 10

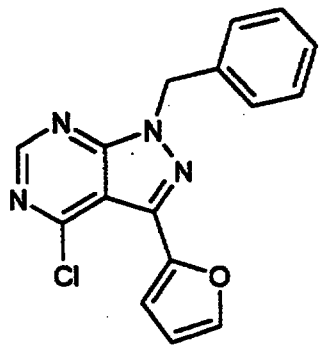
1-Benzyl-3-(2-furyl)-4-hydroxypyrazolo[3,4-d]pyrimidine



6.14 g (23.2 mmol) of 5-amino-1-benzyl-4-cyano-3-(2-furyl)pyrazole (R_f = 0.6) are boiled for 3.75 h in 100 ml of formic acid. The batch is then evaporated in vacuo. The residue is treated with water and the mixture is extracted by shaking with ethyl acetate. The insoluble portion is filtered off with suction and affords 5.1 g of the target compound (m.p. = 242°C, R_f = 0.3, SiO_2, toluene/ethyl acetate = 1:1). By evaporating the organic phase, further quantities can be isolated.

Example 11

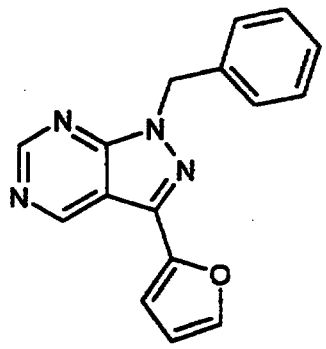
1-Benzyl-4-chloro-3-(2-furyl)pyrazolo[3,4-d]pyrimidine



6.6 g of 1-benzyl-3-(2-furyl)-4-hydroxypyrazolo[3,4-d]pyrimidine are boiled for 12 h in 100 ml of $POCl_3$. The mixture is evaporated in vacuo, the residue is stirred with aqueous K_2HPO_4 solution and the mixture is extracted with ethyl acetate. After drying using Na_2SO_4 and concentrating in a rotary evaporator, 7.47 g of a solid are obtained which can be reacted directly for the next stage (R_f = 0.8, SiO_2, toluene/ethyl acetate = 1:1).

Example 12

1-Benzyl-3-(2-furyl)pyrazolo[3,4-d]pyrimidine

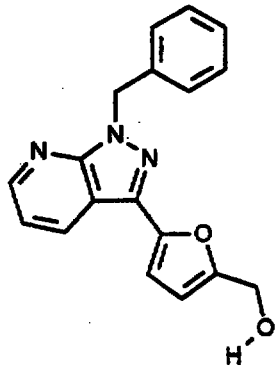


5.81 g of 1-benzyl-4-chloro-3-(2-furyl)pyrazolo[3,4-d]pyrimidine are dissolved in 450 ml of dioxane and hydrogenated in the Parr apparatus at a hydrogen pressure of 3 bar for 5 h using 4 g of 20% $Pd(OH)_2$ on carbon after addition of 2.61 ml of triethyl-

amine. After filtration through kieselguhr, evaporation and chromatography, 2.26 g of yellowish crystals are obtained (m.p. = 106°C, R_f = 0.2 toluene/ethyl acetate = 4:1).

Example 13

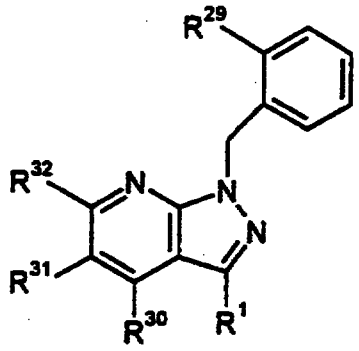
1-Benzyl-3-(5-hydroxymethyl-2-furyl)-1-H-pyrazolo[3,4-b]pyridine



2.69 g (10 mmol) of 5-amino-1-benzyl-3-(5-hydroxymethyl-2-furyl)pyrazole and 1.4 g of malonaldehyde hydrate sodium salt are stirred at 100°C for 30 min in 100 ml of dioxane and slowly treated with 1.9 ml of trifluoroacetic acid during the course of 5.5 hours. The mixture is evaporated in vacuo, the residue is taken up in ethyl acetate, the mixture is extracted by shaking with K_2HPO_4 solution, and the organic phase is dried using Na_2SO_4 and concentrated in vacuo in a rotary evaporator. The residue is chromatographed on silica gel. 200 mg (6.6% of theory) of crystals having a melting point of 104°C are obtained.

The compounds mentioned in Table 3 are prepared in analogy to the abovementioned procedures:

Table 3



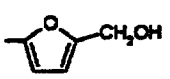
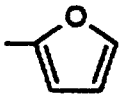
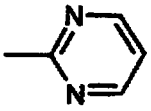
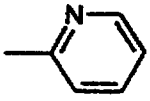
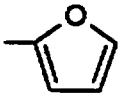
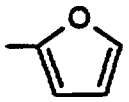
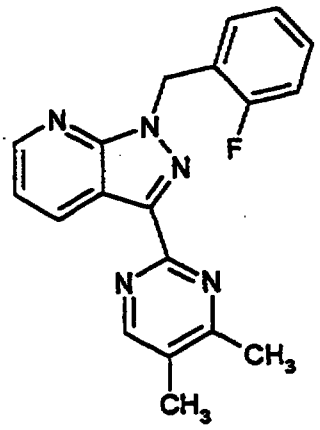
Ex. No.	R^{29}	R^1	R^{30}	R^{31}	R^{32}	m.p. [°C]	R_f	Yield (% of theory)
14	F		H	H	H	115	0.6 (EA)	1.1
15	F		H	H	H	45	0.69 (T1E1)	68
16	F		H	H	H	163	0.33 (T1E1)	11
17	F		H	H	H	71	0.65 (T1E1)	41
18	H		Me	Me	Me	115	0.84 (T1E1)	71

Table 3 - continuation

Ex. No.	R^{29}	R^1	R^{30}	R^{31}	R^{32}	m.p. [°C]	R_f	Yield (% of theory)
19	H		Me	H	Me	78	0.77 (T1E1)	71

Example 20

3-(4,5-Dimethylpyrimidin-2-yl)-1-(2-fluorobenzyl)pyrazolo[3,4-b]pyrimidine



1.4 g (3.59 mmol) of 1-(2-fluorobenzyl)-3-trimethylstannylpyrazolo[3,4-b]pyrimidine are boiled overnight in toluene under argon with 0.51 g (3.58 mmol) of 2-chloro-4,5-dimethylpyrimidine and 0.2 g (0.28 mmol) of bis(triphenylphosphine)dichloropalladium. 3 g of silica gel are added and the solvent is evaporated in vacuo. The residue is then chromatographed on silica gel and eluted with a toluene/ethyl acetate mixture. 0.34 g (28.4% of theory) of the title compound having an m.p. of 167°C and an R_f of 0.08 (SiO_2, T4E) is obtained.

The example shown in Table 4 was prepared in an analogous manner.

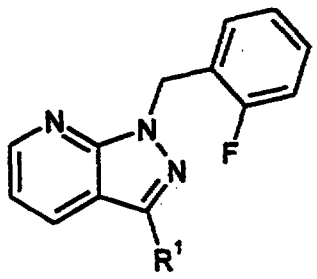
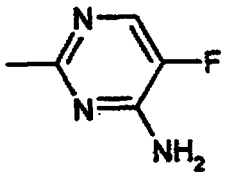
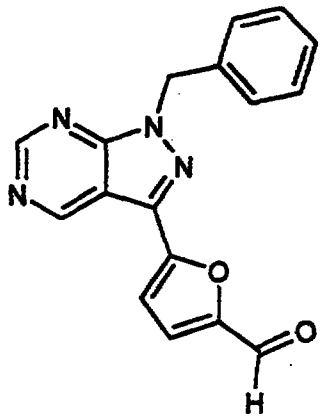


Table 4

Ex. No.	R^1
21	

Example 22

1-Benzyl-3-(5-formyl-2-furyl)pyrazolo[3,4-d]pyrimidine



0.74 ml of $POCl_3$ is added at 0°C to 0.64 ml of DMF. The solidified mixture is allowed to come to room temperature and 14 ml of 1,2-dichloroethane are added. A

solution of 2 g of 1-benzyl-3-(2-furyl)pyrazolo[3,4-d]pyrimidine (R_f = 0.45, SiO_2, toluene/ethyl acetate = 1:1) in 14 ml of 1,2-dichloroethane is added dropwise at 15°C to this solution and it is then warmed to 80°C. After 4 h, the entire batch is added dropwise to further Vilsmeier reagent, which was prepared from 1.5 ml of $POCl_3$ and 1.3 ml of DMF, and stirred at 80°C for 24 h. The mixture is then added to a 50% aqueous solution of K_2HPO_4 and briefly heated to 75°C with stirring. After extraction with ethyl acetate, drying of the organic phase, concentration in a rotary evaporator and chromatography on SiO_2, 0.6 g (27% of theory) of an oil is obtained (R_f = 0.3, SiO_2, toluene/ethyl acetate = 1:1).

The examples from Table 5 are prepared in analogy to the abovementioned procedures.

Table 5

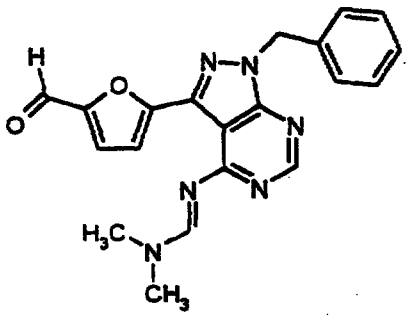
Ex. No.	Structure	m.p. (°C)	Yield (% of theory)	R_f
23		203	56.1	0.17 (EA)

Table 5 - continuation

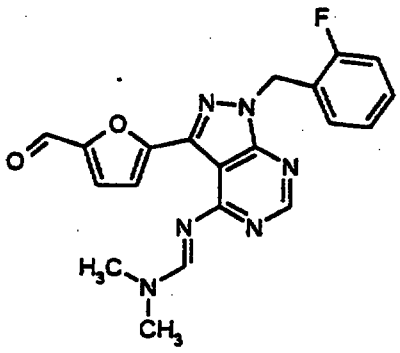
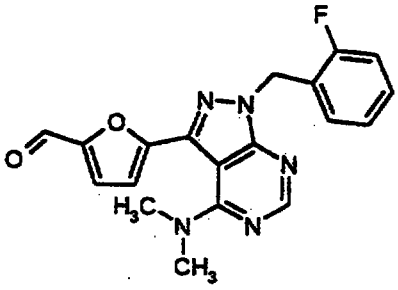
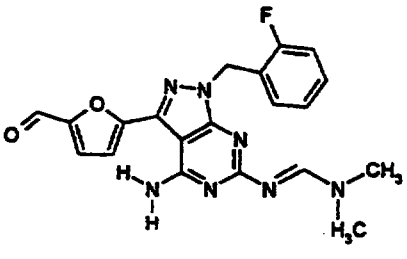
Ex. No.	Structure	m.p. (°C)	Yield (% of theory)	R_f
24		220	80,6	0.23 (EA)
25		205	100	0.61 (EA)
26		225	22.1	0.74 (T/E = 2:1)

Table 5 - continuation

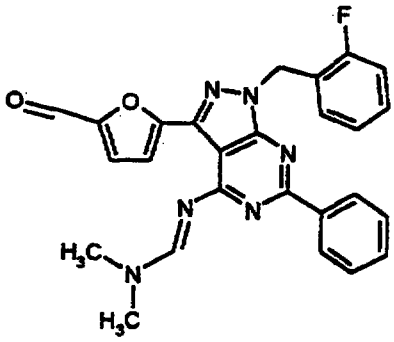
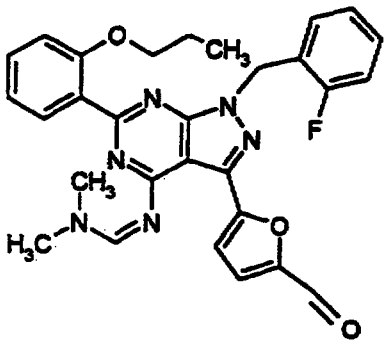
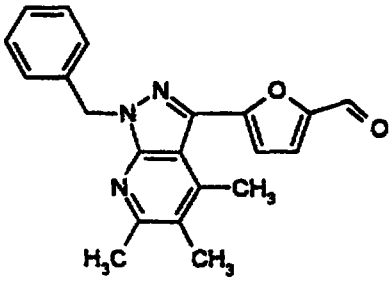
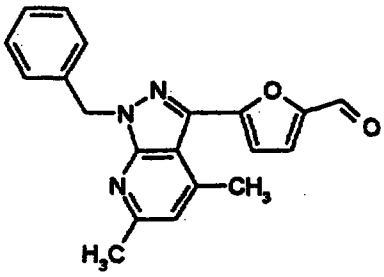
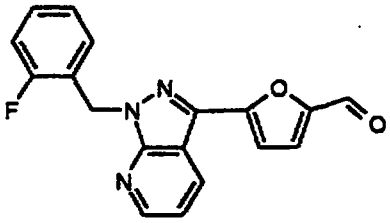
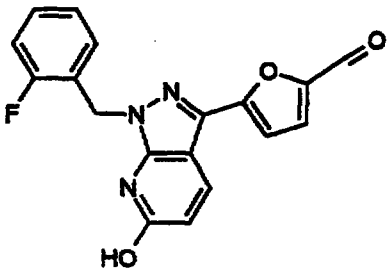
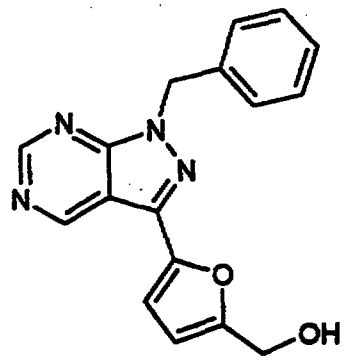
Ex. No.	Structure	m.p. (°C)	Yield (% of theory)	R_f
27		220	75	0.34 (T1E1)
28		157	79	0.44 (T1E1)
29		118	13.09	0.49 (T4:E1)

Table 5 - continuation

Ex. No.	Structure	m.p. (°C)	Yield (% of theory)	R_f
30		125	27.56	0.46 (T4:E1)
31		123	93	0.63 (T1:E1)
32		265	97	0.49 (T1:E1)

Example 33

1-Benzyl-3-(5-hydroxymethyl-2-furyl)pyrazolo[3,4-d]pyrimidine



0.6 g (1.97 mmol) of 1-benzyl-3-(5-formyl-2-furyl)pyrazolo[3,4-d]pyrimidine (R_f = 0.65, SiO_2, ethyl acetate) is treated with 60 mg of $NaBH_4$ with good stirring in 20 ml of 1-propanol at room temperature. After 15 min, 50 ml of water and 2.5 ml of glacial acetic acid are added. After partially concentrating in a rotary evaporator, the mixture is extracted with ethyl acetate, and the extract is dried and concentrated in a rotary evaporator after addition of toluene. After chromatography on SiO_2, 74.8 mg (12.4% of theory) of product are obtained (m.p. 165°C, R_f = 0.43, SiO_2, ethyl acetate).

The compounds shown in Table 6 are prepared in analogy to the procedure of Example 33:

Table 6

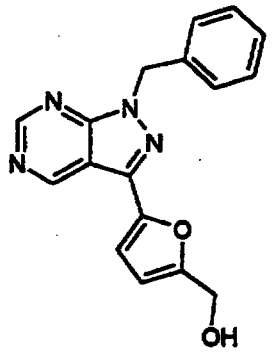
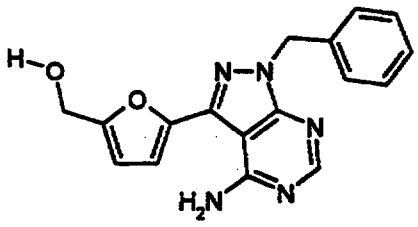
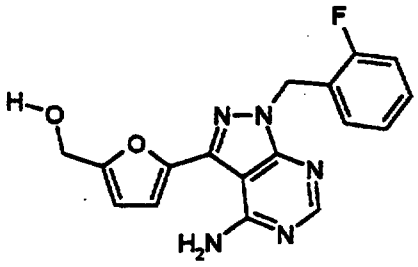
Ex. No.	Structure	m.p. [°C]	Yield (% of theory)	R_f
34		165	43.5	0.37 (EA)
35		213	60	0.15 (EA)
36		207	63	0.21 (EA)

Table 6 - continuation

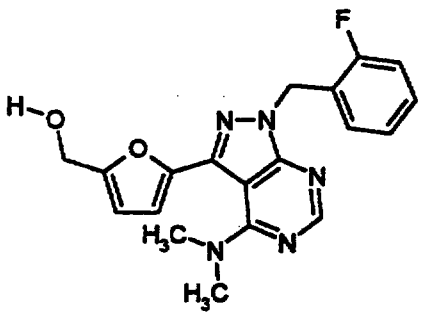
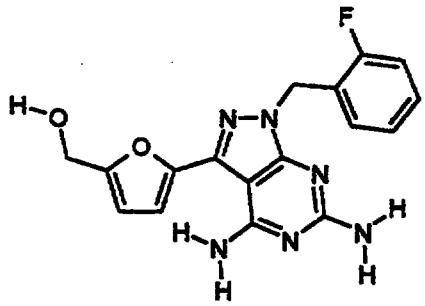
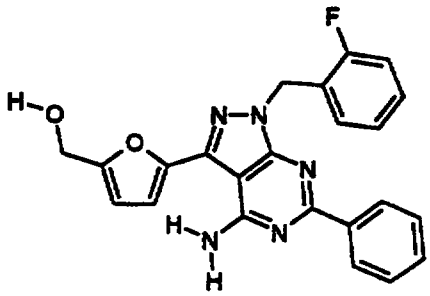
Ex. No.	Structure	m.p. [°C]	Yield (% of theory)	R_f
37		94	30	0.45 (EA)
38		205	27.6	0.11 (EA)
39		225	23.5	0.29 (T1E1)

Table 6 - continuation

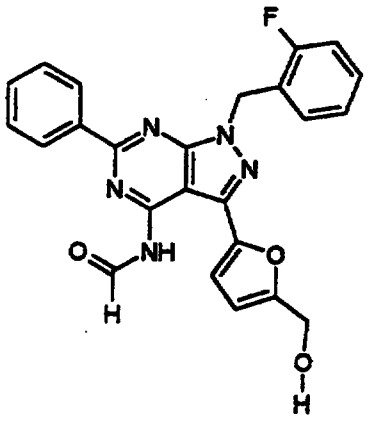
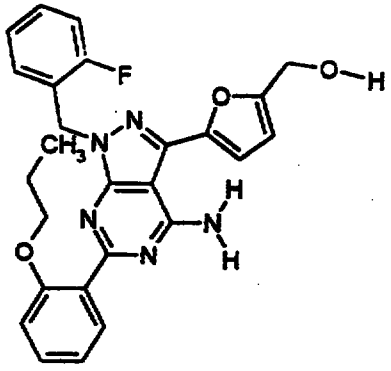
Ex. No.	Structure	m.p. [°C]	Yield (% of theory)	R_f
40		189	23	0.43 (T1E1)
41				

Table 6 - continuation

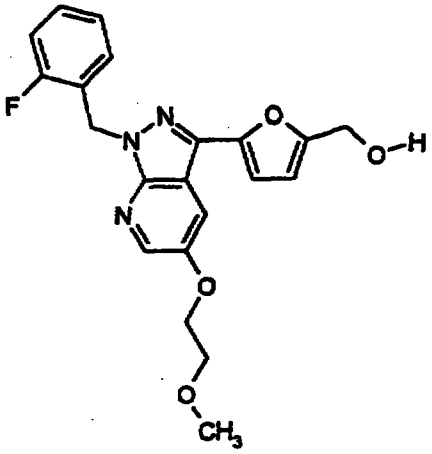
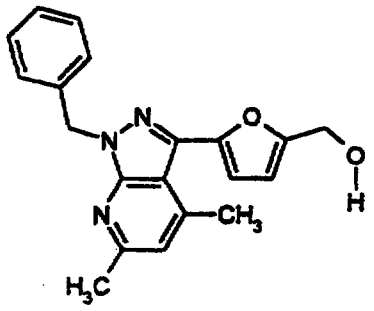
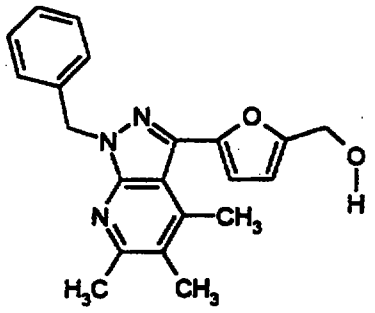
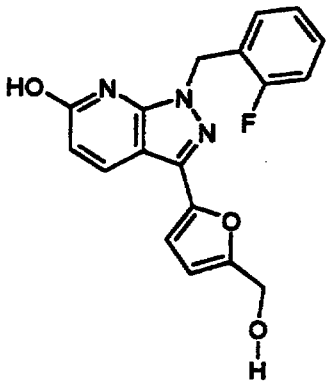
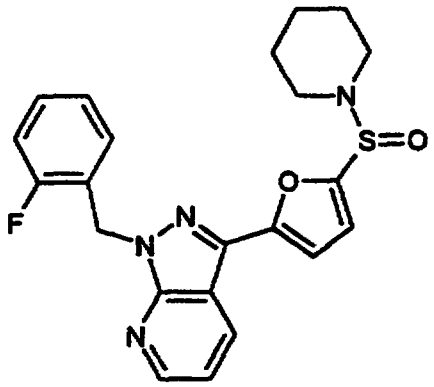
Ex. No.	Structure	m.p. [°C]	Yield (% of theory)	R_f
42		106	15.46	0.25 (T1E1)
43		155	81.73	0.48 (T1E1)

Table 6 - continuation

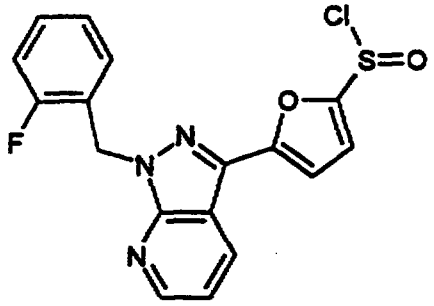
Ex. No.	Structure	m.p. [°C]	Yield (% of theory)	R_f
44		180	72.08	0.53 (T1E1)
45				0.21 (T1E1)

Example 46

Preparation of 1-(2-fluorobenzyl)-3-[5-(piperidine-1-sulphinyl)furan-2-yl]-1H-pyrazolo-[3,4-b]pyridine



a) Preparation of 1-(2-fluorobenzyl)-3-[5-chlorosulphinylfuran-2-yl]pyrazolo[3,4-b]-pyridine



0.85 g (2.86 mmol) of 1-(2-fluorobenzyl)-3-(2-furyl)pyrazolo[3,4-b]pyridine is stirred with 20 ml of thionyl chloride for 25 min at 70°C. The batch is then evaporated in vacuo and reacted further in crude form.

b) The above batch is taken up in 30 ml of dioxane, treated with 0.6 ml (about 6 mmol) of piperidine, vigorously shaken and allowed to stand overnight. It is added to water and the mixture is extracted by shaking with ethyl acetate. After drying the organic phase using Na_2SO_4, it is evaporated and the residue is chromatographed on silica gel using a toluene/ethyl acetate gradient. 0.49 g (40% of theory) of a brown, clear viscous syrup is obtained (R_f (SiO_2; T1E1) = 0.36).

The compounds shown in Table 7 are prepared in analogy to the abovementioned procedures and that of Example 46.

Example 67 is prepared in analogy to the procedure of Example 20.

Table 7

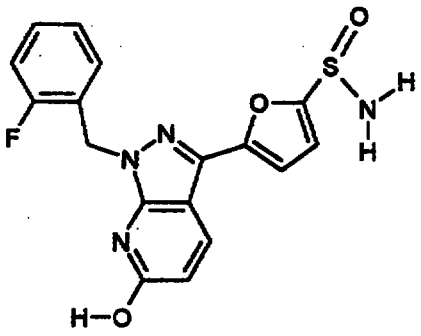
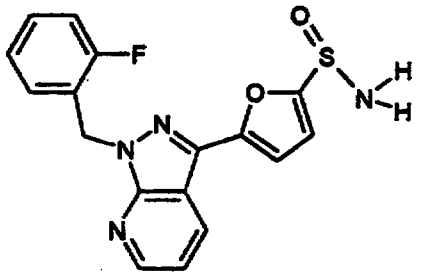
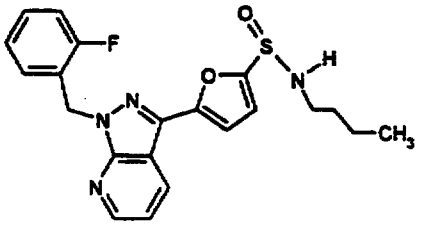
Ex. No.	Structure	m.p. (°C)	Yield (% of theory)	R_f
47			29.34	0.37 EA
48			8.23	0.12 (T1E1)
49		oil	10	0.37 (T1E1)

Table 7 - continuation

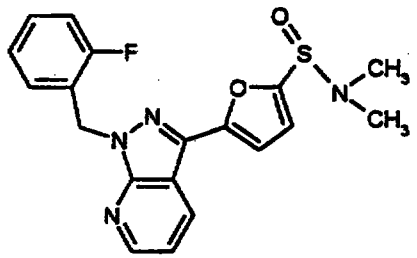
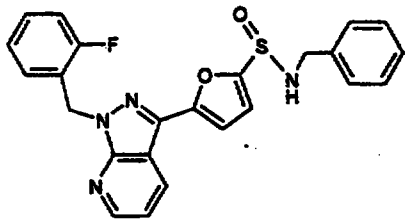
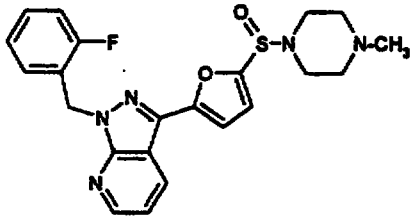
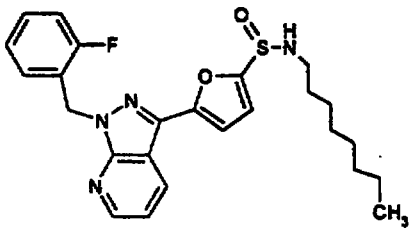
Ex. No.	Structure	m.p. (°C)	Yield (% of theory)	R_f
50		107	37	0.28 (T1E1)
51		126	27	0.43 (T1E1)
52		279	77	0.16 (EA/EtOH = 1:1)
53		69	56	0.49 (T1E1)

Table 7 - continuation

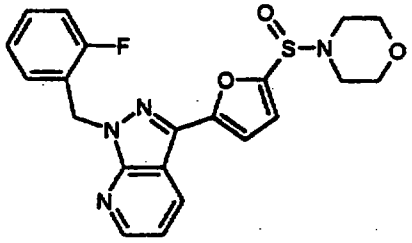
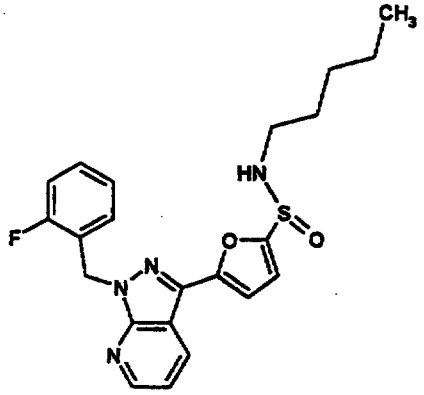
Ex. No.	Structure	m.p. (°C)	Yield (% of theory)	R_f
54		122	34	0.31 (T1:E1)
55		oil	4.2	0.37 (T1E1)

Table 7 - continuation

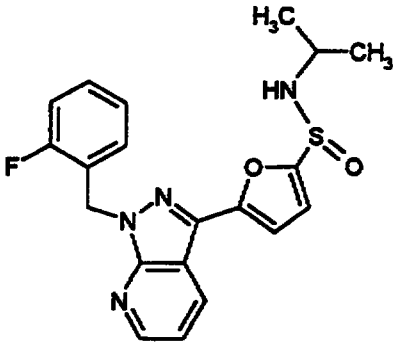
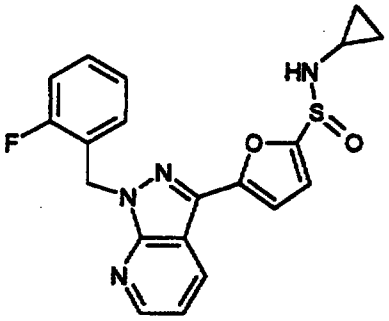
Ex. No.	Structure	m.p. (°C)	Yield (% of theory)	R_f
56		136	76	0.33 (T1E1)
57		138	50	0.31 (T1E1)

Table 7 - continuation

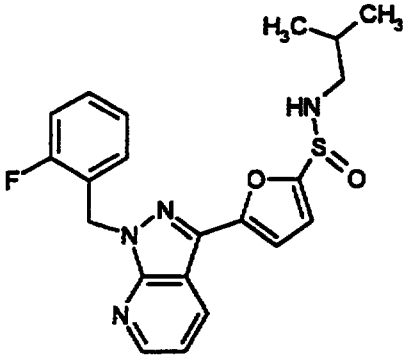
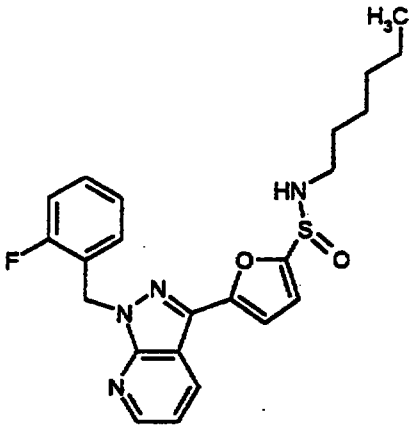
Ex. No.	Structure	m.p. (°C)	Yield (% of theory)	R_f
58		109	59	0.38 (T1E1)
59		114	53	0.45 (T1E1)

Table 7 - continuation

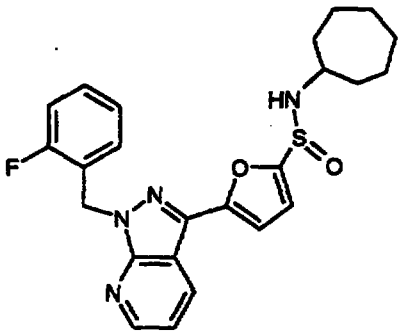
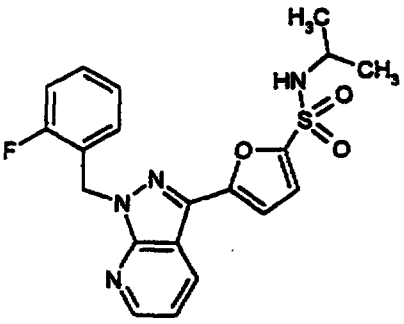
Ex. No.	Structure	m.p. (°C)	Yield (% of theory)	R_f
60		161	40	0.46 (T1E1)
61		109	58	0.58 (T1E1)

Table 7 - continuation

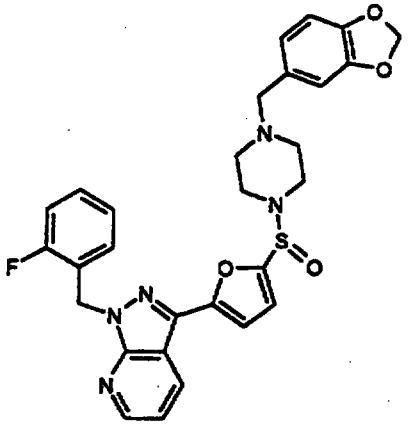
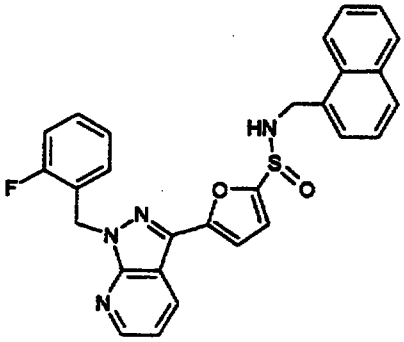
Ex. No.	Structure	m.p. (°C)	Yield (% of theory)	R_f
62		oil	65	0.17 (T1E1)
63		158	66	0.47 (T1E1)

Table 7 - continuation

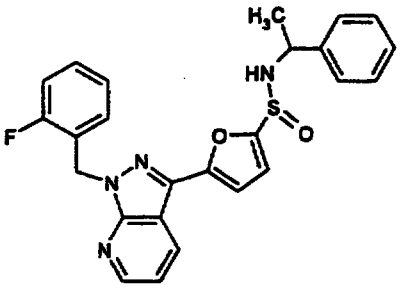
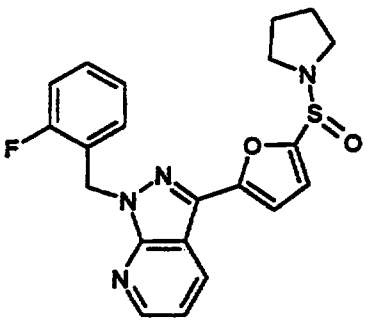
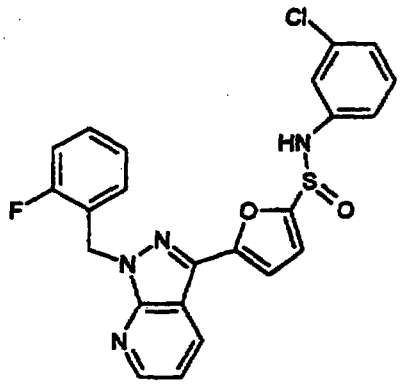
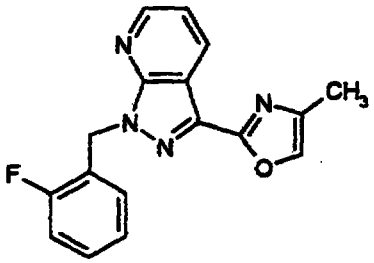
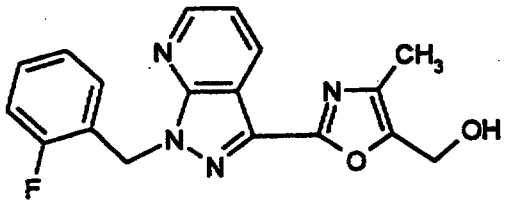
Ex. No.	Structure	m.p. (°C)	Yield (% of theory)	R_f
64		132	60	0.41 (T1E1)
65		107	71	0.4 (T1E1)

Table 7 - continuation

Ex. No.	Structure	m.p. (°C)	Yield (% of theory)	R_f
66		110	62	0.57 (T1E1)
67		106	6	0.23 (hexane:EA 3:1) Al_2O_3

Example 68

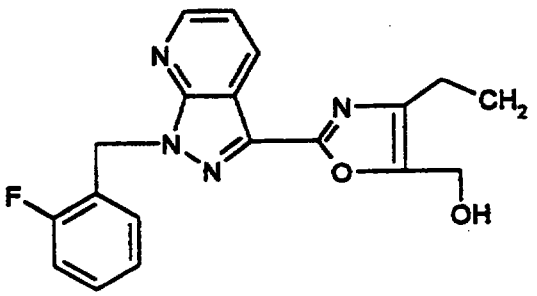
1-(2-Fluorobenzyl)-3-(4-methyl-3-hydroxymethyloxazol-2-yl)pyrazolo[3,4b]pyridine



330 mg of 1-(2-fluorobenzyl)-3-(1,1-dichlorobut-1-en-3-yl-amido)pyrazolo[3,4b]pyridine (0.84 mmol), 1.7 ml of NaOH 1N (1.68 mmol) and 3.3 ml of 1-methyl-2-pyrrolidone are stirred overnight at 50°C, then allowed to cool. The mixture is treated with water and ethyl acetate. The organic phase is separated, dried over Na_2SO_4 and concentrated. The mixture is dried in a high vacuum. The solid is then treated with cyclohexane/EA 2:1, crystals being formed. The crystals are filtered off with suction and stirred at RT with ether. An insoluble impurity is separated. The ethereal solution is concentrated and chromatographically purified. 52.1 mg (18%) of 1-(2-fluorobenzyl)-3-(4-methyl-3-hydroxymethyloxazol-2-yl)pyrazolo[3,4b]pyridine are obtained. M.p. 145°C. R_f: 0.074 (cyclohexane:EA 2:1). MS (ESI-POSITIVE): 339 (100, $[M + H]^+$).

Example 69

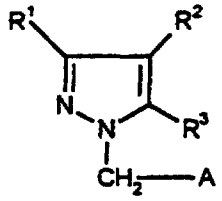
1-(2-Fluorobenzyl)-3-(4-ethyl-3-hydroxymethyloxazol-2-yl)pyrazolo[3,4b]pyridine



The compound is prepared in analogy to the procedure of Example 68. Yield (52% of theory), R_f 0.33 (hexane:EA 1:1).

Patent claims

1. Substituted pyrazole derivatives of the general formula (I)



(I)

in which

R^1 represents a saturated or aromatic 5- or 6-membered heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O, which can be bonded via a nitrogen atom and which is optionally substituted up to 3 times identically or differently by amino, azido, formyl, mercaptyl, carboxyl, hydroxyl, straight-chain or branched acyl, alkoxy, alkylthio or alkoxycarbonyl each having up to 6 carbon atoms, nitro, cyano, halogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl, amino, azido, carboxyl, straight-chain or branched acyl, alkoxy, alkoxycarbonyl or acylamino each having up to 5 carbon atoms or by a radical of the formula $-OR^4$,

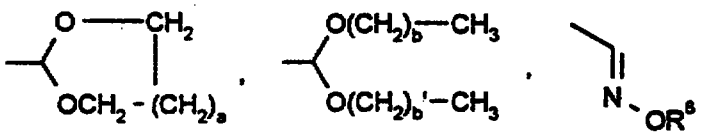
in which

R^4 denotes straight-chain or branched acyl having up to 5 carbon atoms or a group of the formula $-SiR^5R^6R^7$,

in which

R^5, R^6 and R^7 are identical or different and denote aryl having 6 to 10 carbon atoms or alkyl having up to 6 carbon atoms,

and/or is substituted by a radical of the formula



or

$-S(O)_c-NR^9R^{10}$,

in which

a, b and b' are identical or different and denote a number 0, 1, 2 or 3,

R^8 denotes hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

c denotes a number 1 or 2 and

R^9 and R^{10} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 10 carbon atoms, which can optionally be substituted by cycloalkyl having 3 to 8 carbon atoms or by aryl having 6 to 10 carbon atoms, which for its part can be substituted by halogen, or

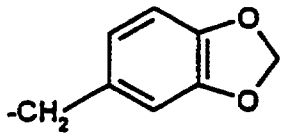
denote aryl having 6 to 10 carbon atoms, which is optionally substituted by halogen, or

denote cycloalkyl having 3 to 7 carbon atoms, or

R^9 and R^{10}, together with the nitrogen atom, form a 5- to 7-membered saturated heterocycle which can optionally contain a further oxygen atom or a radical $-NR^{11}$, in which

* C L M S *

R^{11} denotes hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms or a radical of the formula



or denotes benzyl or phenyl, where the ring systems are optionally substituted by halogen,

R^2 and R^3, including the double bond, form a 6-membered saturated or aromatic heterocycle having up to 3 heteroatoms from the group consisting of N, S and/or O, which is optionally substituted up to 3 times identically or differently by formyl, carboxyl, hydroxyl, mercaptyl, straight-chain or branched acyl, alkylthio or alkoxycarbonyl each having up to 6 carbon atoms, nitro, cyano, halogen or straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms, which for its part can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 5 carbon atoms,

and/or the heterocycle is optionally substituted by a group of the formula $-NR^{12}R^{13}$ or $-S(O)_{c'}NR^{9'}R^{10'}$, in which

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

R^{12} denotes hydrogen and

R^{13} denotes formyl

c', $R^{9'}$ and $R^{10'}$ have the meaning of c, R^9 and R^{10} indicated above and are identical to or different from these

and/or the heterocycle is optionally substituted by phenyl which for its part can be substituted up to 2 times identically or differently by halogen or by straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms

and/or the heterocycle is optionally substituted by a group of the formula $-N=CH-NR^{14}R^{15}$, in which

R^{14} and R^{15} are identical or different and denote hydrogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms,

A represents a 5- or 6-membered aromatic or saturated heterocycle having up to 3 heteroatoms from the group consisting of S, N and/or O or phenyl, each of which is optionally substituted up to 3 times identically or differently by amino, mercaptyl, hydroxyl, formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkyloxyacyl, alkoxy or alkoxycarbonyl each having up to 6 carbon atoms, nitro, cyano, trifluoromethyl, azido, halogen, phenyl or straight-chain or branched alkyl having up to 6 carbon atoms, which for its part can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 5 carbon atoms,

and/or is substituted by a group of the formula $-(CO)_d-NR^{16}R^{17}$,

in which

d denotes a number 0 or 1,

R^{16} and R^{17} are identical or different and

denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl or acyl each having up to 5 carbon atoms,

* C L M S *

and their isomeric forms and salts.

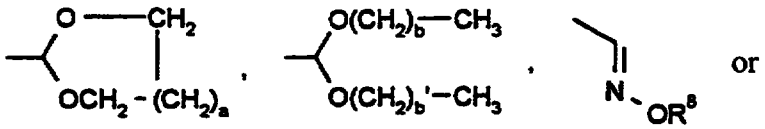
2. Compounds of the general formula (I) according to Claim 1, in which

R^1 represents pyrimidinyl, pyridazinyl, pyridyl, pyrazinyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, thiazolyl, 1,2,3-triazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, isoxazolyl, isothiazolyl, pyranyl or morpholinyl, each of which is optionally substituted up to 3 times identically or differently by amino, formyl, mercaptyl, carboxyl, hydroxyl, straight-chain or branched acyl, alkoxy, alkylthio or alkoxycarbonyl each having up to 5 carbon atoms, nitro, cyano, azido, fluorine, chlorine, bromine, phenyl or straight-chain or branched alkyl having up to 5 carbon atoms, which for its part can be substituted by hydroxyl, amino, azido, carboxyl, straight-chain or branched acyl, alkoxy, alkoxycarbonyl or acylamino each having up to 4 carbon atoms or by a radical of the formula $-OR^4$,

in which

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

and/or by a radical of the formula



or

$-S(O)_c-NR^9R^{10}$,

in which

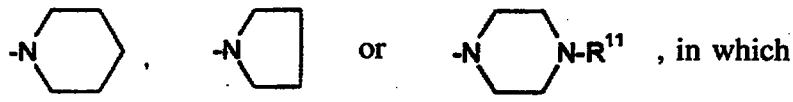
a, b and b' are identical or different and denote a number 0, 1, 2 or 3,

R^8 denotes hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

c denotes a number 1 or 2 and

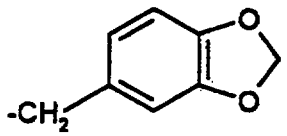
R^9 and R^{10} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 9 carbon atoms, which can optionally be substituted by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or naphthyl or phenyl, which for their part can be substituted by fluorine or chlorine, or
denote phenyl or naphthyl, each of which is optionally substituted by fluorine or chlorine, or
denote cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, or

R^9 and R^{10}, together with the nitrogen atom, form a morpholine ring or a radical of the formula



, in which

R^{11} denotes hydrogen, methyl or a radical of the formula



or denotes benzyl or phenyl,
where the ring systems are optionally substituted by fluorine or chlorine,

R^2 and R^3, including the double bond, form a pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl ring, each of which is optionally substituted up to 3 times identically or differently by formyl, carboxyl, hydroxyl, mercaptyl,

* C L M S *

straight-chain or branched acyl, alkylthio or alkoxycarbonyl each having up to 5 carbon atoms, nitro, cyano, azido, fluorine, chlorine, bromine or straight-chain or branched alkyl or alkoxy each having up to 5 carbon atoms, which for its part can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms,

and/or the abovementioned heterocyclic rings are optionally substituted by a group of the formula $-NR^{12}R^{13}$ or $-S(O)_{c'}NR^{9'}R^{10'}$, in which

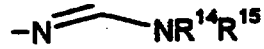
R^{12} and R^{13} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, or

R^{12} denotes hydrogen and

R^{13} denotes formyl

c', $R^{9'}$ and $R^{10'}$ have the meaning of c, R^9 and R^{10} indicated above and are identical to or different from these

and/or the abovementioned heterocyclic rings are optionally substituted by phenyl, which for its part can be substituted by fluorine, chlorine, bromine or by straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms

and/or the abovementioned heterocyclic rings are optionally substituted by a group of the formula , in which

R^{14} and R^{15} denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

* C L M S *

A represents thienyl, tetrahydropyranyl, tetrahydrofuranyl, phenyl, morpholinyl, pyrimidyl, pyrazinyl, pyridazinyl or pyridyl, each of which is optionally substituted up to 2 times identically or differently by hydroxyl, formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkoxyacyl, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl or straight-chain or branched alkyl having up to 4 carbon atoms, which for its part can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms,

and/or by a group of the formula $-(CO)_d-NR^{16}R^{17}$,

in which

d denotes a number 0 or 1,

R^{16} and R^{17} are identical or different and

denote hydrogen, phenyl, benzyl or straight-chain or branched alkyl or acyl each having up to 4 carbon atoms,

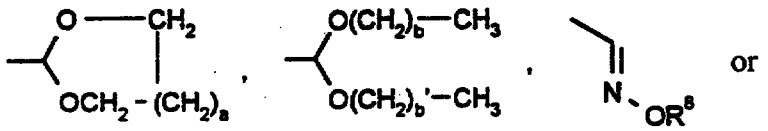
and their isomeric forms and salts.

3. Compounds of the general formula (I) according to Claim 1, in which

R^1 represents imidazolyl, furyl, pyridyl, pyrrolyl, pyrazinyl, pyrimidyl, isoxazolyl, oxazolyl or thiazolyl, each of which is optionally substituted up to 3 times identically or differently by formyl, fluorine, chlorine, amino, mercaptyl, cyano, straight-chain or branched acyl, alkylthio, alkoxy or alkoxycarbonyl each having up to 4 carbon atoms or straight-chain or branched alkyl having up to 4 carbon atoms, which for its part can be substituted by hydroxyl, carboxyl, amino, azido, straight-chain or branched acyl, alkoxy, alkoxycarbonyl or acylamino each having up to

3 carbon atoms,

and/or by a radical of the formula



$-S(O)_c-NR^9R^{10}$,

in which

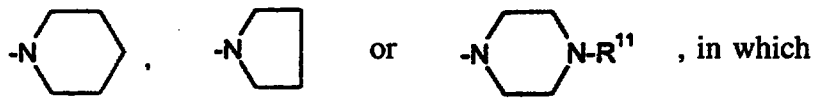
a, b and b' are identical or different and denote a number 0, 1 or 2,

R^8 denotes hydrogen or methyl,

c denotes a number 1 or 2 and

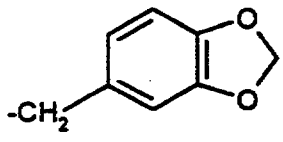
R^9 and R^{10} are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 9 carbon atoms, which can optionally be substituted by phenyl or naphthyl, or
denote phenyl or naphthyl, each of which is optionally substituted by fluorine or chlorine, or
denote cyclopropyl or cycloheptyl, or

R^9 and R^{10}, together with the nitrogen atom, form a morpholine ring or a radical of the formula



, in which

R^{11} denotes hydrogen, methyl or a radical of the formula



or denotes benzyl or phenyl, where the

ring systems are optionally substituted by chlorine,

R^2 and R^3, including the double bond, form a pyridyl, pyrazinyl, pyrimidinyl or pyridazinyl ring, each of which is optionally substituted up to 3 times identically or differently by formyl, mercaptyl, carboxyl, hydroxyl, straight-chain or branched acyl, alkoxy, alkylthio or alkoxycarbonyl each having up to 4 carbon atoms, nitro, cyano, fluorine, chlorine or straight-chain or branched alkyl or alkoxy each having up to 3 carbon atoms, which for its part can be substituted by hydroxyl, amino, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms,

and/or the heterocyclic rings are optionally substituted by amino, N,N-dimethylamino or by a radical of the formula -NH-CHO or $-N=CH-N(CH_3)_2$ and/or by phenyl, which for its part can be substituted by a radical of the formula $-O(CH_2)_2-CH_3$,

A represents tetrahydropyranyl, phenyl, pyrimidyl, thienyl or pyridyl, each of which is optionally substituted up to 2 times identically or differently by formyl, carboxyl, straight-chain or branched acyl, alkylthio, alkyloxyacyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms, fluorine, chlorine, bromine, nitro, cyano, trifluoromethyl or straight-chain or branched alkyl having up to 3 carbon atoms, which for its part can be substituted by hydroxyl, carboxyl, straight-chain or branched acyl, alkoxy or alkoxycarbonyl each having up to 3 carbon atoms,

and their isomeric forms and salts.

4. Process for the preparation of compounds of the general formula (I) according to Claim 1, characterized in that, depending on the various meanings of the heterocycles defined under R^2 and R^3, either

* C L M S *

[A] compounds of the general formula (II)

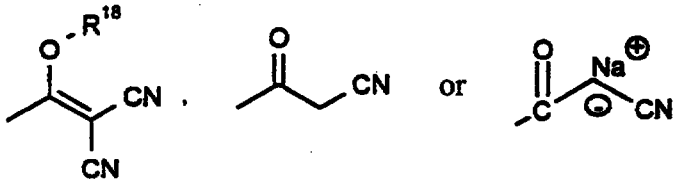
$$R^1\text{-}D \quad (II)$$

in which

R^1 has the meaning indicated above,

and

D represents radicals of the formula



in which

R^{18} represents C_1-C_4-alkyl,

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

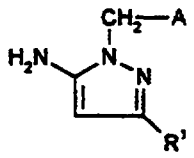
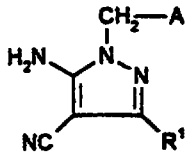
$$A\text{-}CH_2\text{-}NH\text{-}NH_2 \quad (III)$$

in which

A has the meaning indicated above

in inert solvents, if appropriate in the presence of a base, into the compounds of the general formula (IV) or (IVa)

* C L M S *


(IV) and

(IVa)

in which

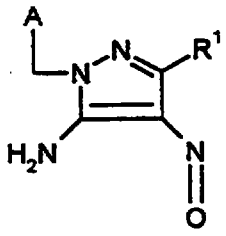
A and R^1 have the meaning indicated above,

and, in the case of the compounds of the general formula (IVa), then cyclized with carboxylic acids, nitriles, formamides or guanidinium salts,

and, in the case of the compounds of the general formula (IV), cyclized with 1,3-dicarbonyl derivatives, their salts, tautomers, enol ethers or enamines, in the presence of acids and, if appropriate, under microwaves,

or

[B] in the case where R^2 and R^3 together form a pyrazine ring, compounds of the general formula (IV) are first converted by nitrosation into the compounds of the general formula (V)

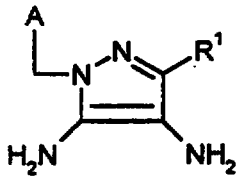

(V),

in which

A and R^1 have the meaning indicated above,

in a second step, by means of a reduction, the compounds of the general

formula (VI)



(VI),

in which

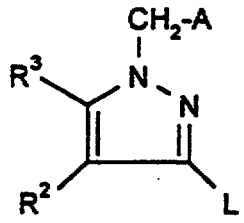
A and R^1 have the meaning indicated above,

are prepared

and finally cyclized with 1,2-dicarbonyl compounds, preferably aqueous glyoxal solution,

or

[C] compounds of the general formula (VII)



(VII)

in which

A^1, R^2 and R^3 have the meaning indicated above,

and

L represents a radical of the formula $-SnR^{19}R^{20}R^{21}$, ZnR^{22}, iodine, bromine or triflate,

in which

* C L M S *

R^{19}, R^{20} and R^{21} are identical or different and denote straight-chain or branched alkyl having up to 4 carbon atoms,

and

R^{22} denotes halogen,

are reacted with compounds of the general formula (VIII)

$$R^1\text{-}T \qquad \text{(VIII)}$$

in which

R^1 has the meaning indicated above

and

if L = $SnR^{19}R^{20}R^{21}$ or ZnR^{22}

T represents triflate or halogen, preferably bromine,

and

if L = iodine, bromine or triflate,

T represents a radical of the formula $SnR^{19'}R^{20'}R^{21'}$, $ZnR^{22'}$ or $BR^{23'}R^{24'}$,

in which

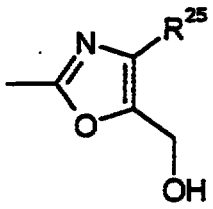
$R^{19'}$, $R^{20'}$, $R^{21'}$ and $R^{22'}$ have the meaning of R^{19}, R^{20}, R^{21} and R^{22} indicated above and are identical to or different from

* C L M S *

these,

$R^{23'}$ and $R^{24'}$ are identical or different and denote hydroxyl, aryloxy having 6 to 10 carbon atoms or straight-chain or branched alkyl or alkoxy each having up to 5 carbon atoms, or together form a 5- or 6-membered carbocyclic ring,

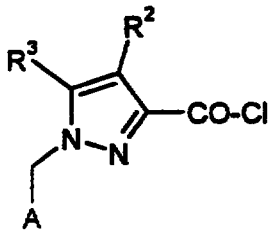
in a palladium-catalysed reaction in inert solvents, if appropriate in the presence of a base,

[D] if R^1 = 

in which

R^{25} denotes (C_1-C_6)-alkyl which is optionally substituted by halogen,

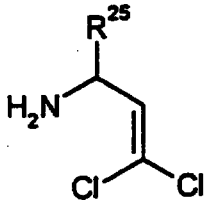
compounds of the general formula (IX)

 (IX),

in which

A, R^2 and R^3 have the meaning indicated above,

are converted either directly by reaction with the compound of the formula (X)



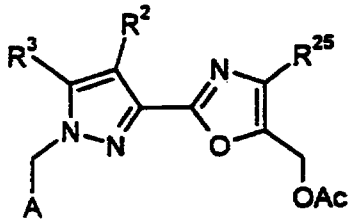
(X)

in which

R^{25} has the meaning indicated above,

in the system NaOCO-CH_3/N-methylpyrrolidine

into the compounds of the general formula (Ia)



(Ia),

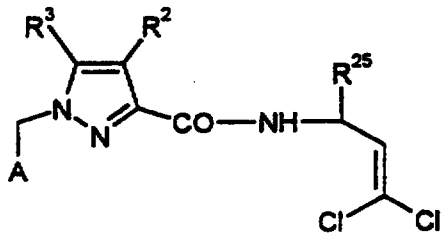
in which

R^2, R^3 and A and R^{25} have the meaning indicated above,

and then, by action of potassium hydroxide in methanol, the acetyl group is removed,

or

first, by reaction of the compounds of the general formula (IX) with the compound of the formula (X), the compounds of the general formula (XI)



(XI),

in which

R^2, R^3, A and R^{25} have the meaning indicated above,

are prepared,

and in a further step, by action of potassium hydroxide, the hydroxymethyl compounds are prepared,

and, if appropriate, converted into the corresponding alkoxy compounds by alkylation according to customary methods,

and in the case of the groups $-S(O)_cNR^9R^{10}$ and $-S(O)_{c'}NR^{9'}R^{10'}$, starting from the unsubstituted compounds of the general formula (I), first reacted with thionyl chloride and in a second step with the appropriate amines

and, if appropriate, the substituents mentioned under R^1, R^2, R^3 and/or A are varied or introduced according to customary methods, preferably by chlorination, catalytic hydrogenation, reduction, oxidation, removal of protective groups and/or nucleophilic substitution.

5. Medicaments comprising at least one compound of the general formula (I) according to Claim 1.

6. Process for the production of medicaments, characterized in that at least one

* C L M S *

compound of the formula (I) according to Claim 1 is converted into a suitable administration form, if appropriate using customary auxiliaries and additives.

7. Medicaments comprising at least one compound of the general formula (I) according to Claim 1 in combination with organic nitrates or NO donors.

8. Medicaments comprising at least one compound of the general formula (I) according to Claim 1 in combination with compounds which inhibit the degradation of cyclic guanosine monophosphate (cGMP).

9. Use of compounds of the general formula (I) according to Claim 1 in the production of medicaments for the treatment of cardiovascular disorders.

10. Use of compounds of the general formula (I) according to Claim 1 in the production of medicaments for the treatment of thromboembolic disorders and ischaemias.

* C L M S *