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(54) Title: FORMULATIONS OF DEACETYLASE INHIBITORS

(57) Abstract: The present invention provides a stable parenteral formulation of histone deacetylase inhibitors.



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FORMULATIONS OF DEACETYLASE INHIBITORS

The present invention relates to pharmaceutical formulations of deacetylase inhibitors suitable for parenteral administration.

Reversible acetylation of histones is a major regulator of gene expression which acts by altering accessibility of transcription factors to DNA. In normal cells, histone deacetylase (HDA) and histone acetyltransferase together control the level of acetylation of histones to maintain a balance. Inhibition of HDA results in the accumulation of hyperacetylated histones, which results in a variety of cellular responses.

Inhibitors of HDA have been studied for their therapeutic effects on cancer cells. For example, butyric acid and its derivatives, including sodium phenylbutyrate, have been reported to induce apoptosis *in vitro* in human colon carcinoma, leukemia and retinoblastoma cell lines. However, butyric acid and its derivatives tend to be metabolized rapidly and have a very short half-life *in vivo*. Other inhibitors of HDA that have been widely studied for their anti-cancer activities are trichostatin A and trapoxin. Trichostatin A is an antifungal and antibiotic and is a reversible inhibitor of mammalian HDA. Trapoxin is a cyclic tetrapeptide, which is an irreversible inhibitor of mammalian HDA. Although trichostatin and trapoxin have been studied for their anti-cancer activities, the *in vivo* instability of the compounds makes them less suitable as anti-cancer drugs.

The present invention is directed to a stable parenteral formulation of an HDA inhibitor compound that is suitable for treating tumors, including cancerous tumors, and for treating cellular proliferative ailments, that is highly efficacious and stable.

Summary of the Invention

The present invention provides a stable parenteral formulation of an HDA inhibitor.

The stable pharmaceutical compositions of the present invention are ones that are efficacious particularly for treating cellular proliferative ailments. The pharmaceutical composition comprises a pharmaceutically effective amount of an HDA inhibitor, and an alcohol selected from the group consisting of propylene glycol, ethanol and glycerine. In addition it has been found that control of the pH in the range of 3.5-4.5 can provide increased stability of the formulation.

Detailed Description of the Invention

The pharmaceutical composition according to the invention is suitable for parenteral administration to mammals, including man, for the treatment of proliferative diseases such as tumors, alone or in combination, with one or more pharmaceutically acceptable excipients or carriers.

The parenteral formulation of the present invention comprises:

- (a) an histone deacetylase inhibitor ("HDAI") compound;
- (b) at least one alcohol compound selected from the group consisting of propylene glycol, ethanol and glycerine;
- 10 (c) a buffer; and
- (d) optional pharmaceutically acceptable excipients including buffers, anti-oxidants, bacteriostats, preserving, stabilizing, wetting or solubilizing agents, and/or excipients for regulating the osmolarity.

In addition, the compositions may also contain other therapeutically active substances.

One embodiment of the present invention is a parenteral formulation comprising an HDAI compound, at least one alcohol compound selected from the group consisting of propylene glycol, ethanol and glycerine, and a buffer.

The parenteral formulation of the present invention comprises at least one alcohol compound which inhibits and reduces the oxidation and hydrolysis of the hydroxamate compound. Examples of alcohol compounds include propylene glycol, ethanol and glycerine. The alcohol compound is present in an amount, by weight, of 1-100%, preferably, of 5-60%, more preferably 20%.

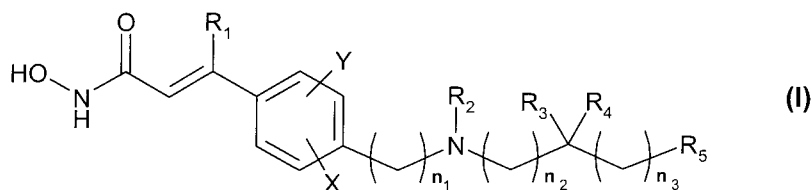
The parenteral formulations of the present invention also comprise a buffer which controls pH and provides solubility and stability. The pH of the formulation of the present invention is maintained in the range of about 3.5 to about 4.5, or preferably pH 4. Any buffer which can control the pH is suitable for the present invention. Non-limiting examples of a buffer suitable for the parenteral formulation of the present invention are selected from a lactate buffer, citrate buffer, acetate buffer, phosphate buffer, tartrate buffer, maleate buffer, maleate buffer and a glycine buffer. In one embodiment the buffer is a lactate buffer. The

buffer is present in an amount, by weight, of about 0.2% to about 1.5%, preferably about 0.96%.

The formulations of the present invention may be sterilized and/or contain adjuvants, such as preservatives, antioxidants, stabilizing, wetting or emulsifying agents, solution
 5 promoters, and/or salts for regulating the osmotic pressure. The formulation may be an aqueous and non-aqueous sterile injection solutions.

The term "pharmaceutically effective amount", as used herein, indicates an amount necessary to administer to a host to achieve a therapeutic result, especially an anti-tumor effect, e.g., inhibition of proliferation of malignant cancer cells, benign tumor cells or other
 10 proliferative cells.

The parenteral formulation of the present invention comprises a pharmaceutically effective amount of an HDAC compound having the following structure (I). HDAC inhibitor compounds of particular interest for use in the inventive combination are hydroxamate compounds described by the formula (I):



15

wherein

- R_1 is H; halo; or a straight-chain C_1 - C_6 alkyl, especially methyl, ethyl or n-propyl, which methyl, ethyl and n-propyl substituents are unsubstituted or substituted by one or more substituents described below for alkyl substituents;
- 20 R_2 is selected from H; C_1 - C_{10} alkyl, preferably C_1 - C_6 alkyl, e.g., methyl, ethyl or $-CH_2CH_2OH$; C_4 - C_9 cycloalkyl; C_4 - C_9 heterocycloalkyl; C_4 - C_9 heterocycloalkylalkyl; cycloalkylalkyl, e.g., cyclopropylmethyl; aryl; heteroaryl; arylalkyl, e.g., benzyl; heteroarylalkyl, e.g., pyridylmethyl; $-(CH_2)_nC(O)R_6$; $-(CH_2)_nOC(O)R_6$; amino acyl; $HON-C(O)-CH=C(R_1)$ -aryl-alkyl-; and $-(CH_2)_nR_7$;
- 25 R_3 and R_4 are the same or different and, independently, H; C_1 - C_6 alkyl; acyl; or acylamino, or
- R_3 and R_4 , together with the carbon to which they are bound, represent $C=O$, $C=S$ or $C=NR_8$, or

- R₂, together with the nitrogen to which it is bound, and R₃, together with the carbon to which it is bound, can form a C₄-C₉heterocycloalkyl; a heteroaryl; a polyheteroaryl; a non-aromatic polyheterocycle; or a mixed aryl and non-aryl polyheterocycle ring;
- R₅ is selected from H; C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; acyl; aryl; heteroaryl; arylalkyl, e.g., benzyl; heteroarylalkyl, e.g., pyridylmethyl; aromatic polycycles; non-aromatic polycycles; mixed aryl and non-aryl polycycles; polyheteroaryl; non-aromatic polyheterocycles; and mixed aryl and non-aryl polyheterocycles;
- n, n₁, n₂ and n₃ are the same or different and independently selected from 0-6, when n₁ is 1-6, each carbon atom can be optionally and independently substituted with R₃ and/or R₄;
- X and Y are the same or different and independently selected from H; halo; C₁-C₄alkyl, such as CH₃ and CF₃; NO₂; C(O)R₁; OR₉; SR₉; CN; and NR₁₀R₁₁;
- R₆ is selected from H; C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; cycloalkylalkyl, e.g., cyclopropylmethyl; aryl; heteroaryl; arylalkyl, e.g., benzyl and 2-phenylethenyl; heteroarylalkyl, e.g., pyridylmethyl; OR₁₂; and NR₁₃R₁₄;
- R₇ is selected from OR₁₅; SR₁₅; S(O)R₁₆; SO₂R₁₇; NR₁₃R₁₄; and NR₁₂SO₂R₆;
- R₈ is selected from H; OR₁₅; NR₁₃R₁₄; C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; aryl; heteroaryl; arylalkyl, e.g., benzyl; and heteroarylalkyl, e.g., pyridylmethyl;
- R₉ is selected from C₁-C₄alkyl, e.g., CH₃ and CF₃; C(O)-alkyl, e.g., C(O)CH₃; and C(O)CF₃;
- R₁₀ and R₁₁ are the same or different and independently selected from H; C₁-C₄alkyl; and -C(O)-alkyl;
- R₁₂ is selected from H; C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; C₄-C₉heterocycloalkylalkyl; aryl; mixed aryl and non-aryl polycycle; heteroaryl; arylalkyl, e.g., benzyl; and heteroarylalkyl, e.g., pyridylmethyl;
- R₁₃ and R₁₄ are the same or different and independently selected from H; C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; aryl; heteroaryl; arylalkyl, e.g., benzyl; heteroarylalkyl, e.g., pyridylmethyl; amino acyl, or
- R₁₃ and R₁₄, together with the nitrogen to which they are bound, are C₄-C₉heterocycloalkyl; heteroaryl; polyheteroaryl; non-aromatic polyheterocycle; or mixed aryl and non-aryl polyheterocycle;

R₁₅ is selected from H; C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; and (CH₂)_mZR₁₂;

R₁₆ is selected from C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; aryl; heteroaryl; polyheteroaryl; arylalkyl; heteroarylalkyl; and (CH₂)_mZR₁₂;

5 R₁₇ is selected from C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; aryl; aromatic polycycles; heteroaryl; arylalkyl; heteroarylalkyl; polyheteroaryl and NR₁₃R₁₄;

m is an integer selected from 0-6; and

Z is selected from O; NR₁₃; S; and S(O),

or a pharmaceutically acceptable salt thereof.

10 As appropriate, "unsubstituted" means that there is no substituent or that the only substituents are hydrogen.

Halo substituents are selected from fluoro, chloro, bromo and iodo, preferably fluoro or chloro.

Alkyl substituents include straight- and branched-C₁-C₆alkyl, unless otherwise noted.

15 Examples of suitable straight- and branched-C₁-C₆alkyl substituents include methyl, ethyl, n-propyl, 2-propyl, n-butyl, sec-butyl, t-butyl and the like. Unless otherwise noted, the alkyl substituents include both unsubstituted alkyl groups and alkyl groups that are substituted by one or more suitable substituents, including unsaturation, i.e., there are one or more double or triple C-C bonds; acyl; cycloalkyl; halo; oxyalkyl; alkylamino; aminoalkyl; acylamino; and
20 OR₁₅, e.g., alkoxy. Preferred substituents for alkyl groups include halo, hydroxy, alkoxy, oxyalkyl, alkylamino and aminoalkyl.

Cycloalkyl substituents include C₃-C₉cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, unless otherwise specified. Unless otherwise noted, cycloalkyl substituents include both unsubstituted cycloalkyl groups and cycloalkyl
25 groups that are substituted by one or more suitable substituents, including C₁-C₆alkyl, halo, hydroxy, aminoalkyl, oxyalkyl, alkylamino and OR₁₅, such as alkoxy. Preferred substituents for cycloalkyl groups include halo, hydroxy, alkoxy, oxyalkyl, alkylamino and aminoalkyl.

The above discussion of alkyl and cycloalkyl substituents also applies to the alkyl portions of other substituents such as, without limitation, alkoxy, alkyl amines, alkyl ketones,
30 arylalkyl, heteroarylalkyl, alkylsulfonyl and alkyl ester substituents and the like.

Heterocycloalkyl substituents include 3- to 9-membered aliphatic rings, such as 4- to 7-membered aliphatic rings, containing from 1-3 heteroatoms selected from nitrogen, sulfur, oxygen. Examples of suitable heterocycloalkyl substituents include pyrrolidyl, tetrahydrofuryl, tetrahydrothiofuryl, piperidyl, piperazyl, tetrahydropyranyl, morpholino, 1,3-diazapane, 1,4-diazapane, 1,4-oxazepane and 1,4-oxathiapane. Unless otherwise noted, the rings are unsubstituted or substituted on the carbon atoms by one or more suitable substituents, including C₁-C₆alkyl; C₄-C₉cycloalkyl; aryl; heteroaryl; arylalkyl, e.g., benzyl; heteroarylalkyl, e.g., pyridylmethyl; halo; amino; alkyl amino and OR₁₅, e.g., alkoxy. Unless otherwise noted, nitrogen heteroatoms are unsubstituted or substituted by H, C₁-C₄alkyl; arylalkyl, e.g., benzyl; heteroarylalkyl, e.g., pyridylmethyl; acyl; aminoacyl; alkylsulfonyl; and arylsulfonyl.

Cycloalkylalkyl substituents include compounds of the formula -(CH₂)_{n5}-cycloalkyl, wherein n5 is a number from 1-6. Suitable alkylcycloalkyl substituents include cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl and the like. Such substituents are unsubstituted or substituted in the alkyl portion or in the cycloalkyl portion by a suitable substituent, including those listed above for alkyl and cycloalkyl.

Aryl substituents include unsubstituted phenyl and phenyl substituted by one or more suitable substituents including C₁-C₆alkyl; cycloalkylalkyl, e.g., cyclopropylmethyl; O(CO)alkyl; oxyalkyl; halo; nitro; amino; alkylamino; aminoalkyl; alkyl ketones; nitrile; carboxyalkyl; alkylsulfonyl; aminosulfonyl; arylsulfonyl and OR₁₅, such as alkoxy. Preferred substituents include including C₁-C₆alkyl; cycloalkyl, e.g., cyclopropylmethyl; alkoxy; oxyalkyl; halo; nitro; amino; alkylamino; aminoalkyl; alkyl ketones; nitrile; carboxyalkyl; alkylsulfonyl; arylsulfonyl and aminosulfonyl. Examples of suitable aryl groups include C₁-C₄alkylphenyl, C₁-C₄alkoxyphenyl, trifluoromethylphenyl, methoxyphenyl, hydroxyethylphenyl, dimethylaminophenyl, aminopropylphenyl, carbethoxyphenyl, methanesulfonylphenyl and tolylsulfonylphenyl.

Aromatic polycycles include naphthyl, and naphthyl substituted by one or more suitable substituents including C₁-C₆alkyl; alkylcycloalkyl, e.g., cyclopropylmethyl; oxyalkyl; halo; nitro; amino; alkylamino; aminoalkyl; alkyl ketones; nitrile; carboxyalkyl; alkylsulfonyl; arylsulfonyl; aminosulfonyl and OR₁₅, such as alkoxy.

Heteroaryl substituents include compounds with a 5- to 7-membered aromatic ring containing one or more heteroatoms, e.g., from 1-4 heteroatoms, selected from N, O and S. Typical heteroaryl substituents include furyl, thienyl, pyrrole, pyrazole, triazole, thiazole,

oxazole, pyridine, pyrimidine, isoxazolyl, pyrazine and the like. Unless otherwise noted, heteroaryl substituents are unsubstituted or substituted on a carbon atom by one or more suitable substituents, including alkyl, the alkyl substituents identified above, and another heteroaryl substituent. Nitrogen atoms are unsubstituted or substituted, e.g., by R_{13} ;
5 especially useful N substituents include H, C_1 - C_4 alkyl, acyl, aminoacyl and sulfonyl.

Arylalkyl substituents include groups of the formula $-(CH_2)_{n5}$ -aryl, $-(CH_2)_{n5}$ -1-(CH-aryl)- $(CH_2)_{n5}$ -aryl or $-(CH_2)_{n5}$ -1CH(aryl)(aryl), wherein aryl and $n5$ are defined above. Such arylalkyl substituents include benzyl, 2-phenylethyl, 1-phenylethyl, tolyl-3-propyl, 2-phenylpropyl, diphenylmethyl, 2-diphenylethyl, 5,5-dimethyl-3-phenylpentyl and the like.
10 Arylalkyl substituents are unsubstituted or substituted in the alkyl moiety or the aryl moiety or both as described above for alkyl and aryl substituents.

Heteroarylalkyl substituents include groups of the formula $-(CH_2)_{n5}$ -heteroaryl, wherein heteroaryl and $n5$ are defined above and the bridging group is linked to a carbon or a nitrogen of the heteroaryl portion, such as 2-, 3- or 4-pyridylmethyl, imidazolylmethyl,
15 quinolylethyl and pyrrolylbutyl. Heteroaryl substituents are unsubstituted or substituted as discussed above for heteroaryl and alkyl substituents.

Amino acyl substituents include groups of the formula $-C(O)-(CH_2)_n-C(H)(NR_{13}R_{14})-(CH_2)_n-R_5$, wherein n , R_{13} , R_{14} and R_5 are described above. Suitable aminoacyl substituents include natural and non-natural amino acids, such as glyciny, D-tryptophanyl, L-lysiny, D- or
20 L-homoseriny, 4-aminobutyric acyl and $\pm$ -3-amin-4-hexenoyl.

Non-aromatic polycycle substituents include bicyclic and tricyclic fused ring systems where each ring can be 4- to 9-membered and each ring can contain zero, one or more double and/or triple bonds. Suitable examples of non-aromatic polycycles include decalin, octahydroindene, perhydrobenzocycloheptene and perhydrobenzo-[f]-azulene. Such
25 substituents are unsubstituted or substituted as described above for cycloalkyl groups.

Mixed aryl and non-aryl polycycle substituents include bicyclic and tricyclic fused ring systems where each ring can be 4- to 9-membered and at least one ring is aromatic. Suitable examples of mixed aryl and non-aryl polycycles include methylenedioxyphenyl, bis-methylenedioxyphenyl, 1,2,3,4-tetrahydronaphthalene, dibenzosuberane,
30 dihydroanthracene and 9H-fluorene. Such substituents are unsubstituted or substituted by nitro or as described above for cycloalkyl groups.

Polyheteroaryl substituents include bicyclic and tricyclic fused ring systems where each ring can independently be 5- or 6-membered and contain one or more heteroatom, e.g., 1, 2, 3 or 4 heteroatoms, chosen from O, N or S such that the fused ring system is aromatic. Suitable examples of polyheteroaryl ring systems include quinoline, isoquinoline, pyridopyrazine, pyrrolopyridine, furopyridine, indole, benzofuran, benzothiofuran, benzindole, benzoxazole, pyrroloquinoline and the like. Unless otherwise noted, polyheteroaryl substituents are unsubstituted or substituted on a carbon atom by one or more suitable substituents, including alkyl, the alkyl substituents identified above and a substituent of the formula $-O-(CH_2CH=CH(CH_3)(CH_2))_{1-3}H$. Nitrogen atoms are unsubstituted or substituted, e.g., by R_{13} , especially useful N substituents include H, C_1 - C_4 alkyl, acyl, aminoacyl and sulfonyl.

Non-aromatic polyheterocyclic substituents include bicyclic and tricyclic fused ring systems where each ring can be 4- to 9-membered, contain one or more heteroatom, e.g., 1, 2, 3 or 4 heteroatoms, chosen from O, N or S and contain zero or one or more C-C double or triple bonds. Suitable examples of non-aromatic polyheterocycles include hexitol, cis-perhydro-cyclohepta[*b*]pyridinyl, decahydro-benzo[*f*][1,4]oxazepinyl, 2,8-dioxabicyclo[3.3.0]octane, hexahydro-thieno[3,2-*b*]thiophene, perhydropyrrolo[3,2-*b*]pyrrole, perhydronaphthyridine, perhydro-1*H*-dicyclopenta[*b,e*]pyran. Unless otherwise noted, non-aromatic polyheterocyclic substituents are unsubstituted or substituted on a carbon atom by one or more substituents, including alkyl and the alkyl substituents identified above. Nitrogen atoms are unsubstituted or substituted, e.g., by R_{13} , especially useful N substituents include H, C_1 - C_4 alkyl, acyl, aminoacyl and sulfonyl.

Mixed aryl and non-aryl polyheterocycles substituents include bicyclic and tricyclic fused ring systems where each ring can be 4- to 9-membered, contain one or more heteroatom chosen from O, N or S, and at least one of the rings must be aromatic. Suitable examples of mixed aryl and non-aryl polyheterocycles include 2,3-dihydroindole, 1,2,3,4-tetrahydroquinoline, 5,11-dihydro-10*H*-dibenz[*b,e*][1,4]diazepine, 5*H*-dibenzo[*b,e*][1,4]diazepine, 1,2-dihydropyrrolo[3,4-*b*][1,5]benzodiazepine, 1,5-dihydro-pyrido[2,3-*b*][1,4]diazepin-4-one, 1,2,3,4,6,11-hexahydro-benzo[*b*]pyrido[2,3-*e*][1,4]diazepin-5-one. Unless otherwise noted, mixed aryl and non-aryl polyheterocyclic substituents are unsubstituted or substituted on a carbon atom by one or more suitable substituents including -N-OH, =N-OH, alkyl and the alkyl substituents identified above. Nitrogen atoms are unsubstituted or substituted, e.g., by R_{13} ; especially useful N substituents include H, C_1 - C_4 alkyl, acyl, aminoacyl and sulfonyl.

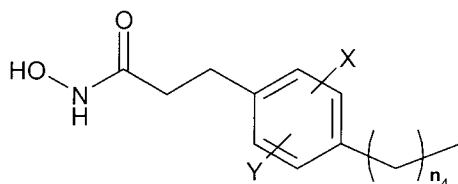
Amino substituents include primary, secondary and tertiary amines and in salt form, quaternary amines. Examples of amino substituents include mono- and di-alkylamino, mono- and di-aryl amino, mono- and di-arylalkyl amino, aryl-arylalkylamino, alkyl-aryl amino, alkyl-arylalkylamino and the like.

- 5 Sulfonyl substituents include alkylsulfonyl and arylsulfonyl, e.g., methane sulfonyl, benzene sulfonyl, tosyl and the like.

Acyl substituents include groups of formula $-C(O)-W$, $-OC(O)-W$, $-C(O)-O-W$ or $-C(O)NR_{13}R_{14}$, where W is R_{16} , H or cycloalkylalkyl.

- Acylamino substituents include substituents of the formula $-N(R_{12})C(O)-W$,
10 $-N(R_{12})C(O)-O-W$ and $-N(R_{12})C(O)-NHOH$ and R_{12} and W are defined above.

The R_2 substituent $HON-C(O)-CH=C(R_1)$ -aryl-alkyl- is a group of the formula:

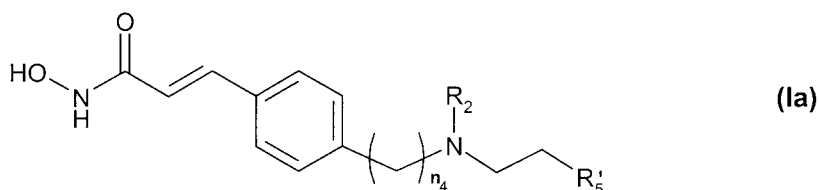


Preferences for each of the substituents include the following:

- R_1 is H, halo or a straight-chain C_1 - C_4 alkyl;
- 15 R_2 is selected from H, C_1 - C_6 alkyl, C_4 - C_9 cycloalkyl, C_4 - C_9 heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, $-(CH_2)_nC(O)R_6$, amino acyl and $-(CH_2)_nR_7$;
- R_3 and R_4 are the same or different and independently selected from H and C_1 - C_6 alkyl, or R_3 and R_4 , together with the carbon to which they are bound, represent $C=O$, $C=S$ or $C=NR_8$;
- 20 R_5 is selected from H, C_1 - C_6 alkyl, C_4 - C_9 cycloalkyl, C_4 - C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, a aromatic polycycle, a non-aromatic polycycle, a mixed aryl and non-aryl polycycle, polyheteroaryl, a non-aromatic polyheterocycle, and a mixed aryl and non-aryl polyheterocycle;
- n , n_1 , n_2 and n_3 are the same or different and independently selected from 0-6, when n_1 is
25 1-6, each carbon atom is unsubstituted or independently substituted with R_3 and/or R_4 ;

- X and Y are the same or different and independently selected from H, halo, C₁-C₄alkyl, CF₃, NO₂, C(O)R₁, OR₉, SR₉, CN and NR₁₀R₁₁;
- R₆ is selected from H, C₁-C₆alkyl, C₄-C₉cycloalkyl, C₄-C₉heterocycloalkyl, alkylcycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, OR₁₂ and NR₁₃R₁₄;
- 5 R₇ is selected from OR₁₅, SR₁₅, S(O)R₁₆, SO₂R₁₇, NR₁₃R₁₄ and NR₁₂SO₂R₆;
- R₈ is selected from H, OR₁₅, NR₁₃R₁₄, C₁-C₆alkyl, C₄-C₉cycloalkyl, C₄-C₉heterocycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl;
- R₉ is selected from C₁-C₄alkyl and C(O)-alkyl;
- 10 R₁₀ and R₁₁ are the same or different and independently selected from H, C₁-C₄alkyl and -C(O)-alkyl;
- R₁₂ is selected from H, C₁-C₆alkyl, C₄-C₉cycloalkyl, C₄-C₉heterocycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl;
- R₁₃ and R₁₄ are the same or different and independently selected from H, C₁-C₆alkyl, C₄-C₉cycloalkyl, C₄-C₉heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and amino acyl;
- 15 R₁₅ is selected from H, C₁-C₆alkyl, C₄-C₉cycloalkyl, C₄-C₉heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and (CH₂)_mZR₁₂;
- R₁₆ is selected from C₁-C₆alkyl, C₄-C₉cycloalkyl, C₄-C₉heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and (CH₂)_mZR₁₂;
- 20 R₁₇ is selected from C₁-C₆alkyl, C₄-C₉cycloalkyl, C₄-C₉heterocycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl and NR₁₃R₁₄;
- m is an integer selected from 0-6; and
- Z is selected from O, NR₁₃, S and S(O);
- or a pharmaceutically acceptable salt thereof.
- 25 Useful compounds of the formula (I), include those wherein each of R₁, X, Y, R₃ and R₄ is H, including those wherein one of n₂ and n₃ is 0 and the other is 1, especially those wherein R₂ is H or -CH₂-CH₂-OH.

One suitable genus of hydroxamate compounds are those of formula (Ia):



wherein

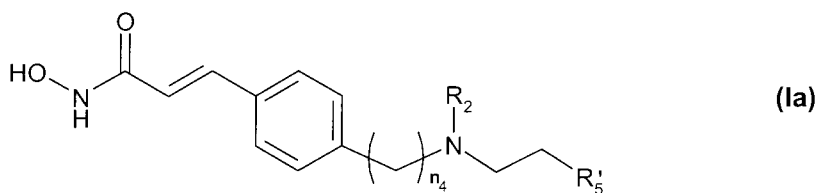
n_4 is 0-3;

5 R_2 is selected from H, C_1 - C_6 alkyl, C_4 - C_9 cycloalkyl, C_4 - C_9 heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, $-(CH_2)_n C(O)R_6$, amino acyl and $-(CH_2)_n R_7$; and

10 R_5' is heteroaryl; heteroarylalkyl, e.g., pyridylmethyl; aromatic polycycles; non-aromatic polycycles; mixed aryl and non-aryl polycycles; polyheteroaryl or mixed aryl; and non-aryl polyheterocycles;

or a pharmaceutically acceptable salt thereof.

Another suitable genus of hydroxamate compounds are those of formula (Ia):



wherein

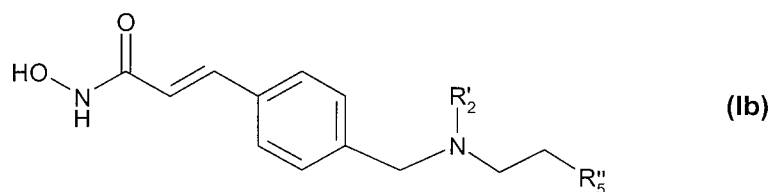
15 n_4 is 0-3;

R_2 is selected from H, C_1 - C_6 alkyl, C_4 - C_9 cycloalkyl, C_4 - C_9 heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, $-(CH_2)_n C(O)R_6$, amino acyl and $-(CH_2)_n R_7$;

20 R_5' is aryl; arylalkyl; aromatic polycycles; non-aromatic polycycles and mixed aryl; and non-aryl polycycles, especially aryl, such as *p*-fluorophenyl, *p*-chlorophenyl, *p*-O- C_1 - C_4 alkylphenyl, such as *p*-methoxyphenyl, and *p*- C_1 - C_4 alkylphenyl; and arylalkyl, such as benzyl, ortho-, meta- or para-fluorobenzyl, ortho-, meta- or para-chlorobenzyl, ortho-, meta- or para-mono, di- or tri-O- C_1 - C_4 alkylbenzyl, such as ortho-, meta- or para-methoxybenzyl, *m,p*-diethoxybenzyl, *o,m,p*-trimethoxybenzyl and ortho-, meta- or para-mono, di- or tri- C_1 - C_4 alkylphenyl, such as *p*-methyl, 25 *m,m*-diethylphenyl;

or a pharmaceutically acceptable salt thereof.

Another interesting genus is the compounds of formula (Ib):



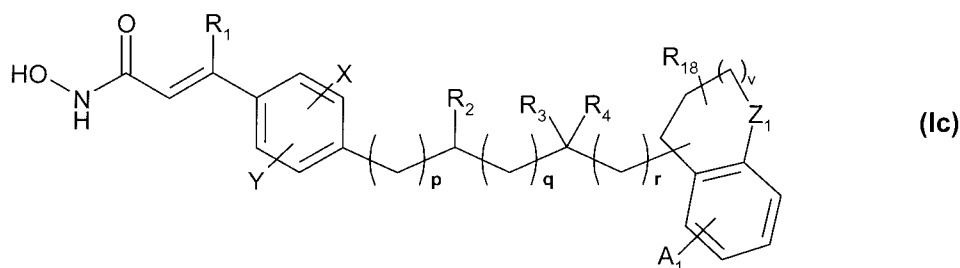
wherein

R'_2 is selected from H; C_1 - C_6 alkyl; C_4 - C_6 cycloalkyl; cycloalkylalkyl, e.g., cyclopropylmethyl;
 5 $(CH_2)_{2-4}OR_{21}$, where R_{21} is H, methyl, ethyl, propyl and *i*-propyl; and

R''_5 is unsubstituted 1*H*-indol-3-yl, benzofuran-3-yl or quinolin-3-yl, or substituted 1*H*-indol-3-yl, such as 5-fluoro-1*H*-indol-3-yl or 5-methoxy-1*H*-indol-3-yl, benzofuran-3-yl or quinolin-3-yl;

or a pharmaceutically acceptable salt thereof.

10 Another interesting genus of hydroxamate compounds are the compounds of formula (Ic):



wherein

the ring containing Z_1 is aromatic or non-aromatic, which non-aromatic rings are
 15 saturated or unsaturated;

Z_1 is O, S or N- R_{20} ;

R_{18} is H; halo; C_1 - C_6 alkyl (methyl, ethyl, *t*-butyl); C_3 - C_7 cycloalkyl; aryl, e.g., unsubstituted phenyl or phenyl substituted by 4-OCH₃ or 4-CF₃; or heteroaryl, such as 2-furanyl, 2-thiophenyl or 2-, 3- or 4-pyridyl;

20 R_{20} is H; C_1 - C_6 alkyl; C_1 - C_6 alkyl- C_3 - C_9 cycloalkyl, e.g., cyclopropylmethyl; aryl; heteroaryl; arylalkyl, e.g., benzyl; heteroarylalkyl, e.g., pyridylmethyl; acyl, e.g., acetyl, propionyl and benzoyl; or sulfonyl, e.g., methanesulfonyl, ethanesulfonyl, benzenesulfonyl and toluenesulfonyl;

A_1 is 1, 2 or 3 substituents which are independently H; C_1 - C_6 alkyl; -OR₁₉; halo;
 25 alkylamino; aminoalkyl; halo; or heteroarylalkyl, e.g., pyridylmethyl;

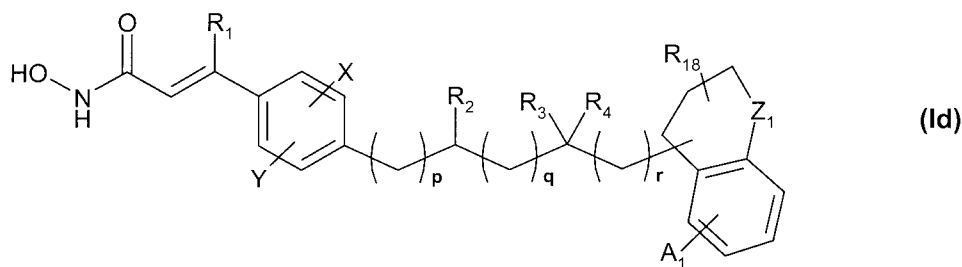
R_{19} is selected from H; C_1 - C_6 alkyl; C_4 - C_9 cycloalkyl; C_4 - C_9 heterocycloalkyl; aryl; heteroaryl; arylalkyl, e.g., benzyl; heteroarylalkyl, e.g., pyridylmethyl and $-(CH_2CH=CH(CH_3)(CH_2))_{1-3}H$;

R_2 is selected from H, C_1 - C_6 alkyl, C_4 - C_9 cycloalkyl, C_4 - C_9 heterocycloalkyl, cycloalkylalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, $-(CH_2)_nC(O)R_6$, amino acyl and $-(CH_2)_nR_7$;
 5 v is 0, 1 or 2;
 p is 0-3; and
 q is 1-5 and r is 0, or
 q is 0 and r is 1-5;

10 or a pharmaceutically acceptable salt thereof. The other variable substituents are as defined above.

Especially useful compounds of formula (Ic), are those wherein R_2 is H, or $-(CH_2)_pCH_2OH$, wherein p is 1-3, especially those wherein R_1 is H; such as those wherein R_1 is H and X and Y are each H, and wherein q is 1-3 and r is 0 or wherein q is 0 and r is 1-3,
 15 especially those wherein Z_1 is $N-R_{20}$. Among these compounds R_2 is preferably H or $-CH_2-CH_2-OH$ and the sum of q and r is preferably 1.

Another interesting genus of hydroxamate compounds are the compounds of formula (Id):



20 wherein

Z_1 is O, S or $N-R_{20}$;

R_{18} is H; halo; C_1 - C_6 alkyl (methyl, ethyl, t-butyl); C_3 - C_7 cycloalkyl; aryl, e.g., unsubstituted phenyl or phenyl substituted by 4- OCH_3 or 4- CF_3 ; or heteroaryl;

R_{20} is H; C_1 - C_6 alkyl, C_1 - C_6 alkyl- C_3 - C_9 cycloalkyl, e.g., cyclopropylmethyl; aryl; heteroaryl; arylalkyl, e.g., benzyl; heteroarylalkyl, e.g., pyridylmethyl; acyl, e.g., acetyl, propionyl and benzoyl; or sulfonyl, e.g., methanesulfonyl, ethanesulfonyl, benzenesulfonyl, toluenesulfonyl);
 25

A_1 is 1, 2 or 3 substituents which are independently H, C_1 - C_6 alkyl, $-OR_{19}$ or halo;

R_{19} is selected from H; C_1 - C_6 alkyl; C_4 - C_9 cycloalkyl; C_4 - C_9 heterocycloalkyl; aryl; heteroaryl; arylalkyl, e.g., benzyl; and heteroarylalkyl, e.g., pyridylmethyl;

p is 0-3; and

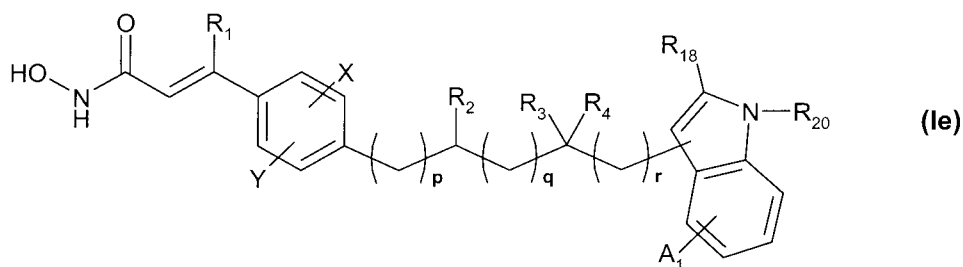
5 q is 1-5 and r is 0, or

q is 0 and r is 1-5;

or a pharmaceutically acceptable salt thereof. The other variable substituents are as defined above.

Especially useful compounds of formula (Id), are those wherein R_2 is H or
 10 $-(CH_2)_pCH_2OH$, wherein p is 1-3, especially those wherein R_1 is H; such as those wherein R_1 is H and X and Y are each H, and wherein q is 1-3 and r is 0 or wherein q is 0 and r is 1-3. Among these compounds R_2 is preferably H or $-CH_2-CH_2-OH$ and the sum of q and r is preferably 1.

The present invention further relates to compounds of the formula (Ie):



15

or a pharmaceutically acceptable salt thereof. The variable substituents are as defined above.

Especially useful compounds of formula (Ie), are those wherein R_{18} is H, fluoro, chloro, bromo, a C_1 - C_4 alkyl group, a substituted C_1 - C_4 alkyl group, a C_3 - C_7 cycloalkyl group,
 20 unsubstituted phenyl, phenyl substituted in the para position, or a heteroaryl, e.g., pyridyl, ring.

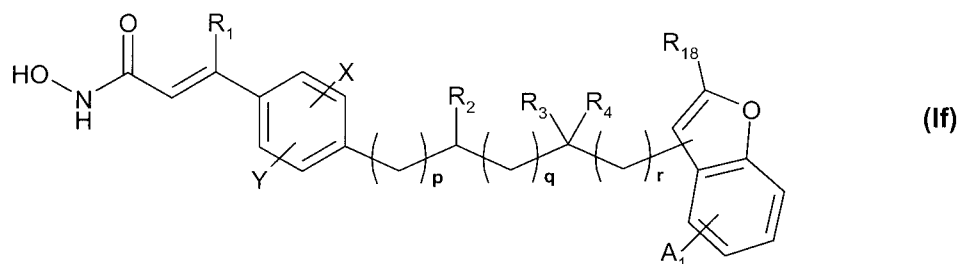
Another group of useful compounds of formula (Ie), are those wherein R_2 is H or $-(CH_2)_pCH_2OH$, wherein p is 1-3, especially those wherein R_1 is H; such as those wherein R_1 is H and X and Y are each H, and wherein q is 1-3 and r is 0 or wherein q is 0 and r is 1-3.
 25 Among these compounds R_2 is preferably H or $-CH_2-CH_2-OH$ and the sum of q and r is preferably 1. Among these compounds p is preferably 1 and R_3 and R_4 are preferably H.

Another group of useful compounds of formula (Ie), are those wherein R_{18} is H, methyl, ethyl, t-butyl, trifluoromethyl, cyclohexyl, phenyl, 4-methoxyphenyl, 4-trifluoromethylphenyl, 2-furanyl, 2-thiophenyl, or 2-, 3- or 4-pyridyl wherein the 2-furanyl, 2-thiophenyl and 2-, 3- or 4-pyridyl substituents are unsubstituted or substituted as described
 5 above for heteroaryl rings; R_2 is H or $-(CH_2)_pCH_2OH$, wherein p is 1-3; especially those wherein R_1 is H and X and Y are each H, and wherein q is 1-3 and r is 0 or wherein q is 0 and r is 1-3. Among these compounds R_2 is preferably H or $-CH_2-CH_2-OH$ and the sum of q and r is preferably 1.

Those compounds of formula (Ie), wherein R_{20} is H or C_1-C_6 alkyl, especially H, are
 10 important members of each of the subgenres of compounds of formula (Ie) described above.

N-hydroxy-3-[4-[[[(2-hydroxyethyl)[2-(1*H*-indol-3-yl)ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, *N*-hydroxy-3-[4-[[[2-(1*H*-indol-3-yl)ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide and *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-
 15 2*E*-2-propenamide or a pharmaceutically acceptable salt thereof, are important compounds of formula (Ie).

The present invention further relates to the compounds of the formula (If):



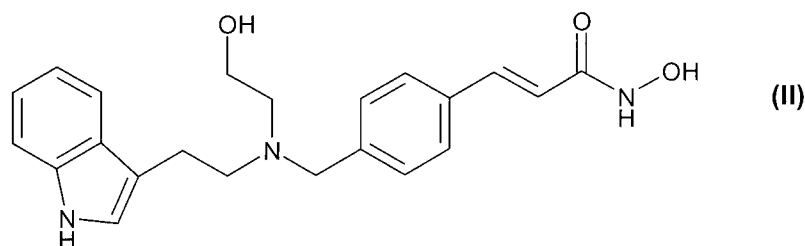
or a pharmaceutically acceptable salt thereof. The variable substituents are as defined
 20 above.

Useful compounds of formula (If), are include those wherein R_2 is H or $-(CH_2)_pCH_2OH$, wherein p is 1-3, especially those wherein R_1 is H; such as those wherein R_1 is H and X and Y are each H, and wherein q is 1-3 and r is 0 or wherein q is 0 and r is 1-3. Among these compounds R_2 is preferably H or $-CH_2-CH_2-OH$ and the sum of q and r is
 25 preferably 1.

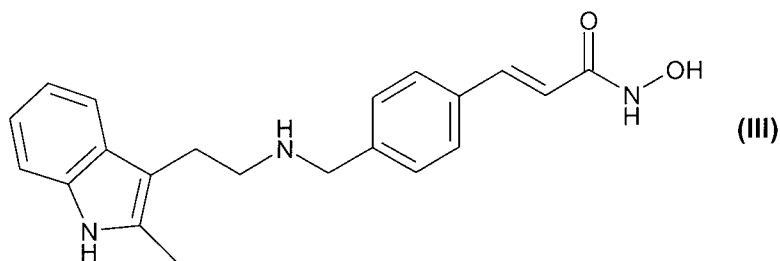
N-hydroxy-3-[4-[[[2-(benzofur-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide or a pharmaceutically acceptable salt thereof, is an important compound of formula (If).

The compounds described above are often used in the form of a pharmaceutically acceptable salt. Pharmaceutically acceptable salts include, when appropriate, pharmaceutically acceptable base addition salts and acid addition salts, e.g., metal salts, such as alkali and alkaline earth metal salts, ammonium salts, organic amine addition salts and amino acid addition salts and sulfonate salts. Acid addition salts include inorganic acid addition salts, such as hydrochloride, sulfate and phosphate; and organic acid addition salts, such as alkyl sulfonate, arylsulfonate, acetate, maleate, fumarate, tartrate, citrate and lactate. Examples of metal salts are alkali metal salts, such as lithium salt, sodium salt and potassium salt; alkaline earth metal salts, such as magnesium salt and calcium salt, aluminum salt and zinc salt. Examples of ammonium salts are ammonium salt and tetramethylammonium salt. Examples of organic amine addition salts are salts with morpholine and piperidine. Examples of amino acid addition salts are salts with glycine, phenylalanine, glutamic acid and lysine. Sulfonate salts include mesylate, tosylate and benzene sulfonic acid salts.

Additional HDAI compounds within the scope of formula (I), and their synthesis, are disclosed in WO 02/22577 published March 21, 2002 which is incorporated herein by reference in its entirety. Two preferred compounds within the scope of WO 02/22577 are:



N-hydroxy-3-[4-[(2-hydroxyethyl){2-(1*H*-indol-3-yl)ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof; and



N-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof.

The HDAI compound is present in the formulation of the present invention in an amount of 1-50% by weight.

An example of the present invention is a formulation comprising propylene glycol, lactate buffer, mannitol and *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof. Preferably the pH of this formulation is pH 4.

Another example of the present invention is a formulation comprising 20% propylene glycol, 0.96% lactate buffer, 5% mannitol and 0.5% of *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof. Preferably the pH of this formulation is pH 4.

The compositions of the present invention are prepared according to conventional methods and may be presented in unit-dose or multi-dose containers, e.g., sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, e.g., water for injections, immediately prior to use. Extemporaneous injection solutions may be prepared from sterile powders, granules and tablets of the kind previously described.

As discussed above, the HDAI compounds of the present invention are useful for treating proliferative diseases. A proliferative disease is mainly a tumor disease (or cancer) (and/or any metastases). The inventive compounds are particularly useful for treating a tumor which is a breast cancer, genitourinary cancer, lung cancer, gastrointestinal cancer, epidermoid cancer, melanoma, ovarian cancer, pancreas cancer, neuroblastoma, head and/or neck cancer or bladder cancer, or in a broader sense renal, brain or gastric cancer; in particular:

- (i) a breast tumor; an epidermoid tumor, such as an epidermoid head and/or neck tumor or a mouth tumor; a lung tumor, e.g., a small cell or non-small cell lung tumor; a gastrointestinal tumor, e.g., a colorectal tumor; or a genitourinary tumor, e.g., a prostate tumor (especially a hormone-refractory prostate tumor); or
- (ii) a proliferative disease that is refractory to the treatment with other chemotherapeutics; or
- (iii) a tumor that is refractory to treatment with other chemotherapeutics due to multi-drug resistance.

In a broader sense, a proliferative disease may furthermore be a hyperproliferative condition, such as leukemias, hyperplasias, fibrosis (especially pulmonary, but also other types of fibrosis, such as renal fibrosis), angiogenesis, psoriasis, atherosclerosis and smooth muscle proliferation in the blood vessels, such as stenosis or restenosis following angioplasty.

Where a tumor, a tumor disease, a carcinoma or a cancer are mentioned, also metastasis in the original organ or tissue and/or in any other location are implied alternatively or in addition, whatever the location of the tumor and/or metastasis.

The HDAI compound is selectively toxic or more toxic to rapidly propifering cells than to normal cells, particularly in human cancer cells, e.g., cancerous tumors, the compound has significant antiproliferative effects and promotes differentiation, e.g., cell cycle arrest and apoptosis. In addition, the hydroxamate compound induces p21, cyclin-CDK interacting protein, which induces either apoptosis or G1 arrest in a variety of cell lines.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereto.

Example 1: Aqueous Formulation Comprising *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide as the Active Ingredient

A solution of 1 mL contains:

- | | | |
|----|---|----------|
| 20 | • N-hydroxy-3-[4-[[[2-(2-methyl-1 <i>H</i> -indol-3-yl)-ethyl]-amino]methyl]phenyl]-2 <i>E</i> -2-propenamide | 5 mg |
| | • Propylene glycol | 200 mg |
| | • Mannitol | 50 mg |
| | • Lactic acid | 9.6 mg |
| 25 | • Water for injection | qs. 1 mL |
| | • HCl or NaOH to adjust pH to 4 | |

This formulation is stable at 5°C up to 13 months.

Example 2: Non-Aqueous Formulation Comprising *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide as the Active Ingredient

A solution of 1 mL contains:

- 5
- N-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide 5 mg
 - Propylene glycol qs. 1 mL

This formulation is stable at room temperature up to 2 years.

What is claimed is:

1. A pharmaceutical formulation suitable for parenteral use comprising:
 - (a) *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino] methyl]phenyl]-2*E*-2-propenamide;
 - 5 (b) an alcohol selected from the group consisting of propylene glycol, ethanol, sorbitol and glycerine;
 - (c) a buffer;
 - (d) water; and
 - (e) a tonicity modifier.
- 10 2. The formulation according to Claim 1, wherein the pH of the formulation is about 3.5 to about 4.5.
3. The formulation according to Claim 2, wherein the pH of the formulation is about 4.
4. The formulation according to Claim 1, wherein the buffer is lactate buffer.
5. The formulation according to Claim 1, wherein the alcohol is propylene glycol.
- 15 6. The formulation according to Claim 1, wherein the tonicity modifier is mannitol.
7. A pharmaceutical formulation suitable for parenteral use comprising propylene glycol, lactate buffer, mannitol and *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof.
8. A pharmaceutical formulation suitable for parenteral use comprising 20% propylene
20 glycol, 0.96% lactate buffer, 5% mannitol and 0.5% of a compound selected from *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof.
9. A method of treating a proliferative disorder in a mammal which comprises administering to said mammal a pharmaceutical composition according to Claim 1.

10. A pharmaceutical formulation suitable for parenteral use comprising:
- (a) *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino] methyl]phenyl]-2*E*-2-propenamide; and
- (b) an alcohol selected from the group consisting of propylene glycol, ethanol,
- 5 sorbitol and glycerine.
11. The formulation according to Claim 10, wherein the pH of the formulation is about 3.5 to about 4.5.
12. The formulation according to Claim 11, wherein the pH of the formulation is about 4.
13. The formulation according to Claim 10, wherein the alcohol is propylene glycol.
- 10 14. A pharmaceutical formulation suitable for parenteral use comprising propylene glycol and *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino] methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof.
15. A method of treating a proliferative disorder in a mammal which comprises administering to said mammal a pharmaceutical composition according to Claim 10.