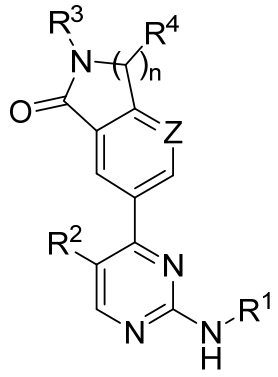
CLAIMS

1. The use of a compound for the manufacture of a medicament for inhibiting the activity of ERK1/2 wherein the compound is a compound having the formula (2):



(2)

or a pharmaceutically acceptable salt or tautomer thereof

wherein

n is 1 or 2;

Z is selected from C-R^z and N;

R^z is selected from hydrogen; halogen; methoxy; and C_{1-3} alkyl optionally substituted with hydroxy or methoxy;

R^1 is selected from:

- -$(Alk^1)_t$-Cyc^1; wherein t is 0 or 1; and Alk^1 is a C_{1-4} straight chain or branched alkylene group optionally substituted with 1 or 2 hydroxy groups; and
- C_{1-6} acyclic hydrocarbon groups which are unsubstituted or substituted with 1, 2 or 3 substituents R^5 selected from hydroxy; oxo; fluorine; and cyano; and wherein 1 or 2 but not all of the carbon atoms of the hydrocarbon group can be replaced by O or N;

Cyc^1 is a cyclic group selected from (a) 3 to 9 membered non-aromatic monocyclic and bicyclic carbocyclic and heterocyclic groups containing 0, 1, 2, or 3 heteroatom ring members selected from O, N, S, S(O) and $S(O)_2$; (b) 5 to 6 membered monocyclic heteroaryl groups containing 1, 2 or 3 heteroatom ring members of which 1 is N and the others, when present, are selected from O, N and S; and (c) 3 to 7 membered monocyclic carbocyclic groups; wherein each cyclic group (a), (b) and (c) is unsubstituted or substituted with 1, 2 or 3 substituents R^6 selected from hydroxy; oxo; fluorine; amino; $NH(Hyd^1)$; $N(Hyd^1)_2$; O-Hyd^1; -C(=O)-Hyd^1; -C(=O)-O-Hyd^1 and Hyd^1; where Hyd^1 is a C_{1-4} non-aromatic hydrocarbon group optionally substituted with one or more substituents selected from fluorine, hydroxyl and methoxy;

R^2 is selected from hydrogen; halogen; and C_{1-3} hydrocarbon groups optionally substituted with one or more fluorine atoms;

R^3 is hydrogen or a group L^1-R^7;

R^4 is selected from hydrogen; methoxy; and C_{1-3} alkyl optionally substituted with hydroxy, amino, mono- or di-C_{1-2} alkylamino, a cyclic amino group or methoxy; wherein the cyclic amino group is a saturated 4-7 membered heterocyclic group containing a nitrogen ring member and optionally a second heteroatom ring member selected from O, N and S, wherein the cyclic amino group is linked via a nitrogen ring member thereof to the C_{1-3} alkyl, and wherein the cyclic amino group is optionally substituted with one or two methyl groups; provided that no more than one R^4 can be other than hydrogen or methyl;

L^1 is selected from a bond; Alk^2, Alk^2–O and Alk^2-C(=O) wherein Alk^2 is a C_{1-4} straight chain or branched alkylene group which is optionally substituted with one or more substituents selected from hydroxy, methoxy, amino, methylamino, dimethylamino and fluorine;

R^7 is selected from:

- hydrogen;
- CO_2H;
- NR^8R^9;
- a carbocyclic or heterocyclic group having from 3 to 12 ring members, of which 0, 1, 2 or 3 are heteroatom ring members selected from O, N and S and oxidised forms of S, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R^{10}; and
- an acyclic C_{1-8} hydrocarbon group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano; carboxy; amino; mono- or di-C_{1-4} alkylamino; and carbocyclic and heterocyclic groups having from 3 to 12 ring members, of which 0, 1, 2 or 3 are heteroatom ring members selected from O, N and S and oxidised forms of S, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R^{10}; wherein one or two but not all of the carbon atoms of the acyclic C_{1-8} hydrocarbon group may optionally be replaced by O, S, SO, SO_2 or NR^{11};

R^8 is selected from hydrogen and a C_{1-4} hydrocarbon group, the C_{1-4} hydrocarbon group being optionally substituted with 1-2 substituents selected from hydroxy, amino, mono- C_{1-4} alkylamino, di-C_{1-4} alkylamino, and 4-7 membered saturated heterocyclic rings containing 1-2 heteroatom ring members selected from O and N, wherein the mono- C_{1-4} alkylamino, di-C_{1-4} alkylamino, and 4-7 membered saturated heterocyclic rings are each optionally substituted with 1-2 hydroxy or C_{1-3} alkyl substituents;

R^9 is selected from:

- hydrogen;
- a carbocyclic or heterocyclic group having from 3 to 12 ring members, of which 0, 1, 2 or 3 are heteroatom ring members selected from O, N and S and oxidised forms of S, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R^{10}; and
- an acyclic C_{1-8} hydrocarbon group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano; carboxy; amino; mono- or di-C_{1-4} alkylamino; and carbocyclic and heterocyclic groups having from 3 to 12 ring members, of which 0, 1, 2 or 3 are heteroatom ring members selected from O, N and S and oxidised forms of S, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R^{10}; wherein one or two but not all of the carbon atoms of the acyclic C_{1-8} hydrocarbon group may optionally be replaced by O, S, SO, SO_2 or NR^{11};

or NR^8R^9 forms a heterocyclic group having from 4 to 12 ring members wherein, in addition to the nitrogen atom of NR^8R^9, the heterocyclic group optionally contains 1 or 2 further heteroatom ring members selected from O, N and S and oxidised forms of S; and wherein the heterocyclic group is optionally substituted with one or more substituents R^{10};

R^{10} is selected from:

- halogen; hydroxy; oxo; cyano;
- OR^{12} wherein R^{12} is C_{1-6} alkyl or C_{3-6} cycloalkyl, each being optionally substituted with halogen;
- an acyclic C_{1-8} hydrocarbon group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano; carboxy; amino; mono- or di-C_{1-4} alkylamino; and carbocyclic and heterocyclic groups having 3 to 7 ring members of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from N, O and S, wherein the carbocyclic and heterocyclic groups are optionally substituted with one or more substituents R^{13} selected from hydroxy; halogen; cyano; amino; -$NH(Hyd^1)$; -$N(Hyd^1)_2$; and –$(O)_v$-Hyd^1 where v is 0 or 1; wherein one or two but not all of the carbon atoms of the acyclic C_{1-8} hydrocarbon group may optionally be replaced by O, S, SO, SO_2 or NR^{11}; and
- carbocyclic and heterocyclic groups having 3 to 7 ring members of which 0, 1, 2, 3 or 4 are heteroatom ring members selected from N, O and S, wherein the carbocyclic and heterocyclic groups are optionally substituted with one or more substituents R^{13}; and

R^{11} is selected from hydrogen and a C_{1-4} hydrocarbon group.

2. A compound having the formula (2) as defined in claim 1 or a pharmaceutically acceptable salt or tautomer thereof for use in medicine.

3. The use of a compound having the formula (2) as defined in claim 1 or a pharmaceutically acceptable salt or tautomer thereof, for the manufacture of a medicament:

   (a) for use in the prophylaxis or treatment of disease states or conditions mediated by ERK1/2; or

   (b) for use in the prophylaxis or treatment of disease states of cancer; or

   (c) for use in the prophylaxis or treatment of disease states or conditions selected from hepatocellular carcinoma, melanoma, oesophageal, renal, colon, colorectal, lung e.g. mesothelioma or lung adenocarcinoma, breast, bladder, gastrointestinal, ovarian and prostate cancers; or

   (d) for use in the prophylaxis or treatment of disease states or condition as described herein; or

   (e) for use in preventing or treating a disease or conditions with mutant Ras, mutant BRAF or mutant MEK; or

   (f) for use in the prophylaxis or treatment of cancer wherein the compound or composition is used in combination with one or more other compounds or therapies; or

   (g) for use in the prophylaxis or treatment of haematological malignancies; or

   (h) for use in the prophylaxis or treatment of leukemias and lymphomas; or

   (i) for use in the prophylaxis or treatment of haematological malignancies and related conditions of lymphoid lineage (for example acute lymphocytic leukemia [ALL], chronic lymphocytic leukemia [CLL], B-cell lymphomas such as diffuse large B-cell lymphoma [DLBCL], follicular lymphoma, Burkitt's lymphoma, mantle cell lymphoma, T-cell lymphomas and leukaemias, natural killer [NK] cell lymphomas, Hodgkin's lymphomas, hairy cell leukaemia, monoclonal gammopathy of uncertain significance, plasmacytoma, multiple myeloma, and post-transplant lymphoproliferative disorders); or

(j) for use in the prophylaxis or treatment of haematological malignancies and related conditions of myeloid lineage (for example acute myelogenous leukemia [AML], chronic myelogenous leukemia [CML], chronic myelomonocytic leukemia [CMML], hypereosinophilic syndrome, myeloproliferative disorders such as polycythaemia vera, essential thrombocythaemia and primary myelofibrosis, myeloproliferative syndrome, myelodysplastic syndrome, and promyelocytic leukemia); or

(k) for use in the prophylaxis or treatment of adenomas and carcinomas; or

(l) the prophylaxis or treatment of disease states or conditions selected from tumours of epithelial origin; haematological malignancies and premalignant haematological disorders and disorders of borderline malignancy; tumours of mesenchymal origin; neural crest cell-derived tumours; tumours of the central or peripheral nervous system; endocrine tumours; ocular and adnexal tumours; germ cell and trophoblastic tumours; and paediatric and embryonal tumours; or syndromes, congenital or otherwise, which leave the patient susceptible to malignancy; or

(m) the prophylaxis or treatment of pancreatic cancers; or

(n) the prophylaxis or treatment of NRas melanoma and NRas AML; or

(o) the prophylaxis or treatment of KRas lung cancer, KRas pancreatic cancer or KRas colorectal cancer (CRC); or

(p) the prophylaxis or treatment of BRAF colorectal cancer (CRC), BRAF lung cancer or BRAF melanoma.

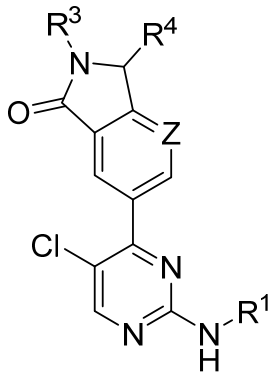
4. The use of a compound for the manufacture of a medicament for treating lung cancer, melanoma, pancreatic cancer, or colorectal cancer wherein the compound is a compound having the formula (2) as defined in claim 1 or a pharmaceutically acceptable salt or tautomer thereof.

5. The use according to claim 4 for the manufacture of a medicament for treating lung cancer, for example adenocarcinoma, small cell lung carcinoma, non-small cell lung carcinomas bronchioalveolar carcinoma, and mesothelioma.

6. The use of a compound in the manufacture of a medicament for treating a subject having a disease state or condition mediated by ERK1/2, wherein the subject is to be screened to establish susceptibility of a disease to ERK inhibition, and wherein a therapeutically effective amount of the compound is to be administered to the subject, wherein the compound is a compound having the formula (2) as defined in claim 1 or a pharmaceutically acceptable salt or tautomer thereof.

7. The use of a compound for the manufacture of a medicament for treating a subject who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with an ERK1/2 inhibitor, wherein the compound is a compound having the formula (2) as defined in claim 1 or a pharmaceutically acceptable salt or tautomer thereof.

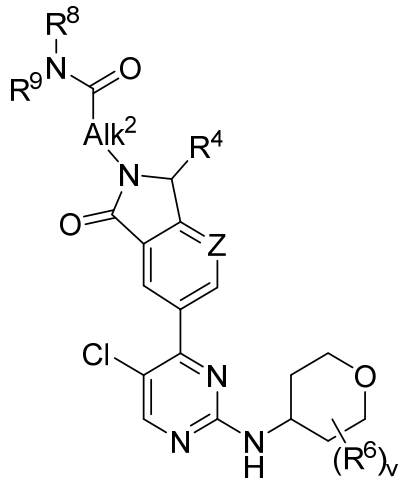
8. The use according to any one of claims 1 to 7 wherein a compound having the formula (5):



(5)

or a pharmaceutically acceptable salt or tautomer thereof is to be administered.

9. The use according to any one of claims 1 to 8 wherein a compound having the formula (9):



(9)

or a pharmaceutically acceptable salt or tautomer thereof, wherein v is 0, 1, 2 or 3, is to be administered.

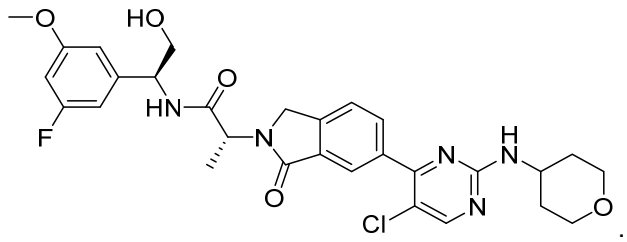
10. The use according to claim 9 wherein:
R^4 is hydrogen;
v is 0;
R^8 is hydrogen;
R^9 is an acyclic saturated C_{1-3} hydrocarbon group optionally substituted with one or more substituents selected from hydroxy and a phenyl group, the phenyl group being optionally substituted with one or more substituents R^{10};
R^{10} is selected from fluorine, methyl, methoxy and dimethylamino;
Alk^2 is selected from CH_2 and $CH(CH_3)$; and
Z is CH.

11. The use according to any one of claims 1 to 7 wherein the compound (2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl]propanamide or a pharmaceutically acceptable salt thereof is to be administered.

12. The use according to any one of claims 1 to 7 wherein the compound (2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl]propanamide is to be administered.

13. The use according to any one of claims 1 to 12 wherein the compound or pharmaceutically acceptable salt or tautomer thereof is to be administered in combination with another therapeutic agent.

14. A compound having the following formula:



15. A pharmaceutical composition comprising a compound of the formula (2) as defined in claim 1 or the compound of claim 14 and a pharmaceutically acceptable excipient, which is suitable for oral administration.

16. A pharmaceutical composition which is a unit dosage form comprising from approximately 1% (w/w) to approximately 95% active ingredient and from approximately 99% (w/w) to approximately 5% (w/w) of a pharmaceutically acceptable excipient or combination of excipients, wherein said active ingredient comprises a compound selected from:

(2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl]propanamide;

(2R)-2-(6-{5-Chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-2-hydroxy-1-(2-methoxypyridin-4-yl)ethyl]propanamide;

(R)-2-(6-(5-chloro-2-((2-methoxypyridin-4-yl)amino)pyrimidin-4-yl)-1-oxoisoindolin-2-yl)-N-((S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl)propanamide;

(R)-2-(6-(5-chloro-2-((2-methylpyrimidin-4-yl)amino)pyrimidin-4-yl)-1-oxoisoindolin-2-yl)-N-((S)-1-(6-(dimethylamino)pyridin-2-yl)-2-hydroxyethyl)propanamide;

(2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-2-hydroxy-1-[6-(4-methylpiperazin-1-yl)pyridin-2-yl]ethyl]propanamide; and

(2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1R)-1-[3-fluoro-5-(4-methylpiperazin-1-yl)phenyl]ethyl]propanamide; and

pharmaceutically acceptable salts and tautomers thereof.

17. A pharmaceutical composition according to claim 16 wherein the unit dosage form comprises from 20% (w/w) to 90% active ingredient and from 80% (w/w) to 10% (w/w) of the pharmaceutically acceptable excipient or combination of excipients.

18. A pharmaceutical composition according to claim 16 or claim 17 wherein said active ingredient is (2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl]propanamide or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition which is a unit dosage form comprising from approximately 1% (w/w) to approximately 95% active ingredient and from approximately 99% (w/w) to approximately 5% (w/w) of a pharmaceutically acceptable excipient or combination of excipients, wherein said active ingredient comprises a compound selected from:

(2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl]propanamide;

(2R)-2-(6-{5-Chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-2-hydroxy-1-(2-methoxypyridin-4-yl)ethyl]propanamide;

(R)-2-(6-(5-chloro-2-((2-methoxypyridin-4-yl)amino)pyrimidin-4-yl)-1-oxoisoindolin-2-yl)-N-((S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl)propanamide;

(R)-2-(6-(5-chloro-2-((2-methylpyrimidin-4-yl)amino)pyrimidin-4-yl)-1-oxoisoindolin-2-yl)-N-((S)-1-(6-(dimethylamino)pyridin-2-yl)-2-hydroxyethyl)propanamide;

(2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-2-hydroxy-1-[6-(4-methylpiperazin-1-yl)pyridin-2-yl]ethyl]propanamide; and

(2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1R)-1-[3-fluoro-5-(4-methylpiperazin-1-yl)phenyl]ethyl]propanamide.

20. A pharmaceutical composition according to claim 19 wherein the unit dosage form comprises from 20% (w/w) to 90% active ingredient and from 80% (w/w) to 10% (w/w) of the pharmaceutically acceptable excipient or combination of excipients.

21. A pharmaceutical composition according to claim 19 or claim 20 wherein said active ingredient is (2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl]propanamide.

22. A combination comprising the compound (2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl]propanamide or a pharmaceutically acceptable salt thereof and an anti-cancer agent selected from:

(i) a kinase inhibitor, or

(ii) drugs targeting the ubiquitin-proteasome pathway; or

(iii) regulators of cell death antagonists; or

(iv) a DNA methyl transferase inhibitor.

23. A combination comprising the compound (2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl]propanamide or a pharmaceutically acceptable salt thereof and another therapeutic agent or therapy selected from:

- Topoisomerase I inhibitors
- Antimetabolites
- Tubulin targeting agents
- DNA binder and topoisomerase II inhibitors
- Alkylating Agents
- Monoclonal Antibodies
- Anti-Hormones
- Signal Transduction Inhibitors
- Ubiquitin-proteasome pathway Inhibitors
- Immunotherapies
- Regulators of Cell Death
- DNA methyl transferase inhibitors
- Cytokines and retinoids
- Chromatin targeted therapies
- Radiotherapy

24. A combination comprising the compound (2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl]propanamide or a pharmaceutically acceptable salt thereof and another therapeutic agent or therapy selected from:

(i) Platinum compounds;

(ii) Taxane compounds;

(iii) Topoisomerase I inhibitors;

(iv) Topoisomerase II inhibitors;

(v) Vinca alkaloids;

(vi) Nucleoside derivatives;

(vii) Antimetabolites;

(viii) Alkylating agents;

(ix) Anthracyclines, anthracenediones and related drugs;

(x) Epothilones;

(xi) DNA methyl transferase inhibitors;

(xii) Antifolates;

(xiii) Cytotoxic antibiotics;

(xiv) Tubulin-binding agents;

(xv) Signal Transduction inhibitors

(xvi) Aurora kinase inhibitors;

(xvii) CDK inhibitors;

(xviii) PKA/B inhibitors and PKB (akt) pathway inhibitors;

(xix) Hsp90 inhibitors;

(xx) Monoclonal Antibodies (unconjugated or conjugated to radioisotopes, toxins or other agents), antibody derivatives and related agents;

(xxi) Estrogen receptor antagonists or selective estrogen receptor modulators (SERMs) or inhibitors of estrogen synthesis;

(xxii) Aromatase inhibitors and related drugs;

(xxiii) Antiandrogens (i.e. androgen receptor antagonists) and related agents;

(xxiv) Hormones and analogues thereof;

(xxv) Steroids,

(xxvi) Steroidal cytochrome P450 17alpha-hydroxylase-17,20-lyase inhibitor (CYP17);

(xxvii) Gonadotropin releasing hormone agonists or antagonists (GnRAs);

(xxviii) Glucocorticoids;

(xxix) Differentiating agents;

(xxx) Farnesyltransferase inhibitors;

(xxxi) Chromatin targeted therapies;

(xxxii) Drugs targeting the ubiquitin-proteasome pathway including proteasome inhibitors;

(xxxiii) Photodynamic drugs;

(xxxiv) Marine organism-derived anticancer agents;

(xxxv) Radiolabelled drugs for radioimmunotherapy;

(xxxvi) Telomerase inhibitors;

(xxxvii) Matrix metalloproteinase inhibitors;

(xxxviii) Recombinant interferons and interleukins ;

(xxxix) Selective immunoresponse modulators;

(xl) Therapeutic Vaccines;

(xli) Cytokine-activating agents;

(xlii) Arsenic trioxide;

(xliii) Inhibitors of G-protein coupled receptors (GPCR);

(xliv) Enzymes such as L-asparaginase, pegaspargase, rasburicase, or pegademase;

(xlv) DNA repair inhibitors such as PARP inhibitors;

(xlvi) Agonists of Death receptor (e.g. TNF-related apoptosis inducing ligand (TRAIL) receptor;

(xlvii) Immunotherapies such as immune checkpoint inhibitors; cancer vaccines and CAR-T cell therapy;

(xlviii) Regulators of Cell death (apoptosis) including Bcl-2 (B-cell lymphoma 2) antagonists;

(xlix) Prophylactic agents (adjuncts); i.e. agents that reduce or alleviate some of the side effects associated with chemotherapy agents, for example

– anti-emetic agents,

– agents that prevent or decrease the duration of chemotherapy-associated neutropenia and prevent complications that arise from reduced levels of platelets, red blood cells or white blood cells, for example interleukin-11 , erythropoietin (EPO) and analogues thereof , colony-stimulating factor analogs such as granulocyte macrophage-colony stimulating factor (GM-CSF) , and granulocyte-colony stimulating factor (G-CSF) and analogues thereof,

– agents that inhibit bone resorption such as denosumab or bisphosphonates,

– agents that suppress inflammatory responses,

– agents used to reduce blood levels of growth hormone and IGF-I (and other hormones) in patients with acromegaly or other rare hormone-producing tumours, such as synthetic forms of the hormone somatostatin,

– antidote to drugs that decrease levels of folic acid,

– agents for pain,

– non-steroidal anti-inflammatory drugs (NSAID) such as COX-2 inhibitors,

– agents for mucositis,

– agents for the treatment of side-effects including anorexia, cachexia, oedema or thromoembolic episodes, such as megestrol acetate; and

(l) radiotherapy for radical, palliative or prophylactic purposes (or, for adjuvant or neoadjuvant purposes).

25. A combination comprising the compound (2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl]propanamide or a pharmaceutically acceptable salt thereof and another therapeutic agent or therapy selected from:

(i) cisplatin (optionally combined with amifostine), carboplatin and oxaliplatin;

(ii) paclitaxel, paclitaxel protein bound particles (Abraxane™), docetaxel, cabazitaxel and larotaxel;

(iii) camptothecin compounds, for example camptothecin, irinotecan(CPT11), SN-38 and topotecan;

(iv) anti-tumour epipodophyllotoxins and podophyllotoxin derivatives for example etoposide, or teniposide;

(v) vinblastine, vincristine, liposomal vincristine (Onco-TCS), vinorelbine, vindesine, vinflunine and vinvesir;

(vi) 5-fluorouracil (5-FU, optionally in combination with leucovorin), gemcitabine, capecitabine, tegafur, UFT, S1, cladribine, cytarabine (Ara-C, cytosine arabinoside), fludarabine, clofarabine, and nelarabine;

(vii) clofarabine, aminopterin, methotrexate, azacitidine, cytarabine, floxuridine, pentostatin, thioguanine, thiopurine, 6-mercaptopurine, hydroxyurea (hydroxycarbamide) and trifluridine (optionally in combination with tipiracil);

(viii) nitrogen mustards and nitrosourea, for example cyclophosphamide, chlorambucil, carmustine (BCNU), bendamustine, thiotepa, melphalan, treosulfan, lomustine (CCNU), altretamine, busulfan, dacarbazine, estramustine, fotemustine, ifosfamide (optionally in combination with mesna), pipobroman, procarbazine, streptozocin, temozolomide, uracil, mechlorethamine, methylcyclohexylchloroethylnitrosurea, or nimustine (ACNU);

(ix) daunorubicin, doxorubicin (optionally in combination with dexrazoxane), liposomal formulations of doxorubicin (eg. Caelyx™, Myocet™, Doxil™), idarubicin, mitoxantrone, epirubicin, amsacrine, and valrubicin;

(x) ixabepilone, patupilone, BMS-310705, KOS-862 and ZK-EPO, epothilone A, epothilone B, desoxyepothilone B (also known as epothilone D or KOS-862), aza-epothilone B (also known as BMS-247550), aulimalide, isolaulimalide, and luetherobin;

(xi) temozolomide, azacytidine, decitabine and guadecitabine (SGI-110);

(xii) methotrexate, pemetrexed disodium, and raltitrexed;

(xiii) antinomycin D, bleomycin, mitomycin C, dactinomycin, carminomycin, daunomycin, levamisole, plicamycin, and mithramycin;

(xiv) combrestatin, colchicines and nocodazole;

(xv) kinase inhibitors for example receptor tyrosine kinase inhibitors (e.g. EGFR (epithelial growth factor receptor) inhibitors, VEGFR (vascular endothelial growth factor receptor) inhibitors, PDGFR (platelet-derived growth factor receptor) inhibitors, Axl inhibitors, MTKI (multi target kinase inhibitors), Raf inhibitors, ROCK inhibitors, mTOR inhibitors, MEK inhibitors or PI3K Inhibitors) for example imatinib mesylate, erlotinib, gefitinib, dasatinib, lapatinib, dovotinib, axitinib, nilotinib, vandetanib, vatalinib, pazopanib, sorafenib, sunitinib, , temsirolimus, everolimus (RAD 001), vemurafenib (PLX4032 or RG7204), dabrafenib, encorafenib, selumetinib (AZD6244), trametinib (GSK121120212), dactolisib (BEZ235), buparlisib (BKM-120; NVP-BKM-120), BYL719, copanlisib (BAY-80-6946), ZSTK-474, CUDC-907, apitolisib (GDC-0980; RG-7422), pictilisib (pictrelisib, GDC-0941, RG-7321), GDC-0032, GDC-0068, GSK-2636771, idelalisib (formerly CAL-101, GS 1101, GS-1101), MLN1117 (INK1117), MLN0128 (INK128), IPI-145 (INK1197), LY-3023414, ipatasertib, afuresertib, MK-2206, MK-8156, LY-3023414, LY294002, SF1126 or PI-103, sonolisib (PX-866), or AT13148;

(xvi) AT9283, barasertib (AZD1152), TAK-901, MK0457 (VX680), cenisertib (R-763), danusertib (PHA-739358), alisertib (MLN-8237), and MP-470;

(xvii) AT7519, roscovitine, seliciclib, alvocidib (flavopiridol), dinaciclib (SCH-727965), 7-hydroxy-staurosporine (UCN-01), JNJ-7706621, BMS-387032 (a.k.a. SNS-032), PHA533533, ZK-304709, or AZD-5438 and including CDK4 inhibitors such as palbociclib (PD332991) and ribociclib (LEE-011);

(xviii) AT13148, AZ-5363, Semaphore, SF1126 and MTOR inhibitors such as rapamycin analogues, AP23841 and AP23573, calmodulin inhibitors (forkhead translocation inhibitors), API-2/TCN (triciribine), RX-0201, enzastaurin HCl (LY317615), NL-71-101, SR-13668, PX-316, and KRX-0401 (perifosine/ NSC 639966);

(xix) onalespib (AT13387), herbimycin, geldanamycin (GA), 17-allylamino-17-desmethoxygeldanamycin (17-AAG) e.g. NSC-330507, Kos-953 and CNF-1010, 17-dimethylaminoethylamino-17-demethoxygeldanamycin hydrochloride (17-DMAG) e.g. NSC-707545 and Kos-1022, NVP-AUY922 (VER-52296), NVP-BEP800, CNF-2024 (BIIB-021 an oral purine), ganetespib (STA-9090), SNX-5422 (SC-102112), and IPI-504 or TAS-116;

(xx) anti-CD, anti-VEGFR, anti-HER2 or anti-EGFR antibodies, for example rituximab (CD20), ofatumumab (CD20), ibritumomab tiuxetan (CD20), GA101

(CD20), tositumomab (CD20), epratuzumab (CD22), lintuzumab (CD33), gemtuzumab ozogamicin (CD33), alemtuzumab (CD52), galiximab (CD80), trastuzumab (HER2 antibody), pertuzumab (HER2), trastuzumab-DM1 (HER2), ertumaxomab (HER2 and CD3), cetuximab (EGFR), panitumumab (EGFR), necitumumab (EGFR), nimotuzumab (EGFR), bevacizumab (VEGF), catumaxumab (EpCAM and CD3), abagovomab (CA125), farletuzumab (folate receptor), elotuzumab (CS1), denosumab (RANK ligand), figitumumab (IGF1R), CP751,871 (IGF1R), mapatumumab (TRAIL receptor), metMAB (met), mitumomab (GD3 ganglioside), naptumomab estafenatox (5T4), or siltuximab (IL6) or immunomodulating agents such as CTLA-4 blocking antibodies and/or antibodies against PD-1 and PD-L1 and/or PD-L2 for example ipilimumab (CTLA4), MK-3475 (pembrolizumab, formerly lambrolizumab, anti-PD-1), nivolumab (a anti-PD-1), BMS-936559 (anti- PD-L1), MPDL320A, AMP-514 or MEDI4736 (anti-PD-L1), or tremelimumab (formerly ticilimumab, CP-675,206, anti-CTLA-4);

(xxi) tamoxifen, fulvestrant, toremifene, droloxifene, faslodex, and raloxifene;

(xxii) exemestane, anastrozole, letrazole, testolactone aminoglutethimide, mitotane and vorozole;

(xxiii) bicalutamide, nilutamide, flutamide, cyproterone, and ketoconazole;

(xxiv) medroxyprogesterone, diethylstilbestrol (a.k.a. diethylstilboestrol) and octreotide;

(xxv) dromostanolone propionate, megestrol acetate, nandrolone (decanoate, phenpropionate), fluoxymestrone and gossypol,

(xxvi) abiraterone;

(xxvii) abarelix, goserelin acetate, histrelin acetate, leuprolide acetate, triptorelin, buserelin, and deslorelin;

(xxviii) prednisone, prednisolone, dexamethasone;

(xxix) retinoids, rexinoids, vitamin D or retinoic acid and retinoic acid metabolism blocking agents (RAMBA) for example accutane, alitretinoin, bexarotene, or tretinoin;

(xxx) tipifarnib;

(xxxi) histone deacetylase (HDAC) inhibitors for example sodium butyrate, suberoylanilide hydroxamide acid (SAHA), depsipeptide (FR 901228),

dacinostat (NVP-LAQ824), R306465/ JNJ-16241199, JNJ-26481585, trichostatin A, vorinostat, chlamydocin, A-173, JNJ-MGCD-0103, PXD-101, or apicidin;

(xxxii) bortezomib, carfilzomib, CEP-18770, MLN-9708, or ONX-0912; NEDD8 inhibitors; HDM2 antagonist and deubiquitinases (DUBs);

(xxxiii) porfimer sodium and temoporfin;

(xxxiv) trabectidin;

(xxxv) Radiolabelled drugs for radioimmunotherapy with a beta particle-emitting isotope (e.g. , Iodine -131, Yittrium -90) or an alpha particle-emitting isotope (e.g., Bismuth-213 or Actinium-225) for example ibritumomab,r Iodine tositumomab or alpha radium;

(xxxvi) telomestatin;

(xxxvii) batimastat, marimastat, prinostat and metastat;

(xxxviii) interferon-γ, interferon α, interleukin 2, aldesleukin, denileukin diftitox, interferon alfa 2a, interferon alfa 2b, and peginterferon alfa 2b;

(xxxix) thalidomide and lenalidomide;

(xl) sipuleucel-T (Provenge) or OncoVex;

(xli) Picibanil, Romurtide, Sizofiran, Virulizin, andThymosin;

(xlii) Arsenic trioxide;

(xliii) atrasentan;

(xliv) Enzymes such as L-asparaginase, pegaspargase, rasburicase, or pegademase;

(xlv) olaparib, velaparib, iniparib, INO-1001, AG-014699, or ONO-2231;

(xlvi) mapatumumab (formerly HGS-ETR1), conatumumab (formerly AMG 655), PRO95780, lexatumumab, dulanermin, CS-1008 , apomab and recombinant TRAIL ligands such as recombinant Human TRAIL/Apo2 Ligand;

(xlvii) Immunotherapies such as immune checkpoint inhibitors; cancer vaccines and CAR-T cell therapy;

(xlviii) venetoclax (ABT-199 or GDC-0199), ABT-737, ABT-263, TW-37, sabutoclax, obatoclax, and MIM1 and IAP antagonists including LCL-161 (Novartis), Debio-1143 (Debiopharma / Ascenta), AZD5582, Birinapant / TL-32711

(TetraLogic), CUDC-427 / GDC-0917 / RG-7459 (Genentech), JP1201 (Joyant), T-3256336 (Takeda), GDC-0152 (Genentech), HGS-1029 / AEG-40826 (HGS/ Aegera) and ASTX-660;

(xlix) Prophylactic agents (adjuncts); i.e. agents that reduce or alleviate some of the side effects associated with chemotherapy agents, for example

– e.g. oprelvekin, darbepoetin alfa, sargramostim, filgrastim and pegfilgrastim,

– zoledronate, zoledronic acid, pamidronate and ibandronate,

– dexamethasone, prednisone, and prednisolone,

– octreotide acetate,

– leucovorin, or folinic acid,

– morphine, diamorphine and fentanyl,

– celecoxib, etoricoxib and lumiracoxib,

– palifermin,

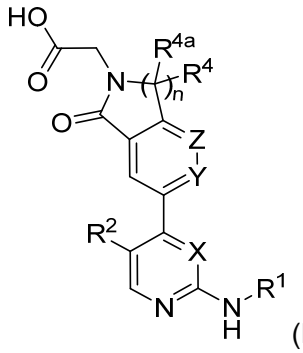
– megestrol acetate; and

(l) radiotherapy for radical, palliative or prophylactic purposes (or, for adjuvant or neoadjuvant purposes).

26. A combination according to any one of claims 22 to 25 comprising the compound (2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl]propanamide and another therapeutic agent or therapy.

27. A method for the preparation of the compound having the formula (2) as defined in claim 1, or a pharmaceutically acceptable salt or tautomer thereof, which method comprises:

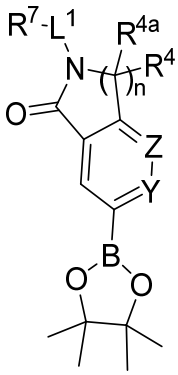
(a) (i) reacting a compound of formula (II):



(II)

with a compound of formula HNR^8R^9 under amide forming conditions; or

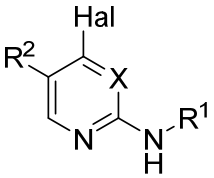
(ii) reacting a compound of formula (III):



(III)

wherein R^{4a} is hydrogen, and Y is CH,

with a compound of formula (IV):

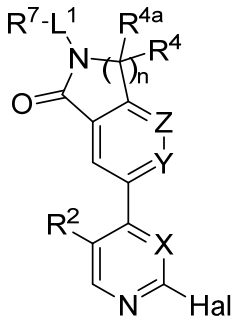


(IV)

wherein Hal is a suitable leaving group,

in the presence of a palladium catalyst; or

(iii) reacting a compound of formula (V):

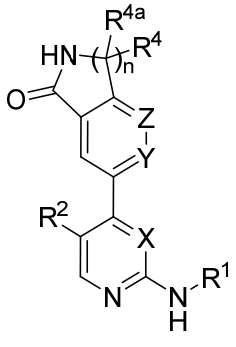


(V)

wherein Hal is a suitable leaving group,

with a compound of formula R^1NH_2; or

(iv) reacting a compound of formula (VI):



(VI)

with a compound of formula R^7L^1-J, wherein J is a suitable leaving group; and/or

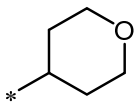
(b) deprotecting a protected derivative of a compound of formula (2); and/or

(c) interconverting a compound of formula (2) or protected derivative thereof to a further compound of formula (2) or protected derivative thereof; and

(d) optionally forming a pharmaceutically acceptable salt of a compound of formulae (2) or (5).

wherein R^1, R^2, R^4, R^7, R^8, R^9, n, L^1, X, Y and Z are as defined in claim 1 and wherein R^{4a} is hydrogen, X is N and Y is CH.

28. The method of claim 27 wherein R^1 is a group AA:



AA.

29. The method of claim 27 or 28 wherein R^2 is chlorine.

30. The method of any one of claims 27 to 29 wherein Z is C-R^z where R^z is hydrogen.

31. The method of any one of claims 27 to 30 wherein R^4 is hydrogen.

32. The method of any one of claims 27 to 31 wherein R^3 is L^1-R^7 wherein L^1 is Alk^2 or Alk^2-C(=O).

33. The method of claim 32 wherein Alk^2 is $CH(CH_3)$.

34. The method of claim 33 wherein R^7 is an acyclic C_{1-8} hydrocarbon group optionally substituted with one or more substituents selected from hydroxy; oxo; halogen; cyano; carboxy; amino; mono- or di-C_{1-4} alkylamino; and carbocyclic and heterocyclic groups having from 3 to 12 ring members, of which 0, 1, 2 or 3 are heteroatom ring members selected from O, N and S and oxidised forms of S, the carbocyclic or heterocyclic group being optionally substituted with one or more substituents R^{10}; wherein one or two but not all of the carbon atoms of the acyclic C_{1-8} hydrocarbon group may optionally be replaced by O, S, SO, SO_2 or NR^{11}.

35. The method of any one of claims 27 to 34 wherein process (a)(i) comprises reacting the compound of formula (II) with the compound of formula HNR^8R^9 in the presence of an amide coupling agent selected from HATU, TBTU, HBTU, and 1-propanephosphonic anhydride.

36. The method of any one of claims 27 to 34 wherein process (a)(ii) comprises reacting the compound of formula (III) with the compound of formula (IV) in the presence of the palladium catalyst and a base in a solvent.

37. The method of any one of claims 27 to 36 wherein:

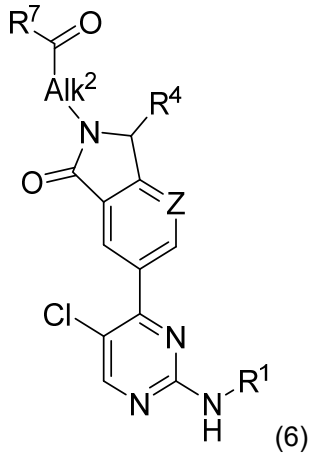
- in formula (IV), Hal is a halide; and
- in formula (V), Hal is a halide.

38. The method of claim 37 wherein:

- in formula (IV), Hal is chloro; and
- in formula (V), Hal is chloro.

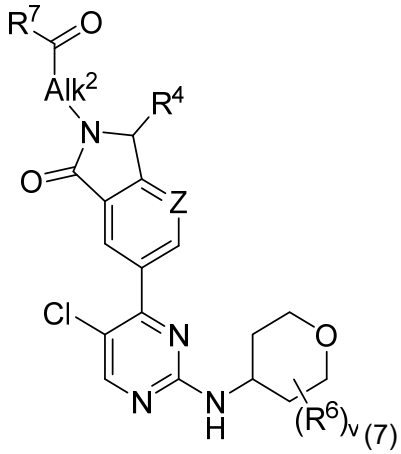
39. The method of any one of claims 27 to 38 for the preparation of a compound selected from:

(a) a compound having the formula (6):



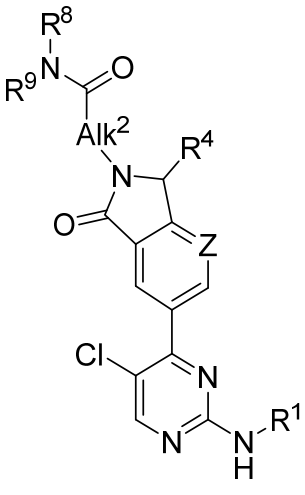
or a pharmaceutically acceptable salt or tautomer thereof;

(b) a compound having the formula (7):



or a pharmaceutically acceptable salt or tautomer thereof, wherein v is 0, 1, 2 or 3; and

(c) a compound having the formula (8):

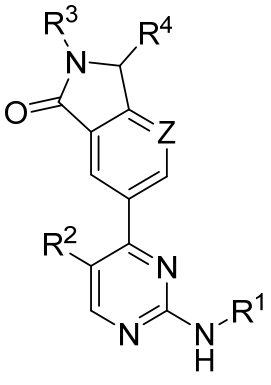


(8)

or a pharmaceutically acceptable salt or tautomer thereof.

40. The method of claim 39 wherein said method comprises the process (a)(ii), which comprises reacting the compound of formula (III) with the compound of formula (IV) in the presence of the palladium catalyst and a base in a solvent.

41. The method of any one of claims 27 to 40 for the preparation of a compound wherein n is 1, said compound having the formula (3):



(3)

or a pharmaceutically acceptable salt or tautomer thereof.

42. The method of any one of claims 27 or 35 to 38 for the preparation of a compound selected from:

(2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl]propanamide;

(2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-2-hydroxy-1-(2-methoxypyridin-4-yl)ethyl]propanamide;

(R)-2-(6-(5-chloro-2-((2-methoxypyridin-4-yl)amino)pyrimidin-4-yl)-1-oxoisoindolin-2-yl)-N-((S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl)propanamide;

(R)-2-(6-(5-chloro-2-((2-methylpyrimidin-4-yl)amino)pyrimidin-4-yl)-1-oxoisoindolin-2-yl)-N-((S)-1-(6-(dimethylamino)pyridin-2-yl)-2-hydroxyethyl)propanamide;

(2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-2-hydroxy-1-[6-(4-methylpiperazin-1-yl)pyridin-2-yl]ethyl]propanamide; and

(2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1R)-1-[3-fluoro-5-(4-methylpiperazin-1-yl)phenyl]ethyl]propanamide; and

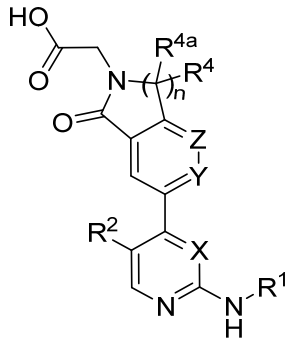
pharmaceutically acceptable salts thereof.

43. The method of claim 42 for the preparation of (2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl]propanamide or a pharmaceutically acceptable salt thereof.

44. The method of claim 42 for the preparation of (2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl]propanamide.

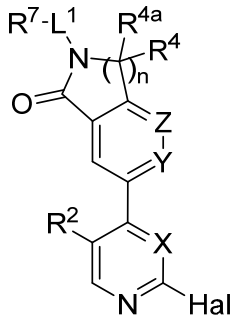
45. A compound selected from a compound of:

(i) formula (II):



(II);

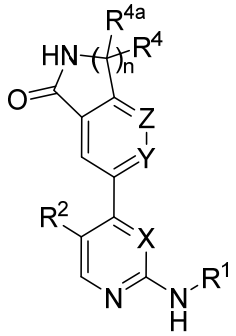
(ii) formula (V):



(V)

wherein Hal is a suitable leaving group such as halide; or

(iii) formula (VI):

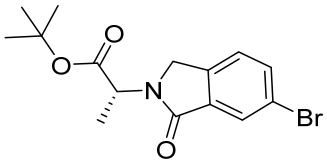


(VI);

wherein R^1, R^2, R^4, R^7, L^1, n, X, Y and Z are as defined in claim 1 and wherein R^{4a} is hydrogen, X is N and Y is CH.

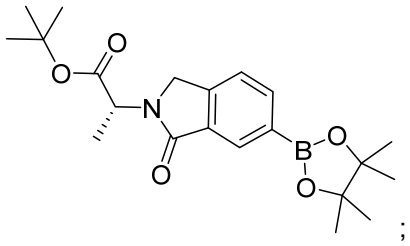
46. A compound selected from:

(i) (R)-tert-butyl 2-(6-bromo-1-oxoisoindolin-2-yl)propanoate having the formula:



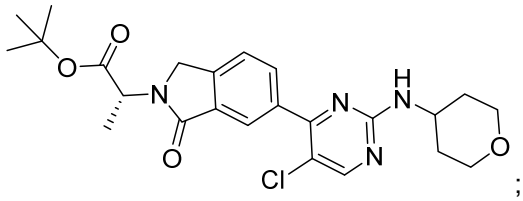
;

(ii) tert-butyl (2R)-2-[1-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-isoindol-2-yl]propanoate having the formula:



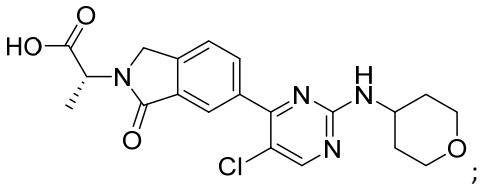
;

(iii) tert-butyl (2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)propanoate having the formula:



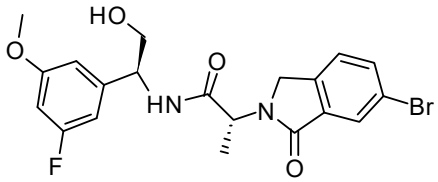
;

(iv) (2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)propanoic acid having the formula:



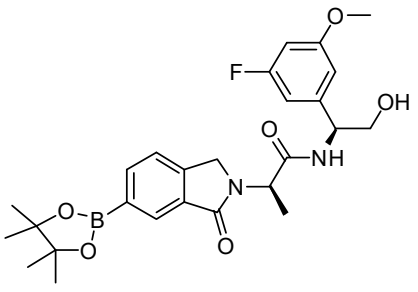
;

(v) (*R*)-2-(6-bromo-1-oxoisoindolin-2-yl)-*N*-((*S*)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl)propanamide having the formula:



; and

(vi) (*R*)-*N*-((*S*)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl)-2-(1-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoindolin-2-yl)propanamide having the formula:



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47. The use of (2R)-2-(6-{5-chloro-2-[(oxan-4-yl)amino]pyrimidin-4-yl}-1-oxo-2,3-dihydro-1H-isoindol-2-yl)-N-[(1S)-1-(3-fluoro-5-methoxyphenyl)-2-hydroxyethyl]propanamide or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer.