



US 20190300496A1

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2019/0300496 A1**  
(43) **Pub. Date: Oct. 3, 2019****STEVENAZZI et al.**(54) **BENZO-N-HYDROXY AMIDE COMPOUNDS  
HAVING ANTITUMOR ACTIVITY***C07D 233/64* (2006.01)*C07D 213/56* (2006.01)*C07D 405/12* (2006.01)*C07D 417/12* (2006.01)*C07D 409/12* (2006.01)*A61P 35/00* (2006.01)(71) Applicant: **ITALFARMACO SPA**, Milano (IT)(72) Inventors: **Andrea STEVENAZZI**, Milano (IT);  
**Giovanni SANDRONE**, Novara (IT);  
**Daniela MODENA**, Monza (IT);  
**Samuele Pietro POZZI**, Legnano (IT);  
**Barbara VERGANI**, Macherio (IT);  
**Maria LATTANZIO**, Milano (IT);  
**Paolo MASCAGNI**, Alicante (ES);  
**Christian STEINKÜHLER**, Roma  
(IT); **Gianluca FOSSATI**, Milano (IT)(52) **U.S. Cl.**CPC ..... *C07D 317/60* (2013.01); *C07C 259/10*  
(2013.01); *C07D 221/04* (2013.01); *C07D*  
*233/64* (2013.01); *A61P 35/00* (2018.01);  
*C07D 405/12* (2013.01); *C07D 417/12*  
(2013.01); *C07D 409/12* (2013.01); *C07D*  
*213/56* (2013.01)(21) Appl. No.: **16/315,576**(22) PCT Filed: **Jul. 14, 2017**(86) PCT No.: **PCT/EP2017/067850**

§ 371 (c)(1),

(2) Date: **Jan. 4, 2019**(30) **Foreign Application Priority Data**

Jul. 18, 2016 (IT) ..... 102016000074606

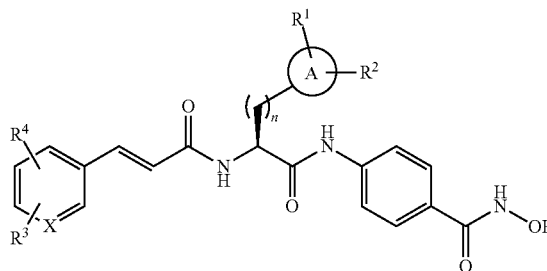
**Publication Classification**(51) **Int. Cl.***C07D 317/60* (2006.01)*C07C 259/10* (2006.01)*C07D 221/04* (2006.01)

(57)

**ABSTRACT**

The present invention relates to new benzo-N-hydroxy amide compounds of formula (I) and pharmaceutically acceptable salts, isomers and prodrugs thereof, which show a significant inhibitory activity on the proliferation of tumor cells and specifically of cancer stem cells.

(I)



## BENZO-N-HYDROXY AMIDE COMPOUNDS HAVING ANTITUMOR ACTIVITY

### FIELD OF THE INVENTION

[0001] The present invention relates to new benzo-N-hydroxy amide compounds having an alpha-amino acidic scaffold carrying an alpha-beta unsaturated carbonyl moiety on the amino-group and to the pharmaceutical compositions thereof.

[0002] The molecules have antitumor activity and are particularly active on cancer stem cells.

### BACKGROUND OF THE INVENTION

[0003] Partial or even complete cancer regression can be achieved in some patients with current cancer treatments. However, such initial responses are almost always followed by relapse, with the recurrent cancer being resistant to further treatments. The discovery of therapeutic approaches that counteract relapse is, therefore, essential for advancing cancer medicine. Cancer cells are extremely heterogeneous, even in each individual patient, in terms of their malignant potential, drug sensitivity, and their potential to metastasize and cause relapse. Indeed, hypermalignant cancer cells, termed cancer stem cells or tumor-initiating cells, that are highly tumorigenic and metastatic have been isolated from cancer patients with a variety of tumor types. Moreover, such stemness-high cancer cells are resistant to conventional chemotherapy and radiation.

[0004] Therefore, development of specific therapies targeted at cancer stem cells holds hope for improvement of survival and quality of life of cancer patients, especially for patients with metastatic disease.

[0005] U.S. Pat. No. 7,635,788 discloses hydroxamic acid derivatives containing an alpha-aminoacyl moiety and having inhibitory activity on the proinflammatory cytokines production, in particular TNF $\alpha$ . Such compounds are useful in the treatment of inflammatory diseases and other disorders characterised by overproduction of TNF $\alpha$  or other proinflammatory cytokines. Said compounds furthermore exhibit a cytotoxicity activity in in vitro testing on human hepatoma cell line Hep-G2.

### Definitions

[0006] Unless otherwise defined, all terms of art, notations and other scientific terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this disclosure pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference; thus, the inclusion of such definitions herein should not be construed to represent a substantial difference over what is generally understood in the art.

[0007] The term "halogen" herein refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I).

[0008] The term "C<sub>1</sub>-C<sub>4</sub> alkyl" herein refers to a branched or linear hydrocarbon containing from 1 to 4 carbon atoms. Examples of C<sub>1</sub>-C<sub>4</sub> alkyl groups include but are not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl.

[0009] The term "aryl" herein refers to aromatic mono- and poly-carbocyclic ring systems, wherein the individual carbocyclic rings in the poly-carbocyclic ring systems may

be fused or attached to each other via a single bond. Suitable aryl groups include, but are not limited to, phenyl, naphthyl and biphenyl.

[0010] The term "aryloxy" herein refers to O-aryl group, wherein "aryl" is defined above.

[0011] The term "alkoxy" herein refers to O-alkyl group, wherein "alkyl" is defined above.

[0012] The term "arylalkyl" herein refers to an aryl radical, as defined herein, attached to an alkyl radical, as defined herein.

[0013] The term "arylcarbonyl" herein refers to —C(O)-aryl, wherein "aryl" is defined above.

[0014] The term "heterocycle" herein refers to a 4-, 5-, 6-, 7- or 8-membered monocyclic ring which is saturated or unsaturated, and which consists of carbon atoms and one or more heteroatoms selected from N, O and S, and wherein the nitrogen and sulphur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heterocycle ring may be attached to any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. The term also includes any bicyclic system in which any of the above heterocyclic rings is fused to an aryl or another heterocycle. When the heterocycle ring is an aromatic heterocycle ring it can be defined "heteroaromatic ring".

[0015] The terms "comprising", "having", "including" and "containing" are to be construed as open-ended terms (i.e. meaning "including, but not limited to") and are to be considered as providing support also for terms as "consist essentially of", "consisting essentially of", "consist of" or "consisting of".

[0016] The terms "consist essentially of", "consisting essentially of" are to be construed as a semi-closed terms, meaning that no other ingredients and/or steps which materially affects the basic and novel characteristics of the invention are included (optional excipients may be thus included).

[0017] The terms "consists of", "consisting of" are to be construed as a closed term.

[0018] The term "pharmaceutically acceptable salts" herein refers to those salts which possess the biological effectiveness and properties of the salified compound and which do not produce adverse reactions when administered to a mammal, preferably a human. The pharmaceutically acceptable salts may be inorganic or organic salts; examples of pharmaceutically acceptable salts include but are not limited to: carbonate, hydrochloride, hydrobromide, sulphate, hydrogen sulphate, citrate, maleate, fumarate, acetate, trifluoroacetate, pamoate, 2-naphthalenesulphonate, and para-toluenesulphonate. Further information on pharmaceutically acceptable salts can be found in Handbook of pharmaceutical salts, P. Stahl, C. Wermuth, WILEY-VCH, 127-133, 2008, herein incorporated by reference.

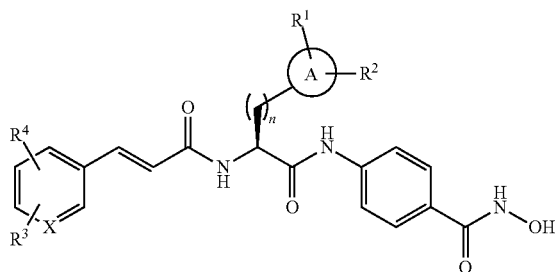
[0019] The term "physiologically acceptable excipient" herein refers to a substance devoid of any pharmacological effect of its own and which does not produce adverse reactions when administered to a mammal, preferably a human. Physiologically acceptable excipients are well known in the art and are disclosed, for instance in the Handbook of Pharmaceutical Excipients, sixth edition 2009, herein incorporated by reference.

[0020] The term "isomers" herein refers to structural (or constitutional) isomers (i.e. tautomers) and stereoisomers (or spatial isomers) i.e. diastereoisomers and enantiomers.

## DESCRIPTION OF THE INVENTION

**[0021]** It has now been found that benzo-N-hydroxy amide compounds having an alpha-amino acidic scaffold carrying an alpha-beta unsaturated carbonyl moiety on the amino-group show a high inhibitory activity on the proliferation of tumor cells and of staminal tumor cells. These compounds are particularly active on cancer stem cells, making them useful in the treatment of human neoplasia.

**[0022]** The present invention provides compounds of the formula (I):



and pharmaceutically acceptable salts, isomers and prodrugs thereof,

**[0023]** wherein:

**[0024]** n is 0, 1 or 2;

**[0025]** A is absent or is a mono or di-carbocyclic residue, optionally partially or totally unsaturated, comprising carbon atoms and optionally one or more heteroatoms selected from N, S or O;

**[0026]** R<sup>1</sup> and R<sup>2</sup> are independently selected from the group comprising —H, —OH, —OMe, —CN, —NH<sub>2</sub>, —NO<sub>2</sub>, —Cl, —COOH, —halogen, —CF<sub>3</sub>, —N(Ra)<sub>2</sub>, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, aryl, arylalkyl, arylcarbonyl, alkoxy, aryloxy residue, sulphonylamino and —CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>;

**[0027]** Ra is a linear or branched C<sub>1</sub>-C<sub>3</sub> alkyl residue;

**[0028]** X can be C or N;

**[0029]** R<sup>3</sup> and R<sup>4</sup> are independently selected from the group comprising —H, —OMe, —OPh, —NO<sub>2</sub>, —NMe<sub>2</sub>, —NH<sub>2</sub>, —halogen, —CF<sub>3</sub>, —N(Ra)<sub>2</sub>, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, aryl, arylalkyl, arylcarbonyl, alkoxy, aryloxy residue and sulphonylamino, or R<sup>3</sup> and R<sup>4</sup> together can form a heteropentacyclic moiety (—OCH<sub>2</sub>O—).

**[0030]** The compounds of the present invention can exist in different isomeric forms: the cis-form and the trans-form.

**[0031]** The preferred isomeric form is the trans-form.

**[0032]** The compounds of the invention contain one or more chiral centers (asymmetric carbon atoms) and may thus exist in enantiomeric and/or diastereoisomeric forms; all possible optical isomers, alone or mixed with one another, fall within the scope of the present invention.

**[0033]** Prodrugs of compounds of formula (I) are included in this invention. Such prodrugs are bioreversible derivatives of compounds (I). They are pharmacologically inactive derivatives, which can undergo in vivo metabolic transformation to afford an active compound included in the general formula of this invention. Many different prodrugs are known in the art [Prodrug approach: an effective solution to overcome side-effects, Patil S. J., Shirote P. J., International Journal of Medical and Pharmaceutical Sciences, 2011, 1-13; Carbamate Prodrug Concept for Hydroxamate HDAC

Inhibitors, Jung, Manfred et al., ChemMedChem, 2011, 1193-1198]. Some compounds of formula (I) present one or more basic or acidic moieties, which can undergo salification by conventional chemical methods, generally treatment of the compounds with organic or inorganic acid, organic or inorganic base, or by ion-exchange chromatography. Examples of pharmaceutically acceptable salts include, but are not limited to, those deriving from inorganic acids such as hydrochloric, hydrobromic, sulfuric, phosphoric, nitric and the like, or from organic acids such as acetic, maleic, propionic, succinic, glycolic, stearic, malic, tartaric, citric, ascorbic, pamoic and the like. Further examples of pharmaceutically acceptable salts include, but are not limited to, those deriving from bases such as aluminium, ammonium, calcium, copper, ferric, lithium, magnesium, potassium, sodium, zinc and the like. Pharmaceutically acceptable salts are well known in the art. Their preparation is well described by Berg et al. in "Pharmaceutica salts", J. Pharm. Sci., 1977, 66, 1-19.

**[0034]** One class of preferred compounds comprises compounds of the formula (I) and pharmaceutically acceptable salts, isomers and prodrugs thereof, in which:

**[0035]** n is 0, 1 or 2;

**[0036]** A is absent or is a mono or di-carbocyclic residue, optionally partially or totally unsaturated, comprising carbon atoms and optionally one or more heteroatoms selected from N, S or O;

**[0037]** R<sup>1</sup> and R<sup>2</sup> are independently selected from the group comprising —H, —OH, —OMe, —CN, —NH<sub>2</sub>, —NO<sub>2</sub>, —Cl, —COOH and —CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>;

**[0038]** X can be C or N;

**[0039]** R<sup>3</sup> and R<sup>4</sup> are independently selected from the group comprising —H, —OMe, —OPh, —NO<sub>2</sub>, —NMe<sub>2</sub> and —NH<sub>2</sub>, or R<sup>3</sup> and R<sup>4</sup> together can form a heteropentacyclic moiety (—OCH<sub>2</sub>O—).

**[0040]** Preferably, A is absent or is a mono or di-carbocyclic residue selected from the group comprising phenyl, naphthyl, pyridyl, indanyl, quinolyl, imidazolyl, indolyl, thiazolyl, benzothiophenyl.

**[0041]** Another class of more preferred compounds comprises compounds of the formula (I) and pharmaceutically acceptable salts, isomers and prodrugs thereof in which:

**[0042]** n is 1, X is C;

**[0043]** R<sup>1</sup> and R<sup>2</sup> are independently —H, —Cl or —OMe;

**[0044]** R<sup>3</sup> and R<sup>4</sup> are independently —H, —NMe<sub>2</sub>, or R<sup>3</sup> and R<sup>4</sup> together can form a heteropentacyclic moiety (—OCH<sub>2</sub>O—).

**[0045]** The following compounds of the formula (I) are particularly preferred:

**[0046]** (2S)-2-[[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(4-methoxyphenyl)propanamide (1D);

**[0047]** (2S)—N-[4-(hydroxycarbamoyl)phenyl]-3-(4-methoxyphenyl)-2-[[[E]-3-phenylprop-2-enoyl]amino]propanamide (2D);

**[0048]** (2S)-2-[[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-phenyl-propanamide (4D);

**[0049]** (2S)—N-[4-(hydroxycarbamoyl)phenyl]-3-phenyl-2-[[[E]-3-phenyl-2-enoyl]amino]propanamide (5D);

**[0050]** (2S)-2-[[[E]-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(4-hydroxyphenyl)propanamide (7D);

- [0051] (E)-3-(2,5-dimethoxyphenyl)-N-[(1R)-2-[4-(hydroxycarbamoyl)anilino]-1-indan-2-yl-2-oxo-ethyl]prop-2-enamide (8D);
- [0052] (2S)-2-[[E]-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-4-phenyl-butanamide (9D);
- [0053] (2S)-2-[[E]-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-phenyl-propanamide (10D);
- [0054] (2S)-2-[[E]-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(2-naphthyl)propanamide (11D);
- [0055] (E)-3-(2,5-dimethoxyphenyl)-N-[2-[4-(hydroxycarbamoyl)anilino]-2-oxo-ethyl]prop-2-enamide (12D);
- [0056] (2S)-2-[[E]-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]propanamide (13D);
- [0057] (2S)-2-[[E]-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(3-quinolyl)propanamide (14D);
- [0058] (2S)-2-[[E]-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(3-pyridyl)propanamide (15D);
- [0059] (2S)-2-[[E]-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(4-nitrophenyl)propanamide (16D);
- [0060] (2S)-2-[[E]-3-(4-aminophenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-phenyl-propanamide (17D);
- [0061] (2S)-3-(4-aminophenyl)-2-[[E]-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]propanamide (18D);
- [0062] (2S)-3-(4-cyanophenyl)-2-[[E]-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]propanamide (19D);
- [0063] (2S)—N-[4-(hydroxycarbamoyl)phenyl]-2-[[E]-3-(4-nitrophenyl)prop-2-enoyl]amino]-3-phenyl-propanamide (20D);
- [0064] (2S)-2-[[E]-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(1H-imidazol-5-yl)propanamide (21D);
- [0065] (2S)-2-[[E]-3-(3,4-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(3-pyridyl)propanamide (22D);
- [0066] (2S)-2-[[E]-3-(3,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(3-pyridyl)propanamide (23D);
- [0067] (2S)-2-[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(3-pyridyl)propanamide (24D);
- [0068] (2S)-2-[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-3-(benzothiophen-3-yl)-N-[4-(hydroxycarbamoyl)phenyl]propanamide (25D);
- [0069] (2S)-2-[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-thiazol-4-yl-propanamide (26D);
- [0070] (2S)-2-[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-4-phenyl-butanamide (27D);
- [0071] (2S)-2-[[E]-3-(3,4-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-phenyl-propanamide (28D);
- [0072] (2S)-2-[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-3-(4-cyanophenyl)-N-[4-(hydroxycarbamoyl)phenyl]propanamide (29D);
- [0073] (2S)-2-[[E]-3-(3,4-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(1H-indol-3-yl)propanamide (30D);
- [0074] (2S)-2-[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(1H-indol-3-yl)propanamide (31D);
- [0075] (2S)-2-[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(4-nitrophenyl)propanamide (32D);
- [0076] (2S)-2-[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-3-(4-chlorophenyl)-N-[4-(hydroxycarbamoyl)phenyl]propanamide (33D);
- [0077] (2S)-3-(4-aminophenyl)-2-[[E]-3-(3,4-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]propanamide (34D);
- [0078] (2S)-3-(4-aminophenyl)-2-[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]propanamide (35D);
- [0079] 4-[(2S)-2-[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-3-[4-(hydroxycarbamoyl)anilino]-3-oxopropyl]benzoic acid (36D);
- [0080] (2S)-2-[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-3-(3,4-dichlorophenyl)-N-[4-(hydroxycarbamoyl)phenyl]propanamide (37D);
- [0081] (2S)—N-[4-(hydroxycarbamoyl)phenyl]-3-(4-methoxyphenyl)-2-[[E]-3-phenylprop-2-enoyl]amino]propanamide (38D);
- [0082] (2S)-2-[[E]-3-(4-dimethylaminophenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-phenyl-propanamide (39D);
- [0083] (2S)-2-[[E]-3-(4-dimethylaminophenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(4-methoxyphenyl)propanamide; 2,2,2-trifluoroacetic acid (40D);
- [0084] (E)-N-[2-[[4-(hydroxycarbamoyl)phenyl]methylamino]-2-oxo-ethyl]-3-phenyl-prop-2-enamide (41D);
- [0085] (E)-3-(1,3-benzodioxol-5-yl)-N-[2-[[4-(hydroxycarbamoyl)phenyl]methylamino]-2-oxo-ethyl]prop-2-enamide (43D);
- [0086] (2S)-3-[4-(diethylaminomethyl)phenyl]-N-[4-(hydroxycarbamoyl)phenyl]-2-[[E]-3-phenylprop-2-enoyl]amino]propanamide; 2,2,2-trifluoroacetic acid (45D);
- [0087] (2S)-2-[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-3-[4-(diethylaminomethyl)phenyl]-N-[4-(hydroxycarbamoyl)phenyl]propanamide; 2,2,2-trifluoroacetic acid (46D);
- [0088] (2S)—N-[4-(hydroxycarbamoyl)phenyl]-3-(2-naphthyl)-2-[[E]-3-(6-phenoxy-3-pyridyl)prop-2-enoyl]amino]propanamide (47D);
- [0089] The following compounds of the formula (I) are more particularly preferred:
- [0090] (2S)-2-[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(4-methoxyphenyl)propanamide (1D);
- [0091] (2S)—N-[4-(hydroxycarbamoyl)phenyl]-3-(4-methoxyphenyl)-2-[[E]-3-phenylprop-2-enoyl]amino]propanamide (2D);
- [0092] (2S)-2-[[E]-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-phenyl-propanamide (4D);

[0093] (2S)—N-[4-(hydroxycarbonyl)phenyl]-3-phenyl-2-[[*(E)*-3-phenyl-2-enyl]amino]propanamide (5D).

[0094] The compounds of the invention may be prepared using methods known to the person skilled in the art.

[0095] All starting materials, building blocks, reagents, acids, bases, solvents and catalysts used to synthesize compounds of the present invention are commercially available.

[0096] Compounds of formula (I) can be prepared both by solid phase synthesis (scheme 1) and by solution synthetic method (scheme 2). In some cases it could be necessary to synthesize the compound in a protected species and to add one or more step for the de-protection.

[0097] Reactions are monitored by HPLC or LC-MS analysis.

[0098] Final products are generally purified by preparative HPLC-MS chromatography or by SPE on reverse phase filled cartridge.

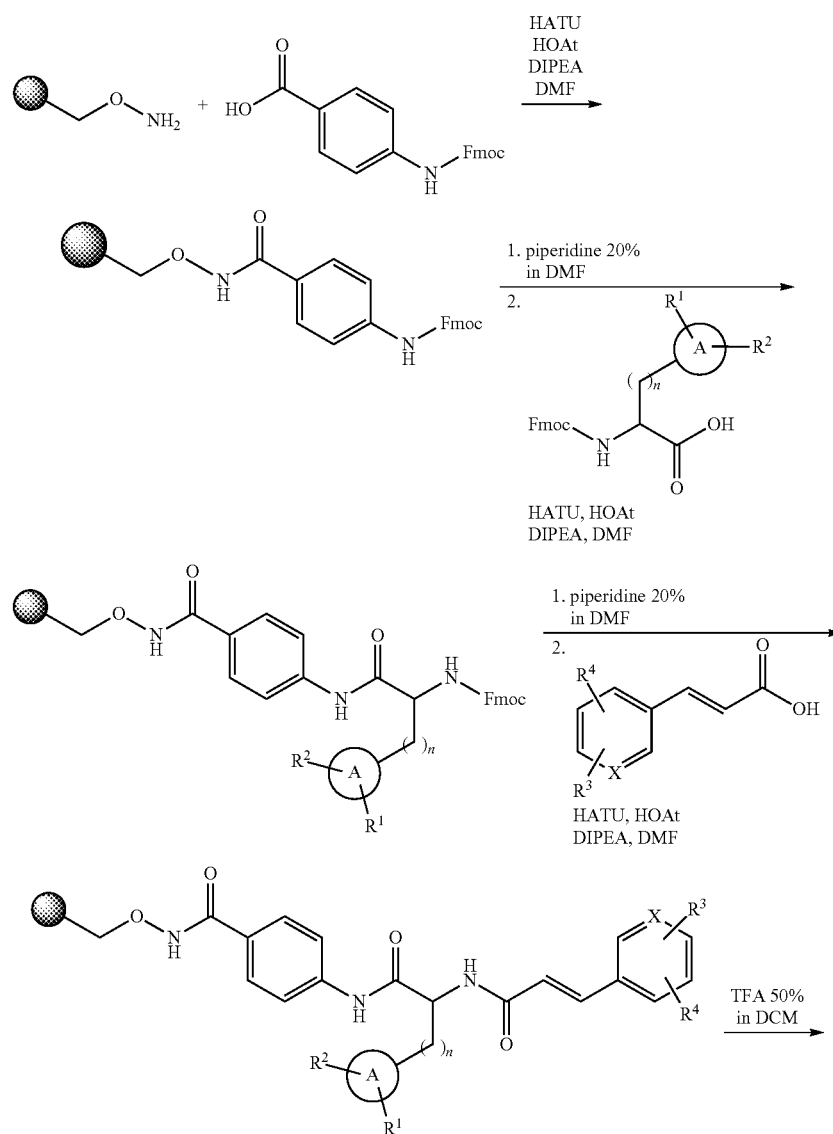
[0099] Solid Phase Synthesis

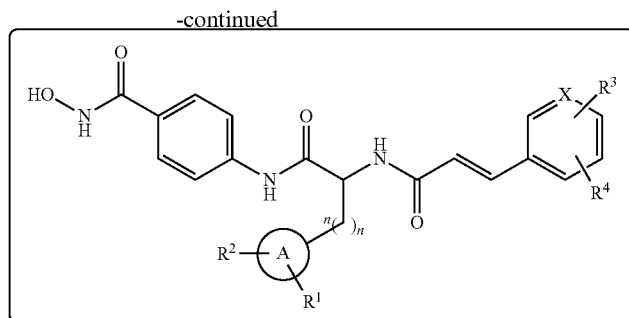
[0100] Compounds of formula (I) can be synthesised by SPS following scheme 1.

[0101] N-fmoc-4-aminobenzoic acid is loaded on hydroxylamine Wang resin after classical activation with HATU, HOAt and DIPEA. The Fmoc-deprotection is performed by treating the resin with piperidine 20% solution in DMF for 15 minutes. A fmoc-amino acid is then coupled to the aromatic amine, after activation with HATU, HOAt and DIPEA. Another fmoc-deprotection step follows and finally the amine group is acylated by treatment of the resin with an activated cinnamic acid derivative. Cleavage of the product from the resin is obtained by treatment with TFA 50% solution in DCM.

[0102] Final products are usually purified by preparative LC-MS chromatography or by SPE on C<sub>18</sub> filled cartridge.

Scheme 1





**[0103]** Solution Phase Synthesis

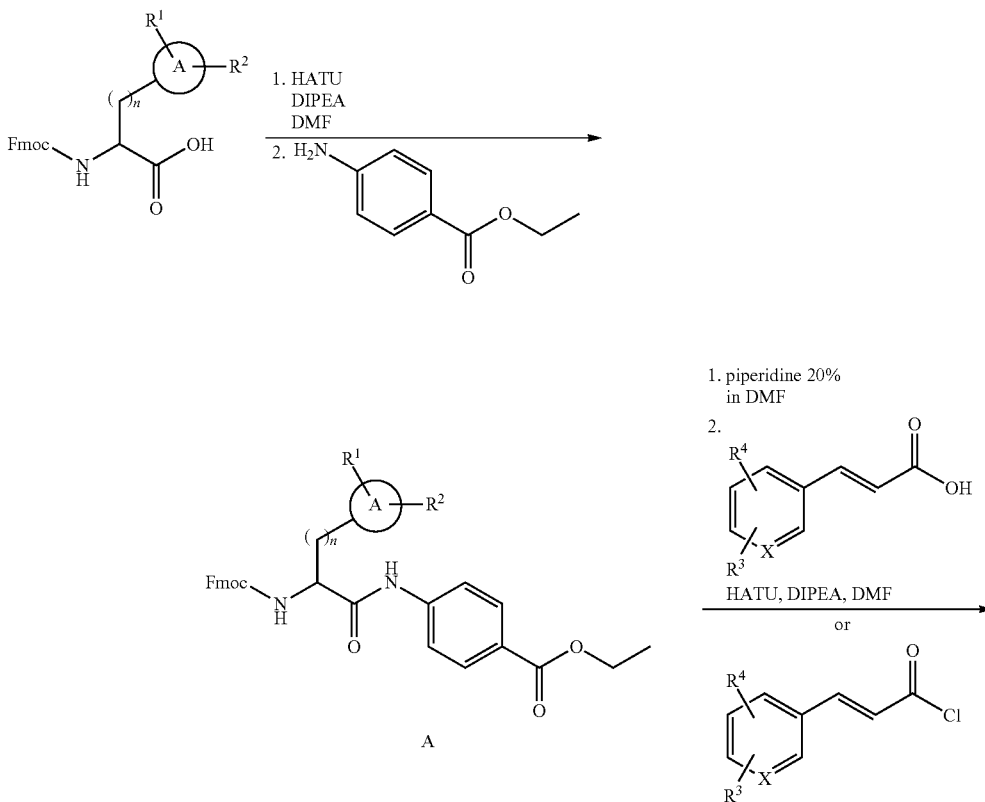
**[0104]** Compounds of formula (I) can also be prepared by classical solution synthesis, as shown in scheme 2. The formation of the amide can be performed using one of the method known to one of skill in the art. For example, after activation of carboxylic moiety with HATU and DIPEA, a Fmoc-amino acid is reacted with ethyl-4-aminobenzoate. The obtained compound A is deprotected by treatment with piperidine 20% in DMF and then acylated by reaction with activated cinnamic acid derivative to give the intermediate B. The final hydroxamic compound can be obtained following different synthetic route. It is possible to perform a direct

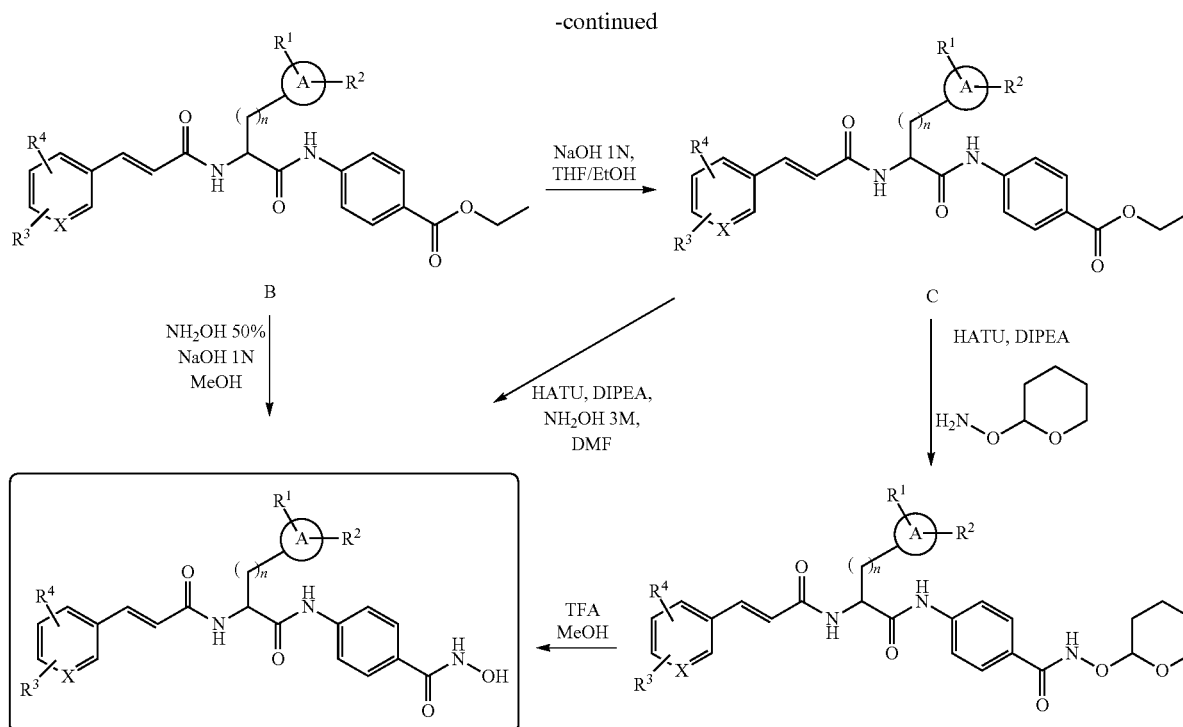
hydroxylaminolysis by treatment of the ester intermediate with hydroxylamine and NaOH in methanol.

**[0105]** Otherwise it is possible to hydrolyse the ester function with NaOH and then to transform the obtained carboxylic acid in hydroxamic acid by reaction with hydroxylamine after activation via HATU.

**[0106]** In some cases it is preferably to transform the carboxylic acid in a protected form of hydroxamate, in order to perform a purification of a compound easier to handle. In this case the final compound is obtained by deprotection with a TFA solution in Methanol.

Scheme 2





wherein A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and X have the same meanings reported above.

**[0107]** Preparative HPLC-MS Chromatography

**[0108]** The purification was performed using a Waters preparative HPLC system, equipped with a mass spectrometer detector (ZQ200). Three different methods have been used for purification, depending on the nature of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> groups.

**[0109]** Crude product was dissolved in DMSO. The solution was filtered through a 0.45 μm PTFE membrane and injected in the preparative system. Fractions corresponding to the peak associated with the expected molecular ion ([M+H]<sup>+</sup>) were collected and concentrated to dryness.

**[0110]** Operating Conditions:

Column:	Waters SunFire™ Prep C18 OBD™ 5□m, 19 × 100 mm
Solv. A	H <sub>2</sub> O
Solv. B	ACN
Solv. C	1% formic acid in H <sub>2</sub> O

**[0111]** HPLC Method 1:

Time (min)	Solv. A	Solv. B	Solv. C	Flow rate (ml/min)
0	55%	35%	10%	20
20	45%	45%	10%	20
22	0%	90%	10%	20
24	0%	90%	10%	20
26	55%	45%	10%	20
30	55%	45%	10%	20

**[0112]** HPLC Method 2:

Time (min)	Solv. A	Solv. B	Solv. C	Flow rate (ml/min)
0	70%	20%	10%	20
20	50%	40%	10%	20
22	0%	90%	10%	20
24	0%	90%	10%	20
26	70%	20%	10%	20
30	70%	20%	10%	20

**[0113]** HPLC Method 3:

Time (min)	Solv. A	Solv. B	Solv. C	Flow rate (ml/min)
0	75%	15%	10%	20
20	55%	35%	10%	20
22	0%	90%	10%	20
24	0%	90%	10%	20
26	75%	15%	10%	20
30	75%	15%	10%	20

**[0114]** Ms Method:

Centroid ES+	ionisation,
Scan time	30 min,
m/z scan	100-1000,
Cone voltage	15 V,
Source temperature	150° C.,
Desolvation temperature	280° C.

[0115] Solid Phase Extraction

[0116] The purification has been performed on reverse phase pre-filled SPE cartridge (Phenomenex Strata C18-E, 55 mm, 70A).

[0117] Crude product was dissolved in DMF and loaded on the cartridge. The product was eluted with ACN/water mixtures at different ratios, depending on the nature of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> groups. Eluted fractions which showed a HPLC purity area over 85% were collected and concentrated to dryness.

[0118] The compounds of the present invention showed high inhibitory activity on the proliferation of cancer stem cells in vitro, with IC<sub>50</sub> values of nanomolar order.

[0119] In vivo studies were also carried out, monitoring the capability of compounds to reduce tumor size and weight as described, for example, in Example 7.

[0120] These compounds may accordingly be used, alone or together with other antitumor drugs, in the prevention and/or treatment of cancer.

[0121] The compounds of the invention are preferably useful for the prevention and/or treatment of solid tumors such as colorectal cancer, lung, brain, prostate or gynecological cancers or hematologic malignancies.

[0122] The compounds of the invention are particularly active on cancer stem cells. Therefore, said compounds are preferably useful for the prevention and/or treatment of metastatic, recurrent and drug-resistant diseases.

[0123] The present invention accordingly also provides pharmaceutical compositions comprising a therapeutically effective quantity of the compounds of the formula (I) or of the pharmaceutically acceptable salts, isomers and prodrugs thereof together with at least one pharmaceutically acceptable excipient.

[0124] Such compositions may be liquid, suitable for enteral or parenteral administration, or solid, for example, in the form of capsules, tablets, coated tablets, powders or granules for oral administration, or in forms suitable for cutaneous administration, such as for example creams or ointments, or inhalatory administration.

[0125] The pharmaceutical compositions provided by the present invention may be prepared using known methods.

[0126] The following examples have the purpose of further illustrating the invention without however limiting it.

#### EXAMPLES

[0127] The abbreviations below are used in the following Examples:

[0128] ACN Acetonitrile

[0129] Boc tert-Butyloxycarbonyl

[0130] DCM dichloromethane

[0131] DEA diethylamine

[0132] DIPEAN, N-diisopropylethylamine

[0133] DMF dimethylformamide

[0134] DMSO dimethylsulfoxide

[0135] EtOAc ethyl acetate

[0136] EtOH Ethanol

[0137] Et<sub>2</sub>O diethyl ether

[0138] ES Electrospray

[0139] Fmoc Fluorenylmethyloxycarbonyl

[0140] HATU O-(7-azabenzotriazol-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

[0141] HOAt 1-hydroxy-7-azabenzotriazole

[0142] HPLC high pressure liquid chromatography

[0143] LC-MS HPLC system equipped with a mass spectrometer

[0144] MeOH methanol

[0145] PTFE Polytetrafluoroethylene

[0146] RT Room Temperature

[0147] SPE solid phase extraction

[0148] SPS solid phase synthesis

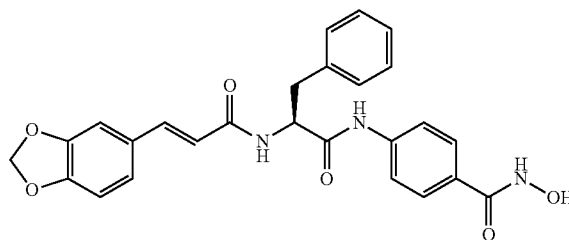
[0149] TFA trifluoroacetic acid

[0150] THF tetrahydrofuran

#### Example 1 (Compound 4D)

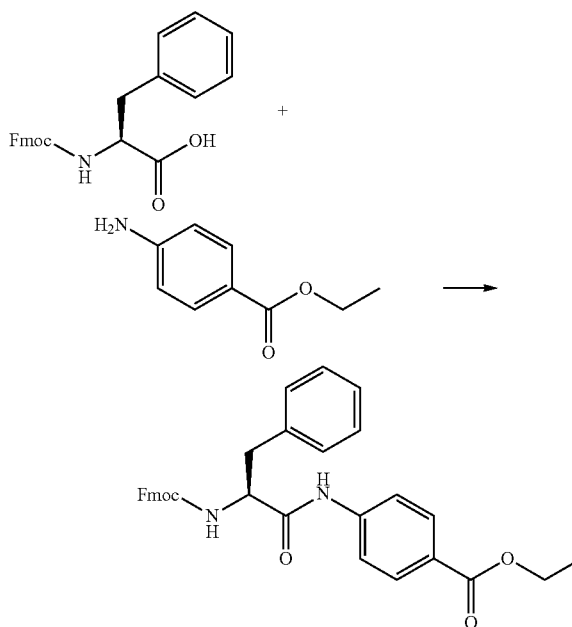
Synthesis of (S,E)-4-(2-(3-(benzo[d][1,3]dioxol-5-yl)acrylamido)-3-phenylpropanamido)-N-hydroxybenzamide

[0151]



Step A: Ethyl (S)-4-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)benzoate

[0152]



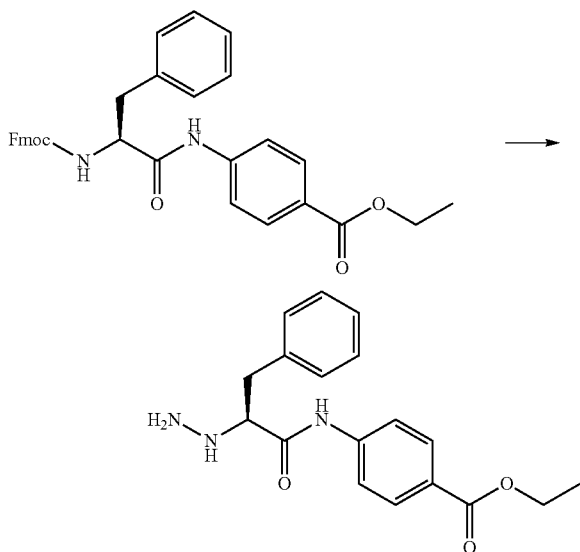
[0153] 3 g of Fmoc-L-Phenylalanine (7.74 mmol, 1 eq.) were dissolved in 15 ml of DMF and the solution was cooled at 0° C. HATU (3.84 g, 1.3 eq.) and DIPEA (1.75 ml, 1.3 eq.) were added and the reaction mixture was stirred for half an hour. Ethyl 4-aminobenzoate (1.40 g, 1 eq.) was then added and the mixture was stirred at RT for 1 h. The reaction was monitored by HPLC analysis. When the reaction was com-



plete, the solution was poured in water (150 ml). The white solid precipitated was filtered and dried. 4 g of pure product was obtained.

Step B: ethyl  
(S)-4-(2-amino-3-phenylpropanamido)benzoate

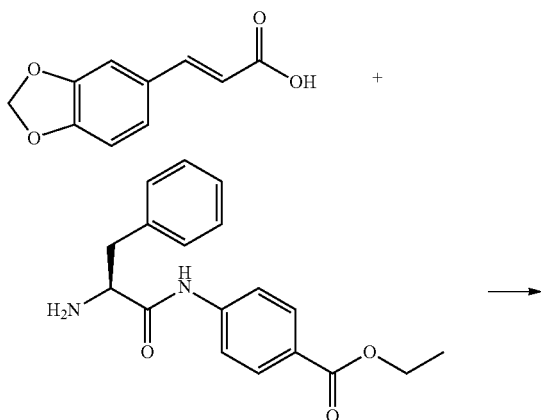
[0154]



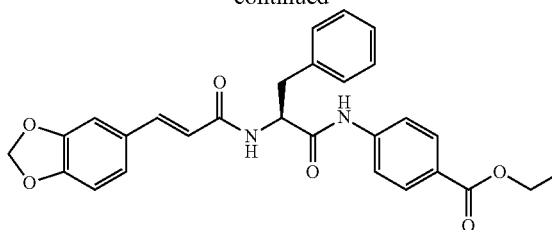
[0155] Compound obtained in step A was treated with 4.6 ml of DEA (6 eq.) in THF at RT for one night, in order to remove the Fmoc-protection. THF was removed and the residue was dissolved in n-hexane until formation of a solid. The solvent was removed and the product was washed twice with fresh n-hexane. 2.2 g of product was obtained.

Step C: ethyl (S,E)-4-(2-(3-(benzo[1,3]dioxol-5-yl)acrylamido)-3-phenylpropanamido)benzoate

[0156]



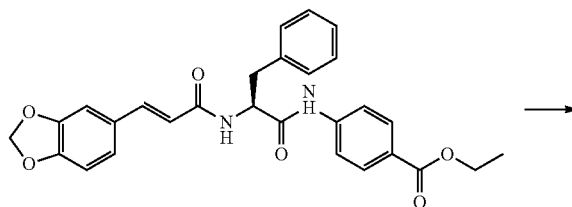
-continued



[0157] (E)-3-(1,3-benzodioxol-5-yl)prop-2-enoic acid (430 mg, 1 eq.) was dissolved in 5 ml of DMF, cooled to 0° C. and HATU (1.3 eq.) and DIPEA (1.3 eq.) were added. After 30 minutes 700 mg of compound obtained in step B was added. The reaction mixture was brought at RT and stirred for 1 h. The solution was then poured in water (50 ml) and the product was extracted with EtOAc. After acidification the solvent was evaporated and the crude product was purified on silica gel column.

Step D: (S,E)-4-(2-(3-(benzo[1,3]dioxol-5-yl)acrylamido)-3-phenylpropanamido)benzoic Acid

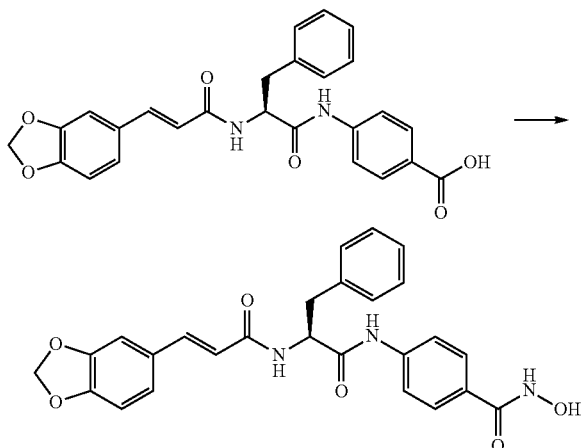
[0158]



[0159] 600 mg of compound obtained in step C were dissolved in 30 ml of EtOH/THF 1:2. NaOH 1N (3 eq.) was added to the solution and the reaction mixture was stirred at reflux for 4 h. Solvents were removed and the crude was dissolved in water. The solution was acidified with HCl 6N and precipitation of product was observed. The filtered solid was suspended in Et<sub>2</sub>O and filtered.

Step E: (S,E)-4-(2-(3-(benzo[d][1,3]dioxol-5-yl)acrylamido)-3-phenylpropanamido)-N-hydroxybenzamide

[0160]

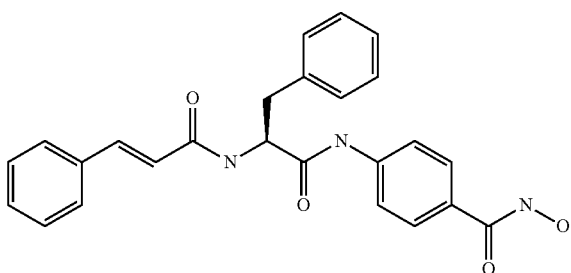


[0161] 400 mg of compound obtained in step D (1 eq.) were dissolved in 2.5 ml of DMF. After cooling in ice bath, HATU (1.3 eq.) and DIPEA (1.3 eq.) were added and the mixture was stirred for 1 h. Finally a solution of  $\text{NH}_2\text{OH}$  3M in DMF (3 eq.) was added and the reaction mixture was stirred at RT for 4 h. the mixture was then poured into water and the precipitated solid was filtered and suspended in dioxane and the mixture was stirred and warmed. The final product was obtained by filtration.

Example 2 (Compound 5D)

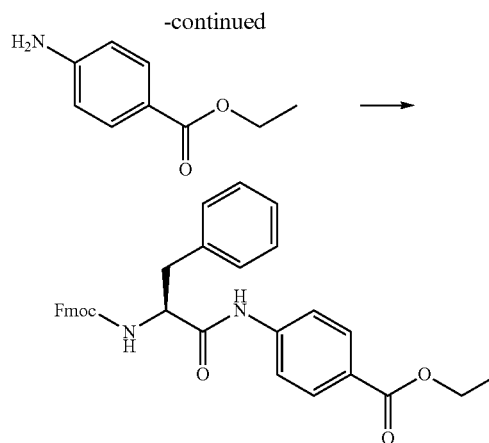
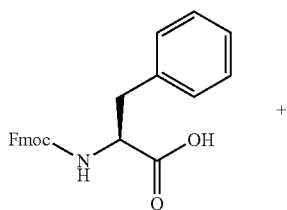
Synthesis of (S)-4-(2-(cinnamamido)-3-phenylpropanamido)-N-hydroxybenzamide

[0162]



Step A: Ethyl (S)-4-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)benzoate

[0163]

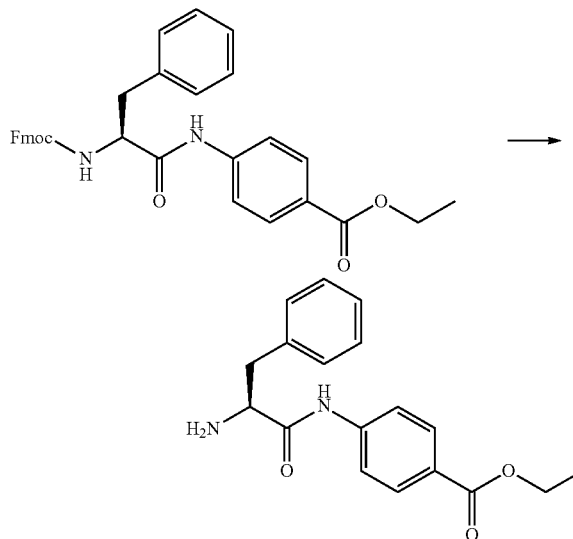


[0164] 3 g of Fmoc-L-Phenylalanine (7.74 mmol, 1 eq.) were dissolved in 15 ml of DMF and the solution was cooled at  $0^\circ\text{C}$ . HATU (3.84 g, 1.3 eq.) and DIPEA (1.75 ml, 1.3 eq.) were added and the reaction mixture was stirred for half an hour. Ethyl 4-aminobenzoate (1.40 g, 1 eq.) was then added and the mixture was stirred at RT for 1 h. The reaction was monitored by HPLC analysis. When the reaction was complete, the solution was poured in water (150 ml). The precipitated white solid was filtered and dried. 4 g of pure product was obtained.

Step B: ethyl

(S)-4-(2-amino-3-phenylpropanamido)benzoate

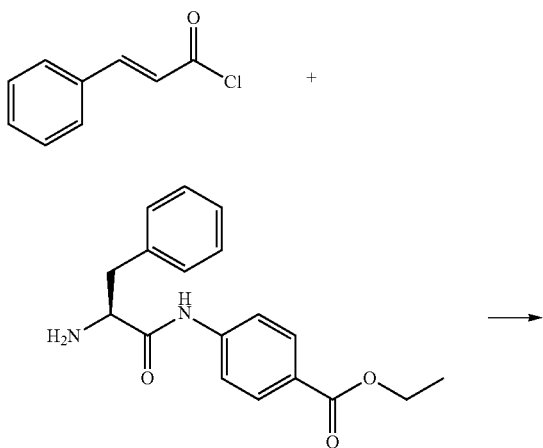
[0165]



[0166] Compound obtained in step A was treated with 4.6 ml of DEA (6 eq.) in THF at RT for one night, in order to remove the Fmoc-protection. THF was removed and the residue was dissolved in n-hexane until formation of a solid. The solvent was removed and the product was washed twice with fresh n-hexane. 2.2 g of product was obtained.

Step C: ethyl  
(S)-4-(2-cinnamamido-3-phenylpropanamido)benzoate

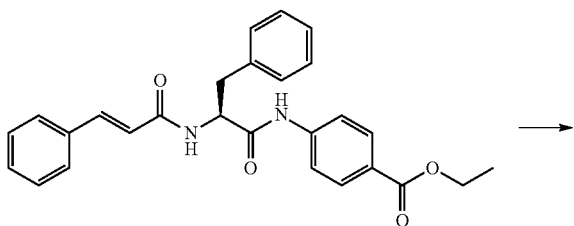
[0167]



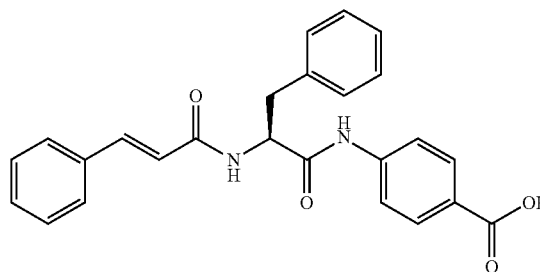
[0168] 900 mg of product obtained in step B (1 eq.) were dissolved in DCM (25 ml) and the solution was cooled at 0° C. TEA was added (1 eq.). Finally a solution of cinnamoyl chloride was added. The reaction mixture was stirred at room temperature for 1 h. After the reaction was complete, the solution was washed with water, HCl 1N and NaHCO<sub>3</sub> 5% in water. The organic phase was dried with CaCl<sub>2</sub>, filtered and evaporated. The crude was purified on silica gel column using a mixture of toluene/EtOH as mobile phase.

Step D:  
(S)-4-(2-cinnamamido-3-phenylpropanamido)benzoic Acid

[0169]



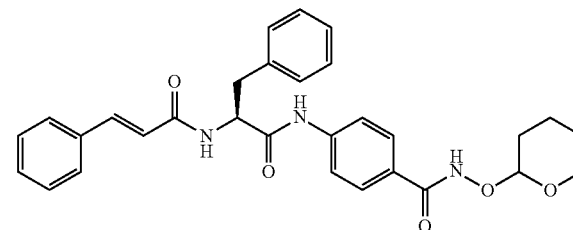
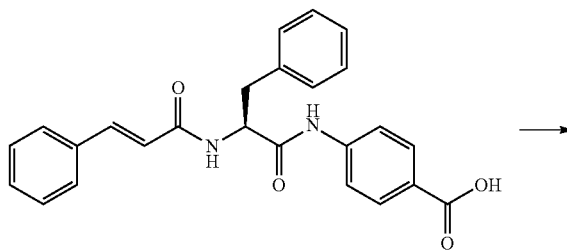
-continued



[0170] Ethyl (S)-4-(2-cinnamamido-3-phenylpropanamido)benzoate obtained in step C (400 mg, 1 eq.) was dissolved in a mixture of THF/EtOH and treated with NaOH 1N (3 eq.) for 1 h. Solvent was removed and crude was dissolved in water. Solution was acidified with conc. HCl. A solid is formed, filtered and used for the next step.

Step E: 4-((S)-2-cinnamamido-3-phenylpropanamido)-N-((tetrahydro-2H-pyran-2-yl)oxy)benzamide

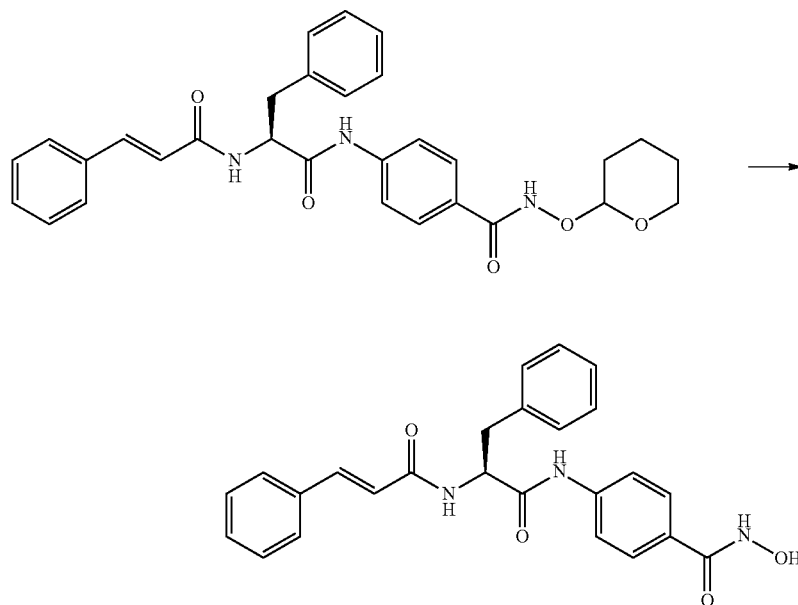
[0171]



[0172] 400 mg of compound obtained in step D (1 eq.) were dissolved in 2.5 ml of DMF. After cooling in ice bath, HATU (1.3 eq.) and DIPEA (1.3 eq.) were added and the mixture was stirred for 1 h. Finally O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (3 eq.) was added and the reaction mixture was stirred at RT for 4 h. The mixture was then poured into water and the precipitated solid was filtered and purified on silica gel column with a mixture of DCM/MeOH/NH<sub>3</sub> 25:1:0.1 as mobile phase.

Step F: (S)-4-(2-cinnamamido-3-phenylpropanamido)-N-hydroxybenzamide

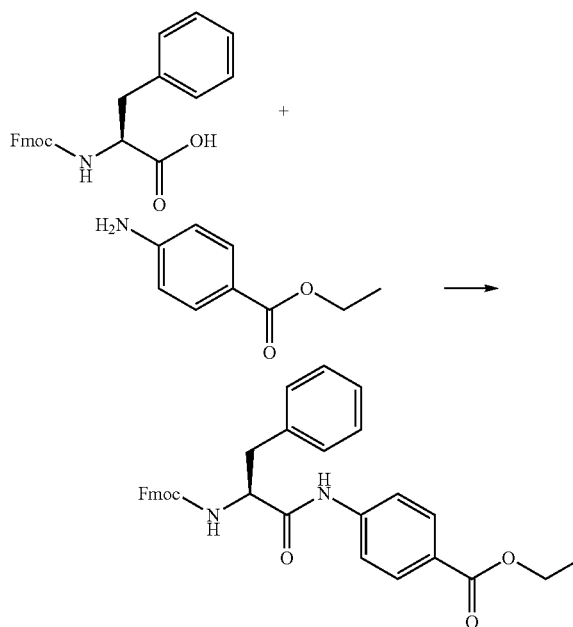
[0173]



[0174] Compound obtained in step E (200 mg, 1 eq.) was dissolved in MeOH (50 ml) and treated with TFA (1.5 ml). The reaction mixture was stirred at RT overnight. The solvent and the exceeding TFA were removed by evaporation and the crude was suspended in Et<sub>2</sub>O and filtered. 120 mg of pure product were obtained.

Step A: Ethyl (S)-4-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)benzoate

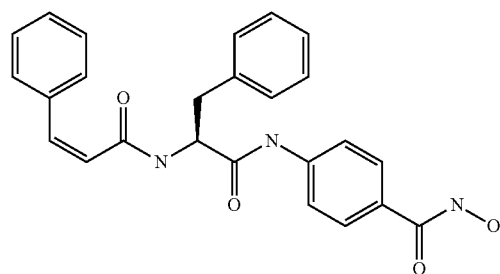
[0176]



Example 3 (Compound 5DZ)

Synthesis of (S,Z)-N-hydroxy-4-(3-phenyl-2-(3-phenylacrylamido)propanamido)benzamide

[0175]

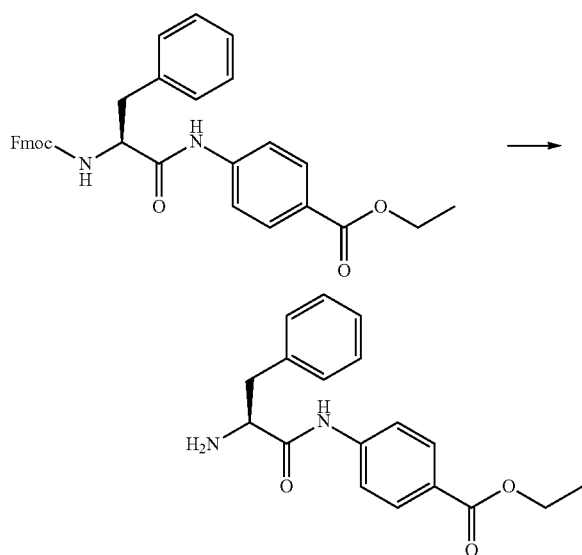


[0177] 3 g of Fmoc-L-Phenylalanine (7.74 mmol, 1 eq.) were dissolved in 15 ml of DMF and the solution was cooled at 0° C. HATU (3.84 g, 1.3 eq.) and DIPEA (1.75 ml, 1.3 eq.) were added and the reaction mixture was stirred for half an hour. Ethyl 4-aminobenzoate (1.40 g, 1 eq.) was then added and the mixture was stirred at RT for 1 h. The reaction was monitored by HPLC analysis. When the reaction was complete, the solution was poured in water (150 ml).

[0178] The precipitated white solid was filtered and dried. 4 g of pure product was obtained.

Step B: ethyl  
(S)-4-(2-amino-3-phenylpropanamido)benzoate

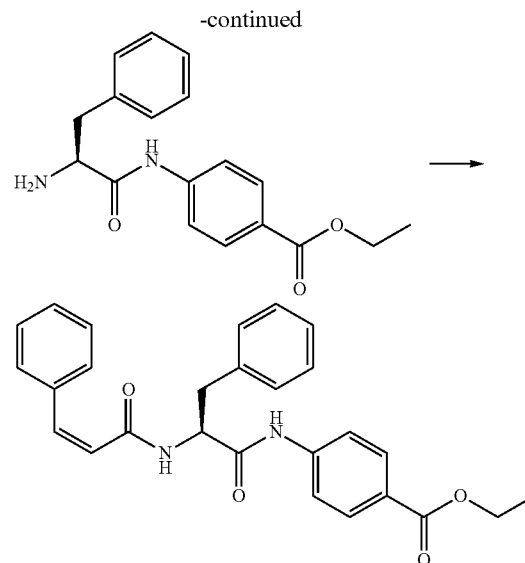
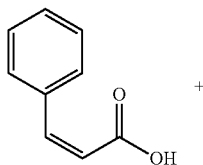
[0179]



[0180] Compound obtained in step A was treated with 4.6 ml of DEA (6 eq.) in THF at RT overnight, in order to remove the Fmoc-protection. THF was removed and the residue was dissolved in n-hexane until formation of a solid. The solvent was removed and the product was washed twice with fresh n-hexane. 2.2 g of product was obtained.

Step C: ethyl (S,Z)-4-(3-phenyl-2-(3-phenylacrylamido)propanamido)benzoate

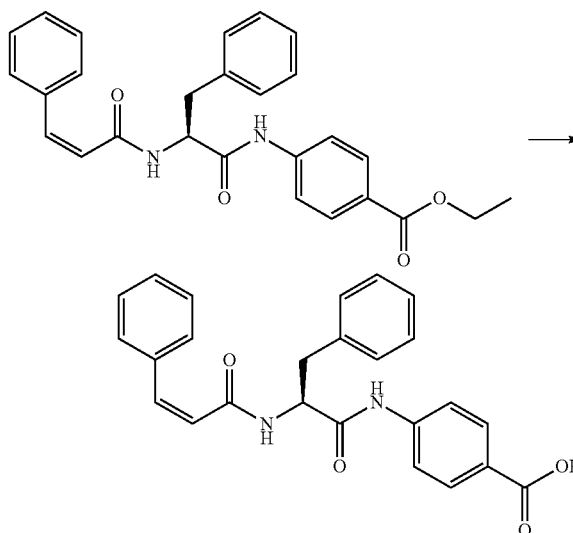
[0181]



[0182] (Z)-3-phenylacrylic acid (1 eq.) was dissolved in 5 ml of DMF and the solution was cooled at 0° C. HATU (1.3 eq.) and DIPEA (1.3 eq.) were added and the reaction mixture was stirred for one hour. Ethyl (S)-4-(2-amino-3-phenylpropanamido)benzoate (1 eq.) obtained in step B was then added and the mixture was stirred at RT overnight. The reaction was monitored by HPLC analysis. When the reaction was complete, the solution was poured in water. Crude product was extracted with EtOAc and purified on silica gel column, using a mixture of toluene/EtOAc 6:4 as mobile phase.

Step D: (S,Z)-4-(3-phenyl-2-(3-phenylacrylamido)propanamido)benzoic acid

[0183]

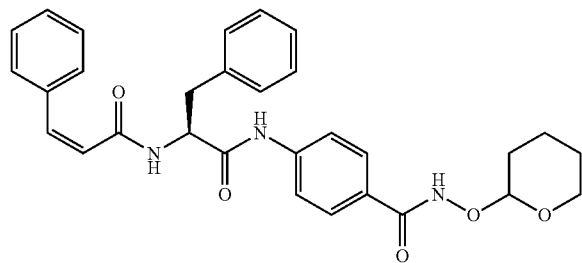
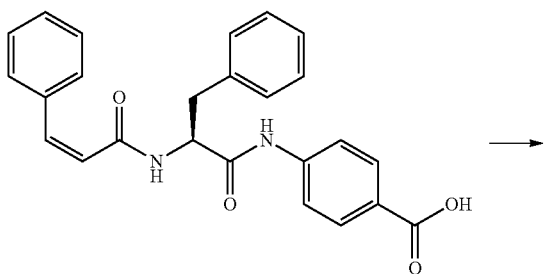


[0184] Ethyl (S,Z)-4-(3-phenyl-2-(3-phenylacrylamido)propanamido)benzoate obtained in step C (250 mg, 1 eq.)

was dissolved in a mixture of THF/EtOH and treated with NaOH 1N (3 eq.) for 24 h. Solvent was removed and crude was dissolved in water. Crude product was purified by silica gel column, eluting with a mixture of Toluene/EtOAc.

Step E: 4-((S)-3-phenyl-2-((Z)-3-phenylacrylamido)propanamido)-N-((tetrahydro-2H-pyran-2-yl)oxy)benzamide

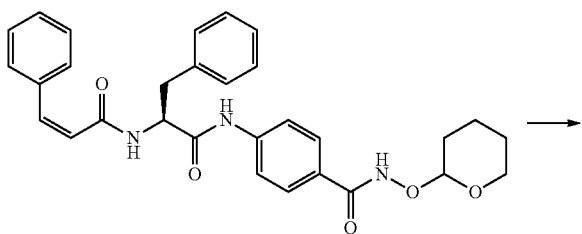
[0185]



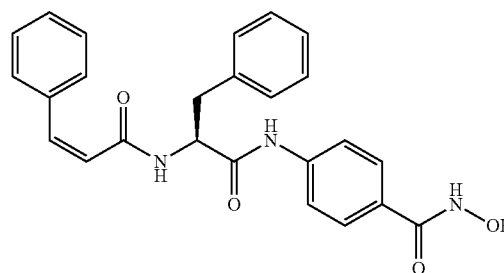
[0186] 200 mg of compound obtained in step D (1 eq.) were dissolved in 1 ml of DMF. After cooling in ice bath, HATU (1.3 eq.) and DIPEA (1.3 eq.) were added and the mixture was stirred for 1 h. Finally O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (1 eq.) was added and the reaction mixture was stirred at RT for 4 h. The mixture was then poured into water and the precipitated solid was filtered and purified on silica gel column with a mixture of EtOAc/Toluene 7:3 as mobile phase.

Step F: (S,Z)—N-hydroxy-4-(3-phenyl-2-(3-phenylacrylamido)propanamido)benzamide

[0187]



-continued

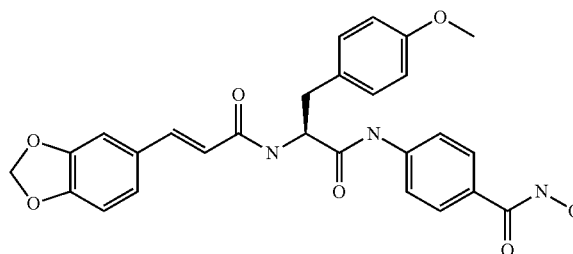


[0188] Compound obtained in step E (110 mg, 1 eq.) was dissolved in MeOH (25 ml) and treated with TFA (1 ml). The reaction mixture was stirred at RT for 4 hours. The solvent and the exceeding TFA were removed by evaporation and the crude was suspended in Et<sub>2</sub>O and filtered. 80 mg of pure product were obtained.

Example 4 (Compound 1D)

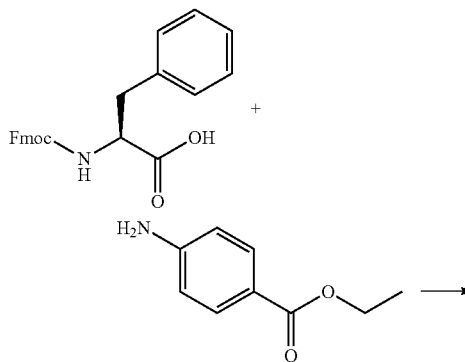
Synthesis of (S,E)-4-(2-(3-(benzo[1,3]dioxol-5-yl)acrylamido)-3-(4-methoxyphenyl)propanamido)-N-hydroxybenzamide

[0189]

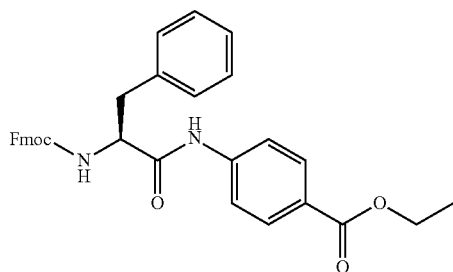


Step A: Ethyl (S)-4-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)benzoate

[0190]

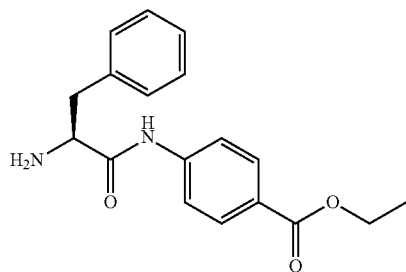
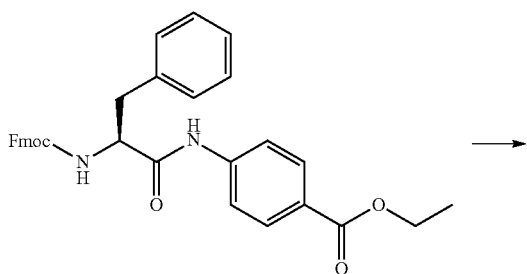


-continued



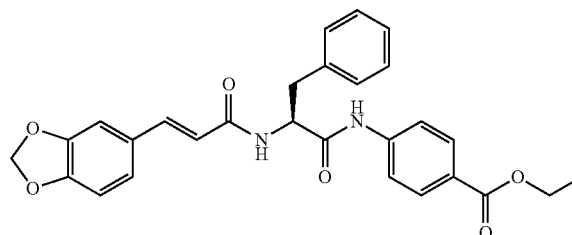
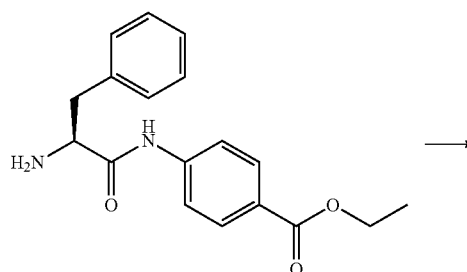
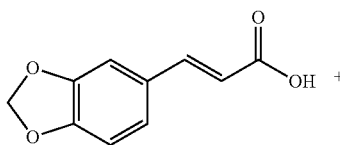
**[0191]** 3 g of Fmoc-L-Phenylalanine (7.74 mmol, 1 eq.) were dissolved in 15 ml of DMF and the solution was cooled at 0° C. HATU (3.84 g, 1.3 eq.) and DIPEA (1.75 ml, 1.3 eq.) were added and the reaction mixture was stirred for half an hour. Ethyl 4-aminobenzoate (1.40 g, 1 eq.) was then added and the mixture was stirred at RT for 1 h. The reaction was monitored by HPLC analysis. When the reaction was complete, the solution was poured in water (150 ml). The precipitated white solid was filtered and dried. 4 g of pure product was obtained.

Step B: ethyl  
(S)-4-(2-amino-3-phenylpropanamido)benzoate

**[0192]**

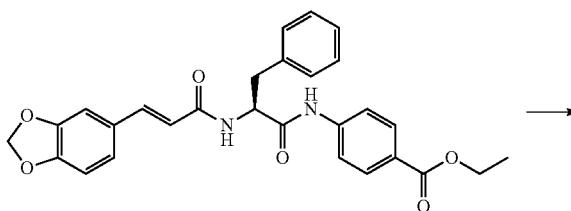
**[0193]** Compound obtained in step A was treated with 4.6 ml of DEA (6 eq.) in THF at RT overnight, in order to remove the Fmoc-protection. THF was removed and the residue was dissolved in n-hexane until formation of a solid. The solvent was removed and the product was washed twice with fresh n-hexane. 2.2 g of product were obtained.

Step C: ethyl (S,E)-4-(2-(3-(benzo[1,3]dioxol-5-yl)acrylamido)-3-phenylpropanamido)benzoate

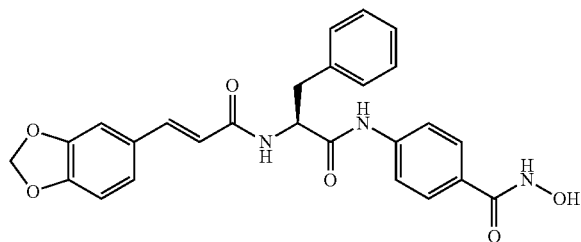
**[0194]**

**[0195]** (E)-3-(1,3-benzodioxol-5-yl)prop-2-enoic acid (430 mg, 1 eq.) was dissolved in 5 ml of DMF, cooled to 0° C. and reacted with HATU (1.3 eq.) and DIPEA (1.3 eq.). After 30 minutes 700 mg of compound obtained in step B was added. The reaction mixture was brought at RT and stirred for 1 h. The solution was then poured in water (50 ml) and the product was extracted with EtOAc. After acidification the solvent was evaporated and the crude product was purified on silica gel column.

Step D: (S,E)-4-(2-(3-(benzo[1,3]dioxol-5-yl)acrylamido)-3-(4-methoxyphenyl)propanamido)-N-hydroxybenzamide

**[0196]**

-continued

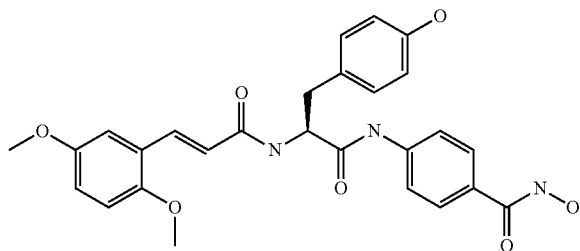


[0197] A solution of compound obtained in step D in MeOH was cooled in ice bath. A solution of hydroxylamine 50% in water (15 eq.) and NaOH 1N (10 eq.) were added and the reaction mixture was stirred at RT for 1 h. The solution was then neutralised with HCl 1N. A precipitation was observed. The pure product was obtained by simple filtration.

## Example 5 (Compound 7D)

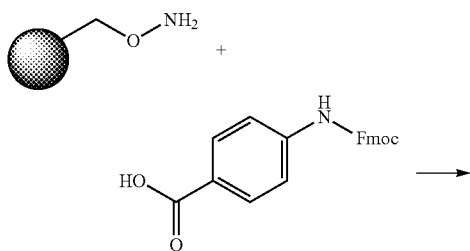
Synthesis of (S,E)-4-(2-(3-(2,5-dimethoxyphenyl)acrylamido)-3-(4-hydroxyphenyl)propanamido)-N-hydroxybenzamide

[0198]

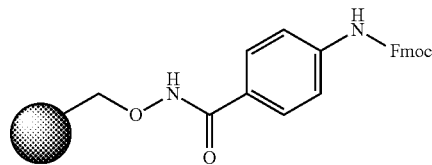


Step A: loading of (9H-fluoren-9-yl)methyl (4-(hydroxycarbonyl)phenyl)carbamate on Hydroxylamine Wang Resin

[0199]



-continued

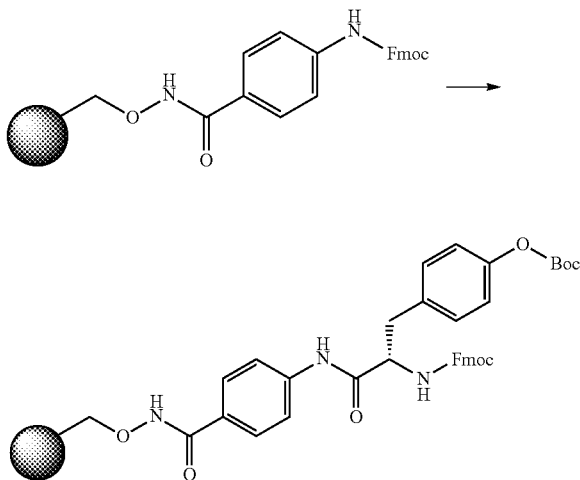


[0200] The reaction was performed in an empty SPE plastic filter tube, using an Activotec PLS 4x6 Organic Synthesizer.

[0201] After swelling of the resin with DCM and DMF, a solution of 4-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)benzoic acid (4 eq.), HATU (4 eq.), HOAt (4 eq.) and DIPEA (8 eq.) in DMF was added. The reaction mixture was shaken at RT overnight. The resin was then filtered and washed with DMF and DCM.

## Step B: First Coupling

[0202]

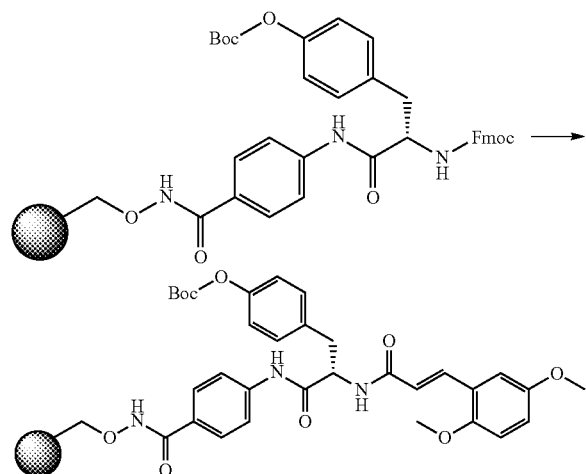


[0203] Resin from step A (200 mg, 1 eq.) was swelled in DMF, then filtered. Fmoc-deprotection was carried out by a double treatment of the resin with a solution of piperidine 20% in DMF for 30 minutes. The solution was filtered off and the resin was washed with DMF. A solution of (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-(tert-butoxycarbonyloxy)phenyl)propanoic acid (4 eq.), HATU (4 eq.), HOAt (4 eq.) and DIPEA (8 eq.) in DMF was added to the resin. The reaction mixture was shaken at RT overnight. The resin was filtered and washed with DMF and DCM.



## Step C: Second Coupling

[0204]



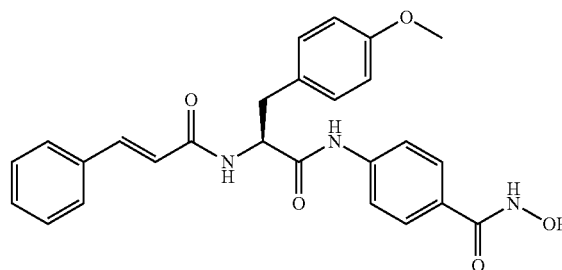
[0207] Cleavage of the product from the resin was obtained by treatment with TFA 50% in DCM at RT for 30 minutes. During this step the Boc-protection was also removed.

[0208] Crude was purified on SPE cartridge.

## Example 6

[0209] The following compounds were prepared using the procedure described in example 5:

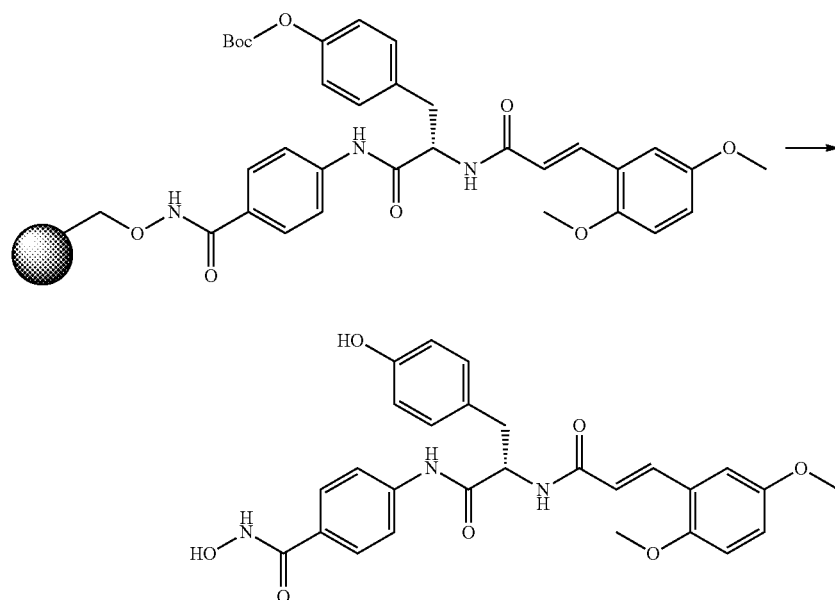
Compound 2D



[0205] Resin from step B (1 eq.) was swelled in DMF, then filtered. Fmoc-deprotection was performed by a double treatment of the resin with a solution of piperidine 20% in DMF for 30 minutes. The solution was filtered off and the resin was washed with DMF. A solution (E)-3-(2,5-dimethoxyphenyl)acrylic acid (4 eq.), HATU (4 eq.), HOAt (4 eq.) and DIPEA (8 eq.) in DMF was added to the resin. The reaction mixture was shaken at RT overnight. The resin was filtered and washed with DMF and DCM.

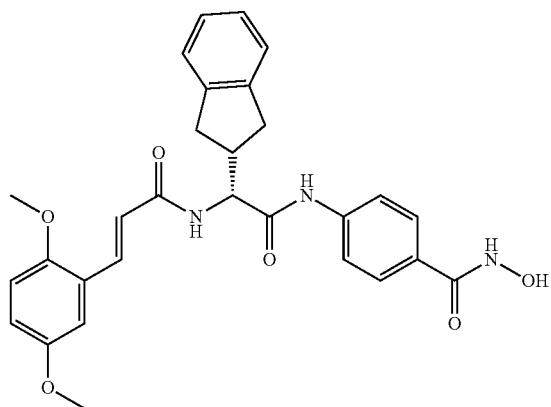
## Step D: Cleavage

[0206]

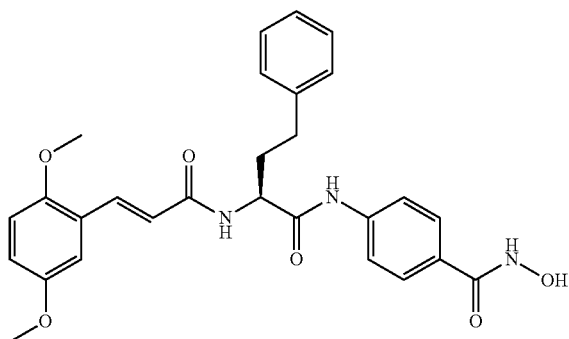


-continued

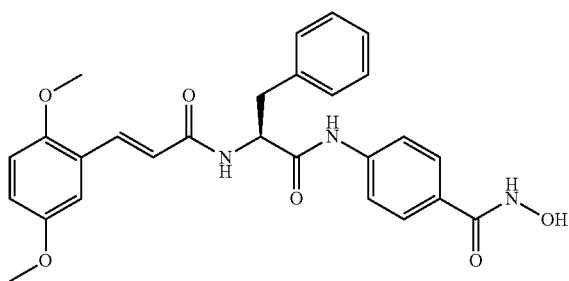
Compound 8D



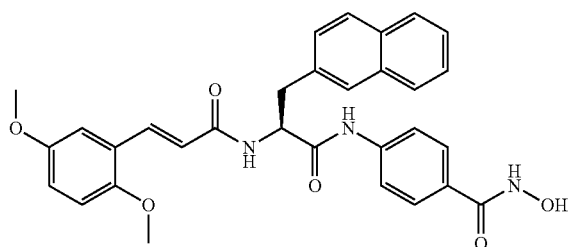
Compound 9D



Compound 10D



Compound 11D



2

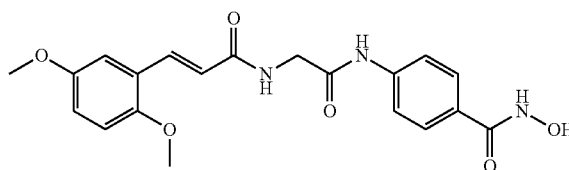
3

4

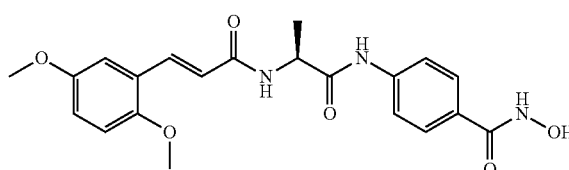
5

-continued

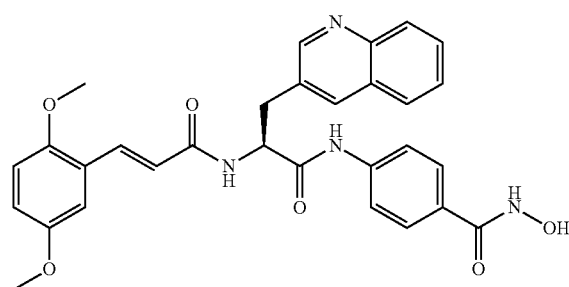
Compound 12D



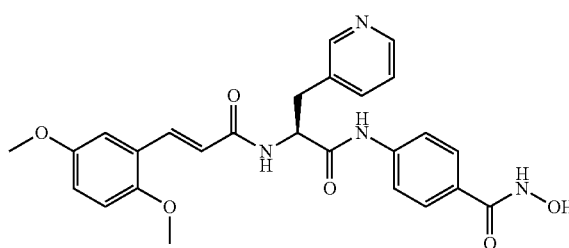
Compound 13D



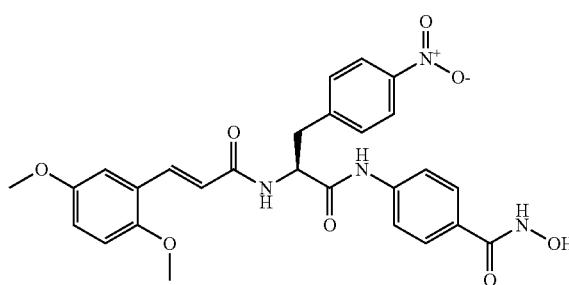
Compound 14D



Compound 15D



Compound 16D



6

7

8

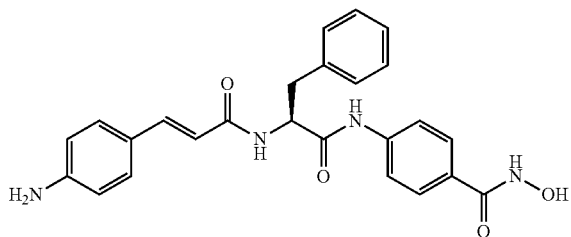
9

10

-continued

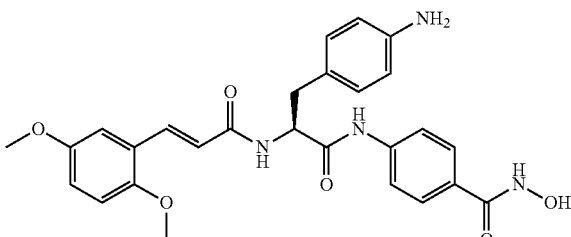
Compound 17D

11



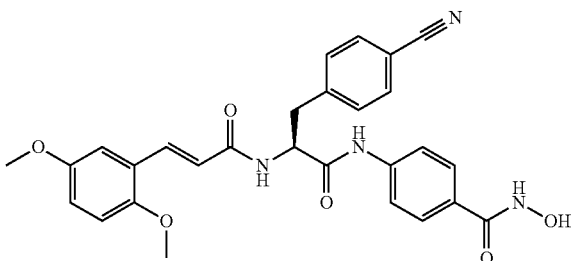
Compound 18D

12



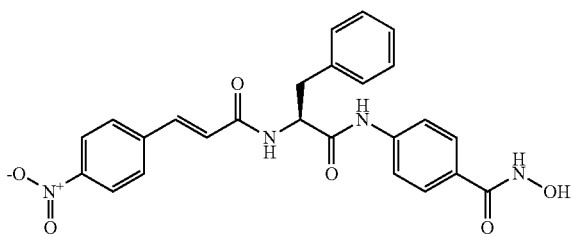
Compound 19D

13



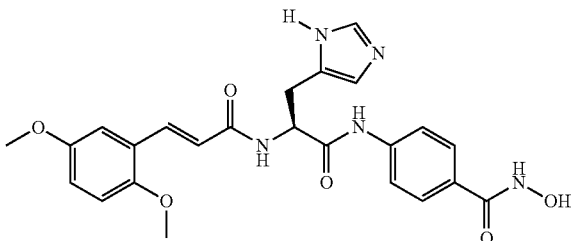
Compound 20D

14



Compound 21D

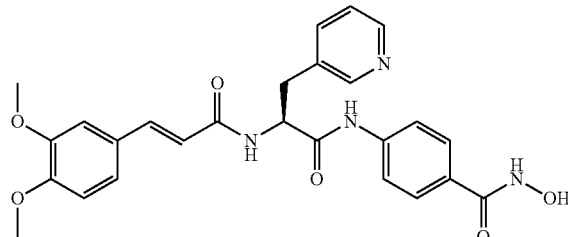
15



-continued

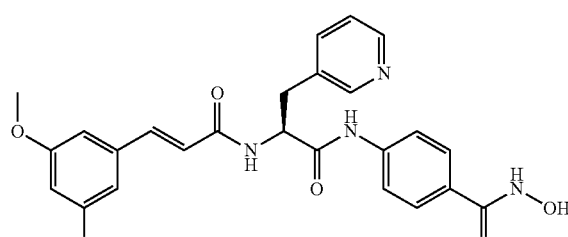
Compound 22D

16



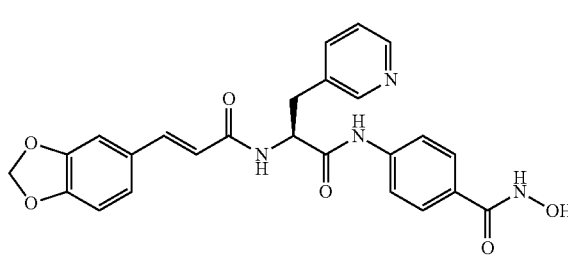
Compound 23D

17



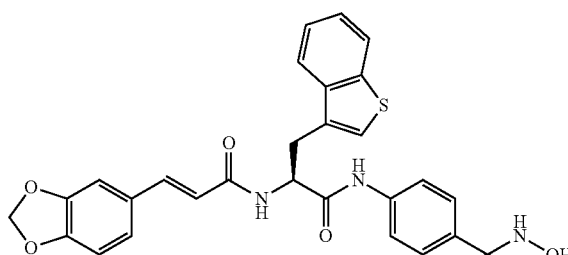
Compound 24D

18



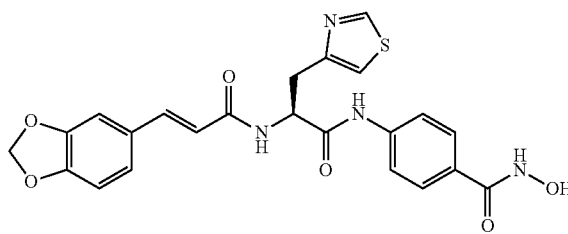
Compound 25D

19



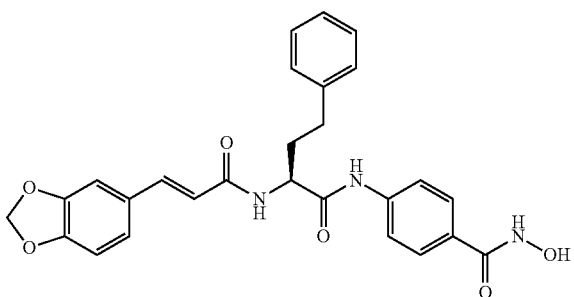
Compound 26D

20



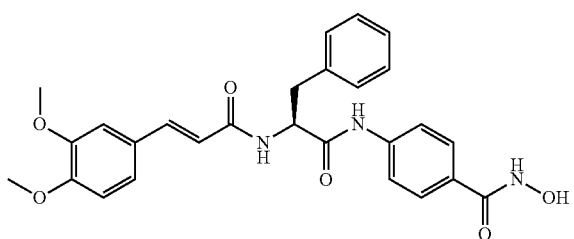
-continued

Compound 27D



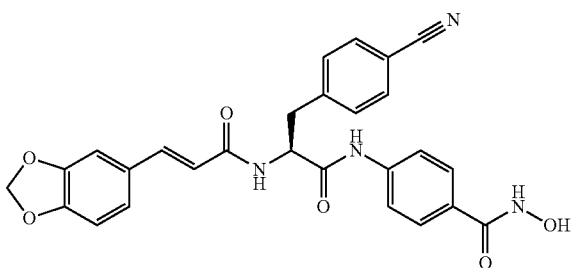
21

Compound 28D



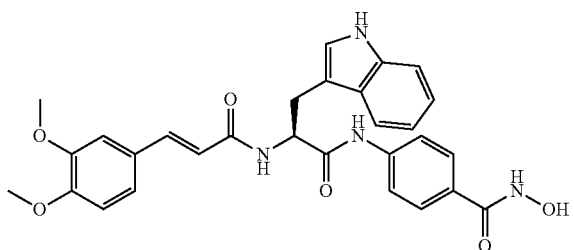
22

Compound 29D



23

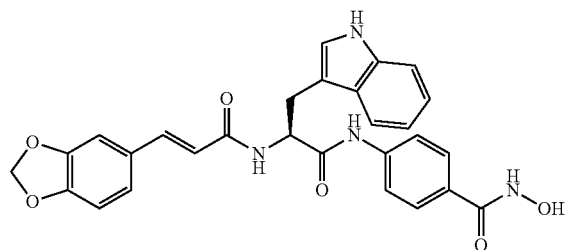
Compound 30D



24

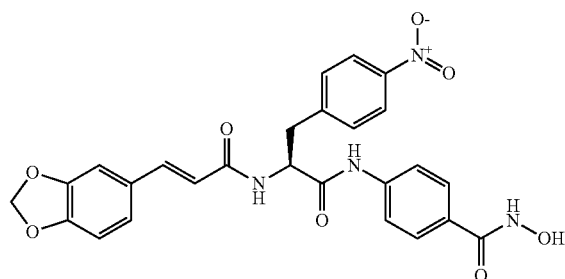
-continued

Compound 31D



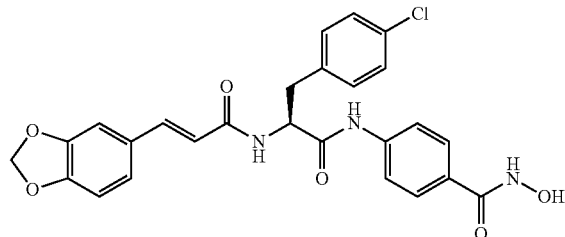
25

Compound 32D



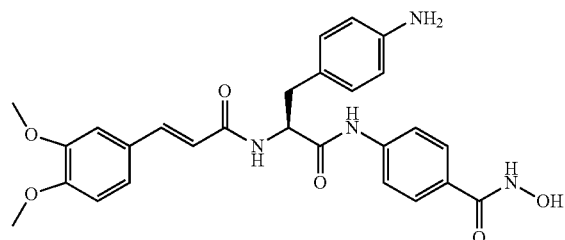
26

Compound 33D



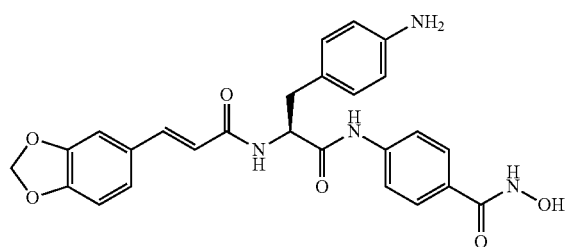
27

Compound 34D



28

Compound 35D

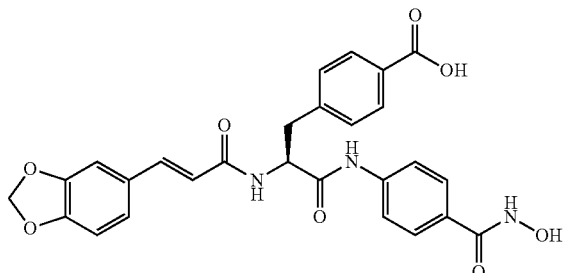


29

-continued

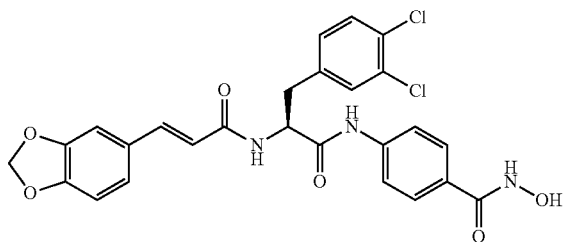
Compound 36D

30



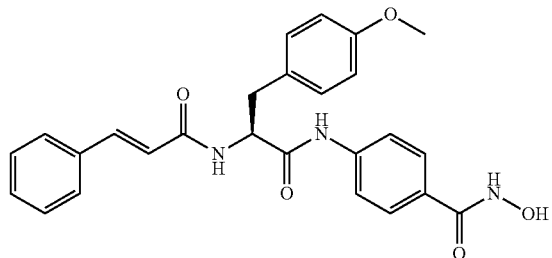
Compound 37D

31



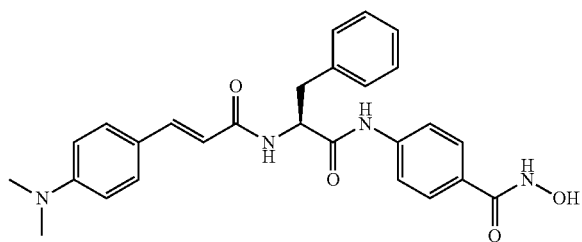
Compound 38D

32



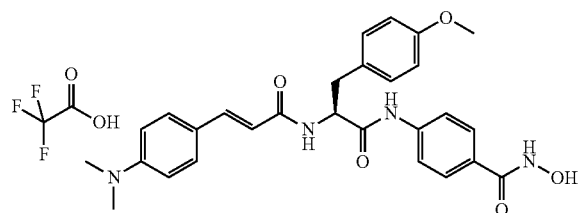
Compound 39D

33



Compound 40D

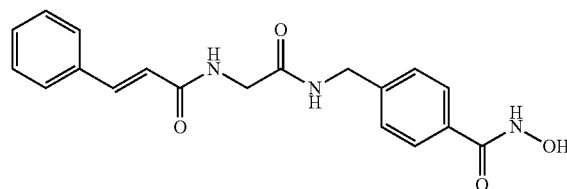
34



-continued

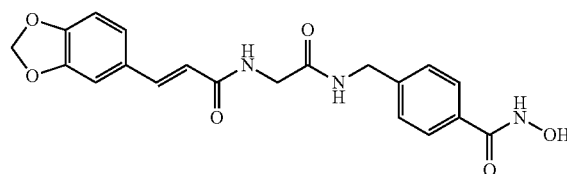
Compound 41D

35



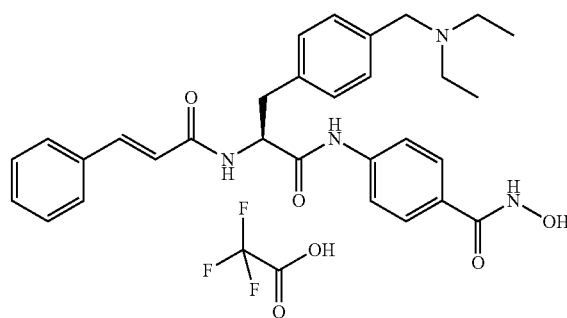
Compound 43D

36



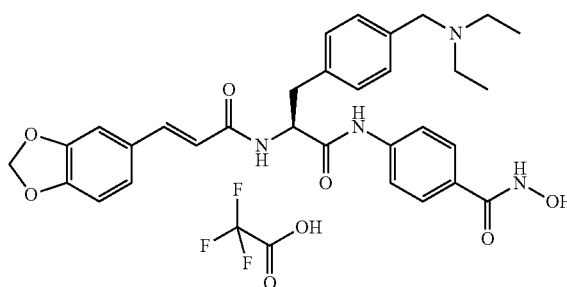
Compound 45D

37



Compound 46D

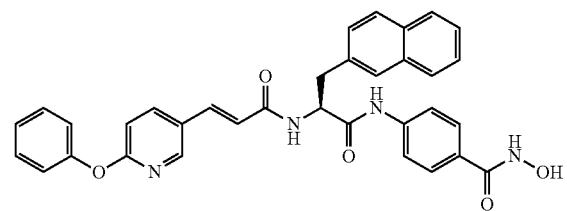
38



Compound 47D

39

AND Enantiomer



## Example 7

## Cytotoxicity Activity In Vitro

**[0210]** The compounds of the present invention are small molecules of formula (I), characterised by the presence of a metal chelating moiety, the benzohydroxamate, an  $\alpha$ -amino-acidic N-acylated central core and an  $\alpha,\beta$ -unsaturation at the acyl-moiety. This particular structural feature seems responsible for the high inhibitory activity on cancer stem cell lines and on HCT116 cells (ATCC CCL-247), a human colorectal carcinoma cell line widely used in cancer biology both in vitro and in vivo (Botchkina Cancer Genom Proteom 6, 19-30, 2009; Yeung PNAS 107, 3722-3727, 2010).

**[0211]** The cytotoxicity activity was evaluated as follows:

**[0212]** Pre-B leukemia cell line 697 was seeded at  $2 \times 10^5$  c/well;

**[0213]** Colon carcinoma cell lines HCT116, HT29 and COLO2015 were seeded at  $4 \times 10^3$ ,  $4 \times 10^3$  and  $10 \times 10^3$  c/well respectively;

**[0214]** Primary human kidney cells were seeded at  $1.5 \times 10^3$  and  $6.5 \times 10^3$  in two separate experiments;

**[0215]** Human PBMC were seeded at  $5 \times 10^5$  c/well;

**[0216]** Colon cancer stem cells (CSC) were seeded at  $3 \times 10^3$ ;

**[0217]** Testing compounds were added after 24 h and incubated for 72 h (48 h for 697 cell line). The concentrations of molecules ranged from 10000 nM to 1.5 nM (10000 to 1 nM for 697 cell line). The cytotoxic activity of compounds was evaluated using the CellTiter 96® Aqueous One Solution Cell Proliferation Assay (Promega) which mea-

sures the functionality of mitochondria according to manufacturer's instructions. For Colon cancer stem cells viability was determined with CellTiter-Glo Luminescent cell viability assay (Promega).

**[0218]** In the primary cytotoxicity screening performed on 697 cell line the activity of compounds D was similar or higher than that of saturated compounds.

**[0219]** The proliferation inhibitory activity of the unsaturated compounds of the present invention on HCT116 cells is 30 to 80 fold higher than the one exhibited by saturated analogues of the prior art U.S. Pat. No. 7,635,788, while it is at least similar or 3.5 to 40 fold higher on the stem cells (see table 1). In particular, all the compounds of the invention are resulted more active than the saturated analogues of the prior art on HCT116 cells.

**[0220]** The compound cytotoxicity was confirmed by further assays on two other colon cancer cell lines HT29 (ATCC HTB38) and Colo205 (ATCC CCL222) and on colon cancer stem cells (CSCs) (see table 2 and 3). It is worth noting that cytotoxic activity toward human primary kidney cells and peripheral blood mononuclear cells (PBMC) isolated from healthy donors was lower compared to tumor cells cytotoxicity (see table 4).

**[0221]** The cis-form prepared according to Example 3 is resulted less potent of the trans-form on HCT116 cells.

**[0222]** Furthermore the cis- form is chemically less stable than the trans. In a force degradation test all the compounds in the trans-form show high stability even at high temperatures (15 days at 80° C.) and at low pH (15 days at pH 2), while cis-analogue was little less stable at 80° C. and definitely less stable at pH 2.

TABLE 1

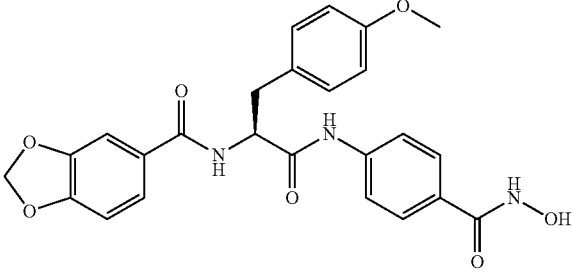
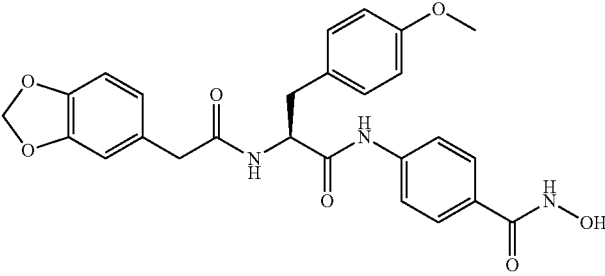
Comparison results on colon cancer cell lines			
COMPOUND	HCT116 (nM)	CSC1 (nM)	CyTox697 (nM)
	24	24	21
Compound 1A			
	554	280	168
Compound 1B			

TABLE 1-continued

Comparison results on colon cancer cell lines			
COMPOUND	HCT116 (nM)	CSC1 (nM)	CyTox697 (nM)
 Compound 1C	702	400	496
 Compound 1D	18	192	3
 Compound 2A	76	48	54
 Compound 2B	316	160	72

TABLE 1-continued

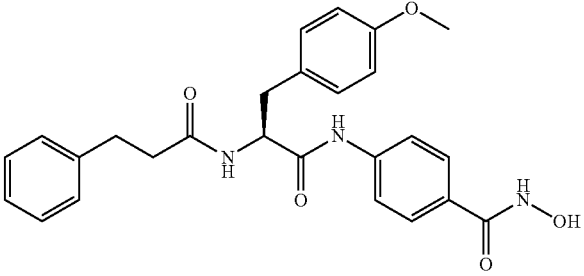
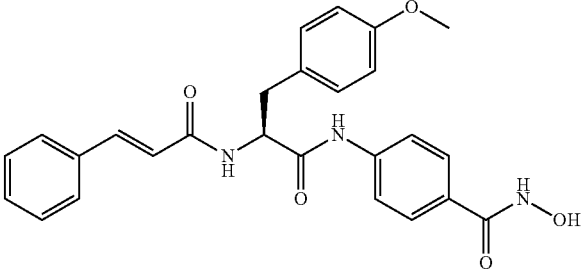
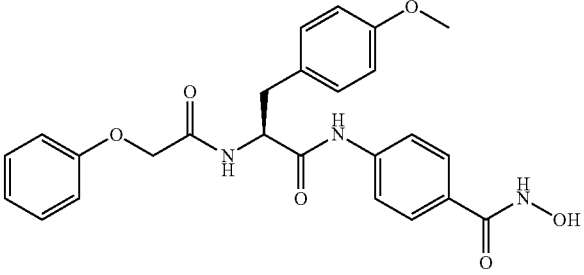
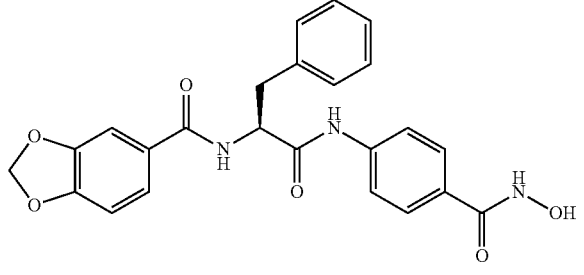
Comparison results on colon cancer cell lines			
COMPOUND	HCT116 (nM)	CSC1 (nM)	CyTox697 (nM)
 Compound 2C	431	136	53
 Compound 2D	13	40	22
 Compound 3E	194	na	44
 Compound 4A	79	na	18



TABLE 1-continued

Comparison results on colon cancer cell lines			
COMPOUND	HCT116 (nM)	CSC1 (nM)	CyTox697 (nM)
 Compound 4B	1072	208	127
 Compound 4C	900	336	203
 Compound 4D	11	37	85
 Compound 5A	184	96	105

TABLE 1-continued

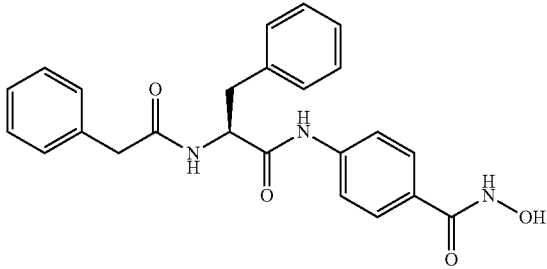
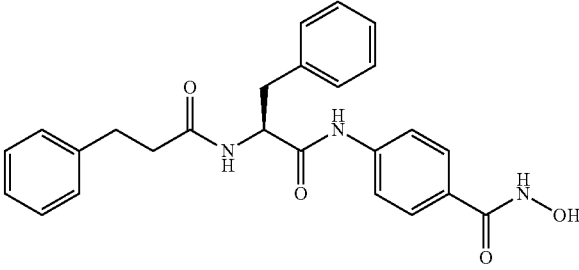
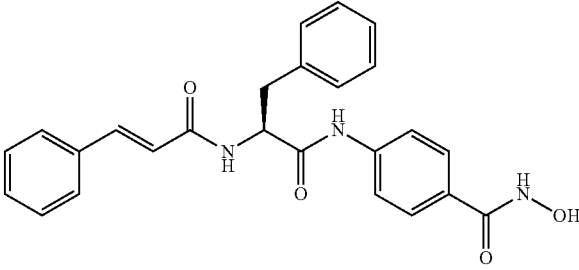
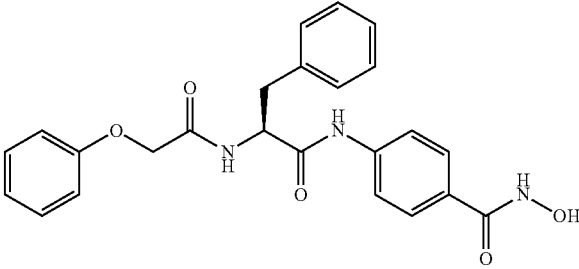
Comparison results on colon cancer cell lines			
COMPOUND	HCT116 (nM)	CSC1 (nM)	CyTox697 (nM)
 Compound 5B	237	192	90
 Compound 5C	806	332	770
 Compound 5D	10	73	45
 Compound 6E	466	424	59

TABLE 2

Cytotoxic activity of compounds on colon cancer cell lines			
Compound	HCT-116 IC 50 (nM)	HT29 IC 50 (nM)	COLO205 IC 50 (nM)
5D	14	197	221
4D	19	215	201
1D	18	157	146
2D	14	61	73

[0223] na=not available

[0224] The activity of compounds at any dose is calculated as percentage of inhibition versus vehicle-treated control (=0). The IC50s are extrapolated from the inhibition dose/response curve using GraphPad Prism program.

TABLE 3

Cytotoxic activity of compounds on colon cancer stem cell			
Compound	CSC1 IC 50 (nM)	CSC2 IC 50 (nM)	CSC3 IC 50 (nM)
5D	26	102	230
4D	13	102	91
1D	19	114	85
2D	50	100	70

TABLE 4

Cytotoxic activity of compounds on primary renal cells and PBMC				
Compound	PBMC 1 IC 50 (nM)	PBMC 2 IC 50 (nM)	Renal.ep1 IC 50 (nM)	Renal.ep2 IC 50 (nM)
5D	147	595	1061	511
4D	359	601	778	na
1D	80	152	462	321
2D	89	42	na	na

[0225] Antitumor Activity In Vivo

[0226] The compounds of this invention also showed activity in vivo in a xenograft model of colon cancer where the human HTC116 colorectal carcinoma cell line was injected subcutaneously (sc) in CD1 nude female mice (see table 5).

[0227] Female CD-1 nude mice, 5 weeks of age and 20 to 22 g of weight, were housed in the animal house of the Italfarmaco Research Centre. Mice were maintained in micro isolator cages and supplied with sterile food and water under standard conditions.

[0228] Xenografts were generated by sc injection of  $7 \times 10^6$  HCT116 cells in the right flank of the animals.

[0229] Tumor sizes were determined by caliper measurements and tumor volumes were calculated according to the following formula:

$$\text{Tumor volume (mm}^3\text{)} = (w \times l^2) / 2$$

where "w" is the width and "l" is the length of the carcinoma in mm.

[0230] Tumor growth was followed by volume measurement three times a week.

[0231] Tumor mass reached a measurable size three weeks after transplantation, at this time, treatments began.

[0232] Two reference compounds were also used in the experiment. The cinnamic hydroxamic acid panobinostat and 5-FU. The compounds were administered at the MTD according to previous experiments or as described in the literature. As shown in table 5, the compounds of this invention were able to reduce tumor size and volume, their activity being comparable to that of the two reference compounds.

[0233] Of note, the treatment with the reference compound 5-FU lead to a remarkable leukopenia (70.4%) at the end of the treatment while compound 4D showed a comparable effectiveness (54% reduction of tumor compared to 61% obtained with 5-FU) but a much less pronounced leukopenia (23.7%).

[0234] Furthermore, no thrombocytopenia and no weight loss were observed at the end of the treatment indicating that at the effective doses, the compounds object of this invention exhibited a favourable therapeutic window in this animal model.

[0235] The compounds of the present invention show good in vitro metabolic stability, both when incubated with human S9-fraction and in human plasma. They also show a good pharmacokinetic profile in preliminary studies in pre-clinical species.

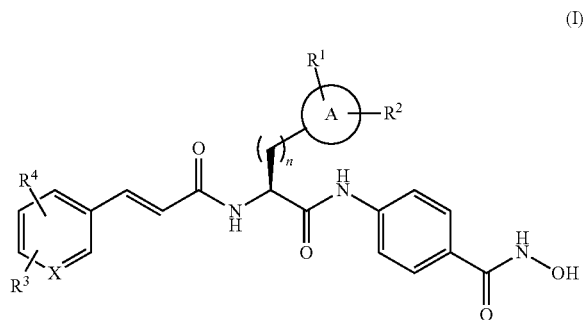
TABLE 5

Summary of the anti-tumor in vivo activity					
Compound	Dose, route of administration	% inhib tumor vs CTRL after 44 days of treatment	% inhib WBC vs CTRL T <sub>0</sub> after 44 days of treatment (vs predose)	% inhib PLT vs CTRL T <sub>0</sub> after 44 days of treatment (vs predose)	% of Body Weight variation intragroup After 65 days of treatment
Panobinostat	1 mg/kg, ip	34	36.8 (-7.2)	-4.2 (-20.3)	-1.08
5D	5 mg/kg, ip	46	31.8 (-15.7)	-6.4; (-22.9)	1.73
4D	5 mg/kg, ip	54	23.7 (-29.4)	-10.3; (-27.3)	-0.97
4D	10 mg/kg, ip	39	25.2 (-26.9)	-6.3, (-22.7)	1.24
1D	0.5 mg/kg, ip	23	-11.7 (-89.4)	-14.3; (-31.9)	-0.41

TABLE 5-continued

Summary of the anti-tumor in vivo activity					
Compound	Dose, route of administration	% inhib tumor vs CTRL after 44 days of treatment	% inhib WBC vs CTRL T <sub>0</sub> after 44 days of treatment (vs predose)	% inhib PLT vs CTRL T <sub>0</sub> after 44 days of treatment (vs predose)	% of Body Weight variation intragroup After 65 days of treatment
1D	1 mg/kg, ip	22	16.2; (-42.1)	-8.3; (-25)	1.42
2D	1 mg/kg, ip	33	1.6; (-67)	2.8; (-12.2)	-1.84
5-FU	10 mg/kg, ip	36	26; (-25.5)	1.9; (-13.2)	-3.22
5-FU	70 mg/kg, ip, once a week	61	70.4; (49.7)	-12.4; (-29.8)	1.57
CTRL	Vehicle, 200 $\mu$ L/mice	na	(69.6)	(-15.4)	6.7

1. A compound of the formula (I)



and pharmaceutically acceptable salts, isomers and prodrugs thereof,

wherein:

n is 0, 1 or 2;

A is absent or is a mono or di-carbocyclic residue, optionally partially or totally unsaturated, comprising carbon atoms and optionally one or more heteroatoms selected from N, S or O;

R<sup>1</sup> and R<sup>2</sup> are independently selected from the group comprising —H, —OH, —OMe, —CN, —NH<sub>2</sub>, —NO<sub>2</sub>, —Cl, —COOH, -halogen, —CF<sub>3</sub>, —N(Ra)<sub>2</sub>, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, aryl, arylalkyl, arylcarbonyl, alkoxy, aryloxy residue, sulfonylamino and —CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>;

Ra is a linear or branched C<sub>1</sub>-C<sub>3</sub> alkyl residue;

X can be C or N;

R<sup>3</sup> and R<sup>4</sup> are independently selected from the group comprising —H, —OMe, —OPh, —NO<sub>2</sub>, —NMe<sub>2</sub>, —NH<sub>2</sub>, -halogen, —CF<sub>3</sub>, —N(Ra)<sub>2</sub>, linear or branched C<sub>1</sub>-C<sub>4</sub> alkyl, aryl, arylalkyl, arylcarbonyl, alkoxy, aryloxy residue and sulfonylamino, or R<sup>3</sup> and R<sup>4</sup> together can form a heteropentacyclic moiety (—OCH<sub>2</sub>O—).

2. A compound according to claim 1, in which: n is 0, 1 or 2;

A is absent or is a mono or di-carbocyclic residue, optionally partially or totally unsaturated, comprising carbon atoms and optionally one or more heteroatoms selected from N, S or O;

R<sup>1</sup> and R<sup>2</sup> are independently selected from the group comprising —H, —OH, —OMe, —CN, —NH<sub>2</sub>, —NO<sub>2</sub>, —Cl, —COOH and —CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>;

Ra is a linear or branched C<sub>1</sub>-C<sub>3</sub> alkyl residue;

X can be C or N;

R<sup>3</sup> and R<sup>4</sup> are independently selected from the group comprising —H, —OMe, —OPh, —NO<sub>2</sub>, —NMe<sub>2</sub>, and —NH<sub>2</sub>, or R<sup>3</sup> and R<sup>4</sup> together can form a heteropentacyclic moiety (—OCH<sub>2</sub>O—).

3. A compound according to claim 1, in which n is 1, X is C;

R<sup>1</sup> and R<sup>2</sup> are independently —H, —Cl or —OMe;

R<sup>3</sup> and R<sup>4</sup> are independently —H, —NMe<sub>2</sub>, or R<sup>3</sup> and R<sup>4</sup> together can form a heteropentacyclic moiety (—OCH<sub>2</sub>O—).

4. A compound selected from the group consisting of:

(2S)-2-[[[(E)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbonyl)phenyl]-3-(4-methoxyphenyl)propanamide (1D);

(2S)—N-[4-(hydroxycarbonyl)phenyl]-3-(4-methoxyphenyl)-2-[[[(E)-3-phenylprop-2-enoyl]amino]propanamide (2D);

(2S)-2-[[[(E)-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbonyl)phenyl]-3-phenylpropanamide (4D);

(2S)—N-[4-(hydroxycarbonyl)phenyl]-3-phenyl-2-[[[(E)-3-phenylprop-2-enoyl]amino]propanamide (5D);

(2S)-2-[[[(E)-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbonyl)phenyl]-3-(4-hydroxyphenyl)propanamide (7D);

(E)-3-(2,5-dimethoxyphenyl)-N-[(1R)-2-[4-(hydroxycarbonyl)anilino]-1-indan-2-yl-2-oxo-ethyl]prop-2-enamide (8D);

(2S)-2-[[[(E)-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbonyl)phenyl]-4-phenylbutanamide (9D);

- (2S)-2-[[*(E)*-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-phenylpropanamide (10D);
- (2S)-2-[[*(E)*-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(2-naphthyl)propanamide (11D);
- (*E*)-3-(2,5-dimethoxyphenyl)-N-[2-[4-(hydroxycarbamoyl)anilino]-2-oxo-ethyl]prop-2-enamide (12D);
- (2S)-2-[[*(E)*-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]propanamide (13D);
- (2S)-2-[[*(E)*-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(3-quinolyl)propanamide (14D);
- (2S)-2-[[*(E)*-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(3-pyridyl)propanamide (15D);
- (2S)-2-[[*(E)*-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(4-nitrophenyl)propanamide (16D);
- (2S)-2-[[*(E)*-3-(4-aminophenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-phenylpropanamide (17D);
- (2S)-3-(4-aminophenyl)-2-[[*(E)*-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]propanamide (18D);
- (2S)-3-(4-cyanophenyl)-2-[[*(E)*-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]propanamide (19D);
- (2S)—N-[4-(hydroxycarbamoyl)phenyl]-2-[[*(E)*-3-(4-nitrophenyl)prop-2-enoyl]amino]-3-phenylpropanamide (20D);
- (2S)-2-[[*(E)*-3-(2,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(1H-imidazol-5-yl)propanamide (21D);
- (2S)-2-[[*(E)*-3-(3,4-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(3-pyridyl)propanamide (22D);
- (2S)-2-[[*(E)*-3-(3,5-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(3-pyridyl)propanamide (23D);
- (2S)-2-[[*(E)*-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(3-pyridyl)propanamide (24D);
- (2S)-2-[[*(E)*-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-3-(benzothiophen-3-yl)-N-[4-(hydroxycarbamoyl)phenyl]propanamide (25D);
- (2S)-2-[[*(E)*-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-thiazol-4-ylpropanamide (26D);
- (2S)-2-[[*(E)*-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-4-phenylbutanamide (27D);
- (2S)-2-[[*(E)*-3-(3,4-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-phenylpropanamide (28D);
- (2S)-2-[[*(E)*-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-3-(4-cyanophenyl)-N-[4-(hydroxycarbamoyl)phenyl]propanamide (29D);
- (2S)-2-[[*(E)*-3-(3,4-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(1H-indol-3-yl)propanamide (30D);
- (2S)-2-[[*(E)*-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(1H-indol-3-yl)propanamide (31D);
- (2S)-2-[[*(E)*-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(4-nitrophenyl)propanamide (32D);
- (2S)-2-[[*(E)*-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-3-(4-chlorophenyl)-N-[4-(hydroxycarbamoyl)phenyl]propanamide (33D);
- (2S)-3-(4-aminophenyl)-2-[[*(E)*-3-(3,4-dimethoxyphenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]propanamide (34D);
- (2S)-3-(4-aminophenyl)-2-[[*(E)*-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]propanamide (35D);
- 4-[(2S)-2-[[*(E)*-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-3-[4-(hydroxycarbamoyl)anilino]-3-oxo-propyl]benzoic acid (36D);
- (2S)-2-[[*(E)*-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-3-(3,4-dichlorophenyl)-N-[4-(hydroxycarbamoyl)phenyl]propanamide (37D);
- (2S)—N-[4-(hydroxycarbamoyl)phenyl]-3-(4-methoxyphenyl)-2-[[*(E)*-3-phenylprop-2-enoyl]amino]propanamide (38D);
- (2S)-2-[[*(E)*-3-(4-dimethylaminophenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-phenylpropanamide (39D);
- (2S)-2-[[*(E)*-3-(4-dimethylaminophenyl)prop-2-enoyl]amino]-N-[4-(hydroxycarbamoyl)phenyl]-3-(4-methoxyphenyl)propanamide; 2,2,2-trifluoroacetic acid (40D);
- (*E*)-N-[2-[[4-(hydroxycarbamoyl)phenyl]methylamino]-2-oxo-ethyl]-3-phenylprop-2-enamide (41D);
- (*E*)-3-(1,3-benzodioxol-5-yl)-N-[2-[[4-(hydroxycarbamoyl)phenyl]methylamino]-2-oxo-ethyl]prop-2-enamide (43D);
- (2S)-3-[4-(diethylaminomethyl)phenyl]-N-[4-(hydroxycarbamoyl)phenyl]-2-[[*(E)*-3-phenylprop-2-enoyl]amino]propanamide; 2,2,2-trifluoroacetic acid (45D);
- (2S)-2-[[*(E)*-3-(1,3-benzodioxol-5-yl)prop-2-enoyl]amino]-3-[4-(diethylaminomethyl)phenyl]-N-[4-(hydroxycarbamoyl)phenyl]propanamide; 2,2,2-trifluoroacetic acid (46D);
- (2S)—N-[4-(hydroxycarbamoyl)phenyl]-3-(2-naphthyl)-2-[[*(E)*-3-(6-phenoxy-3-pyridyl)prop-2-enoyl]amino]propanamide (47D).
5. A compound according to claim 1, in which the isomeric form is the trans-form.
  6. A compound according to claim 1, for use as a medicament.
  7. A compound for use according to claim 6, in the prevention and/or treatment of cancer.
  8. A compound for use according to claim 7, in the prevention and/or treatment of colorectal cancer, lung, brain, prostate or gynecological cancers or hematologic malignancies.
  9. A compound for use according to claim 6, in the prevention and/or treatment of metastatic, recurrent and drug-resistant diseases.
  10. A pharmaceutical composition comprising a therapeutically effective quantity of at least one of the compounds of the formula (I) or pharmaceutically acceptable salts, isomers and prodrugs thereof according to claim 1 together with at least one pharmaceutically acceptable excipient.

**11.** A pharmaceutical composition according to claim **10**, suitable to be administered by enteral route, parenteral route, oral route, topical route, or inhalatory route.

**12.** A pharmaceutical composition according to claim **10**, in the form of a liquid or a solid, preferably in the form of capsules, tablets, coated tablets, powders, granules, creams or ointments.

\* \* \* \* \*