

WO 03/097602

CYANOGUANIDINE PRODRUGS

FIELD OF INVENTION

- 5 The present invention relates to novel pyridyl cyanoguanidine prodrugs and their inclusion in pharmaceutical compositions, as well as their use in the manufacture of medicaments.

BACKGROUND OF THE INVENTION

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Pyridyl cyanoguanidines such as pinacidil (N-1,2,2-trimethylpropyl-N'-cyano-N''-(4-pyridyl)guanidine) were originally discovered to be potassium channel openers and were consequently developed as antihypertensive agents. Replacement of the side chain of pinacidil by longer aryl-containing
15 side chains caused a loss of the antihypertensive activity, but such compounds were, on the other hand, found to show antitumour activity on oral administration in a rat model carrying Yoshida ascites tumours.

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Different classes of pyridyl cyanoguanidines with antiproliferative activity are disclosed in, for instance, EP 660 823, WO 98/54141, WO 98/54143, WO 98/54144, WO 98/54145, WO 00/61559 and WO 00/61561. The structure-activity relationships (SAR) of such compounds are discussed in C. Schou et al., *Bioorganic and Medicinal Chemistry Letters* 7(24), 1997, pp. 3095-3100, in which the antiproliferative effect of a number of pyridyl cyanoguanidines
25 was tested *in vitro* on different human lung and breast cancer cell lines as well as on normal human fibroblasts. The compounds were also tested *in vivo* in nude mice carrying a human lung cancer tumour xenograft. Based on the SAR analysis, a specific compound (N-(6-(4-chlorophenoxy)hexyl)-N'-cyano-N''-(4-pyridyl)guanidine) was selected for its high antiproliferative
30 activity *in vitro* and potent antitumour activity in the nude mouse model.

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P-J V Hjarnaa et al., *Cancer Res.* 59, 1999, pp. 5751-5757, report on the results of further testing of the compound N-(6-(4-chlorophenoxy)hexyl)-N'-cyano-N''-(4-pyridyl)guanidine in *in vitro* and *in vivo* tests. The compound
exhibited a potency *in vitro* which was comparable to that of the reference cytostatic agents daunorubicin and paclitaxel, while showing considerably less antiproliferative activity on normal human endothelial cells. In *in vivo* tests using nude mice transplanted with human tumour cells, the compound

showed substantial antitumour activity, also against tumour cells that were resistant to conventional anticancer drugs such as paclitaxel.

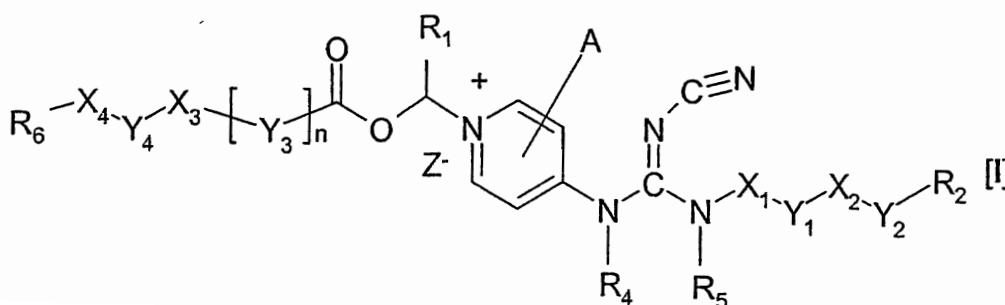
SUMMARY OF THE INVENTION

While, as indicated above, pyridyl cyanoguanidines are promising antitumour agents with an extremely interesting activity profile, they are highly lipophilic and consequently sparingly soluble compounds and are, as such, generally available for oral administration only. However, many cancer patients are in a severely debilitated condition as a result of their illness giving rise to problems with patient compliance with respect to oral administration of drugs.

It is therefore an object of the present invention to provide pyridyl cyanoguanidines in the form of prodrugs with an improved solubility profile which prodrugs may be included in pharmaceutical compositions suitable for parenteral administration, i.e. liquid compositions in which the prodrug is dissolved in sufficient amounts to be converted to therapeutically effective quantities of the active compound on administration of the composition. The compounds of the present invention exhibit good solubility in water, even at pH values around physiological pH making them ideal candidates for parenteral administration.

Furthermore, it has been found that pyridyl cyanoguanidine prodrugs of the invention exhibit an improved gastrointestinal absorption on oral administration. Consequently, it is another object of the invention to provide oral formulations of pyridyl cyanoguanidines as prodrugs with improved bioavailability.

Accordingly, the present invention relates to a compound of the general formula I



wherein X_1 is a straight, branched and/or cyclic hydrocarbon diradical, optionally substituted with one or more hydroxy, halogen, nitro, amino, cyano;

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X_2 is a bond; a straight, branched and/or cyclic hydrocarbon diradical, optionally substituted with one or more hydroxy, halogen, nitro, amino, cyano, aminosulfonyl, alkylsulfonylamino, alkylcarbonyl, formyl, aminocarbonyl or alkylcarbonylamino; a heteroarylene or non-aromatic heterocyclic hydrocarbon diradical, all of which are optionally substituted with one or more straight, branched and/or cyclic non-aromatic hydrocarbon radical, hydroxyl, halogen, amino, nitro, cyano, aminosulfonyl, alkylsulfonylamino, alkylcarbonyl, formyl, aminocarbonyl or alkylcarbonylamino;

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X_3 is a straight, branched and/or cyclic hydrocarbon diradical, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, nitro, amino, cyano, aminosulfonyl, alkylsulfonylamino, alkylcarbonyl, formyl, aminocarbonyl or alkylcarbonylamino;

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X_4 is a bond or a straight, branched and/or cyclic hydrocarbon diradical, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, nitro, amino, cyano, aminosulfonyl, alkylsulfonylamino, alkylcarbonyl, formyl, aminocarbonyl or alkylcarbonylamino;

Y_1 is a bond, O, S, S(O), S(O)₂, C(O), NH-C(O) or C(O)-NH;

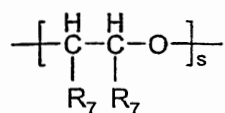
Y_2 is a bond, an ether diradical (R'-O-R''), an amine diradical (R'-N-R''), O, S, S(O), S(O)₂, C(O), NH-C(O), C(O)-NH, SO₂-N(R') or N(R')-SO₂ wherein R' and R'' are independently straight or branched hydrocarbon diradicals containing up to 4 carbon atoms;

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Y_3 is O;

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Y_4 is O, S, C(O) or



wherein s is an integer from 1 to 100 and R_7 is hydrogen or methyl;

R_1 is hydrogen or straight, branched and/or cyclic alkyl, optionally substituted with phenyl; or an aromatic hydrocarbon radical;

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R_2 is hydrogen, or aryl or heteroaryl, both of which are optionally substituted with one or more substituent selected from the group consisting of halogen, trifluoromethyl, hydroxy, C_{1-4} alkoxy, nitro, cyano, C_{1-4} hydroxyalkyl or C_{1-4} alkyl, optionally substituted with halogen, hydroxyl, cyano or nitro; tetrahydropyranyloxy, di- $(C_{1-4}$ alkoxy)phosphinoyloxy or C_{1-4} alkoxycarbonylamino;

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R_4 and R_5 are independently hydrogen; a straight, branched and/or cyclic hydrocarbon radical, optionally substituted with halogen, hydroxyl, halogen, amino, nitro or cyano;

15

R_6 is an amino group or a heterocyclic ring or condensed ring system with 3-10 ring atoms, wherein at least 1 ring atom constitutes an aliphatic amine;

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A is hydrogen, an optionally substituted, straight, branched and/or cyclic hydrocarbon radical, hydroxy, halogen, nitro, cyano, heteroaryl, heteroaralkyl or thiol;

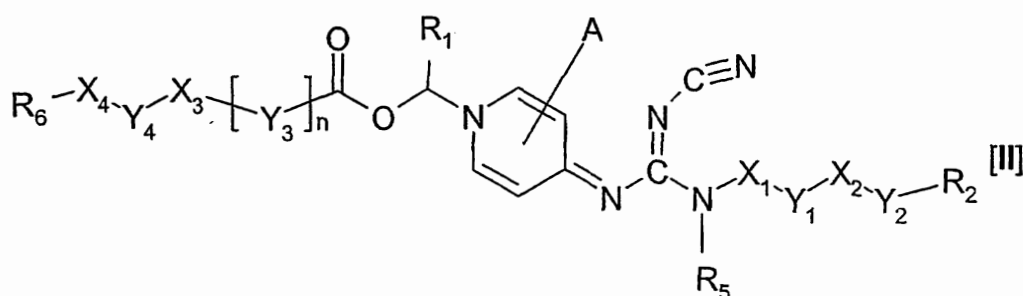
n represents 0 or 1; and

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Z^- is a pharmaceutically acceptable anion, such as chloride, bromide, iodide, sulfate, methanesulfonate, p-toluenesulfonate, nitrate or phosphate.

Furthermore, the invention relates to a compound of formula II, which is the free base form of the compounds of formula I, provided R_4 is hydrogen

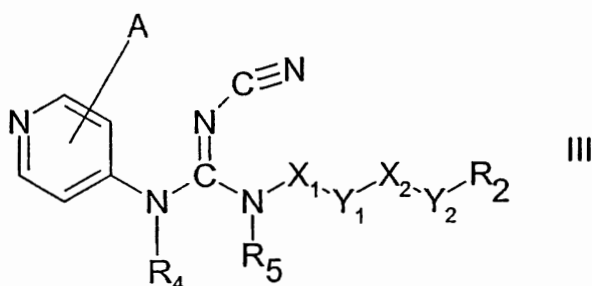
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wherein A , R_1 , R_2 , R_5 , R_6 , X_1 , X_2 , X_3 , X_4 , Y_1 , Y_2 , Y_3 , Y_4 and n are as indicated above.

It is understood that the compounds of the present invention include any tautomeric forms, optical isomers or diastereoisomers thereof, either in pure form or as mixtures thereof. It is further understood that the invention includes pharmaceutically acceptable salts of compounds of formula I or II.

On administration of a compound of formula I or formula II to a patient, the ester or carbonate group $R_6-X_4-Y_4-X_3-(Y_3)_n-C(O)O-CHR_1-$ is hydrolysed enzymatically to liberate the active compound of formula III



wherein A, R_2 , R_4 , R_5 , X_1 , X_2 , Y_1 , and Y_2 are as indicated above, together with the aldehyde R_1CHO .

DETAILED DESCRIPTION OF THE INVENTION

Definitions

In the present context, the term "prodrug" is intended to indicate a derivative of an active compound which does not, or does not necessarily, exhibit the physiological activity of the active compound, but which may be subjected to enzymatic cleavage such as hydrolysis *in vivo* so as to release the active compound on administration of the prodrug. In this particular instance, the prodrug comprises the active compound which in itself is highly lipophilic provided with a side chain with predominantly hydrophilic properties imparting improved solubility characteristics to the prodrug, thereby making it more suitable for parenteral administration in the form of a solution or for oral administration to obtain an improved bioavailability. More specifically, the hydrophilic side chain selected for the compounds of the present invention comprises an ester or carbonate group of formula $R_6-X_4-Y_4-X_3-(Y_3)_n-C(O)O-CHR_1-$ (wherein R_1 , R_6 , X_3 , X_4 , Y_3 , Y_4 and n are as indicated above).

The term "alkyl" is intended to indicate a univalent radical derived from straight, branched or cyclic alkane by removing a hydrogen atom from any carbon atom, preferably comprising 1-8 carbon atoms. The term includes the subclasses primary, secondary and tertiary alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.-butyl, isobutyl, tert.-butyl, isopentyl, isohexyl, cyclohexyl, cyclopentyl and cyclopropyl.

The term "aryl" is intended to indicate radicals of carbocyclic aromatic rings, optionally fused bi-, tri- or tetra-cyclic rings wherein at least one ring is aromatic, e.g. phenyl, naphthyl, indanyl, indenyl, 1,4-dihydronaphthyl, flourenyl or tetralinyl.

The term "heteroaryl" is intended to indicate radicals of heterocyclic aromatic rings, in particular 5- or 6-membered rings with 1-3 heteroatoms selected from O, S and N, or optionally fused bicyclic rings, of which at least one is aromatic, with 1-4 heteroatoms, e.g. pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, pyridyl, pyrimidyl, purinyl, quinolinyl, chromenyl or carbazolyl.

The term "aralkyl" is intended to indicate an aromatic ring with an alkyl side chain as defined above, e.g. benzyl.

The term "halogen" is intended to indicate fluoro, chloro, bromo or iodo.

The term "aminosulfonyl" indicates a radical of the formula $-S(O)_2NR^a$, wherein each R^a independently represents either hydrogen or alkyl as defined above.

The term "alkylsulfonylamino" indicates a radical of the formula $-NR^a_2-S(O)_2-R^b$, wherein each R^a independently represents hydrogen or alkyl as defined above, and R^b represents alkyl as defined above.

The term "alkylcarbonyl" indicates a radical of the formula $-C(O)R^b$, wherein R^b is as just described.

The term "amino" indicates a radical of the formula $-N(R^a)_2$, wherein each R^a independently represents hydrogen or alkyl as defined above.

The term "alkylcarbonylamino" indicates a radical of the formula $\text{-NR}^a\text{C(O)R}^b$, wherein R^a and R^b are as just described.

5 The term "alkoxy" indicates a radical of the formula OR^b , wherein R^b is as just described.

The term "alkoxycarbonyl" is intended to indicate a radical of the formula -C(O)-OR^b , wherein R^b is as indicated above.

10 The term "aminoacylamino" is intended to indicate a radical of the formula $\text{-NH-C(O)-R}^c\text{-NH}_2$, wherein R^c is a diradical known from any natural amino acid, $\text{H}_2\text{N-R}^c\text{-COOH}$, or its enantiomer.

15 The term "aminocarbonyl" is intended to indicate a radical of the formula -C(O)-NR^a_2 , wherein each R^a independently represent hydrogen or alkyl as defined above.

The term "alkoxycarbonylamino" is intended to indicate a radical of the formula $\text{-NR}^a\text{-C(O)-OR}^b$, wherein R^a and R^b are as indicated above.

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The term "hydrocarbon" is intended to indicate a compound comprising only hydrogen and carbon atoms, it may contain one or more double or triple carbon-carbon bonds, and it may comprise cyclic moieties in combination with branched or linear moieties. Preferably, said hydrocarbon comprises 1-18 carbon atoms, e.g. 1-12 carbon atoms. The term may be qualified as "non-aromatic heterocyclic", which is intended to indicate saturated or partly saturated cyclic compounds with 1-3 heteroatoms selected from O, S or N or optionally fused bicyclic rings with 1-4 heteroatoms, such as pyrrolidinyl, 3-pyrrolinyl, tetrahydrofuranyl, tetrahydrothiophenyl, 27 piperidinyl or piperazinyl.

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The term "a heterocyclic ring or condensed ring system with 3-10 ring atoms, wherein at least 1 ring atom constitutes an aliphatic amine" is intended to include radicals, such as pyrrolidinyl, piperidyl, hexahydro-1H-azapinyl, imidazolidinyl, piperazinyl, decahydro-isoquinolinyl, octahydro-isoindolyl, 1,2,3,4-tetrahydro-isoquinolinyl, 2,3-dihydro-1H-isoindolyl or morpholinyl.

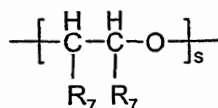
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The term "pharmaceutically acceptable salt" is intended to indicate salts prepared by reacting a compound of formula I or II comprising a basic group with a suitable inorganic or organic acid, e.g. hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric, acetic, phosphoric, lactic, maleic, phthalic, citric, propionic, benzoic, glutaric, gluconic, methanesulfonic, salicylic, succinic, tartaric, toluenesulfonic, sulfamic or fumaric acid.

Preferred embodiments of the compound of formula I or II

- 10 In a preferred embodiment of the invention, X_2 and Y_1 are both bonds, while X_1 is a straight, branched or cyclic, saturated or unsaturated hydrocarbon diradical with 4 to 20 carbon atoms;
 Y_2 is O, S, C(O) or a bond;
 R_2 is aryl or heteroaryl, optionally substituted with one or more substituent
 15 selected from the group consisting of halogen, trifluoromethyl, hydroxy, C_{1-4} alkoxy, nitro, cyano, C_{1-4} hydroxyalkyl or C_{1-4} alkyl, optionally substituted with halogen, hydroxyl, cyano or nitro; tetrahydropyranyloxy, di- $(C_{1-4}$ alkoxy)phosphinoyloxy or C_{1-4} alkoxycarbonylamino;
 X_3 or a straight hydrocarbon comprising from 1 to 4 carbon atoms;
 20 X_4 or a bond;
 n is 1 and Y_4 is O;
 R_6 or $-NH_2$ or piperidyl, attached at the 2, 3 or 4 position to X_3 , and in particular at the 4 position;
 R_1 is hydrogen, straight or branched C_{1-4} alkyl, aralkyl or aryl;
 25 A, R_4 and R_5 are all hydrogen;
 and Z^- is a pharmaceutically acceptable anion, such as chloride, bromide, iodide, sulfate, methanesulfonate, p-toluenesulfonate or nitrate.

In embodiments where Y_4 is



s is preferably an integer of from 1 to 75, more preferably from 1 to 50, in particular from 1 to 30, such as from 1 to 25, from 1 to 20, from 1 to 15 or from 1 to 10.

- 35 In a preferred embodiment of the compounds of formula I or II, R_2 is aryl and in particular phenyl, optionally substituted by one or more substituent selected from the group consisting of halogen, trifluoromethyl, hydroxy,

C₁₋₄alkoxy, nitro, cyano, C₁₋₄hydroxyalkyl or C₁₋₄alkyl, optionally substituted with halogen, hydroxyl, cyano or nitro. A particular preferred substituent is halogen, such as chloro.

- 5 In a preferred embodiment of the compounds of formula I or II, Y₁ is a bond and Y₂ is O.

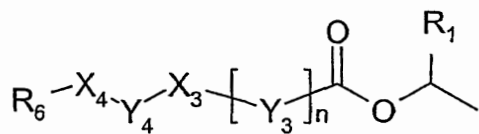
In a further preferred embodiment of the compounds of formula I or II, X₁ is a C₄₋₁₂ hydrocarbon diradical and X₂ is a bond.

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Specific examples of compounds according to formula I are

- 1-[2-(4-Piperidyloxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chloro-phenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride, hydrochloride;
 15 1-[2-(2-aminoethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride, hydrochloride;
 1-[2-(2-(2-aminoethoxy)-ethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride, hydrochloride; and
 20 1-[2-(2-(2-(2-aminoethoxy)-ethoxy)-ethoxy)-ethoxy)-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride, hydrochloride.

As described above, an advantage of the prodrug forms of cyanoguanidines of the present invention is an increased solubility compared to the solubility of the cyanoguanidines themselves. Said increase may be ascribed to at least two factors, i.e. the positive charge at the pyridine nitrogen, and the hydrophilic character of the prodrug moiety, i.e.



- . Pyridines in general have pK_B values
 30 around 9. This indicates that if pH is raised from acid pH values, e.g. 3 to physiological pH then the compounds of the present invention will be transformed from compounds of formula I to the corresponding free base, i.e. to compounds of formula II. At physiological pH, the positive charge at the pyridine nitrogen has thus largely disappeared, and this will lower the
 35 solubility of the compounds. It is believed to be a particular advantage of the compounds of the present invention that the prodrug moiety at R₆ bears

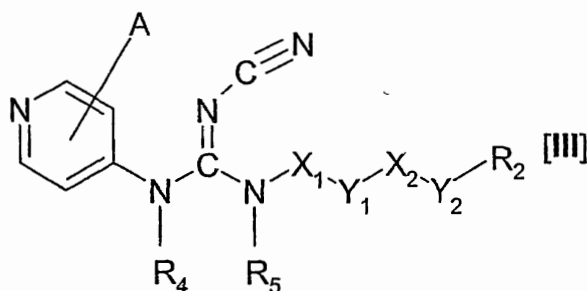
a unit charge, or at least a fraction of a unit charge, at physiological pH. As defined, R_6 comprises an aliphatic amine moiety, and it is well-known that aliphatic amines have pK_B values in the 3-5 range [Frenna, *J.Chem.Soc. Perkin Trans. II*, 1865, 1985], which implies that the amine moiety is mainly protonated at physiological pH. The protonation gives rise to a charge which increases solubility.

Moreover, the following compounds are found to be particular useful in the preparation of compound of formula I or II

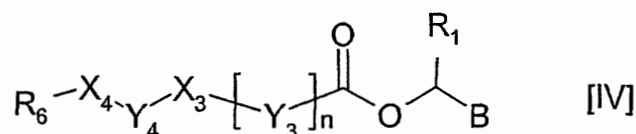
Chloromethyl 2-(1-(tert-butoxycarbonyl)-4-piperidyloxy)-ethyl carbonate;
 Iodomethyl 2-(1-(tert-butoxycarbonyl)-4-piperidyloxy)-ethyl carbonate;
 1-[2-[1-(tert-Butoxycarbonyl)-4-piperidyloxy]-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium iodide;
 Chloromethyl 2-(2-azidoethoxy)-ethyl carbonate;
 Chloromethyl 2-(2-(2-azidoethoxy)-ethoxy)-ethyl carbonate;
 Chloromethyl 2-(2-(2-(2-azidoethoxy)-ethoxy)-ethoxy)-ethyl carbonate;
 Iodomethyl 2-(2-azidoethoxy)-ethyl carbonate;
 Iodomethyl 2-(2-(2-azidoethoxy)-ethoxy)-ethyl carbonate;
 Iodomethyl 2-(2-(2-(2-azidoethoxy)-ethoxy)-ethoxy)-ethyl carbonate;
 1-[2-(2-azidoethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride;
 1-[2-(2-(2-azidoethoxy)-ethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride; and
 1-[2-(2-(2-(2-azidoethoxy)-ethoxy)-ethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride.

General methods of preparation

Compounds of formula I may be prepared by reacting a compound of formula III



wherein A, R₂, R₄, R₅, X₁, X₂, Y₁ and Y₂ are as indicated in formula I, with a compound of formula IV



wherein R₁, R₆, X₃, X₄, Y₃, Y₄ and n are as indicated in formula I, and B is a leaving group, such as Cl, Br or I. In addition R₆, X₃, and X₄ may optionally contain protecting groups and R₆ may be a precursor of an amino group, e.g. an azido group.

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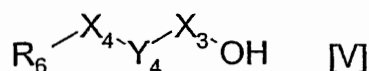
The reaction of a compound of formula III with a compound of formula IV may be performed in a solvent-free environment or in an inert solvent such as acetonitrile at a temperature between room temperature and 150°C to afford a compound of formula I optionally after removal of protecting groups and/or conversion of precursors of amino groups into amino groups by methods well known to persons skilled in the art.

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The compounds of formula IV are known from the literature or may be prepared by methods well known to persons skilled in the art.

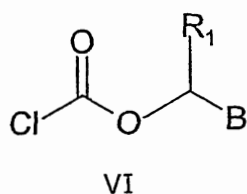
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When n is 1, compounds of formula IV may be prepared by reacting a compound of formula V



wherein R₆, X₃, X₄ and Y₄ are as indicated in formula IV, with a compound of formula VI

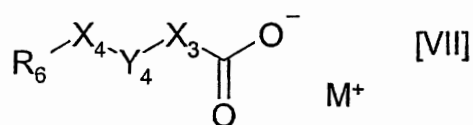
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wherein R₁ and B are as indicated above.

The reaction between a compound of formula V and a compound of formula VI may be performed at a temperature between room temperature and -70°C in an inert organic solvent, such as dichloromethane, in the presence of a suitable base such as pyridine.

When n is zero, compounds of formula IV in which B is chlorine may be prepared by reacting a compound of formula VII



wherein R_6 , X_3 , X_4 and Y_4 are as indicated in formula IV and M^+ is a suitable metal kation, e. g. an alkali metal kation, or a tertiary ammonium ion, with a compound of formula VIII



wherein R₁ is as indicated above and X is iodo, bromo or chlorosulfonyloxy.

The reaction between VII and VIII may be performed in a suitable solvent such as dimethylformamide at a suitable temperature, e.g. at room temperature, when X is iodo or bromo. When X is chlorosulfonyloxy the reaction may be performed under phase transfer conditions as described in Synthetic Communications 14, 857-864 (1984).

Compounds of formula IV in which B is chloro may be transformed into the corresponding compounds in which B is iodo by reaction with sodium iodide in acetone or acetonitrile.

The compounds of formulae V, VI, VII, VIII are either known from the literature or may be prepared by methods well known to persons skilled in the art.

Compounds of formula III are known from the literature and may be prepared by any one of the methods disclosed in, for instance, EP 660 823,

WO 98/54141, WO 98/54143, WO 98/54144, WO 98/54145, WO 00/61559 and WO 00/61561.

5 A compound of formula I, provided that R₄ is hydrogen may be converted into the corresponding free base of formula II by treating a solution of a compound of formula I in an appropriate inert solvent, e.g. dichloromethane, with a suitable base, e.g. aqueous sodium bicarbonate. The free base of formula II may be reconverted into a salt of formula I by
10 treating a solution of a compound of formula II in an appropriate inert solvent, e.g. dichloromethane, with a suitable acid of formula ZH, wherein Z is as indicated above.

Pharmaceutical compositions

15 In another aspect, the invention relates to pharmaceutical formulations of a compound of formula I or II intended for the treatment of proliferative diseases. The formulations of the present invention, both for veterinary and for human medical use, comprise active ingredients in association with a
20 pharmaceutically acceptable carrier(s) and optionally other therapeutic ingredient(s). The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

25 Conveniently, the active ingredient comprises from 0.1-100% by weight of the formulation. Conveniently, a dosage unit of a formulation contain between 0.07 mg and 1 g of a compound of formula I or II.

30 By the term "dosage unit" is meant a unitary, i.e. a single dose which is capable of being administered to a patient, and which may be readily handled and packed, remaining as a physically and chemically stable unit dose comprising either the active material as such or a mixture of it with solid or liquid pharmaceutical diluents or carriers.

35 The formulations include e.g. those in a form suitable for oral (including sustained or timed release), rectal, parenteral (including subcutaneous, intraperitoneal, intramuscular, intraarticular and intravenous), transdermal, ophthalmic, topical, nasal or buccal administration.

The formulations may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy, e.g. as disclosed in Remington, The Science and Practice of Pharmacy, 20th ed., 2000. All methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be in the form of discrete units, such as capsules, sachets, tablets or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or a suspension in an aqueous liquid or non-aqueous liquid, such as ethanol or glycerol; or in the form of an oil-in-water emulsion or a water-in-oil emulsion. Such oils may be edible oils, such as e.g. cottonseed oil, sesame oil, coconut oil or peanut oil. Suitable dispersing or suspending agents for aqueous suspensions include synthetic or natural gums such as tragacanth, alginate, acacia, dextran, sodium carboxymethylcellulose, gelatin, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, carbomers and polyvinylpyrrolidone. The active ingredients may also be administered in the form of a bolus, electuary or paste.

A tablet may be made by compressing or moulding the active ingredient optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient(s) in a free-flowing form such as a powder or granules, optionally mixed by a binder, such as e.g. lactose, glucose, starch, gelatine, acacia gum, tragacanth gum, sodium alginate, carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, polyethylene glycol, waxes or the like; a lubricant such as e.g. sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride or the like; a disintegrating agent such as e.g. starch, methylcellulose, agar, bentonite, croscarmellose sodium, sodium starch glycollate, crospovidone or the like or a dispersing agent, such as polysorbate 80. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered active ingredient and suitable carrier moistened with an inert liquid diluent.

Formulations for rectal administration may be may in the form of suppositories in which the compound of the present invention is admixed with low melting water soluble or insoluble solids such as cocoa butter, hydrogenated vegetable oils, polyethylene glycol or fatty acids esters of polyethylene glycols, while elixirs may be prepared using myristyl palmitate.

Formulations suitable for parenteral administration conveniently comprise a sterile oily or aqueous preparation of the active ingredients, which is preferably isotonic with the blood of the recipient, e.g. isotonic saline, isotonic glucose solution or buffer solution. The formulation may be conveniently sterilised by for instance filtration through a bacteria retaining filter, addition of sterilising agent to the formulation, irradiation of the formulation or heating of the formulation. Liposomal formulations as disclosed in e.g. Encyclopedia of Pharmaceutical Technology, vol.9, 1994, are also suitable for parenteral administration.

Alternatively, the compound of formula I may be presented as a sterile, solid preparation, e.g. a freeze-dried powder, which is readily dissolved in a sterile solvent immediately prior to use.

Transdermal formulations may be in the form of a plaster or a patch.

Formulations suitable ophthalmic administration may be in the form of a sterile aqueous preparation of the active ingredients, which may be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems e.g. as disclosed in Encyclopedia of Pharmaceutical Technology, vol.2, 1989, may also be used to present the active ingredient for ophthalmic administration.

Formulations suitable for topical or ophthalmic administration include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops.

Formulations suitable for nasal or buccal administration include powder, self-propelling and spray formulations, such as aerosols and atomisers.

In addition to the aforementioned ingredients, the formulations of a compound of formula I or II may include one or more additional ingredients such as diluents, buffers, flavouring agents, colourant, surface active agents, thickeners, preservatives, e.g. methyl hydroxybenzoate (including anti-oxidants), emulsifying agents and the like.

In the systemic treatment using the present invention daily doses of from 0.001-500 mg per kilogram body weight, preferably from 0.002-100 mg/kg of mammal body weight, for example 0.003-20 mg/kg or 0.003 to 5 mg/kg of a compound of formula I or II is administered, typically corresponding to a daily dose for an adult human of from 0.01 to 37000 mg. However, the present invention also provides compounds and compositions intended for administration with longer intervals, e.g. every week, every three weeks or every month. In the topical treatment of dermatological disorders, ointments, creams or lotions containing from 0.1-750 mg/g, and preferably from 0.1-500 mg/g, for example 0.1-200 mg/g of a compound of formula I or II is administered. For topical use in ophthalmology ointments, drops or gels containing from 0.1-750 mg/g, and preferably from 0.1-500 mg/g, for example 0.1-200 mg/g of a compound of formula I or II is administered. The oral compositions are formulated, preferably as tablets, capsules, or drops, containing from 0.07-1000 mg, preferably from 0.1-500 mg, of a compound of formula I or II per dosage unit.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising a compound of formula I or II in combination with one or more other pharmacologically active compounds used in the treatment of proliferative diseases. Examples of compounds used in the treatment of proliferative diseases which may be used together with compounds of the present invention include S-triazine derivatives such as altretamine; enzymes such as asparaginase; antibiotic agents such as bleomycin, dactinomycin, daunorubicin, doxorubicin, idarubicin, mitomycin, epirubicin and plicamycin; alkylating agents such as busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, ifosfamide, lomustine, mechlorethamine, melphalan, procarbazine and thiotepa; antimetabolites such as cladribine, cytarabine, floxuridine, fludarabine, fluorouracil, hydroxyurea, mercaptopurine, methotrexate, gemcitabin, pentostatin and thioguanine; antimitotic agents such as etoposide, paclitaxel, teniposide, vinblastine, vinorelbin and vincristine; hormonal agents, e.g. aromatase inhibitors such as aminoglutethimide,

corticosteroids, such as dexamethasone and prednisone, and luteinizing hormone releasing hormone (LH-RH); antiestrogens such as tamoxifen, formestane and letrozole; antiandrogens such as flutamide; biological response modifiers, e.g. lymphokines such as aldesleukin and other
5 interleukines; interferon such as interferon- α ; growth factors such as erythropoietin, filgrastim and sargramostim; differentiating agents such as vitamin D derivatives, e.g. seocalcitol, and all-trans retinoic acid; immunoregulators such as levamisole; and monoclonal antibodies, tumour necrosis factor α and angiogenesis inhibitors. Finally, ionising radiation,
10 although not readily defined as a compound, is heavily depended on in the treatment of neoplastic diseases, and may be combined with the compounds of the present invention. Due to the severe side effects often experienced by patients receiving anti-neoplastic treatment it is often desirable also to administer therapeutics which are not themselves anti-neoplastic, but rather
15 help relieving the side effects of anti-neoplastic therapy. Such compounds include amifostin, leucovorin and mesna.

In particular, anti-neoplastic compounds, such as paclitaxel, fluorouracil, etoposide, cyclophosphamide, cisplatin, carboplatin, vincristine, gemcitabine,
20 vinorelbine, chlorambucil, doxorubicin, melphalan and seocalcitol appear beneficial in the combination compositions of the present invention.

It is envisaged that the combination composition of the present invention may be provided as mixtures of the compounds or as individual compounds
25 intended for simultaneous or sequential administration. It lies within the capabilities of a skilled physician or veterinarian to decide time intervals in a sequential administration regime.

In a further aspect, the invention relates to a method of treating or
30 ameliorating proliferative diseases or conditions, the method comprising administering, to a patient in need thereof, a pharmaceutical composition comprising a compound of formula I or II, which compound is hydrolysed enzymatically upon administration to provide a compound of formula III, in an amount sufficient to effect treatment or amelioration of said proliferative
35 disease or condition, optionally together with another anti-neoplastic compound and/or ionising radiation.

In particular, proliferative diseases or conditions to be treated by the present method include a variety of cancers and neoplastic diseases or

conditions including leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia, chronic lymphatic leukaemia, myelodysplasia, multiple myeloma, Hodgkin's disease or non-Hodgkin's lymphoma, small or non-small cell lung carcinoma, gastric, intestinal or colorectal cancer, prostate, ovarian or breast cancer, brain, head or neck cancer, cancer in the urinary tract, kidney or bladder cancer, malignant melanoma, liver cancer, uterine or pancreatic cancer.

Cyanoguanidines are also believed to be useful in the treatment of inflammatory diseases. In one aspect, the invention thus provides a method of treating or ameliorating inflammatory diseases, the method comprising administering to a patient in need thereof an effective amount of a compound of the present invention, either alone or in combination with other therapeutically active compounds.

The invention also relates to the use of compounds of formula I or II, optionally together with other anti-neoplastic compounds, as indicated above, in the manufacture of medicaments. In particular, said medicament is intended to be used for the treatment of proliferative diseases, e.g. cancers as mentioned above.

As indicated above, it is preferred to administer the compounds of the invention parenterally, such as in a liquid, preferably aqueous, solution intended for intravenous injection or infusion. A suitable dosage of the compound of the invention will depend, inter alia, on the age and condition of the patient, the severity of the disease to be treated and other factors well known to the practising physician. The compound may be administered either orally or parenterally according to different dosing schedules, e.g. daily or with weekly intervals. In general a single dose will be in the range from 0.1 to 400 mg/kg bodyweight. Parenterally, the compound may be administered as a bolus (i.e. the entire dose is administered at once) or in divided doses two or more times a day or preferably as an intravenous infusion.

The invention is described in further detail in the following examples which are not in any way intended to limit the scope of the invention as claimed.

EXAMPLES

For ^1H nuclear magnetic resonance (NMR) spectra (300 MHz) and ^{13}C NMR (75.6 MHz) chemical shift values are quoted relative to internal tetramethylsilane ($\delta=0.00$) or chloroform ($\delta=7.25$) or deuteriochloroform ($\delta=76.81$ for ^{13}C NMR) standards. The value of a multiplet, either defined (singlet (s), doublet (d), triplet (t), quartet (q)) or not (broad (br)), at the approximate midpoint is given unless a range is quoted. The organic solvents used were anhydrous.

Preparation 1Chloromethyl 2-(1-(tert-butoxycarbonyl)-4-piperidyloxy)-ethyl carbonate

Pyridine (1.03 ml) was added to a dry-ice cooled solution of 2-(1-(tert-butoxycarbonyl)-4-piperidyloxy)-ethanol (2.62 g) in dichloromethane (20 ml) followed by a solution of chloromethyl chloroformate (1.05 ml) in dichloromethane (5 ml) at such a rate that the temperature was kept below $-60\text{ }^\circ\text{C}$. After stirring for 1 hour the cooling bath was removed and the temperature was allowed to rise to room temperature. The reaction mixture was then washed twice with 0.5 M HCl followed by water and aqueous sodium bicarbonate. The organic phase was dried over magnesium sulfate, filtered and evaporated in vacuo to yield the title compound as a colourless oil.

^{13}C NMR (CDCl_3) δ = 154.8, 153.4, 79.5, 75.1, 72.2, 68.3, 65.3, 41.0, 30.8, 28.4

Preparation 2Iodomethyl 2-(1-(tert-butoxycarbonyl)-4-piperidyloxy)-ethyl carbonate

Chloromethyl 2-(1-(tert-butoxycarbonyl)-4-piperidyloxy)-ethyl carbonate (3.15 g) was added to a solution of sodium iodide (5.6 g) in acetone (20 ml). After stirring at $40\text{ }^\circ\text{C}$ for 2.5 hours the reaction mixture was cooled to room temperature, diluted with dichloromethane, washed with aqueous sodium bicarbonate and sodium thiosulfate and evaporated in vacuo. The residue was taken up in ether and washed with water. The organic phase was dried and evaporated in vacuo to yield the title compound as a light yellow oil.

^{13}C NMR (CDCl_3) δ = 154.8, 153.2, 79.5, 75.1, 68.3, 65.4, 41.0, 33.9, 30.9, 28.5

Preparation 3

1-[2-[1-(tert-Butoxycarbonyl)-4-piperidyloxy]-ethoxy-carbonyloxymethyl]-
4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium
5 iodide

A solution of iodomethyl 2-[1-(tert-butoxycarbonyl)-4-piperidyloxy]-ethyl carbonate (3.3 g) in acetonitrile (15 ml) was added to a hot solution of N-(6-(4-chlorophenoxy)-1-hexyl)-N'-cyano-N''-(4-pyridyl)-guanidine (1.9 g) 10 in acetonitrile (75 ml) followed by reflux for 20 minutes. After cooling to room temperature and concentration in vacuo, the title compound crystallised by the addition of ethyl acetate and was isolated by filtration as light yellow crystals.

^{13}C NMR (CDCl_3) δ = 157.7, 154.9, 154.8, 153.8, 143.8, 129.3, 125.2,
15 115.9, 114.4, 114.1, 80.5, 79.6, 75.3, 69.4, 68.1, 65.0, 41.1, 30.8, 29.2, 28.9, 28.5, 26.3, 25.5

Preparation 4

Chloromethyl 2-(2-azidoethoxy)-ethyl carbonate

20 Chloromethyl chloroformate (1.2 ml) was added to an ice-cold solution of 2-(2-azidoethoxy)-ethanol (1.6 g) in dichloromethane (12 ml) followed by pyridine (1.2 ml) at such a rate that the temperature was kept below 10 °C. After stirring for four hours at room temperature water was added and after 25 a further 5 minutes the reaction mixture was washed twice with 0.5 M HCl followed by water and aqueous sodium bicarbonate. Drying over magnesium sulfate, filtration and evaporation in vacuo gave the title compound as a light yellow oil which was used in the next step without further purification.

^1H NMR (CDCl_3) δ = 5.74 (s,2H), 4.39 (m,2H), 3.76 (m,2H), 3.68 (t,2H),
30 3.39 (t,2H)

Preparation 5

Chloromethyl 2-(2-(2-azidoethoxy)-ethoxy)-ethyl carbonate.

35 The title compound is prepared as described in Preparation 4 but substituting 2-(2-(2-azidoethoxy)-ethoxy)-ethanol for 2-(2-azidoethoxy)-ethanol.

Preparation 6Chloromethyl 2-(2-(2-(2-azidoethoxy)-ethoxy)-ethoxy)-ethyl carbonate

The title compound is prepared as described in Preparation 4 but

- 5 substituting 2-(2-(2-(2-azidoethoxy)-ethoxy)-ethoxy)-ethanol for 2-(2-azidoethoxy)-ethanol.

Preparation 7Iodomethyl 2-(2-azidoethoxy)-ethyl carbonate

10

Chloromethyl 2-(2-azidoethoxy)-ethyl carbonate (2.6 g) was added to a solution of sodium iodide (7 g) in acetone (20 ml). After stirring at 40 °C for 2.5 hours the reaction mixture was cooled to room temperature, filtered and evaporated in vacuo. The residue was taken up in dichloromethane, washed
15 with aqueous sodium bicarbonate and sodium thiosulfate, dried over magnesium sulfate, filtered and evaporated in vacuo. Purification on silica gel with hexane/ethyl acetate (2:1) as eluent gave the title compound as a colourless oil.

^{13}C NMR (CDCl_3) δ = 70.2, 68.7, 67.9, 50.7, 33.9

20

Preparation 8Iodomethyl 2-(2-(2-azidoethoxy)-ethoxy)-ethyl carbonate.

The title compound is prepared as described in Preparation 7 but

25 substituting chloromethyl 2-(2-(2-azidoethoxy)-ethoxy)-ethyl carbonate for chloromethyl 2-(2-azidoethoxy)-ethyl carbonate.

Preparation 9Iodomethyl 2-(2-(2-(2-azidoethoxy)-ethoxy)-ethoxy)-ethyl carbonate.

30

The title compound is prepared as described in Preparation 7 but substituting chloromethyl 2-(2-(2-(2-azidoethoxy)-ethoxy)-ethoxy)-ethyl carbonate for chloromethyl 2-(2-azidoethoxy)-ethyl carbonate.

35 Preparation 101-[2-(2-azidoethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium iodide.

A solution of iodomethyl 2-(2-azidoethoxy)-ethyl carbonate (3.2 g) in

acetonitrile (15 ml) was added to a hot solution of N-(6-(4-chlorophenoxy)-1-hexyl)-N'-cyano-N''-(4-pyridyl)-guanidine (2.47 g) in acetonitrile (80 ml) followed by reflux for 20 minutes. After cooling to room temperature and concentration in vacuo, the title compound crystallised by the addition of ethyl acetate and was isolated by filtration as light yellow crystals.

¹H NMR (CDCl₃) δ = 11.2 (br,1H), 8.54 (d,2H), 8.25 (br,2H), 7.8 (br,1H), 7.20 (d,2H), 6.83 (d,2H), 6.17 (s,2H), 4.39 (m,2H), 3.94 (t,2H), 3.85 – 3.70 (m,4H), 3.67 (t,2H), 3.35 (t,2H), 1.86 – 1.70 (m,4H), 1.60 – 1.47 (m,4H)

Preparation 11

1-[2-(2-(2-azidoethoxy)-ethoxy-carbonyloxymethyl)-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride

1-[2-(2-(2-azidoethoxy)-ethoxy-carbonyloxymethyl)-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium iodide was dissolved in dichloromethane, washed with an excess of aqueous sodium bicarbonate and sodium thiosulfate, dried over magnesium sulfate and filtered. The resulting solution was treated with an excess of HCl in ether, the solvents were evaporated in vacuo and the residue was redissolved in a small volume of dichloromethane. Addition of isopropanol followed by removal of dichloromethane in vacuo gave the crystalline title compound.

Preparation 12

1-[2-(2-(2-(2-azidoethoxy)-ethoxy)-ethoxy-carbonyloxymethyl)-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride

This compound is prepared as described in Preparations 10 and 11 but substituting iodomethyl 2-(2-(2-(2-azidoethoxy)-ethoxy)-ethyl carbonate for iodomethyl 2-(2-azidoethoxy)-ethyl carbonate

Preparation 13

1-[2-(2-(2-(2-(2-azidoethoxy)-ethoxy)-ethoxy)-ethoxy-carbonyloxymethyl)-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride

This compound is prepared as described in Preparations 10 and 11 but substituting iodomethyl 2-(2-(2-(2-(2-azidoethoxy)-ethoxy)-ethoxy)-ethyl carbonate for iodomethyl 2-(2-azidoethoxy)-ethyl carbonate.

Example 1

1-[2-(4-Piperidyloxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chloro-phenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride, hydrochloride.

5

A solution of 1-[2-[1-(tert-butoxycarbonyl)-4-piperidyloxy]-ethoxy-carbonyloxy-methyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium iodide (2.4 g) in dichloromethane was shaken with an excess of aqueous sodium bicarbonate and sodium thiosulfate. The organic
10 phase was dried over magnesium sulfate and filtered. After concentration in vacuo to about 25 ml the clear filtrate was cooled in ice with stirring and treated with an excess of hydrogen chloride in ether. The ice bath was removed and after stirring for 4 hours, the solvent was removed in vacuo. The residue was treated with ether followed by evaporation in vacuo. The
15 residue crystallised from methanol upon the addition of ether to yield the title compound as colourless crystals.

¹H NMR (DMSO) δ = 12.0 (br, 1H), 9.17 (br, 1H), 9.03 (br, 2H), 8.76 (d, 2H), 7.60 (br, 2H), 7.31 (d, 2H), 6.95 (d, 2H), 6.23 (s, 2H), 4.28 (m, 2H), 3.93 (t, 2H), 3.62 (m, 2H), 3.57 (m, 1H), 3.40 (br, 2H), 3.06 (m, 2H), 2.91
20 (m, 2H), 2.0-1.3 (m, 12H)

Example 2

1-[2-(2-aminoethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride, hydrochloride.

25

Triphenylphosphine (0.58 g) is added to a stirred solution of 1-[2-(2-azido-ethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride (1.19 g) in dichloromethane (20 ml) at room temperature. When the evolution of
30 nitrogen has ceased, water (0.036 ml) is added and stirring is continued overnight at room temperature. 2M HCl in ether (1 ml) is added and the solvents are removed in vacuo. The residue is stirred with ethyl acetate (10 ml) and the solvent is removed by filtration or decantation. After drying in vacuo the title compound is obtained as a colourless powder.

35

Example 3

1-[2-(2-(2-aminoethoxy)-ethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride, hydrochloride.

5

The title compound is prepared as described in Example 2 but substituting 1-[2-(2-(2-azidoethoxy)-ethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride for 1-[2-(2-azido-ethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride.

10

Example 4

1-[2-(2-(2-(2-aminoethoxy)-ethoxy)-ethoxy)-ethoxy)-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride, hydrochloride.

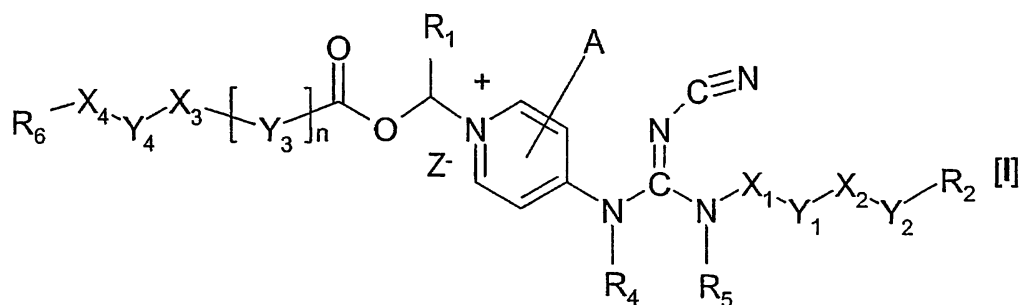
15

The title compound is prepared as described in Example 2 but substituting 1-[2-(2-(2-(2-azidoethoxy)-ethoxy)-ethoxy)-ethoxy)-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride for 1-[2-(2-azido-ethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride.

20

CLAIMS

1. A compound of general formula I



wherein X_1 is a straight, branched and/or cyclic hydrocarbon diradical, optionally substituted with one or more hydroxy, halogen, nitro, amino, cyano;

X_2 is a bond; a straight, branched and/or cyclic hydrocarbon diradical, optionally substituted with one or more hydroxy, halogen, nitro, amino, cyano, aminosulfonyl, alkylsulfonylamino, alkylcarbonyl, formyl, aminocarbonyl or alkylcarbonylamino; a heteroarylene or non-aromatic heterocyclic hydrocarbon diradical, all of which are optionally substituted with one or more straight, branched and/or cyclic non-aromatic hydrocarbon radical, hydroxyl, halogen, amino, nitro, cyano, aminosulfonyl, alkylsulfonylamino, alkylcarbonyl, formyl, aminocarbonyl or alkylcarbonylamino;

X_3 is a straight, branched and/or cyclic hydrocarbon diradical, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, nitro, amino, cyano, aminosulfonyl, alkylsulfonylamino, alkylcarbonyl, formyl, aminocarbonyl or alkylcarbonylamino;

X_4 is a bond or a straight, branched and/or cyclic hydrocarbon diradical, optionally substituted with one or more substituents selected from the group consisting of hydroxy, halogen, nitro, amino, cyano, aminosulfonyl, alkylsulfonylamino, alkylcarbonyl, formyl, aminocarbonyl or alkylcarbonylamino;

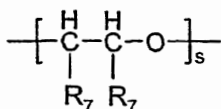
Y_1 is a bond, O, S, S(O), S(O)₂, C(O), NH-C(O) or C(O)-NH;

Y_2 is a bond, an ether diradical ($R'-O-R''$), an amine diradical ($R'-N-R''$), O, S, $S(O)$, $S(O)_2$, $C(O)$, $NH-C(O)$, $C(O)-NH$, $SO_2-N(R')$ or $N(R')-SO_2$ wherein R' and R'' are independently straight or branched hydrocarbon diradicals containing up to 4 carbon atoms;

5

Y_3 is O;

Y_4 is O, S, $C(O)$ or



10 wherein s is an integer from 1 to 100 and R_7 is hydrogen or methyl;

R_1 is hydrogen or straight, branched and/or cyclic alkyl, optionally substituted with phenyl; or an aromatic hydrocarbon radical;

15 R_2 is hydrogen, or aryl or heteroaryl, both of which are optionally substituted with one or more substituent selected from the group consisting of halogen, trifluoromethyl, hydroxy, C_{1-4} alkoxy, nitro, cyano, C_{1-4} hydroxyalkyl or C_{1-4} alkyl, optionally substituted with halogen, hydroxyl, cyano or nitro; tetrahydropyranyloxy, di- $(C_{1-4}$ alkoxy)phosphinoyloxy or C_{1-4} alkoxycarbonylamino C_{1-4} ;

20

R_4 and R_5 are independently hydrogen; a straight, branched and/or cyclic hydrocarbon radical, optionally substituted with halogen, hydroxyl, halogen, amino, nitro or cyano;

25

R_6 is an amino group or a heterocyclic ring or condensed ring system with 3-10 ring atoms, wherein at least 1 ring atom constitutes an aliphatic amine;

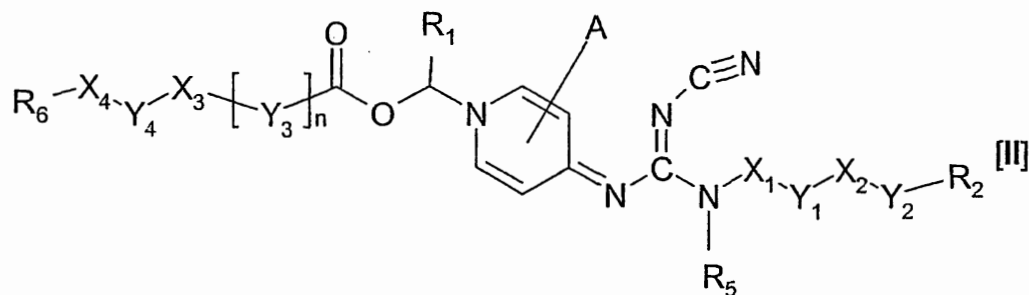
A is hydrogen, an optionally substituted, straight, branched and/or cyclic hydrocarbon radical, hydroxy, halogen, nitro, cyano, heteroaryl, heteroaralkyl or thiol;

30

n is 0 or 1; and

35 Z^- is a pharmaceutically acceptable anion, such as chloride, bromide, iodide, sulfate, methanesulfonate, p-toluenesulfonate, nitrate or phosphate.

2. A compound of the general formula II



wherein A, R₁, R₂, R₅, R₆, X₁, X₂, X₃, X₄, Y₁, Y₂, Y₃, Y₄ and n are as indicated in claim 1.

5

3. A compound according to claim 1 or 2, wherein X₂ and Y₁ are both bonds;

X₁ is a straight, branched or cyclic, saturated or unsaturated hydrocarbon diradical with 4 to 20 carbon atoms;

- 10 Y₂ is O, S, C(O) or a bond;

R₂ is aryl or heteroaryl, optionally substituted with one or more substituent selected from the group consisting of halogen, trifluoromethyl, hydroxy, C₁₋₄alkoxy, nitro, cyano, C₁₋₄hydroxyalkyl or C₁₋₄alkyl, optionally substituted with halogen, hydroxyl, cyano or nitro; tetrahydropyranyloxy, di-(C₁₋₄alkoxy)phosphinoyloxy or C₁₋₄alkoxycarbonylamino;

- 15 X₃ is a straight hydrocarbon comprising from 1 to 4 carbon atoms;

X₄ is a bond;

n is 1;

Y₄ is O;

R₆ is -NH₂ or piperidyl, attached at the 2, 3 or 4 position to X₃

R₁ is hydrogen, straight or branched C₁₋₄alkyl, aralkyl or aryl;

A, R₄ and R₅ are all hydrogen;

and Z⁻ is a pharmaceutically acceptable anion, such as chloride, bromide, iodide, sulfate, methanesulfonate, p-toluenesulfonate or nitrate.

25

4. A compound according to claim 1-3, wherein R₂ is aryl, optionally substituted by one or more substituents selected from the group consisting of halogen, trifluoromethyl, hydroxy, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkoxycarbonyl, nitro, cyano, amino, aminocarbonyl, sulfamoyl or C₁₋₄hydroxyalkyl.

30

5. A compound according to any of claims 1-3, wherein R₂ is phenyl or phenyl substituted by one or more substituents selected from the group consisting of halogen, trifluoromethyl, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄alkoxycarbonyl, nitro, cyano, amino, aminocarbonyl, sulfamoyl or C₁₋₄hydroxyalkyl.
6. A compound according to claim 5, wherein said substituent is chloro.
7. A compound according to any claims 1-6, wherein Y₁ is a bond, and Y₂ is O.
8. A compound according to any claims 1-7, wherein X₁ is a C₄₋₁₂ hydrocarbon diradical, and X₂ is a bond.
9. A compound according to claim 1 which is 1-[2-(4-Piperidyloxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chloro-phenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride, hydrochloride; 1-[2-(2-aminoethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride, hydrochloride; 1-[2-(2-(2-aminoethoxy)-ethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride, hydrochloride; and 1-[2-(2-(2-(2-aminoethoxy)-ethoxy)-ethoxy)-ethoxy)-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride, hydrochloride.
10. A pharmaceutical composition comprising a compound of formula I or II according to any one of claims 1-9 together with a pharmaceutically acceptable excipient or diluent.
11. A composition according to claim 10, wherein the compound is dissolved in an appropriate, pharmaceutically acceptable solvent, e.g. selected from the group consisting of water, isotonic saline, isotonic glucose solution, or a buffer solution.
12. A composition according to claim 11 for parenteral administration, intravenous injection or infusion.

13. A composition according to any one of claims 10-12 further comprising one or more other anti-neoplastic compounds.
14. A composition according to claim 13, wherein said other antineoplastic compound(s) is selected from the list consisting of S-triazin derivatives, antibiotic agents, alkylating agents, anti-metabolites, anti-mitotic agents, hormonal agents, differentiating agents, biological response modifiers and angiogenesis inhibitors.
15. A composition according to claim 14, wherein the compound of formula I or II is 1-[2-(4-Piperidyloxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chloro-phenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride, hydrochloride, and wherein the other anti-neoplastic agent(s) is selected from the group consisting of paclitaxel, fluorouracil, etoposide, cyclophosphamide, cisplatin, carboplatin, vincristine, gemcitabine, vinorelbine, chlorambucil, doxorubicin, melphalan and seocalcitol.
16. A pharmaceutical composition comprising, in separate containers and intended for sequential or simultaneous administration, a compound of formula I or II according to any one of claims 1-9 and one or more other anti-neoplastic compounds, together with pharmaceutically acceptable excipients or diluents.
17. Use of a compound of formula I or II according to any one of claims 1-9, optionally together with one or more other anti-neoplastic compound, for the preparation of a medicament for the treatment or amelioration of proliferative diseases or conditions.
18. The use according to claim 17, wherein the proliferative disease is a cancer.
19. The use according to claim 17, wherein said proliferative disease is selected from the group consisting of leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia, chronic lymphatic leukaemia, myelodysplasia, multiple myeloma, Hodgkin's disease or non-Hodgkin's lymphoma, small or non-small cell lung carcinoma, gastric, intestinal or colorectal cancer, prostate, ovarian or breast cancer, brain head, or neck cancer, cancer of the urinary tract, kidney or bladder cancer, malignant melanoma, liver cancer, uterine or pancreatic cancer.

20. The use according to any one of claims 17-19, wherein said other anti-neoplastic compound(s) is selected from the group consisting of S-triazin derivatives, antibiotic agents, alkylating agents, anti-metabolites, anti-mitotic agents, hormonal agents, differentiating agents, biological response modifiers and angiogenesis inhibitors.
21. The use according to any one of claims 17-20, wherein the compound of formula I or II is 1-[2-(4-piperidyloxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chloro-phenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride, hydrochloride, and wherein said other anti-neoplastic compound is selected from the group consisting of paclitaxel, fluorouracil, etoposide, cyclophosphamide, cisplatin, carboplatin, vincristine, gemcitabine, vinorelbine, chlorambucil, doxorubicin, melphalan and seocalcitol.
22. A compound selected from the group consisting of
 Chloromethyl 2-(1-(tert-butoxycarbonyl)-4-piperidyloxy)-ethyl carbonate;
 Iodomethyl 2-(1-(tert-butoxycarbonyl)-4-piperidyloxy)-ethyl carbonate;
 1-[2-[1-(tert-butoxycarbonyl)-4-piperidyloxy]-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium iodide;
 Chloromethyl 2-(2-azidoethoxy)-ethyl carbonate;
 Chloromethyl 2-(2-(2-azidoethoxy)-ethoxy)-ethyl carbonate;
 Chloromethyl 2-(2-(2-(2-azidoethoxy)-ethoxy)-ethoxy)-ethyl carbonate;
 Iodomethyl 2-(2-azidoethoxy)-ethyl carbonate;
 Iodomethyl 2-(2-(2-azidoethoxy)-ethoxy)-ethyl carbonate;
 Iodomethyl 2-(2-(2-(2-azidoethoxy)-ethoxy)-ethoxy)-ethyl carbonate;
 1-[2-(2-azidoethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride;
 1-[2-(2-(2-azidoethoxy)-ethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride; and
 1-[2-(2-(2-(2-azidoethoxy)-ethoxy)-ethoxy)-ethoxy-carbonyloxymethyl]-4-[N'-cyano-N''-(6-(4-chlorophenoxy)-1-hexyl)-N-guanidino]-pyridinium chloride.