

United States Patent [19][11] **Patent Number:** **5,614,535****Juraszyk et al.**[45] **Date of Patent:** **Mar. 25, 1997**

[54] **ADHESION RECEPTOR ANTAGONISTS**

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[30] **Foreign Application Priority Data**

Aug. 19, 1994 [DE] Germany 44 29 461.1

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[52] **U.S. Cl.** **514/326**; 514/212; 514/255; 514/364; 514/374; 540/603; 544/369; 546/208; 548/134; 548/135; 548/230

[58] **Field of Search** 540/603; 544/369; 546/208; 548/134, 135, 230; 514/212, 255, 326, 364, 374

[56] **References Cited****U.S. PATENT DOCUMENTS**

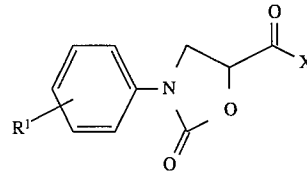
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[57] **ABSTRACT**

Compounds of the formula I



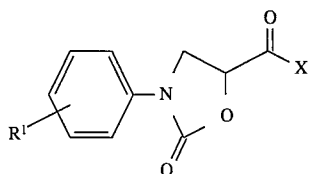
in which R¹ and X have the meanings herein defined, their physiologically unobjectionable salts and/or solvates inhibit the binding of fibrinogen to the corresponding receptor and can be employed for the treatment of thromboses, osteoporosis, tumoral diseases, apoplexy, cardiac infarction, inflammations, arteriosclerosis and osteolytic disorders.

20 Claims, No Drawings

ADHESION RECEPTOR ANTAGONISTS

SUMMARY OF THE INVENTION

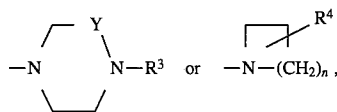
The invention relates to oxazolidinonecarboxylic acid derivatives of the formula I



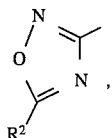
wherein

R¹ is NO₂, NR⁶R⁷, CN, CONR⁶R⁷, CSNR⁶R⁷, C(=NH)SA, C(=NH)OA, C(=NH)SAr, C(=NH)NHOH, C(=NR⁶R⁷), CH₂NR⁶R⁷, CH₂NHC(=NH)NR⁶R⁷, NHC(=NH)NR⁶R⁷, CH₂NHCO—alk—NR⁶R⁷, CH₂NHCO—Ph—E, CH₂NHCO—Ph—CH₂NR⁶R⁷, CH₂NHCONH—Ph—E or D,

X is OH, OA, AS, AS—AS',



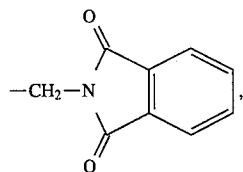
D is



E is —CN, —C(=NH)OA, —CSNH₂, —C(=NH)SA or —C(=NH)NH₂,

Y is CH₂, CHOR⁵ or C=O,

R² is H, A, Ar, OH, OA, CF₃, CCl₃, NR⁶R⁷, —alk—NR⁶R⁷, —alk(CH₂Ar)NR⁶R⁷, or



R³ is —(CH₂)_m—COOR⁵,

R⁴ is —(CH₂)_p—COOR⁵ or —(CH₂)_q—O—(CH₂)_r—COOR⁵,

AS or AS' is in each case, independent of the other, an amino-acid residue selected from Ala, β-Ala, Arg, Asn, Asp, Gln, Glu, Gly, Leu, Lys, Orn, Phe, Pro, Sar, Ser, Thr, Tyr, Tyr (OMe), Val, C-allyl-Gly, C-propargyl-Gly, N-benzyl-Gly, N-phenethyl-Gly, N-benzyl-β-Ala, N-methyl-β-Ala and N-phenethyl-β-Ala, it being possible for free amino or carboxyl groups also to be provided with conventional protective groups which are known per se,

R⁵, R⁶ and R⁷ are each, independent of one another, H or A,

m is 1, 2 or 3,

n is 1, 2, 3 or 4,

p is 0, 1 or 2,

q is 0 or 1,

r is 1 or 2,

A is alkyl of 1 to 6 carbon atoms,

—alk— is alkylene of 1 to 6 carbon atoms,

Ar is phenyl or benzyl, and

Ph is phenylene,

and their physiologically unobjectionable salts and/or solvates.

Compounds having a similar activity profile are known from EP-A1-0 381 033.

An object of the invention is to provide novel compounds having valuable properties, in particular those compounds which can be used for preparing medicaments.

Upon further study of the specification and appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

These objects are achieved by the invention. It has been found that the compounds of the formula I and their solvates and salts possess valuable pharmacological properties while being well tolerated. In particular, they inhibit the binding of fibrinogen, fibronectin and the von Willebrand factor to the fibrinogen receptor of blood platelets (glycoprotein IIb/IIIa), as well as the binding of these proteins and of further adhesive proteins, such as vitronectin, collagen and laminin, to the corresponding receptors on the surface of various cell types. The compounds consequently influence cell-cell and cell-matrix interactions. They prevent the development of blood-platelet thrombi in particular, and can therefore be used for the treatment of thromboses, apoplexy, cardiac infarction, inflammations and arteriosclerosis. In addition, the compounds have an effect on tumor cells, by preventing them from forming metastases. Consequently, they can also be used as antitumor agents.

There is evidence that tumor cells spreading from a solid tumor into the vasculature are carried by microthrombi, i.e., microaggregates of tumor cells and platelets. As a result, the tumor cells in the microthrombi are protected from being detected by cells of the immune system. The second step of attachment to the vessel wall seems to be facilitated by microthrombi as well. Since the formation of thrombi is mediated by fibrinogen binding to the fibrinogen receptor (glycoprotein IIb/IIIa) on activated platelets, fibrinogen-binding inhibitors are expected to be effective as antimetastatics.

Also, since fibrinogen-binding inhibitors are ligands with fibrinogen receptor on platelets, they can be used as diagnostic tools for detection and localization of thrombi in the vascular in vivo. Thus, for example, in accordance with known procedures, the fibrinogen-binding inhibitors can be labeled with a signal generating or detectable moiety whereby, once the labeled fibrinogen-binding inhibitor is bound to a fibrinogen receptor on platelets, it is possible to detect and locate thrombi.

Fibrinogen-binding inhibitors are also very effective as research tools for studying the metabolism of platelets in the different activation states or intracellular signalling mechanisms of the fibrinogen receptor. For example, as described above, fibrinogen-binding inhibitor can be labeled with a signal generating or detectable moiety. The fibrinogen-binding inhibitor-signal generating/detectable moiety conjugate can then be employed in vitro as a research tool. By binding the conjugate to fibrinogen receptors, it is possible to monitor and study the metabolism of platelets, as well as the activation states and signalling mechanisms of the fibrinogen receptors.

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Furthermore, the compounds are suitable for the prophylaxis and treatment of osteolytic disorders, especially osteoporosis and restenosis following angioplasty. In addition, they have antiangiogenic properties.

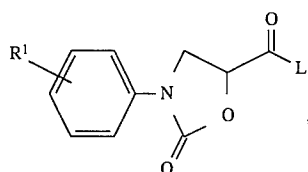
Moreover, the compounds display an antimicrobial action and can be employed in treatments and interventions in which it is necessary to prevent microbial infection. Antimicrobial activity of the compounds can be demonstrated by the procedure described by P. Valentin-Weigan et al., *Infection and Immunity*, 2851-2855 (1988).

The properties of the compounds can be demonstrated by methods which are described in EP-A1-0 462 960. The inhibition of the binding of fibrinogen to the fibrinogen receptor can be demonstrated by the method indicated in EP-A1-0 381 033. The inhibitory effect on blood-platelet aggregation can be demonstrated in vitro by the method of Born (*Nature*, 4832:927-929 (1962)). The inhibition of the interactions of β_3 -integrin receptors with suitable ligands can be demonstrated by the method of J. W. Smith et al., *J. Biol. Chem.*, 265:12267-12271 (1990).

The invention relates to compounds of the indicated formula I, to their salts and solvates, and to a process for the preparation of these compounds, characterized in that

(a) a compound of the formula I is liberated from one of its functional derivatives by treatment with a solvolysis or hydrogenolyzing agent, or in that

(b) a compound of the formula II



in which

R^1 has the meaning given and

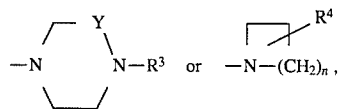
L is Cl, Br, OH or a reactive esterified OH group or a leaving group which is readily capable of undergoing nucleophilic substitution,

is reacted with a compound of the formula III



in which

X' is AS, AS-AS',



where Y, R^3 , R^4 and n have the meanings given, or in that

c) a radical X is converted into a different radical X by hydrolyzing an ester of the formula I or esterifying a carboxylic acid of the formula I, or in that

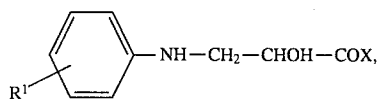
d) a radical R^1 is converted into a different radical R^1 by catalytically hydrogenating a NO_2 and/or CN group, or converting a nitrile group by reaction with ammonia into a $C(=NH)-NH_2$ group, or converting a nitrile group into a thiocarbonyl group, or

converting a thiocarbonyl group into an alkylsulfimido group, or

converting a carbonyl group into an alkylimido group, or

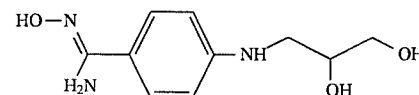
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converting a methylsulfimido group into an amidine group, or
 converting a nitrile group by reaction with NH_2OH into a $C(=NH)-NHOH$ group, or
 converting a NH_2 group into a guanidinyll group, or
 converting a $C(=NH)-NHOH$ group into an amidine group, or
 converting a CH_2NH_2 group into an alkanoylaminoethyl, $CH_2NHC(=NH)NR^6R^7$, $CH_2NHCO-Ph-C(=NH)NH_2$, $CH_2NHCO-Ph-CH_2NR^6R^7$ or a $CH_2NHCONH-Ph-E$ group, or
 converting a 1,2,4-oxadiazole or 1,2,4-oxadiazolinone group into an amidine group,
 e) or in that a compound of the formula IV



in which

R^1 and X have the given meanings, is reacted with a reactive derivative of carbonic acid, and/or in that f) a compound of the formula V



is reacted with 2 equivalents of a reactive carbonic acid derivative and then oxidized, or in that

g) a compound of the formula I is converted by treatment with an acid or a base into one of its salts.

The abbreviations given above and below for amino-acid residues are the residues of the following amino acids:

Ala	alanine
β -Ala	β -alanine
Arg	arginine
Asn	asparagine
Asp	aspartic acid
Asp(O But)	aspartic acid β -butyl ester
Gln	glutamine
Glu	glutamic acid
Gly	glycine
Leu	leucine
Lys	lysine
Orn	ornithine
Phe	phenylalanine
Pro	proline
Sar	sarcosine (N-methylglycine)
Ser	serine
Thr	threonine
Tyr	tyrosine
Tyr(OMe)	2-amino-3-p-methoxyphenylpropionic acid
Val	valine.

Further abbreviations used below are:

BOC	tert-butoxycarbonyl
CBZ	benzyloxycarbonyl
DCCI	dicyclohexylcarbodiimide
DMF	dimethylformamide
EDCI	N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride
Et	ethyl
Me	methyl
OMe	methyl ester
OEt	ethyl ester
TFA	trifluoroacetic acid

Above and below, the radicals R^1 and X have the meanings given for the formula I. Where a compound of the

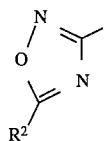
formula I possesses a chiral center, it may occur in a plurality of enantiomeric forms. All of these forms and mixtures thereof, especially racemates, are included by the invention.

In the formula above and below, the group A has 1-6, preferably 1, 2, 3 or 4, carbon atoms. Specifically, A is preferably methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, and also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, or 1-, 2- or 3-methylpentyl.

X is preferably $-\text{OH}$, $-\text{OCH}_3$, $-\text{O}-\text{CH}_2-\text{CH}_3$, 4-carboxypiperidino, 4-carboxyalkylpiperidino, 4-carboxyalkoxy-piperidino and the corresponding alkyl ester groups of the radicals mentioned, 4-alkoxycarbonylpiperidino, 4-carboxymethylpiperazino, 4-carboxyethylpiperazino or, particularly preferably, is an amino-acid residue or a dipeptide residue which is attached to the carbonyl group via an amide bond. If X is an amino-acid residue or dipeptide residue, the following are particularly preferred: Ala, β -Ala, Gly, Arg and β -Ala-Asp, Phe, N-phenethylglycine, N-phenethyl- β -alanine or Sar.

The C-terminal amino-acid residue can in this case likewise be attached to a conventional protective group. An esterification is particularly suitable.

The group R^1 is preferably $-\text{NH}_2$, $-\text{C}(=\text{NH})-\text{NH}_2$, $-\text{CH}_2-\text{NH}_2$, $-\text{CH}_2-\text{NH}-\text{CO}-\text{alk}-\text{NH}_2$, $-\text{CH}_2-\text{NH}-\text{CO}-\text{Ph}-\text{C}(=\text{NH})-\text{NH}_2$, $-\text{CH}_2-\text{NH}-\text{CO}-\text{alk}-\text{C}(=\text{NH})-\text{NH}_2$, $-\text{CH}_2-\text{NH}-\text{CO}-\text{Ph}-\text{CH}_2-\text{NH}_2$, NO_2 or CN . In addition, R^1 is also preferably $-\text{C}(=\text{NH})-\text{S}-\text{A}$, $-\text{CSNH}_2$, $-\text{C}(=\text{NH})-\text{NHOH}$ or



The radical Ar is unsubstituted benzyl or phenyl.

The parameters m and n are preferably 1, but also, in addition, preferably 2 or 3. The variable p is preferably 0 or 1, whereas q and r are preferably 1.

Among the compounds of the formula I, preference is given to those in which at least one of the indicated radicals, groups and/or parameters has one of the preferred meanings given. Some groups of preferred compounds are those of the formulae Ia to If, which correspond to the formula I except that

in Ia R^1 is $\text{C}(=\text{NH})\text{NH}_2$ and X is OH or OA;

in Ib R^1 is $\text{C}(=\text{NH})\text{NH}_2$ and X is 4-carboxypiperidino, 4-carboxylalkylpiperidino or 4-carboxyalkoxy-piperidino;

in Ic R^1 is $\text{C}(=\text{NH})\text{NH}_2$ and X is β -Ala, Asp, Tyr, Tyr(OMe), N-phenethyl- β -Ala or Phe, and the corresponding esterified derivatives;

in Id R^1 is $\text{C}(=\text{NH})\text{NH}_2$ and X is 4-alkoxycarbonylpiperidino, 4-alkoxycarbonylpiperazino, 4-alkoxycarbonylalkylpiperidino, 4-alkoxycarbonylalkoxy-piperazino or 4-alkoxycarbonylalkoxy-piperidino;

in Ie R^1 is $\text{C}(=\text{NH})\text{NH}_2$ and X is 4-carboxypiperazino or 4-carboxyalkylpiperazino;

in If R^1 is $\text{C}(=\text{NH})\text{NHOH}$ and X is one of the radicals mentioned under Ia to Ie.

Furthermore, the invention includes all those compounds which have a NH_2 group within which this NH_2 group is provided with a protective group which is known per se.

The compounds of the formula I, and also the starting compounds for their preparation, are otherwise prepared by

methods which are known per se, as described in the literature (e.g., in the standard works such as Houben-Weyl, Methoden der organischen Chemie [Methods for Organic Chemistry], Georg-Thieme-Verlag, Stuttgart; and also J. March, Adv. Org. Chem., 3rd Ed. (1985), J. Wiley & Sons), specifically under reaction conditions which are known and suitable for the stated reactions. In this context, use can also be made of variants which are known per se which are not mentioned here in more detail.

If desired, the starting compounds can also be formed in situ, such that they are not isolated from the reaction mixture but, instead, are reacted further immediately to give the compounds of the formula I.

The compounds of the formula I can be obtained by liberating them from their functional derivatives by solvolysis, in particular hydrolysis, or by hydrogenolysis.

Preferred starting compounds for the solvolysis or hydrogenolysis are those which, while otherwise corresponding to the formula I, contain corresponding protected amino and/or hydroxyl groups in place of one or more free amino and/or hydroxyl groups, preferably those which carry an amino-protective group in place of a hydrogen atom which is linked to a nitrogen atom, in particular those which carry, in place of an HN group, a group $\text{R}'-\text{N}$ in which R' is an amino-protective group, and/or those which carry, instead of the hydrogen atom of a hydroxyl group, a hydroxy-protective group, for example those which correspond to the formula I but, instead of a $-\text{COOH}$ group, carry a group $-\text{COOR}''$ in which R'' is a hydroxy-protective group.

It is also possible for two or more—identical or different—protected amino and/or hydroxyl groups to be present in the molecule of the starting compound. If the protective groups present are different from one another, they can in many cases be eliminated selectively.

The expression "amino-protective group" is well known and relates to groups which are suitable for protecting (or blocking) an amino group from chemical reactions but which are readily removable once the desired chemical reaction has been carried out at another site of the molecule.

Typical groups of this kind are, in particular, unsubstituted or substituted acyl, aryl (e.g., 2,4-dinitrophenyl (DNP)), aralkoxymethyl (e.g., benzyloxymethyl (BOM)) or aralkyl groups (e.g., benzyl, 4-nitrobenzyl or triphenylmethyl). Since the amino-protective groups are removed after the desired reaction (or sequence of reactions), their nature and size is otherwise not critical; however, preference is given to those having 1-20, especially 1-8 carbon atoms. In connection with the present process, the expression "acyl group" should be interpreted in the broadest sense. It embraces acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids and also, in particular, alkoxycarbonyl, aryloxycarbonyl and, especially, aralkoxycarbonyl groups. Examples of such acyl groups are alkanoyl such as acetyl, propionyl, butyryl; aralkanoyl such as phenylacetyl; aroyl such as benzoyl or tolyl; aryloxyalkanoyl such as phenoxyacetyl; alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl (BOC) and 2-iodoethoxycarbonyl; aralkyloxycarbonyl such as benzyloxycarbonyl (CBZ), 4-methoxybenzyloxycarbonyl and 9-fluorenylmethoxycarbonyl (Fmoc). Preferred amino-protective groups are BOC, DNP and BOM, and also CBZ, benzyl and acetyl.

The expression "hydroxy-protective group" is likewise well known and relates to groups which are suitable for protecting a hydroxyl group against chemical reactions, but which are readily removable once the desired chemical

reaction has been carried out at another site of the molecule. Typical groups of this kind are the abovementioned unsubstituted or substituted aryl, aralkyl or acyl groups, and also alkyl groups. The nature and size of the hydroxy-protective groups is not critical, since after the desired chemical reaction or sequence of reactions they are removed again; preference is given to groups having 1–20, especially 1–10, carbon atoms. Examples of hydroxy-protective groups include tert-butyl, benzyl, p-nitrobenzoyl, p-toluenesulfonyl and acetyl, with particular preference being given to benzyl and acetyl.

The functional derivatives of the compounds of the formula I, which derivatives are to be used as starting compounds, can be prepared by conventional methods as described, for example, in the standard works and Patent Applications mentioned, for example by reaction of compounds which correspond to the formulae II and III but in which at least one of these compounds contains a protective group instead of a hydrogen atom.

The liberation of the compounds of the formula I from their functional derivatives is achieved—depending on the protective group used—by employing, for example, strong acids, advantageously using trifluoroacetic or perchloric acid, but also with other strong inorganic acids such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids such as trichloroacetic acid or sulfonic acids such as benzene- or p-toluenesulfonic acid. The presence of an additional inert solvent is possible, but not always necessary.

Suitable inert solvents are preferably organic, for example carboxylic acids such as acetic acid, ethers such as tetrahydrofuran (THF) or dioxane, amides such as dimethylformamide (DMF), halogenated hydrocarbons such as dichloromethane, and also alcohols such as methanol, ethanol or isopropanol, and water. Also suitable are mixtures of the abovementioned solvents. Trifluoroacetic acid is preferably used in excess without the addition of a further solvent, perchloric acid in the form of mixture of acetic acid and 70% perchloric acid in a ratio of 9:1. The reaction temperatures for the cleavage are advantageously between about 0° and about 50°; it is preferably carried out at between 15° and 30° (room temperature).

The BOC group may, for example, preferably be eliminated using 40% trifluoroacetic acid in dichloromethane or with from about 3 to 5N HCl in dioxane at 15°–60°, and the Fmoc group removed using an approximately 5–20% solution of dimethylamine, diethylamine or piperidine in DMF at 15°–50°. Elimination of the DNP group is also achieved, for example, with an approximately 3–10% solution of 2-mercaptoethanol in DMF/water at 15°–30°.

Protective groups which can be removed by hydrogenolysis (e.g., BOM, CBZ or benzyl) may, for example, be eliminated by treatment with hydrogen in the presence of a catalyst (e.g., a noble metal catalyst such as palladium, advantageously on a support such as charcoal). In this case suitable solvents are those indicated above, particular examples being alcohols such as methanol or ethanol, or amides such as DMF. The hydrogenolysis is generally carried out at temperatures of between 0° and 100° and at pressures of between 1 and 200 bar, preferably 20°–30° and 1–10 bar. Hydrogenolysis of the CBZ group is readily achieved, for example, over 5–10% Pd-C in methanol at 20°–30°.

It is also possible, for example, to perform a hydrogenolytic conversion of a 1,2,4-oxadiazolin-5-on-3-yl or a 5-alkyl-1,2,4-oxadiazol-3-yl group into amidine group by catalytic hydrogenation.

Compounds of the formula I can also be obtained, preferably, by reaction of an oxazolidinone of the formula II

with a compound of the formula III. In this case use is advantageously made of the methods which are known per se of nucleophilic substitution and/or of the N-alkylation of amines or the reactions for amide formation.

The leaving group L in the formula II is preferably Cl, Br or OH, or a group which can be derived therefrom, for example the trifluoromethanesulfonyloxy, toluenesulfonyloxy or methanesulfonyloxy group.

The reaction is preferably carried out in the presence of an additional base, for example an alkali metal or alkaline-earth metal hydroxide or carbonate, such as sodium hydroxide, potassium hydroxide or calcium hydroxide, sodium carbonate, potassium carbonate or calcium carbonate, in an inert solvent, for example a halogenated hydrocarbon such as dichloromethane, an ether such as THF or dioxane, an amide such as DMF or dimethylacetamide, or a nitrile such as acetonitrile, at temperatures of between about –10° and 200°, preferably between 0° and 120°. The addition of an iodide such as potassium iodide may favor the progress of the reaction.

The starting compounds of the formula II are in general known or can be prepared in an analogy to known compounds. Their preparation is described, for example, in DE 37 23 797 (EP 300 272). They can be prepared, for example, by reacting an appropriately substituted aniline with allyl chloride, subsequently converting the double bond into a diol, reacting this diol with a reactive derivative of carbonic acid, for example phosgene, N-N-carbonyldiimidazole, a dialkyl carbonate or diphosgene, oxidizing the product to 5-oxazolidinonecarboxylic acid and, if desired, carrying out further activation by derivatizing the acid group,

In a compound of the formula II it is possible to convert a radical L into a different radical L' by, for example, reacting an OH group (Y=OH) with SOCl₂, SOBr₂, methanesulfonylchloride or p-toluenesulfonyl chloride.

The compounds of the formula III are, in general, known and commercially available

The reaction of the oxazolidinones of the formula II with the compounds of the formula III is carried out in a manner known per se, preferably in a protic or aprotic polar inert solvent at temperatures of between 20° and the boiling point of the solvent. The reaction times are from 10 min to 24 h, preferably from 2 h to 10 h.

Suitable solvents include, in particular, alcohols such as methanol, ethanol, isopropanol, n-butanol and tert-butanol; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) and dioxane; glycol ethers such as ethylene glycol monomethyl and monoethyl ether (methyl glycol or ethyl glycol), and ethylene glycol dimethyl ether (diglyme); ketones such as acetone and butanone; nitriles such as acetonitrile; nitro compounds such as nitromethane and nitrobenzene; esters such as ethyl acetate and hexamethylphosphoric triamide; sulfoxides such as dimethyl sulfoxide (DMSO); chlorinated hydrocarbons such as dichloromethane, chloroform, trichloroethylene, 1,2-dichloroethane and carbon tetrachloride; and hydrocarbons such as benzene, toluene and xylene. Also suitable are mixtures of these solvents with one another. N-methylpyrrolidone is particularly suitable.

Derivatives having a free primary or secondary amino group are advantageously converted into a protected form. Suitable protective groups are those mentioned above.

It is also possible to obtain a compound of the formula I by converting a radical X into a different radical X'. For example, a free acid group (X=OH) can be esterified (X=OA) or linked by a peptide bond to an amino acid or a dipeptide. Furthermore, it is also possible, for example, to convert an acid into an amide.

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