TITLE OF THE INVENTION

SUBSTITUTED PYRAZOLO-QUINAZOLINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE AS KINASE INHIBITORS

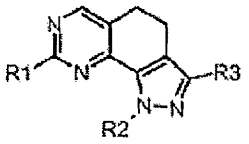
The present invention relates to certain substituted pyrazolo-quinazoline compounds, which modulate the activity of protein kinases. The compounds of this invention are therefore useful in treating diseases caused by dysregulated protein kinase activity. The present invention also provides methods for preparing these compounds, pharmaceutical compositions comprising these compounds, and methods of treating diseases utilizing pharmaceutical compositions comprising these compounds.

The use of mitotic inhibitors in cancer therapy is a widely accepted clinical strategy for the treatment of a broad range of human cancers. Taxanes (Paclitaxel and Docetaxel) and Vinca Alkaloids (Vincristine and Vinblastine) work by either stabilizing or destabilizing microtubules with catastrophic consequences in cells progressing through mitosis. They are first line therapeutics for several tumour types and second line in cisplatin-refractory ovarian, breast, lung, bladder and esophagus cancers (Taxanes). However, due to the role of microtubules in processes such as cell movement, phagocytosis and axonal transport certain toxicities such as peripheral neuropathy are frequently observed with these agents. Progression through mitosis is a requirement of all proliferating cells and hence cancer therapies that have targets in mitosis are generally applicable to a wide range of tumour types. Several protein kinases play key roles in the orchestration of the cell cycle and some of them are already subject to targeted therapies in the oncology setting including Cdk-2 and Aurora-A. The fidelity of mitosis is of paramount importance and several "checkpoints" exist in normal cells to maintain chromosome integrity during the cell cycle. These checkpoints often go away during oncogenic transformation and this permits cancer cells to tolerate anueploidy and chromosomal instability. Inhibition of mitosis in "checkpoint compromised" tumour cells should have catastrophic consequences as cancer cells try to carry forward an aberrant mitosis.

The Polo-like kinase family, comprising 4 serine / threonine kinases (Plk-1-4), are predominantly involved in the entry into, progression through and exit from mitosis. These kinases are characterized by having an n-terminal kinase domain and a unique,

CLAIMS

1. A compound of formula (I):



(I)

wherein

Rl is an ortho-substituted-arylamino;

R2 is hydrogen or an optionally substituted group selected from straight or branched Ci-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and heterocyclyl;

R3 is CO-OR' or CO-NR'R", wherein R' and R" are, each independently, hydrogen or an optionally substituted group selected from straight or branched Ci-C_6 alkyl, C_3-C_6 cycloalkyl and heterocyclyl, or R' and R" taken together with the nitrogen atom to which they are bonded, may form an optionally substituted heterocyclyl group optionally containing one additional heteroatom selected among N, O or S, provided that:

ethyl 1-methyl-8-(2-methoxy-phenylamino)-4,5-dihydro-lH-pyrazolo[4,3-h]quinazoline-3-carboxylate and 1 -methyl-8-(2-methoxyphenylamino)-4,5-dihydro-lH-pyrazolo[4,3-h]quinazoline-3-carboxamide are excluded;

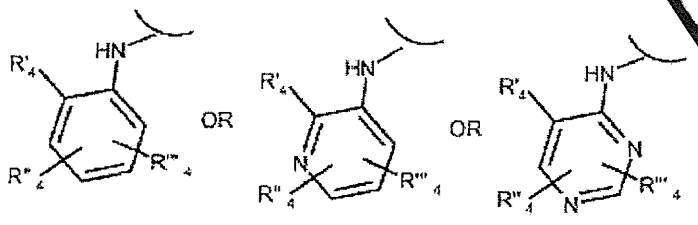
and isomers, tautomers, hydrates, solvates, complexes, metabolites, prodrugs, carriers, N-oxides and pharmaceutically acceptable salts thereof.

2. A compound of formula (I) as defined in claim 1 wherein:

R3 is CO-OH or CO-NRR", wherein R' and R" are as defined in claim 1.

3. A compound of formula (I) as defined in claims 1 or 2 wherein:

Rl is an ortho-substituted-arylamino of the formula:

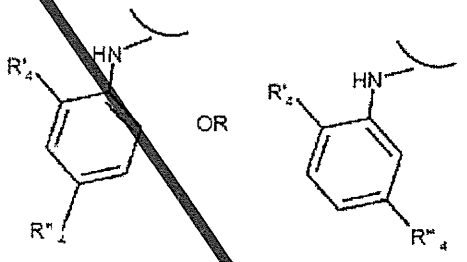


wherein R'_4, R^M_4 and R^m_4 are independently selected from a group consisting of:

halogen, nitro, cyano, Ci-C $_6$ alkyl, polyfluorinated alkyl, polyfluorinated alkoxy, alkenyl, alkynyl, hydroxyalkyl, aryl, arylalkyl, heterocyclyl , C $_3$ -C $_6$ cycloalkyl, hydroxy, alkoxy, aryloxy, heterocyclyloxy, methylenedioxy, alkylcarbonyloxy, arylcarbonyloxy, cycloalkenyloxy, heterocyclylcarbonyloxy, alkylideneaminooxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, amino, ureido, alkylamino, dialkylamino, arylamino, diarylamino, heterocyclylamino, formylamino, alkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylamino carbonyl, heterocyclylaminocarbonyl, alkoxy carbonylamino, hydroxyaminocarbonyl, alkoxyimino, alkylsulfonylamino, arylsulfonylamino, heterocyclylsulfonylamino, formyl, alkylcarbonyl, arylcarbonyl, cycloalkylcarbonyl, heterocyclylcarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, heterocyclylaminosulfonyl, arylthio, alkylthio, phosphonate and alkylphosphonate.

4. A compound of formula (I) as defined in claims 1 to 3 wherein:

Rl is an Ortho-Substituted-arylamino of the formula:



wherein R'4 and R^M4 are as defined in claim 3 and

R2 is an optionally substituted straight or branched C_1-C_6 alkyl or or C_2-C_6 alkenyl.

5. A compound of formula (I) as defined in claims 1 to 4 wherein:

R3 is CO-NR'R", wherein R' and R" are as defined in claim 1.

6. A compound or a pharmaceutically acceptable salt thereof wich is selected from the group consisting of:

l-Methyl-8-(2-methylphenylamino)-4,5-dihydro-lH-pyrazolo[4,3-h]quinazoline-3-carboxamide (A4B1C1Z);

l-Methyl-8-(2-methylamino-phenylamino)-4,5-dihydro-lH-pyrazolo[4,3-hjquinazo line-3 - carboxamide (A27B 1 C 1 Z);

8-(2-Acetyl-phenylamino)-l-(2-fluoro-ethyl)-4,5-dihydro-lH-pyrazolo[4,3-h]quinazoline-3-carboxamide (A2B2C1Z);

8-[2-Acetyl-5-(4-methyl-piperazin- 1 -yl)-phenylamino]- 1 -methyl-4,5-dihydro- IH-pyrazolo[4,3-h]quinazoline-3-carboxamide (A39B1C1Z);

8-[2-Acetyl-5-(4-methyl-piperazin- 1 -yl)-phenylamino]- 1 -(2-fluoro-ethyl)-4,5-dihydro-lH-pyrazolo[4,3-h]quinazoline-3-carboxamide (A39B2C1Z);

l-Methyl-8-(2-trifluoromethoxy-phenylamino)-4,5-dihydro-lH-pyrazolo[4,3-h]quinazoline-3-carboxamide (A45B1C1Z);

1 -Methyl-8-[5-(4-methyl-piperazin- 1 -yl)-2-trifluoromethoxy-phenylamino]-4,5-dihy dro - 1 H-pyrazo lo [4 , 3 -h] quinazo line-3 -carboxamide (A51 B 1 C 1 Z) ;

Ethyl 1 -methyl-8-[5-(4-methyl-piperazin- 1 -yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-lH-pyrazolo[4,3-h]quinazoline-3-carboxylate (A51B1C2Z);

1 -Methyl-8-[2-methoxy-5-(4-methyl-piperazin- 1 -yl)-phenylamino]- 1 -methyl-4,5-dihy dro - 1 H-pyrazo Io [4 , 3 -h] quinazo line-3 -carboxamide (A85 B 1 C 1 Z) ;

8-[5-(4-Methyl-piperazin- 1 -yl)-2-trifluoromethoxy-phenylamino]- 1 -(2-fluoro-ethyl)- 4,5-dihydro-lH-pyrazolo[4,3-h]quinazoline-3-carboxamide (A51B2C1Z);

1 -Methyl-8-[4-(4-methyl-piperazin- 1 -yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-lH-pyrazolo[4,3-h]quinazoline-3-carboxamide (A48B1C1Z);

1 -Methyl-8-(2-trifluoromethoxy-5-piperazin- 1 -yl-phenylamino]-4,5-dihydro- IH-pyrazolo[4,3-h]quinazoline-3-carboxamide (A97B1C1Z);

1 -Methyl-8-[2-methyl-5-(4-methyl-piperazin- 1 -yl)-phenylamino]-4,5-dihydro- IH-pyrazolo[4,3-h]quinazoline-3-carboxamide (A98B1C1Z);

1 -Methyl-8-[5-(4-pyrrolidin- 1 -yl-piperidin- 1 -yl)-2-trifluoromethoxy phenylamino]- 4,5-dihydro-lH-lH-pyrazolo[4,3-h]quinazoline-3-carboxamide (A99B IClZ);

1 -Methyl-8-[5-(4-methyl-piperazin- 1 -yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-lH-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide (A51B1C4Z);

1 -Methyl-8-[5-(4-methyl-piperazin- 1 -yl)-2-methoxy-phenylamino]-4,5-dihydro- IH-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide (A85B1C4Z);

1 -Methyl-8-[2-methyl-5-(4-methyl-piperazine- 1 -carbonyl)-phenylamino]-4,5-dihy dro - 1 H-pyrazo Io [4 , 3 -h] quinazo line-3 -carboxamide (A87B 1 C 1 Z) ;

1 -Methyl-8-[2-methyl-4-(4-methyl-piperazine- 1 -carbonyl)-phenylamino]-4,5-dihy dro - 1 H-pyrazo Io [4 , 3 -h] quinazo line-3 -carboxamide (A86B 1 C 1 Z) ;

l-Methyl-8-{2-trifluoromethoxy-5-[(l-methyl-piperidine-4-carbonyl)-amino]-phenyl lamino } -4 , 5 -dihy dro - 1 H-pyrazo Io [4 , 3 -h] quinazo line-3 -carboxamide

(A82B1C1Z);

Ethyl 1 -methyl- 8 -(2-trifluoromethoxy-pheny lamino)-4 , 5 -dihy dro - 1 H-pyrazo Io [4 , 3-h]quinazoline-3-carboxylate (A45B1C2Z);

Potassium 8-[5-(4-methyl-piperazin- 1 -yl)-2-trifluoromethoxy-phenylamino]- 1 -methyl-4,5-dihydro-lH-pyrazolo[4,3-h]quinazoline-3-carboxylate (A51B1C3Z);

Potassium 8-(2-trifluoromethoxy-phenylamino) -4,5-dihydro-LH-Pyrazole [4.3-h] quinazoline-3-carboxylate
(A45B5C IZ)

1-Ethyl-8-[5 - (4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino] -4,5-dihydro-LH-Pyrazole [4.3-h] quinazoline -3-carboxamide (A51B7C1Z)

1-Methyl-8-[5 - (4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino] -4,5-dihydro-LH-Pyrazole [4.3 - h] quinazoline-3-carboxylic acid (2,2,2-trifluoro-ethyl)-amide (A51BlC7Z)

1 - (2-Hydroxy-ethyl) -8 - [5 - (4-methyl-piperazin-1 1-yl)-2-trifluoromethoxy-phenylamino] - 1-vinyl-4 ,5-dihydro-LH-Pyrazole [4.3-h] quinazoline-3-carboxamide (A5 IB IZ 1 ° C), 1 - (2-Chloro -ethyl) -8 - [5 - (4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino] - 4.5-dihydro-LH-Pyrazole [4.3-h] quinazoline-3-carboxamide (A51B8C1Z) Potassium 1 - (2-hydroxy-ethyl) -8 - [5 - (4-methyl-piperazin-1 1 - (2-hydroxy-ethyl) -8 - [5 - (4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino] - 4.5-dihydro-LH-Pyrazole [4.3-h] quinazoline-3-carboxylate (A51B5C2Z) l-Methyl-8-[5 - (l-methyl-1,2,3,

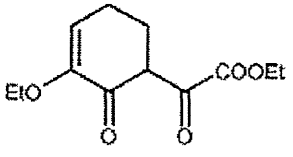
l-Methyl-8-[5-(l-methyl-piperidin-4-yl)-2-trifluoromethoxy-phenylamino]-4,5-dihy dro - 1 H-pyrazo Io [4 , 3 -h] quinazo line-3 -carboxamide (A114B1C1Z);

8-(5-Bromo-2-trifluoromethoxy-phenylamino)-l-methyl-4,5-dihydro-lH-pyrazolo[4,3-h]quinazoline-3-carboxamide (A49B1C1Z), and

8-(5-Bromo-2-trifluoromethoxy-phenylamino)-4,5-dihydro-lH-pyrazolo[4,3-h]quinazoline-3-carboxamide (A49B8C1Z).

7. A process for preparing a compound of formula (I) as defined in claim 1, wich process comprises:

st.1) reacting the compound of formula (II):

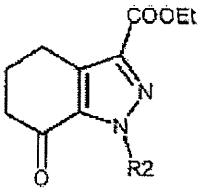


(II)

with a hydrazine derivative of formula (III):

$R2\text{-}NHNH_2$ (III)

wherein R2 is as defined in claim 1 , in the presence of acetic acid to give a compound of formula (IV):



(IV)

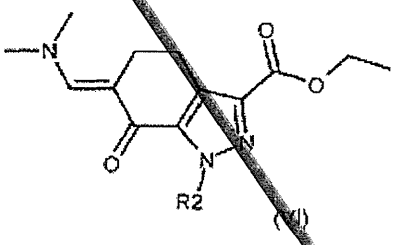
wherein R2 is as defined above;

optionally alkylating a compound of formula (IV) wherein R2 is hydrogen with the compounds of formula (V):

R2-Y (V)

wherein Y is a suitable leaving group such as mesyl, tosyl, halogen, and R2 is as defined above but not hydrogen, to give a compound of formula (IV) wherein R2 is as defined above but not hydrogen;

st.2) reacting the compound of formula (IV) with dimethylformamide-di-te/t-butylacetale or dimethylformamide-diisopropylacetale to give a compound of formula (VI):



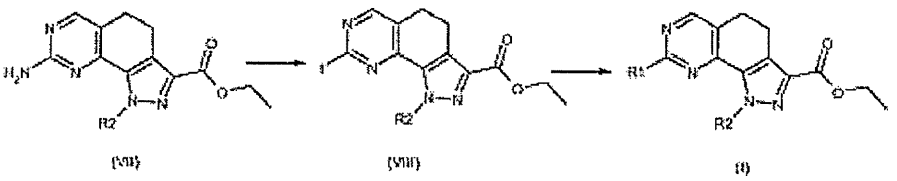
(VI)

wherein R2 is as defined above; and

st3.) reacting the compound of formula (VI) according to any one of the alternative steps (st.3a) or (st.3b):

st.3a) with guanidine to give a compound of formula (VII), wherein R2 is as defined above; converting the amino group of the resulting compound of formula (VII) to iodine, and then reacting the resulting iodo-derivative of formula (VIII) with an ortho-substituted-arylamine of formula R1-H (IX) wherein R1 is as defined in claim

1, to give a compound of formula (I):

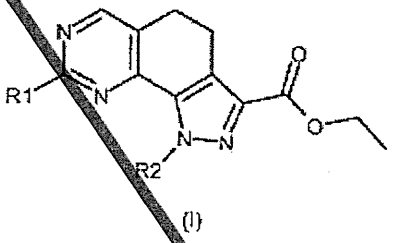


wherein Rl and R2 are as defined above;

st.3b) with a guanidine derivative of formula (X):

R1-C(=NH)NH_2 (X)

wherein Rl is as defined above, to give a compound of formula (I):

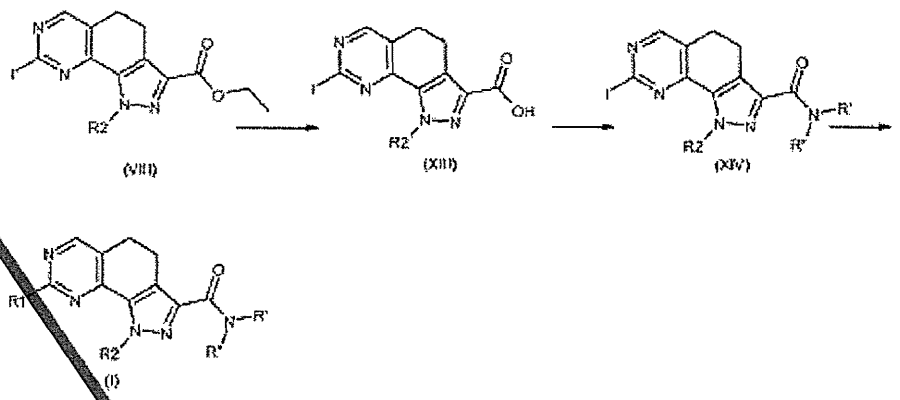


wherein Rl and R2 are as defined above, and

optionally converting it into other derivatives of formula (I) and/or into pharmaceutically acceptable salts thereof.

8. A process for preparing a compound of formula (I) according to claim 7, characterized in that the compound of formula (I) is prepared according to a process which comprises:

st.4.) converting the ethoxycarbonyl group of the compound of formula (VIII) as defined in claim 7, to a compound of formula (XIII) or corresponding salt through acidic or basic hydrolysis; converting the resulting compound of formula (XIII) or corresponding salt into the compound of formula (XIV) through reaction under basic conditions and in presence of a suitable condensing agent, with an amine of formula R'R"-NH (XI) wherein R' and R" are as defined in claim 1; reacting the compound of formula (XIV) with an ortho-substituted-arylamine of formula Rl-H (IX) wherein Rl is as defined in claim 1, to obtain a compound of formula (I):

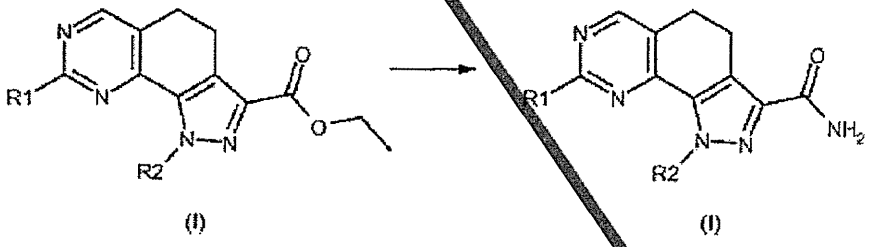


wherein Rl, R2, R and R' are as defined above and

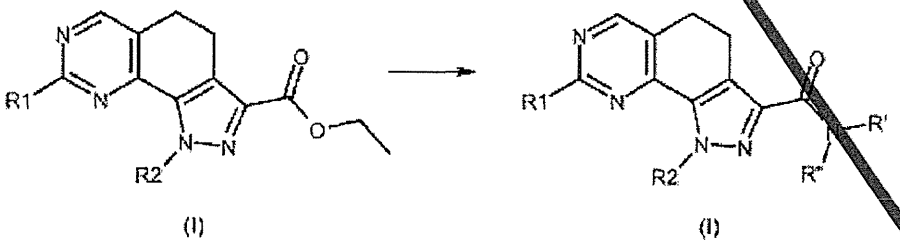
optionally converting it into other derivatives of formula (I) and/or into pharmaceutically acceptable salts thereof.

9. A process for preparing a compound of formula (I) according to claim 7 or 8, characterized in that the optional conversion of a compound of formula (I) into another compound of formula (I), is carried out by one or more of the following reactions:

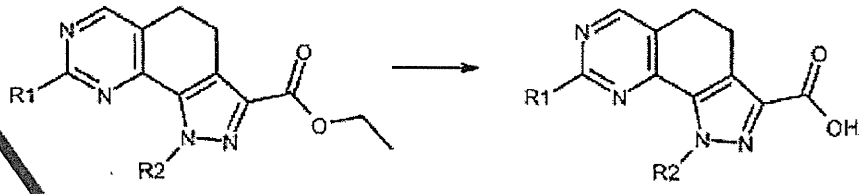
a) converting a compound of formula (I) wherein R3 is ethoxycarbonyl into a compound of formula (I) wherein R3 is aminocarbonyl by treatment with ammonium hydroxide:



b) converting a compound of formula (I) wherein R3 is ethoxycarbonyl into a compounda of formula (I) wherein R3 is a group CO-NR'R" by treatment with an amine of formula RR" - NH (XI), wherein R' and R" are as defined in Claim 1 :

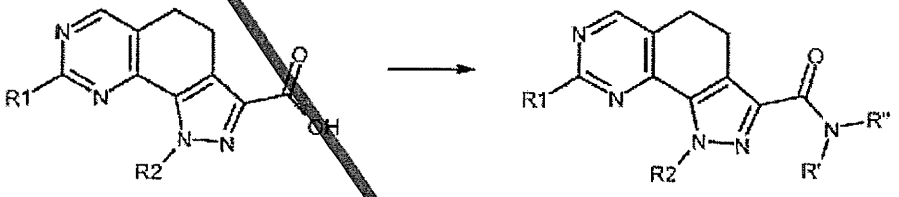


c) converting a compound of formula (I) wherein R3 is ethoxycarbonyl into a compound of formula (I) wherein R3 is a group CO-OH or corresponding salt through acidic or basic hydrolysis:



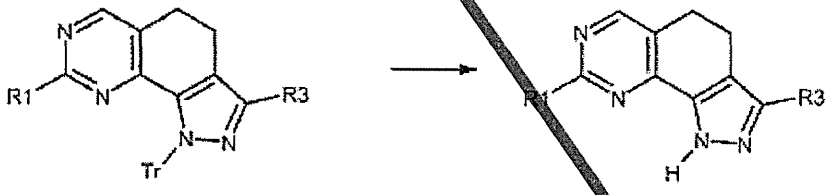
(I) (I)

d) converting a compound of formula (I) wherein R3 is CO-OH or corresponding salt into a compound of formula (I) wherein R3 is a group CO-NRR", through reaction with an amine of formula RR" -NH (XI) under basic conditions and in the presence of a suitable condensing agent, wherein R and R" are as defined above:



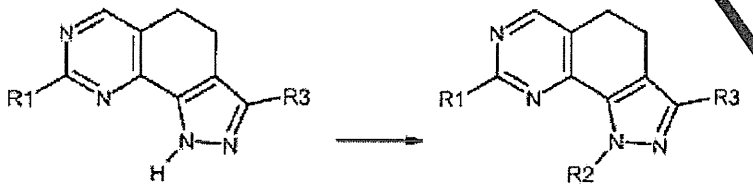
(I) (I)

e) converting a compound of formula (I) wherein R2 is Trityl into a compound of formula (I) wherein R2 is hydrogen, under acidic conditions:



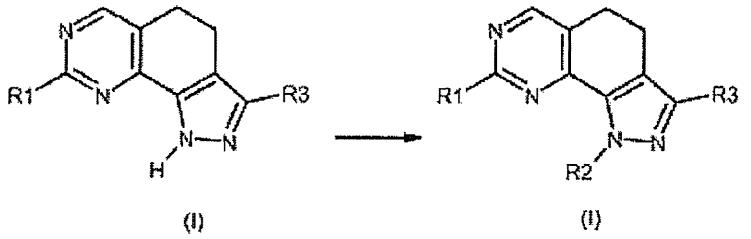
(I) (I)

f) converting a compound of formula (I) wherein R2 is hydrogen into a compound of formula (I) wherein R2 is as defined in Claim 1 but not hydrogen, through reaction with an alcohol of formula R2-OH (XII) wherein R2 is as defined above but not hydrogen:



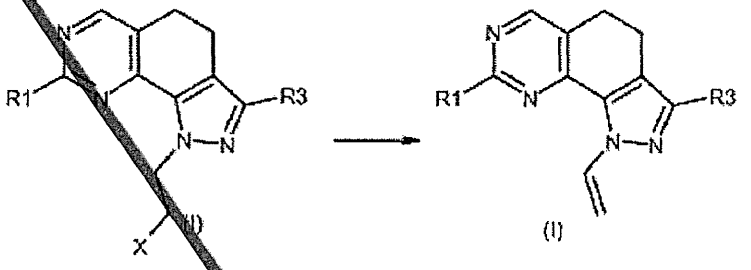
(I) (I)

g) converting a compound of formula (I) wherein R2 is hydrogen into a compound of formula (I) wherein R2 is as defined in claim 1 but not hydrogen, through reaction with a compound of formula R2-X (XV) wherein R2 is as defined above but not hydrogen and X is halogen:



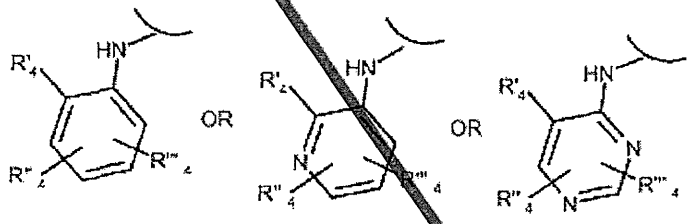
(I) (I)

h) converting a compound of formula (I) wherein R2 is an haloethyl into a compound of formula (I) wherein R2 is vinyl:



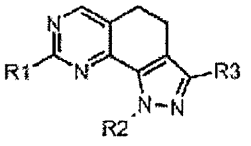
(I) (I)

i) converting a compound of formula (I) wherein Rl is an o/t/zo-substituted-arylamino of the formula:



wherein R'4, or R^M_4 or R^m_4 is bromine, into a compound of formula (I) wherein R'4, or R"4 or R'"4 is a group -NRR" by treatment with an amine of formula RR"-NH (XI), wherein R and R" are as defined in claim 1.

10. A library of two or more compounds of formula (I):



(I)

wherein

Rl is an ortho-substituted-arylamino;

R2 is hydrogen or an optionally substituted group selected from straight or branched Ci-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl and heterocyclyl;

R3 is CO-OR' or CO-NRR", wherein R' and R" are, each independently, hydrogen or an optionally substituted group selected from straight or branched Ci-C_6 alkyl, C_3-C_6 cycloalkyl and heterocyclyl, or R' and R" taken together with the nitrogen atom to which they are bonded, may form an optionally substituted heterocyclyl group optionally containing one additional heteroatom selected among N, O or S, provided that: ethyl l-methyl-8-(2-methoxy-phenylamino)-4,5-dihydro-lH-pyrazolo[4,3-h]quinazoline-3-carboxylate and 1 -methyl-8-(2-methoxyphenylamino)-4,5-dihydro-lH-pyrazolo[4,3-h]quinazoline-3-carboxamide are excluded;

and isomers, tautomers, hydrates, solvates, complexes, metabolites, prodrugs, carriers, N-oxides and pharmaceutically acceptable salts thereof.

11. A method for treating a disease caused by and/or associated with a dysregulated protein kinase activity which comprises administering to a mammal in need thereof an effective amount of a compound of formula (I) as defined in claim 1.

12. The method according to claim 11 for treating a disease caused by and/or associated with a dysregulated PLK-I, Aurora-2 or Cdk2/cyclin A activity.

13. The method according to claim 12 for treating a disease caused by and/or associated with a dysregulated PLK-I activity.

14. The method according to claim 11 wherein the disease is selected from the group consisting of cancer, cell proliferative disorders, viral infections, autoimmune and neurodegenerative disorders.

15. The method according to claim 14 wherein the cancer is selected from the group consisting of carcinoma such as bladder, breast, colon, kidney, liver, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage including leukaemia, acute lymphocitic leukaemia, acute lymphoblastic leukaemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukaemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma neuroblastoma, glioma and schwannomas; other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma.

16. The method according to claim 14 for treating viral infections in HIV-infected individuals.

17. The method according to claim 11 which provides tumor angiogenesis and metastasis inhibition as well as the treatment of organ transplant rejection and host versus graft disease.

18. The method according to claim 11 further comprising subjecting the mammal in need thereof to a radiation therapy or chemotherapy regimen in combination with at least one cytostatic or cytotoxic agent.

19. The method according to claim 11 wherein the mammal in need thereof is a human.

20. A method for inhibiting the activity po PLK-I protein which comprises contacting said protein with an effective amount of a compound as defined in claim 1.

21. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1, and at least one pharmaceutically acceptable excipient, carrier and/or diluent.

22. A pharmaceutical composition according to claim 22 further comprising one or more chemotherapeutic agents.

23. A product or kit comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1, or pharmaceutical compositions thereof as defined in claim 22 and one or more chemotherapeutic agent, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

24. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1 , for use as a medicament. .

25. A compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1 , for use in a method for treating cancer.

26. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in claim 1 , in the manufacture of a medicament with anticancer activity.

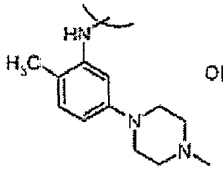
27. An intermediate of formula (X'):

$$R\Gamma\text{-}C(=NH)NH_2 \quad (X')$$

or of formula (IX):

$$Rl'\text{-}H \quad (IX)$$

wherein Rl' is



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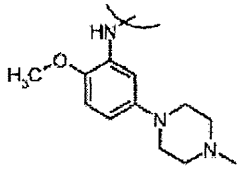

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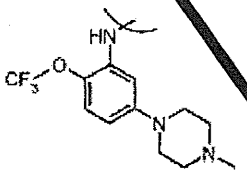


TITLE OF THE INVENTION

SUBSTITUTED PYRAZOLO-QUINAZOLINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE AS KINASE INHIBITORS

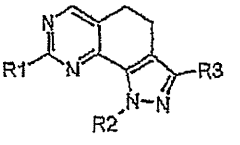
The present invention relates to certain substituted pyrazolo-quinazoline compounds, which modulate the activity of protein kinases. The compounds of this invention are therefore useful in treating diseases caused by dysregulated protein kinase activity. The present invention also provides methods for preparing these compounds, pharmaceutical compositions comprising these compounds, and methods of treating diseases utilizing pharmaceutical compositions comprising these compounds.

The use of mitotic inhibitors in cancer therapy is a widely accepted clinical strategy for the treatment of a broad range of human cancers. Taxanes (Paclitaxel and Docetaxel) and Vinca Alkaloids (Vincristine and Vinblastine) work by either stabilizing or destabilizing microtubules with catastrophic consequences in cells progressing through mitosis. They are first line therapeutics for several tumour types and second line in cisplatin-refractory ovarian, breast, lung, bladder and esophagus cancers (Taxanes). However, due to the role of microtubules in processes such as cell movement, phagocytosis and axonal transport certain toxicities such as peripheral neuropathy are frequently observed with these agents. Progression through mitosis is a requirement of all proliferating cells and hence cancer therapies that have targets in mitosis are generally applicable to a wide range of tumour types. Several protein kinases play key roles in the orchestration of the cell cycle and some of them are already subject to targeted therapies in the oncology setting including Cdk-2 and Aurora-A. The fidelity of mitosis is of paramount importance and several "checkpoints" exist in normal cells to maintain chromosome integrity during the cell cycle. These checkpoints often go away during oncogenic transformation and this permits cancer cells to tolerate anueploidy and chromosomal instability. Inhibition of mitosis in "checkpoint compromised" tumour cells should have catastrophic consequences as cancer cells try to carry forward an aberrant mitosis.

The Polo-like kinase family, comprising 4 serine / threonine kinases (Plk-1-4), are predominantly involved in the entry into, progression through and exit from mitosis. These kinases are characterized by having an n-terminal kinase domain and a unique,

CLAIMS:

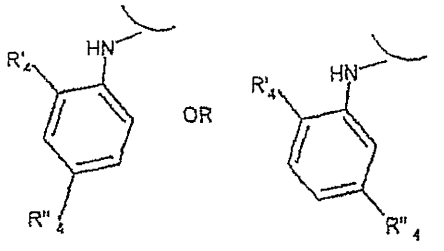
1. A compound of formula (I):



(I)

wherein

R1 is an ortho-substituted-arylamino of the formula:



wherein R'_4 and R''_4 are independently selected from: halogen, nitro, cyano, C_1-C_6 alkyl, polyfluorinated alkyl, polyfluorinated alkoxy, alkenyl, alkynyl, hydroxyalkyl, aryl, arylalkyl, heterocyclyl, C_3-C_6 cycloalkyl, hydroxy, alkoxy, aryloxy, heterocyclyloxy, methylenedioxy, alkylcarbonyloxy, arylcarbonyloxy, cycloalkenyloxy, heterocyclylcarbonyloxy, alkylideneaminooxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, amino, ureido, alkylamino, dialkylamino, arylamino, diarylamino, heterocyclylamino, formylamino, alkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, heterocyclylaminocarbonyl, alkoxycarbonylamino, hydroxyaminocarbonyl, alkoxyimino, alkylsulfonylamino, arylsulfonylamino, heterocyclylsulfonylamino, formyl, alkylcarbonyl, arylcarbonyl, cycloalkylcarbonyl, heterocyclylcarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl,

dialkylaminosulfonyl, arylaminosulfonyl, heterocyclylaminosulfonyl, arylthio, alkylthio, phosphonate or alkylphosphonate;

R2 is hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or heterocyclyl;

R3 is CO-OR' or CO-NR'R", wherein R' and R" are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocyclyl, or R' and R" taken together with the nitrogen atom to which they are bonded, may form an optionally substituted heterocyclyl group optionally containing one additional heteroatom selected among N, O or S;

or an optional isomer, tautomer, hydrate, solvate, N-oxide or pharmaceutically acceptable salt thereof.

2. A compound of formula (I) as defined in claim 1 wherein:

R3 is CO-OH or CO-NR'R", wherein R' and R" are as defined in claim 1.

3. A compound of formula (I) as defined in claim 1 or 2 wherein:

R2 is an optionally substituted straight or branched C_1-C_6 alkyl or C_2-C_6 alkenyl.

4. A compound of formula (I) as defined in any one of claims 1 to 3 wherein:

R3 is CO-NR'R", wherein R' and R" are as defined in claim 1.

5. A compound or a pharmaceutically acceptable salt thereof which is selected from the group consisting of: 8-[2-acetyl-5-(4-methyl-piperazin-l-yl)-phenylamino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A39B1CI Z);

8-[2-acetyl-5-(4-methyl-piperazin-l-yl)-phenylamino]-1-(2-fluoro-ethyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A39B2C1Z);

1-methyl-8-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A51B1C1Z);

1-methyl-8-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (A51B1C2Z);

1-methyl-8-[2-methoxy-5-(4-methyl-piperazin-1-yl)-phenylamino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A85B1C1Z);

8-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino]-1-(2-fluoro-ethyl)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A51B2C1Z);

1-methyl-8-[4-(4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A48B1C1Z);

1-methyl-8-[2-trifluoromethoxy-5-piperazin-1-yl-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A97B1C1Z);

1-methyl-8-[2-methyl-5-(4-methyl-piperazin-1-yl)-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A98B1C1Z);

1-methyl-8-[5-(4-pyrrolidin-1-yl-piperidin-1-yl)-2-trifluoromethoxy phenylamino]-4,5-dihydro-1H-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A99B1C1Z);

1-methyl-8-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide (A51B1C4Z);

1-methyl-8-[5-(4-methyl-piperazin-1-yl)-2-methoxy-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid methylamide (A85B1C4Z);

1-methyl-8-[2-methyl-5-(4-methyl-piperazine-1-carbonyl)-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A87B1C1Z);

1-methyl-8-[2-methyl-4-(4-methyl-piperazine-1-carbonyl)-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A86B1C1Z);

1-methyl-8-{2-trifluoromethoxy-5-[(1-methyl-piperidine-4-carbonyl)-amino]-phenylamino}-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A82B1C1Z);

8-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino]-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (A51B1C3Z);

1-ethyl-8-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A51B7C1Z);

1-methyl-8-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylic acid (2,2,2-trifluoro-ethyl)-amide (A51B1C7Z);

1-(2-hydroxy-ethyl)-8-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A51B5C1Z);

8-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino]-1-vinyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A51B10C1Z);

1-(2-chloro-ethyl)-8-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A51B9C1Z);

8-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A51B8C1Z);

1-(2-hydroxy-ethyl)-8-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (A51B5C3Z);

1-(2-hydroxy-ethyl)-8-[5-(4-methyl-piperazin-1-yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxylate (A51B5C2Z);

1-methyl-8-[5-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A113B1C1Z);

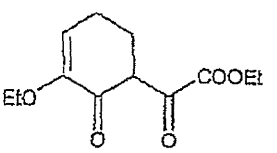
1-methyl-8-[5-(1-methyl-piperidin-4-yl)-2-trifluoromethoxy-phenylamino]-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A114B1C1Z);

8-(5-bromo-2-trifluoromethoxy-phenylamino)-1-methyl-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A49B1C1Z), and

8-(5-bromo-2-trifluoromethoxy-phenylamino)-4,5-dihydro-1H-pyrazolo[4,3-h]quinazoline-3-carboxamide (A49B8C1Z).

6. A process for preparing a compound of formula (I) as defined in claim 1, which process comprises:

st.1) reacting a compound of formula (II):

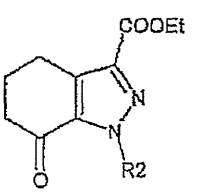


(II)

with a hydrazine derivative of formula (III):

$R2\text{-}NHNH_2$ (III)

wherein R2 is as defined in claim 1, in the presence of acetic acid to give a compound of formula (IV):



(IV)

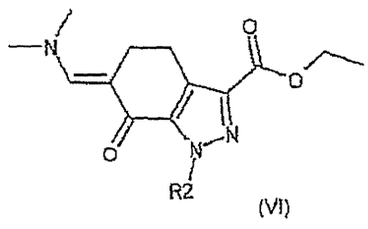
wherein R2 is as defined above;

optionally alkylating a compound of formula (IV) wherein R2 is hydrogen with the compounds of formula (V):

R2-Y (V)

wherein Y is a suitable leaving group, to give a compound of formula (IV) wherein R2 is as defined above but not hydrogen;

st.2) reacting the compound of formula (IV) with dimethylformamide-di-*tert*-butylacetate or dimethylformamide-diisopropylacetate to give a compound of formula (VI):

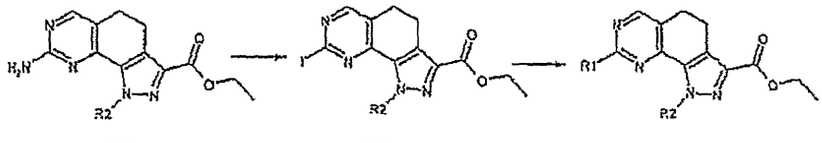


(VI)

wherein R2 is as defined above; and

st3.) reacting the compound of formula (VI) according to any one of the alternative steps (st.3a) or (st.3b):

st.3a) with guanidine to give a compound of formula (VII), wherein R2 is as defined above; converting the amino group of the resulting compound of formula (VII) to iodine, and then reacting the resulting iodo-derivative of formula (VIII) with an ortho-substituted-arylamine of formula R1-H (IX) wherein R1 is as defined in claim 1, to give a compound of formula (I):



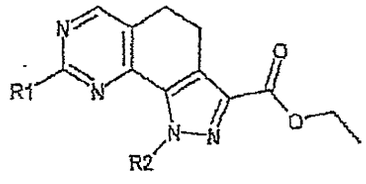
(VII) (VIII) (I)

wherein R1 and R2 are as defined above;

st.3b) with a guanidine derivative of formula (X):

R1-C(=NH)NH$_2$ (X)

wherein R1 is as defined above, to give a compound of formula (I):



(I)

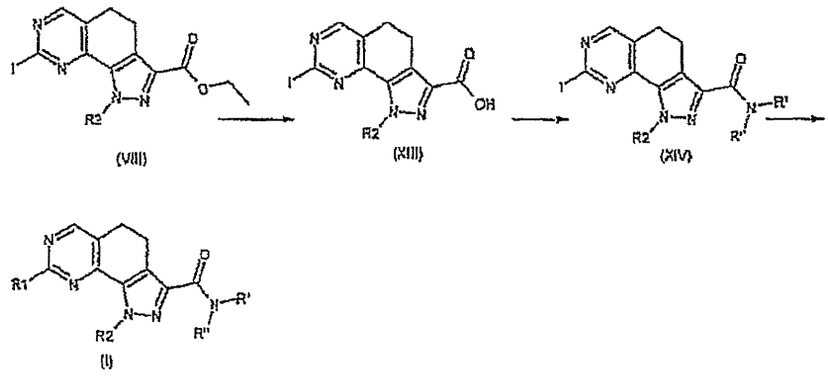
wherein R1 and R2 are as defined above, and

optionally converting it into other derivatives of formula (I) and/or into a pharmaceutically acceptable salt thereof.

7. A process according to claim 6 , wherein the leaving group in the definition of Y in st.I) is mesyl, tosyl, halogen or R2 as defined in claim 1 but not hydrogen.

8. A process for preparing a compound of formula (I) according to claim 6 , wherein the compound of formula (I) is prepared according to a process which comprises:

st.4.) converting the ethoxycarbonyl group of the compound of formula (VIII) as defined in claim 6 , to a compound of formula (XIII) or corresponding salt through acidic or basic hydrolysis; converting the resulting compound of formula (XIII) or corresponding salt into the compound of formula (XIV) through reaction under basic conditions and in presence of a suitable condensing agent, with an amine of formula R'R"-NH (XI) wherein R' and R" are as defined in claim 1; reacting the compound of formula (XIV) with an ortho-substituted-arylamine of formula R1-H (IX) wherein R1 is as defined in claim 1, to obtain a compound of formula (I):

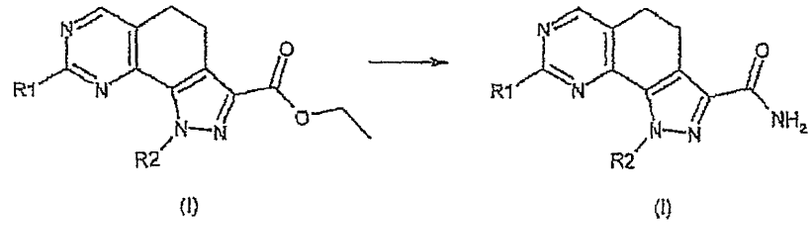


wherein R1, R' and R" are as defined above and R2 is as defined in claim 1 and

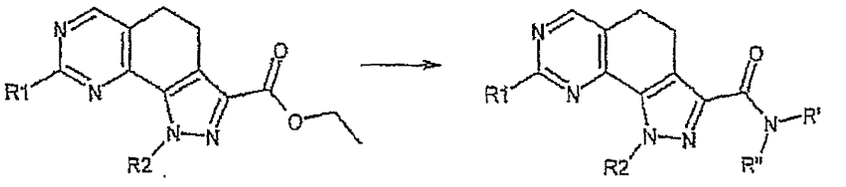
optionally converting it into other derivatives of formula (I) and/or into a pharmaceutically acceptable salt thereof.

9. A process for preparing a compound of formula (I) according to any one of claims 6 to 8 , wherein the optional conversion of a compound of formula (I) into another compound of formula (I), is carried out by one or more of the following reactions:

a) converting a compound of formula (I) wherein R3 is ethoxycarbonyl into a compound of formula (I) wherein R3 is aminocarbonyl by treatment with ammonium hydroxide:

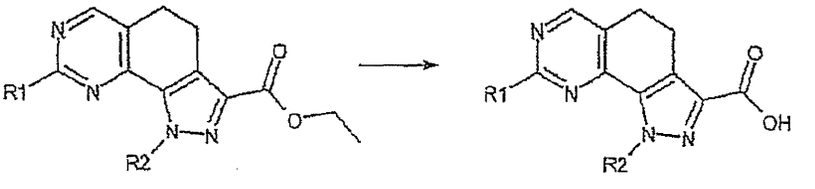


b) converting a compound of formula (I) wherein R3 is ethoxycarbonyl into a compound of formula (I) wherein R3 is a group CO-NR'R" by treatment with an amine of formula R'R"-NH (XI), wherein R' and R" are as defined in claim 1:



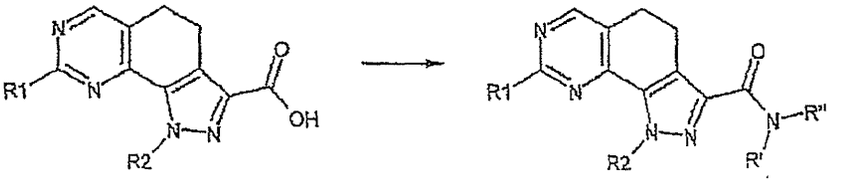
(I) (I)

c) converting a compound of formula (I) wherein R3 is ethoxycarbonyl into a compound of formula (I) wherein R3 is a group CO-OH or corresponding salt through acidic or basic hydrolysis:



(I) (I)

d) converting a compound of formula (I) wherein R3 is CO-OH or corresponding salt into a compound of formula (I) wherein R3 is a group CO-NR'R", through reaction with an amine of formula R'R"-NH (XI) under basic conditions and in the presence of a suitable condensing agent, wherein R' and R" are as defined above:



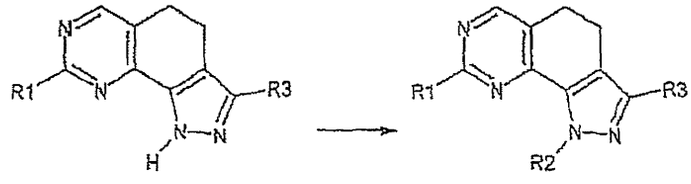
(I) (I)

e) converting a compound of formula (I) wherein R2 is Trityl into a compound of formula (I) wherein R2 is hydrogen, under acidic conditions:



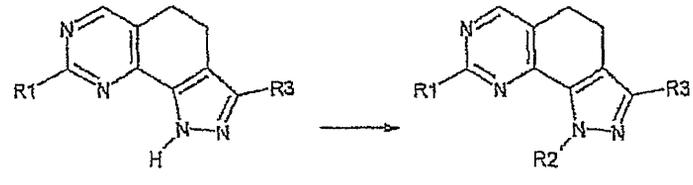
(I) (I)

f) converting a compound of formula (I) wherein R2 is hydrogen into a compound of formula (I) wherein R2 is as defined in claim 1 but not hydrogen, through reaction with an alcohol of formula R2-OH (XII) wherein R2 is as defined above but not hydrogen:



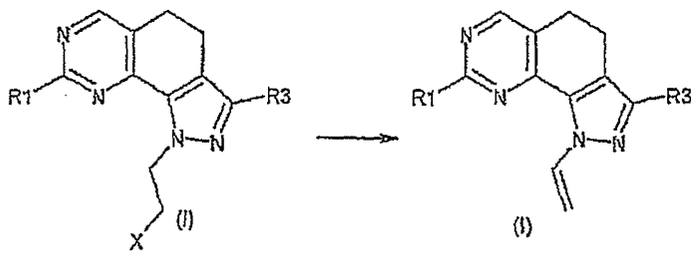
(I) (I)

g) converting a compound of formula (I) wherein R2 is hydrogen into a compound of formula (I) wherein R2 is as defined in claim 1 but not hydrogen, through reaction with a compound of formula R2-X (XV) wherein R2 is as defined above but not hydrogen and X is halogen:

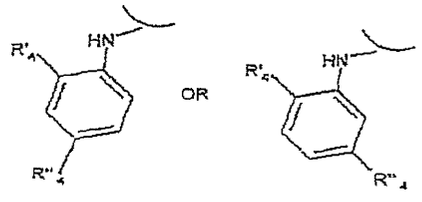


(I) (I)

h) converting a compound of formula (I) wherein R2 is a haloethyl into a compound of formula (I) wherein R2 is vinyl:

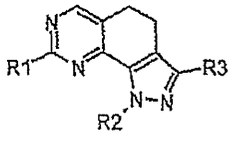


i) converting a compound of formula (I) wherein R1 is an *ortho*-substituted-arylamino of the formula:



wherein R'_4 or R''_4 is bromine, into a compound of formula (I) wherein R'_4 or R''_4 is a group -NR'R'' by treatment with an amine of formula R'R''-NH (XI), wherein R' and R'' are as defined in claim 1.

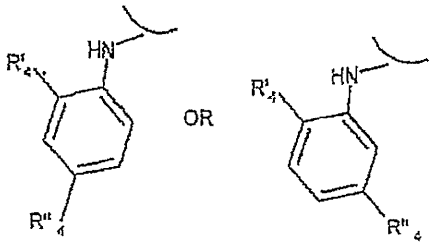
10. A library of two or more compounds of formula (I):



(I)

wherein

R1 is an ortho-substituted-arylamino of the formula:



wherein R'_4 and R''_4 are independently selected from: halogen, nitro, cyano, C_1-C_6 alkyl, polyfluorinated alkyl, polyfluorinated alkoxy, alkenyl, alkynyl, hydroxyalkyl, aryl, arylalkyl, heterocyclyl, C_3-C_6 cycloalkyl, hydroxy, alkoxy, aryloxy, heterocyclyloxy, methylenedioxy, alkylcarbonyloxy, arylcarbonyloxy, cycloalkenyloxy, heterocyclylcarbonyloxy, alkylideneaminooxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, cycloalkyloxycarbonyl, heterocyclyloxycarbonyl, amino, ureido, alkylamino, dialkylamino, arylamino, diarylamino, heterocyclylamino, formylamino, alkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, heterocyclylaminocarbonyl, alkoxycarbonylamino, hydroxyaminocarbonyl, alkoxyimino, alkylsulfonylamino, arylsulfonylamino, heterocyclylsulfonylamino, formyl, alkylcarbonyl, arylcarbonyl, cycloalkylcarbonyl, heterocyclylcarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylaminosulfonyl, dialkylaminosulfonyl, arylaminosulfonyl, heterocyclylaminosulfonyl, arylthio, alkylthio, phosphonate or alkylphosphonate;

R2 is hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, straight or branched C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or heterocyclyl;

R3 is CO-OR' or CO-NR'R", wherein R' and R" are, each independently, hydrogen or an optionally substituted group selected from straight or branched C_1-C_6 alkyl, C_3-C_6 cycloalkyl or heterocyclyl, or R' and R" taken together with the nitrogen atom to which they are bonded, may form an optionally substituted heterocyclyl group optionally containing one additional heteroatom selected among N, O or S;

or an optional isomer, tautomer, hydrate, solvate, N-oxide or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 5 , and at least one pharmaceutically acceptable excipient, carrier and/or diluent.

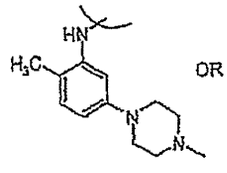
12. A compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 5 , for use in treating cancer.

13. Use of a compound or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 5 , in the manufacture of a medicament for the treatment of cancer.

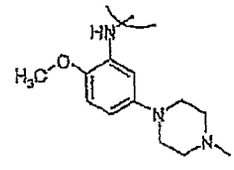
14. An intermediate of formula (X'):

$$R1'\text{-}C(=NH)NH_2 \qquad (X')$$

wherein R1' is



OR



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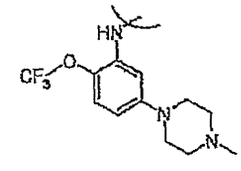

or of formula (IX'):

$$R1'\text{-}H \qquad (IX')$$

wherein R1' is

