

NOVEL TRIAZINE COMPOUNDS FOR THE TREATMENT OF CANCER

DESCRIPTION:

The present invention relates to novel triazene compounds, to a
5 process for their preparation, to pharmaceutical compositions
comprising them, and to the use thereof in the treatment of
cancer diseases in humans. The novel triazene compounds are
distinguished, as compared with the known triazene compounds,
by an improved therapeutic breadth, that is to say by fewer
10 side-effects with a high anti-tumour action.

INTRODUCTION:

Triazenes were thoroughly investigated in the 1970s for their
cytostatic activity and the resulting possibility of treating
15 cancer diseases. However, because of the considerable side-
effects and toxicity of these cytostatics, which belong to the
alkylating agents, they never became widely used for combating
tumours. One exception is dacarbazin (DTIC), which is a prodrug
of monomethyl-triazeno-imidazole-carboxamide (MTIC) and is used
20 mainly for combating melanomas (Montgomery JA (1976) Cancer
Treat Rep 60, 205-211).

Because of the sensitivity of dacarbazin to light and in
particular because of its side-effects, among which nausea,
25 vomiting and leuko- and thrombo-poenia are to be given special
mention, a large number of arylalkyltriazenes have been
synthesised with the aim of developing more potent and better
tolerated triazenes (Montgomery JA (1976) Cancer treatment
reports 60: 125-134; Spassova MK and Golovinsky EV (1985)
30 Pharmac Ther 27: 333-352; Derry E. V. Wilman and Phyllis M.
Goddard; J. Med. Chem. 1980. 23, 1052-1024). Despite these
efforts, dacarbazin and temozolomid (for the treatment of
glioblastomas) have hitherto remained the only triazenes or
triazene prodrug in clinical use.

THOMAS A. CONNORS, PHYLLIS M. GODDARD, KANTI MERAI, WALTER C. J. ROSS and DERRY E. V. WILMAN; Biochemical Pharmacology, Vol. 25. pp 241-246. Pergamon Press 1976 described the

5 structural requirements for an anti-tumour action. When the triazene-carrying group is an imidazole radical, the compounds are unstable and decompose spontaneously. If the imidazole radical is replaced by different groups, in particular by groups carrying aromatic compounds, the stability of the

10 triazenes increases without changing their activity. However, attempts at developing novel and therapeutically more active triazenes for tumour therapy by means of structure-action relationships have shown that differences in the anti-tumour action did not correlate with the physico-chemical properties

15 of aromatic triazene model compounds. A further difficulty was that alkylating agents having different properties are formed depending on substituents. No improvement in the therapeutic index was found within the tested compounds.

20 An approach for overcoming the problems of tolerability of selected triazenes has been described in DE 1793 115 and DE 2147 781. By the introduction of strongly polar functional groups it was possible to bring about a considerable improvement not only in the water solubility of triazene

25 derivatives but also in the rapid excretion of the substances. The typical side-effects mentioned above, in particular suppression of the blood-forming system, could be reduced considerably. However, the price of this was a considerable metabolic load on the excretory organs the liver and kidneys.

30 Because of tolerability problems on long-term administration, the tolerable dose range was limiting, so that the highly promising therapeutic potential of this class of compound could not be put into practice. Because such triazenes possess relatively high cytostatic activity, however, they would

nevertheless be valuable for combating tumours provided that the mentioned side-effects could be reduced or even eliminated.

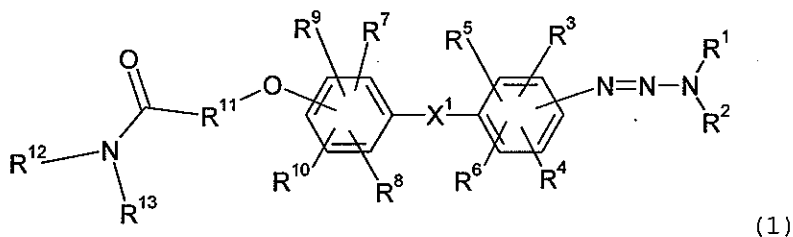
Further documents relating to triazenes, which are mentioned here for the sake of completeness, are the following: DE 1768720, WO91/17753 and WO2004/106258 A1 (which likewise relate to the use of triazene derivatives in the treatment of tumours), EP-A-0627325 (which relates to the use of triazenes as dyes), EP-A-0037948 and EP-A-0 071 901 (which relate to processes for the preparation of triazenyl compounds), and F. Schmidt et al.; J. Med. Chem. 1994, 37, 3812-3818 (which relates to the antineoplastic action of peptide-bonded 1,3-dialkyl-3-acyltriazenes).

15 OBJECT:

Accordingly, the object of the present invention was to find cytostatic triazene derivatives having reduced toxicity and improved activity, in order to make them available for therapy in humans, in particular for the therapy of cancer diseases in humans.

DESCRIPTION OF THE INVENTION

The inventors have found novel triazenyl compounds having high cytostatic activity and the toxicity of which is markedly reduced. The invention accordingly provides compounds of formula (1):



wherein

R^1 and R^2 are identical or different and are in each case selected from the group consisting of:

- optionally substituted alkyl,
- optionally substituted alkenyl,
- optionally substituted aryl,
- optionally substituted alkylaryl;

R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are identical or different and are in each case selected from the group consisting of:

- hydrogen,
- halogen,
- cyano,
- nitro,
- carboxyl,
- aminocarbonyl,
- sulfonic acid radical ($-SO_3H$),
- aminosulfonyl,
- optionally substituted alkyl,
- optionally substituted alkoxy,
- optionally substituted alkenyl,
- optionally substituted aryl,
- optionally substituted alkylaryl;

R^{11} is optionally substituted alkanediyl or optionally substituted alkenediyl;

R^{12} is hydrogen and R^{13} is optionally substituted alkyl or hydroxy, or

R^{13} is hydrogen and R^{12} is optionally substituted alkyl or hydroxy, or

R^{12} and R^{13} are each alkyl, wherein at least one of the alkyl groups has at least one substituent, or R^{12} and R^{13} , together with the nitrogen atom to which they are bonded, form a saturated or unsaturated, optionally substituted 5- to 8-membered ring which can optionally contain further heteroatoms; and

X^1 is selected from the group consisting of:

- a single bond,
- carbonyl,
- sulfur,
- oxygen,
- sulfoxy,
- sulfonyl,
- azo and
- an optionally substituted, saturated or unsaturated aliphatic divalent radical having from 1 to 6 carbon atoms,

or pharmaceutically acceptable salts thereof.

In the general formula (1), R^1 and R^2 are identical or different and are in each case selected from the group consisting of:

- optionally substituted alkyl,
- optionally substituted alkenyl,
- optionally substituted aryl and
- optionally substituted alkylaryl.

Within the scope of the invention as a whole, i.e. also in connection with the other groups of substituents (wherein further possibilities can be included where indicated, as in the case of R^{12} and R^{13}), optionally substituted alkyl

preferably includes:

Straight-chained or branched alkyl having from 1 to 8, preferably from 1 to 6, carbon atoms, cycloalkyl having from 3 to 8, preferably 5 or 6, carbon atoms, or alkyl having from 1 to 4 carbon atoms which is substituted by cycloalkyl, which in each case can optionally carry preferably from 1 to 3 substituents which are preferably selected from the group consisting of: hydroxy, halogen and cyano. Here and within the scope of the present invention, halogen includes fluorine, chlorine, bromine and iodine, preferably fluorine or chlorine. Furthermore, one or more, more preferably from 1 to 3, carbon atoms can be replaced by heteroanalogous groups containing nitrogen, oxygen or sulfur. This means in particular that, for example, one or more methylene groups in the alkyl radicals can be replaced by NH, O or S.

Examples of alkyl radicals having from 1 to 8 carbon atoms include: a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, an n-pentyl group, an isopentyl group, a sec-pentyl group, a tert-pentyl group, a 2-methylbutyl group, an n-hexyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 4-methylpentyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 3-ethylbutyl group, a 1,1-dimethylbutyl group, a 2,2-dimethylbutyl group, a 3,3-dimethylbutyl group, a 1-ethyl-1-methylpropyl group, an n-heptyl group, a 1-methylhexyl group, a 2-methylhexyl group, a 3-methylhexyl group, a 4-methylhexyl group, a 5-methylhexyl group, a 1-ethylpentyl group, a 2-ethylpentyl group, a 3-ethylpentyl group, a 4-ethylpentyl group, a 1,1-dimethylpentyl group, a 2,2-dimethylpentyl group, a 3,3-dimethylpentyl group, a 4,4-dimethylpentyl group, a 1-propylbutyl group, an n-octyl group, a 1-methylheptyl group, a 2-methylheptyl group, a 3-methylheptyl group, a 4-methylheptyl

group, a 5-methylheptyl group, a 6-methylheptyl group, a 1-ethylhexyl group, a 2-ethylhexyl group, a 3-ethylhexyl group, a 4-ethylhexyl group, a 5-ethylhexyl group, a 1,1-dimethylhexyl group, a 2,2-dimethylhexyl group, a 3,3-dimethylhexyl group, a 4,4-dimethylhexyl group, a 5,5-dimethylhexyl group, a 1-propylpentyl group, a 2-propylpentyl group, etc. Preference is given to those having from 1 to 6 carbon atoms, in particular methyl, ethyl and n-propyl. Methyl is most preferred.

10 Examples of alkyl groups which are formed by replacement with one or more heteroanalogous groups, such as -O-, -S- or -NH-, are preferably those in which one or more methylene groups have been replaced by -O- to form an ether group, such as methoxymethyl, ethoxymethyl, 2-methoxyethylene, etc. According
15 to the invention, polyether groups are also included in the definition of alkyl.

Cycloalkyl radicals having from 3 to 8 carbon atoms preferably include: a cyclopropyl group, a cyclobutyl group, a cyclopentyl
20 group, a cyclohexyl group, a cycloheptyl group, a cyclooctyl group, etc. Preference is given to a cyclopropyl group, a cyclobutyl group, a cyclopentyl group and a cyclohexyl group. Heterocyclic alkyl radicals which are formed from cycloalkyl by replacement of methylene by heteroanalogous groups are, for
25 example, 5- or 6-membered heterocyclic radicals, such as tetrahydrofuryl, pyrrolidinyl, piperidinyl or tetrahydropyranyl, which can optionally be fused with aromatic rings, etc.

30 Examples of a halo-substituted linear or branched alkyl radical having from 1 to 8 carbon atoms include in particular:
a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a chloromethyl group, a dichloromethyl group, a trichloromethyl group, a bromomethyl group, a dibromomethyl

group, a tribromomethyl group, a 1-fluoroethyl group, a 1-chloroethyl group, a 1-bromoethyl group, a 2-fluoroethyl group, a 2-chloroethyl group, a 2-bromoethyl group, a 1,2-difluoroethyl group, a 1,2-dichloroethyl group, a 1,2-dibromoethyl group, a 2,2,2-trifluoroethyl group, a heptafluoroethyl group, a 1-fluoropropyl group, a 1-chloropropyl group, a 1-bromopropyl group, a 2-fluoropropyl group, a 2-chloropropyl group, a 2-bromopropyl group, a 3-fluoropropyl group, a 3-chloropropyl group, a 3-bromopropyl group, a 1,2-difluoropropyl group, a 1,2-dichloropropyl group, a 1,2-dibromopropyl group, a 2,3-difluoropropyl group, a 2,3-dichloropropyl group, a 2,3-dibromopropyl group, a 3,3,3-trifluoropropyl group, a 2,2,3,3,3-pentafluoropropyl group, a 2-fluorobutyl group, a 2-chlorobutyl group, a 2-bromobutyl group, a 4-fluorobutyl group, a 4-chlorobutyl group, a 4-bromobutyl group, a 4,4,4-trifluorobutyl group, a 2,2,3,3,4,4,4-heptafluorobutyl group, a perfluorobutyl group, a 2-fluoropentyl group, a 2-chloropentyl group, a 2-bromopentyl group, a 5-fluoropentyl group, a 5-chloropentyl group, a 5-bromopentyl group, a perfluoropentyl group, a 2-fluorohexyl group, a 2-chlorohexyl group, a 2-bromohexyl group, a 6-fluorohexyl group, a 6-chlorohexyl group, a 6-bromohexyl group, a perfluorohexyl group, a 2-fluoroheptyl group, a 2-chloroheptyl group, a 2-bromoheptyl group, a 7-fluoroheptyl group, a 7-chloroheptyl group, a 7-bromoheptyl group, a perfluoroheptyl group, etc.

Examples of a hydroxy-substituted alkyl radical include the above-mentioned alkyl radicals with from 1 to 3 hydroxy radicals, such as, for example, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, etc.

Within the scope of the invention as a whole, optionally substituted alkenyl preferably includes:

Straight-chained or branched-chained alkenyl having from 2 to 8

carbon atoms and cycloalkenyl having from 3 to 8 carbon atoms, which can optionally be substituted by preferably from 1 to 3 substituents, such as hydroxy, halogen or alkoxy. Examples include: vinyl, 1-methylvinyl, allyl, 1-butenyl, isopropenyl, 5 cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl. Vinyl or allyl are preferred.

Within the scope of the invention as a whole, optionally substituted aryl preferably includes:

10 Aromatic hydrocarbon radicals having from 6 to 14 carbon atoms (wherein the carbon atoms of the substituents are not included) and 5- to 10-membered aromatic heterocyclic radicals having up to 3 heteroatoms from the group S, O, N, which can be mono- or bi-cyclic and which can be substituted by preferably from 1 to 15 3 substituents selected from hydroxy, halogen, cyano, alkyl, acyl and alkoxy. With regard to the definition of alkyl and halogen, reference may be made to the definitions and examples hereinbefore.

Here and in the following, alkoxy as a substituent of aryl 20 includes, for example: An alkyl radical mentioned hereinbefore which is bonded to aryl via an oxygen atom, such as a linear or branched alkoxy radical having up to 6 carbon atoms, such as a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, an isobutoxy group, a sec- 25 butoxy group, a tert-butoxy group, an n-pentoxy group, an isopentoxy group, a sec-pentoxy group, a tert-pentoxy group, a 2-methylbutoxy group, an n-hexyloxy group, an isohexyloxy group, a tert-hexyloxy group, a sec-hexyloxy group, a 2-methylpentoxy group, a 3-methylpentoxy group, a 1-ethylbutoxy 30 group, a 2-ethylbutoxy group, a 1,1-dimethylbutoxy group, a 2,2-dimethylbutoxy group, a 3,3-dimethylbutoxy group, a 1-ethyl-1-methylpropoxy group, etc. Preference is given to a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, an isobutoxy group, a sec-

butoxy group, a tert-butoxy group, etc.

Here and in the following, acyl as a substituent of aryl includes: aliphatic acyl, aromatic acyl, such as C1 to C6 alkanoyl, such as formyl, acetyl, propionyl, butyryl, 5 isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc., and also C6 to C10 aroyl, such as benzoyl, toluoyl, xyloyl, etc.

Aromatic hydrocarbon radicals having from 6 to 14 carbon atoms include, for example: phenyl, naphthyl, phenanthrenyl and 10 anthracenyl, which can optionally be substituted. Phenyl is preferred.

Heteroaromatic radicals include, for example: pyridyl, pyridyl N-oxide, pyrimidyl, pyridazinyl, pyrazinyl, thienyl, furyl, 15 pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl or isoxazolyl, indoliziny, indolyl, benzo(b)thienyl, benzo(b)-furyl, indazolyl, quinolyl, isoquinolyl, naphthyridinyl, quinazolinyl. Preference is given to 5- or 6-membered aromatic heterocycles such as, for example, pyridyl, pyridyl N-oxide, 20 pyrimidyl, pyridazinyl, furyl and thienyl.

Within the scope of the invention as a whole, optionally substituted alkylaryl preferably includes:

Straight-chained or branched alkyl having from 1 to 8, 25 preferably from 1 to 4, carbon atoms, as described above, which is substituted with aryl, as described above. The preferred arylalkyl is benzyl.

Particularly preferably, R^1 and R^2 are in each case alkyl and 30 are preferably identical (preferred) or different and in each case straight-chained or branched alkyl having from 1 to 6, preferably from 1 to 4, more preferably from 1 to 3, carbon atoms, preference being given to linear alkyl. R^1 and R^2 are preferably methyl or ethyl. R^1 and R^2 are most preferably

methyl.

In the general formula (1), R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are identical or different and are in each case selected from the

5 group consisting of:

- hydrogen,
- halogen,
- cyano,
- nitro,
- 10 - carboxyl,
- aminocarbonyl,
- sulfonic acid ($-\text{SO}_3\text{H}$),
- aminosulfonyl,
- optionally substituted alkyl,
- 15 - optionally substituted alkoxy,
- optionally substituted alkenyl,
- optionally substituted aryl,
- optionally substituted alkylaryl.

20 With regard to the definition of said substituents and their preferred meanings, reference may be made to the comments made above in respect of the corresponding substituents in connection with the definition of R^1 and R^2 . In addition, within the scope of the invention as a whole, aminocarbonyl
25 preferably represents carbamoyl ($\text{H}_2\text{NCO}-$) or mono- or di-alkylaminocarbonyl ($\text{H}(\text{alkyl})\text{NCO}-$ or $(\text{alkyl})_2\text{NCO}-$), wherein, with regard to the definition of alkyl, reference may be made to the comments made above and optionally substituted alkyl is also included. Furthermore, aminosulfonyl within the scope of
30 the invention as a whole represents in particular sulfamoyl ($\text{H}_2\text{N}-\text{SO}_2-$) or mono- or di-alkylaminosulfonyl $(\text{alkyl})_2\text{N}-\text{SO}_2$, wherein, with regard to the definition of alkyl, reference may be made to the comments made above and optionally substituted

alkyl is also included. Optionally substituted alkoxy includes alkoxy as exemplified above as a substituent of aryl, which can optionally be substituted by preferably from 1 to 3 substituents which are preferably selected from the group
5 halogen, hydroxy and cyano.

Preferably, R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are selected from:

- hydrogen,
- halogen,
- 10 - cyano,
- nitro,
- carboxyl,
- aminocarbonyl,
- sulfonic acid ($-SO_3H$),
- 15 - aminosulfonyl,
- optionally substituted alkyl and
- optionally substituted alkoxy.

More preferably, R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are selected
20 from:

- hydrogen,
- halogen and
- optionally substituted alkoxy.

25 Preferably at least 6, more preferably at least 7, of the radicals R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} represent hydrogen. Most preferably, all the radicals R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} represent hydrogen.

30 R^{11} in the general formula (1) is optionally substituted alkanediyl or optionally substituted alkenediyl. Optionally substituted alkanediyl is preferably a divalent straight-chained or branched alkanediyl radical having from 1 to 7,

preferably from 1 to 6, more preferably from 1 to 4, carbon atoms, which can optionally carry from 1 to 3 substituents selected from the group consisting of hydroxy, halogen and cyano. The following may be mentioned as preferred examples:

5 methylene, 1,2-ethanediyl, ethane-1,1-diyl, 1,3-propylene, propane-1,1-diyl, propane-1,2-diyl, propane-2,2-diyl, 1,4-butylene, butane-1,2-diyl, butane-1,3-diyl, butane-2,3-diyl, pentane-1,5-diyl, pentane-2,4-diyl, 3-methyl-pentane-2,4-diyl and hexane-1,6-diyl. A preferred substituted alkanediyl radical

10 is a hydroxy-substituted alkanediyl radical. Optionally substituted alkenediyl is preferably a divalent straight-chained or branched alkenediyl radical having from 2 to 7, more preferably from 2 to 6, still more preferably from 2 to 4, carbon atoms, which can optionally carry from 1 to 3

15 substituents selected from the group consisting of hydroxy, halogen and cyano. The following may be mentioned as preferred examples: ethene-1,1-diyl, ethene-1,2-diyl, propene-1,1-diyl, propene-1,2-diyl, propene-1,3-diyl, but-1-ene-1,4-diyl, but-1-ene-1,3-diyl, but-2-ene-1,4-diyl, buta-1,3-diene-1,4-diyl,

20 pent-2-ene-1,5-diyl, hex-3-ene-1,6-diyl and hexa-2,4-diene-1,6-diyl.

Within the scope of the present invention, R^{11} is particularly preferably alkanediyl, more preferably alkanediyl having from 1

25 to 3 carbon atoms, still more preferably 1,2-ethanediyl ($-\text{CH}_2\text{CH}_2-$) or 1,3-propanediyl ($-\text{CH}_2\text{CH}_2\text{CH}_2-$). R^{11} is most preferably 1,2-ethanediyl ($-\text{CH}_2\text{CH}_2-$).

In the general formula (1), X^1 is selected from the group

30 consisting of:

- a single bond,
- carbonyl ($-\text{CO}-$),
- sulfur ($-\text{S}-$),
- oxygen ($-\text{O}-$),

- sulfoxy (-SO-),
 - sulfonyl (-SO₂-),
 - azo (-N=N-) and
 - an optionally substituted, saturated or unsaturated
- 5 aliphatic radical having from 1 to 6 carbon atoms.

Within the scope of the present invention, an optionally substituted, saturated or unsaturated aliphatic radical having from 1 to 6 carbon atoms for X¹ includes: optionally

10 substituted alkanediyl as defined above, optionally substituted alkenediyl as defined above, and alkynediyl. X¹ is preferably alkanediyl, alkenediyl or alkynediyl having up to 4, having up to 2 carbon atoms, such as methylene (-CH₂-), which can optionally be substituted by hydroxyl (such as, for example, -

15 CH(OH)-).

Compounds of the general formula (1) in which X¹ is carbonyl (-CO-) are most preferred.

20 Within the scope of the present invention, the groups R¹² and R¹³ in the general formula (1) are selected from the following alternatives:

- 1) R¹² is hydrogen and R¹³ is optionally substituted alkyl or
- 25 hydroxyl, or
- R¹³ is hydrogen and R¹² is optionally substituted alkyl or hydroxyl.

The alternatives mentioned under 1) are equivalent. They

30 correspond to the case in which one substituent of R¹² or R¹³ is hydrogen and the other substituent is optionally substituted alkyl or hydroxyl.

- 2) R¹² and R¹³ are each alkyl, wherein at least one of the

alkyl groups has at least one substituent, that is to say R^{12} and R^{13} are substituted alkyl, or

- 3) R^{12} and R^{13} , together with the nitrogen atom to which they are bonded, form a saturated or unsaturated, optionally substituted 5- to 8-membered ring which can optionally contain further heteroatoms.

Alternative 1):

- 10 Alternative 1) mentioned hereinbefore is a preferred alternative within the scope of the present invention. More preferably, within the scope of this alternative:

- R^{12} is hydrogen and R^{13} is substituted alkyl, or
15 R^{13} is hydrogen and R^{12} is substituted alkyl.

- Alkyl here includes straight-chained or branched alkyl having from 1 to 8, preferably from 1 to 6, carbon atoms, cycloalkyl having from 3 to 8, preferably 5 or 6, carbon atoms, or alkyl
20 having from 1 to 4 carbon atoms which is substituted by cycloalkyl. With regard to possible examples of alkyl, reference may be made to the examples mentioned above for R^1 and R^2 . Particularly preferably, alkyl is here a C1 to C6, preferably C1 to C5, alkyl group which can be branched or
25 straight-chained, such as in particular methyl, ethyl, propyl, 2-methylpropane, butyl, such as n-butyl, 2-methylbutyl, 3-methylbutyl, pentyl, such as n-pentyl, or n-hexyl. Said alkyl groups are substituted by at least one substituent. Preferred substituents of alkyl are polar functional groups containing
30 one or more heteroatoms, which are preferably selected from: N, O, S, halogen, such as Cl, F, Br and I. In the definition of R^{12} and R^{13} , substituents of alkyl include in particular:

A group of the formula:

$-X^2-R^{14}$, wherein

X^2 is selected from the group consisting of:

- 5 - carbonyl,
- sulfoxy and
- sulfonyl, and

R^{14} is selected from the group consisting of:

- hydroxy,
- 10 - optionally substituted amino and
- optionally substituted alkoxy.

Preferably, X^2 is carbonyl and R^{14} is hydroxy.

When R^{14} is hydroxy, the substituent group $-X^2R^{14}$ is carboxy.

- 15 When R^{14} is optionally substituted amino, the substituent group $-X^2R^{14}$ is, for example, $-CONH_2$, that is to say carbamoyl in the case of R^{14} = amino, or $-X^2R^{14}$ = mono- or di-alkylaminocarbonyl in the case of R^{14} = alkylamino or dialkylamino. When R^{14} is optionally substituted alkoxy, the substituent group $-X^2R^{14}$ is,
- 20 for example, alkoxycarbonyl in the case of R^{14} = alkoxy, that is to say an ester group. Substituents of alkyl in the definition of R^{12} and R^{13} preferably contain at least one group, preferably one or two groups, of the formula $-X^2R^{14}$.

- 25 In addition to the group $-X^2R^{14}$ that is preferably present, further preferred substituents of alkyl in the definition of R^{12} and R^{13} include the following substituents:

- guanidino,
- 30 - thiol (-SH),
- alkylthio, such as in particular methylthio,
- amino ($-NH_2$),
- mono- or di-alkylamino,

- acylamino, wherein acyl is in particular as defined above,
- saturated, unsaturated or aromatic, mono- or bi-cyclic, optionally substituted heterocyclic radicals, such as, for example, the optionally substituted heteroaromatic radicals mentioned hereinbefore, preferably imidazolyl, such as imidazol-5-yl, 1H-indolyl, such as 1H-indol-3-yl,
- optionally substituted aryl, as described above, in particular phenyl, hydroxyphenyl, such as 4-hydroxyphenyl, alkoxyphenyl, such as methoxyphenyl,
- hydroxyl,
- alkoxy, as described hereinbefore.

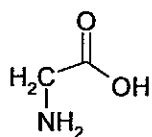
15 Alkyl in the definition of R^{12} and R^{13} preferably has one or two substituents, of which preferably at least one substituent is the group $-X^2R^{14}$.

In a preferred form of alternative 1) mentioned hereinbefore:

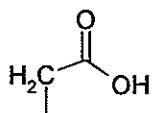
20 R^{12} is hydrogen and R^{13} is a radical A of a compound of the formula H_2N-A , or
 R^{13} is hydrogen and R^{12} is a radical A of a compound of the formula H_2N-A , wherein
25 A is a radical which is derived formally by cleavage of an amino group ($-NH_2$) from a natural or synthetic amino acid, a natural or synthetic amino acid derivative or a polyamino acid or polyamino acid derivative.

30 For the purposes of illustration:

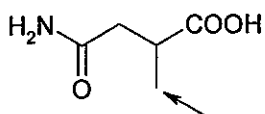
If the amino acid H_2N-A is, for example, glycine:



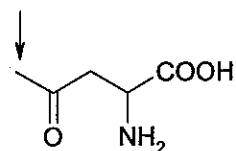
, then $A = R^{12}$ or R^{13} is a radical of the formula:



- 5 More preferred are compounds according to the invention wherein A is the radical derived formally by cleavage of the amino group from an amino acid or amino acid derivative (for clarification: The formal cleavage of the amino group from an amino acid does not mean the cleavage of an amino group from an amide group (H_2N-CO-) that is optionally present but of an amino group bonded to a carbon atom that does not carry further substituents other than H or C. That is to say, the corresponding radical R^{12} or R^{13} formed by cleavage of an amino group from asparagine would be:



(the arrow denotes the binding site) and not:

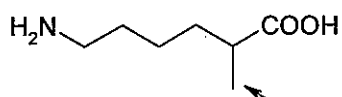


(the arrow denotes the binding site)).

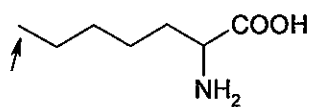
- 20 Still more preferably, the radical A is formed from the cleavage of a H_2N group from the group of the following amino acids:

- alanine, corresponding to the case where R^{12} or R^{13} is ethyl substituted by carboxy,

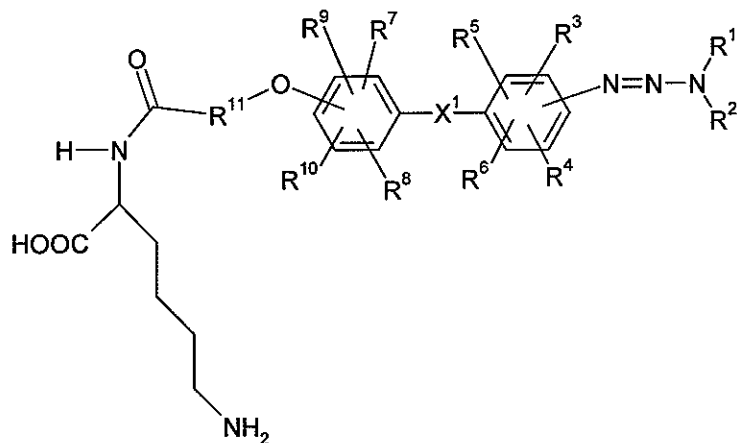
- arginine (less preferred), corresponding to the case where R^{12} or R^{13} is butyl substituted by carboxy and guanidino,
- asparagine, corresponding to the case where R^{12} or R^{13} is ethyl substituted by aminocarbonyl (carbamoyl) and carboxy,
- 5 - aspartic acid, corresponding to the case where R^{12} or R^{13} is ethyl substituted by two carboxy groups,
- cysteine (less preferred), corresponding to the case where R^{12} or R^{13} is ethyl substituted by thio (-SH) and carboxy,
- 10 - glutamine, corresponding to the case where R^{12} or R^{13} is propyl substituted by aminocarbonyl (carbamoyl) and carboxy,
- glutamic acid, corresponding to the case where R^{12} or R^{13} is propyl substituted by two carboxy groups,
- 15 - glycine, corresponding to the case where R^{12} or R^{13} is methyl substituted by carboxy,
- histidine, corresponding to the case where R^{12} or R^{13} is ethyl substituted by carboxy and imidazolyl,
- isoleucine, corresponding to the case where R^{12} or R^{13} is 2-methylbutyl substituted by carboxy,
- 20 - leucine, corresponding to the case where R^{12} or R^{13} is 3-methylbutyl substituted by carboxy,
- lysine, corresponding to the case where R^{12} or R^{13} is n-pentyl substituted by carboxy and amino, wherein binding
- 25 can take place via the amino group adjacent to the carboxyl group:



(arrow indicates the bond line or binding site) or via the terminal amino group:

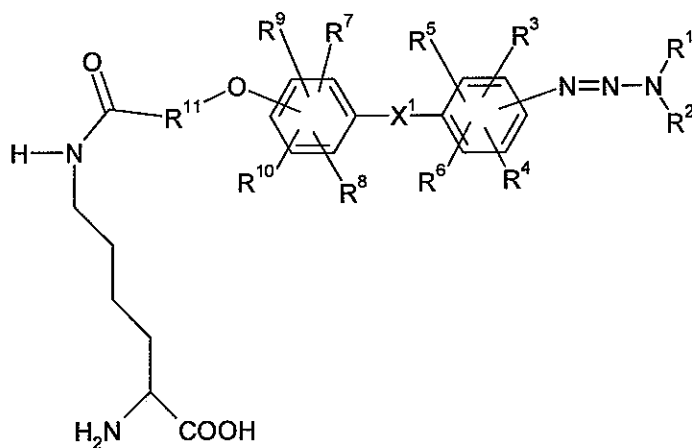


(arrow indicates the bond line or binding site), so that the corresponding compounds of formula (1) look like this:



5

or



10

(this applies analogously to other basic amino acids having more than one amino group),

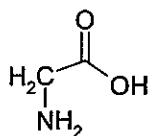
- methionine, corresponding to the case where R^{12} or R^{13} is n-propyl substituted by carboxy and methylthio,

- phenylalanine, corresponding to the case where R^{12} or R^{13} is ethyl substituted by carboxy and phenyl,
 - serine, corresponding to the case where R^{12} or R^{13} is ethyl substituted by carboxy and hydroxy,
 - 5 - threonine, corresponding to the case where R^{12} or R^{13} is n-propyl substituted by carboxy and hydroxy,
 - tryptophan, corresponding to the case where R^{12} or R^{13} is ethyl substituted by carboxy and indolyl,
 - tyrosine, corresponding to the case where R^{12} or R^{13} is ethyl substituted by carboxy and hydroxyphenyl, and
 - 10 - valine, corresponding to the case where R^{12} or R^{13} is 2-methylpropyl substituted by carboxy,
- or derivatives, such as in particular esters or amides, thereof, corresponding to the case where R^{14} is alkoxy or
- 15 optionally substituted amino, or derivatives or polyamino acids thereof, which are formed by peptidic linking with one or more further amino acids to the amino acids mentioned hereinbefore or hereinafter.
- 20 Further amino acid compounds, or derivatives thereof, from which a radical R^{12} or R^{13} is formed formally by cleavage of an amino group include: creatine (less preferred), creatinine, taurine, or derivatives or polyamino acids thereof, which are formed by peptidic linking with one or more further amino acids
- 25 to the amino acids mentioned hereinbefore or hereinafter. Also included are so-called non-proteinogenic amino acids, such as, for example: 4-aminobutyric acid (GABA), L-homoserine (2-amino-4-hydroxybutyric acid), ornithine (2,5-diaminovaleric acid), L-(+)-citrulline (N5-(aminocarbonyl)-L-ornithine), 5-
- 30 hydroxytryptophan (5-HTP), β -alanine (3-aminopropionic acid), β -methylamino-alanine, D-valine, D-alanine, D-glutamic acid and 2,6-diaminopimelic acid.

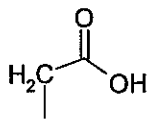
The derivatives of the above-mentioned amino acid compounds H_2N-A are in particular those which have been formed by replacement of a hydrogen atom by a hydroxyl function.

5 Very preferred are compounds according to the invention wherein the radical A is derived formally by cleavage of the H_2N group from the group of the amino acids glycine and its derivatives and histidine and its derivatives.

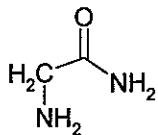
10 Most preferred are compounds according to the invention wherein the radical A is derived by cleavage of the H_2N group from the group of the following amino acids or amino acid derivatives: glycine:



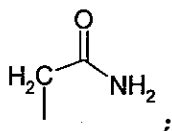
15 corresponding to R^{12} or $R^{13} =$



glycineamide:

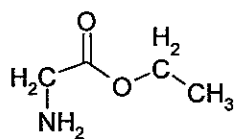


(2-amino-acetamide), corresponding to R^{12} or $R^{13} =$

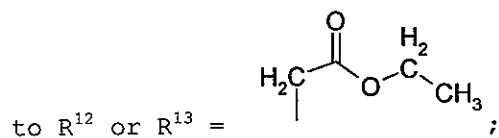


20

glycine ethyl ester:

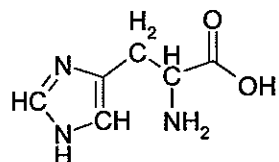


(amino-acetic acid ethyl ester), corresponding

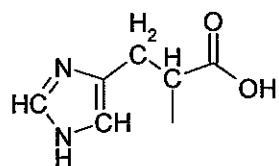


histidine:

5

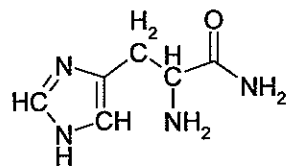


corresponding to R^{12} or $\text{R}^{13} =$



10 ;

or histidineamide:



(2-amino-3-(1H-imidazol-4-yl)-propionamide),

15

corresponding to R^{12} or $\text{R}^{13} =$

Alternative 2:

In alternative 2) mentioned hereinbefore, wherein R^{12} and R^{13} are each alkyl, wherein at least one of the alkyl groups has at least one substituent, preferably one or two substituents, reference may be made with regard to the definitions and examples of alkyl to those given above for R^1 or R^2 or for R^{12} and R^{13} in alternative 1). Substituents of alkyl accordingly include examples given for "optionally substituted alkyl" in the definition of R^1 and R^2 , such as hydroxy, halogen and cyano. In addition, possible substituents of alkyl in alternative 2) also include the examples given for R^{12} and R^{13} in alternative 1) described hereinbefore, such as

- guanidino,
- thiol (-SH),
- alkylthio, such as in particular methylthio,
- amino (-NH₂),
- mono- or di-alkylamino,
- acylamino, wherein acyl is in particular as defined above,
- saturated, unsaturated or aromatic, mono- or bi-cyclic, optionally substituted heterocyclic radicals, such as, for example, the above-mentioned optionally substituted heteroaromatic radicals, preferably imidazolyl, such as imidazol-5-yl, 1H-indolyl, such as 1H-indol-3-yl,
- optionally substituted aryl, as described above, in particular phenyl, hydroxyphenyl, such as 4-hydroxyphenyl, alkoxyphenyl, such as methoxyphenyl,
- hydroxy,
- alkoxy, as described hereinbefore, and
- a group of the formula:
 $-X^2-R^{14}$, wherein X^2 and R^{14} are as defined above,

and, in particular, also the radicals which result formally from the cleavage of the NH_2 group from the amino acids $\text{NH}_2\text{-A}$.

Alternative 3):

5 In alternative 3) mentioned hereinbefore, wherein R^{12} and R^{13} , together with the nitrogen atom to which they are bonded, form a saturated or unsaturated, optionally substituted 5- to 8-membered ring which can optionally contain further heteroatoms, possible ring systems consisting of R^{12} and R^{13} and the nitrogen
10 atom to which they are bonded preferably include 5- or 6-membered, optionally substituted rings, such as piperidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, pyrrolidin-1-yl, oxazolidin-3-yl, thiazolidin-3-yl, 2-carboxyl-pyrrolidin-1-yl (prolyl), 3- or 4-hydroxy-carboxyl-pyrrolidin-1-yl (3- or 4-
15 hydroxy-prolyl), etc. Prolyl and hydroxy-prolyl are particularly preferred.

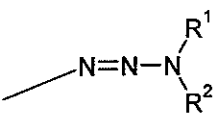
Triazene compounds that are particularly preferred according to the invention are those wherein R^1 and R^2 are in each case
20 alkyl, preferably alkyl having from 1 to 6 carbon atoms, particularly preferably methyl.

Triazene compounds that are particularly preferred according to the invention are those wherein R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10}
25 are in each case hydrogen.

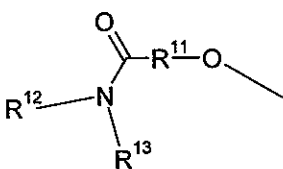
Triazene compounds that are particularly preferred according to the invention are those wherein X^1 is carbonyl.

30 Triazene compounds that are particularly preferred according to the invention are those wherein R^{11} is alkanediyl, preferably linear alkanediyl having from 1 to 6 carbon atoms, particularly preferably methylene ($-\text{CH}_2-$) or ethane-1,2-diyl.

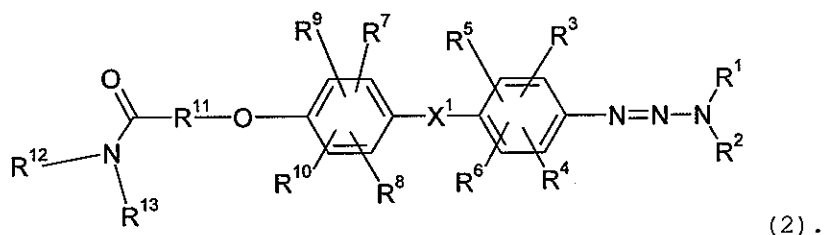
Triazene compounds that are particularly preferred according to the invention are those wherein the radicals

X¹ and the radical  on the phenylene radical are in the para-position relative to one another.

Triazene compounds that are particularly preferred according to the invention are those wherein the radicals

X¹ and the radical  on the phenylene radical are in the para-position relative to one another.

Particular preference is given according to the invention to compounds of formula (2):



Particular preference is given according to the invention to compounds of formula (1) or (2) wherein

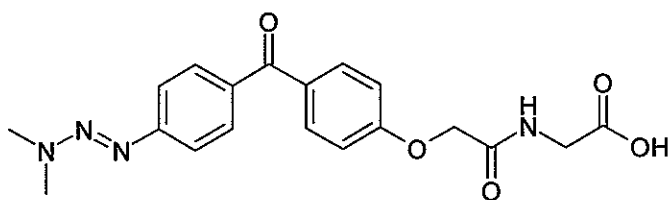
R¹ and R² are in each case alkyl,
 R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ are in each case hydrogen,
 R¹¹ is alkanediyl,
 R¹² is hydrogen and R¹³ is a radical A of a compound of the

formula H_2N-A or

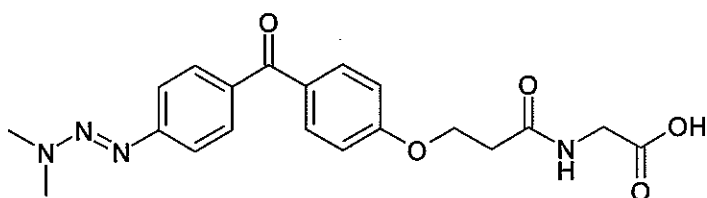
R^{13} is hydrogen and R^{12} is a radical A of a compound of the formula H_2N-A , wherein

A is a radical derived by cleavage of the amino group
5 $(-NH_2)$ from a natural or synthetic amino acid, a
natural or synthetic amino acid derivative or a
polyamino acid or polyamino acid derivative, and
 X^1 is carbonyl $(-CO-)$.

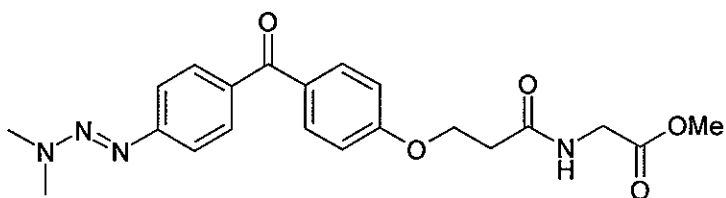
10 Most preferred are compounds selected from the group consisting
of:



(Example 4)

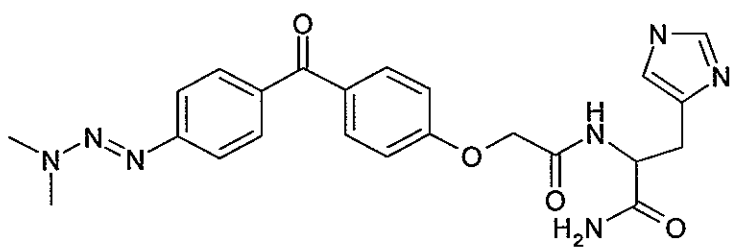


(Example 2)

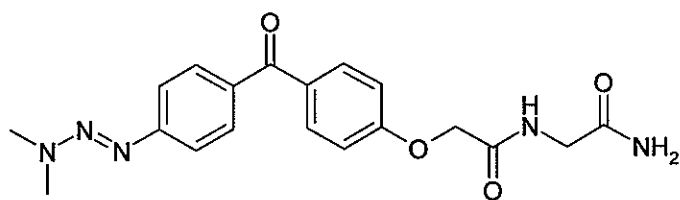


(Example 1)

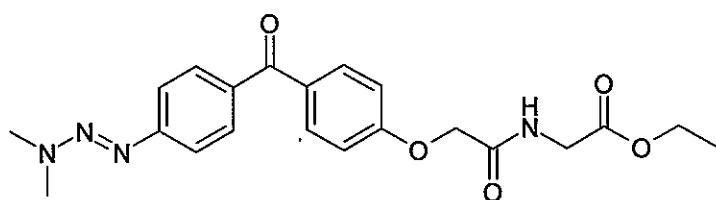
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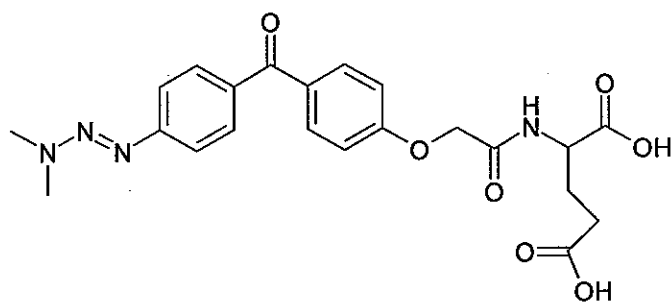
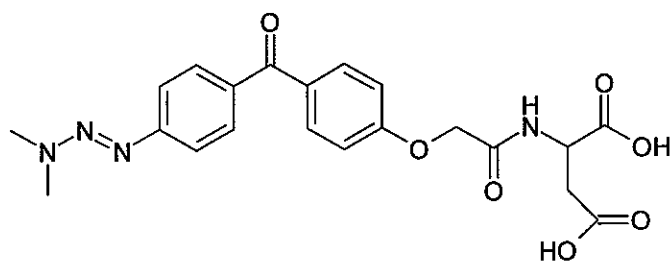
(Example 5)

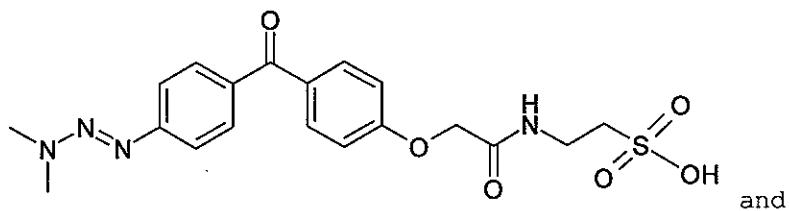


(Example 6)

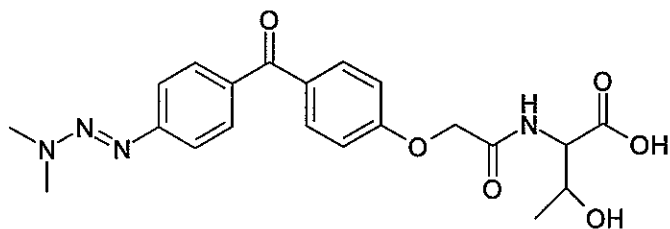


(Example 3)





and

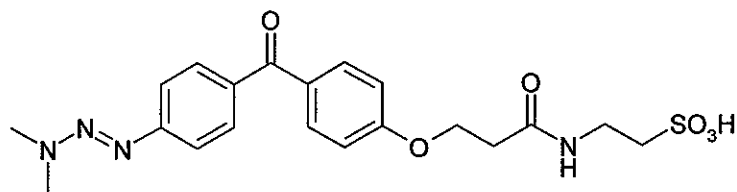


5

or pharmaceutically acceptable salts thereof.

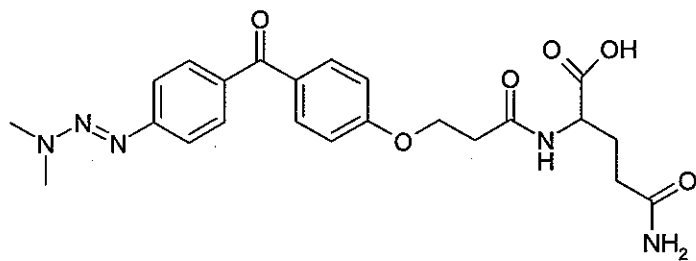
The preferred compounds further include the following compounds:

10



(free acid of

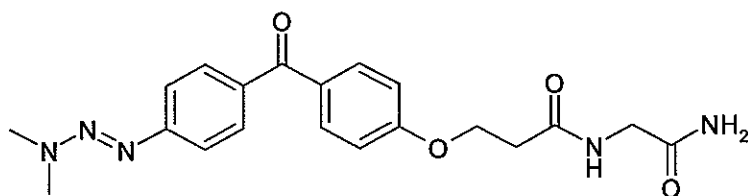
Example 9),



(free acid

of Example 7) and

15



(Example 8)

and their pharmaceutically acceptable salts.

5 (In these structural formulae, a structural element of the

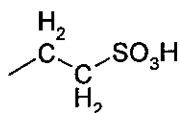
formula , for example, denotes a dimethylamino group, that is to say the methyl groups are represented by single lines, a notation which is well known to the person skilled in the art.

Analogously,  represents an abbreviated notation for a
10 methylene radical (-CH₂-).

Preference is further given according to the invention to compounds of formula (1) wherein

15 R¹² is hydrogen and R¹³ is substituted alkyl, or
R¹³ is hydrogen and R¹² is substituted alkyl, wherein

substituted alkyl is an alkyl group having at least one
sulfonic acid radical, sulfonic acid ester radical or
20 sulfonamido radical. Particular preference is given in this connection to compounds in which substituted alkyl in the definition of R¹² or R¹³ is a radical of the formula:



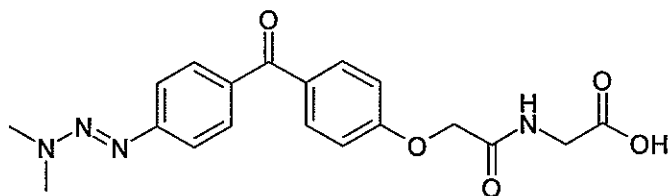
which is derived from taurine (2-aminoethane-
25 sulfonic acid).

Triazene compounds according to the invention that contain basic groups can be used in the form of their pharmaceutically acceptable salts with pharmaceutically acceptable acids, such as, for example, salts with mineral acids, carboxylic acids and sulfonic acids, such as, for example, with hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, phosphoric acid, tartaric acid, methanesulfonic acid, hydroxyethanesulfonic acid, aceturic acid (acetylglycine), maleic acid, propionic acid, fumaric acid, toluenesulfonic acid, benzenesulfonic acid, trifluoroacetic acid, naphthalene-1,5-disulfonic acid, salicylic acid, benzoic acid, lactic acid, malic acid, 3-hydroxy-2-naphthoic acid, citric acid or acetic acid.

Triazene compounds according to the invention that contain acidic groups can be used in the form of their pharmaceutically acceptable salts with pharmaceutically acceptable bases, such as, for example, salts with alkali or alkaline earth hydroxides, such as NaOH, KOH, Ca(OH)₂, Mg(OH)₂, etc., amine compounds, such as ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, ethanolamine, diethanolamine, triethanolamine, methylglucamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, arginine, lysine, ethylenediamine, N-methylpiperidine, 2-amino-2-methyl-1-propanol, 2-amino-2-methyl-1,3-propanediol, 2-amino-2-hydroxyl-methyl-1,3-propanediol (TRIS), etc.

The water solubility, or the solubility in physiological saline, and accordingly optionally also the activity, of the compounds according to the invention can be influenced significantly by salt formation in general, specifically also

by the choice of counter-ion. For example, the sodium salt of the compound



5

(Example 4a) has a solubility in water at 25°C of about 4 g/litre, whereas the TRIS salt has a solubility in water at 25°C of about 250 g/litre.

10 However, the water solubility, or the solubility in physiological saline, and accordingly optionally also the activity, of the compounds according to the invention is also significantly dependent under certain circumstances on the basic structure of the compounds themselves. For example, the
15 compound of Example 2a) surprisingly has very good water solubility of 500 g/litre at room temperature (25°C), which is much higher than that of the compound of Example 4a) (4 g/litre), even though it contains one more methylene group.

20 A high degree of water solubility of the compounds according to the invention is not absolutely critical because the predominant proportion of the substance is probably in protein-bound form in the bloodstream. Rather, it is generally important that the substances are recognised as substrate for a
25 transport system in the body. In connection with the present invention, the so-called OATs (organic anion transporters) and OATPs (organic anion transporter proteins) are presumably of particular importance. However, these do not have 100 % specificity for anions. An example thereof of digitoxin.

30 Peptide transporters can also be discussed as relevant uptake

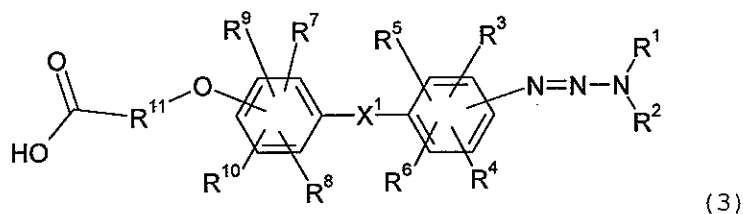
and excretion mechanisms which recognise the amino acid or amino acid amide radical.

The use of 2-amino-2-hydroxyl-methyl-1,3-propanediol (TRIS) and sodium salts is preferred against the background of increasing the water solubility of the compounds according to the invention.

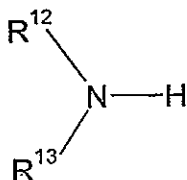
Depending on their structure, the compounds according to the invention can exist in stereoisomeric forms (enantiomers, diastereoisomers) when asymmetric carbon atoms are present. The invention therefore also includes the use of the enantiomers or diastereoisomers and mixtures thereof. The enantiomerically pure forms can optionally be obtained by conventional processes of optical resolution, such as by fractional crystallisation of diastereoisomers thereof by reaction with optically active compounds. Where the compounds according to the invention can occur in tautomeric forms, the present invention includes the use of all tautomeric forms.

The present invention relates further to a process for the preparation of the compounds of formula (1), which comprises the step:

reaction of a compound of formula (3):



or a salt thereof, such as in particular the sodium, potassium or calcium salt thereof, with a compound of formula (4)

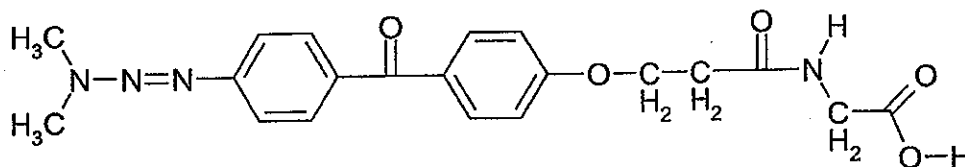


wherein R^1 to R^{13} and X^1 are as defined hereinbefore.

5

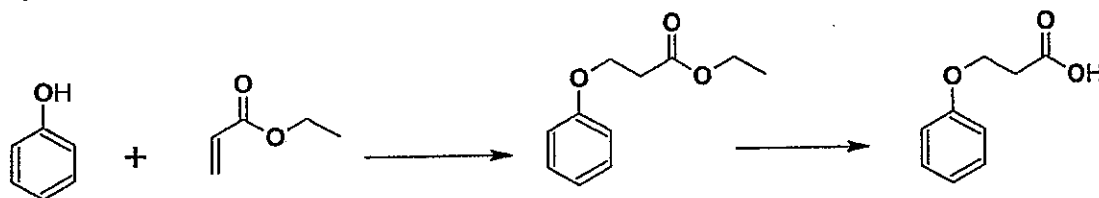
The preparation of the triazene compounds (3) can be carried out analogously to the preparation method described in DE 1793115 A1 by diazotisation of the underlying amino compound, which in turn is obtained by reduction from the corresponding

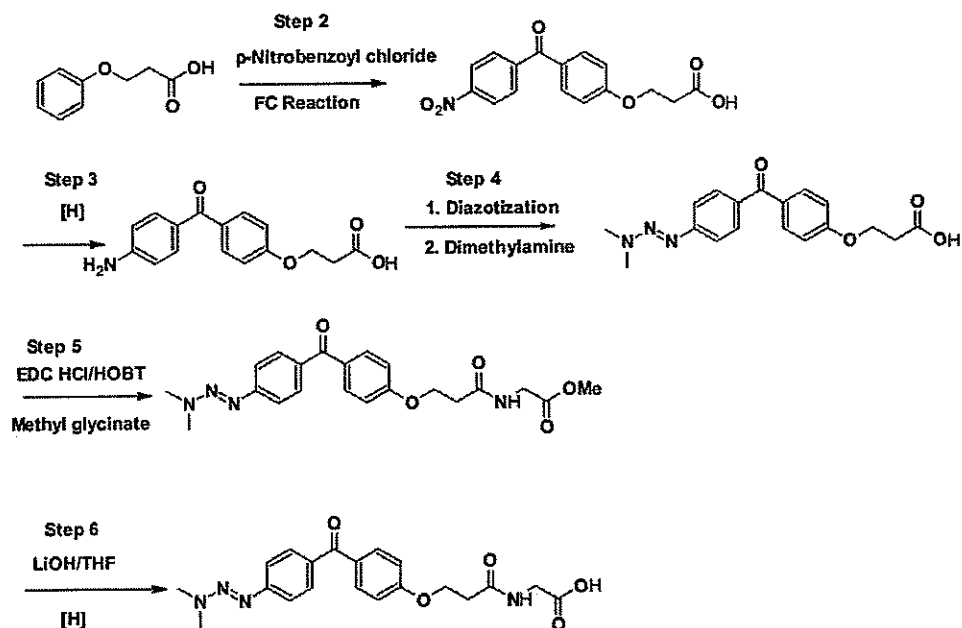
10 nitro compound. The following scheme illustrates the preparation process using the example of {2-[4-(4-[(1E)-3,3-dimethyl-1-triazenyl]-benzoyl)-phenoxy]-propionylamino}acetic acid:



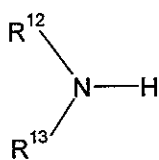
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Step 1



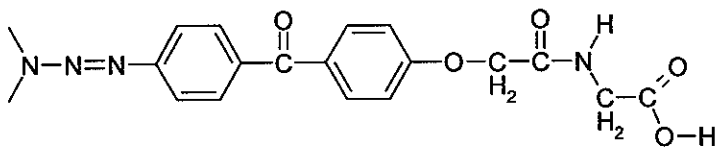


The steps shown are types of reaction which are known *per se* (Friedel Crafts acylation, hydrogenation or reduction of the nitro group, diazotisation, amidation and saponification) and which can be carried out in a manner known *per se*. The corresponding salt is obtained by reaction with a pharmaceutically acceptable base. Instead of methyl glycinate it is also possible to use in step 5 other amino compounds of the formula:



in particular also other amino acids or derivatives thereof.

Analogously to the above scheme there is obtained

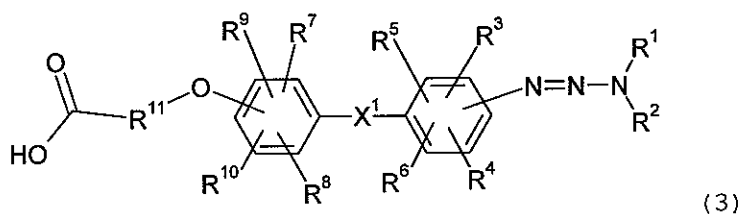


{2-[4-(4-[(1E)-3,3-dimethyl-1-triazenyl]-benzoyl)-phenoxy]-
acetylamino}acetic acid and salts thereof starting from
5 phenoxyacetic acid, which is reacted in step 2 with p-
nitrobenzoyl chloride in a Friedel-Crafts reaction.

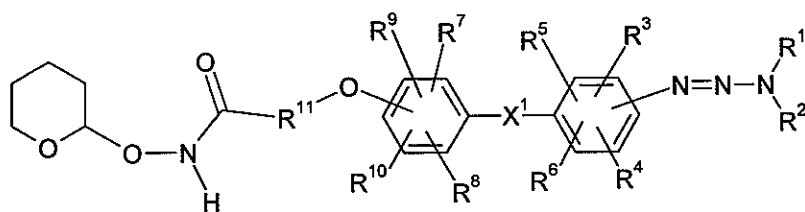
With regard to the stilbene derivatives, in which $X^1 = -CH=CH-$,
reference may be made, for example, to WO2004/106358. The
10 preparation of further starting compounds is described in DE
1793115 A1, which has already been mentioned, in DE 2147781 A1
and in DE 1768720 A1.

With regard to preferred reaction conditions, reference may be
15 made to the examples.

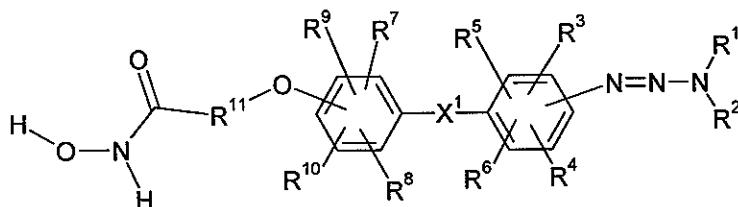
The hydroxamic acid derivatives, in which one of R^{12} and R^{13} is
hydrogen and the other is hydroxyl, can be reacted, for
example, analogously to US 20070135424 A (for example
20 intermediate 24) by reaction of the acid:



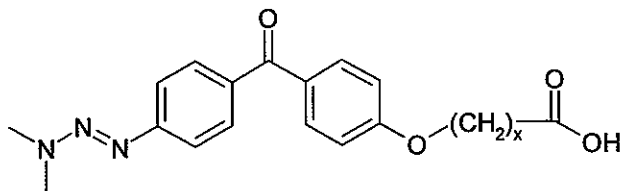
with O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine to give the
25 compound of the formula:



which can subsequently be converted into the corresponding hydroxamic acid by reaction with trifluoroacetic acid, for example:



Some of the intermediates used according to the invention are novel and contribute towards the properties of the end products by the structural elements they contribute. Accordingly, the invention relates also to novel intermediates, such as in particular of formula (3'):



wherein x is from 2 to 6, preferably 2, and salts thereof.

The present invention relates further to compounds of formula (1) for use as medicaments, and to the use of the

compounds of formula (1) in the preparation of a medicament, in particular for the treatment of cancer diseases.

The compounds according to the invention can be used, for example, in the treatment of the following types of tumour: adenocarcinoma, uveal melanoma, acute leukaemia, acoustic neuroma, ampullary carcinoma, anal carcinoma, astrocytomas, basalioma, pancreatic cancer, connective tissue tumour, bladder cancer, bronchial carcinoma, non-small cell bronchial carcinoma, breast cancer, Burkitt's lymphoma, corpus carcinoma, CUP syndrome, colon cancer, cancer of the small intestine, ovarian cancer, endometrial carcinoma, ependymoma, epithelial cancer types, Ewing's tumours, gastrointestinal tumours, gallbladder cancer, gallbladder carcinomas, uterine cancer, cervical cancer, glioblastoma, gynaecological tumours, neck, nose and ear tumours, haematological neoplasias, hairy cell leukaemia, urethral cancer, skin cancer, brain tumours (gliomas), brain metastases, testicular cancer, hypophysis tumour, carcinoids, Kaposi's sarcoma, laryngeal cancer, germ cell tumour, bone cancer, colorectal carcinoma, head/neck tumours (tumours of the neck, nose and ear region), colon carcinoma, craniopharyngeoma, cancer in the mouth region and on the lip, liver cancer, liver metastases, leukaemia, lid tumour, lung cancer, lymph gland cancer (Hodgkin's/non-Hodgkin's), lymphomas, stomach cancer, malignant melanoma, malignant neoplasma, malignomas of the gastrointestinal tract, mammary carcinoma, rectal cancer, medulloblastomas, melanoma, meningiomas, Merkel cell carcinoma, Hodgkin's disease, Mycosis fungoides, cancer of the nose, neurinoma, neuroblastoma, kidney cancer, renal cell carcinomas, non-Hodgkin's lymphomas, oligodendroglioma, oesophageal carcinoma, osteolytic carcinomas and osteoplastic carcinomas, osteosarcoma, ovarian carcinoma, pancreatic carcinoma, penile cancer, plasmocytoma, squamous cell carcinomas of the head and neck, prostate cancer,

pharyngeal cancer, rectal carcinoma, retinoblastoma, vaginal cancer, thyroid carcinoma, Schneeberg lung disease, oesophageal cancer, spinalioma, T-cell lymphoma (Mycosis fungoides), thymoma, tube carcinoma, tumours of the eye, urethral cancer, 5 urological tumours, urothelial carcinoma, vulval cancer, wart involvement, tumours of soft parts, soft part sarcoma, Wilms' tumour, cervical carcinoma and tongue cancer. Reference can additionally be made to the list of cancer types in, for example, WO2007061978 (page 16, line 22 to page 18, line 2) or 10 in US2007135424A1 (page 9, left-hand column, section 122), which are to be regarded as part of the disclosure of the present invention. The compounds of the present invention can also be used in further indications, such as those mentioned in US2007135424A1 in sections 123 to 142.

15 The compounds according to the invention are used particularly preferably for the treatment of breast cancer, intestinal cancer or melanomas.

20 The compounds according to the invention are used particularly preferably for the treatment of breast cancer.

The invention relates further to the use of the compounds of formula (1) in combination with at least one further 25 chemotherapeutic agent for the treatment of cancer.

The compounds of the present invention can accordingly also be used in combination with further chemotherapeutic agents known in the treatment of cancer or tumours and/or in combination 30 with medicaments which are administered together with the chemotherapeutic agents during chemotherapy. Examples of such chemotherapeutic agents which can be used in combination and of other medicaments used in chemotherapy will be found, for example, in WO2007061978 under the heading "Combination

Therapy" (page 23, line 1 to page 30, line 18) or in US2007135424A1 (sections 153 to 171), to the whole of the contents of which reference is accordingly made.

5 The present invention relates further to pharmaceutical compositions comprising at least one of the compounds of formula (1) together with at least one pharmacologically acceptable carrier, auxiliary substance or solvent. These are conventional pharmaceutical carriers, auxiliary substances or
10 solvents. The mentioned pharmaceutical compositions are, for example, suitable for inhalation or for intravenous, intraperitoneal, intramuscular, intravaginal, intrabuccal, percutaneous, subcutaneous, mucocutaneous, oral, rectal, transdermal, topical, intradermal, intragastral or
15 intracutaneous administration and are in the form of, for example, pills, tablets, enteric-coated tablets, film-coated tablets, layered tablets, retard formulations for oral, subcutaneous or cutaneous administration (in particular in plaster form), depot formulation, dragées, suppositories, gels,
20 ointments, syrup, powders for inhalation, granules, suppositories, emulsions, dispersions, microcapsules, microformulations, nanoformulations, liposomal formulations, capsules, enteric-coated capsules, powders, powders for inhalation, microcrystalline formulations, sprays for
25 inhalation, powders, drops, nasal drops, nasal sprays, aerosols, ampoules, solutions, juices, suspensions, emulsions, infusion solutions or injection solutions, etc.

The compounds according to the invention can be administered in
30 pharmaceutical compositions that can comprise various organic or inorganic carriers and/or auxiliary materials as are conventionally used for pharmaceutical purposes, in particular for solid medicament forms, such as, for example, excipients (such as sucrose, starch, mannitol, sorbitol, lactose, glucose,

cellulose, talc, calcium phosphate, calcium carbonate), binders (such as cellulose, methylcellulose, hydroxypropylcellulose, polypropylpyrrolidone, gelatin, gum arabic, polyethylene glycol, sucrose, starch), disintegrators (such as starch, hydrolysed starch, carboxymethylcellulose, calcium salt of carboxymethylcellulose, hydroxypropyl starch, sodium glycol starch, sodium bicarbonate, calcium phosphate, calcium citrate), glidants and lubricants (such as magnesium stearate, talc, sodium lauryl sulfate), an agent that forms a good taste (such as citric acid, menthol, glycine, orange powder), preservatives (such as sodium benzoate, sodium bisulfite, methylparaben, propylparaben), stabilisers (such as citric acid, sodium citrate, acetic acid, and multicarboxylic acids from the Titriplex group, such as, for example, diethylene-triaminepentaacetic acid (DTPA)), suspending agents (such as methylcellulose, polyvinylpyrrolidone, aluminium stearate), dispersing agents, diluents (such as water, organic solvents), beeswax, cocoa butter, polyethylene glycol, white petrolatum, etc.

20

Liquid medicament forms, such as solutions, suspensions and gels, conventionally comprise a liquid carrier, such as water and/or pharmaceutically acceptable organic solvents. Such liquid formulations can also comprise pH-adjusting agents, emulsifiers or dispersing agents, buffering agents, preservatives, wetting agents, gelling agents (for example methylcellulose), colourings and/or flavourings. The compositions can be isotonic, that is to say they can have the same osmotic pressure as blood. The isotonicity of the composition can be adjusted by the use of sodium chloride or other pharmaceutically acceptable agents, such as, for example, dextrose, maltose, boric acid, sodium tartrate, propylene glycol or other inorganic or organic soluble substances. The viscosity of the liquid compositions can be adjusted using a

30

pharmaceutically acceptable thickener, such as methylcellulose. Other suitable thickeners include, for example, xanthan, carboxymethylcellulose, hydroxypropylcellulose, carbomer and the like. The preferred concentration of the thickener will
5 depend on the chosen agent. Pharmaceutically acceptable preservatives can be used to increase the life of the liquid composition. Benzyl alcohol can be suitable, although a large number of preservatives including, for example, paraben, thimerosal, chlorobutanol or benzalkonium chloride can likewise
10 be used.

Diethylenetriaminepentaacetic acid (DTPA) in particular is found to be a suitable stabiliser for the solid or liquid pharmaceutical formulations of the compounds according to the
15 invention, such as in particular the compound of Example 2a).

The active ingredient can be administered, for example, in a unit dose of from 0.01 mg/kg to 500 mg/kg body weight, for example up to 1 to 4 times per day. However, the dosage can be
20 increased or reduced according to the age, weight and condition of the patient, the severity of the disease or the mode of administration.

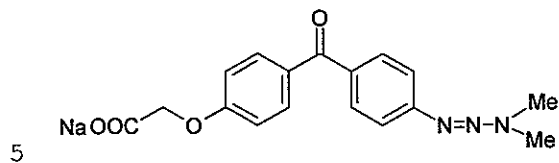
The invention is illustrated in detail by the following
25 examples. The examples merely constitute exemplifications, and the person skilled in the art is able to extend the specific examples to further claimed compounds.

EXAMPLES:

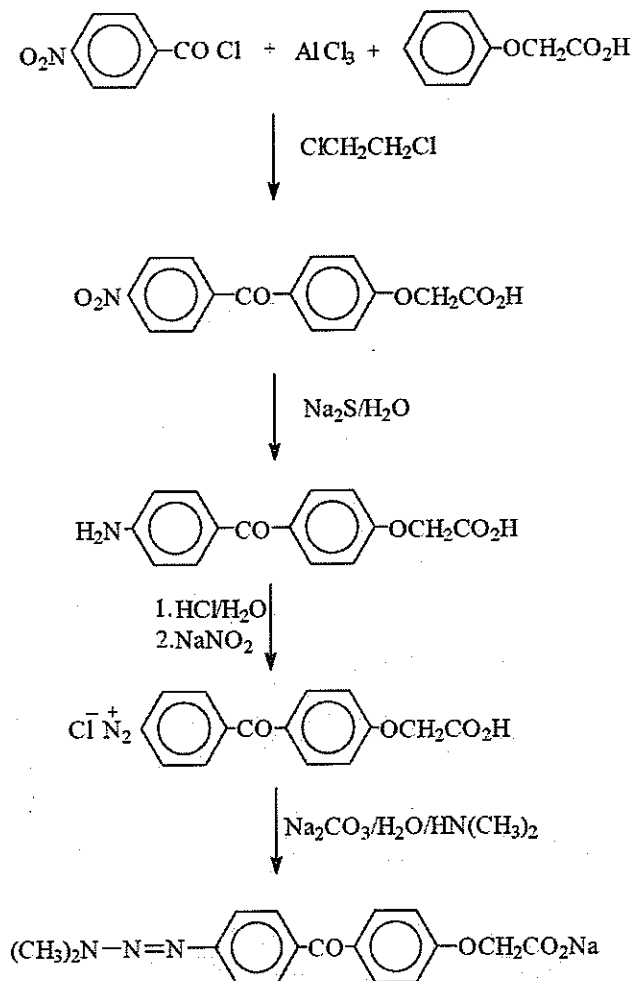
STARTING PREPARATIONS:

Preparation 1:

The preparation of the starting compound

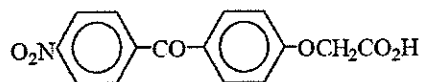


is carried out according to the following reaction scheme:



All the starting materials are well known and documented. The NMR spectra of all the synthesised products are in agreement with the structure.

5 **Stage I**



MW: 301; C₁₅H₁₁NO₆

10 0.5 mol

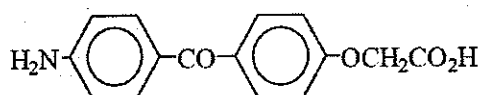
102 g of p-nitrobenzoyl chloride (0.55 mol) dissolved in 300 ml of dichloroethane are slowly added dropwise at 0°-5°C, with stirring, to a suspension of 235 g of AlCl₃ in 1 litre of dichloroethane. 76 g of phenoxyacetic acid are introduced in
15 portions into the solution at 5°C. Stirring is then carried out for 4 hours at 10°C and for 10 hours at room temperature.

Working up:

600 ml of dichloroethane are distilled off, and 600 ml of ligroin are added. The mixture is then poured onto 2 litres of
20 ice/water. The aqueous phase is separated off and the resulting crystalline product is filtered off with suction, washed with water and dried.

Yield: 100 g; m.p.: 186°C, white product.

25 **Stage II**



MW: 271; C₁₅H₁₃NO₄; Lit.: Houben Weyl 11/1 p. 417

30 0.5 mol

320 g of I are boiled at reflux, with stirring, in 1 litre of ethanol. A solution of 350 g of Na₂S and 350 ml of water is carefully added dropwise thereto (strongly exothermic, H₂S absorption). Boiling is then carried out for 2 hours at reflux.

- 5 The reaction mixture is then allowed to stand for about 10 hours at room temperature.

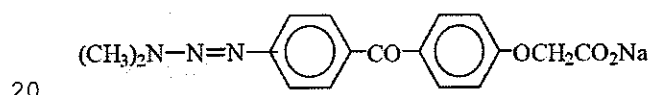
Working up:

- 10 The alcohol is distilled off and the residue is extracted, with stirring, with 3 litres of hot water and filtered off with suction while hot. The filtrate is acidified with glacial acetic acid and the resulting product is filtered off with suction, washed with water, filtered off with suction again and dried.

Purification: from ethanol

- 15 Yield: 200 g = 74 %, weakly yellow product;
M.p.: 172°C.

Stage III:



MW: 349; C₁₇H₁₆N₃O₄Na

0.1 mol

- 25 A solution of 6.9 g of NaNO₂ in 20 ml of water is added dropwise at 0°C, with stirring, to a solution of 27.1 g of II, 350 ml of water and 10.4 g of concentrated HCl (37 %), and stirring is carried out for a further 15 minutes at 0°C.

- 30 The resulting diazonium salt solution is added dropwise at 0-5°C, with stirring, to a solution, placed in a vessel, of 15 g of Na₂CO₃ and 10 g of a 45 % aqueous dimethylamine solution and 50 ml of water.

Working up:

The reaction mixture is kept cold, and the resulting salt is filtered off with suction and recrystallised from water.

Purification:

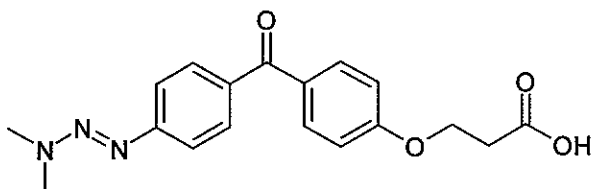
- 5 Recrystallisation from water. Solubility: 1 g in 25 ml of water.

Yield: 10 g = 28 %, beige; m.p. of the acid: 160°C. The acid is obtained by dissolving the salt in water and precipitating with acetic acid.

10

PREPARATION 2:

The preparation of the phenoxypropionyl starting compound



is carried out as shown in the scheme in the description.

15

Step 1:

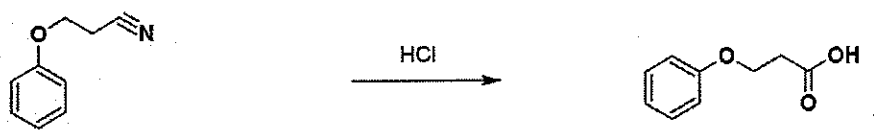
The following materials were used in the indicated amounts:

	Amount	Molecular weight	Mol	Eq.
Phenol	1 kg	94.11	10.62	1
Ethyl acrylate	2.7 kg	100	27	2.54
Triton B	1 ml			
NaOH (10 %)	3 l	40	7.5	0.705
Ethyl acetate	5 l			
Conc. HCl	3.5 l			

- 20 Phenol and ethyl acrylate were introduced into a 5-litre three-necked glass flask equipped with a thermal element and an overhead stirrer. Triton B was added, and heating was carried

- out for 48 hours under reflux (120°C). TLC showed that a small amount of phenol was still present. The reaction composition was worked up as follows. Ethyl acrylate was removed, and the residue was dissolved in ethyl acetate, washed with aqueous
- 5 NaOH (10 %) followed by water (3.0 litres) and dried over anhydrous sodium sulfate. The dried organic layer was concentrated to give a residue. The residue was placed in a 10.0-litre round-bottomed glass flask, concentrated HCl was added, and heating was carried out for 24 hours under reflux.
- 10 The TLC was checked and the reaction composition was cooled to 25°C. The solids were filtered off and washed thoroughly with water (5 litres). The product was dried overnight at 30°C in vacuo in an oven.
- 15 Yield: 450 g (27 % of theory)
Purity (HPLC): 98.32 %

- (Alternatively, the product can also be prepared by saponification of the underlying nitrile according to the
- 20 following scheme:



Step 2:

- 25 The following materials were used in the indicated amounts:

	Amount	Molecular weight	Mol	Eq.
4-Nitrobenzoic acid	300 g	167	1.796	1
Thionyl chloride	1.5 l	119	20.62	11.5
DMF	0.05 ml			

Dichloroethane	12.5 l			
AlCl ₃	720 g	133.3	5.4	3
Step 1 product	280 g	166	1.687	0.94
Hexane	8 l			
Ice-water	15 l			

4-Nitrobenzoic acid, thionyl chloride and DMF were placed in a 3-litre 4-necked glass flask and heated for 2 hours at 78°C under reflux. The end of the reaction was monitored by the clarity of the reaction mixture. There was a clear solution at the end of the reaction. Thionyl chloride was removed under reduced pressure. Dichloroethane (1 litre) was added, and evaporation was carried out to yield 4-nitrobenzoyl chloride in the form of a solid. The solid was dissolved in dichloroethane (1 litre). Dichloroethane (10 litres) was introduced into a 20-litre glass flask and cooled to 0°C. Aluminium chloride was added at 0-5°C. The 4-nitrobenzoyl chloride prepared above, dissolved in dichloroethane, was then added dropwise at 0-5°C. Phenoxypropionic acid was added in portions to the reaction composition at 0.5°C, and stirring was carried out overnight at 25°C. The TLC was checked and the reaction composition was quenched in a mixture of hexane (8 litres) and ice-water (15 litres). The composition was stirred and the solids were filtered off. The product was washed with hexane and dried.

Yield: 400 g (70 % of theory)

Purity: 92.8 % by HPLC.

Step 3

The following materials were used in the indicated amounts:

	Amount	Molecular weight	Mol	Eq.
Step 2 product	400 g	315	1.26	1
Na ₂ S	400 g	78	5.13	4
Ethanol	4 l			
Water	1 l			

The product from step 2 was taken up in ethanol and cooled to 10°C. An aqueous solution of the sodium sulfide was added dropwise at 10-15°C, and stirring was carried out overnight at 5 25°C. Ethanol was removed, and water (4 litres) was added under reduced pressure. Acetic acid was added in order to adjust the pH to 6. The pH of the filtrate was adjusted to 3 with acetic acid, and extraction with ethyl acetate (3 litres) was carried out. The organic layer was dried and concentrated to give a 10 residue.

Yield: 168 g

Purity: > 70 % by HPLC.

15 A similar batch was prepared with 230 g of the product from step 2.

Yield: 108 g

Purity: 66.1 % by HPLC.

20

The above two batches of the product were mixed and recrystallised from ethanol.

Combined yield: 110 g (19.3 % of theory)

25 Purity: 95.6 % by HPLC.

Step 4:

The following materials were used in the indicated amounts:

	Amount	M.W.	Mol	Eq.
Step 3 product	110 g	285	0.3859	1
Conc. HCl	130 ml	36.5	1.31	3.4
Water	2 l			
NaNO ₂	30 g	69	0.04347	1.12
Na ₂ CO ₃	67.5 g	106	0.6367	1.65
Dimethylamine (40 %)				

Mixed product from step 3, water (2 litres) and concentrated HCl were cooled to 0°C. Sodium nitrite was dissolved in water
5 (150 ml) and added at 0-5°C, and stirring was carried out for 30 minutes.

In another glass flask, sodium carbonate was dissolved in water (160 ml); dimethylamine was added and the mixture was cooled to
10 0°C. The sodium diazonium salt was added slowly at 0-5°C to the solution prepared above, and stirring was carried out for one hour. The TLC was checked and the reaction was completed. The pH of the reaction composition was adjusted to 3 with acetic acid, and extraction with ethyl acetate (1.2 litres) was
15 carried out. The organic layer was washed with water (200 ml x 2), dried over anhydrous sodium sulfate and concentrated to give a solid.

Crude yield: 109.5 g
20 Purity: 84.7 %

The crude product was purified by column chromatography (20 % THF in ethyl acetate).

25 Yield: 85 g (64.6 % of theory)

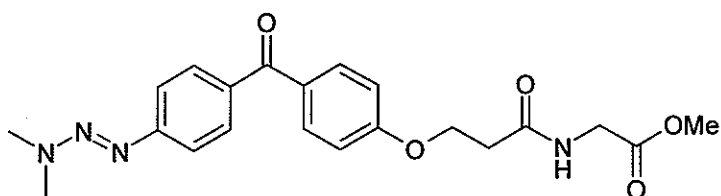
Purity: 93.3 % by HPLC.

The product of Preparation 2 has a melting point of from 124.5 to 125.8°C.

5

Figure 19 shows the ¹H-NMR spectrum of the resulting compound.

Example 1:



5 (Step 5 of the above scheme):

The following materials were used in the indicated amounts:

	Amount	Molecular weight	Mol	Eq.
Step 4 product	85 g	341.36	0.249	1
EDC HCl	52.5 g	191.7	0.274	1.1
HOBT	8 g			
Methyl glycinate HCl	31.23 g	125.8	0.249	0.99
TEA	75.89	101	0.7514	3
DCM	850 ml			

10 The product from step 4 was dissolved in DCM and cooled to 10°C. HCl and HOBT were added to the EDC, and stirring was carried out for 30 minutes. Methyl glycinate was added at 10°C, and stirring was carried out overnight at 27°C. The TLC was checked and it was found that the reaction was complete. Water (1 litre) was added and the layer was separated. The organic
15 layer was dried over sodium sulfate and concentrated to give a residue.

Crude yield: 110 g

Purity: 91.3 % by HPLC

The crude product was purified further by column chromatography (10 % ethyl acetate in hexane).

Yield: 89 g (86 % of theory)

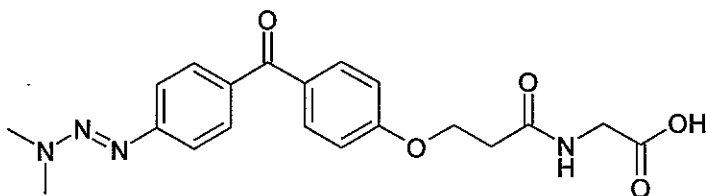
5 Purity: 95.4 % by HPLC.

The product is a pink-coloured powder having a melting point of 104.0 to 105.0°C. A main peak is observed in the mass spectrum at 413.5 (M+1).

10 Figure 1 shows the ¹H-NMR spectrum (400 MHz) of the compound of Example 1.

Figure 2 shows the ¹³C-NMR spectrum (100 MHz) of the compound of Example 1.

15 Example 2:



(Step 6 of the above scheme)

20 The following materials were used in the indicated amounts:

	Amount	Molecular weight	Mol	Eq.
Step 5 product	89 g	412	0.2157	1
LiOH H ₂ O	9.5 g	41.96	0.2264	1.05
THF	890 ml			
Water	178 ml			

The product of step 5, THF and water were mixed and cooled to 0°C. Lithium hydroxide (4.5 g) was added in portions at 0°C,

and stirring was carried out for 20 minutes. The TLC was checked, the reaction had not begun. A further batch of LiOH (4.5 g) was added, and stirring was carried out for 30 minutes. The TLC was checked and it was found that the reaction had
5 begun. The reaction composition was maintained for one hour, and the TLC was checked. A very small amount of the substrate remained. Yet a further batch of lithium hydroxide (0.5 g) was added. The TLC was checked after 30 minutes and the substrate had disappeared. THF was removed *in vacuo* and the residue was
10 diluted with ethyl acetate (2 litres). The pH was adjusted to 5-6, a clear solution was obtained. Washing with water (200 ml x 2) was carried out, followed by drying over sodium sulfate and concentration to give a residue.

15 Yield: 72 g

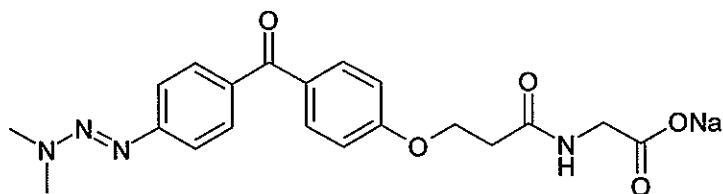
The crude product was purified further by column chromatography (DCM/methanol).

20 Yield: 46 g (53.5 % of theory)
Purity: 95.9 %.

The product is a yellow hygroscopic solid. A main peak is observed in the mass spectrum at 399.1 (M+1).

25 Figure 3 shows the ^1H -NMR spectrum (400 MHz) of the compound of Example 2.

Example 2 a):



5 A solution of sodium carbonate (1.49 g, 0.0140 mol) in water (3.75 ml) was added to 7 g of the compound obtained in Example 2. Ethyl acetate (50 ml) was added thereto and stirring was carried out. The resulting product was stirred overnight (about 12 hours) with tetrahydrofuran (100 ml) at room
10 temperature (25°C). The solid was filtered off and washed with dichloromethane (50 ml) and ethyl acetate (100 ml). The solid was dried overnight (about 12 hours) at 50°C *in vacuo*, and the sodium salt of the compound of Example 2 was obtained.

15 Yield: 5.7 g (56 % of theory)
Purity HPLC: 97.4 %

The product is a weakly orange-coloured crystalline powder. It surprisingly has a very good water solubility of 500 g/l at
20 room temperature (25°C), which in particular is very much higher than that of the compound of Example 4a), even though it has one more methylene group.

Figure 4 shows the ¹H-NMR spectrum (400 MHz - D₂O) of the
25 compound obtained in Example 2a).

Figure 5 shows the ¹³C-NMR spectrum (100 MHz - d⁶-DMSO) of the compound obtained in Example 2a).

Example 3

Starting from Preparation 1 with ethyl glycinate, the following compound was obtained analogously to Example 1 in the form of a yellow powder having a purity of > 95 % (HPLC).

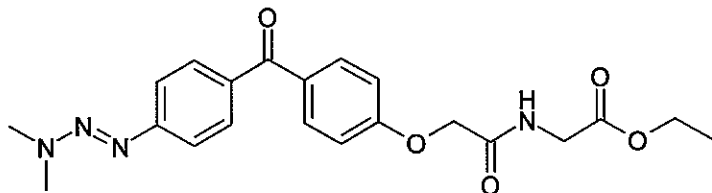
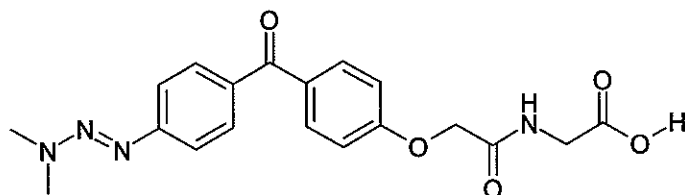


Figure 6 shows the result of the HPLC of the compound obtained in Example 3.

Example 4

Starting from Example 3, the following compound was obtained analogously to Example 2:



Yellow solid; purity (HPLC) > 99 %; melting point 130.7 to 131.2°C.

Figure 7 shows the ^1H -NMR spectrum (400 MHz - d^6 -DMSO) of the compound obtained in Example 4.

Figure 8 shows the ^{13}C -NMR spectrum (100 MHz - d^6 -DMSO) of the compound obtained in Example 4.

Example 4a)

The sodium salt of the compound of Example 4 was obtained analogously to Example 2a) by reaction with sodium carbonate.

5

It is a cream-coloured powder having a melting point of 253.2 to 253.9°C.

Figure 9 shows the ^1H -NMR spectrum (400 MHz - D_2O) of the compound obtained in Example 4a).

10

Figure 10 shows the ^{13}C -NMR spectrum (100 MHz - d^6 -DMSO) of the compound obtained in Example 4a).

Further salts of the compound of Example 4 can be obtained in an analogous manner by reaction with other bases, such as TRIS (tris(hydroxymethyl)-aminomethane or 2-amino-2-(hydroxymethyl)-propane-1,3-diol).

15

The TRIS salt in particular exhibits markedly higher water solubility at room temperature than the sodium salt (250 g/litre, corresponding to a factor of about 60 compared with the sodium salt), which in addition exhibits a pronounced salting-out effect in 0.9 % NaCl.

20

25 Example 5

Starting from Preparation 1 with histidineamide, the following compound was obtained analogously to Example 1 in the form of a yellow powder having a purity of > 95 % (HPLC):

30

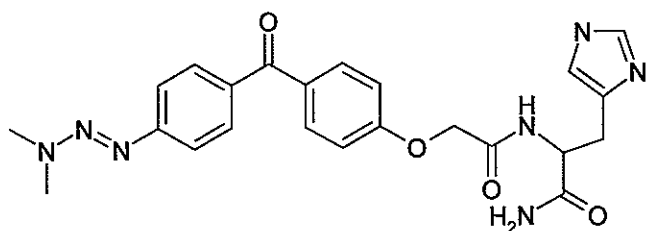


Figure 11 shows the result of the HPLC of the compound obtained in Example 5.

5

Example 6

Starting from glycineamide, the following compound was obtained analogously to Example 1 in the form of a light-brown powder in a purity of > 95 % (HPLC):

10

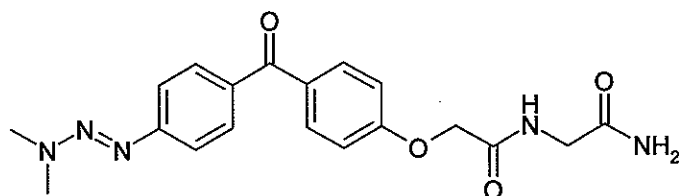
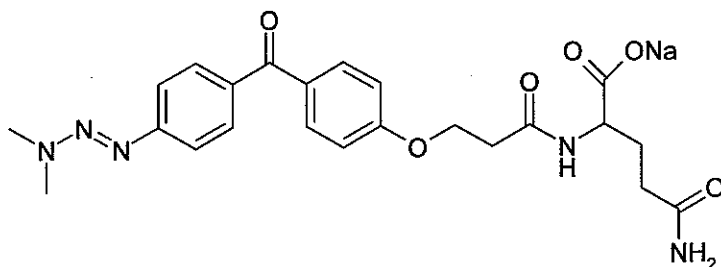


Figure 12 shows the result of the HPLC of the compound obtained in Example 6.

15

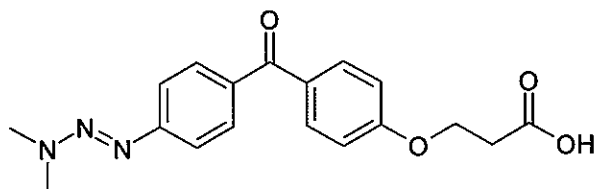
Example 7



(4-carbamoyl-2-{3-[4-(4-[(1E)-3,3-dimethyl-1-triazenyl]-benzoyl)-phenoxy]-propionylamino}-butanoic acid sodium salt)

was prepared as follows starting from

5



(3-{4-[4-[(1E)-3,3-dimethyl-1-triazenyl]-benzoyl]-phenoxy}-propionic acid):

10

In a one-litre three-necked round-bottomed flask having a thermal element pocket and a stirrer, (3-{4-[4-[(1E)-3,3-dimethyl-1-triazenyl]-benzoyl]-phenoxy}propionic acid) (40 g, 0.1173 mol) as starting compound, HOBT (3.7 g, 0.0274 mol) and dioxane (300 ml) were added to an ice-water bath. A solution of DCC (40.66 g, 0.1970 mol) in dioxane (100 ml) was added dropwise thereto over a period of 5 to 6 hours, whereby the temperature was maintained at 20 to 25°C. In another 2-litre three-necked round-bottomed flask having a thermal element pocket and a stirrer, L-glutamine (43.20 g, 0.2956 mol) and saturated sodium bicarbonate solution (432 ml) were added to an ice-water bath. The dioxane solution prepared above was added thereto, and stirring was carried out for 16 hours at 10 to 15°C. The start of the reaction was monitored by TLC (thin-layer chromatography) (MDC:MeOH, 1:1). After 16 hours, TLC showed that the starting compound had reacted completely. The pH of the reaction mixture was adjusted to 6.8 using HCl (1.5 N), and the reaction mixture was concentrated under reduced pressure at 50°C. Water (200 ml) was added to the residue, and stirring was carried out at 25°C. The suspension

15

20

25

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was filtered and the pH of the filtrate was adjusted to 3.08 using HCl (1.5 N). The reaction mixture was extracted with ethyl acetate (200 ml) and the phases were separated. The organic layer was dried over sodium sulfate (25 g). The organic
5 layer was rinsed for 2 hours with dry ammonia (a rubber-like residue was formed) and the supernatant liquid was decanted off. The residue was rinsed with a mixture of THF:EtOAc (1:1, 100 ml) and decanted off. The process was repeated five times (after this treatment, the residue was a movable solid) and
10 filtration was then carried out. The crude solid was maintained under reflux (78 to 80°C) for one hour in ethanol (100 ml). The hot suspension was filtered and the filtrate was cooled to 20°C for 2 hours. After 2 hours, the suspension was filtered and the filter cake (12 g) was dissolved in water (120 ml). The pH of
15 the solution was adjusted to 3.0 using HCl (1.5 N), and extraction with ethyl acetate (120 ml) was carried out. The phases were separated and the organic layer was washed with water (60 ml). The organic layer was dried over sodium sulfate (20 g), and a solution of sodium carbonate (2.6 g) in water
20 (8 ml) was added. THF (120 ml) was added thereto, and stirring was carried out for 2 hours. The suspension was filtered and dried for 16 hours in a VTD (vacuum tray drier) at 50°C. The dried product was analysed.
Yield: 11.2 g (19.44 % of theory)

25

The compound is obtained in the form of a weakly orange-coloured powder having a melting point of 181.0 to 182.5°C.

The solubility in water at 25°C is about 400 g/litre.

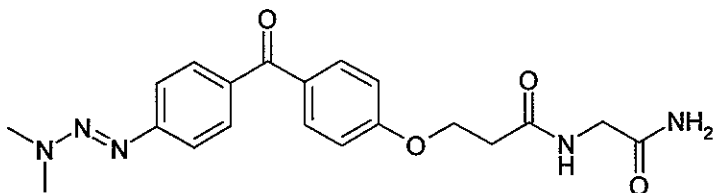
30

Other salts can be obtained analogously by reaction with corresponding bases, such as TRIS, instead of sodium carbonate.

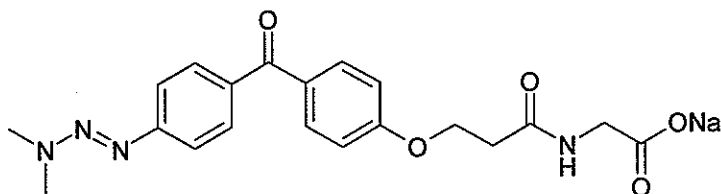
Figure 13 shows the ^1H -NMR spectrum of the compound obtained in Example 7.

Figure 14 shows the ^{13}C -NMR spectrum of the compound obtained in Example 7.

Example 8



was prepared as follows starting from



(compound of Example 2a)):

A 5.0 litre three-necked round-bottomed flask with a thermal element and a stirrer was arranged on an ice-water bath. The compound of Example 2a) (200 g, 0.476 mol) and water (2.0 litres) were added thereto. The reaction mixture was stirred until a clear solution was obtained, and the pH of the solution was adjusted to 3.5 using 1.5 N HCl. Ethyl acetate (2.0 litres) was then added. The reaction mixture was stirred for 30 minutes in order to extract the free acid, and the layers were separated. Washing water (1.0 litre) was added to the organic layer (i.e. the ethyl acetate layer). The organic layer was dried over sodium sulfate (100 g) and concentrated at

50°C *in vacuo*, followed by the addition of dichloromethane (1.0 litre) to the residue. The reaction mass was transferred to a 2.0 litre three-necked round-bottomed flask with a thermal element and a stirrer. The reaction mass was cooled to 0 to 5°C using an ice-bath. EDC.HCl (1-ethyl 3-(3-dimethyl-aminopropyl)carbodiimide - 109.5 g, 0.5714 mol) was added, followed by the addition of HOBT (11 g, 0.17 mol) at 0 to 5°C. Dry ammonia was passed in for 2 hours, and then the reaction mixture was checked for the presence of the starting compound by TLC (MDC:MEOH = 8:2). The reaction mixture was concentrated to dryness *in vacuo* at a temperature of below 50°C. Ethyl acetate (1.0 litre) and water (1.0 litre) were added to the residue, and the layers were separated. Washing water (1.0 litre) was added to the organic layer. The organic layer was dried over sodium sulfate (100 g) and concentrated *in vacuo* at 50°C. Isopropanol (800 ml) was added to the residue (80 g), and the mixture was heated to 80°C in order to obtain a clear solution. The solution was gradually cooled to 25°C. The product was filtered off and washed with isopropanol (50 ml). The product was dried for 12 hours in a VTD at 50°C.

Yield: 56 g (29.6 % of theory)

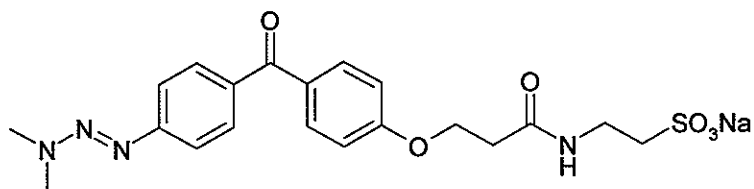
The compound was obtained in the form of a yellow- to orange-coloured solid having a melting point of 145.2 to 147.0°C. The solubility in DMSO at room temperature was 833 g/litre.

Figure 15 shows the ¹H-NMR spectrum of the compound obtained in Example 8.

Figure 16 shows the ¹³C-NMR spectrum of the compound obtained in Example 8.

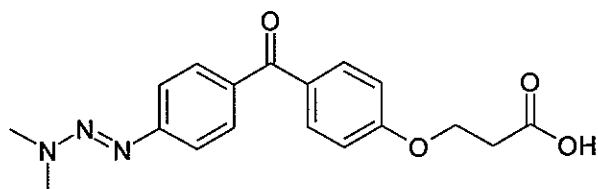
Example 9:

The compound of the formula:



5

was prepared as follows starting from the compound of Preparation 2:



10

Taurine (5.5 g, 0.044 mol) and 4N NaOH (1.76 g NaOH in 11 ml of water) were introduced into a 50 ml round-bottomed flask, and stirring was carried out in order to obtain a clear solution. The solution was concentrated by evaporation *in vacuo* at 50°C in order to obtain a white residue. The residue was stripped repeatedly with methanol (2 x 100 ml) at 58°C.

The sodium salt of taurine prepared above, and methanol (750 ml) were introduced into a further 2-litre three-necked round-bottomed flask connected to an overhead stirrer and having a thermal element pocket. 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ, 16.31 g, 0.066 mol) was added thereto, and stirring was carried out at 25°C (a clear solution formed). The compound of Preparation 2 (15 g, 0.044 mol) was added thereto, and stirring was carried out for 48 hours at 25°C. The progress of the reaction was monitored by thin-layer

chromatography (TLC) (MDC:MEOH 8:2). After 48 hours, the TLC showed that the starting compound had reacted completely. The reaction mixture was concentrated *in vacuo* at 50°C to give a reddish-yellow solid.

5

The crude product was dissolved in methanol (150 ml), and methyl tert-butyl ether (MTBE, 1500 ml) was slowly added thereto over a period of 30 minutes. The resulting solids were filtered off and washed with MTBE (100 ml). The product was

10 dried for 12 hours in a vacuum tray drier (VTD) at 50°C and was then analysed.

The product was obtained in the form of an orange powder. The solubility in water at room temperature was 666 g/litre.

15

Yield: 12.5 g (60.46 % of theory)

Figure 17 shows the ^1H -NMR spectrum of the compound obtained in Example 9.

20 Figure 18 shows the ^{13}C -NMR spectrum of the compound obtained in Example 9.

PHARMACOLOGICAL ACTIVITY TESTS:

All the tests were carried out using female nude mice under standard conditions for the keeping of animals with controlled illumination and temperature. The animals were given water and food as desired.

Breast tumours (MAXF 401) were implanted subcutaneously into the rear members of the mice aged 10 weeks. The increase in the volume of the individual tumours was measured using microcallipers, and the size of the tumour was calculated according to the formula $a \cdot b^2 / 2$ (where a is the largest diameter of the tumour and b is the vertical axis). When the tumour volume had increased to 80 - 120 mm³, the animals were allocated at random into test groups of in each case 6 animals.

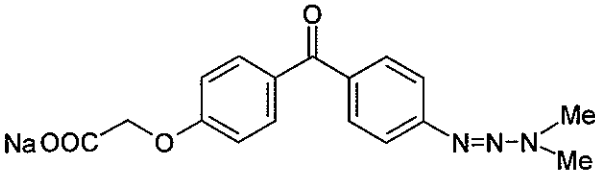
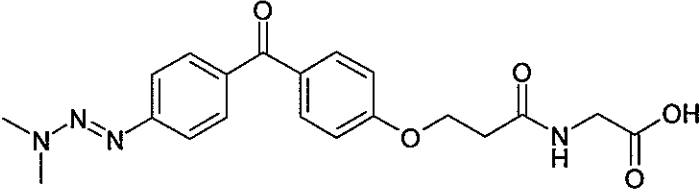
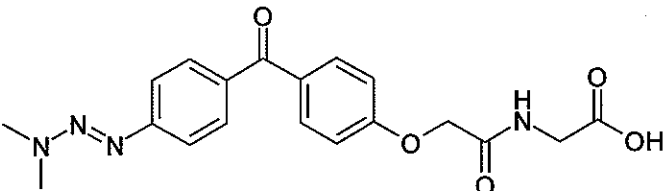
The test compounds (in the form of sodium salts) were dissolved in a saline solution, and 5 % Klucel (hydroxypropylcellulose) was added in order to dissolve all the test compounds in the same carrier. The compounds were administered by intraperitoneal injection in equimolar doses corresponding to 350 mg/kg of the comparison compound (according to Example 30 of DE 1793115A). This dose level was chosen corresponding to a dose of the comparison compound that led under the test conditions to a 50 % reduction in the tumour volume development. A volume of 10 ml/kg body weight was injected. Animals that received only the carrier served as control. The test compounds were treated according to the scheme of twice weekly administration over a period of 5 weeks. The tumour volume and the body weight were checked twice weekly, and the relative tumour volumes were calculated as the ratio of tumour size to body weight. The test was ended when the tumour volume of the control group had reached a size which required the

animals to be sacrificed in order to satisfy the regulations relating to animal protection.

On the basis of the relative tumour volumes of the animals
5 treated with the test compounds compared with the tumour
volumes of the controls treated only with the carrier, the T/C
values were calculated and were used as the index of anti-
tumour activity. (The T/C index here represents the ratio of
the tumour size of treated and untreated animals. The smaller
10 the ratio, the better the activity. 100 % would be no activity:
tumour is the same size).

As is shown in Table 1, the substances of Examples 2 and 4 have
improved anti-tumour activity under the test conditions. A
15 marked tumour remission was observed within 4 weeks of
treatment with both derivatives. In addition, the compositions
were well tolerated. In comparison with the control group,
there were no instances of death in the substance-treated
animals over the test period.

Table 1: Comparative anti-tumour activity and mortality in tumour heterotransplanted mice

Test composition	T/C value	Mortality
Ex. 30 of DE 1793115A 	48.5	2/6
Example 2 	3.4	0/6
Example 4 	12.6	0/6

5

Figure 20 shows a comparison of the anti-tumour activity of the sodium salt (Example 4a) and the TRIS salt of the compound of Example 4 in the MAXF 401 xenograft model in the nude mouse. Subcutaneous implantation of the tumour and the determination of the tumour volume were carried out as described hereinbefore. The above-mentioned salts of the test substance were administered by ip injection twice weekly in the mentioned doses in the form of an aqueous solution, over a period of 4 weeks. The figure shows the dose-dependent progression over

10

time of the anti-tumour action of the test substance as the T/C value. When 400 mg/kg of the sodium salt of the compound of Example 4 were administered, a T/C value of 12 was achieved after 4 weeks' therapy; after administration of 500 mg/kg of the salt, complete remission was achieved within 3 weeks of treatment. If, on the other hand, the same substance was administered in the form of the TRIS salt in equimolar doses of 360, 400 and 500 mg/kg of the sodium salt, complete remission was observed with all the doses used. These results show that the two salts differ in terms of their bioavailability. It is probable that the different anti-tumour action of the sodium salt and the TRIS salt is attributable to different peak concentrations of the compound of Example 4 after administration of the different salts.

FURTHER ACTIVITY DATA:

Further pharmacological activity data of the test compounds (sodium salts) were obtained.

5

SELECTIVITY OF THE ANTI-TUMOUR ACTIVITY:

Figure 21 shows the selectivity of the anti-tumour activity of the substance of Example 2a (sodium salt) on different tumours.

10

The anti-tumour activity of the substance of Example 2a (sodium salt) was tested in a xenograft tumour panel. To this end, xenografts of human tumours derived from prostate, uterine, lung, pancreatic, bladder and "head and neck" cancers were implanted in nude mice. The implantation and the determination of tumour volumes were carried out as described hereinbefore. Groups of 5 to 8 animals were used. The test substance was administered by ip injection twice weekly in the mentioned doses in the form of the sodium salt as an aqueous solution.

15

20

The tumour xenografts used, the doses used, the duration of the therapy and a classification of observed anti-tumour actions are summarised in Table 2 below.

25

Table 2:

Xenograft	Tissue	Dose range [mg/kg] Ex. 2a)	Duration of treatment [d]	Max. effect
BXF 1218	Bladder	450-540	7*	Inhibition < 50% n.s.
CXF 280	Colon	450-540	28	Remission ***
HNXF 536	Head & neck	450-540	28	Inhibition < 50% **
LXFL 529	Lung	450-540	10*	Inhibition < 50% *
MAXF 401	Breast	300-540	28	Remission ***
MEXF 462	Melanoma	100-540	28	Remission ***
MEXF 276	Melanoma	450-540	21*	Inhibition > 50% ***
PAXF 1657	Pancreas	450-540	21*	No anti-tumour action n.s.
PRXF 22RV1	Prostate	450-540	28	Inhibition < 50% **
PRXF DU145	Prostate	385-590	28	Inhibition > 50% **
UXF 1138	Uterus	450-540	21*	Inhibition > 50% **

(* The control group was ended as soon as the tumour volume in individual animals exceeds > 1500 mm², N=5-8; statistical significance: n.s.: not significantly different from the control, *: p<0.05; ** p<0.01; ***: p>0.005)

The graph of Figure 21 shows the dose dependency of the anti-tumour action and the different response of different tumours. 0 % anti-tumour action corresponds to the growth of control

tumours and 100 % of the complete remission of tumours under therapy. The anti-tumour action of the test substance decreased in the sequence MEXF 462 >> CXF 280 ~ MAXF 401 > UXF 1138 ~ MEXF 276 ~ PRXF 22RV1 ~ PRXF DU 145 > LXFL 529 ~ HNXF536 > BXF 1218 ~ PAXF 1657. The results show that the test substance has a pronounced (i.e. remission-inducing) and specific anti-tumour action in particular in tumour types including melanoma, breast cancer and colon carcinoma.

10 Figure 22 shows the dose dependency of the anti-tumour action of the substance of Example 2a in breast tumours (MAXF 401 - xenograft in nude mice).

The anti-tumour activity of the substance of Example 2a (sodium salt) was studied in the MAXF-401 xenograft tumour model in the nude mouse. Subcutaneous implantation of the tumour and the determination of tumour volumes were carried out as described hereinbefore. The test substance was administered by ip injection twice weekly in the mentioned doses in the form of the sodium salt as an aqueous solution, over a period of 4 weeks. The figure shows the dose-dependent progression over time of the anti-tumour action of the test substance as the T/C value. A dose of 300 mg/kg was determined as the threshold dose, 450 mg/kg as the ED50 and 500 mg/kg as the ED90 of the anti-tumour action. At the highest dose, remission of the tumours was observed under therapy. The substance was well tolerated in the dose range used.

Figure 23 shows the anti-tumour action of the substance of Example 2a (sodium salt) in a colon carcinoma xenograft model.

The anti-tumour activity of the substance of Example 2a was thereby determined in the CXF280 xenograft model in the nude mouse. Subcutaneous implantation of the tumour and the

determination of tumour volumes were carried out as described hereinbefore. The test substance was administered by ip injection twice weekly in the mentioned doses in the form of the sodium salt as an aqueous solution, over a period of 5 4 weeks. Groups of in each case 8 animals were used. After administration in doses of 450, 500 or 540 mg/kg of Example 2a, a pronounced anti-tumour action was observed in all the doses used, with complete inhibition of tumour growth and the induction of remissions to obliteration of the tumour in the 10 high dose group. ED20, ED50 and ED90 doses were extrapolated to 330, 390 and 490 mg/kg of the active substance. The substance was well tolerated in the dose range used and was not associated with a significant weight loss in the animals.

15 Table 3 below shows a comparison of the anti-tumour action of a further two selected compounds, which are referred to hereinbelow as the compound of Example 6 and the compound of Example 7, in comparison with the compound of Example 2a in a melanoma xenograft model.

20 The anti-tumour activity of the compounds was determined in the MEXF 462 xenograft tumour model in the nude mouse. Subcutaneous implantation of the tumour and the determination of tumour volumes were carried out as described hereinbefore. Groups of 25 in each case 8 animals were used.

The test substances according to Example 7 and Example 2a were administered by ip injection twice weekly in equimolar doses in the form of an aqueous solution, over a period of 4 weeks. 30 Equimolar amounts of the compound of Example 8 were administered ip twice weekly in the form of a 5 % DMSO solution over the mentioned period.

The progression over time of the anti-tumour action, expressed in % of the tumour volume at the beginning of the test, over the period of therapy is shown in Table 3.

5 **Table 3:**

Time	Control		Compound of Ex. 2a (300 mg/kg)		Compound of Ex. 7 (350 mg/kg)		Compound of Ex. 8 (285 mg/kg)	
[d]	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0	100	0	100	0	100	0	100	0
3	593	149	316	109	278	75	293	90
7	1126	381	240	144	172	45	369	115
11	2441	700	187	230	73	15	174	91
14			166	245	49	13	134	63
18			83	112	24	13	107	69
21			67	113	6	8	151	189
25			40	87	2	3	172	247
28			30	73	0.3	0.8	271	434

The control group was ended after day 11 for ethical reasons owing to the high tumour volume. In the treatment groups, on
10 treatment with equimolar doses, partial remission was observed with the compound of Example 2a, complete remission was observed on treatment with the compound of Example 7, and a pronounced slowing down of tumour growth was observed on
15 treatment with the compound of Example 8. All the substances were found to be well tolerated in the dose range used, a significant weight increase was observed in all the animals receiving therapy.

In summary, the compounds according to the invention, or the
20 pharmaceutical compositions thereof, are found to be potent

anti-tumour medicaments having improved therapeutic breadth and fewer side-effects.

Example 2 (nephrological tolerability):

5

Tumour-carrying mice were treated as described above with the comparison compound of Example 30 of DE 1793115A or with the derivative according to the invention of Example 2a, at an equimolar dose level corresponding to 450 mg of stock
10 composition per ip injection. A control group was treated only with the carrier according to a twice weekly treatment scheme.

When the 28-day treatment period had ended, a post-mortem was carried out on the mice. In the animals treated with the stock
15 composition, macroscopic changes (swelling, local discolouration) of the kidneys were observed, while the kidneys of the other treatment group, which received the substance from Example 2a, and the control group remained without pathological findings. The kidneys of all the animals in the test groups
20 were removed by operation, fixed in formalin according to standard methods, embedded in paraffin and processed for HE staining. The histological results of the tissue slices of the test groups are summarised in Table 4:

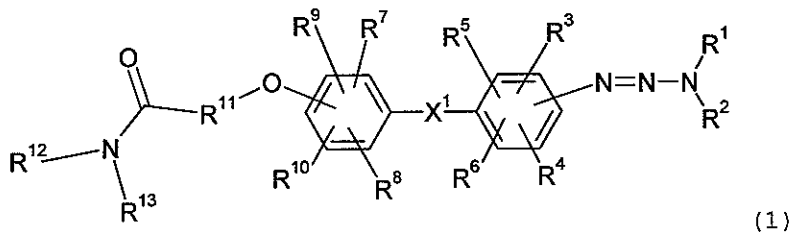
25 Table 4:

Composition	Acute single-cell necrosis	Focal tubular necrosis
Control	0/6	0/6
Compound of Ex. 30 of DE 1793115A	4/9	3/9
Compound of Ex. 2a	0/9	0/9

Marked focal tubular necrosis of the kidneys was observed in the animals treated with the comparison compound. No necrotic changes were found in the kidneys of the animals treated with the compound according to the invention. This emphasises that
5 administration of the comparison compound is associated with a change in renal histology, which limits its use as an anti-tumour agent for long-term administration and confirms the excellent tolerability profile of the compounds according to the invention.

PATENT CLAIMS:

1. Compounds of formula (1):



wherein

10 R^1 and R^2 are identical or different and are in each case selected from the group consisting of:

- optionally substituted alkyl,
- optionally substituted alkenyl,
- optionally substituted aryl,
- optionally substituted alkylaryl;

15 R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are identical or different and are in each case selected from the group consisting of:

- hydrogen,
- 20 - halogen,
- cyano,
- nitro,
- carboxyl,
- aminocarbonyl,
- 25 - sulfonic acid radical ($-\text{SO}_3\text{H}$),
- aminosulfonyl,
- optionally substituted alkyl,
- optionally substituted alkoxy,

- optionally substituted alkenyl,
- optionally substituted aryl,
- optionally substituted alkylaryl;

5 R^{11} is optionally substituted alkanediyl or optionally substituted alkenediyl;

R^{12} is hydrogen and R^{13} is optionally substituted alkyl or hydroxyl, or

10 R^{13} is hydrogen and R^{12} is optionally substituted alkyl or hydroxyl, or

R^{12} and R^{13} are each alkyl, wherein at least one of the alkyl groups has at least one substituent, or

15 R^{12} and R^{13} , together with the nitrogen atom to which they are bonded, form a saturated or unsaturated, optionally substituted 5- to 8-membered ring which can optionally contain further heteroatoms; and

X^1 is selected from the group consisting of:

- 20 -
- a single bond,
 - carbonyl,
 - sulfur,
 - oxygen,
 - sulfoxy,
 - 25 -
 - sulfonyl,
 - azo and
 - an optionally substituted, saturated or unsaturated aliphatic radical having from 1 to 6 carbon atoms,

30 or pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1, wherein

R^{12} is hydrogen and R^{13} is substituted alkyl, or

R^{13} is hydrogen and R^{12} is substituted alkyl.

3. Compounds according to claim 2, wherein

5 substituted alkyl is an alkyl group which contains at least one group of the formula

$-X^2-R^{14}$, wherein

X^2 is selected from the group consisting of:

- 10
- carbonyl,
 - sulfoxy and
 - sulfonyl, and

R^{14} is selected from the group consisting of:

- 15
- hydroxy,
 - optionally substituted amino and
 - optionally substituted alkoxy.

4. Compounds according to any one of claims 1, 2 or 3, wherein

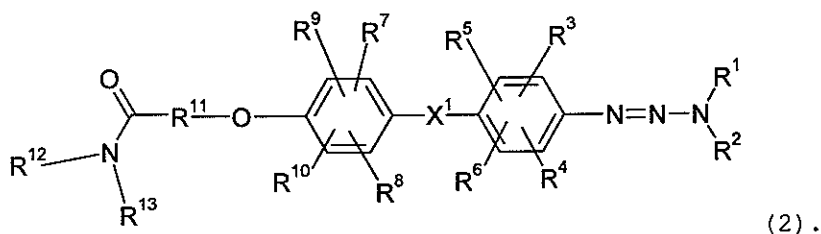
20

R^{12} is hydrogen and R^{13} is a radical A of a compound of the formula H_2N-A , or

R^{13} is hydrogen and R^{12} is a radical A of a compound of the formula H_2N-A , wherein

25 A is a radical that is derived by cleavage of the amino group ($-NH_2$) from a natural or synthetic amino acid, a natural or synthetic amino acid derivative or a polyamino acid or polyamino acid derivative.

30 5. Compounds according to one or more of claims 1 to 4, of formula (2):



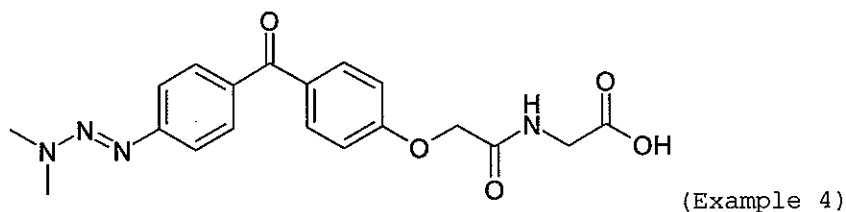
6. Compounds according to any one of claims 1 to 5, wherein

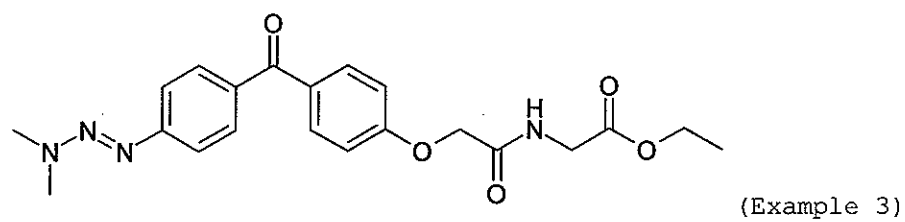
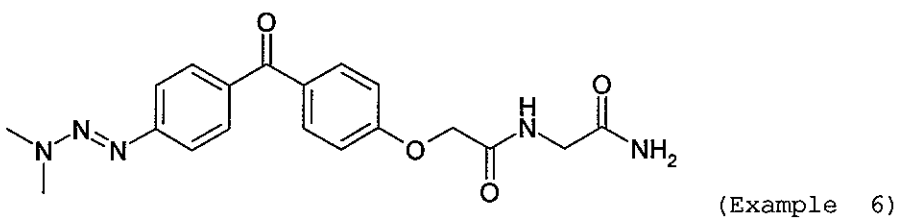
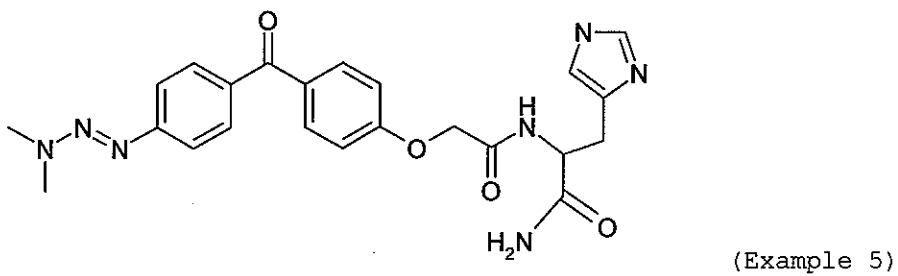
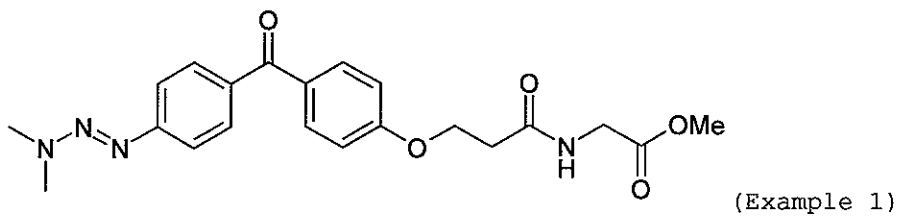
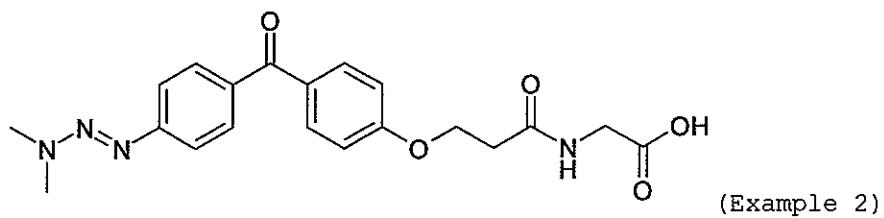
- 5 R^1 and R^2 are in each case alkyl,
 R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 and R^{10} are in each case hydrogen,
 R^{11} is alkanediyl,
 R^{12} is hydrogen and R^{13} is a radical A of a compound of the
formula H_2N-A or
10 R^{13} is hydrogen and R^{12} is a radical A of a compound of the
formula H_2N-A , wherein

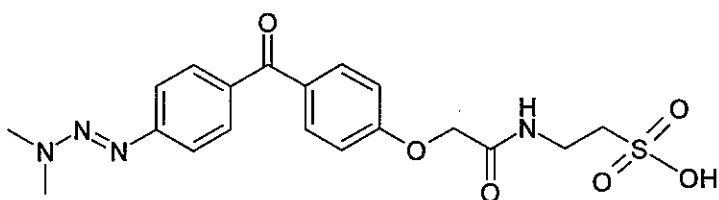
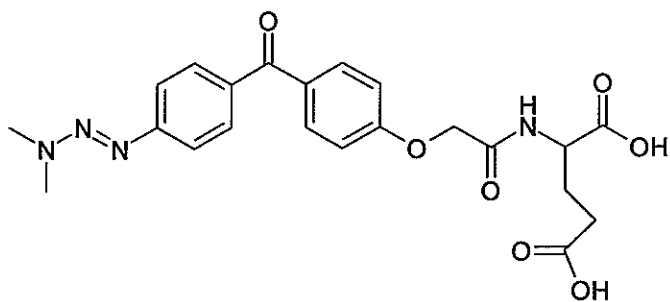
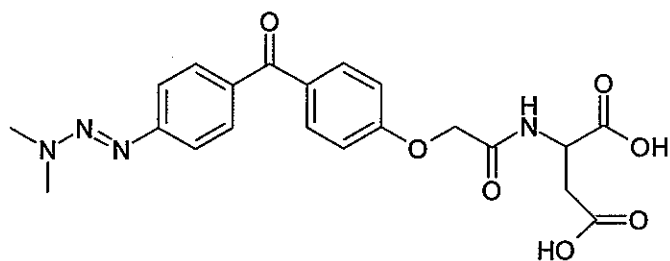
A is in each case a radical that is derived by
cleavage of the amino group ($-NH_2$) from a natural or
synthetic amino acid, a natural or synthetic amino
15 acid derivative or a polyamino acid or polyamino acid
derivative, and

X^1 is carbonyl ($-CO-$).

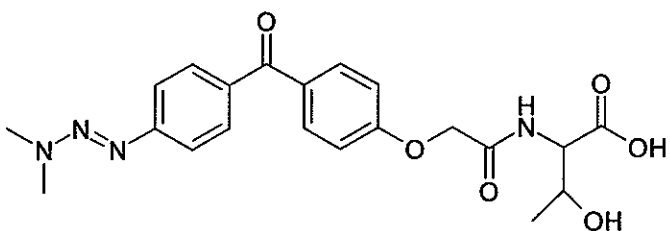
7. Compounds according to one or more of claims 1 to 6,
20 selected from the group consisting of:







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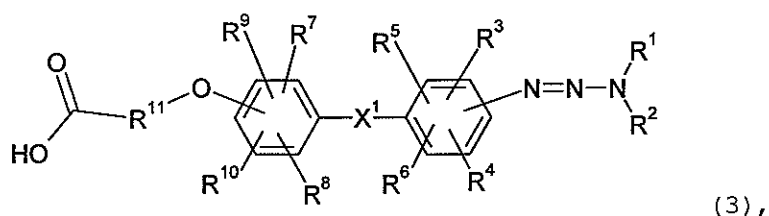


or pharmaceutically acceptable salts thereof.

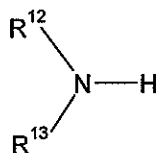
10

8. Process for the preparation of compounds of formula (1) according to one or more of claims 1 to 7, which comprises the step:

reaction of a compound of formula (3):



5 or a salt thereof, with a compound of formula (4)



10 wherein R¹ to R¹³ and X¹ are as defined in one or more of claims 1 to 7.

9. Compounds of formula (1) according to one or more of claims 1 to 7 for use as a medicament.
- 15 10. Use of the compounds of formula (1) according to one or more of claims 1 to 7 in the preparation of a medicament for the treatment of cancer diseases.