Heterocyclylamide-substituted thiazoles, pyrroles and thiophenes

The invention relates to heterocyclylamide-substituted thiazoles, pyrroles and thiophenes and methods for their preparation, their use for the treatment and/or prophylaxis of diseases as well as their use for the production of medicaments for the treatment and/or prophylaxis of diseases, in particular for use as antiviral agents, especially against cytomegaloviruses.

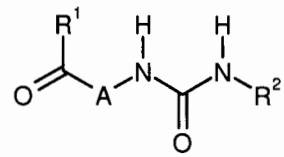
WO 99/23091 describes aromatic heterocyclic compounds as antiinflammatory agents which, inter alia, may also be suitable for the treatment of viral infections and WO 04/052852 describes 3-pyrrolylurea derivatives as antiviral agents which carry a carbocycle as a substituent on the urea.

Although structurally different agents having antiviral activity are available on the market, the therapies currently available with ganciclovir, valganciclovir, foscarnet and cidofovir are associated with severe side effects, for example nephrotoxicity, neutropenia or thrombocytopenia. In addition, it is always possible for resistances to develop. Novel agents for an effective therapy are therefore desirable.

One object of the present invention is therefore to provide novel compounds having the same or improved antiviral activity for the treatment of viral infectious diseases in humans and animals.

It has surprisingly been found that the substituted heterocycles described in the present invention have high antiviral activity.

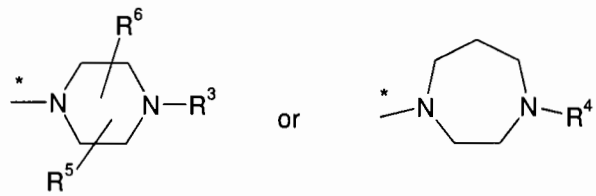
The present invention relates to compounds of formula



(I),

in which

R^1 represents a group of formula



whereby

* represents the linkage site to the carbonyl group,

R^3 represents phenyl or 5- or 6-membered heteroaryl,

wherein phenyl and heteroaryl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, oxo, nitro, cyano, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, trifluoromethylthio, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

R^4 represents phenyl or 5- or 6-membered heteroaryl,

wherein phenyl and heteroaryl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, oxo, nitro, cyano, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, trifluoromethylthio, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

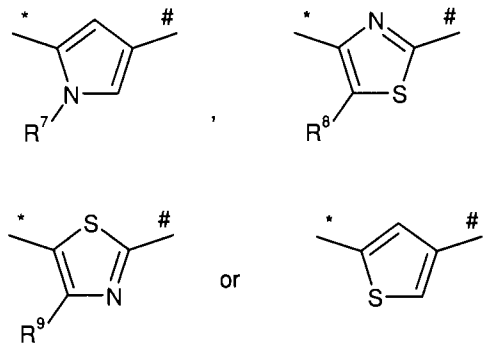
and

R^5 and R^6 independently of one another represent hydrogen, methyl or ethyl,

R^2 represents phenyl,

whereby phenyl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, trifluoromethylthio, C_1-C_6-alkyl and C_1-C_6-alkoxy,

A represents a group of formula



whereby

* represents the linkage site to the carbonyl group,

\# represents the linkage site to the nitrogen atom of the urea,

R^7 represents C_1-C_6-alkyl,

whereby alkyl may be substituted with a substituent, whereby the substituent is selected from the group consisting of C_3-C_6-cycloalkyl, C_6-C_{10}-aryl and 5- or 6-membered heteroaryl,

wherein cycloalkyl, aryl and heteroaryl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, oxo, nitro, cyano, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, trifluoromethylthio, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

and

R^8 and R^9 independently of one another represent hydrogen, halogen or C_1-C_6-alkyl,

whereby alkyl may be substituted with a substituent, whereby the substituent is selected from the group consisting of C_3-C_6-cycloalkyl, C_6-C_{10}-aryl and 5- or 6-membered heteroaryl,

wherein cycloalkyl, aryl and heteroaryl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, oxo, nitro, cyano, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, trifluoromethylthio, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

and their salts, their solvates and the solvates of their salts.

Compounds of the invention are the compounds of formula (I) and their salts, solvates and solvates of the salts; the compounds of the formulae mentioned below and encompassed by formula (I) and their salts, solvates and solvates of the salts as well as the compounds encompassed by formula (I) and mentioned below as exemplary embodiments and their salts, solvates and solvates of the salts, insofar as the compounds mentioned below, and encompassed by formula (I), are not already salts, solvates and solvates of the salts.

The compounds of the invention may, depending on their structure, exist in stereoisomeric forms (enantiomers, diastereomers). The invention therefore relates to the enantiomers or diastereomers and their respective mixtures. The stereoisomeri-

cally uniform constituents can be isolated in a known manner from such mixtures of enantiomers and/or diastereomers.

Where the compounds of the invention can exist in tautomeric forms, the present invention encompasses all tautomeric forms.

Salts preferred for the purpose of the present invention are physiologically acceptable salts of the compounds of the invention. Also included, however, are salts which themselves are not suitable for pharmaceutical applications but which can be used, for example, for the isolation or purification the compounds of the invention.

Physiologically acceptable salts of the compounds of the invention include acid addition salts of mineral acids, carboxylic acids and sulfonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically acceptable salts of the compounds of the invention also include salts of usual bases, such as, by way of example and preferably, alkali metal salts (for example sodium and potassium salts), alkaline earth metal salts (for example calcium and magnesium salts) and ammonium salts derived from ammonia or organic amines having 1 to 16 carbon atoms, such as, by way of example and preferably, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, arginine, lysine, ethylenediamine and N-methylpiperidine.

Solvates for the purpose of the present invention, refer to those forms of the compounds of the invention which in the solid or liquid state form a complex by

coordination with solvent molecules. Hydrates are a special form of solvates in which the coordination takes place with water.

Furthermore, the present invention also extends to prodrugs of the compounds of the invention. The term "prodrugs" encompasses compounds which themselves may be biologically active or inactive but which, during their residence time in the body, are converted into compounds of the invention (for example metabolically or hydrolytically).

For the purpose of the present invention, the substituents have the following meaning, unless specified otherwise:

Alkyl per se and "alk" and "alkyl" in alkoxy, alkylamino, alkoxycarbonyl and alkylaminocarbonyl represent a linear or branched alkyl radical generally having 1 to 6 ("C_1-C_6-alkyl"), preferably 1 to 4, particularly preferably 1 to 3, carbon atoms, by way of example and preferably methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

Alkoxy, by way of example and preferably, represents methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

Alkylamino represents an alkylamino radical having one or two alkyl substituents (selected independently of one another), by way of example and preferably methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexylamino, *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-n-propylamino, *N*-isopropyl-*N*-n-propylamino, *N*-t-butyl-*N*-methylamino, *N*-ethyl-*N*-n-pentylamino and *N*-n-hexyl-*N*-methylamino. C_1-C_3-Alkylamino represents, for example, a monoalkylamino radical having 1 to 3 carbon atoms or a dialkylamino radical having 1 to 3 carbon atoms per alkyl substituent.

Alkoxycarbonyl, by way of example and preferably, represents methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, n-pentoxycarbonyl and n-hexoxycarbonyl.

Alkylaminocarbonyl represents an alkylaminocarbonyl radical having one or two alkyl substituents (selected independently of one another), by way of example and preferably methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, n-hexylaminocarbonyl, *N,N*-dimethylaminocarbonyl, *N,N*-diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-methyl-*N*-n-propylaminocarbonyl, *N*-isopropyl-*N*-n-propylaminocarbonyl, *N*-tert-butyl-*N*-methylaminocarbonyl, *N*-ethyl-*N*-n-pentylaminocarbonyl and *N*-n-hexyl-*N*-methylaminocarbonyl. C_1-C_3-Alkylaminocarbonyl represents, for example, a monoalkylaminocarbonyl radical having 1 to 3 carbon atoms or a dialkylaminocarbonyl radical having 1 to 3 carbon atoms per alkyl substituent.

Aryl represents a mono- or bicyclic aromatic carbocyclic radical generally having 6 to 10 carbon atoms; by way of example and preferably phenyl and naphthyl.

For the purpose of the invention, 5- or 6-membered heteroaryl generally represents an aromatic monocyclic radical having 5 or 6 ring atoms and up to 4 heteroatoms from the series S, O and/or N. The heteroaryl radical may be attached via a carbon atom or a heteroatom. The following radicals may be mentioned by way of example and preferably: thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, pyrazolyl, imidazolyl, pyridyl, pyrimidyl and pyridazinyl.

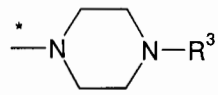
Cycloalkyl represents a cycloalkyl group generally having 3 to 6 carbon atoms, by way of example and preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Halogen represents fluorine, chlorine, bromine and iodine.

For the purpose of the present invention, preference is given to compounds of formula (I),

in which

R^1 represents a group of formula



whereby

* represents the linkage site to the carbonyl group,

R^3 represents phenyl or 5- or 6-membered heteroaryl,

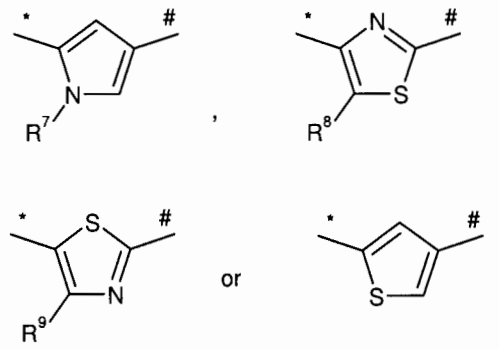
wherein phenyl and heteroaryl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, oxo, nitro, cyano, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, trifluoromethylthio, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

R^2 represents phenyl,

whereby phenyl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, trifluoromethyl, difluoromethyl, trifluorometh-

oxy, difluoromethoxy, monofluoromethoxy, trifluoromethylthio, C_1-C_6-alkyl and C_1-C_6-alkoxy,

A represents a group of formula



whereby

* represents the linkage site to the carbonyl group,

\# represents the linkage site to the nitrogen atom of the urea,

R^7 represents C_1-C_6-alkyl,

whereby alkyl may be substituted with a substituent, whereby the substituent is selected from the group consisting of C_3-C_6-cycloalkyl, C_6-C_{10}-aryl, and 5- or 6-membered heteroaryl,

wherein cycloalkyl, aryl and heteroaryl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, oxo, nitro, cyano, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, tri-

fluoromethylthio, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

and

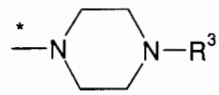
R^8 and R^9, independently of one another, represent hydrogen, halogen or C_1-C_6-alkyl,

and their salts, their solvates and the solvates of their salts.

For the purpose of the present invention, preference is also given to compounds of formula (I),

in which

R^1 represents a group of formula



whereby

* represents the linkage site to the carbonyl group,

R^3 represents phenyl or pyridyl,

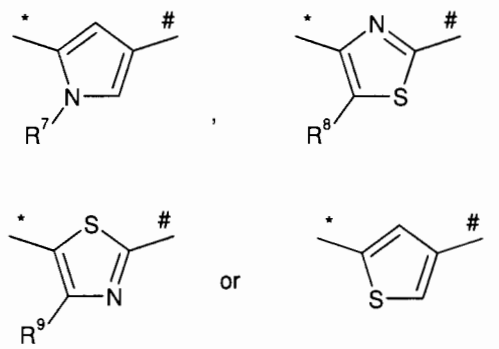
wherein phenyl and pyridyl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, nitro, cyano, trifluoro-

methyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, C_1-C_4-alkyl and C_1-C_4-alkoxy,

R^2 represents phenyl,

whereby phenyl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of fluorine, chlorine, trifluoromethoxy, difluoromethoxy, trifluoromethylthio and methyl,

A represents a group of formula



whereby

* represents the linkage site to the carbonyl group,

\# represents the linkage site to the nitrogen atom of the urea,

R^7 represents methyl, ethyl or n-butyl,

whereby methyl, ethyl and n-butyl may be substituted with a substituent, whereby the substituent is selected from the group consisting of cyclopropyl and phenyl,

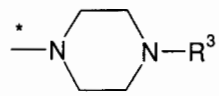
wherein phenyl may be substituted with a trifluoromethyl substituent,

and

R^8 and R^9, independently of one another, represent hydrogen, bromine, chlorine, methyl or ethyl,

and their salts, their solvates and the solvates of their salts.

For the purpose of the present invention, preference is also given to compounds of formula (I) in which R^1 represents a group of formula



whereby

* represents the linkage site to the carbonyl group, and

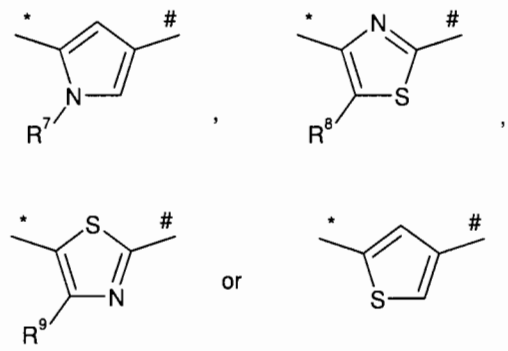
R^3 represents phenyl or pyridyl,

wherein phenyl and pyridyl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, nitro, cyano, trifluoro-

methyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, C_1-C_4-alkyl and C_1-C_4-alkoxy.

For the purpose of the present invention, preference is also given to compounds of formula (I) in which R^2 represents phenyl, whereby phenyl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of fluorine, chlorine, trifluoromethoxy, difluoromethoxy, trifluoromethylthio and methyl.

For the purpose of the present invention, preference is also given to compounds of formula (I), in which A represents a group of formula



whereby

* represents the linkage site to the carbonyl group,

\# represents the linkage site to the nitrogen atom of the urea,

R^7 represents methyl, ethyl or n-butyl,

whereby methyl, ethyl and n-butyl may be substituted with a substituent, whereby the substituent is selected from the group consisting of cyclopropyl and phenyl,

wherein phenyl may be substituted with a trifluoromethyl substituent,

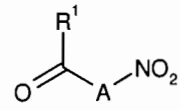
R^8 represents hydrogen, bromine, chlorine or methyl,

and

R^9 represents hydrogen.

The invention furthermore relates to a method for preparing the compounds of formula (I) whereby

according to method [A] compounds of formula



(II),

in which

R^1 has the meaning indicated above,

are reacted in the first step with a reducing agent and in the second step in the presence of a carbonic acid derivative with compounds of formula

$$H_2N—R^2 \quad (III),$$

in which

R^2 has the meaning indicated above,

or

according to method [B] compounds of formula (II) are reacted in the first step with a reducing agent and in the second step with compounds of formula

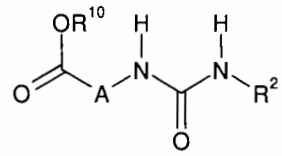
$$OCN\text{-}R^2 \qquad (IV),$$

in which

R^2 has the meaning indicated above,

or

according to method [C] compounds of formula



(V),

in which

R^2 has the meaning indicated above, and

R^{10} represents methyl or ethyl,

are reacted in the first step with a base and in the second step with compounds of formula

$$R^1\text{-}H \qquad (VI),$$

in which

R^1 has the meaning indicated above,

in the presence of dehydrating reagents.

The compounds of formulae (III), (IV) and (VI) are known or can be synthesized by known methods from the corresponding starting materials.

For methods [A] and [B], 1. stage, the following applies:

The reaction generally takes place in inert solvents, preferably in a temperature range from 0°C to the reflux of the solvents under atmospheric pressure to 3 bar.

Reducing agents are, for example, palladium-on-carbon and hydrogen, formic acid/triethylamine/palladium-on-carbon, zinc, zinc/hydrochloric acid, iron, iron/hydrochloric acid, iron(II) sulfate/hydrochloric acid, sodium sulfide, sodium disulfide, sodium dithionite, ammonium polysulfide, sodium borohydride/nickel chloride, tin dichloride, titanium trichloride or Raney nickel and an aqueous hydrazine solution; preference is given to Raney nickel and an aqueous hydrazine solution, palladium-on-carbon and hydrogen or formic acid/triethylamine/palladium-on-carbon.

Inert solvents are, for example, ethers, such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, alcohols, such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol, hydrocarbons, such as benzene, xylene, toluene, hexane,

cyclohexane or mineral oil fractions, or other solvents, such as dimethylformamide, dimethylacetamide, acetonitrile or pyridine, in the case of water-miscible solvents also mixtures of the same with water; preferred solvents are methanol, ethanol, isopropanol or, in the case of Raney nickel and an aqueous hydrazine solution, tetrahydrofuran.

For method [A], 2. stage, the following applies:

The reaction generally takes place in inert solvents, preferably in a temperature range of from room temperature to 40°C under atmospheric pressure.

Carbonic acid derivatives are, for example, N,N-carbonyldiimidazole, phosgene, diphosgene, triphosgene, phenyl chloroformate or 4-nitrophenyl chloroformate; preference is given to N,N-carbonyldiimidazole.

Inert solvents are, for example, halohydrocarbons, such as methylene chloride, trichloromethane, carbon tetrachloride, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, ethers, such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, hydrocarbons, such as benzene, xylene, toluene, hexane, cyclohexane or mineral oil fractions, or other solvents, such as ethyl acetate, acetone, dimethylformamide, dimethylacetamide, 2-butanone, dimethyl sulfoxide, acetonitrile or pyridine, in the case of water-miscible solvents also mixtures of the same with water; preference is given to dimethyl sulfoxide.

For method [B], 2. stage, the following applies:

The reaction generally takes place in inert solvents, optionally in the presence of a base, preferably in a temperature range of from room temperature to the reflux of the solvents under atmospheric pressure.

Inert solvents are, for example, halohydrocarbons, such as methylene chloride, trichloromethane, carbon tetrachloride, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, ethers, such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, hydrocarbons, such as benzene, xylene, toluene, hexane, cyclohexane or mineral oil fractions, or other solvents, such as ethyl acetate, acetone, dimethylformamide, dimethylacetamide, 2-butanone, dimethyl sulfoxide, acetonitrile or pyridine; preference is given to tetrahydrofuran or methylene chloride.

Bases are, for example, alkali metal carbonates, such as caesium carbonate, sodium carbonate or potassium carbonate, or potassium tert-butoxide, or other bases, such as sodium hydride, DBU, triethylamine or diisopropylethylamine, preferably triethylamine.

For method [C], 1. stage, the following applies:

The reaction generally takes place in inert solvents, preferably in a temperature range of from 0°C to the reflux of the solvents under atmospheric pressure.

Bases are, for example, alkali metal hydroxides, such as sodium hydroxide, lithium hydroxide or potassium hydroxide, or alkali metal carbonates, such as caesium carbonate, sodium carbonate or potassium carbonate, preferably sodium hydroxide.

Inert solvents are, for example, halohydrocarbons, such as methylene chloride, trichloromethane, carbon tetrachloride, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, ethers, such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, alcohols, such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol, hydrocarbons, such as benzene, xylene, toluene, hexane, cyclohexane or mineral oil fractions, or other solvents, such as

dimethylformamide, dimethylacetamide, dimethyl sulfoxide, acetonitrile or pyridine, or mixtures of solvents with water; the preferred solvent is a mixture of ethanol and water.

For method [C], 2. stage, the following applies:

The reaction generally takes place in inert solvents, optionally in the presence of a base, preferably in a temperature range of from -70°C to 40°C under atmospheric pressure.

Suitable dehydrating reagents hereby include, for example, carbodiimides, such as, for example, N,N'-diethyl-, N,N'-dipropyl-, N,N'-diisopropyl-, N,N'-dicyclohexyl-carbodiimide, N-(3-dimethylaminoisopropyl)-N'-ethylcarbodiimide hydrochloride (EDC), N-cyclohexylcarbodiimide-N'-propyloxymethyl-polystyrene (PS-carbodiimide) or carbonyl compounds, such as carbonyldiimidazole, or 1,2-oxazolium compounds, such as 2-ethyl-5-phenyl-1,2-oxazolium-3-sulfate or 2-tert-butyl-5-methylisoxazolium perchlorate, or acylamino compounds, such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, or propanephosphonic anhydride, or isobutyl chloroformate, or bis(2-oxo-3-oxazolidinyl)phosphoryl chloride or benzotriazolyloxytri(dimethyl-amino)phosphonium hexafluorophosphate, or O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), 2-(2-oxo-1-(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), or 1-hydroxybenzo-triazole (HOBt), or benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluo-rophosphate (BOP), or mixtures of these, with bases.

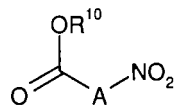
Bases are, for example, alkali metal carbonates, such as, for example, sodium carbon-ate or potassium carbonate, or sodium bicarbonate or potassium bicarbonate, or organic bases, such as trialkylamines, for example triethylamine, N-methyl-morpholine, N-methylpiperidine, 4-dimethylaminopyridine (DMAP) or diisopro-pylethylamine, or DBU, DBN, pyridine; preference is given to triethylamine.

The condensation is preferably carried out using TBTU and DMAP.

Inert solvents are, for example, halohydrocarbons, such as methylene chloride, trichloromethane, carbon tetrachloride, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, ethers, such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, hydrocarbons, such as benzene, xylene, toluene, hexane, cyclohexane or mineral oil fractions, or other solvents, such as ethyl acetate, acetone, dimethylformamide, dimethylacetamide, 2-butanone, dimethyl sulfoxide, acetonitrile or pyridine, in the case of water-miscible solvents also mixtures of the same with water; preference is given to dimethylformamide.

In an alternative method, the carboxylic acids obtained from the first stage of method [C], may in the second stage first be reacted with a chlorinating reagent such as, for example, thionyl chloride to form the carboxylic chloride and subsequently with compounds of formula (VI) in the presence of a base to form compounds of formula (I).

The compounds of formula (II) are known or can be prepared by reacting compounds of formula



(VII),

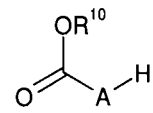
in which

R^{10} has the meaning indicated above,

in the first stage with a base and in the second stage with compounds of formula (VI), in the presence of dehydrating reagents.

The reaction takes place as described in method [C].

The compounds of formula (VII) are known or can be prepared by reacting compounds of formula



(VIII),

in which

R^{10} has the meaning indicated above,

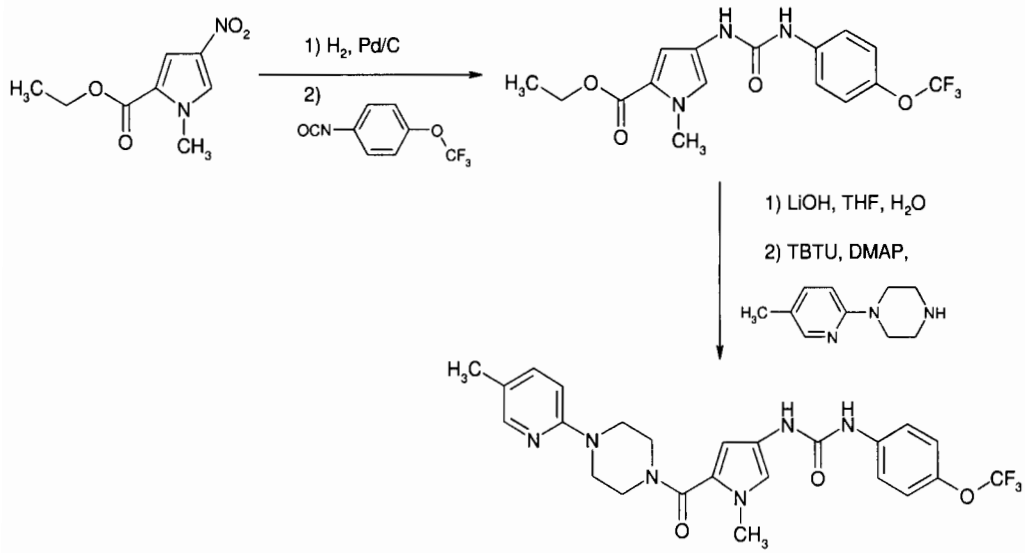
with fuming nitric acid, concentrated nitric acid, nitrating acid or other mixing ratios of sulfuric acid and nitric acid, optionally in acetic anhydride as solvent, preferably in a temperature range of from room temperature to 60°C under atmospheric pressure.

The compounds of formula (VIII) are known or can be prepared by known methods from the corresponding starting materials.

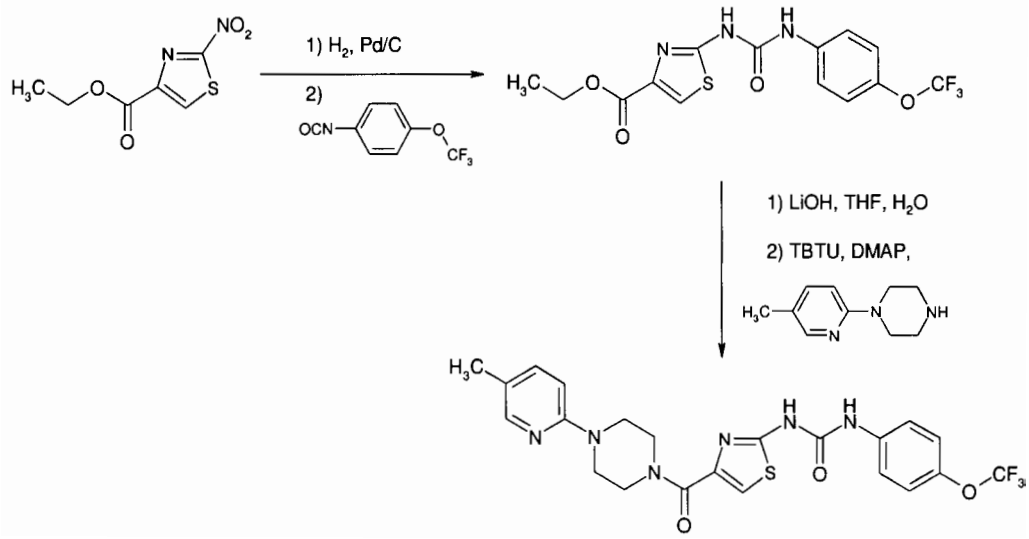
The compounds of formula (V) are known or can be prepared by reacting compounds of formula (VII) in the first stage with a reducing agent and in the second stage in the presence of a carbonic acid derivative with compounds of formula (III) or in the second stage with compounds of formula (IV).

The reaction takes place as described in methods [A] and [B].

Synthesis scheme 1:



Synthesis scheme 2:



The compounds of general formula (I) of the invention show an unforeseeable, surprising spectrum of activity. They have an antiviral activity on representatives of the group of the Herpes viridae (herpes viruses), especially on cytomegaloviruses (CMV), in particular on the human cytomegalovirus (HCMV). They are therefore suitable for the treatment and prophylaxis of diseases, especially infections with viruses, in particular the viruses mentioned above, and the infectivous diseases caused thereby. Hereinafter, a viral infection is to be understood as meaning both an infection with a virus and a disease caused by an infection with a virus.

Due to their particular properties, the compounds of general formula (I) can be used for the production of medicaments suitable for the prophylaxis and/or treatment of diseases, in particular viral infections.

Areas of indication which may be mentioned by way of example are:

1) Treatment and prophylaxis of HCMV infections in AIDS patients (retinitis, pneumonitis, gastrointestinal infections).

2) Treatment and prophylaxis of cytomegalovirus infections in bone-marrow and organ transplant patients who develop often life-threatening HCMV pneumonitis or encephalitis, as well as gastrointestinal and systemic HCMV infections.

3) Treatment and prophylaxis of HCMV infections in neonates and infants.

4) Treatment of an acute HCMV infection in pregnant women.

5) Treatment of an HCMV infection in immunosuppressed patients associated with cancer and cancer therapy.

6) Treatment of HCMV-positive cancer patients with the aim of reducing HCMV-mediated tumour progression (cf. J. Cinatl, et al., *FEMS Microbiology Reviews* **2004**, *28*, 59-77).

The compounds of the invention are preferably used for the production of medicaments suitable for the prophylaxis and/or treatment of infections with a representative of the group of the Herpes viridae, in particular a cytomegalovirus, especially the human cytomegalovirus.

Due to their pharmacological properties, the compounds of the invention can be used alone and, if required, also in combination with other active compounds, in particular antiviral active compounds, such as, for example, ganciclovir, valganciclovir or aciclovir, for the treatment and/or prevention of viral infections, in particular HCMV infections.

The present invention furthermore relates to the use of the compounds of the invention for the treatment and/or prophylaxis of diseases, preferably of viral infections, in particular of infections with the human cytomegalovirus (HCMV) or another representative of the group of the Herpes viridae.

The present invention furthermore relates to the use of the compounds of the invention for the treatment and/or prophylaxis of diseases, in particular the diseases mentioned above.

The present invention furthermore relates to the use of the compounds of the invention for the production of a medicament for the treatment and/or prophylaxis of diseases, in particular the diseases mentioned above.

The present invention furthermore relates to a method for the treatment and/or prophylaxis of diseases, in particular the diseases mentioned above, using an antivirally effective amount of the compounds of the invention.

The compounds of the invention can act systemically and/or locally. For this purpose, they can be administered in a suitable way, such as, for example, orally, parenterally, pulmonarily, nasally, sublingually, lingually, buccally, rectally, dermally, transdermally, conjunctivally or otically, or as an implant or stent.

For these administration routes, the compounds of the invention can be administered in suitable administration forms.

Suitable for oral administration are administration forms which function according to the prior art and release the compounds of the invention rapidly and/or in modified form, and which contain the compounds of the invention in crystalline and/or amorphicized and/or dissolved form, such as, for example, tablets (uncoated or coated tablets, for example having enteric coatings or coatings which dissolve with delay or which are insoluble and which control the release of the compound of the invention), tablets or films/wafers which disintegrate rapidly in the oral cavity, films/lyophilizates, capsules (for example hard or soft gelatin capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration can take place with avoidance of an absorption step (for example intravenously, intraarterially, intracardially, intraspinally or intralumbarly) or with inclusion of an absorption (for example intramuscularly, subcutaneously, intracutaneously, percutaneously or intraperitoneally). Administration forms suitable for parenteral administration are, inter alia, preparations for injection and infusion in the form of solutions, suspensions, emulsions, lyophilizates or sterile powders.

Examples suitable for the other administration routes are pharmaceutical forms for inhalation (inter alia powder inhalers, nebulizers), nasal drops/solutions/sprays; tablets, films/wafers or capsules to be administered lingually, sublingually or buccally, suppositories, preparations for the ears or eyes, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems, milk, pastes, foams, dusting powders, implants or stents.

The compounds of the invention can be converted into the stated administration forms. This can take place in a manner known per se by mixing with inert nontoxic, pharmaceutically acceptable excipients. These excipients include, inter alia, carriers (for example microcrystalline cellulose, lactose, mannitol), solvents (for example liquid polyethylene glycols), emulsifiers and dispersants or wetting agents (for example sodium dodecyl sulfate, polyoxysorbitan oleate), binders (for example polyvinylpyrrolidone), synthetic and natural polymers (for example albumin), stabilizers (for example antioxidants, such as, for example, ascorbic acid), colors (for example inorganic pigments, such as, for example, iron oxides) and taste- and/or odor- corrigents.

The present invention furthermore relates to medicaments comprising at least one compound of the invention, usually together with one or more inert nontoxic, pharmaceutically acceptable excipients, and their use for the purposes mentioned above.

In general, it has proved advantageous to administer on intravenous administration amounts of from about 0.001 to 10 mg/kg, preferably from about 0.01 to 5 mg/kg, of body weight to achieve effective results, and the dosage on oral administration is from about 0.01 to 25 mg/kg, preferably 0.1 to 10 mg/kg, of body weight.

It may nevertheless be necessary, where appropriate, to deviate from the stated amounts, specifically depending on body weight, administration route, the individual response to the active compound, the type of preparation and the time or interval over which the administration takes place. Thus, in some cases it may be sufficient to make do with less than the aforementioned minimum amount, whereas in other cases the upper limit mentioned must be exceeded. In the case of an administration of larger amounts, it may be advisable to divide these into a plurality of individual doses over the day.

The percentage data in the following tests and examples are percentages by weight unless otherwise indicated; parts are parts by weight. Solvent ratios, dilution ratios and concentration data of liquid/liquid solutions are in each case based on volume.

A. Examples

Abbreviations used:

aqu.	aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
CD_3CN	deuteroacetonitrile
conc.	concentrated
DCI	direct chemical ionization (in MS)
DCM	dichloromethane
DIEA	*N,N*-diisopropylethylamine (Hünig's base)
dil.	dilute
DMAP	4-*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EA	ethyl acetate
EDCI x HCl	N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride
EI	electron impact ionization (in MS)
ESI	electrospray ionization (in MS)
Ex.	example
h	hour
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HBTU	*O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HPLC	high pressure, high performance liquid chromatography
LC-MS	liquid chromatography-coupled mass spectroscopy
LDA	lithium diisopropylamide
lit.	literature (reference)
m.p.	melting point
MS	mass spectroscopy
NMR	nuclear magnetic resonance spectroscopy
RP-HPLC	reverse phase HPLC

RT	room temperature
R_t	retention time (in HPLC)
sat.	saturated
sol.	solution
TBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
THF	tetrahydrofuran
TLC	thin-layer chromatography

HPLC and LC-MS methods:

Method 1 (LC-MS): MS instrument type: Micromass ZQ; HPLC instrument type: Waters Alliance 2795; column: Phenomenex Synergi 2µ Hydro-RP Mercury 20 mm x 4 mm; eluent A: 1 l of water + 0.5 ml of 50% formic acid, eluent B: 1 l of acetonitrile + 0.5 ml of 50% formic acid; gradient: 0.0 min 90%A → 2.5 min 30%A → 3.0 min 5%A → 4.5 min 5%A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV detection: 210 nm.

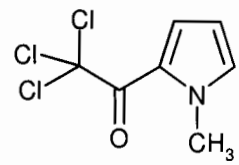
Method 2 (LC-MS): Instrument: Micromass Quattro LCZ with HPLC Agilent series 1100; column: Phenomenex Synergi 2µ Hydro-RP Mercury 20 mm x 4 mm; eluent A: 1 l of water + 0.5 ml of 50% formic acid, eluent B: 1 l of acetonitrile + 0.5 ml of 50% formic acid; gradient: 0.0 min 90%A → 2.5 min 30%A → 3.0 min 5%A → 4.5 min 5%A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2 ml/min; oven: 50°C; UV detection: 208-400 nm.

Method 3 (LC-MS): MS instrument type: Micromass ZQ; HPLC instrument type: HP 1100 series; UV DAD; column: Phenomenex Synergi 2µ Hydro-RP Mercury 20 mm x 4 mm; eluent A: 1 l of water + 0.5 ml of 50% formic acid, eluent B: 1 l of acetonitrile + 0.5 ml of 50% formic acid; gradient: 0.0 min 90%A → 2.5 min 30%A → 3.0 min 5%A → 4.5 min 5%A; flow rate: 0.0 min 1 ml/min, 2.5 min/3.0 min/4.5 min 2ml/min; oven: 50°C; UV detection: 210 nm.

Starting compounds

Example 1A

1-Methyl-2-trichloroacetyl-1H-pyrrole



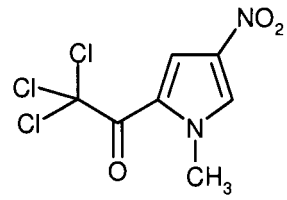
Under argon, 1.09 ml (12.3 mmol) of trichloroacetyl chloride are provided in 5 ml of DCM, and a solution of N-methylimidazole in 3 ml of DCM is added dropwise at RT over a period of 30 min. The reaction solution is stirred at RT overnight, then concentrated, and the residue is purified over a flash frit (cyclohexane, cyclohexane/ethyl acetate 40:1). The product is obtained as a liquid.

Yield: 2.12 g (76% of theory)

LC-MS (Method 1): R_t = 2.34 min.; MS (EI^+): m/z = 225 (M^+)

Example 2A

1-Methyl-4-nitro-2-trichloroacetyl-1H-pyrrole



2.12 g (9.34 mmol) of 1-methyl-2-trichloroacetyl-1H-pyrrole are dissolved in 9.5 ml of acetic anhydride, cooled to -20°C, and 0.43 ml (9.34 mmol) of nitric acid are added. The mixture is slowly warmed to RT and stirred at RT for 1 h. The reaction mixture is poured onto 95 g of ice and stirred vigorously for 2.5 h (initially oily deposit then crystallization). The precipitate is collected by suction filtration, triturated with 20 ml of methanol, filtered and dried in vacuo overnight. To remove the regioisomer, which is also formed, the mixture is triturated with 10 ml of acetic acid/water 1:1 for 2 h, and the solid is collected by suction filtration and dried in vacuo. A solid is obtained.

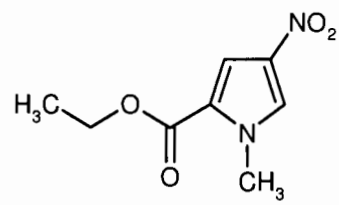
Yield: 1.71 g (67% of theory)

LC-MS (Method 2): R_t = 2.51 min.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.58 (d, 1H), 7.80 (d, 1H), 4.00 (s, 3H).

Example 3A

Ethyl 1-methyl-4-nitro-1H-pyrrole-2-carboxylate



0.50 g (1.84 mmol) of 1-methyl-4-nitro-2-trichloroacetyl-1H-pyrrole are provided in 5 ml of ethanol, 0.26 ml (1.84 mmol) of triethylamine are added and the mixture is stirred at RT for 2 h. 5 ml of water are added, the reaction mixture is stirred at 0°C for 30 min and the precipitate is subsequently collected by suction filtration and dried in vacuo.

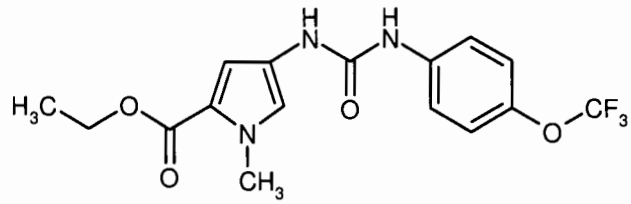
Yield: 321 mg (88% of theory)

LC-MS (Method 3): R_t = 2.25 min.; MS (ESI^+): m/z = 119 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.29 (d, 1H), 7.31 (d, 1H), 4.27 (q, 2H), 3.92 (s, 3H), 1.30 (t, 3H).

Example 4A

Ethyl 1-methyl-4-[({[4-(trifluoromethoxy)phenyl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylate



304 mg (1.53 mmol) of ethyl 1-methyl-4-nitro-1H-pyrrole-2-carboxylate are provided in 6 ml of ethyl acetate/ethanol (1:1), 163 mg (0.15 mmol) of palladium (10% on activated carbon) and 580 mg (9.20 mmol) of ammonium formate are added, and the mixture is stirred at 80°C for 1 h. After cooling, the mixture is filtered through kieselguhr, the filtercake is rinsed with ethanol and the filtrate is freed from the solvent in vacuo. The residue is dissolved in 6 ml of THF, 374 mg (1.84 mmol) of 4-trifluoromethoxyphenyl isocyanate are added and the mixture is stirred at RT for 1 h. The reaction solution is concentrated and the residue is purified by RP-HPLC (acetonitrile/water). A solid is obtained.

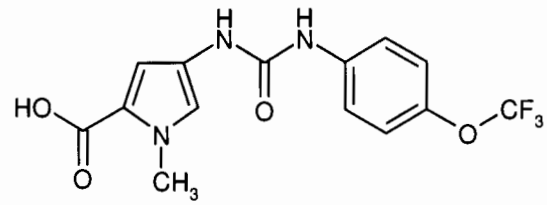
Yield: 486 mg (85% of theory)

LC-MS (Method 3): R_t = 2.61 min.; MS (ESI^+): m/z = 372 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.80 (s, 1H), 8.39 (s, 1H), 7.53 (m, 2H), 7.26 (d, 2H), 7.20 (d, 1H), 6.72 (d, 1H), 4.20 (q, 2H), 3.82 (s, 3H), 1.28 (t, 3H).

Example 5A

1-Methyl-4-[({[4-(trifluoromethoxy)phenyl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid



470 mg (1.27 mmol) of ethyl 1-methyl-4-[({[4-(trifluoromethoxy)phenyl]amino}-carbonyl)amino]-1H-pyrrole-2-carboxylate are provided in 5 ml of THF, 152 mg (6.33 mmol) of lithium hydroxide in 1 ml of water are added and the mixture is stirred under reflux overnight. The reaction mixture is concentrated, the residue is acidified with 2M hydrochloric acid and the precipitate formed is collected by suction filtration and dried in vacuo. A solid is obtained.

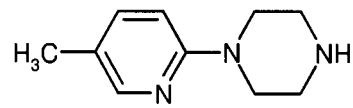
Yield: 429 mg (98% of theory)

LC-MS (Method 2): R_t = 2.09 min.; MS (ESI^+): m/z = 344 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.16 (bs, 1H), 9.01 (s, 1H), 8.58 (s, 1H), 7.53 (m, 2H), 7.25 (d, 2H), 7.18 (d, 1H), 6.63 (d, 1H), 3.80 (s, 3H).

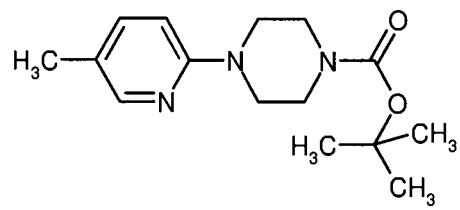
Example 6A

1-(5-Methylpyridin-2-yl)piperazine



Stage 1

1-(tert-Butyloxycarbonyl)-4-(5-methylpyridin-2-yl)piperazine



Under an argon atmosphere, 2.50 g (19.6 mmol) of 2-methyl-5-chloropyridine and 4.38 g (23.5 mmol) of N-(tert-butyloxycarbonyl)piperazine are dissolved in 50 ml of absolute toluene. 2.26 g (23.5 mmol) of sodium tert-butoxide, 0.37 g (0.59 mmol) of BINAP and 0.36 g (0.39 mmol) of tris(dibenzylideneacetone)dipalladium are subsequently added, and the mixture is heated at 70°C for 12 h. After cooling, diethyl ether is added to the reaction mixture, the mixture is washed three times with a saturated sodium chloride solution, dried over sodium sulfate and freed from the solvent in vacuo. The residue was purified by flash chromatography (cyclohexane/ethyl acetate 9:1).

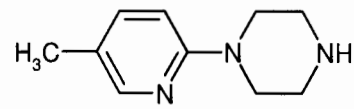
Yield: 5.27 g (97% of theory).

LC-MS (Method 1): R_t = 1.26 min.; MS (ESI^+): m/z = 278 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, 1H), 7.34 (dd, 1H), 6.59 (d, 1H), 3.55 (m, 4H), 3.45 (m, 4H), 2.21 (s, 3H), 1.49 (s, 9H).

Stage 2

1-(5-Methylpyridin-2-yl)piperazine



3.47 g (12.5 mmol) of 1-(tert-butyloxycarbonyl)-4-(5-methylpyridin-2-yl)piperazine are dissolved in 10 ml of dioxane, and 31 ml (125 mmol) of hydrogen chloride in dioxane (4 molar) are added. The mixture is stirred at RT for 2 h. The mixture is subsequently concentrated, the residue is rendered alkaline using a 1M aqueous sodium hydroxide solution and extracted several times with dichloromethane. The combined organic phases are dried over sodium sulfate, concentrated and dried in vacuo.

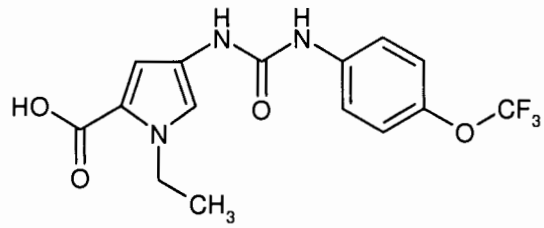
Yield: 2.18 g (98% of theory).

LC-MS (Method 3): R_t = 0.38 min.; MS (ESI^+): m/z = 177 $(M+H)^+$

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, 1H), 7.32 (dd, 1H), 6.59 (d, 1H), 3.45 (m, 4H), 3.00 (m, 4H), 2.20 (s, 3H).

Example 7A

1-Ethyl-4-[({[4-(trifluoromethoxy)phenyl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid

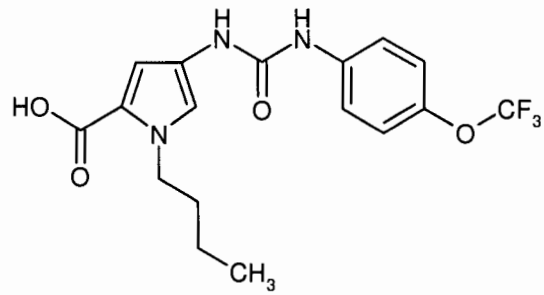


The preparation takes place in analogy to Example 5A.

LC-MS (Method 2): R_t = 2.10 min.; MS (ESI^+): m/z = 358 $(M+H)^+$

Example 8A

1-Butyl-4-[({[4-(trifluoromethoxy)phenyl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid



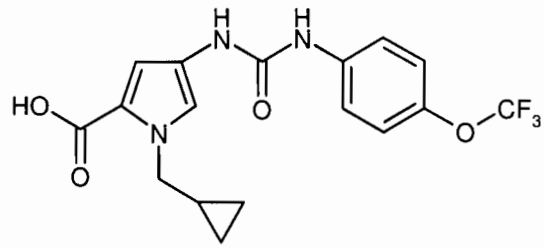
The preparation takes place in analogy to Example 5A.

LC-MS (Method 3): R_t = 2.47 min.; MS (ESI^+): m/z = 386 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.90 (bs, 1H), 8.48 (bs, 1H), 7.54 (d, 2H), 7.26 (d, 2H), 7.24 (d, 1H), 6.73 (d, 1H), 4.21 (t, 2H), 1.62 (quint., 2H), 1.25 (sext., 2H), 0.88 (t, 3H).

Example 9A

1-(Cyclopropylmethyl)-4-[({[4-(trifluoromethoxy)phenyl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid



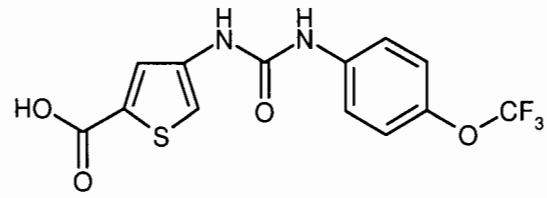
The preparation takes place in analogy to Example 5A.

LC-MS (Method 2): R_t = 2.33 min.; MS (ESI$^+$): m/z = 384 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.86 (bs, 1H), 8.45 (bs, 1H), 7.55 (m, 2H), 7.23-7.32 (m, 3H), 6.68 (d, 1H), 4.11 (d, 2H), 1.21 (m, 1H), 0.45 (m, 2H), 0.32 (m, 2H).

Example 10A

4-[({[4-(Trifluoromethoxy)phenyl]amino}carbonyl)amino]thiophene-2-carboxylic acid



The preparation takes place in analogy to Example 4A and 5A starting with methyl 4-aminothiophene-2-carboxylate (synthesized according to A.A. Kiryano et al., *Tetrahedron Lett.* **2001**, (42), 8797-8800).

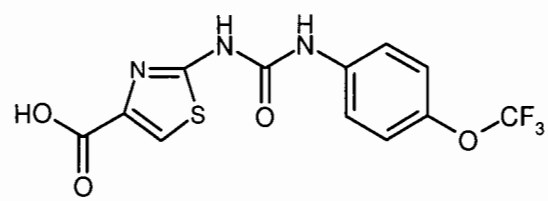
Yield: 72 mg (27% of theory, 2 stages)

LC-MS (Method 2): R_t = 2.25 min.; MS (ESI^+): m/z = 347 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 13.1 (bs, 1H), 9.10 (bs, 1H), 8.98 (bs, 1H), 7.69 (s, 1H), 7.53-7.60 (m, 3H), 7.29 (d, 2H).

Example 11A

2-[({[4-(Trifluoromethoxy)phenyl]amino}carbonyl)amino]-1,3-thiazole-4-carboxylic acid



The preparation takes place in analogy to Example 4A and 5A starting with ethyl 2-amino-1,3-thiazole-4-carboxylate (commercially available from ACROS).

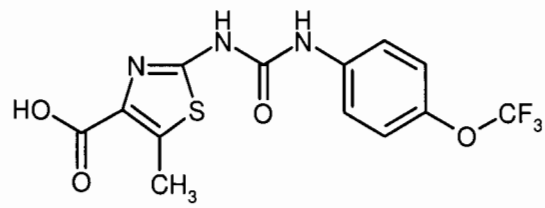
Yield: 290 mg (61% of theory, 2 stages)

LC-MS (Method 2): R_t = 2.05 min.; MS (ESI^+): m/z = 348 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.8 (bs, 1H), 10.9 (bs, 1H), 9.22 (bs, 1H), 7.91 (s, 1H), 7.60 (d, 2H), 7.32 (d, 2H).

Example 12A

5-Methyl-2-[({[4-(trifluoromethoxy)phenyl]amino}carbonyl)amino]-1,3-thiazole-4-carboxylic acid



The preparation takes place in analogy to Example 4A and 5A starting with methyl 2-amino-5-methyl-1,3-thiazole-4-carboxylate (commercially available from Tyger Scientific).

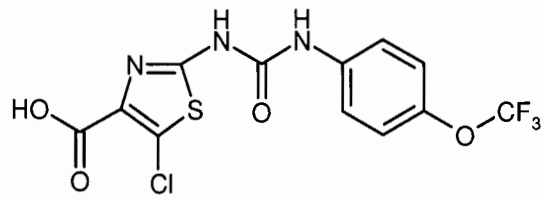
Yield: 148 mg (40% of theory, 2 stages)

LC-MS (Method 3): R_t = 2.47 min.; MS (ESI^+): m/z = 362 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.7 (bs, 1H), 10.7 (bs, 1H), 9.18 (bs, 1H), 7.59 (d, 2H), 7.32 (d, 2H), 3.34 (s, 3H).

Example 13A

5-Chloro-2-[({[4-(trifluoromethoxy)phenyl]amino}carbonyl)amino]-1,3-thiazole-4-carboxylic acid



The preparation takes place in analogy to Example 4A and 5A starting with ethyl 2-amino-5-chloro-1,3-thiazole-4-carboxylate (synthesis described in K.J. Hodgetts et al., *Org. Lett.* **2002**, (4), 1363-1366).

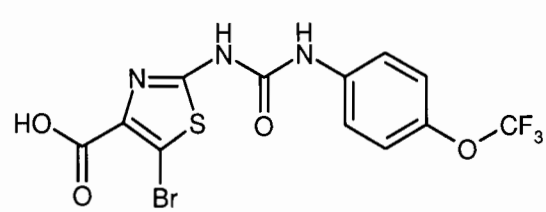
Yield: 365 mg (89% of theory, 2 stages)

LC-MS (Method 3): R_t = 2.51 min.; MS (ESI^+): m/z = 382 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 13.2 (bs, 1H), 11.2 (bs, 1H), 9.28 (bs, 1H), 7.58 (m, 2H), 7.33 (m, 2H).

Example 14A

5-Bromo-2-[({[4-(trifluoromethoxy)phenyl]amino}carbonyl)amino]-1,3-thiazole-4-carboxylic acid



The preparation takes place in analogy to Example 4A and 5A starting with ethyl 2-amino-5-bromo-1,3-thiazole-4-carboxylate (synthesis described in J.F. Okonya et al., *Tetrahedron Lett.*, **2002**, (43), 7051-7054).

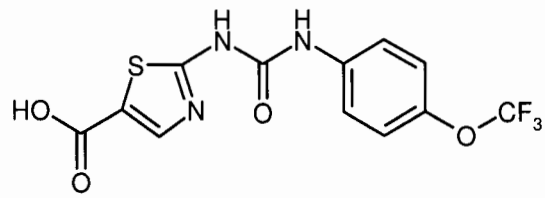
Yield: 343 mg (74% of theory, 2 stages)

LC-MS (Method 2): R_t = 2.22 min.; MS (ESI^+): m/z = 426 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 13.1 (bs, 1H), 11.2 (bs, 1H), 9.28 (bs, 1H), 7.58 (m, 2H), 7.32 (m, 2H).

Example 15A

2-[({[4-(Trifluoromethoxy)phenyl]amino}carbonyl)amino]-1,3-thiazole-5-carboxylic acid



The preparation takes place in analogy to Example 4A and 5A starting with ethyl 2-amino-1,3-thiazole-5-carboxylate (commercially available from RareChem).

Yield: 200 mg (55% of theory, 2 stages)

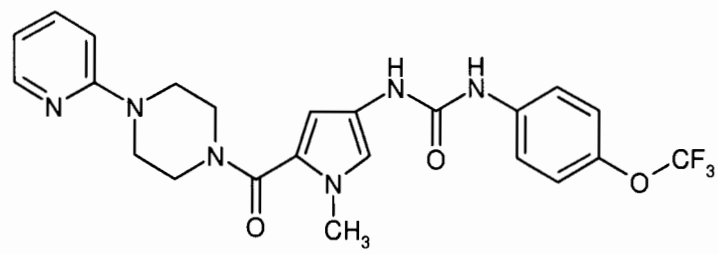
LC-MS (Method 3): R_t = 2.36 min.; MS (ESI^+): m/z = 348 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.8 (bs, 1H), 10.9 (bs, 1H), 9.21 (bs, 1H), 7.92 (s, 1H), 7.60 (d, 2H), 7.33 (d, 2H).

Exemplary emboidments

Example 1

N-{1-Methyl-5-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]-1H-pyrrol-3-yl}-N'-[4-(trifluoromethoxy)phenyl]urea



50 mg (0.15 mmol) of 1-methyl-4-[({[4-(trifluoromethoxy)phenyl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid (Example 5A) are provided in 1 ml of DMF, and 56 mg (0.18 mmol) of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) and 8.9 mg (0.07 mmol) of 4-(dimethylamino)pyridine (DMAP) are added. 29 mg (0.18 mmol) of 1-(2-pyridyl)piperazine are subsequently added, and the mixture is stirred at RT for 8 h. The reaction solution is purified by RP-HPLC (acetonitrile/water). A solid is obtained.

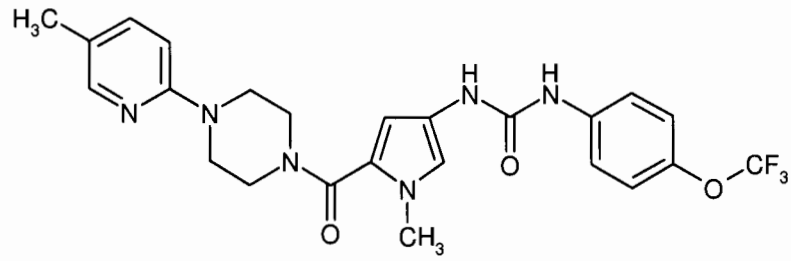
Yield: 54 mg (76% of theory)

LC-MS (Method 1): R_t = 1.61 min.; MS (ESI^+): m/z = 489 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.75 (s, 1H), 8.32 (s, 1H), 8.13 (dd, 1H), 7.50-7.59 (m, 3H), 7.25 (d, 2H), 7.02 (d, 1H), 6.86 (d, 1H), 6.68 (dd, 1H), 6.28 (d, 1H), 3.72 (m, 4H), 3.64 (s, 3H), 3.55 (m, 4H).

Example 2

N-(1-Methyl-5-{[4-(5-methylpyridin-2-yl)piperazin-1-yl]carbonyl}-1H-pyrrol-3-yl)-N'-[4-(trifluoromethoxy)phenyl]urea



The preparation takes place in analogy to Example 1 from Example 5A and 6A.

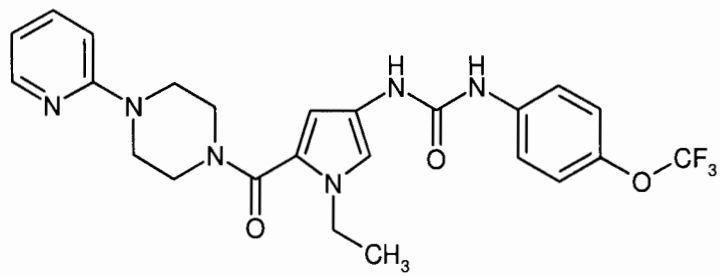
Yield: 50 mg (68% of theory)

LC-MS (Method 1): R_t = 1.66 min.; MS (ESI^+): m/z = 503 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.75 (bs, 1H), 8.32 (bs, 1H), 7.98 (d, 1H), 7.53 (m, 2H), 7.42 (dd, 1H), 7.25 (d, 2H), 7.02 (d, 1H), 6.80 (d, 1H), 6.28 (d, 1H), 3.68-3.76 (m, 4H), 3.63 (s, 3H), 3.45-3.53 (m, 4H), 2.17 (s, 3H).

Example 3

N-{1-Ethyl-5-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]-1H-pyrrol-3-yl}-N'-[4-(trifluoromethoxy)phenyl]urea



The preparation takes place in analogy to Example 1 from Example 7A and 6A.

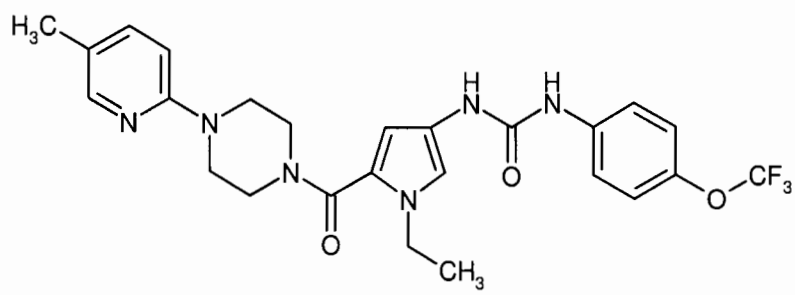
Yield: 29 mg (43% of theory)

LC-MS (Method 2): R_t = 1.79 min.; MS (ESI^+): m/z = 503 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.74 (bs, 1H), 8.32 (bs, 1H), 8.13 (d, 1H), 7.49-7.60 (m, 3H), 7.22-7.28 (m, 2H), 7.08 (s, 1H), 6.87 (d, 1H), 6.68 (dd, 1H), 6.26 (s, 1H), 4.04 (q, 2H), 3.68-3.77 (m, 4H), 3.50-3.58 (m, 4H), 1.26 (t, 3H).

Example 4

N-(1-Ethyl-5-{[4-(5-methylpyridin-2-yl)piperazin-1-yl]carbonyl}-1H-pyrrol-3-yl)-N′-[4-(trifluoromethoxy)phenyl]urea



The preparation takes place in analogy to Example 1 from Example 7A and 6A.

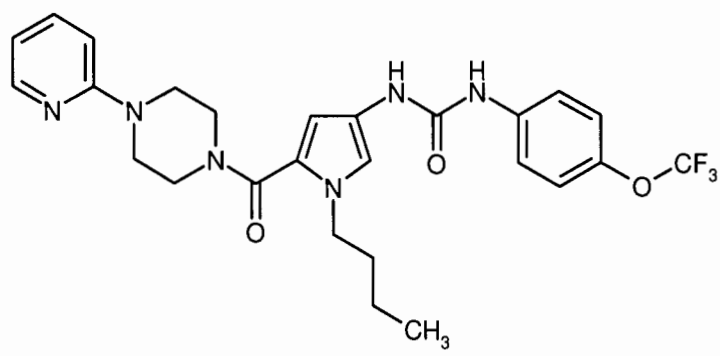
Yield: 26 mg (39% of theory)

LC-MS (Method 2): R_t = 1.80 min.; MS (ESI^+): m/z = 517 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.75 (bs, 1H), 8.32 (bs, 1H), 7.98 (m, 1H), 7.54 (m, 2H), 7.42 (m, 1H), 7.26 (m, 2H), 7.08 (m, 1H), 6.80 (d, 1H), 6.25 (s, 1H), 4.03 (q, 2H), 3.68-3.76 (m, 4H), 3.44-3.52 (m, 4H), 2.18 (s, 3H), 1.25 (t, 3H).

Example 5

N-{1-Butyl-5-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]-1H-pyrrol-3-yl}-N'-[4-(trifluoro-methoxy)phenyl]urea



The preparation takes place in analogy to Example 1 from Example 8A.

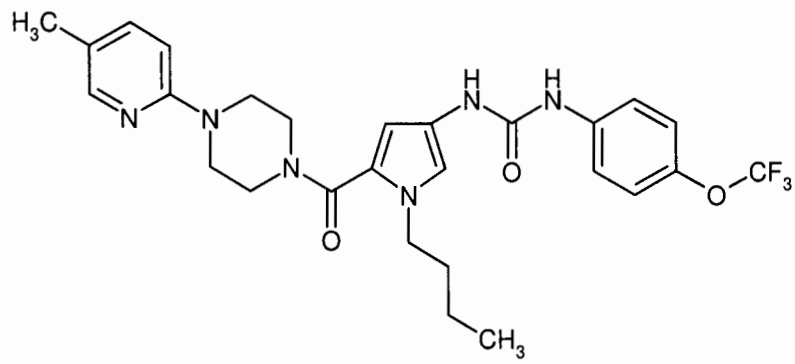
Yield: 41 mg (69% of theory)

LC-MS (Method 2): R_t = 2.11 min.; MS (ESI^+): m/z = 531 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.75 (bs, 1H), 8.33 (bs, 1H), 8.12 (d, 1H), 7.58 (m, 1H), 7.54 (d, 2H), 7.26 (d, 2H), 7.07 (d, 1H), 6.87 (d, 1H), 6.68 (dd, 1H), 6.26 (d, 1H), 4.02 (t, 2H), 3.72 (m, 4H), 3.53 (m, 4H), 1.59 (quint., 2H), 1.18 (sext., 2H), 0.84 (t, 3H).

Example 6

N-(1-Butyl-5-{[4-(5-methylpyridin-2-yl)piperazin-1-yl]carbonyl}-1H-pyrrol-3-yl)-N'-[4-(trifluoromethoxy)phenyl]urea



The preparation takes place in analogy to Example 1 from Example 8A and 6A.

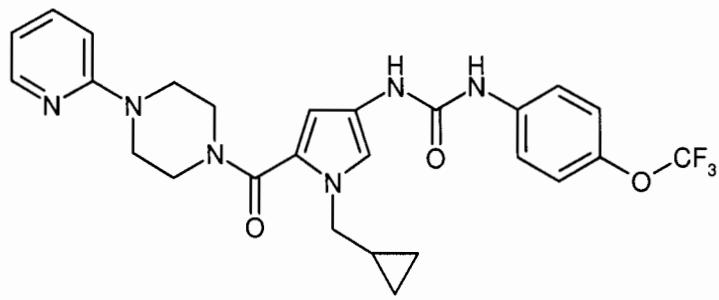
Yield: 19 mg (20% of theory)

LC-MS (Method 2): R_t = 1.97 min.; MS (ESI^+): m/z = 545 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.74 (bs, 1H), 8.32 (bs, 1H), 7.98 (d, 1H), 7.53 (d, 2H), 7.41 (dd, 1H), 7.25 (d, 2H), 7.07 (d, 1H), 6.80 (d, 1H), 6.25 (d, 1H), 4.02 (t, 2H), 3.72 (m, 4H), 3.47 (m, 4H), 2.16 (s, 3H), 1.59 (quint., 2H), 1.18 (sext., 2H), 0.83 (t, 3H).

Example 7

N-{1-(Cyclopropylmethyl)-5-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]-1H-pyrrol-3-yl}-N'-[4-(trifluoromethoxy)phenyl]urea



The preparation takes place in analogy to Example 1 from Example 9A.

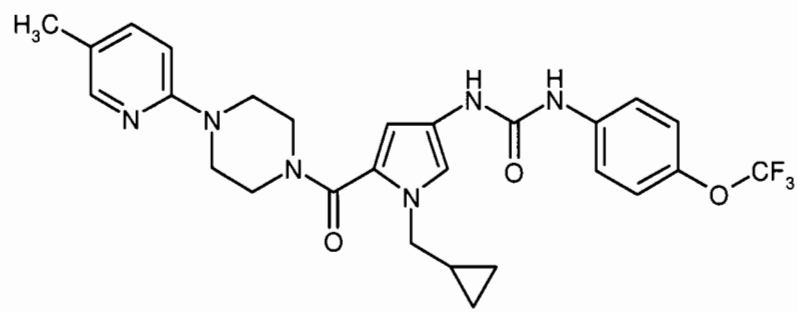
Yield: 51 mg (86% of theory)

LC-MS (Method 1): R_t = 1.84 min.; MS (ESI^+): m/z = 529 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.75 (bs, 1H), 8.33 (bs, 1H), 8.13 (dt, 1H), 7.51-7.61 (m, 3H), 7.27 (d, 2H), 7.13 (d, 1H), 6.88 (d, 1H), 6.69 (dd, 1H), 6.28 (d, 1H), 3.90 (d, 2H), 3.73 (m, 4H), 3.53 (m, 4H), 1.12 (m, 1H), 0.45 (m, 2H), 0.28 (m, 2H).

Example 8

N-(1-(Cyclopropylmethyl)-5-{[4-(5-methylpyridin-2-yl)piperazin-1-yl]carbonyl}-1H-pyrrol-3-yl)-N′-[4-(trifluoromethoxy)phenyl]urea



The preparation takes place in analogy to Example 1 from Example 9A and 6A.

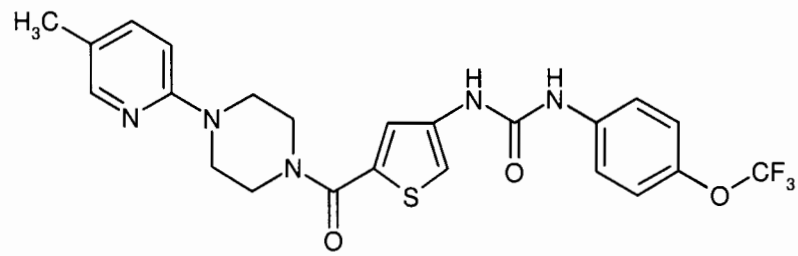
Yield: 52 mg (85% of theory)

LC-MS (Method 1): R_t = 1.86 min.; MS (ESI^+): m/z = 543 $(M+H)^+$

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.77 (bs, 1H), 8.34 (bs, 1H), 7.98 (d, 1H), 7.54 (d, 2H), 7.41 (dd, 1H), 7.25 (d, 2H), 7.12 (d, 1H), 6.80 (d, 1H), 6.27 (d, 1H), 3.89 (d, 2H), 3.72 (m, 4H), 3.48 (m, 4H), 2.16 (s, 3H), 1.12 (m, 1H), 0.45 (m, 2H), 0.28 (m, 2H).

Example 9

N-(5-{[4-(5-Methylpyridin-2-yl)piperazin-1-yl]carbonyl}-3-thienyl)-N′-[4-(trifluoro-methoxy)phenyl]urea



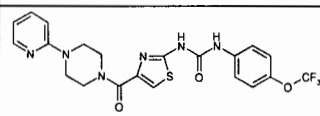
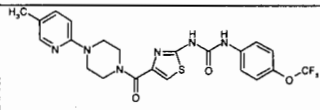
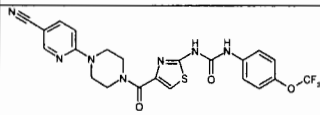
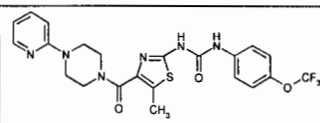
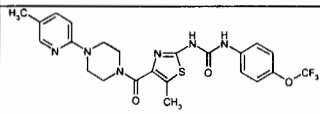
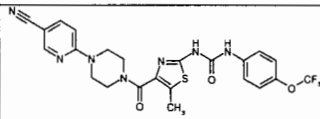
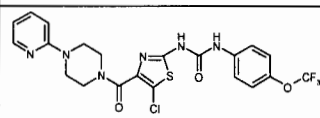
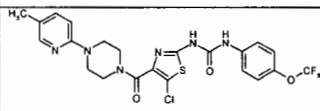
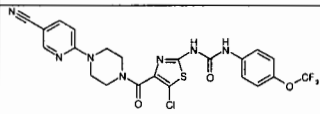
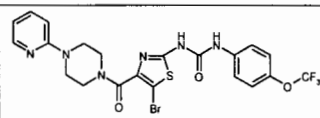
The preparation takes place in analogy to Example 1 from Example 10A and 6A.

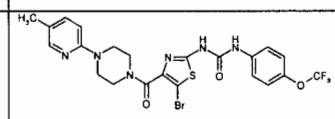
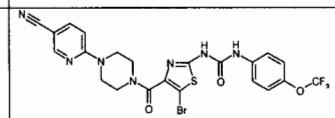
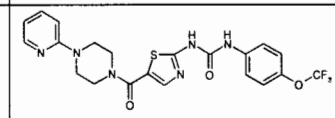
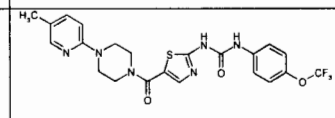
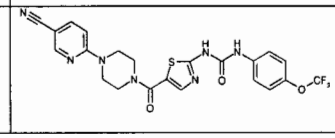
Yield: 60 mg (63% of theory)

LC-MS (Method 3): R_t = 2.05 min.; MS (ESI^+): m/z = 506 $(M+H)^+$

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.05 (bs, 1H), 8.95 (bs, 1H), 7.98 (d, 1H), 7.56 (d, 2H), 7.47 (s, 1H), 7.39-7.44 (m, 2H), 7.29 (d, 2H), 6.80 (d, 1H), 3.75 (m, 4H), 3.51 (m, 4H), 2.16 (s, 3H).

The following compounds are synthesized in analogy to Example 1 from the corresponding starting compounds:

Ex. No.	Structure	Starting compound	Yield	LC-MS R_t [min]	MS $(M+H)^+$
10		Example 11A	36 mg (51% of theory)	1.95 (Method 3)	493
11		Example 11 A	49 mg (67% of theory)	2.02 (Method 3)	507
12		Example 11A	43 mg (58% of theory)	2.52 (Method 3)	518
13		Example 12A	33 mg (48% of theory)	2.00 (Method 3)	507
14		Example 12A	50 mg (70% of theory)	2.01 (Method 3)	521
15		Example 12A	52 mg (71% of theory)	2.60 (Method 3)	532
16		Example 13A	43 mg (58% of theory)	2.21 (Method 3)	527
17		Example 13A	35 mg (49% of theory)	2.24 (Method 3)	541
18		Example 13A	42 mg (52% of theory)	2.76 (Method 3)	552
19		Example 14A	45 mg (59% of theory)	2.22 (Method 3)	571

Ex. No.	Structure	Starting compound	Yield	LC-MS R_t [min]	MS $(M+H)^+$
20		Example 14A	50 mg (68% of theory)	2.27 (Method 3)	585
21		Example 14A	41 mg (50% of theory)	2.77 (Method 3)	596
22		Example 15A	34 mg (49% of theory)	1.90 (Method 3)	493
23		Example 15A	47 mg (65% of theory)	1.93 (Method 3)	507
24		Example 15A	47 mg (64% of theory)	2.53 (Method 3)	518

B. Assessment of the physiological activity

The in vitro activity of the compounds of the invention can be shown in the following assays:

Anti-HCMV (anti-human cytomegalovirus) cytopathogenicity tests

The test compounds are employed as 50 millimolar (mM) solutions in dimethyl sulfoxide (DMSO). Ganciclovir, foscarnet and cidofovir are used as reference compounds. After the addition of in each case 2 µl of the 50, 5, 0.5 and 0.05 mM DMSO stock solutions to 98 µl portions of cell culture medium in row 2 A-H for duplicate determinations, 1:2 dilutions are carried out with 50 µl portions of medium up to row 11 of the 96-well plate. The wells in rows 1 and 12 each contain 50 µl of medium. Then 150 µl portions of a suspension of 1×10^4 cells (human prepuce fibroblasts [NHDF]) are pipetted into each of the wells (row 1 = cell control) and, in rows 2-12, a mixture of HCMV-infected and uninfected NHDF cells (M.O.I. = 0.001 – 0.002), i.e. 1-2 infected cells per 1000 uninfected cells. Row 12 (without substance) serves as virus control. The final test concentrations are 250-0.0005 µM. The plates are incubated at 37°C/5% CO_2 for 6 days, i.e. until all the cells in the virus controls are infected (100% cytopathogenic effect [CPE]). The wells are then fixed and stained by adding a mixture of formalin and Giemsa's dye (30 minutes), washed with double-distilled water and dried in a drying oven at 50°C. The plates are then assessed visually using an overhead microscope (Plaque Multiplier from Technomara).

The following data can be acquired from the test plates:

CC_{50} (NHDF) = maximum substance concentration in µM at which no visible cytostatic effects on the cells are evident compared with the untreated cell control;

EC_{50} (HCMV) = substance concentration in µM which inhibits the CPE (cytopathic effect) by 50% compared with the untreated virus control;

SI (selectivity index) = CC_{50} (NHDF) / EC_{50} (HCMV).

Representative in vitro activity data of the compounds of the invention are shown in Table A:

Table A

Example No.	NHDF CC_{50} [µM]	HCMV EC_{50} [µM]	SI HCMV
4	21	0.0007	28767
9	21	0.0059	3559
14	11	0.0016	7333
23	11	0.0054	2637

The suitability of the compounds of the invention for the treatment of HCMV infections can be shown in the following animal model:

HCMV Xenograft Gelfoam® model

Animals:

3-4-week old female immunodeficient mice (16-18 g), Fox Chase SCID or Fox Chase SCID-NOD or SCID beige, are purchased from commercial breeders (Bomholtgaard, Jackson). The animals are kept under sterile conditions (including bedding and feed) in isolators.

Virus growing:

Human cytomegalovirus (HCMV), Davis strain, is grown in vitro on human embryonic prepuce fibroblasts (NHDF cells). After the NHDF cells have been infected with a multiplicity of infection (M.O.I.) of 0.01, the virus-infected cells are harvested 5-7 days later and stored in the presence of minimal essential medium (MEM), 10% foetal calf serum (FCS) with 10% DMSO at -40°C. After serial ten-fold dilutions of the virus-infected cells, the titre is determined on 24-well plates of confluent NHDF cells after vital staining with Neutral Red, or fixing and staining with a formalin/Giemsa mixture (as described above).

Preparation of the sponges, transplantation, treatment and evaluation:

Collagen sponges 1×1×1 cm in size (Gelfoam®; Peasel & Lorey, order No. 407534; K.T. Chong et al., Abstracts of 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1999, p. 439; P.M. Kraemer et al., Cancer Research 1983, (43): 4822-4827) are initially wetted with phosphate-buffered saline (PBS), the trapped air bubbles are removed by degassing, and then stored in MEM + 10% FCS. 1×10^6 virus-infected NHDF cells (infection with HCMV Davis M.O.I. = 0.01) are detached 3 hours after infection and added dropwise in 20 µl of MEM, 10% of FCS to a moist sponge. 12-13 hours later, optionally, 5 ng/µl of basic fibroblast growth factor (bFGF) in 25 µl of PBS /0.1% BSA/1 mM DTT are added onto the infected sponges and the sponges are incubated for 1 h. For the transplantation, the immunodeficient mice are anaesthetized with avertin or a mixture of azepromazine/xylazine and ketamine, the fur on the back is removed using a dry shaver, the epidermis is opened 1-2 cm, unstressed and the moist sponges are transplanted under the dorsal skin. The surgical wound is closed with tissue glue. 24 hours after the transplantation, the mice are treated with substance perorally three times a day (7.00 h and 14.00 h and 19.00 h), two times a day (8.00 h and 17.00 h) or once a day (14.00 h) over a period of 8 days. The dose is 3 or 10 or 30 or 100 mg/kg of body weight, the volume administered is 10 ml/kg of body weight. The formulation of the substances takes place in the form

of a 0.5% Tylose suspension, optionally with 2% DMSO. 9 days after transplantation and 16 hours after the last administration of substance, the animals are painlessly sacrificed and the sponge is removed. The virus-infected cells are released from the sponge by collagenase digestion (330 U/1.5 ml) and stored in the presence of MEM, 10% foetal calf serum, 10% DMSO at -140°C. Evaluation takes place after serial ten-fold dilutions of the virus-infected cells by determining the titre on 24-well plates of confluent NHDF cells after vital staining with Neutral Red or after fixing and staining with a formalin/Giemsa mixture (as described above). The number of infectious virus particles after the substance treatment compared with the placebo-treated control group is determined.

C. Exemplary embodiments of pharmaceutical compositions

The compounds of the invention can be converted into pharmaceutical preparations in the following ways:

Tablet:

Composition:

100 mg of the compound of Example 1, 50 mg of lactose (monohydrate), 50 mg of corn starch (native), 10 mg of polyvinylpyrrolidone (PVP 25) (BASF, Ludwigshafen, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg. Diameter 8 mm, radius of curvature 12 mm.

Production:

The mixture of active compound, lactose and starch is granulated with a 5% solution (m/m) of the PVP in water. After drying the granules are mixed with the magnesium stearate for 5 min. This mixture is compressed using a conventional tablet press (see above for the format of the tablet). A guideline for the compressive force used for the compression is 15 kN.

Suspension which can be administered orally:

Composition:

1000 mg of the compound of Example 1, 1000 mg of ethanol (96%), 400 mg of Rhodigel (xanthan gum from FMC, Pennsylvania, USA) and 99 g of water.

10 ml of oral suspension correspond to a single dose of 100 mg of the compound of the invention.

Production:

The Rhodigel is suspended in ethanol, and the active compound is added to the suspension. The water is added while stirring. The mixture is stirred for about 6 h until the swelling of the Rhodigel is complete.

Solution which can be administered intravenously:

Composition:

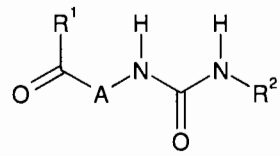
1 mg of the compound of Example 1, 15 g of polyethylene glycol 400 and 250 g of water for injection.

Production:

The compound of the invention is dissolved together with polyethylene glycol 400 in the water with stirring. The solution is sterilized by filtration (pore diameter 0.22 µm) and dispensed under aseptic conditions into heat-sterilized infusion bottles. The latter are closed with infusion stoppers and crimped caps.

Claims

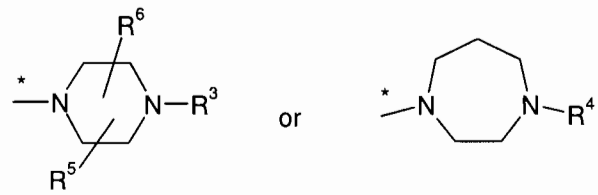
1. Compound of formula



(I),

in which

R^1 represents a group of formula



whereby

* represents the linkage site to the carbonyl group,

R^3 represents phenyl or 5- or 6-membered heteroaryl,

wherein phenyl and heteroaryl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, oxo, nitro, cyano, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, trifluoromethylthio, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl,

C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

R^4 represents phenyl or 5- or 6-membered heteroaryl,

wherein phenyl and heteroaryl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, oxo, nitro, cyano, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, trifluoromethylthio, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

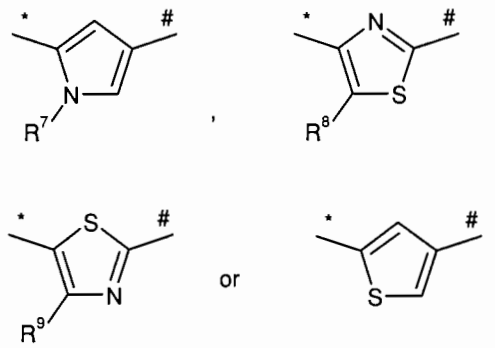
and

R^5 and R^6 independently of one another represent hydrogen, methyl or ethyl,

R^2 represents phenyl,

whereby phenyl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, trifluoromethylthio, C_1-C_6-alkyl and C_1-C_6-alkoxy,

A represents a group of formula



whereby

* represents the linkage site to the carbonyl group,

\# represents the linkage site to the nitrogen atom of the urea,

R^7 represents C_1-C_6-alkyl,

whereby alkyl may be substituted with a substituent, whereby the substituent is selected from the group consisting of C_3-C_6-cycloalkyl, C_6-C_{10}-aryl and 5- or 6-membered heteroaryl,

wherein cycloalkyl, aryl and heteroaryl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, oxo, nitro, cyano, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, trifluoromethylthio, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-

alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

and

R^8 and R^9, independently of one another, represent hydrogen, halogen or C_1-C_6-alkyl,

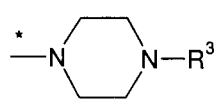
whereby alkyl may be substituted with a substituent, whereby the substituent is selected from the group consisting of C_3-C_6-cycloalkyl, C_6-C_{10}-aryl and 5- or 6-membered heteroaryl,

wherein cycloalkyl, aryl and heteroaryl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, oxo, nitro, cyano, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, trifluoromethylthio, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

or one of its salts, its solvates or the solvates of its salts.

2. Compound according to Claim 1, characterized in that

R^1 represents a group of formula



,

whereby

* represents the linkage site to the carbonyl group,

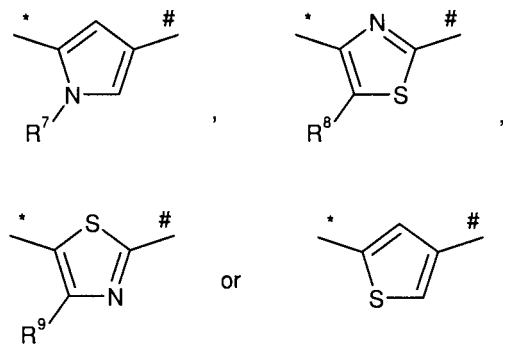
R^3 represents phenyl or 5- or 6-membered heteroaryl,

wherein phenyl and heteroaryl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, oxo, nitro, cyano, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, trifluoromethylthio, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

R^2 represents phenyl,

whereby phenyl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, trifluoromethylthio, C_1-C_6-alkyl and C_1-C_6-alkoxy,

A represents a group of formula



whereby

* represents the linkage site to the carbonyl group,

\# represents the linkage site to the nitrogen atom of the urea,

R^7 represents C_1-C_6-alkyl,

whereby alkyl may be substituted with a substituent, whereby the substituent is selected from the group consisting of C_3-C_6-cycloalkyl, C_6-C_{10}-aryl, and 5- or 6-membered heteroaryl,

wherein cycloalkyl, aryl and heteroaryl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, hydroxy, oxo, nitro, cyano, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, trifluoromethylthio, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

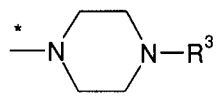
and

R^8 and R^9, independently of one another, represent hydrogen, halogen or C_1-C_6-alkyl,

or one of its salts, its solvates or the solvates of its salts.

3. Compound according to Claim 1 or 2, characterized in that

R^1 represents a group of formula



whereby

* represents the linkage site to the carbonyl group,

R^3 represents phenyl or pyridyl,

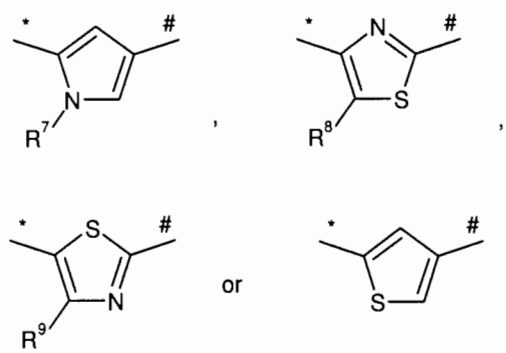
wherein phenyl and pyridyl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the group consisting of halogen, nitro, cyano, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, monofluoromethoxy, C_1-C_4-alkyl and C_1-C_4-alkoxy,

R^2 represents phenyl,

whereby phenyl may be substituted with 1 to 3 substituents, whereby the substituents are selected independently of one another from the

group consisting of fluorine, chlorine, trifluoromethoxy, difluoromethoxy, trifluoromethylthio and methyl,

A represents a group of formula



whereby

* represents the linkage site to the carbonyl group,

\# represents the linkage site to the nitrogen atom of the urea,

R^7 represents methyl, ethyl or n-butyl,

whereby methyl, ethyl and n-butyl may be substituted with a substituent, whereby the substituent is selected from the group consisting of cyclopropyl and phenyl,

wherein phenyl may be substituted with a trifluoromethyl substituent,

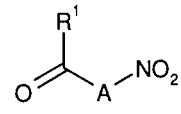
and

R^8 and R^9, independently of one another, represent hydrogen, bromine, chlorine, methyl or ethyl,

or one of its salts, its solvates or the solvates of its salts.

4. Method for preparing a compound of formula (I) according to Claim 1, characterized in that

according to method [A] a compound of formula



(II),

in which

R^1 has the meaning indicated in Claim 1,

is reacted in the first stage with a reducing agent and in the second stage in the presence of a carbonic acid derivative with a compound of formula

$$H_2N—R^2 \quad (III),$$

in which

R^2 has the meaning indicated in Claim 1,

or

according to method [B] a compound of formula (II) is reacted in the first stage with a reducing agent

and in the second stage with a compound of formula

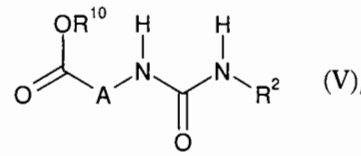
$$OCN\text{-}R^2 \qquad (IV),$$

in which

R^2 has the meaning indicated in Claim 1,

or

according to method [C] a compound of formula



(V),

in which

R^2 has the meaning indicated in Claim 1, and

R^{10} represents methyl or ethyl,

is reacted in the first stage with a base and in the second stage with a compound of formula

$$R^1\text{-}H \qquad (VI),$$

in which

R^1 has the meaning indicated in Claim 1,

in the presence of dehydrating reagents.

5. Compound according to any one of Claims 1 to 3 for the treatment and/or prophylaxis of diseases.

6. Medicament, comprising a compound according to any one of Claims 1 to 3 in combination with at least one inert nontoxic, pharmaceutically acceptable excipient.

7. Use of a compound according to any one of Claims 1 to 3 for the production of a medicament for the treatment and/or prophylaxis of viral infections.

8. Use according to Claim 7, characterized in that the viral infection is an infection with the human cytomegalovirus (HCMV) or another representative of the group of Herpes viridae.

9. Medicament according to Claim 6 for the treatment and/or prophylaxis of viral infections.

10. Method for controlling viral infections in humans and animals by administering an antivirally effective amount of at least one compound according to any one of Claims 1 to 3, a medicament according to Claim 6 or a medicament obtained according to Claim 7 or 8.