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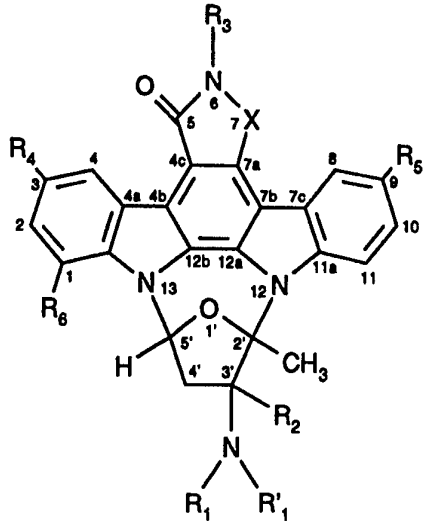
(54) Title: TRINDENE COMPOUNDS

(57) Abstract

Described are trindene derivatives of formula (I), wherein X is methylene or carbonyl, R_1 is hydrogen, acyl or unsubstituted or substituted alkyl, R'_1 is hydrogen or lower alkyl, R_2 is carboxy or functionally modified carboxy, R_3 is hydrogen, halogen, amino, acyl, alkyl or aralkyl, R_4 and R_5 independent of each other are hydrogen, hydroxy, nitro, amino, lower alkyl, lower alkoxy, carbamoyl or halogen, and R_6 is hydrogen or nitro, and salts thereof, a process for the preparation of these compounds, pharmaceutical compositions comprising these compounds and the preparation thereof, and the use of these compounds and compositions for the therapeutic treatment of the human or animal body.



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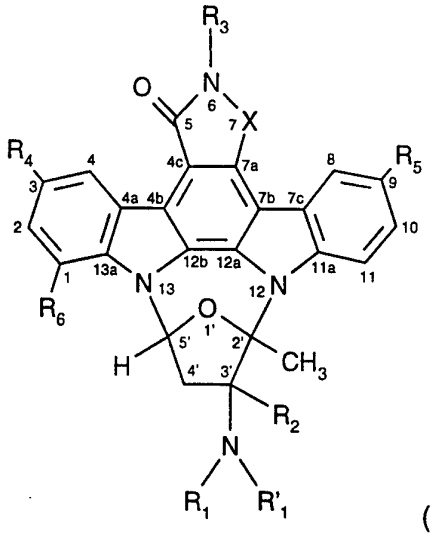
TRINDENE COMPOUNDS

The invention relates to novel trindene compounds of formula I



(I),

wherein X is methylene or carbonyl, R_1 is hydrogen, acyl or unsubstituted or substituted alkyl, R'_1 is hydrogen or lower alkyl, R_2 is carboxy or functionally modified carboxy, R_3 is hydrogen, halogen, amino, acyl, alkyl or aralkyl, R_4 and R_5 independent of each other are hydrogen, hydroxy, nitro, amino, lower alkyl, lower alkoxy, carbamoyl or halogen, and R_6 is hydrogen or nitro, and salts thereof, to a process for the preparation of these compounds, to pharmaceutical compositions comprising these compounds and the preparation thereof, and to the use of these compounds and compositions for the therapeutic treatment of the human or animal body.

Within the scope of this description, the definitions used hereinbefore and hereinafter have preferably the following meanings and, unless indicated to the contrary, organic radicals referred to as "lower" contain from one to seven, and preferably from one to four, carbon atoms. For example, "lower alkyl" stands for C_{1-7}alkyl, preferably C_{1-4}alkyl, "lower alkoxy" represents C_{1-7}alkoxy, preferably C_{1-4}alkoxy.

"Amino" stands for an amino group of the formula $-N(R_7)(R_8)$, wherein R_7 and R_8 independently of each other are hydrogen or C_{1-6}alkyl, preferably hydrogen or C_{1-4}alkyl, mostly preferred hydrogen.

"Halogen" stands for a halogen atom, preferably for chlorine or fluorine, but also for bromine or iodine.

Within the meaning of R_1 and R_3 "acyl" is an acyl radical derived from a free or functionally modified carboxylic acid and is characterised especially by the partial formula Z-C(=W)-, wherein W is oxygen or sulfur and Z is hydrogen, hydrocarbyl, hydrocarbyloxy, an amino group, especially one of the formula -N(R_7)(R_8), as definded above, or chlorine.

Hydrocarbyl Z in such an acyl radical has a total of preferably not more than 30, and especially not more than 19, carbon atoms and is an aliphatic hydrocarbon, aryl or heteroaryl radical, or also an araliphatic or heteroaraliphatic radical.

An aliphatic unsubstituted hydrocarbon radical Z is saturated or unsaturated. Unsaturated hydrocarbon radicals Z are those which contain one or more, especially conjugated and/or non-conjugated multiple bonds (double and/or triple bonds). There is preferred as an aliphatic hydrocarbon radical Z a straight-chain or branched lower alkyl, lower alkenyl or lower alkinyl radical. Lower alkyl is e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl; lower alkenyl is e.g. allyl, propenyl or isopropenyl; lower alkinyl is e.g. propargyl or 2-butinyl. In corresponding unsaturated radicals, the double bond is preferably not situated in the α-position with respect to the free valency.

An aryl radical Z is a carbocyclic radical in which at least one ring is in the form of a 6-membered aromatic ring (i.e. a benzene ring). Preferred are phenyl, naphthyl, such as 1- or 2-naphthyl, biphenylyl, such as, especially, 4-biphenylyl, anthryl and fluorenyl and also such ring systems having one or more fused saturated rings.

An araliphatic radical Z is an aryl-substituted alkyl radical. Preferred are aryl-lower alkyl and aryl-lower alkenyl radicals, e.g. phenyl-lower alkyl or phenyl-lower alkenyl having a terminal phenyl radical, e.g. benzyl, 1- or 2-phenethyl, 1-, 2- or 3-phenylpropyl, diphenylmethyl (benzhydryl), trityl and cinnamyl, and also 1- or 2-naphthylmethyl.

The term "heteroaryl" embraces heterocyclic compounds of aromatic character, e.g. those in which at least one 5- or 6-membered heterocyclic ring contains the maximum number of non-cumulative double bonds.

A heteroaryl radical Z is especially a monocyclic, but also a bicyclic, aza-, thia-, oxa-, thiaza-, oxaza-, diaza-, triaza- or tetraza-cyclic radical of aromatic character the free valency of which must extend from one of its carbon atoms. More especially, it is a monocyclic radical containing one nitrogen, oxygen or sulfur atom, such as pyrrolyl, e.g. 2-pyrrolyl or 3-pyrrolyl, pyridyl, e.g. 2-, 3- or 4-pyridyl, thienyl, e.g. 2- or 3-thienyl, or furyl, e.g. 2-furyl; analogous bicyclic radicals containing one nitrogen, oxygen or sulfur atom are e.g. indolyl, such as 2- or 3-indolyl, quinolyl, such as 2- or 4-quinolyl, isoquinolyl, such as 3- or 5-isoquinolyl, benzofuranyl, such as 2-benzofuranyl, chromenyl, such as 3-chromenyl, or benzothienyl, such as 2- or 3-benzothienyl; preferred monocyclic and bicyclic radicals containing several hetero atoms are e.g. imidazolyl, such as 2-imidazolyl, pyrimidinyl, such as 2- or 4-pyrimidinyl, oxazolyl, such as 2-oxazolyl, isoxazolyl, such as 3-isoxazolyl, or thiazolyl, such as 2-thiazolyl, and benzimidazolyl, such as 2-benzimidazolyl, benzoxazolyl, such as 2-benzoxazolyl, or quinazolyl, such as 2-quinazolinyl, respectively.

Heteroaraliphatic radicals Z are preferably derived from aliphatic radicals having not more than 7, and preferably not more than 4, carbon atoms, e.g. those mentioned above, such as lower alkyl, especially methyl or ethyl, and may carry one, two or more heteroaryl radical(s), e.g. those mentioned above, it also being possible for the ring to be bonded to the aliphatic radical by a nitrogen atom.

Hydrocarbyl Z can be substituted by one, two or more identical or different substituents, especially by two or three substituents. Suitable substituents are especially the following: free, etherified and esterified hydroxy groups; mercapto, lower alkylthio and unsubstituted or substituted phenylthio groups; halogen atoms, such as chlorine and fluorine, but also bromine and iodine; oxo groups that are also in the form of corresponding acetals or ketals; azido and nitro groups; primary, secondary and, preferably, tertiary amino groups, primary or secondary amino groups protected by conventional protecting groups, acylamino groups and diacylamino groups, and free or functionally modified sulfo groups, such as sulfamoyl groups or sulfo groups in salt form. Preferably, the functional groups are not situated at the carbon atom from which the free valency extends but are separated therefrom by two or even more carbon atoms. The hydrocarbyl radical can also be substituted by free and functionally modified carboxy groups, such as carboxy groups in salt form or esterified carboxy groups, by carbamoyl, ureido or guanidino groups each unsubstituted or carrying one or two hydrocarbon radicals, such as lower alkyl, and by cyano groups. Other substituents of aryl or heteroaryl radicals Z are, for example, lower alkyl, such as methyl, ethyl, n-propyl, n-butyl and isobutyl, and halo-substituted lower alkyl, e.g. trifluoromethyl.

An etherified hydroxy group present as a substituent in the hydrocarbyl radical Z is e.g. a lower alkoxy group, such as a methoxy, ethoxy, propoxy, isopropoxy, butoxy or tert-butoxy group, which may also be substituted. For example, such a lower alkoxy group may be substituted by halogen atoms, e.g. by one, two or more halogen atoms, especially in the 2-position, such as in the 2,2,2-trichloroethoxy, 2-chloroethoxy or 2-iodoethoxy radical, or by hydroxy or lower alkoxy radicals, preferably by one in each case, especially in the 2-position, such as in the 2-methoxyethoxy radical. An especially preferred form of etherified hydroxy group is an oxaalkyl radical, in which, in a preferably linear alkyl, one or more carbon atoms are replaced by oxygen atoms which are preferably separated from one another by several (especially 2) carbon atoms so that they form a group $Y-(O-CH_2CH_2-)_n-$ wherein n= 1 to 14 and Y is hydrogen or lower alkyl, such as methyl or ethyl. Such etherified hydroxy groups are also unsubstituted or substituted phenoxy radicals and phenyl-lower alkoxy radicals, such as especially benzyloxy, benzhydryloxy and triphenylmethoxy (trityloxy), and heterocyclyloxy radicals, such as especially 2-tetrahydro-pyranyloxy. A special etherified hydroxy group is the grouping methylenedioxy or ethylene-dioxy; the former as a rule bridges 2 adjacent carbon atoms, especially in aryl radicals, and the latter is bonded to one and the same carbon atom and is to be regarded as a protecting group for oxo. Etherified hydroxy groups are also to be understood in this context as including silylated hydroxy groups, such as, for example, in tri-lower alkylsilyloxy, such as trimethylsilyloxy and dimethyl-tert-butylsilyloxy, or phenyl-di-lower alkylsilyloxy or lower alkyl-diphenylsilyloxy.

An esterified hydroxy group present as a substituent in the hydrocarbyl radical Z carries an acyl radical characterised above, especially an acyl radical having not more than 12 carbon atoms, or is lactonised by a carboxy group also present in the hydrocarbyl radical Z.

An esterified carboxy group present as a substituent in the hydrocarbyl radical Z is one in which the hydrogen atom has been replaced by one of the hydrocarbon radicals character-ised above, especially by a lower alkyl or phenyl-lower alkyl radical; as examples of an esterified carboxy group there may be mentioned lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl which is unsubstituted or substituted in the phenyl moiety, especially the methoxy-, ethoxy-, tert-butoxy- or benzyloxy-carbonyl group, and also a lactonised carboxy group.

A primary amino group $-NH_2$ as a substituent of the hydrocarbyl radical Z may also be in protected form as an acylamino group corresponding to that amino group. A secondary

amino group carries instead of one of the two hydrogen atoms a hydrocarbyl radical, preferably an unsubstituted hydrocarbyl radical, such as one of those mentioned above, especially lower alkyl, and may also be in a protected form as an acylamino group derived therefrom and having a monovalent acyl radical characterised hereinbelow. It is characteristic of protecting groups that they can be removed readily, i.e. without undesired side-reactions taking place, for example by solvolysis, reduction, photolysis or under physiological conditions. Amino-protecting groups and their introduction and removal are known *per se* and described, for example, in T.W. Greene "Protective Groups in Organic Syntheses", Wiley, New York 1984.

An acyl radical serving as an amino-protecting group is preferably derived from a carbonic acid semi-derivative and is preferably lower alkoxycarbonyl or aryl-lower alkoxycarbonyl each of which is unsubstituted or substituted, especially by lower alkyl, lower alkoxy, nitro and/or by halogen, such as methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, 2,2,2--trichloroethoxycarbonyl, 2-iodoethoxycarbonyl, lower alkenyloxycarbonyl, e.g. allyloxy-carbonyl, benzyloxycarbonyl, 4-nitro- or 4-methoxy-benzyloxycarbonyl, 2-phenyl-2-propoxy-carbonyl, 2-p-tolyl-2-propoxycarbonyl, 2-(p-biphenylyl)-2-propoxycarbonyl or 9-fluor-enyl-methoxycarbonyl.

A tertiary amino group occurring as a substituent in the hydrocarbyl radical Z carries two different or, preferably, identical hydrocarbyl radicals (including the heteroaryl radicals), such as the unsubstituted hydrocarbyl radicals characterised above, especially lower alkyl.

A preferred amino group as a substituent of a hydrocarbyl radical Z is one of the formula $N(R_7)(R_8)$, wherein each of R_7 and R_8 independently of the other is hydrogen, unsubstituted aliphatic C_1-C_7hydrocarbyl, such as, especially, C_1-C_4alkyl or C_1-C_4alkenyl, or monocyclic unsubstituted or C_1-C_4alkyl-, C_1-C_4alkoxy-, halo- and/or nitro-substituted aryl, aralkyl or aralkenyl having not more than 10 carbon atoms, it being possible for carbon-containing radicals R_7 and R_8 to be bonded to each other by a carbon-carbon bond or by an oxygen atom, by a sulfur atom or by a nitrogen atom which is unsubstituted or substituted by hydrocarbyl, such as lower alkyl. In such a case, they form together with the nitrogen atom of the amino group a nitrogen-containing heterocyclic ring. The following may be mentioned as examples of especially preferred amino groups: lower alkylamino, such as methylamino or ethylamino, di-lower alkylamino, such as dimethylamino or diethylamino, pyrrolidino, piperidino, morpholino, thiomorpholino, piperazino or 4-methylpiperazino, or phenylamino,

diphenylamino, benzylamino and dibenzylamino each unsubstituted or substituted, especially in the phenyl moiety, e.g. by lower alkyl, lower alkoxy, halogen and/or by nitro; protected amino groups are preferably in the form of lower alkoxycarbonylamino, e.g. tert-butoxycarbonylamino, phenyl-lower alkoxycarbonylamino, e.g. 4-methoxybenzyloxy-carbonylamino, and 9-fluorenylmethoxycarbonylamino.

In an acyl of the formula Z-C(=W)- wherein Z is an aliphatic hydrocarbon radical characterised above, the latter may carry especially from one to three substituents selected from the following: a carboxy group, which may also be in salt form or in the form of a cyano group or a C_1-C_4alkyl ester (C_1-C_4alkoxycarbonyl group) and which is preferably in the ω-position, an amino group of the formula -N(R_7)(R_8), defined above, preferably one in which each of R_7 and R_8 is hydrogen and which is then preferably in the 1-position, or one or more halogen atoms, especially fluorine or chlorine, which are preferably situated in the vicinity of the carbonyl group.

A preferred acyl is a bicyclic or, especially, a monocyclic aroyl, especially benzoyl, which may also carry one or more of the following substituents: halogen atoms, especially chlorine or fluorine, nitro groups, C_1-C_4alkyl radicals, especially methyl, hydroxy groups and etherified hydroxy groups, especially C_1-C_4alkoxy, such as methoxy, phenoxy and methylenedioxy, and carboxy groups which may also be in salt form or in the form of a cyano group or a C_1-C_4alkyl ester (C_1-C_4alkoxycarbonyl). The aroyl radicals carry preferably not more than two and especially only one of such substituents. Also preferred are analogous heteroaroyl radicals Ac_0, especially those that are derived from pyridine, furan, thiophene and imidazole and the analogues thereof having a fused benzene ring (such as quinoline, isoquinoline, benzofuran, benzothiophene and benzimidazole) and that are unsubstituted or also substituted as indicated above. Other preferred acyl radicals are derived also from monocyclic aryl-alkyl or aryl-alkenyl, e.g. benzyl and styryl (i.e. phenacetyl and cinnamoyl). These, too, may be substituted in the manner indicated above. For example, corresponding acyl radicals Ac_0 are derived from the following carboxylic acids: aliphatic monocarboxylic acids having not more than 10 carbon atoms, such as lower alkanecarboxylic acids, e.g. propionic, butyric, isobutyric, valeric, isovaleric, caproic, trimethylacetic, oenanthic and diethylacetic acid and, especially, acetic acid, but also corresponding halogenated lower alkanecarboxylic acids, such as chloroacetic acid, trifluoroacetic acid or trichloroacetic acid, bromoacetic acid or α-bromoisovaleric acid, aromatic carbocyclic carboxylic acids, e.g. benzoic acid, which may be mono- or poly-substi-

tuted as indicated above; aryl- or aryloxy-lower alkanecarboxylic acids and analogues thereof that are unsaturated in the chain, e.g. phenylacetic or phenoxyacetic acids, phenylpropionic acids and cinnamic acids each unsubstituted or substituted as indicated above for benzoic acid; and heteroaryl acids, e.g. furan-2-carboxylic acid, 5-tert-butylfuran-2-carboxylic acid, thiophene-2-carboxylic acid, nicotinic or isonicotinic acid, 4-pyridinepropionic acid, and pyrrole-2- or -3-carboxylic acids which are unsubstituted or substituted by lower alkyl radicals; also corresponding α-amino acids, especially naturally occurring α-amino acids, e.g. glycine and the α-amino acids of the L series, such as phenylglycine, alanine, phenylalanine, proline, leucine, isoleucine, serine, threonine, valine, tyrosine, arginine, histidine, lysine, aspartic acid, glutamic acid, glutamine and asparagine, preferably in an N-protected form, i.e. in a form in which the amino group is substituted by a conventional amino-protecting group, e.g. one of those mentioned above, and also dicarboxylic acids, such as oxalic acid, malonic acid, mono- or di-lower alkylmalonic acids, succinic acid, glutaric acid, adipic acid, maleic acid, or phthalic acid which is unsubstituted or substituted by halogen, such as fluorine, chlorine or bromine, lower alkyl, hydroxy, lower alkoxy and/or by nitro. As mentioned, the second carboxy group not only may be free but also may be functionally modified, for example may be present in the form of a C_1-C_4alkyl ester group or in the form of a salt.

Hydrocarbyl in a hydrocarbyloxy radical Z has the same general and preferred meanings as those indicated above.

A corresponding preferred acyl is derived from monoesters of carbonic acid (hydrocarbyloxycarbonyl). This acyl accordingly forms with the basic structure of the compounds of formula I corresponding N-disubstituted urethanes. Among especially preferred hydrocarbyl radicals in those derivatives there may be mentioned, for example, the following: aliphatic hydrocarbyl, especially a C_1-C_{20}alkyl, preferably a linear C_1-C_{20} alkyl, that may be substituted by a carboxy group which is preferably in a functionally modified form, such as in the form of a salt, cyano or a C_1-C_4alkyl ester, and is preferably situated in the ω-position, a branched lower alkyl, e.g. tert-butyl, or unsubstituted or substituted phenyl and benzyl radicals, e.g. those mentioned above as being preferred.

Another preferred acyl R_1 is derived from amides of carbonic acid (or also thiocarbonic acid) and is characterised by the formula $(R_7)(R_8)$N-C(=W)-, wherein R_7 and R_8 are as defined above and W is sulfur or, especially, oxygen. This acyl radical accordingly forms with the

basic structure of the compounds of formula I corresponding ureas or thioureas. Among preferred compounds according to the invention that carry this acyl, prominence is to be given especially to those wherein W is oxygen, one of the radicals R_7 and R_8 is hydrogen and the other is phenyl or C_1-C_7alkyl each of which may be substituted by hydroxy, mercapto, methylthio, phenyl, p-hydroxyphenyl, p-methoxyphenyl and, especially, by carboxy (in free form or in a functionally modified form, such as C_1-C_4alkoxycarbonyl, carbamoyl or amidino). Prominence is also to be given to compounds wherein W is sulfur, one of the radicals R_7 and R_8 is hydrogen and the other is C_1-C_7alkyl or, especially, C_1-C_7alkenyl in which the free valency extends from a carbon atom other than that from which the double bond extends, such as allyl.

Prominence is also to be given to the compounds of formulal according to the invention wherein X and R_2 are as defined above and R_1 is chloroformyl or thiochloroformyl, which compounds are distinguished especially by being advantageous intermediates for the preparation of modified carbonic acid acyl esters.

Especially preferred are acyl groups of the partial formula Z-C(=W)- wherein W is oxygen and Z is C_1-C_7alkyl, especially C_1-C_4alkyl, such as methyl, propyl or tert-butyl, which may also be substituted by halogen, such as fluorine or chlorine, carboxy or by C_1-C_4 alkoxy-carbonyl, such as methoxycarbonyl, such as trifluoromethyl or trichloromethyl, 2-carboxy- or 2-methoxycarbonyl-ethyl, or phenyl or benzyl each of which may be unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, such as fluorine or chlorine, nitro, trifluoro-methyl, carboxy, C_1-C_4alkoxycarbonyl, methylenedioxy and/or by cyano.

Especially preferred as the radical R_1 is a C_1-C_7alkoxycarbonyl, especially a C_1-C_4alkoxy carbonyl, radical or a phenyloxycarbonyl radical which is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, nitro, trifluoromethyl, carboxy, C_1-C_4alkoxycarbonyl, methylenedioxy and/or by cyano.

Especially preferred are acyl radicals of the partial formula $(R_7)(R_8)$N-C(=W)-, wherein W is sulfur or, especially, oxygen, R_7 is hydrogen and R_8 is C_1-C_7alkyl, especially C_1-C_4alkyl, or phenyl each of which is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, nitro, trifluoromethyl, carboxy, C_1-C_4alkoxycarbonyl, methylenedioxy and/or by cyano.

Especially preferred as the radical R_1 are acyl radicals that are derived from an α-amino acid, especially a naturally occurring α-amino acid of the L series.

Especially preferred are acyl radicals that are derived from an α-amino acid selected from glycine, phenylglycine, alanine, phenylalanine, proline, leucine, isoleucine, serine, threonine, valine, tyrosine, arginine, histidine, lysine, glutamine, glutamic acid, aspartic acid and asparagine.

Especially preferred are those acyl radicals R_1 that are derived from an α-amino acid in which the α-amino group is protected by an amino-protecting group, e.g. tert-butoxy-carbonyl.

Alkyl R_1 is an unsubstituted or substituted radical that has a total of not more than 19 carbon atoms, especially a straight-chain or branched lower alkyl radical. Lower alkyl is e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl or tert.-butyl. Alkyl R_1 can be substituted by one, two or more identical or different substituents, e.g. those mentioned above for hydrocarbyl. Preferred alkyl radicals R_1 are C_1-C_7alkyl, C_2-C_7hydroxyalkyl in which the hydroxy group is in any position other than the 1-position and is preferably in the 2-position, cyano-[C_1-C_7]alkyl in which the cyano group is preferably in the 1- or the ω-position, or carboxy-[C_1-C_7]alkyl in which the carboxy group is preferably in the 1- or the ω-posi tion and may also be in salt form or in the form of a C_1-C_4alkyl ester (C_1-C_4alkoxycarbonyl) or benzyl ester (benzyloxycarbonyl).

A functionally modified carboxy group R_2 preferably means that the carboxy group may also be in the form of esterified carboxy that can be cleaved under physiological conditions or in the form of cyano, or that the hydroxyl radical of the carboxy group has been replaced by amino (carbamoyl) or the hydrogen atom of the carboxy group has been replaced by alkyl (alkoxycarbonyl).

Esterified carboxy groups R_2 that can be cleaved under physiological conditions (i.e. metabolisable esterified carboxy groups R_2) are known from the chemistry of antibiotics. Suitable groups are especially acyloxymethoxycarbonyl groups wherein acyl is, for example, the radical of an organic carboxylic acid, especially an unsubstituted or substituted lower alkanecarboxylic acid, or wherein acyloxymethyl forms the radical of a lactone. Such groups are e.g. lower alkanoyloxymethoxycarbonyl, e.g. acetoxymethoxycarbonyl or pivaloyloxymethoxycarbonyl, amino-lower alkanoyloxymethoxycarbonyl, especially α-amino-

lower alkanoyloxymethoxycarbonyl, and 4-crotonolactonyl. Other esterified carboxy groups R_2 that can be cleaved under physiological conditions are e.g. 5-indanyloxycarbonyl, phthalidyloxycarbonyl, 1-lower alkoxycarbonyloxy-lower alkoxycarbonyl, 1-lower alkoxy-lower alkoxycarbonyl, e.g. 1-ethoxycarbonyloxyethoxycarbonyl or also 2-oxo-1,3-dioxolan-4-ylmethoxycarbonyl that in the 5-position of the dioxolene ring is unsubstituted or is substituted by lower alkyl or by phenyl.

In an alkoxycarbonyl group R_2 alkyl has the same general and preferred meanings as those given above.

Preferred as the radical R_2 is carboxy or functionally modified carboxy that is in the form of an alkoxycarbonyl group, especially a lower alkoxycarbonyl group, for example ethoxy-carbonyl and, especially, methoxycarbonyl.

The compounds according to the invention may also be in the form of salts, especially pharmaceutically acceptable, i.e. physiologically tolerable, salts. For isolation or purification it is also possible to use pharmaceutically unsuitable salts. Only pharmaceutically acceptable salts are used therapeutically and are preferred.

For example, compounds having free acid groups, for example a free sulfo or carboxy-group, especially one in the acyl radical Ac_0 or one that acts as the substituent R_2, may be in the form of salts, preferably physiologically tolerable salts, with a salt-forming basic component. Suitable salts are especially metal or ammonium salts, such as alkali metal and alkaline earth metal salts, e.g. sodium, potassium, magnesium or calcium salts, and ammonium salts with ammonia or suitable organic amines, especially tertiary mono amines and heterocyclic bases, e.g. triethylamine, tri-(2-hydroxyethyl)-amine, N-ethylpiperidine or N,N'-dimethylpiperazine. Such an acid group can also form an internal salt with the amino nitrogen of the staurosporin basic structure or with another amino group that may be present.

Compounds according to the invention of basic character may also be in the form of addition salts, especially in the form of acid addition salts with inorganic or organic acids. For example, compounds of formula I that carry in the radical R_1 or R_2 a basic group, such as an amino group, as substituent can form acid addition salts with common acids. Special prominence is to be given to addition salts that are formed by acid addition to the 9-amino group of the compounds of formula I, with physiologically tolerable salts being preferred.

The following common acids, for example, are suitable for salt formation: hydrohalic acids, e.g. hydrochloric and hydrobromic acid, sulfuric acid or phosphoric acid, and aliphatic, alicyclic, aromatic or heterocyclic carboxylic or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, fumaric, maleic, hydroxymaleic, oxalic, pyruvic, phenylacetic, benzoic, p-aminobenzoic, anthranilic, p-hydroxybenzoic, salicylic, 4-aminosalicylic, embonic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenedisulfonic, halobenzenesulfonic, toluenesulfonic or sulfanilic acid, and also amino acids, such as methionine, tryptophan, lysine or arginine, and ascorbic acid.

Compounds of formula I may contain one or more further chiral centres in the radicals R_1 and R_2. Accordingly, the invention relates to mixtures of diastereoisomers and especially to the novel diastereoisomers of compounds of formula I that have additional chiral centres in the radicals R_1 and/or R_2.

The invention relates especially to compounds of formula I wherein X is methylene or carbonyl, R_1 is hydrogen, acyl of the partial formula Z-C(=W)-, wherein W is oxygen or sulfur and Z is C_1-C_7alkyl, especially C_1-C_4alkyl, such as methyl, propyl or tert-butyl, which may be unsubstituted or substituted by phenyl, phenyloxy, amino, halogen, such as fluorine or chlorine, carboxy, cyano and/or by C_1-C_4alkoxycarbonyl, such as methoxycarbonyl, such as aminomethyl, 2-aminoethyl, trifluoro- or trichloro-methyl, 2-carboxy- or 2-methoxycarbonyl-ethyl, or 3-carboxypropyl, phenyl which is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, such as fluorine or chlorine, nitro, trifluoromethyl, carboxy, C_1-C_4alkoxycarbonyl, methylenedioxy and/or by cyano, C_1-C_{20}alkoxy, especially tert-butoxy, phenyloxy or benzyloxy each of which is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, such as fluorine or chlorine, nitro, trifluoromethyl, carboxy, C_1-C_4alkoxycarbonyl, methylenedioxy and/or by cyano, acyl of the partial formula $(R_7)(R_8)N$-C(=W)-, wherein W is sulfur or, especially, oxygen, R_7 is hydrogen and R_8 is C_1-C_7alkyl, especially C_1-C_4alkyl, or phenyl each of which is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, nitro, trifluoromethyl, carboxy, C_1-C_4alkoxycarbonyl, methylenedioxy and/or by cyano, or is an acyl radical derived from an α-amino acid, especially an acyl radical derived from glycine, phenylglycine, alanine, phenylalanine, proline, leucine, isoleucine, serine, threonine, valine, tyrosine, arginine, histidine, lysine, glutamine, glutamic acid, aspartic acid or asparagine, in which the α-amino group is free or protected by an amino-protecting group and it being possible, in corresponding amino acids having an additional carboxy group, for the carboxy group also to be esterified, or wherein R_1 is C_1-C_7alkyl,

C_2-C_7hydroxyalkyl in which the hydroxy group is in any position other than the 1-position and is preferably in the 2-position, cyano-[C_1-C_7]alkyl in which the cyano group is preferably in the 1- or the ω-position or carboxy-[C_1-C_7]alkyl in which the carboxy group is preferably in the 1- or the ω-position and may also be in salt form or in the form of a C_1-C_4alkyl ester (C_1-C_4alkoxycarbonyl) or a benzyl ester (benzyloxycarbonyl), R_2 is carboxy, C_1-C_7alkoxycarbonyl, carbamoyl, cyano or esterified carboxy that can be cleaved under physiological conditions, and R_3, R_4, R_5, and R_6 are defined as under formula I; or a salt thereof.

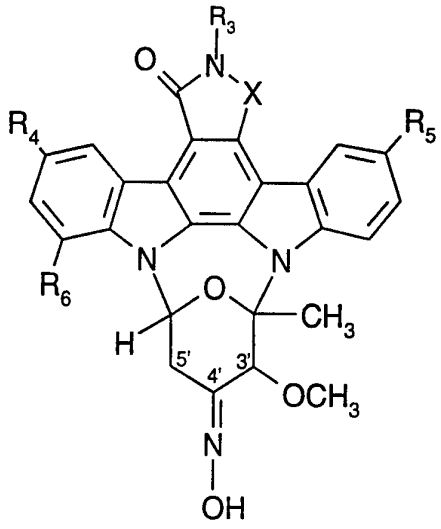
The invention relates chiefly to compounds of formula I wherein X is methylene or carbonyl, R_1 is hydrogen, acyl of the partial formula Z-C(=O)-, wherein Z is C_1-C_7alkyl, such as methyl, ethyl or n-propyl, which is unsubstituted or substituted by phenyl, phenyloxy, halogen, such as fluorine or chlorine, carboxy and/or by C_1-C_4alkoxycarbonyl, such as methoxycarbonyl or ethoxycarbonyl, or phenyl, C_1-C_7alkoxy, such as methoxy, ethoxy, n-propoxy, isobutoxy or tert-butoxy, or phenyloxy each of which is unsubstituted or is substituted by halogen, such as fluorine or chlorine, carboxy, C_1-C_4alkoxycarbonyl, such as methoxycarbonyl, C_1-C_4alkoxy, such as methoxy, C_1-C_4alkyl, such as methyl, and/or by nitro, or the acyl radical of a naturally occurring α-amino acid, such as glycine, alanine, serine or phenylalanine, in which the amino group may be protected by an amino-protecting group, such as lower alkoxycarbonyl, e.g. tert-butoxycarbonyl, or wherein R_1 is C_1-C_4alkyl, cyano-C_1-C_4alkyl, such as cyanoethyl, carboxy-C_1-C_4alkyl, such as carboxymethyl, R_2 is carboxy or lower alkoxycarbonyl, and R_3, R_4, R_5, and R_6 are defined as under formula I; or a salt thereof.

The invention relates more especially to compounds of formula I wherein X is methylene or carbonyl, R_1 is hydrogen, benzoyl, C_1-C_4alkoxycarbonyl, such as tert-butoxycarbonyl, or glycyl or L-alanyl in each of which the amino group may be protected by C_1-C_4alkoxy-carbonyl, R_2 is carboxy or C_1-C_4alkoxycarbonyl, and R_3, R_4, R_5, and R_6 are defined as under formula I; or a salt thereof.

Especially preferred are compounds of the formula I, wherein R_3, R_4, R_5, and R_6 are hydrogen, and X, R_1, R_1' and R_2 are defined as under formula I or as in any one of the preceding subgroups; or a salt thereof.

The invention relates most especially to the compounds of formula I described in the Examples and their salts.

The compounds of formula I are prepared by a novel process which comprises subjecting a compound of the formula II



(II),

wherein X is methylene or carbonyl, to the conditions of a Beckmann rearrangement and, if desired, converting a compound of formula I obtainable according to the process wherein R_1 is hydrogen, R_2 is methoxycarbonyl and R_3 is hydrogen, acyl, alkyl or aralkyl into a different compound of formula I according to a process known *per se*, and/or separating a resulting mixture of diastereoisomeric compounds of formula I into the individual diastereoisomers, and/or converting a compound of formula I obtained in free form into a salt thereof or a compound of formula I obtained in the form of a salt into its free form or into a different salt.

The process according to the invention is carried out under the conditions conventionally used for a Beckmann rearrangement by reacting an oxime of formula II with an organic or inorganic acid or an acid chloride at room temperature or at slightly reduced or, preferably, slightly elevated temperature, e.g. in a temperature range of from approximately 0 to approximately 150°C, preferably in a temperature range of from approximately 25 to approximately 100°C, in an inert solvent, such as a protic solvent, e.g. water or glacial acetic acid, an aprotic solvent, e.g. dioxane, THF, acetonitrile or diethyl ether, or in expedient mixtures of such solvents. Preferably small amounts of water are added to the solvents.

Suitable acids are, especially, concentrated mineral acids, e.g. sulfuric acid, and also Lewis acids, for example boron trifluoride. Boron trifluoride can also be used in the form of

adducts, for example as an acetic acid or ether adduct. A suitable acid chloride is, for example, phosphorylchloride.

In compounds of formula II wherein X is as defined, under the conditions of a Beckmann rearrangement there is surprisingly neither an enlargement of the ring to form the corresponding lactam nor a fragmentation to form the corresponding nitriloaldehyde, but, with a contraction of the ring, a compound of formula I wherein X is methylene or carbonyl, R_1 is hydrogen and R_2 is methoxycarbonyl is formed.

A compound of formula I obtained according to the invention wherein X is methylene or carbonyl, R_1 is hydrogen and R_2 is methoxycarbonyl can, if desired, be converted into a different compound of formula I according to methods known *per se*. For example, an acyl or alkyl group can be introduced into a compound of formula I wherein R_1 is hydrogen and X and R_2 are as defined above.

Acylation of the primary amino group is carried out, advantageously in the presence of an acid-binding agent, with a reagent of the formula Ac-Y_1, wherein Ac has the meanings given above for acyl R_1, and Y_1 is a hydroxy group or a reactively activated hydroxy group, under process conditions that are generally customary in organic chemistry for the substitution of amines, usually at temperatures between the freezing point and the boiling point of the reaction mixture, such as in a temperature range of from approximately -10 to approximately +160°C, especially from approximately +20 to approximately +50°C, at atmospheric or elevated pressure, in heterogeneous phase (such as suspension), with stirring or rotary shaking, or especially in homogeneous liquid phase, such as in an excess of liquid reagent or, especially, in the presence of solvents, especially organic solvents, and, where appropriate, in the presence of acid-binding inorganic or organic agents. Suitable solvents are, for example, aprotic organic solvents, such as aliphatic and aromatic hydrocarbons of the dioxane and benzene type, respectively, and halogenated, especially chlorinated, aliphatic hydrocarbons, such as chloroform and dichloromethane, and, especially, polar aprotic solvents, such as aliphatic and cyclic ethers, e.g. diethyl ether, 1,2-dimethoxyethane, and dioxane and tetrahydrofuran, respectively, lower aliphatic esters and amides, such as ethyl acetate and N,N-dimethylacetamide and dimethylformamide, respectively, and also acetonitrile, dimethyl sulfoxide and hexamethylphosphoric acid triamide. The solvents may also be used in advantageous combinations, e.g. in order to increase the solubility of components.

It is possible in principle to use any basic compound as an acid-binding agent, such as, on the one hand, an organic nitrogen-containing base, e.g. a tertiary amine of the type triethylamine, ethyldiisopropylamine, N,N-dimethylaniline, N-ethylpiperidine or N,N'- dimethylpiperazine, or aromatic heterocyclic bases of the type pyridine, collidine, quinoline or 4-dimethylaminopyridine, or, on the other hand, inorganic compounds giving a basic reaction, especially alkali metal hydroxides, carbonates and hydrogen carbonates, and alkali metal salts of carboxylic acids, such as sodium or potassium acetate.

A reactively activated hydroxyl group will already be present in the free carboxy group of a carboxylic acid of the formula Ac-COOH if, owing to the particular nature of its structure, such as in trifluoroacetic acid or, especially, formic acid, it has a sufficient reactivity, but especially if it is temporarily activated by the action of activating reagents, e.g. carbodiimides, such as, especially, dicyclohexylcarbodiimide or carbonyl-di-(2-imidazolyl), and analogous compounds and, where appropriate, in the presence of auxiliaries that form active esters, such as substituted phenols and especially N-hydroxyamino compounds of the type 1-hydroxybenzotriazole, N-hydroxyphthalimide and N-hydroxymaleimide or -succinimide.

If the acyl radical is derived, for example, from one of the α-amino acids defined at the beginning, or from one of their N-protected derivatives, there is used as starting material especially the relevant amino acid or a salt, which is treated with one of the conventional activating agents, for example one of those mentioned above, thus enabling the carboxy group to be temporarily activated. The reaction is advantageously carried out in situ without isolating the activated intermediate stages. Preferred activating agents are dicyclohexylcarbodiimide and N-hydroxysuccinimide.

An activated hydroxyl group that is advantageous for the acylation is a reactive hydroxyl group esterified by strong acids that forms with the acyl radical a mixed acid anhydride. Particular prominence is to be given to mixed anhydrides with hydrohalic acids, especially with hydrobromic acid and more especially hydrochloric acid, i.e. acid bromides and acid chlorides, e.g. those of the formula Z-C(=W)-Hal, wherein Hal is bromine and preferably chlorine, and Z and W are as defined above.

In acyl radicals Ac of carboxylic acids (including the acyl radical of a functionally modified carbonic acid), the reactive esterified hydroxyl group may also be esterified either by the radical of a different carboxylic acid, especially a stronger carboxylic acid, such as formic

acid, chloroacetic acid or, most especially, trifluoroacetic acid, (mixed anhydride) or, alternatively, by the same acyl radical and form a symmetrical carboxylic acid anhydride of the formula Ac-O-Ac.

The preparation of a compound of formula I wherein X and R_2 are as defined above and R_1 is acyl of the partial formula Z-(C=S)-, wherein Z is as defined above, is effected in a manner known *per se*.

The removal of acyl groups that are not a component part of the desired end product of formula I but serve as amino-protecting groups is effected in a manner known *per se*, e.g. by means of solvolysis, especially hydrolysis.

In a compound of formula I obtainable according to the invention wherein R_2 and X are as defined above and R_1 is hydrogen, the primary amino group can be converted in known manner into an N-alkylated secondary amino group.

In order to prepare compounds of formula I wherein X and R_2 are as defined above and R_1 is unsubstituted or substituted alkyl, a compound of formula I wherein R_1 is hydrogen is reacted, for example, with a reagent of the formula Y_2-Alk wherein Alk is unsubstituted or substituted alkyl as defined above and Y_2 is a reactively esterified hydroxy group.

Y_2 is a reactive esterified hydroxyl group (as a special form of the above-mentioned reactively activated hydroxyl group), i.e. one that is esterified by a strong inorganic acid, such as a hydrohalic acid (e.g. hydrochloric, hydrobromic or hydriodic acid), an oxygen-containing mineral acid, such as phosphoric acid and, especially, sulfuric acid, or a strong organic, such as aliphatic or aromatic, sulfonic acid (e.g. methane- and ethane-sulfonic acid and benzene-, p-toluene-, p-nitrobenzene- and p-chlorobenzene-sulfonic acid, respectively). The reaction is carried out in the presence of one of the acid-binding agents mentioned above. In order to prevent alkylation of the desired N-alkylated secondary amine to the tertiary amine, it may be advisable to protect the primary amino group in a compound of formula I wherein X and R_2 are as defined and R_1 is hydrogen by introducing a monovalent protecting group, e.g. an acyl group, especially one of those mentioned above, and to remove the protecting group in a manner known *per se* after the alkylation.

A functional group present in the radical R_1 can be converted into a different functional group, e.g. a protected amino group can be converted into its free form, or a reactive

chlorine atom (such as that in the chloroformyl radical) can be replaced by the radical Z-O-, wherein Z is as defined above, or by R_7-N(-R_8)-, wherein R_7 and R_8 are the substituents defined above. The freeing of the amino group is effected in a manner known *per se*, e.g. by solvolysis, especially hydrolysis, preferably in an acid medium. The conversion of a chloroformyl (Cl-CO-) group into a hydrocarbyloxycarbonyl group (Z-O-CO-) or an amino-carbonyl-(carbamoyl) group [R_7-N(-R_8)-CO-] is effected under conditions known *per se* by, for example, reacting 3'-chloroformylamino-3'-methoxycarbonyl-"cycloocta trinden"-5-one with an alcohol of the formula Z-OH- or with an amine (including ammonia) of the formula R_7-NH-R_8, respectively, preferably in the presence of an acid-binding agent, such as an organic base (e.g. one of the tertiary amines mentioned above).

In a compound of formula I wherein R_1 and X are as defined above and R_2 is a methoxy-carbonyl group, the latter can be converted into the free carboxy group or into a different functionally modified form defined above. The conversion into the free carboxy group is generally effected by conventional hydrolysis, especially under the action of bases, especially alkali metal hydroxides, carbonates or hydrogen carbonates. A corresponding acid amide can be produced from the methoxycarbonyl compound by ammonolysis, and an alkyl ester, especially a C_2-C_7alkyl ester or a compound of formula I wherein X and R_1 are as defined and R_2 is an esterified carboxy group that can be cleaved under physiological conditions is obtained by alcoholysis (transesterification) of the methoxycarbonyl compound. On the other hand, compounds of formula I wherein R_2 is carboxy can also be converted into compounds of formula I wherein R_2 is an esterified carboxy group that can be cleaved under physiological conditions. Such esters can be prepared, for example, by reacting a salt of the acid, which may be formed *in situ*, with a reactive ester of a corresponding alcohol and a strong inorganic acid, such as sulfuric acid, or a strong organic sulfonic acid, such as 4-toluenesulfonic acid. The preparation of a compound of formula I wherein X and R_1 are as defined and R_2 is cyano is effected in a manner known *per se*, e.g. by dehydration of the corresponding acid amide.

Furthermore, a compound of formula I wherein R_1 and R_2 are as defined and X is methylene can be converted with a suitable oxidising agent into a corresponding compound of formula I wherein X is carbonyl. Such an oxidising agent is one of the customary oxidising agents suitable for the oxidation of an activated methylene group, such as a benzyl group, to a carbonyl group, for example a compound of hexavalent chromium, such as an alkali metal chromate or dichromate, e.g. potassium chromate or potassium dichromate, and anhydrides of chromic acid, e.g. chromium trioxide, and complexes thereof, such as the chromium

trioxide-pyridine complex, chromyl chloride or chromyl acetate, and esters of chromic acid, e.g. chromic acid tri-tert-butyl ester, a compound of quadrivalent to heptavalent manganese, e.g. manganese dioxide and potassium permanganate, ruthenium tetroxide and the like. Other suitable oxidising agents are peracids, their salts and hydroperoxides, e.g. potassium peroxodisulfate, which are to be used in the presence of catalytic amounts of manganese(II) or manganese(III) salts, and, in a photooxidation, atmospheric oxygen in the presence of catalytic amounts of titanium(IV)oxide.

The oxidation is carried out in a manner known *per se* in an inert solvent, such as a protic solvent, such as water or glacial acetic acid (e.g. when using chromium trioxide or an oxidising salt), an aprotic solvent, such as benzene, pyridine, acetone, diethyl ether, carbon tetrachloride, methylene chloride, carbon disulfide and the like (e.g. when using chromyl chloride, chromium trioxide-pyridine complex etc.), or in mixtures of such solvents, and, when using two immiscible solvents, such as water and benzene, also in the presence of a phase-transfer catalyst, such as a quaternary ammonium compound, e.g. benzyltrimethyl-ammonium chloride, tetrabutylammonium chloride or cetyltrimethylammonium bromide, and, when using an oxidising salt, e.g. potassium permanganate, also in the presence of a crown ether, e.g. dicyclohexyl-18-crown-6, and, where appropriate, for example when using an oxidising salt, e.g. potassium dichromate, also in the presence of an equimolar amount of a strong inorganic acid, e.g. sulfuric acid, and, depending upon the nature of the oxidising agent used, at room temperature or at reduced or elevated temperature, e.g. in a temperature range of from approximately 0° to approximately 100°C. When using chromyl chloride or chromyl acetate as oxidising agent, the initially formed adduct must, when reaction is complete, be hydrolysed with water to form the desired compound of formula II.

Mixtures of diastereoisomeric compounds obtainable according to the process are separated by means of physico-chemical methods known *per se* into the individual diastereoisomers. Such methods include, for example, fractional crystallisation, liquid chromatography and adsorption chromatography.

The formation of salts and the freeing of the fundamental forms of the compounds of formula I from their salts, which may be carried out if desired, is effected in a conventional manner that is known *per se*. For example, compounds of formula I carrying carboxy are converted into corresponding salts, especially alkali metal salts, by treatment with a corresponding base, especially a compound giving an alkaline reaction, such as an alkali metal hydroxide, carbonate or hydrogen carbonate; the salts can be converted into free carboxy

compounds by acidification, e.g. with inorganic acids, such as, especially, hydrohalic acids. Compounds of formula I containing primary, secondary or tertiary amino groups can be converted into their salts with acids, e.g. by treatment with an acid suitable for forming salts, such as one of those mentioned above; conversely, by treatment with agents giving a basic reaction, such as with inorganic alkali metal hydroxides, carbonates and hydrogen carbonates, organic bases or ion-exchangers, such a basic fundamental form of an amine of formula I is freed.

Suitable compounds of the present invention may also form internal salts, e.g. by conventional titration to the neutral point or to the isoelectric point.

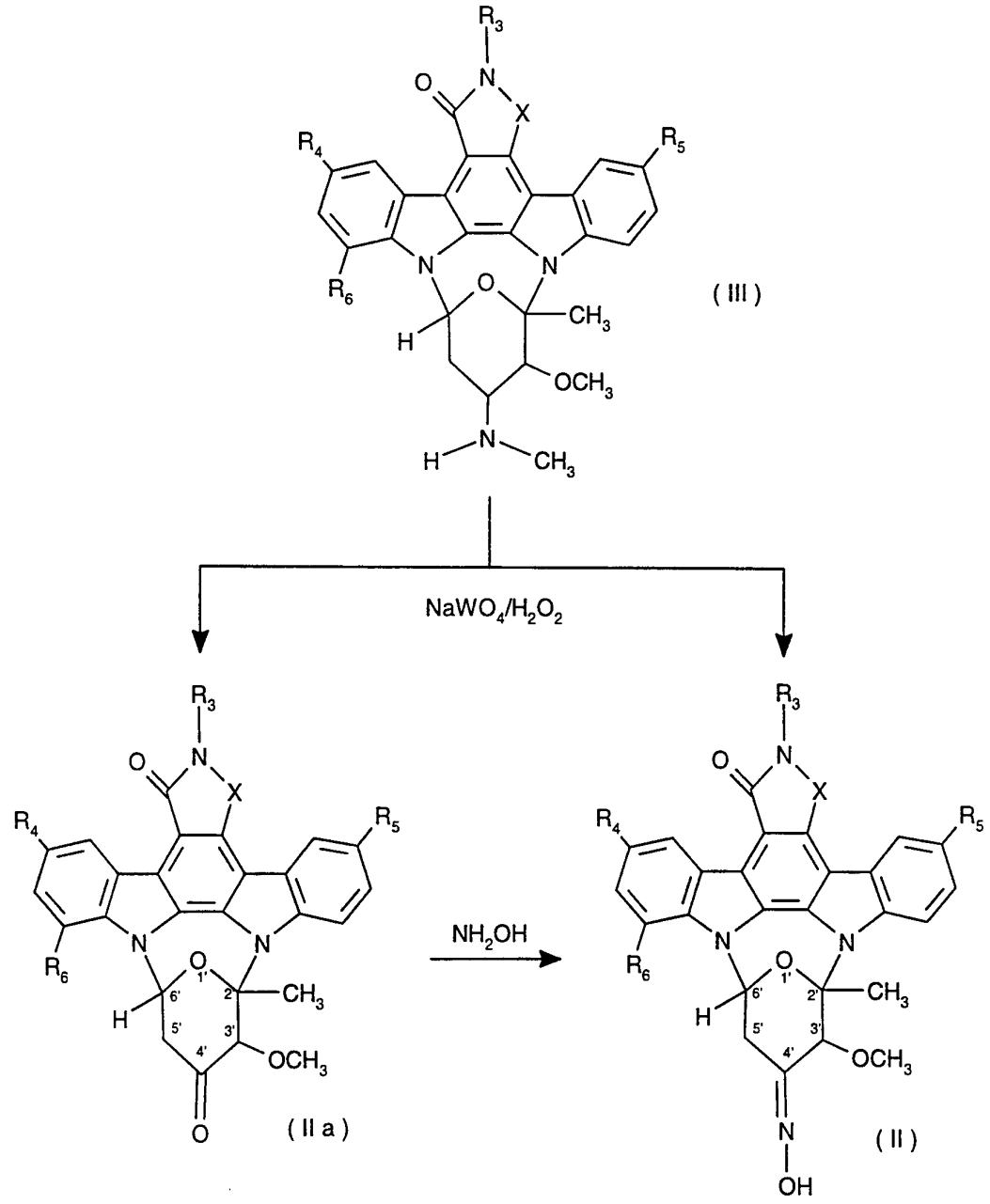
The latter or other salts of the novel compounds, e.g. the picrates, can also be used to purify the resulting compounds, by converting the free compounds into salts, separating the latter and recovering the free compounds from the salts again. In view of the close relationship between the compounds in free form and in the form of their salts, herein before and hereinafter any reference to the free compounds should be understood as including also the corresponding salts, as appropriate and expedient.

The invention relates also to those forms of the process according to which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining steps are carried out or a starting material is used in the form of a derivative, e.g. a salt, or is formed under the reaction conditions.

In the processes of the present invention, there are used starting materials that are known or that can be obtained by known methods, preferably those which result in the compounds described at the beginning as being especially valuable.

The reactions described above can be carried out under reaction conditions known *per se*, in the absence or, usually, in the presence of solvents or diluents, preferably those which are inert towards the reagents used and are solvents thereof, in the absence or presence of catalysts, condensation agents or neutralising agents, and, depending upon the nature of the reaction and/or the reactants, at reduced, normal or elevated temperature, e.g. in a temperature range of from approximately -80°C to approximately 190°C, preferably from approximately -20° to approximately 150°C, e.g. at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, e.g. under a nitrogen atmosphere.

A compound of the formula II can be prepared according to the following reaction scheme by reacting a compound of the formula III, wherein R_3, R_4, R_5 and R_6 are defined as under Formula I in the presence of a suitable oxidising agent like sodium tungstate dihydrate:



This reaction leads to a mixture of a ketone of the formula IIa and an oxime of the formula II. The ketones of the formula IIa can be reduced with a suitable reducing agent such as $NaWO_4$ to oximes of the formula II. Due to the reactive group in 4' position - keto group in

IIa and the oxime group in II - the compounds of the formula II and IIa represent valuable starting compounds for the production of novel pharmaceuticals.

The preparation of compounds of the formula IIa and IIb can be carried out either by starting from compounds of the formula III wherein R_3, R_4, R_5 and R_6 are hydrogen or wherein R_3, R_4, R_5 and R_6 have the other meanings given under formula I. In the first case the resulting compounds of the formula IIa and II are unsubstituted and the substituents can be introduced afterwards. It goes without saying that the reactivity of all reactive groups has to be taken into account if a substituent R_3, R_4, R_5 or R_6 is introduced into the molecule. Whereas, in the second case the resulting compounds of the formula IIa and II are already substituted and no further substitution is necessary.

The starting compound of the formula III wherein X stands for methylene and R_3, R_4, R_5 and R_6 are hydrogen is the antibiotic "staurosporine" which is a fermentation product produced by the strain *Streptomyces staurosporeus* [S. Omura et al. , J. Antibiot. 30, 275-281 (1977)]. Staurosporine is commercially available. Said *Streptomyces* strain was deposited with the Fermentation Research Institute, Japan, under the number FERM P-3725 in connection with the JP 57/53076, that was published on 11.11.82. Further compounds of the formula III wherein X is methylene or C=O, R_4, R_5 and R_6 are hydrogen and R_3 represents hydrogen, lower alkyl, formyl or amino are described in EP-0,383,919 which was published on 29.08.90. A compound of the formula III wherein X is a carbonyl group can also be prepared from the compound of the formula III wherein X stands for methylene by oxidation analogously to the oxidation described for compounds of formula I. In the same manner one can oxidize the methylene group X in the compound of the formula IIa or II in order to obtain their carbonyl analogues.

The starting compound of the formula III wherein R_3, R_4, R_5 and R_6 have other meanings than hydrogen can be obtained from their hydrogen analogues analogously to the reactions described in EP-0,303,697 and US-4,877,776 for the compound K-252 or KT-5556. Further reactions for introducing the substituents R_4 and R_5 are described in the Japanese patent application J0 3072-485 A or can be carried out in accordance with reactions used in organic chemistry for introducing substituents in aromatic ring systems. It goes without saying that it may be advantageous to protect reactive centers with suitable groups prior to the introduction of a further substituent.

The starting compound of formula II wherein X is methylene (staurosporin-4'-one oxime) is known from Tanida, S. *et al.*, J. Antibiot. (1989) 42, 1619-1630 where it is described as a fermentation product. The access to the starting material is exemplified in Example A presented below.

The compounds of the present invention exert a pronounced inhibiting action on protein kinase C. Protein kinase C, which is dependent upon phospholipids and calcium, occurs in cells in several forms and participates in various fundamental processes, such as signal transmission, proliferation and differentiation, and in the release of hormones and neuro-transmitters. These enzymes are known to be activated either by receptor-mediated hydro-lysis of phospholipids of the cell membrane or by direct interaction with certain tumor--promoting substances. The sensitivity of a cell to receptor-mediated signal transmission is considerably influenced by the inhibition of the activity of protein kinase C (as the signal transmitter).

The protein kinase C inhibiting action is determined using protein kinase C from pigs' brains, which is purified by the procedure described by T.Uchida and C.R.Filburn in J.Biol. Chem. 259, 12311-4 (1984). The protein kinase C inhibiting action of the compounds of formula I is determined according to the method of D. Fabbro *et al.*, Arch. Biochem. Biophys. 239, 102-111 (1985). In that test, the compounds of formula I inhibit protein kinase C at a concentration IC_{50} of as little as approximately from 0.01 to 0.2 µmol/litre.

The compounds of formula I also exhibit good inhibiting action (IC_{50} approximately from 0.005 to 0.2µmol/litre) on protein phosphorylase kinase. Other enzymes, e.g.(EGF-R) protein tyrosine kinase, on the other hand, are inhibited by the compounds of formula I only at a far higher, e.g. from 10 to 100 times higher, concentration.

Accordingly, the compounds of formula I and their pharmaceutically acceptable salts can be used e.g. as medicaments, especially for the treatment of tumour diseases. In addition, the compounds of formula I possess anti-inflammatory, immuno-modulating, especially immunosuppressive, and antibacterial properties and can further be used as compositions against AIDS, arteriosclerosis and diseases of the cardiovascular system and the central nervous system.

The immunosuppressive properties of the compounds of the formula I and their pharmaceutically acceptable salts can be demonstrated by various biological tests, e.g. the inhibition of T lymphocyte proliferation. For example, human peripheral blood lymphocytes (PBL) from donors which are sensitive to an antigen, like purified protein derivative (PPD) from M. tuberculosis, are separated by Ficoll method and incubated with PPD in the presence or absence of a compound of the formula I for 6 days in culture. In order to measure antigen induced T cell proliferation, the cultures are pulsed with ^{3}H-thymidine for the last 20 hours of the culture period. In this assay, the compounds of the formula I show IC_{50}-values between about 0.005 and 0.1 μM, e.g. the compound of the formula I, wherein R_1 is hydrogen, R_2 is methoxycarbonyl and X is methylene shows an IC_{50}-value of 0.04 μM.

When tested in a similar assay in the mouse which utilizes lymphocytes from antigen (ovalbumin) sensitized animals, said test being described in detail in Eur. J. Immunol. 8 (1978) 112, the compounds of the formula I show IC_{50}-values between about 0.00001 and 0.001 μM, e.g. the compound of the formula I, wherein R_1 is hydrogen, R_2 is methoxycarbonyl and X is methylene shows an IC_{50}-value of 0.0001 μM. In the same test cyclosporine A has an IC_{50}-value of 0.03 μM and dexamethasone has an IC_{50}-value of 0.003 μM.

Therefore the present invention relates also to a method of suppressing the immune system by administering to a warm-blooded animal in need of such treatment, e.g. when transplanting organs, an immunosuppressing effective amount, especially an amount suppressing the proliferation of T lymphocytes, of a compound of the formula I or of a pharmaceutically acceptable salt thereof.

The present invention further relates to the use of the compounds according to the invention for the preparation of medicaments, e.g. for the applications described above, for the therapeutic and prophylactic treatment of the human, and also the animal, body.

In view of the above-described pharmacological properties of the novel compounds, the present invention also includes the use of the active ingredients according to the invention on their own, where appropriate together with excipients, or in combination with other active ingredients, e.g. antibiotics or chemotherapeutic drugs, as compositions for the treatment of diseases in which, as described above, cell growth is of importance, both prophylactically and curatively. When used as medicaments, the active ingredients according to the invention are administered in prophylactically or curatively effective amounts, preferably in the form of pharmaceutical compositions together with conven tional pharmaceutical

carriers or excipients. There will be administered, for example, to a warm-blooded animal weighing approximately 70 kg, depending upon the species, body weight, age and individual condition, and depending upon the method of administration and especially also the particular syndrome, daily doses of approximately from 0.1 to 5000 mg, which, in acute cases, may be exceeded, especially from 70 mg to 5000 mg, preferably from 70 to 700 mg. The invention also includes accordingly the corresponding method of medical treatment.

The invention relates further to pharmaceutical compositions comprising the compounds of the present invention as active ingredients, and to processes for the preparation of those compositions.

The pharmaceutical compositions according to the invention are, for example, for enteral, such as peroral or rectal, and for parenteral administration to warm-blooded animals. Corresponding unit dose forms, especially for peroral administration, e.g. dragées, tablets or capsules, preferably comprise approximately from 5 to 500 mg, especially approxi mately from 10 to 100 mg, of active ingredient together with pharmaceutically acceptable carriers or excipients.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and binders, such as starch pastes (using, for example, corn, wheat, rice or potato starch), gelatin, gum tragacanth, methylcellulose and/or, if desired, disintegrators, such as the above-mentioned starches, also cyclodextrins, carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores can be provided with suitable coatings which may be enteric coatings, there being used, inter alia, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycols and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Other orally administrable pharmaceutical compositions are dry-filled capsules consisting of gelatin, and also soft sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, where appropriate, stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may also be added.

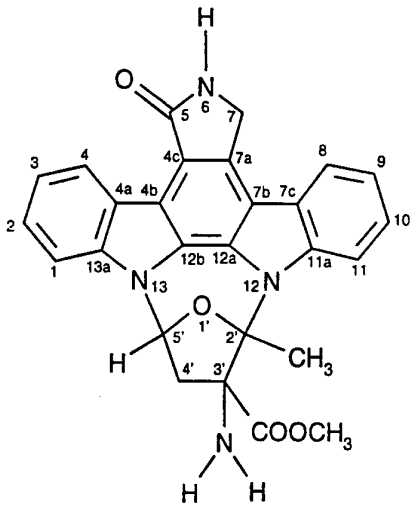
Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. There may also be used gelatin rectal capsules that comprise a combination of the active ingredient with a base; suitable bases are, for example, liquid triglycerides, polyethylene glycols and paraffin hydrocarbons.

For parenteral administration there are suitable, especially, aqueous solutions of a form of the active ingredient that is soluble in water, e.g. a water-soluble salt, or aqueous injection suspensions comprising viscosity-increasing substances, for example sodium carboxy-methylcellulose, sorbitol and/or dextran, and, where appropriate, stabilisers. The active ingredient, where appropriate together with excipients, may also be in the form of a lyophilisate and may be dissolved by the addition of suitable solvents prior to parenteral administration.

The pharmaceutical compositions of the present invention are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture and processing the mixture or granules, if desired or necessary after the addition of suitable excipients, to form tablets or dragée cores.

The following Examples illustrate the invention described above, but do not imply any limitation of the scope thereof. Temperatures are given in degrees Celsius. The following abbreviations are used: TFA = trifluoroacetic acid, BOC= tert-butoxycarbonyl.

The product of formula Ia

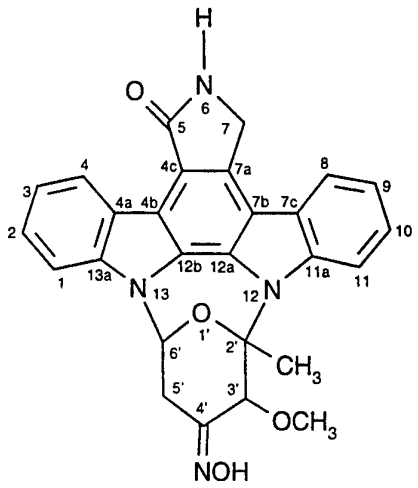


(Ia),

which falls within the scope of formula I is called in accordance with IUPAC rules 3'-amino-3'-methoxycarbonyl-2'-methyl-6,7,3',4'-tetrahydro-2',5'-epoxy-5H,2'H,5'H- 6,12,13-triaza-benzo[a,g]cycloocta[cde]trinden-5-one.

In the present application the 2'-methyl-6,7,3',4'-tetrahydro-2',5'-epoxy-5H,2'H,5'H- 6,12,13-triazabenzo[a,g]cycloocta[cde]trinden-5-one structure is called, in short, cyclooctatrinden-5-one. In order to avoid confusion with the unsubstituted cyclooctatrindene the latter term is placed in quotation marks. The numbering of the positions follows that of formula I.

Example A: Starting Compound: 4'-demethylamino-4'-hydroximino staurosporine of the formula



5.0 g of technical grade staurosporine containing 84.7 % of pure compound (10.9 mmole) is dissolved in 120 ml of methanol and 120 ml of methylene chloride. After addition of 0.6 g (1.8 mmole) of sodium tungsten dihydrate and 4.0 ml of a 30 % hydrogen peroxide solution (39 mmole) the reaction mixture is stirred at room temperature for 60 h under protection from light. The reaction is then quenched by addition of 150 ml of saturated aquous sodium bisulfite solution under cooling. The yellow oil obtained after evaporation of the solvent is redissolved in 80 ml of methanol and 80 ml of methylene chloride. Under stirring and cooling with an ice-bath 1.33 g (19.2 mmole) of hydroxylamine hydrochloride and 12 ml of pyridine are added to the suspension. The reaction mixture is stirred for 2 h at 0°C and subsequently diluted with water and an additional volume of methylene chloride. The aqueous layer is separated and extracted twice with 120 ml of methylene chloride containing 5 % of methanol. The organic phase is washed twice with water, dried over anhydrous sodium sulfate and concentrated in vacuo on a rotatory evaporator. The residue is recrystallized from methanol yielding 3.68 g (87.5 %) of pale yellow crystals. Further recrystallization from ethyl acetate/methanol leads to almost colorless crystals, m.p. 238-244°C.

Example 1: 3'-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one

In a 50ml round-bottom flask, 250 mg of staurosporin-4'-one oxime are dissolved in 20ml of dioxane (Merck; for spectroscopy; 99.5%) by brief heating. After the addition of 56µl of

sulfuric acid (conc.; 96%) the reaction mixture is stirred under reflux for 40 minutes, during which, after about 10 minutes, a light-yellow precipitate begins to form. The precipitate is dissolved with a small quantity of methanol and methylene chloride, then 50 ml each of methylene chloride and saturated Na_2CO_3 solution are added to the reaction mixture, and the aqueous phase is extracted twice with 25 ml of methylene chloride. The organic phases are washed with a small quantity of water, combined and dried with a silicone folded filter. After removal of the solvent, a yellow-brown crude product is obtained which, upon chromatography on silica gel (LiChroprep Si60, 15-25 µm; methylene chloride (indust.), H_2O saturated; 130 ml column), is eluted in the fractions from 200ml to 600ml. Depending upon the quality of the methylene chloride, it is necessary to add 0.5 % isopropanol to the eluant. Removal of the solvent and recrystallisation from 0.5ml of methylene chloride and 6ml of methanol yield the title compound of m.p. 283-290°C (with decomp.). Good yields are obtained if dioxane-water (99:1) is used as a solvent and the solution is kept for 60 minutes at 80°C.

Example 2: 3'-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one

The title compound is obtained analogously to Example 1 by adding 3.2ml of dioxane, 27µl of H_2O and 0.32ml of boron trifluoride-acetic acid (36%) to 40mg of staurosporin-4'-one oxime and stirring under reflux for 100minutes.

Example 3: 3'-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one

The title compound is obtained analogously to Example 1 by dissolving 30 mg of stauro sporin-4'-one oxime in 2.4 ml of dioxane and adding, to 400 µl of that solution, 50µl of boron trifluoride etherate (48 %). The reaction batch is stirred under reflux for 2hours.

Example 4: 3'-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one

The title compound is obtained analogously to Example 1 by dissolving 30 mg of stauro sporin-4'-one oxime in 2.4ml of dioxane and adding, to 400 µl of that stock solution, 4.5 mg of phosphoryl chloride. The reaction batch is stirred under reflux for 30minutes.

Example 5: 3'-benzoylamino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one

In a 5 ml pointed flask under argon equipped with a magnetic stirrer, 3.8 µl of triethylamine and 15 µl of benzoyl chloride are added to 10 mg of 3'-amino-3'-methoxycarbonyl-"cyclooctatrinden"-1-one in 2.5 ml of methylene chloride and 100 µl of pyridine. The reaction mixture is stirred at room temperature for 1hour, then 25ml of methylene chloride and 5 ml of saturated Na_2CO_3 solution are added, and the aqueous phase is extracted twice with 25

ml of methylene chloride. The organic phases are washed with a small quantity of water, combined and dried with a silicone folded filter. Removal of the solvent and final purification by semi-preparative HPLC on silica gel (Nucleosil 100-5, 5 µm; 8x250 mm; methylene chloride / isopropanol 99.5:0.5, H_2O saturated; 6 ml/min; detection: 310 nm; retention times: product: 11.8 min, educt: 24 min) yield the title compound in the form of a colourless substance, m.p. 205-208°C.

Example 6: 3'-amino-3'-carboxy-"cyclooctatrinden"-5-one

A solution of 9 mg of 3'-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one in dioxane (1ml) and 400 µl of 0.1N NaOH is stirred at 55° for 30 minutes. The reaction is stopped by the addition of 5 µl of TFA and the solvent is almost completely driven off with a stream of nitrogen. The mixture is dissolved by the addition of 300 µl of methanol. Purification is carried out by semi-preparative HPLC on a reversed-phase column (Nucleosil 100-5 C-18, 5 µm; 8x250 mm; eluant A: 0.1 % TFA, eluant B: acetonitrile/ water/TFA 80:20:0.08; gradient of 35 % eluant B to 47 % B in 12minutes; 5 ml/min; detection: 310 nm; retention time: 8.4 min.) and yields the colourless title compound, m.p. >300°C.

Example 7: 3'-amino-3'-methoxycarbonyl-7-oxo-"cyclooctatrinden"-5-one

In a 25 ml round-bottom flask, 66 mg of chromium trioxide-pyridine complex (Fieser & Fieser, Reagents for Organic Synthesis, vol.1, Wiley, 1967, page145) are added at 0 °C to 12 mg of 3'-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one in 10 ml of methylene chloride. The reaction mixture is stirred at room temperature for 19 hours. 5 ml of water are added to the mixture which is then rendered basic with 1 ml of saturated Na_2CO_3 solution and extracted twice with 25 ml of methylene chloride. The organic phases are washed with a small quantity of water, combined and dried with a silicone folded filter. Removal of the solvent, drying under a high vacuum and final purification by semi- preparative HPLC (Nucleosil C_{18}, 5 µm, 8 x 250 mm, methylene chloride/isopropanol [99.5/0.5], H_2O saturated, 6 ml/minute, 300 nm, 3runs) yield the title compound; retention time: 4.6 minutes (educt: 19 minutes), EI-MS: 480 (M^+), 437, 420, 367, 351, 325.

Example 8: 3'-BOC-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one

In a 50 ml flask under argon equipped with a magnetic stirrer 33 µl of triethylamine and 58 mg of di-tert-butyl dicarbonate are added to 50mg of 3'-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one in 25 ml of methylene chloride. The reaction mixture is stirred under reflux for 4 hours. The mixture is adjusted to pH 2 with 2N HCl, 25 ml of methylene chloride and 5 ml of water are added and the aqueous phase is extracted twice with 25ml of

methylene chloride. The organic phases are combined and dried with a silicone folded filter. Removal of the solvent yields the title compound which can be used directly in the next Example. EI-MS: 566 (M^+), 466, 406, 353, 311.

Example 9: 3'-BOC-amino-3'-methoxycarbonyl-7-oxo-"cyclooctatrinden"-5-one

In a 250 ml round-bottom flask, 2.8 g of chromium trioxide-pyridine complex in 40 ml of CH_2Cl_2 are added at 4 °C to 60 mg of 3'-BOC-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one in 25 ml of methylene chloride and the mixture is stirred overnight. 100 ml of water are added to the mixture which is then extracted twice with 100 ml of methylene chloride. The combined organic phases are dried with a silicone folded filter. Removal of the solvent yields the title compound in the form of a yellow substance. EI-MS: 580 (M+), 480, 420, 351, 325.

Example 10: 3'-amino-3'-methoxycarbonyl-7-oxo-"cyclooctatrinden"-5-one

10 ml of TFA are added dropwise at 0 °C to 520 mg of 3'-BOC-amino-3'-methoxycarbonyl-7-oxo-"cyclooctatrinden"-1-one (Example 9) in 10 ml of methylene chloride. After 60 minutes, the reaction mixture is neutralised with 100ml of saturated Na_2CO_3 solution and is extracted twice with 100 ml of methylene chloride. The combined organic phases are dried with a silicone folded filter. Removal of the solvent yields the title compound.

Example 11: 3'-(BOC-glycylamino)-3'-methoxycarbonyl-"cyclooctatrinden"-5-one

23.2 mg of dicyclohexylcarbodiimide in 2 ml of methylene chloride are added to 54 mg of 3'-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one and 21.6 mg of BOC-glycine in 4 ml of methylene chloride. After stirring overnight at room temperature, the urea is removed by filtration and the filtrate is diluted with methylene chloride. The organic phase is washed with 1N HCl and saturated Na_2CO_3 solution and dried with a silicone folded filter, and the solvent is removed. Chromatography on silica gel (LiChroprep Si60, 15-25 µm; first methylene chloride, then methylene chloride / acetone 90:10, 50 ml column) yields the title compound. FAB-MS:623 (M+H), 524, 450, 406.

The NMR data of some of the compounds of formulal are indicated in Table1. The numbers follow that of staurosporin, assigning 1' to the oxygen.

Table 1: ^{1}H-NMR chemical shifts (in ppm)

Proton	Example1		Example 5		Example 6		Example 7		Example 12	
1	8.03*	d	8.04	d	8.08	d	7.98	d	7.90*	d
2	7.47	t	7.49	≈ t	7.49	m	7.52*	≈ t	7.48	t
3	7.27*	t	≈ 7.3*	m	7.28*	t	7.39*	t	7.27*	t
4	9.23	d	9.22	d	9.22	d	9.22	d	9.21	d
6	8.29	s br	8.65*	s br	8.70	s br	11.1	s br	8.61	d
7	4.98	≈ d	5.0	≈ d	5.02	≈ d			4.99	br,s
8	8.06*	d	7.88	d	8.16	d	9.01	d	8.03*	d
9	7.35*	t	≈7.4*	m	7.40*		7.60*	≈ t	7.35*	t
10	7.47	t	7.42	t	7.49	m	7.39*	t	7.46	t
11	7.83	d	7.86	d	7.92	d	8.13	d	8.08	d
2'-CH_3	2.15	s	2.66	s	2.26	s	2.10	s	2.16	s
3'-$COOCH_3$	3.92	s	3.80	s			3,89	s	3.93	s
3'-NH_2	2.10	s br					2.27	s		
3'-NH			8.47*	s br					2.44	q
4'a	3.36	dd	3.42	dd	3.47	m	3.36	dd	3.39	dd
4'b	2.04	dd	2.79	dd	2.15	dd	2.13	dd	2.03	dd
5'	7.07	dd	7.25	m	7.18	dd	7.13	dd	7.18	dd
C_6H_5COO			7.4-7.25							
CH_3-N									1.92	d

Solvent: DMSO-d_6. Allocations marked with an asterisk may be exchanged.

Example 12: 3'-methylamino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one

A solution of 233 mg of 3'-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one and 87 µl of trifluoroacetic anhydride in 2ml of dry pyridine is stirred for 2hours. After the addition of 100 ml of methylene chloride, the organic phase is washed in succession with 0.1 normal hydrochloric acid, cold, saturated potassium hydrogen carbonate solution and a small quantity of water and is dried with a silicone folded filter, and the solvent is removed. 50 µl of methyl iodide and 28 mg of potassium hydroxide are added to a solution of the resulting product in 5 ml of acetone and the mixture is stirred overnight. For hydrolysis, 1ml of aqueous 0.5 normal potassium hydroxide solution is added and stirring is continued for 30 minutes. After the addition of 100 ml of methylene chloride, the organic phase is washed

with water and dried with a silicone folded filter and the solvent is removed. HPLC chromatography (Nucleosil C_{18}, 5µm, 16 x 250 mm, eluant A: water, eluant B: acetonitrile/water [80/20], 70% B [isocratic], 10 ml/minute, 290 nm, 40 runs) yields the title compound; retention time: 23 minutes, m.p. 154-156°C.

Example 13: 3'- Ethoxycarbonylmethylcarbimidyl-3'-methoxycarbonyl-"cyclooctatrinden"-5-one

170 µl isocyanateaceticethylester and a catalytic amount of 4-dimethylaminopyridine are added to a solution consisting of 232 mg 3'-amino-3'-methoxycarbonyl-3-cyclooctatrien-5-one in 120 ml methylenechloride and 70 µl triethylamine. The resulting solution is stirred for two days at room temperature. Then the reagent is destroyed by addition of methanol. The solution is washed with a small quantity of aqueous NaCl solution and dried with a silicon coated filter. After removal of the solvent, the crude product is obtained which, upon chromatography on silica gel (LiChroprep Si60, 15-25 µm; 150 ml column; methylene chloride (indust.) / 2-propanol 98:2,), is eluted in the fractions from 400 ml to 800 ml. Removal of the solvent and recrystallisation from methanol yield the title compound of m.p. 205-206°C.

Example 14: Tablets each comprising 20mg of active ingredient (e.g. 3'-amino-3'- methoxy-carbonyl-"cyclooctatrinden"-5-one) are prepared in the customary manner, for example in the following composition:

Composition:

active ingredient	20 mg
wheat starch	60 mg
lactose	50 mg
colloidal silica	5 mg
talc	9 mg
magnesium stearate	1 mg
	145 mg

Preparation:

The active ingredient is mixed with a portion of the wheat starch, with lactose and colloidal silica and the mixture is forced through a sieve. A further portion of the wheat starch is made into a paste with 5 times the amount of water on a water bath and the powder mixture is kneaded with the paste until a slightly plastic mass is obtained.

The plastic mass is pressed through a sieve of about 3 mm mesh size and dried, and the resulting dry granules are forced through a sieve once more. Then, the remainder of the wheat starch, the talc and the magnesium stearate are admixed and the mixture is pressed to form tablets each weighing 145 mg and having a breaking notch.

Example 15: Tablets each comprising 1mg of active ingredient (e.g. 3'-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one) are prepared in the customary manner in the following composition:

Composition:

active ingredient	1 mg
wheat starch	60 mg
lactose	50 mg
colloidal silica	5 mg
talc	9 mg
magnesium stearate	1 mg
	126 mg

Preparation:

The active ingredient is mixed with a portion of the wheat starch, with lactose and colloidal silica and the mixture is forced through a sieve. A further portion of the wheat starch is made into a paste with 5 times the amount of water on a water bath and the powder mixture is kneaded with the paste until a slightly plastic mass is obtained.

The plastic mass is pressed through a sieve of about 3 mm mesh size and dried, and the resulting dry granules are forced through a sieve once more. Then, the remainder of the wheat starch, the talc and the magnesium stearate are admixed and the mixture is pressed to form tablets each weighing 126 mg and having a breaking notch.

Example 16: Capsules each comprising 10mg of active ingredient (e.g. 3'-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one) are prepared in the customary manner as follows:

Composition:

active ingredient	2500 mg
talc	200 mg
colloidal silica	50 mg

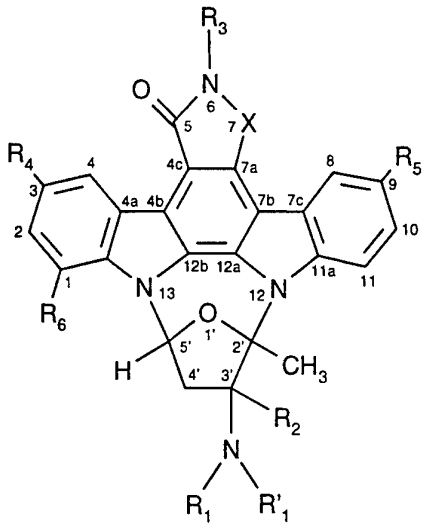
Preparation:

The active ingredient is homogeneously mixed with talc and colloidal silica, and the mixture is forced through a sieve of 0.5 mm mesh size and introduced in portions of 11 mg into hard gelatine capsules of a suitable size.

Example 17: It is also possible to prepare pharmaceutical compositions comprising as active ingredient another of the compounds of formulal described in Examples 1 to 13 instead of the compositions described in Examples 14 to 16.

What is claimed is:

1. A compound of the formula I



(I),

wherein X is methylene or carbonyl, R_1 is hydrogen, acyl or unsubstituted or substituted alkyl, R'_1 is hydrogen or lower alkyl, R_2 is carboxy or functionally modified carboxy, R_3 is hydrogen, halogen, amino, acyl, alkyl or aralkyl, R_4 and R_5 independent of each other are hydrogen, hydroxy, nitro, amino, lower alkyl, lower alkoxy, carbamoyl or halogen, and R_6 is hydrogen or nitro, and salts thereof.

2. A compound of formula I according to claim 1, wherein X is methylene or carbonyl, R_1 is hydrogen, acyl of the partial formula Z-C(=W)-, wherein W is oxygen or sulfur and Z is C_1-C_7alkyl which is unsubstituted or substituted by phenyl, phenyloxy, carboxy, cyano, C_1-C_4alkoxycarbonyl, amino and/or by halogen, phenyl which is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, nitro, trifluoromethyl, carboxy, C_1-C_4 alkoxycarbonyl, methylenedioxy and/or by cyano, C_1-C_{20}alkoxy, phenyloxy or benzyloxy each of which is unsubstituted or substituted by C_1-C_4alkyl, C_1-C_4alkoxy, halogen, nitro, trifluoromethyl, carboxy, C_1-C_4alkoxycarbonyl, methylenedioxy and/or by cyano,acyl of the partial formula $(R_7)(R_8)$N-C(=W)-, wherein W is sulfur or oxygen, R_7 is hydrogen and R_8 is C_1-C_7alkyl or phenyl each of which is unsubstituted or substituted by C_1-C_4 alkyl, C_1-C_4alkoxy, halogen, nitro, trifluoromethyl, carboxy, C_1-C_4alkoxycarbonyl, methylenedioxy and/or by cyano, or is an acyl radical derived from an α-amino acid selected from glycine, phenylglycine, alanine, phenylalanine, proline, leucine, isoleucine, serine, threonine, valine, tyrosine, arginine, histidine, lysine, glutamine, glutamic acid, aspartic acid and asparagine, in which the α-amino group is free or protected by an amino-protecting group and it being possible, in

corresponding amino acids having an additional carboxy group, for the carboxy group also to be esterified, or wherein R_1 is C_1-C_7alkyl, C_2-C_7hydroxyalkyl in which the hydroxy group is in any position other than the 1-position, cyano-[C_1-C_7]alkyl or carboxy-[C_1-C_7]alkyl in which the carboxy group is in the form of a C_1-C_4alkyl ester or a benzyl ester, R_2 is carboxy, alkoxycarbonyl, carbamoyl, cyano or esterified carboxy that can be cleaved under physio logical conditions, and R_3, R_4, R_5, and R_6 are defined as under formula I; or a salt thereof.

3. A compound of formula I according to claim 1, wherein X is methylene or carbonyl, $R_1$is hydrogen, acyl of the partial formula Z-C(=O)-, wherein Z is C_1-C_7alkyl which is unsubstituted or substituted by phenyl, phenyloxy, halogen, carboxy and/or by C_1-C_4 alkoxycarbonyl, or phenyl, C_1-C_7alkoxy or phenyloxy each of which is unsubstituted or is substituted by halogen, carboxy, C_1-C_4alkoxycarbonyl, C_1-C_4alkoxy, C_1-C_4alkyl and/or by nitro, or the acyl radical of a naturally occurring α-amino acid selected from glycine, alanine, serine and phenylalanine in which the amino group may be protected by an amino-protecting group, or wherein R_1 is C_1-C_4alkyl, cyano-C_1-C_4alkyl or carboxy- C_1-C_4alkyl, R_2 is carboxy or C_1-C_7alkoxycarbonyl, and R_3, R_4, R_5, and R_6 are defined as under formula I; or a salt thereof.

4. A compound of formula I according to claim 1, wherein X is methylene or carbonyl, $R_1$is hydrogen, benzoyl, C_1-C_4alkoxycarbonyl, or glycyl or L-alanyl in each of which the amino group may be protected by C_1-C_4alkoxycarbonyl, R_2 is carboxy or C_1-C_4 alkoxycarbonyl and R_3, R_4, R_5, and R_6 are defined as under formula I; or a salt thereof.

5. A compound of the formula I of any one of claims 1 to 4, wherein R_3, R_4, R_5, and R_6 are hydrogen.

6. A pharmaceutically acceptable salt of a compound of formula I according to claim 1.

7. A compound of the formula I according to claim1 or a pharmaceutically accept able salt thereof, selected from the group of compounds consisting of:
3'-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one;
3'-benzoylamino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one;
3'-amino-3'-carboxy-"cyclooctatrinden"-5-one;
3'-BOC-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one;
3'-(BOC-glycyl)-amino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one;
3'-amino-3'-methoxycarbonyl-7-oxo-"cyclooctatrinden"-5-one;
3'-BOC-amino-3'-methoxycarbonyl-7-oxo-"cyclooctatrinden"-5-one; and

3'-methylamino-3'-methoxycarbonyl-"cyclooctatrinden"-5-one.

8. A pharmaceutical composition comprising a compound of formulal or a pharmaceuti cally acceptable salt thereof according to any one of claims 1 to 7 together with a pharmaceutical carrier.

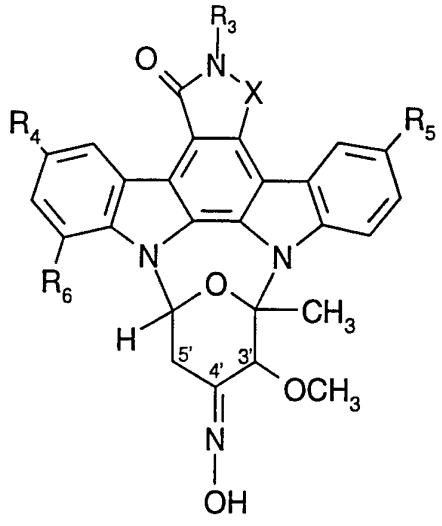
9. A compound of formula I or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 7 for use in a method for the therapeutic treatment of the human or animal body.

10. The use of a compound of formula I according to any one of claims 1 to 7 for the preparation of a pharmaceutical composition to be used for the inhibition of protein kinase C.

11. A method for the treatment of warm-blooded animals, including humans, suffering from abnormally increased cell proliferation, wherein a compound of formula I or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 7 is administered to such a warm-blooded animal at a dosage that retards said cell proliferation.

12. A method of suppressing the immune system of warm-blooded animals comprising administering to a warm-blooded animal in need of such treatment an immunosuppressing effective amount of a compound of the formula I or of a pharmaceutically acceptable salt thereof according to any one of claims 1 to 7.

13. A process for the preparation of a compound of formula I as defined in claim 1, which comprises subjecting a compound of formula II



(II),

wherein X is methylene or carbonyl, to the conditions of a Beckmann rearrangement and, if desired, converting a compound of formula I obtainable according to the process wherein R_1 is hydrogen, R_2 is methoxycarbonyl and R_3 is hydrogen, acyl, alkyl or aralkyl into a different compound of formula I, and/or separating a resulting mixture of diastereoisomeric compounds of formula I into the individual diastereoisomers, and/or converting a compound of formula I obtained in free form into a salt thereof or a compound of formula I obtained in the form of a salt into its free form or into a different salt.

14. A process according to claim 13 for the preparation of a compound of formula I, which comprises treating a compound of formula II with sulfuric acid, boron trifluoride or phosphoryl chloride.

15. A compound obtainable by the process according to claim 14.

INTERNATIONAL SEARCH REPORT

Inter ɔnal Application No
PCT/EP 96/03163

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D498/22 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,94 04541 (THE UPJOHN COMPANY) 3 March 1994 see abstract; claim 1 ---	1-10, 13-15
Y	EP,A,0 508 792 (SCHERING CORPORATION) 14 October 1992 see abstract; claim 1 ---	1-10, 13-15
Y	WO,A,95 07911 (CEPHALON INC.) 23 March 1995 see abstract; claim 1 ---	1-10, 13-15
Y	EP,A,0 643 966 (KYOWA HAKKO KOGYO KABUSHIKI KAISHA) 22 March 1995 see abstract; claim 1 ---	1-10, 13-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
8 November 1996	21.11.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Frelon, D

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INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/EP 96/03163

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE WPI Week 9526 Derwent Publications Ltd., London, GB; AN 95-196729 XP002018017 & JP,A,07 112 987 (ASAHI KASEI KOGYO KK) , 2 May 1995 see abstract -----	1-10, 13-15

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Inter ›nal Application No
PCT/EP 96/03163

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