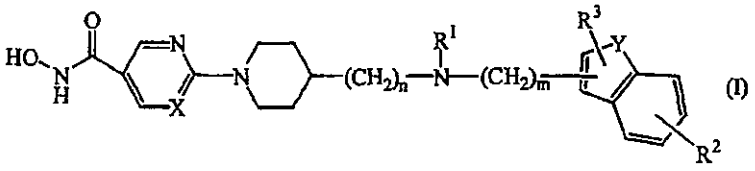
Claims

1. A compound of formula (I),



(I)

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

each n is an integer with value 0, 1 or 2 and when n is 0 then a direct bond is intended;

each m is an integer with value 1 or 2;

each X is independently N or CH;

each Y is independently O, S, or NR^4; wherein

each R^4 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylmethyl, phenylC_{1-6}alkyl, -C(=O)-CHR^5R^6 or -$S(=O)_2$-$N(CH_3)_2$; wherein

each R^5 and R^6 is independently hydrogen, amino, C_{1-6}alkyl or aminoC_{1-6}alkyl; and

when Y is NR^4 and R^2 is on the 7-position of the indolyl then R^2 and R^4 together can form the bivalent radical

$-(CH_2)_2-$ (a-1), or

$-(CH_2)_3-$ (a-2);

R^1 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylcarbonyl or mono- or di(C_{1-6}alkyl)aminosulfonyl;

R^2 is hydrogen, hydroxy, amino, halo, C_{1-6}alkyl, cyano, C_{2-6}alkenyl, polyhaloC_{1-6}alkyl, nitro, phenyl, C_{1-6}alkylcarbonyl, hydroxycarbonyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyloxy, or mono- or di(C_{1-6}alkyl)amino;

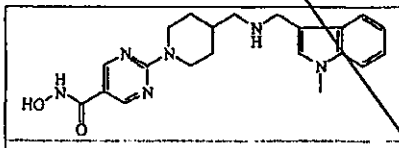
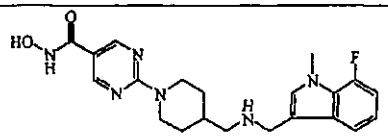
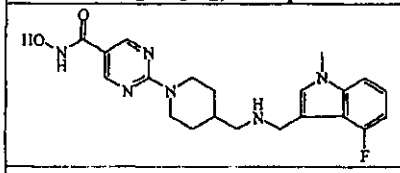
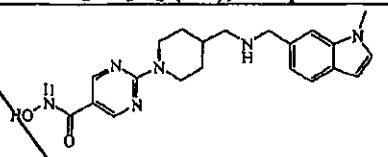
R^3 is hydrogen, C_{1-6}alkyl, or C_{1-6}alkyloxy; and

when R^2 and R^3 are on adjacent carbon atoms, they can form the bivalent radical –O-CH_2-O-.

2. A compound according to claim 1 wherein
each n is an integer with value 0 or 1; each R^4 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{3-6}cycloalkyl or phenylC_{1-6}alkyl; R^1 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl or C_{1-6}alkylsulfonyl; and R^2 is hydrogen, halo, C_{1-6}alkyl, cyano, nitro, poly haloC_{1-6}alkyl or C_{1-6}alkyloxy.

3. A compound according to claim 1 and 2 wherein
wherein each n is an integer with value 1; each m is an integer with value 1; each X is independently N; each Y is independently NR^4; each R^4 is C_{1-6}alkyl; R^1 is hydrogen; R^2 is hydrogen or halo; and R^3 is hydrogen.

4. A compound as claimed in claim 1, 2 and 3 wherein said compound is compound No.1a, compound No.30, compound No.39 and compound No.50.

	
$C_2HF_3O_2$; Compound 1a	$C_2HF_3O_2$ (1:1); compound 30
	
$C_2HF_3O_2$ (1:1); compound 39	compound 50

5. A pharmaceutical composition comprising pharmaceutically acceptable carriers and as an active ingredient a therapeutically effective amount of a compound as claimed in claim 1 to 4.

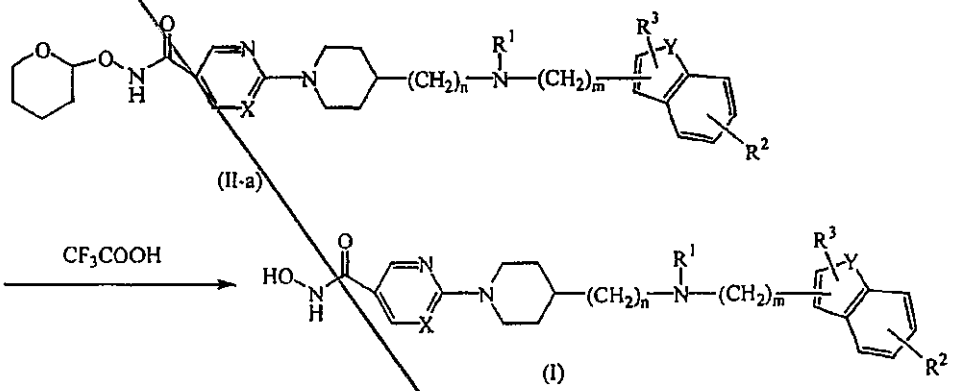
6. A compound as claimed in any of claims 1 to 4 for use as a medicine.

7. Use of a compound as claimed in any of claims 1 to 4 for the manufacture of a medicament for the treatment of proliferative diseases.

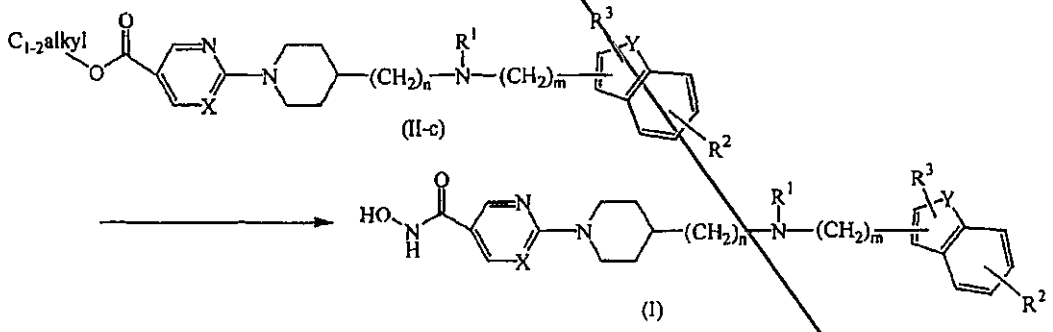
8. A combination of an anti-cancer agent and a HDAC inhibitor as claimed in any of claims 1 to 4.

9. A process for preparing a compound as claimed in claim 1, characterized by

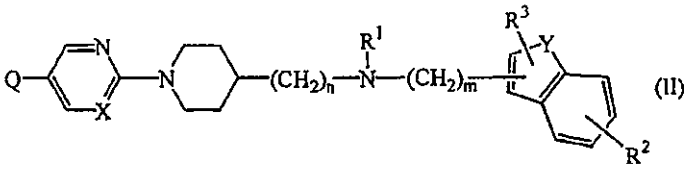
a) reacting an intermediate of formula (II), wherein Q is tetrahydropyranyloxyaminocarbonyl, herein referred to as an intermediate of formula (II-a), with an appropriate acid, such as for example, trifluoro acetic acid, yielding a hydroxamic acid of formula (I).



b) reacting an intermediate of formula (II), wherein Q is C_{1-2}alkyloxycarbonyl, herein referred to as intermediates of formula (II-c), with hydroxylamine, in the presence of a base and in an appropriate solvent with the production of a hydroxamic acid of formula (I)



10. A compound of formula (II),



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

each n is an integer with value 0, 1 or 2 and when n is 0 then a direct bond is intended;

each m is an integer with value 1 or 2;

each X is independently N or CH;

each Y is independently O, S, or NR^4; wherein
each R^4 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylmethyl, phenylC_{1-6}alkyl, $-C(=O)-CHR^5R^6$ or $-S(=O)_2-N(CH_3)_2$; wherein
each R^5 and R^6 is independently hydrogen, amino, C_{1-6}alkyl or aminoC_{1-6}alkyl; and

when Y is NR^4 and R^2 is on the 7-position of the indolyl then R^2 and R^4 together can form the bivalent radical

$-(CH_2)_2-$ (a-1), or
$-(CH_2)_3-$ (a-2);

R^1 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylcarbonyl or mono- or di(C_{1-6}alkyl)aminosulfonyl;

R^2 is hydrogen, hydroxy, amino, halo, C_{1-6}alkyl, cyano, C_{2-6}alkenyl, polyhaloC_{1-6}alkyl, nitro, phenyl, C_{1-6}alkylcarbonyl, hydroxycarbonyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyloxy, or mono- or di(C_{1-6}alkyl)amino;

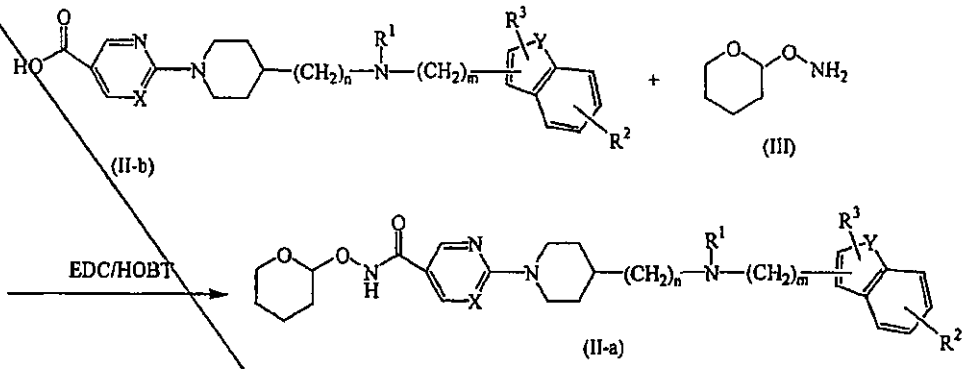
R^3 is hydrogen, C_{1-6}alkyl, or C_{1-6}alkyloxy;

when R^2 and R^3 are on adjacent carbon atoms, they can form the bivalent radical $-O-CH_2-O-$; and

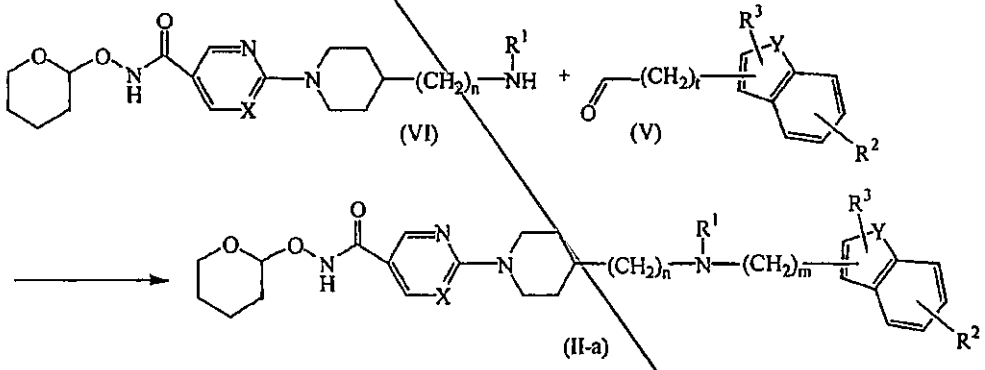
Q is C_{1-2}alkyloxycarbonyl, hydroxycarbonyl or tetrahydropyranyloxyaminocarbonyl.

11. A process for preparing a compound as claimed in claim 10, characterized by
a) reacting a compound of formula (II), wherein Q is hydroxycarbonyl, herein referred to as compounds of formula (II-b), with an intermediate of formula (III) in the

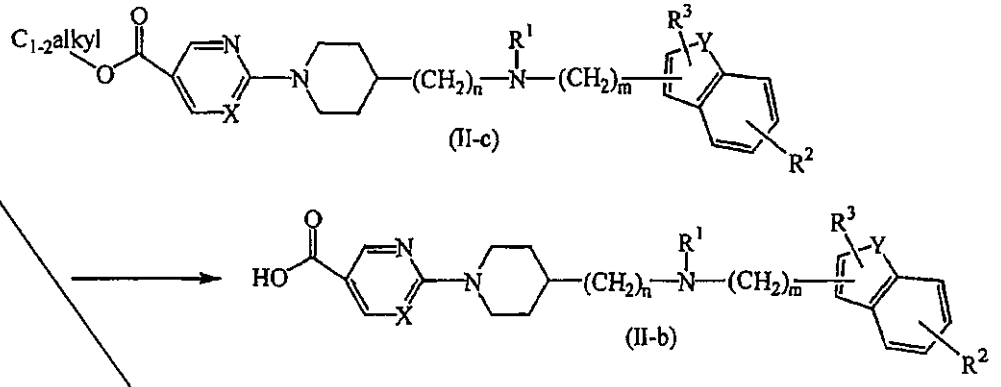
presence of appropriate reagents such as *N'*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine, monohydrochloride (EDC) and 1-hydroxy-1*H*-benzotriazole (HOBT) with the formation of a compound of formula (II-a),



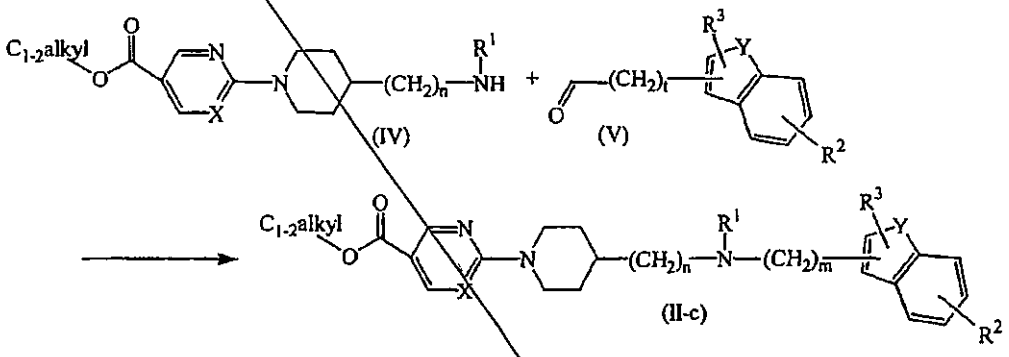
b) reacting an intermediate of formula (VI) with the appropriate carboxaldehyde of formula (V), wherein t is an integer with value 0 or 1, and when t is 0 then a direct bond is intended, in the presence of an appropriate reagent, with the formation of a compound of formula (II-a),



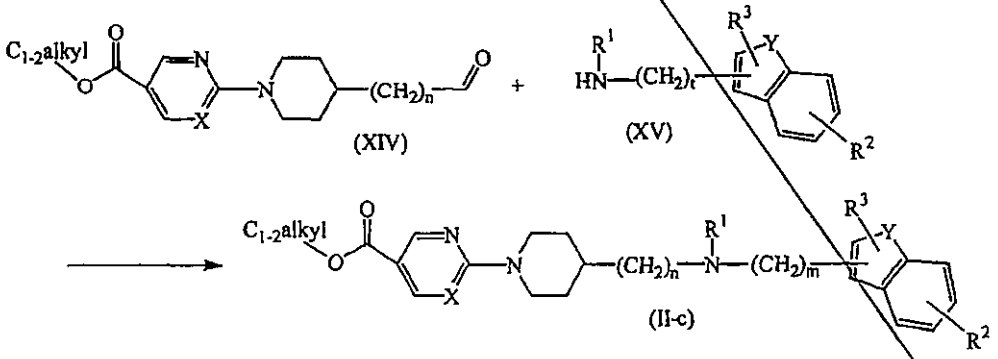
c) reacting a compound of formula (II), wherein Q is methyl- or ethyloxycarbonyl (C_{1-2}alkyl), herein referred to as compounds of formula (II-c), with an appropriate acidic solution or basic solution, with the formation of a compound of formula (II-b),



d) reacting the carboxylic acid ethyl ester of formula (IV) with the appropriate carboxaldehyde of formula (V), in the presence of an appropriate reagent, with the formation of a compound of formula (II-c),

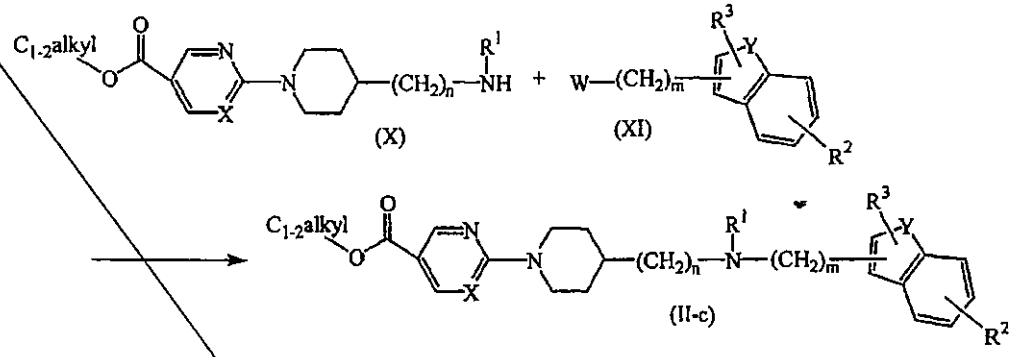


e) reacting an intermediate od formula (XIV) with the appropriate intermediate of formula (XV), in the presence of an appropriate reagent, in a suitable solvent, with the formation of a compound of formula (II-c),

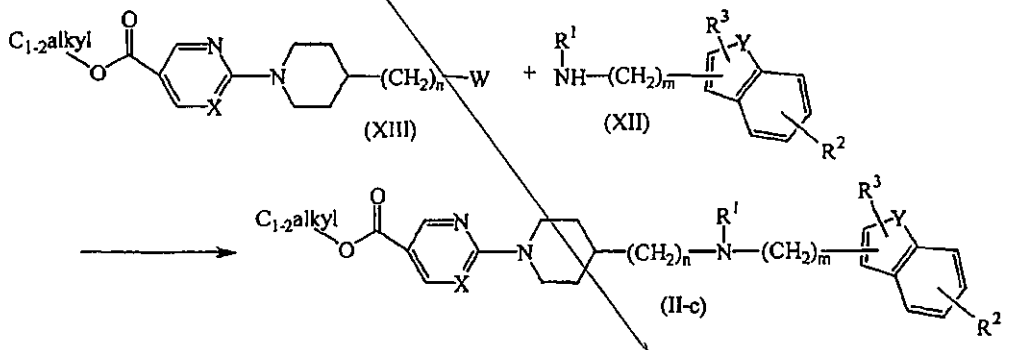


f) reacting an intermediate of formula (X) with an intermediate of formula (XI) wherein W is an appropriate leaving group such as, for example, halo, e.g. fluoro, chloro,

bromo or iodo, or a sulfonyloxy radical such as methylsulfonyloxy, with the formation of a compound of formula (II-c), or

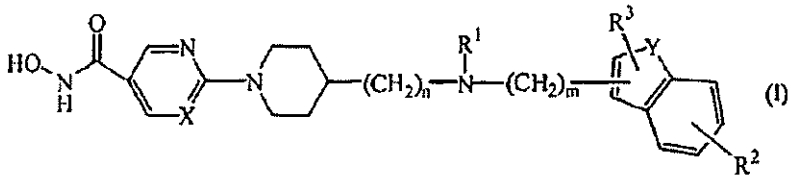


g) reacting an intermediate of formula (XII) with an intermediate of formula (XIII), wherein W is an appropriate leaving group as described above, with the formation of a compound of formula (II-c).



Claims:

1. A compound of formula (I),



(I)

the N-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein
each n is an integer with value 0, 1 or 2 and when n is 0 then a direct bond is intended; each m is an integer with value 1 or 2;
each X is independently N or CH;
each Y is independently O, S, or NR^4; wherein
each R^4 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylmethyl, phenylC_{1-6}alkyl, -C(=O)-CHR^5R^6 or -$S(=O)_2$-$N(CH_3)_2$; wherein
each R^5 and R^6 is independently hydrogen, amino, C_{1-6}alkyl or aminoC_{1-6}alkyl; and
when Y is NR^4 and R^2 is on the 7-position of the indolyl then R^2 and R^4 together can form the bivalent radical

$-(CH_2)_2-$ (a-1),

or

$-(CH_2)_3-$ (a-2);

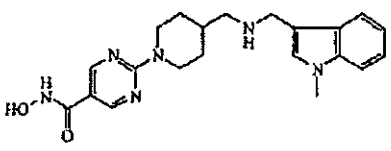
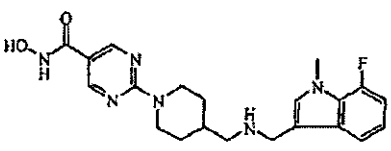
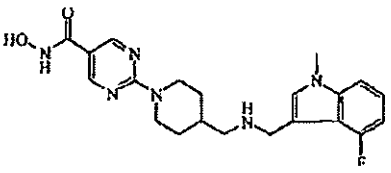
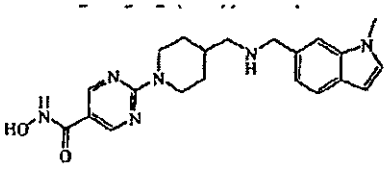
R^1 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylcarbonyl or mono- or di(C_{1-6}alkyl)aminosulfonyl;
R^2 is hydrogen, hydroxy, amino, halo, C_{1-6}alkyl, cyano, C_{2-6}alkenyl, polyhaloC_{1-6}alkyl, nitro, phenyl, C_{1-6}alkylcarbonyl, hydroxycarbonyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyloxy, or mono- or di(C_{1-6}alkyl)amino;
R^3 is hydrogen, C_{1-6}alkyl, or C_{1-6}alkyloxy; and
when R^2 and R^3 are on adjacent carbon atoms, they can form the bivalent radical -O-CH_2-O-.

2. A compound according to claim 1 wherein
each n is an integer with value 0 or 1; each R^4 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{3-6}cycloalkyl or phenylC_{1-6}alkyl; R^1 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl or C_{1-6}alkylsulfonyl; and R^2 is hydrogen, halo, C_{1-6}alkyl, cyano, nitro, polyhaloC_{1-6}alkyl or C_{1-6}alkyloxy.

3. A compound according to claim 1 and 2 wherein
wherein each n is an integer with value 1; each m is an integer with value 1; each X is independently N; each Y is independently NR^4; each R^4 is C_{1-6}alkyl; R^1 is hydrogen; R^2 is hydrogen or halo; and R^3 is hydrogen.

4. A compound as claimed in claim 1, 2 and 3 wherein said compound is compound No. 1a, compound No. 30, compound

No.39 and compound No.50.

	
$C_2HF_3O_2$; Compound 1a	$C_2HF_3O_2$ (1:1); compound 30
	
$C_2HF_3O_2$ (1:1); compound 39	compound 50

5. A pharmaceutical composition comprising pharmaceutically acceptable carriers and as an active ingredient a therapeutically effective amount of a compound as claimed in claim 1 to 4.

6. A process of preparing a pharmaceutical composition as claimed in claim 5 wherein the pharmaceutically acceptable carriers and a compound as claimed in claim 1 to 4 are intimately mixed.

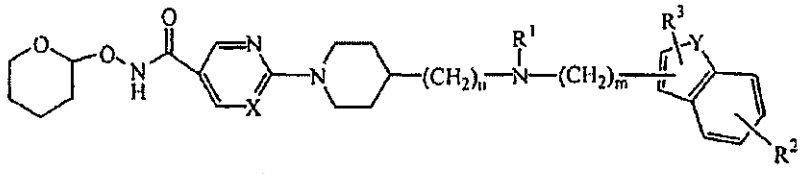
7. A compound as claimed in any of claims 1 to 4 for use as a medicine.

8. Use of a compound as claimed in any of claims 1 to 4 for the manufacture of a medicament for the treatment of proliferative diseases.

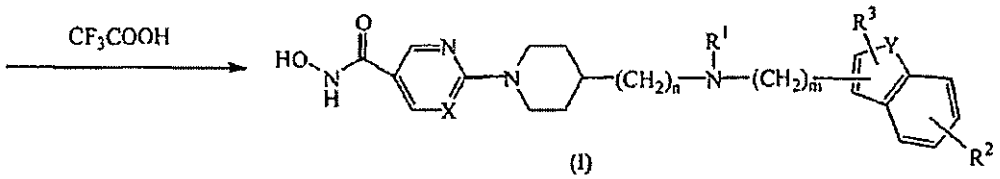
9. A combination of an anti-cancer agent and a HDAC inhibitor as claimed in any of claims 1 to 4.

10. A process for preparing a compound as claimed in claim 1, **characterized by**

a) reacting an intermediate of formula (II), wherein Q is tetrahydropyranyloxyaminocarbonyl, herein referred to as an intermediate of formula (II-a), with an appropriate acid, such as for example, trifluoro acetic acid, yielding a hydroxamic acid of formula (I).

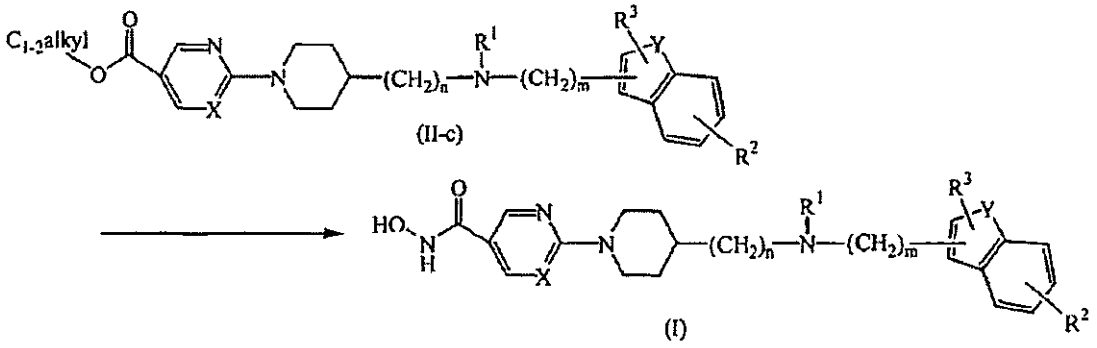


(II-a)



(I)

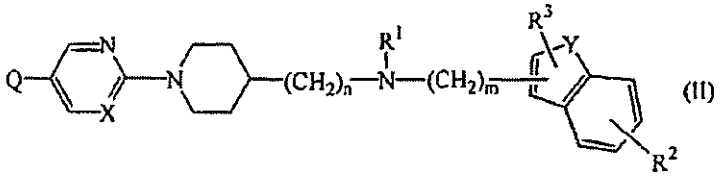
b) reacting an intermediate of formula (II), wherein Q is C_{1-2}alkyloxycarbonyl, herein referred to as intermediates of formula (II-c), with hydroxylamine, in the presence of a base and in an appropriate solvent with the production of a hydroxamic acid of formula (I)



(II-c)

(I)

11. A compound of formula (II),



(II)

the N-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein
each n is an integer with value 0, 1 or 2 and when n is 0 then a direct bond is intended; each m is an integer with value 1 or 2;
each X is independently N or CH;
each Y is independently O, S, or NR^4; wherein
each R^4 is hydrogen, C_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylmethyl, phenylC_{1-6}alkyl, -C(=O)-CHR^5R^6 or -S(=O)$_2$-$N(CH_3)_2$; wherein
each R^5 and R^6 is independently hydrogen, amino, C_{1-6}alkyl or aminoC_{1-6}alkyl; and
when Y is NR^4 and R^2 is on the 7-position of the indolyl then R^2 and R^4 together can form the bivalent radical

$-(CH_2)_2-$ (a-1),

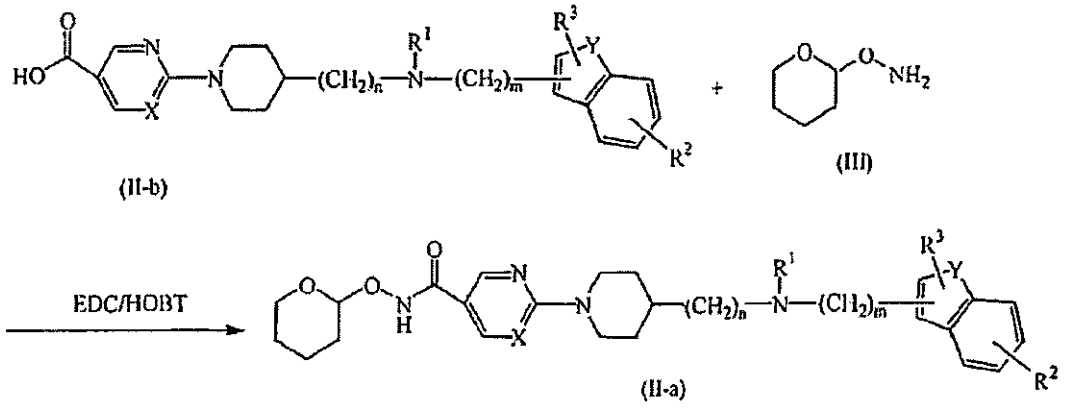
or

$-(CH_2)_3-$ (a-2);

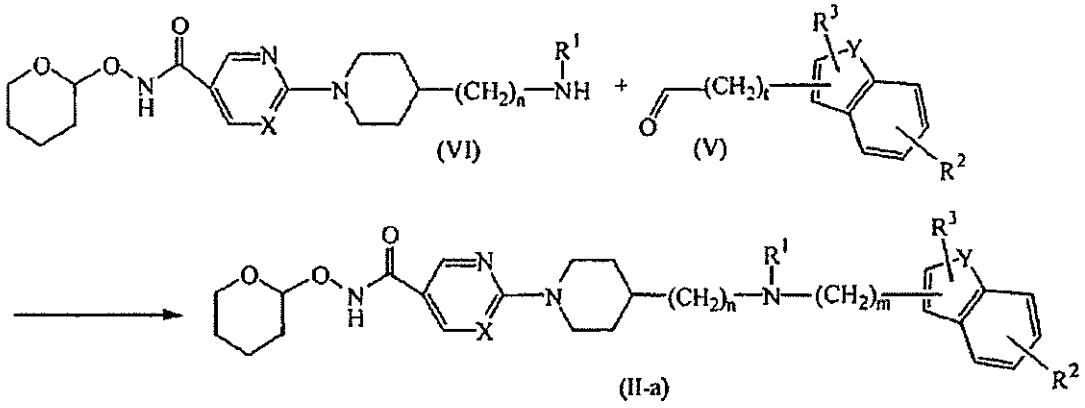
R^1 is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylsulfonyl, C_{1-6}alkylcarbonyl or mono- or di(C_{1-6}alkyl)aminosulfonyl;
R^2 is hydrogen, hydroxy, amino, halo, C_{1-6}alkyl, cyano, C_{2-6}alkenyl, polyhaloC_{1-6}alkyl, nitro, phenyl, C_{1-6}alkylcarbonyl, hydroxycarbonyl, C_{1-6}alkylcarbonylamino, C_{1-6}alkyloxy, or mono- or di(C_{1-6}alkyl)amino;
R^3 is hydrogen, C_{1-6}alkyl, or C_{1-6}alkyloxy;
when R^2 and R^3 are on adjacent carbon atoms, they can form the bivalent radical -O-CH_2-O-; and
Q is C_{1-2}alkyloxycarbonyl, hydroxycarbonyl or tetrahydropyranyloxyaminocarbonyl.

12. A process for preparing a compound as claimed in claim 11, **characterized by**

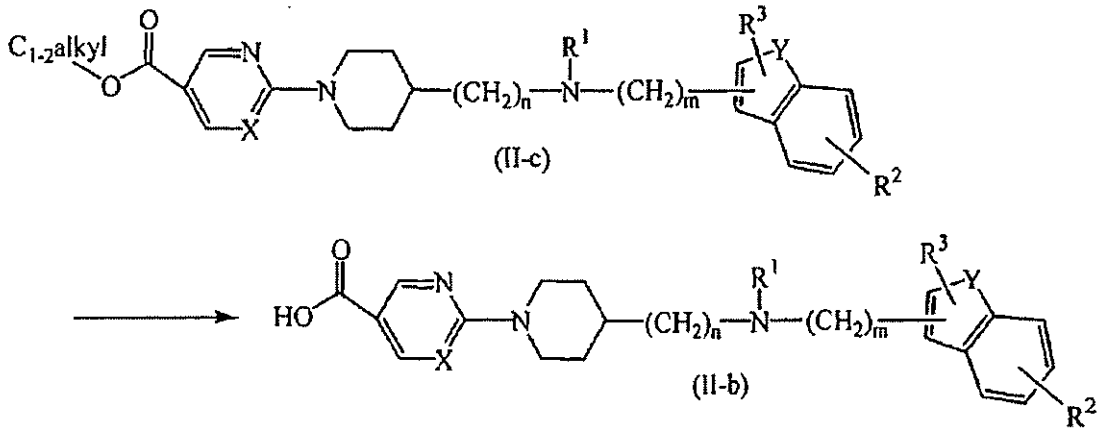
a) reacting a compound of formula (II), wherein Q is hydroxycarbonyl, herein referred to as compounds of formula (II-b), with an intermediate of formula (III) in the presence of appropriate reagents such as *N*'-(ethylcarbonimidoyl)-*N*,*N*-dimethyl-1,3-propanediamine, monohydrochloride (EDC) and 1-hydroxy-1*H*-benzotriazole (HOBT) with the formation of a compound of formula (II-a),



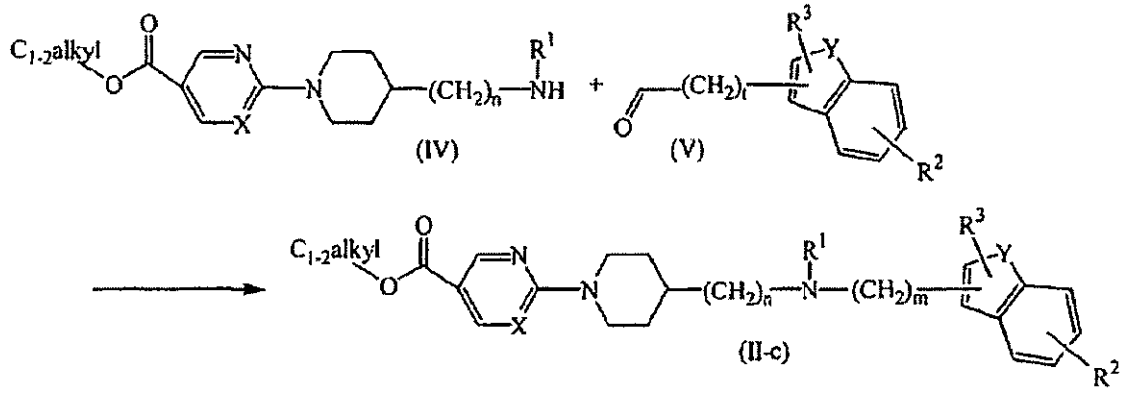
b) reacting an intermediate of formula (VI) with the appropriate carboxaldehyde of formula (V), wherein t is an integer with value 0 or 1, and when t is 0 then a direct bond is intended, in the presence of an appropriate reagent, with the formation of a compound of formula (II-a),



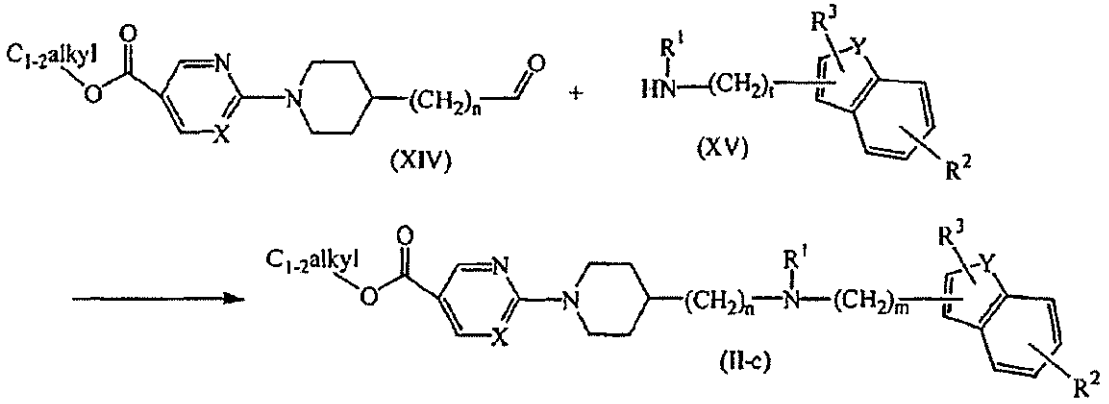
c) reacting a compound of fonnula (II), wherein Q is methyl- or ethyloxycarbonyl (C_{1-2}alkyl), herein referred to as compounds of formula (II-c), with an appropriate acidic solution or basic solution, with the formation of a compound of formula (II-b),



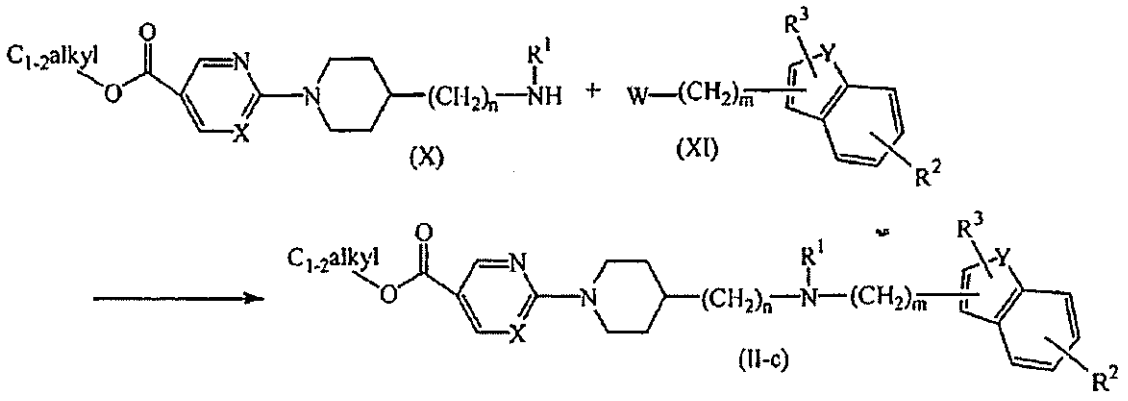
d) reacting the carboxylic acid ethyl ester of formula (IV) with the appropriate carboxaldehyde of formula (V), in the presence of an appropriate reagent, with the formation of a compound of formula (II-c),



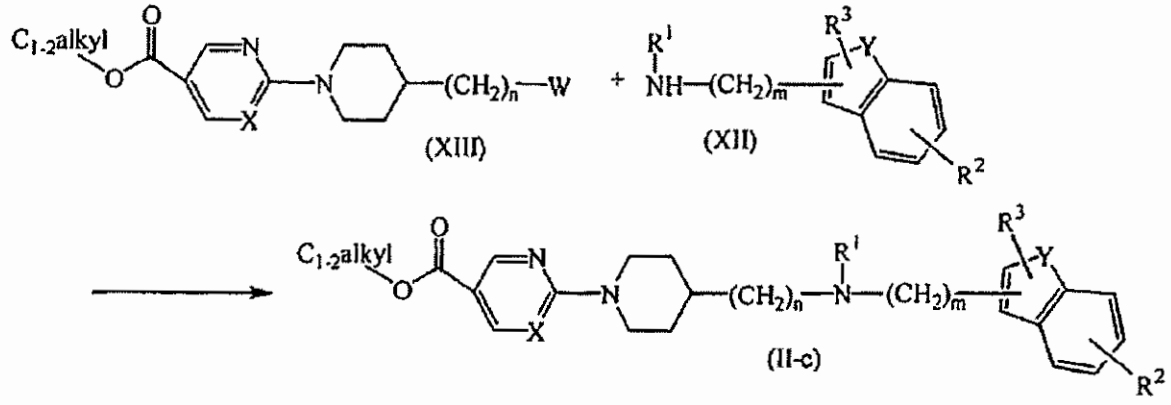
e) reacting an intermediate od formula (XIV) with the appropriate intermediate of formula (XV), in the presence of an appropriate reagent, in a suitable solvent, with the formation of a compound of formula (II-c),



f) reacting an Intermediate of formula (X) with an intermediate of formula (XI) wherein W is an appropriate leaving group such as, for example, halo, e.g. fluoro, chloro, bromo or iodo, or a sulfonyloxy radical such as methylsulfonyloxy, with the formation of a compound of formula (II-c), or



g) reacting an intermediate of formula (XII) with an intermediate of formula (XIII), wherein W is an appropriate leaving group as described above, with the formation of a compound of formula (II-c).


C1-2alkyl
O
N
X
N
(CH2)n—W
(XIII)
+
R1
NH—(CH2)m
R3
Y
R2
(XII)
C1-2alkyl
O
N
X
N
(CH2)n—N—(CH2)m
R1
R3
Y
R2
(II-c)