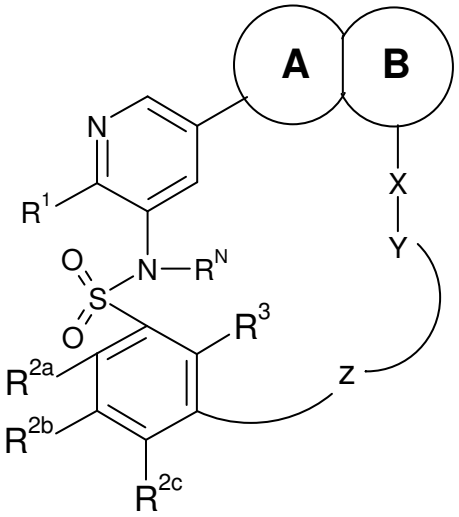
CLAIMS

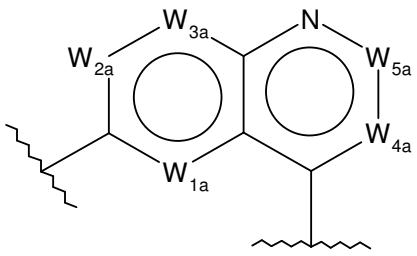
1. A compound of formula I,



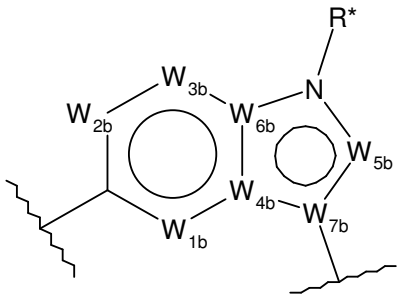
I

wherein:

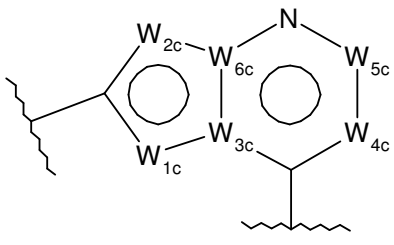
ring A and ring B represent a fused bicyclic group of any one of the following formulae:



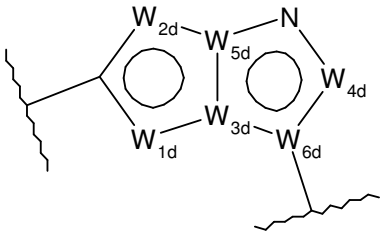
IA



IB



IC



ID

wherein

in formula IA: W^{1a} is CH, CF or N; W^{2a} is CH, CF or N; W^{3a} is CR^{4a} or N; W^{4a} is CR^{5a} or N; W^{5a} is CR^{6a} or N;

in formula IB: W^{1b} is CH, CF or N; W^{2b} is CH, CF or N; W^{3b} is CR^{4b} or N; W^{4b} is C or N; W^{5b} is CR^{6b} or N; W^{6b} is C or N; W^{7b} is C or N, and wherein when W^{3b} represents N, W^{4b} and W^{6b} represent C and W^{5b} represents C or N, then R* is hydrogen (in all other cases R* is absent);

in formula IC: W^{1c} is CH, CR^{t1}, N, NR^{q1}, O or S; W^{2c} is CH, CR^{t2}, N, NR^{q2}, O or S; W^{3c} is C or N; W^{4c} is CR^{5c} or N; W^{5c} is CR^{6c} or N; W^{6c} is C or N;

in formula ID: W^{1d} is CH, CR^{t3}, N, NR^{q3}, O or S; W^{2d} is CH, CR^{t4}, N, NR^{q4}, O or S; W^{3d} is C or N; W^{4d} is CR^{5d} or N; W^{5d} is C or N; W^{6d} is C or N;

each R^{t1}, R^{t2}, R^{t3} and R^{t4} is independently selected from halo, C_{1-3} alkyl (e.g. acyclic C_{1-3} alkyl or cyclopropyl), a 3- to 5-membered heterocycloalkyl group, $-OR^{s1}$, -CN, $-N(R^{s2})R^{s3}$, $-S(O)_{w1}CH_3$ or $-C(O)CH_3$;

w1 represents 0, 1 or 2;

each R^{s1}, R^{s2} and R^{3s} independently represent hydrogen or C_{1-2} alkyl;

each R^{q1}, R^{q2}, R^{q3} and R^{q4} is independently selected from C_{1-3} alkyl (e.g. acyclic C_{1-3} alkyl or cyclopropyl), a 3- to 5-membered heterocycloalkyl group or $-C(O)CH_3$;

each R^1, R^{2a}, R^{2b}, R^{2c}, R^3, R^{4a}, R^{5a}, R^{6a}, R^{4b}, R^{6b}, R^{5c}, R^{6c} and R^{5d} are independently selected from hydrogen or a substituent selected from halo, -CN, $-C(O)N(R^{f1})R^{f2}$, $-C(O)R^{f3}$, $-N(R^{f4})R^{f5}$, $-C(O)OR^{f6}$, $-OR^{f7}$, $-OC(O)-R^{f8}$, $-S(O)_{w2}CH_3$ or C_{1-8} alkyl (e.g. acyclic C_{1-6} alkyl or C_{3-7} cycloalkyl) and a 3- to 8-membered heterocycloalkyl groups, both of which (i.e. alkyl and heterocycloalkyl groups) are optionally substituted by one or more substituents selected from =O and E^1;

w2 represents 0, 1 or 2;

R^{f1}, R^{f2}, R^{f4}, R^{f5} and R^{f7} independently represent hydrogen or C_{1-6} alkyl optionally substituted by one or more substituents selected from =O and E^2; or

R^{f1} and R^{f2} and/or R^{f4} and R^{f5} may be linked together to form a 4- to 8- (e.g. 5- to 6-) membered ring optionally substituted by one or more substituents selected from C_{1-3} alkyl and halo;

R^{f3}, R^{f6} and R^{f8} independently represent C_{1-6} alkyl optionally substituted by one or more substituents selected from =O and E^2;

X represents a direct bond, $-C(R^a)(R^b)-$, -O-, -S-, $-N(R^c)-$, $-N(R^d)C(O)-$, $-C(O)N(R^e)-$ or $-N(R^f)-C(O)-N(R^g)-$;

Y represents -arylene-, -heteroarylene- (which latter two groups are optionally substituted by one or more substituents selected from E^3), -heterocycloalkylene- or -C_{1-12}alkylene- (which latter two groups are optionally substituted by one or more substituents selected from =O and E^4);

R^N represents hydrogen or C_{1-6} alkyl optionally substituted by one or more substituents selected from =O and E^5;

Z represents $-(A^x)_{1-7}-$, wherein each A^x independently represents $-C(R^{x1})(R^{x2})-$, $-N(R^{x3})-$, -C(O)-, -O-, -S-, -S(O)- or $-S(O)_2-$;

R^{x1}, R^{x2} and R^{x3} each independently represent hydrogen or a substituent selected from E_x;

each E_x independently represents halo, $-C(O)R^{y1}$, $-N(R^{y2})-C(O)-N(R^{y3})(R^{y4})$, C_{1-6} alkyl or heterocycloalkyl (both of which latter two groups are optionally substituted by one or more halo atoms);

R^{y1}, R^{y2}, R^{y3} and R^{y4} each independently represent hydrogen or C_{1-3} alkyl optionally substituted by one or more halo atoms;

each R^a, R^b, R^c, R^d, R^e, R^f and R^g independently represent hydrogen or C_{1-6} alkyl optionally substituted by one or more halo atoms;

each E^1, E^2, E^3, E^4 and E^5 independently represents, on each occasion when used herein:
(i) Q^4;

(ii) C_{1-12} alkyl or heterocycloalkyl, both of which are optionally substituted by one or more substituents selected from =O and Q^5;

any two E^1, E^2, E^3, E^4 and/or E^5 groups (for example on C_{1-12} alkyl groups, e.g. when they are attached to the same or adjacent carbon atoms, or, on aromatic groups, when attached to adjacent atoms), may be linked together to form a 3- to 12-membered ring, optionally containing one or more (e.g. one to three) unsaturations (preferably, double bonds), and which ring is optionally substituted by one or more substituents selected from =O and J^1;

each Q^4 and Q^5 independently represent, on each occasion when used herein:
halo, -CN, $-N(R^{20})R^{21}$, $-OR^{20}$, $-C(=Y^1)-R^{20}$, $-C(=Y^1)-OR^{20}$, $-C(=Y^1)N(R^{20})R^{21}$, $-C(=Y^1)N(R^{20})-O-R^{21a}$, $-OC(=Y^1)-R^{20}$, $-OC(=Y^1)-OR^{20}$, $-OC(=Y^1)N(R^{20})R^{21}$, $-OS(O)_2OR^{20}$, $-OP(=Y^1)(OR^{20})(OR^{21})$, $-OP(OR^{20})(OR^{21})$, $-N(R^{22})C(=Y^1)R^{21}$, $-N(R^{22})C(=Y^1)OR^{21}$, $-N(R^{22})C(=Y^1)N(R^{20})R^{21}$, $-NR^{22}S(O)_2R^{20}$, $-NR^{22}S(O)_2N(R^{20})R^{21}$, $-S(O)_2N(R^{20})R^{21}$, $-SC(=Y^1)R^{20}$, $-SC(=Y^1)OR^{20}$, $-SC(=Y^1)N(R^{20})R^{21}$, $-S(O)_2R^{20}$, $-SR^{20}$, $-S(O)R^{20}$, $-S(O)_2OR^{20}$, C_{1-6} alkyl or heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from =O and J^2);

each Y^1 independently represents, on each occasion when used herein, =O, =S, $=NR^{23}$ or =N-CN;

each R^{21a} represents C_{1-6} alkyl or heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from J^4 and =O);

each R^{20}, R^{21}, R^{22} and R^{23} independently represent, on each occasion when used herein, hydrogen, C_{1-6} alkyl or heterocycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from J^4 and =O); or

any relevant pair of R^{20}, R^{21} and R^{22}, may (for example, when attached to the same atom, adjacent atom (i.e. 1,2-relationship) or to atoms that are two atoms apart, i.e. in a 1,3-relationship) be linked together to form (e.g. along with the requisite nitrogen atom to which they may be attached) a 4- to 20- (e.g. 4- to 12-) membered ring, optionally containing one or more heteroatoms (for example, in addition to those that may already be present, e.g. (a) heteroatom(s) selected from oxygen, nitrogen and sulfur), optionally containing one or more unsaturations (preferably, double bonds),

and which ring is optionally substituted by one or more substituents selected from J^6 and =O;

each J^1, J^2, J^4 and J^6 independently represents, on each occasion when used herein:
(i) Q^7;
(ii) C_{1-6} alkyl or heterocycloalkyl, both of which are optionally substituted by one or more substituents selected from =O and Q^8;

each Q^7 and Q^8 independently represents, on each occasion when used herein:
halo, -CN, $-N(R^{50})R^{51}$, $-OR^{50}$, $-C(=Y^a)-R^{50}$, $-C(=Y^a)-OR^{50}$, $-C(=Y^a)N(R^{50})R^{51}$, $-N(R^{52})C(=Y^a)R^{51}$, $-NR^{52}S(O)_2R^{50}$, $-S(O)_2N(R^{50})R^{51}$, $-N(R^{52})-C(=Y^a)-N(R^{50})R^{51}$, $-S(O)_2R^{50}$, $-SR^{50}$, $-S(O)R^{50}$, C_{1-6} alkyl (optionally substituted by one or more fluoro atoms) or heterocycloalkyl (optionally substituted by one or more substituents selected from halo, $-OR^{60}$ and $-N(R^{61})R^{62}$);

each Y^a independently represents, on each occasion when used herein, =O, =S, $=NR^{53}$ or =N-CN;

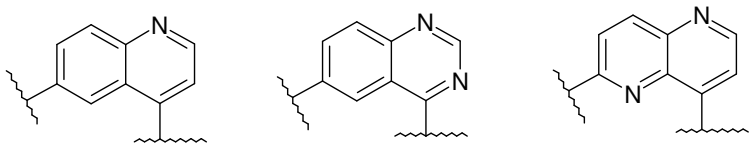
each R^{50}, R^{51}, R^{52} and R^{53} independently represents, on each occasion when used herein, hydrogen or C_{1-6} alkyl optionally substituted by one or more substituents selected from fluoro, $-OR^{60}$ and $-N(R^{61})R^{62}$; or
any relevant pair of R^{50}, R^{51} and R^{52} may (for example when attached to the same or adjacent atoms) be linked together to form, a 3- to 8-membered ring, optionally containing one or more heteroatoms (for example, in addition to those that may already be present, heteroatoms selected from oxygen, nitrogen and sulfur), optionally containing one or more unsaturations (preferably, double bonds), and which ring is optionally substituted by one or more substituents selected from =O and C_{1-3} alkyl;

R^{60}, R^{61} and R^{62} independently represent hydrogen or C_{1-6} alkyl optionally substituted by one or more fluoro atoms;

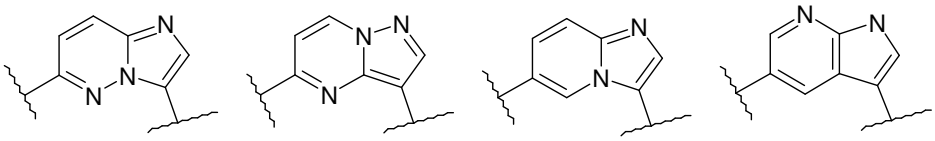
or a pharmaceutically acceptable ester, amide, solvate or salt thereof.

2. A compound as claimed in Claim 1, wherein, ring A and ring B represents a fused bicyclic group of the following structure (optional substituents are not shown):

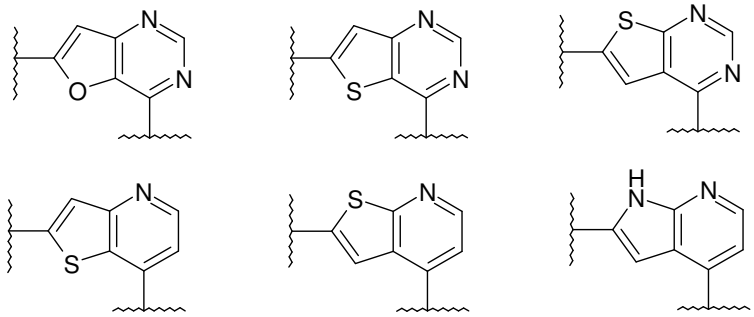
Formula IA:



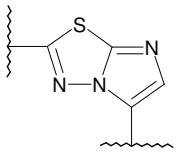
Formula IB:



Formula IC:



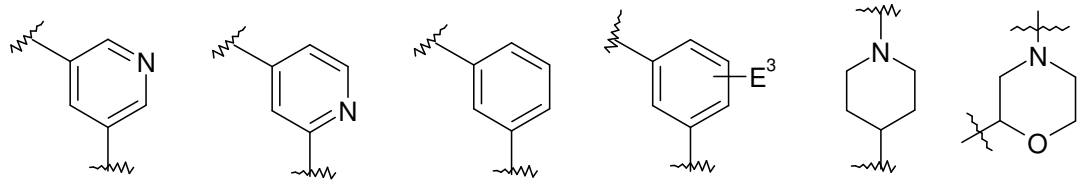
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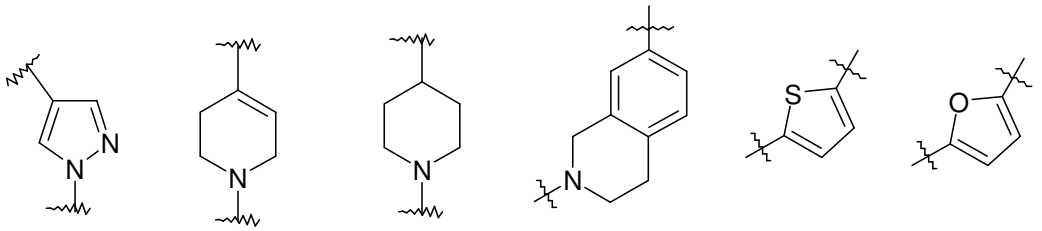
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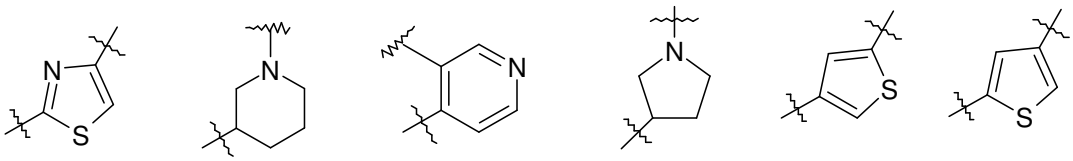
3. A compound as claimed in Claim 1 or Claim 2, wherein

Y represents arylene, heteroarylene, heterocycloalkylene or C_{1-6}alkylene, all of which groups are optionally substituted as defined herein, for instance one of the following groups:



(E^3 = halo, e.g. Cl, F)





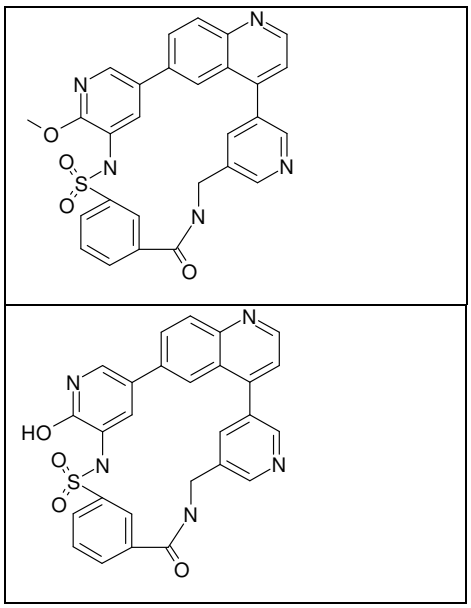
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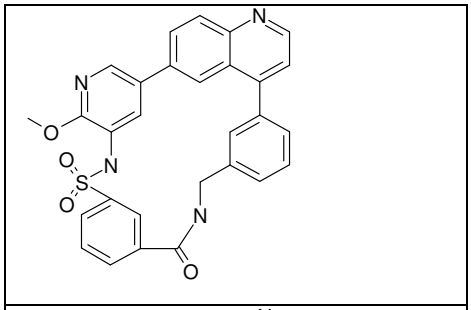
4. A compound as claimed in any one of the preceding claims, wherein

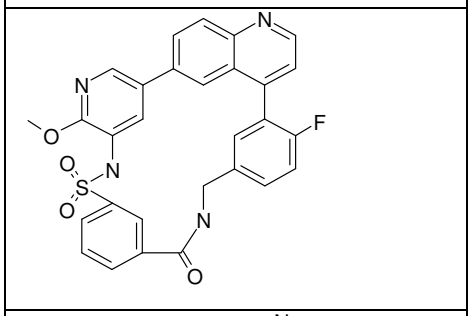
X represents -N(R^c)- or a direct bond; and/or

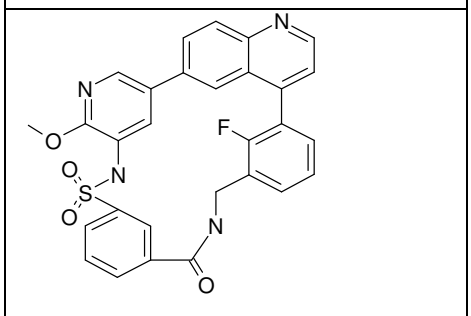
Z represents -C(O)-[T^1]- or -C(O)N(R^{x3})-[T^1]-, in which T^1 represents -$(CH_2)_{0-4}$-T^2- and T^2 represents a direct bond or -C(O)-N(H)-CH_2-.

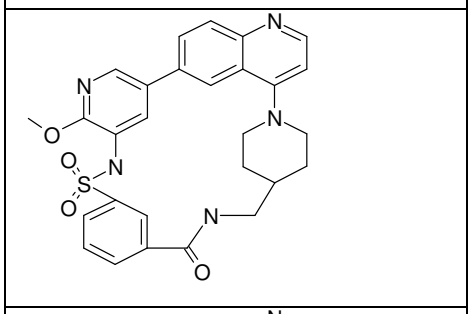
5. A compound according to claim 1, selected from the following:

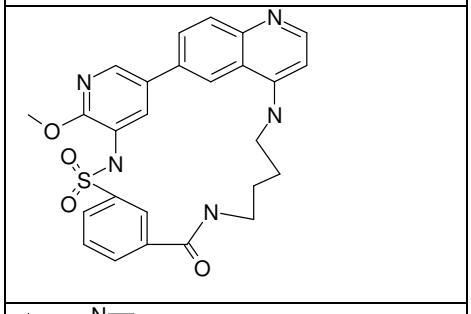


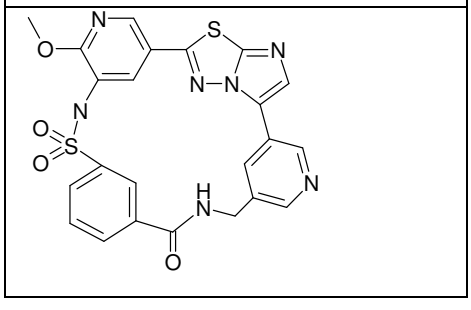


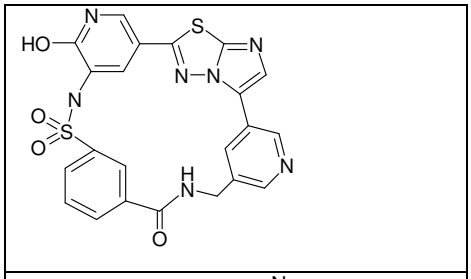


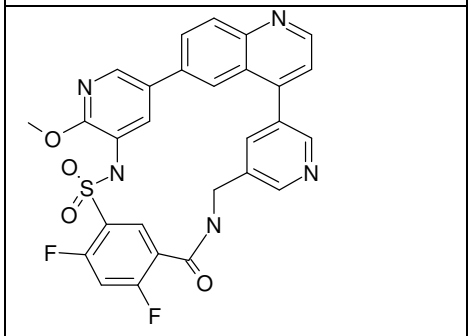


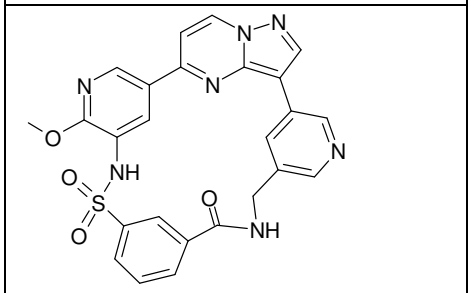


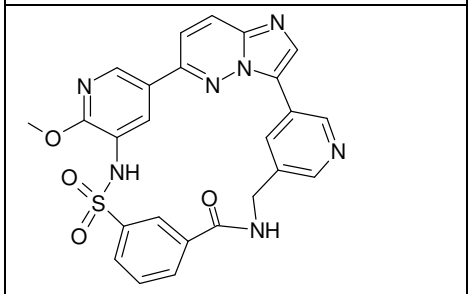


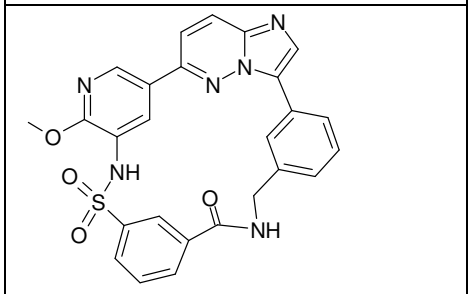


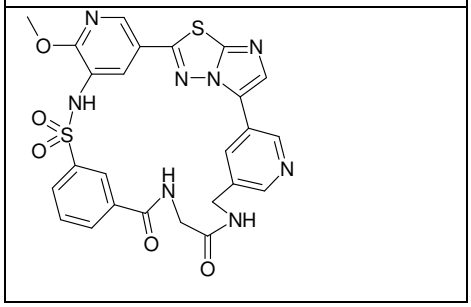


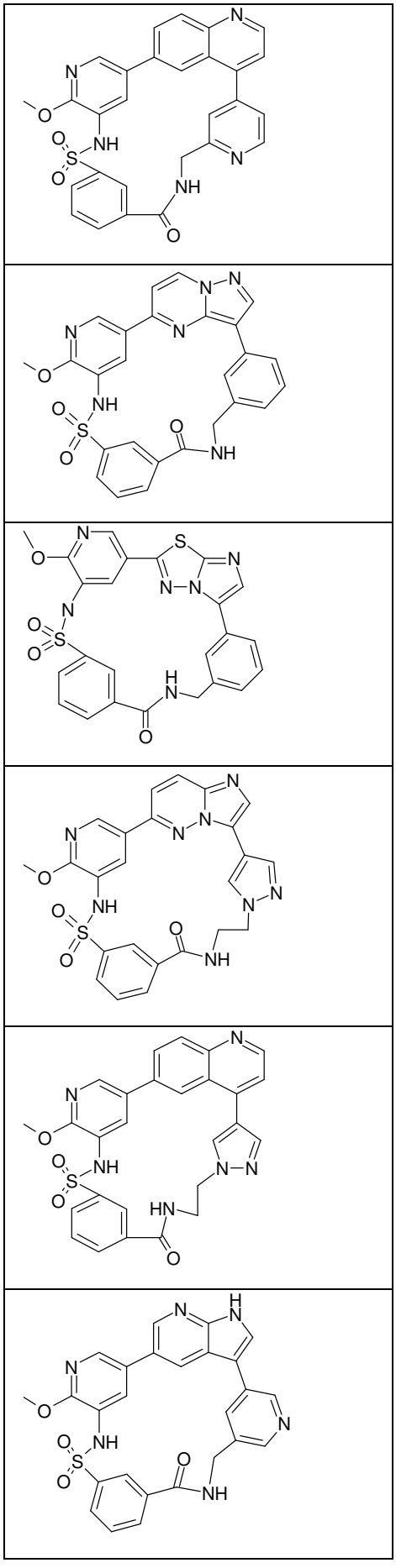


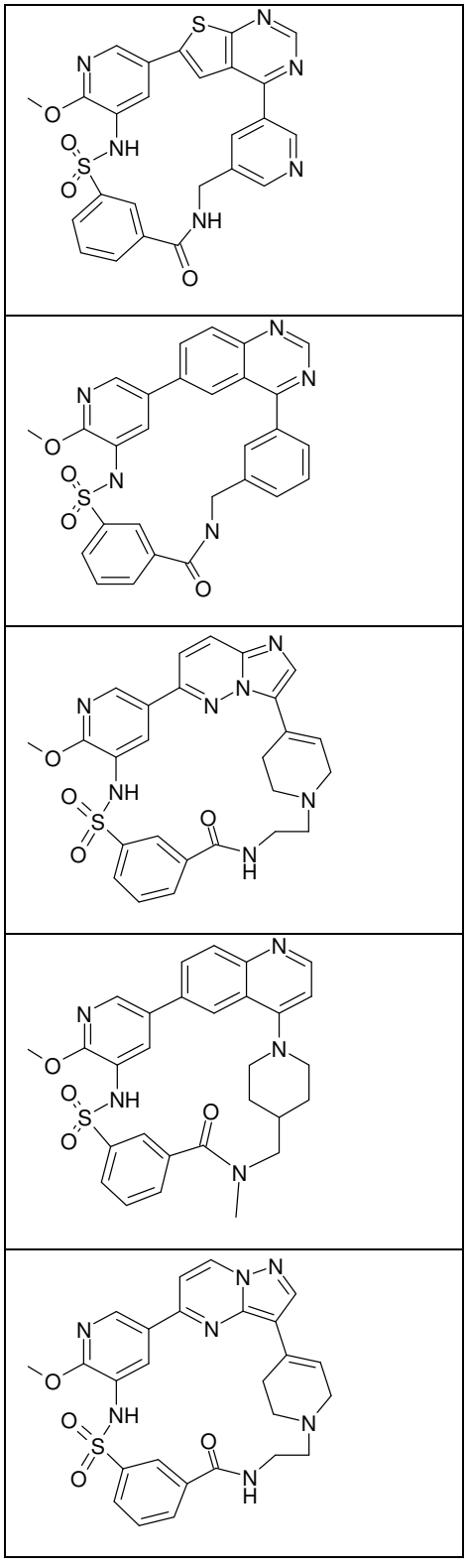


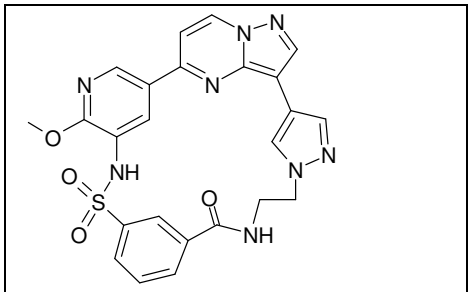


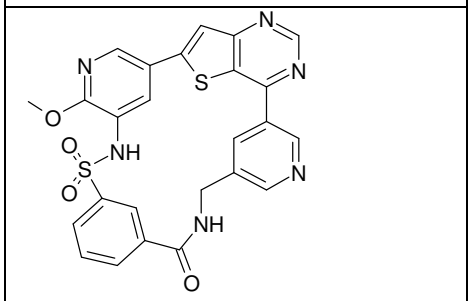


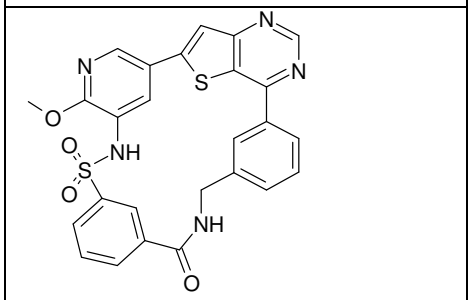


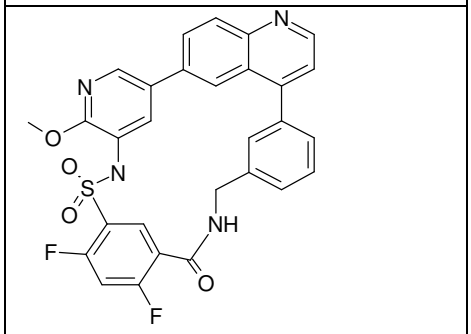


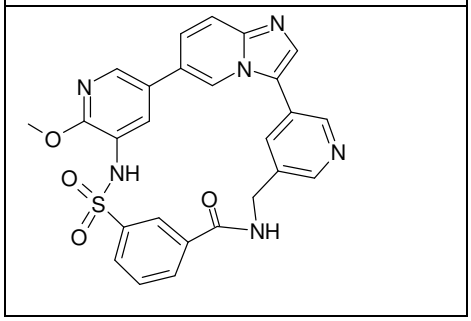


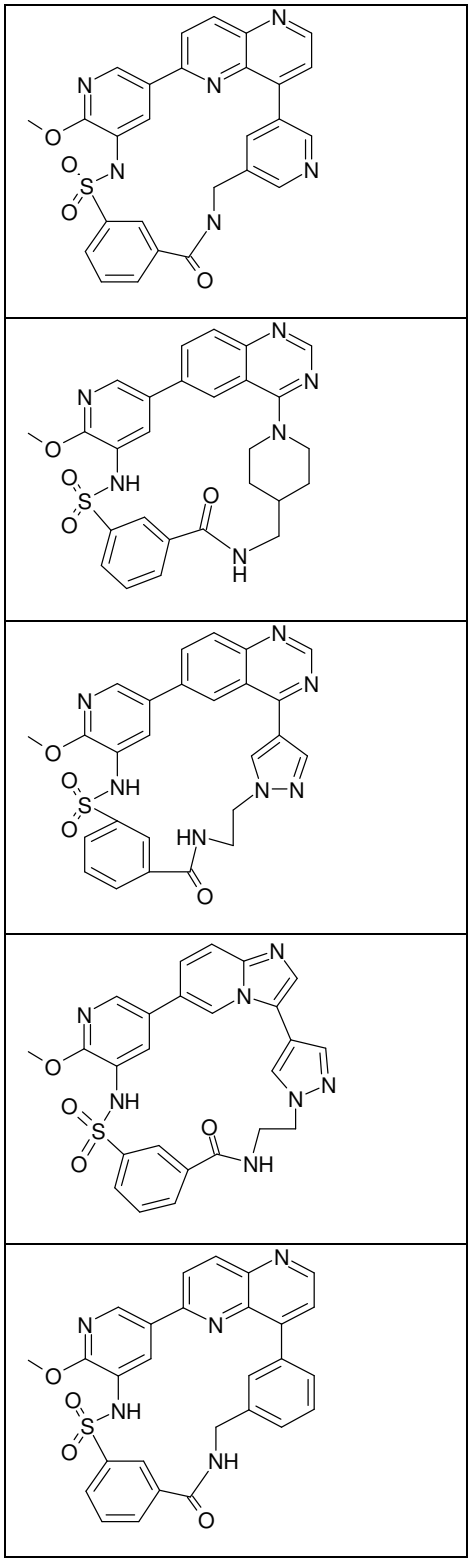


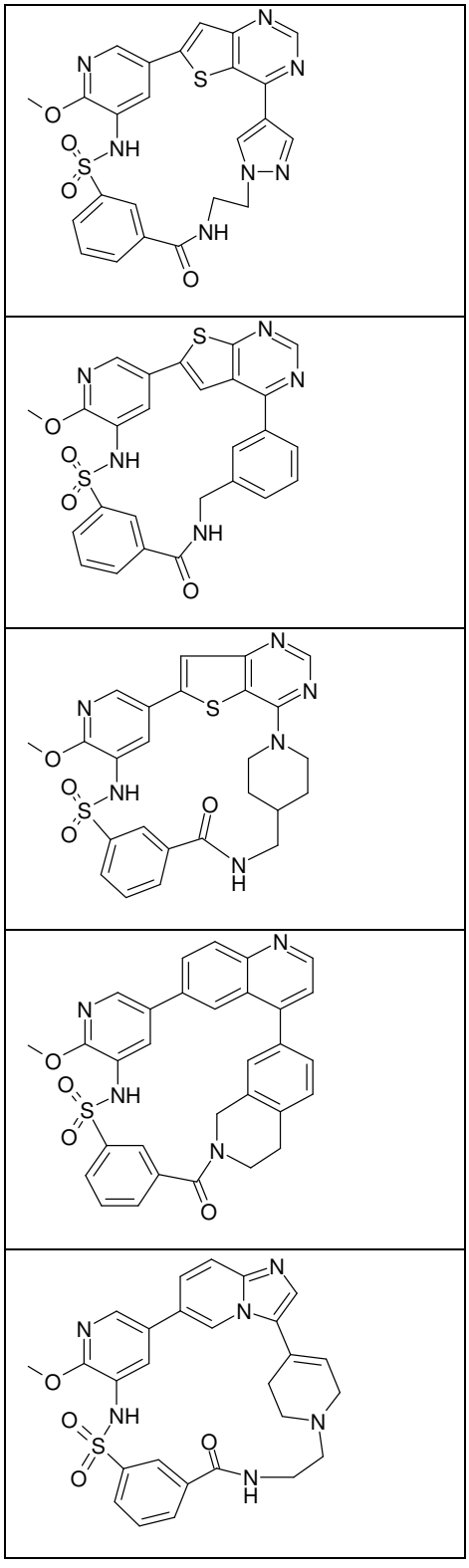


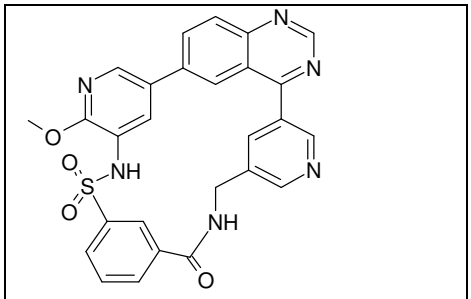


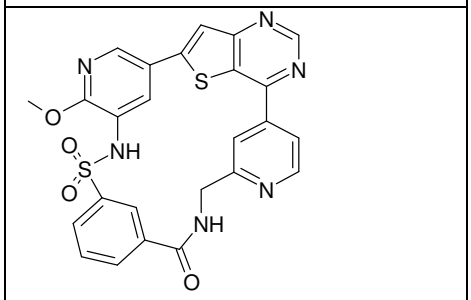


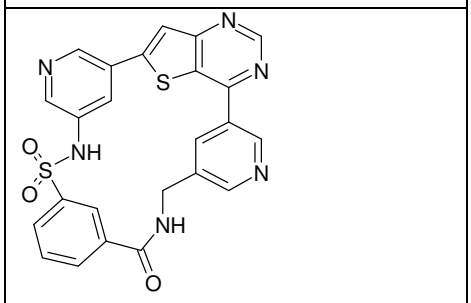


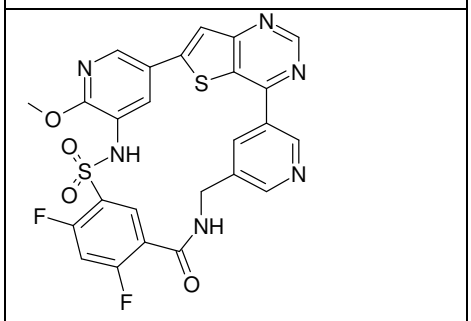


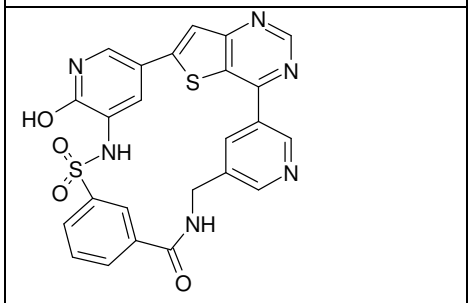


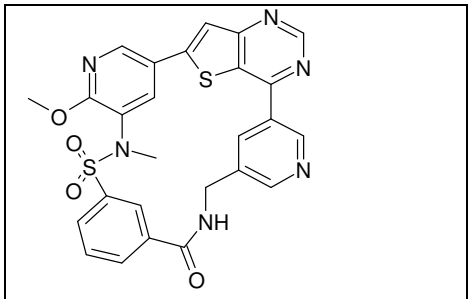


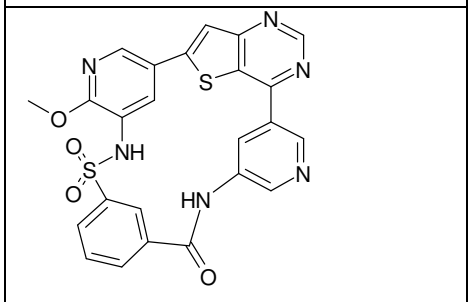


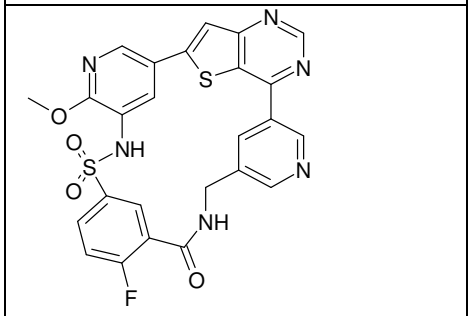


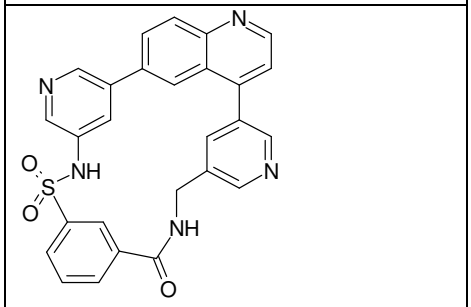


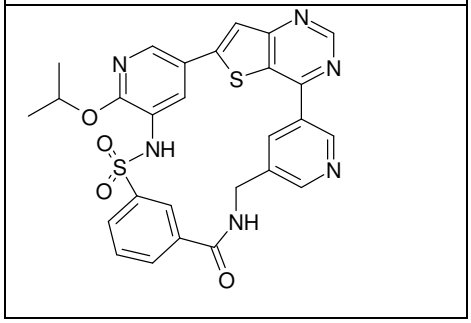


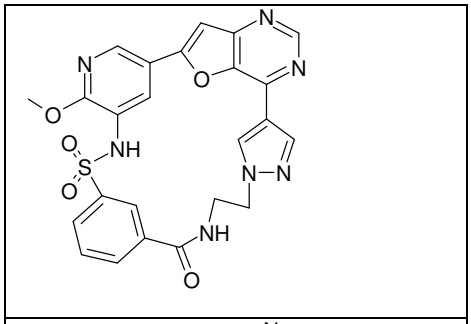


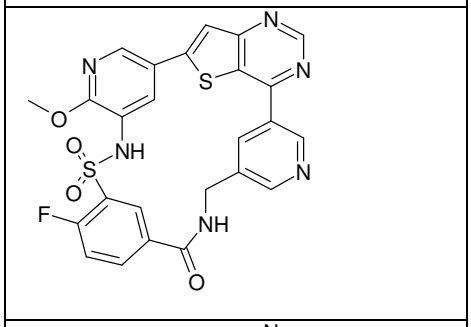


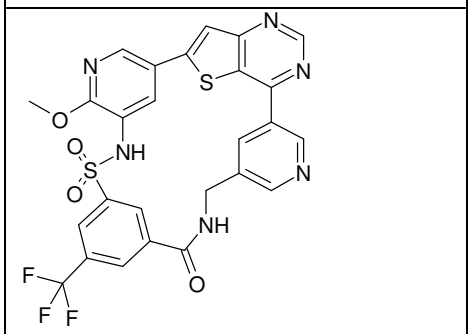


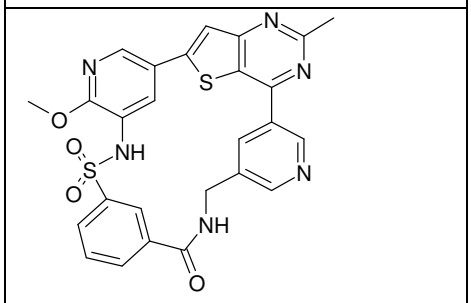


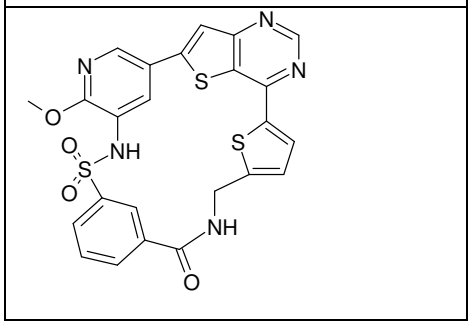


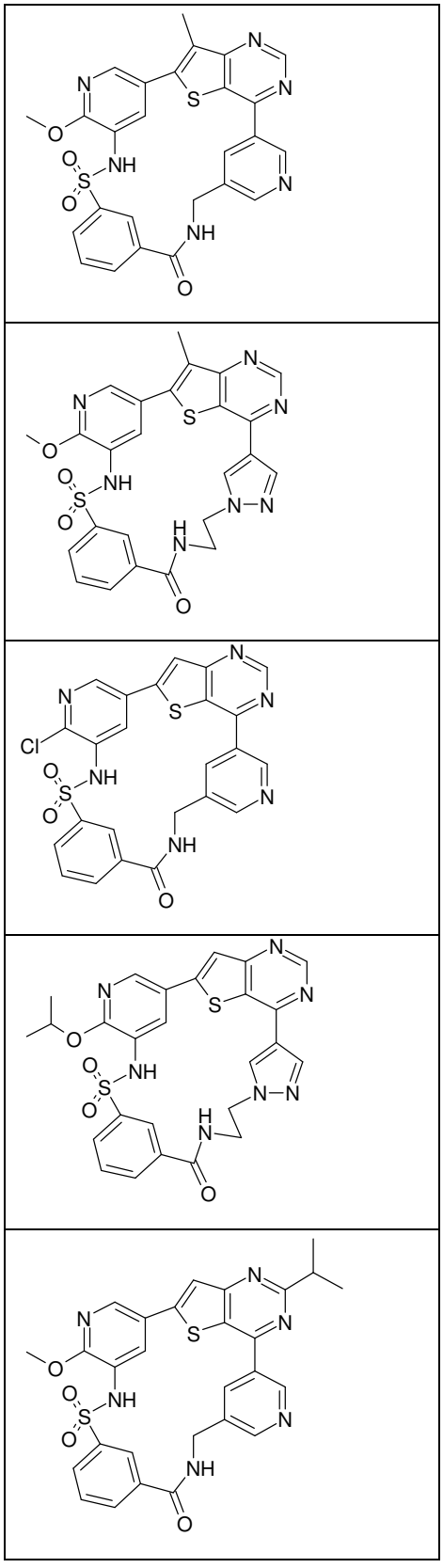


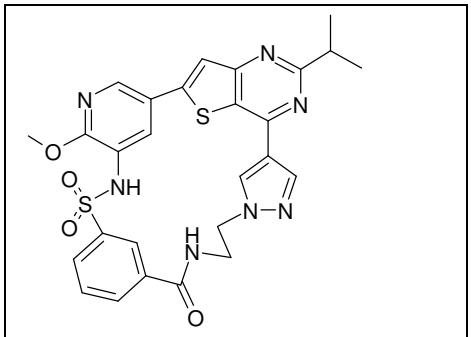


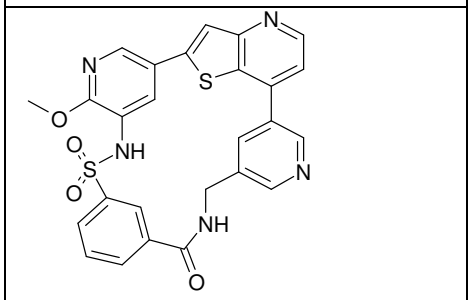


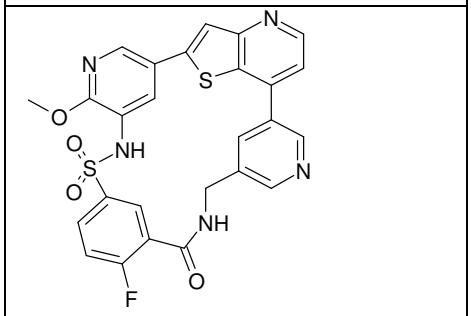


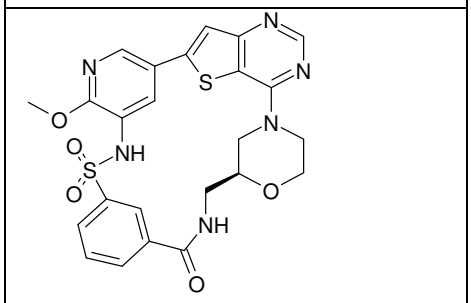


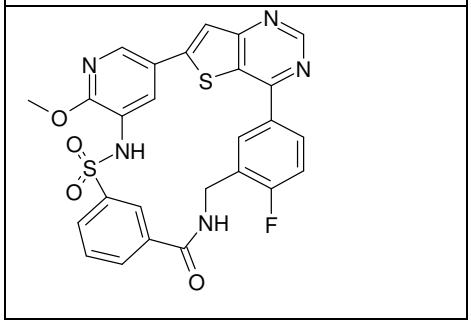


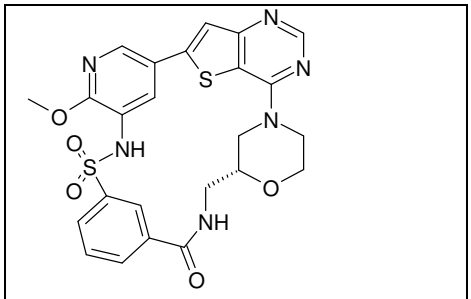


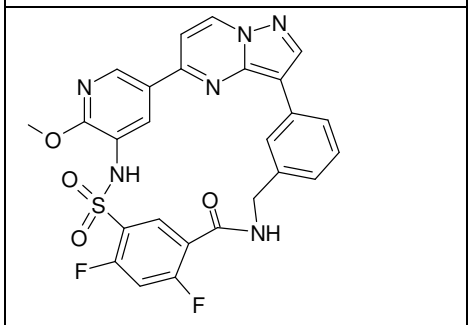


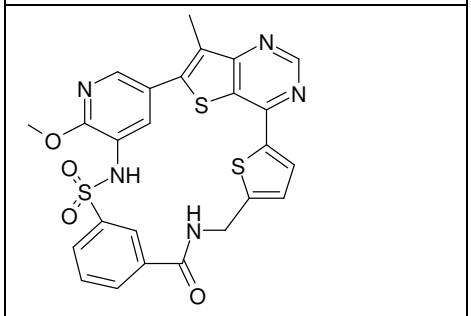


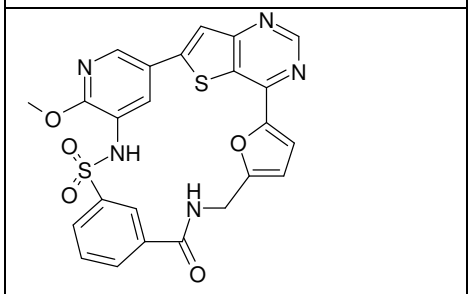


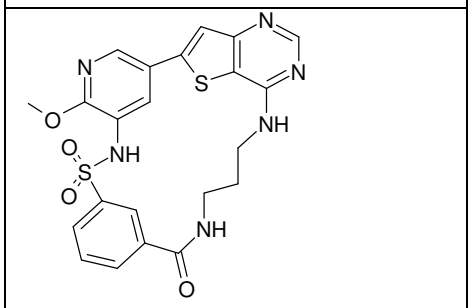


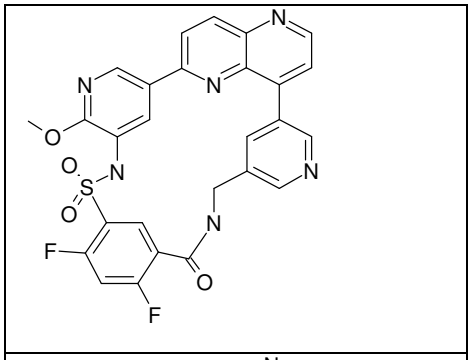


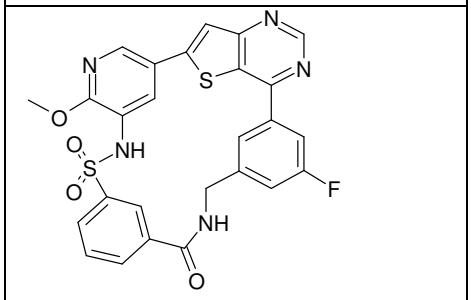


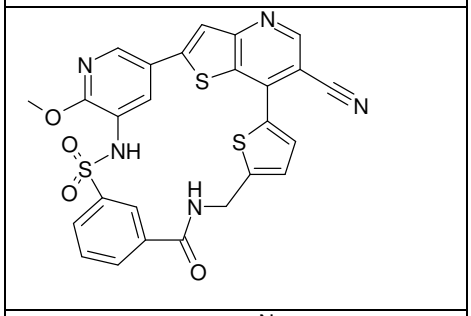


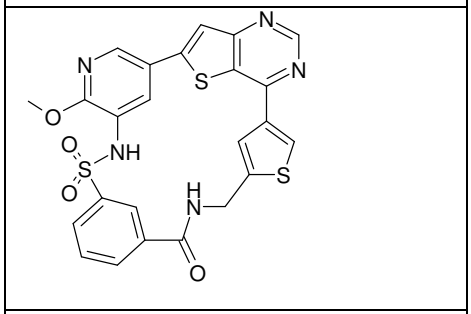


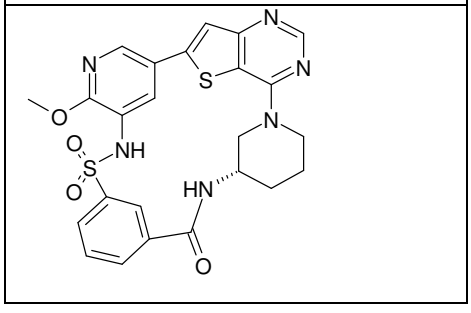


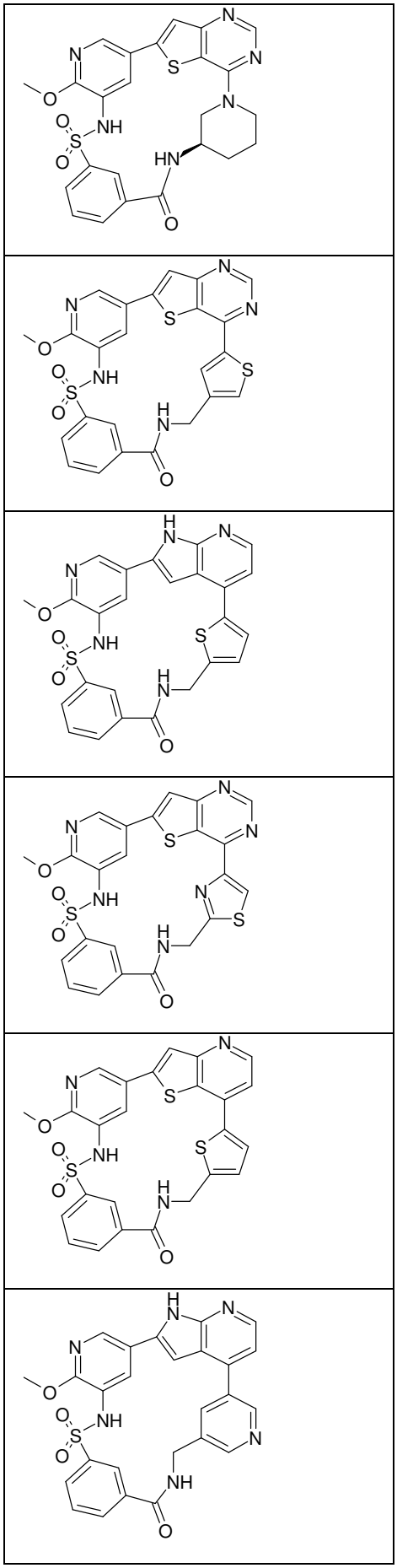


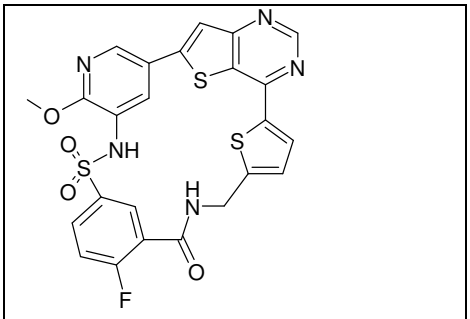


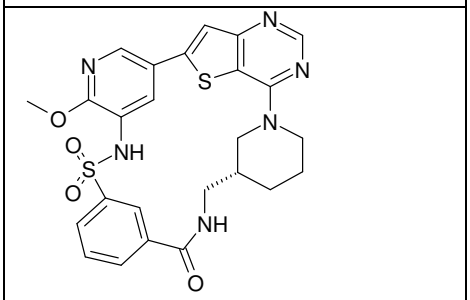


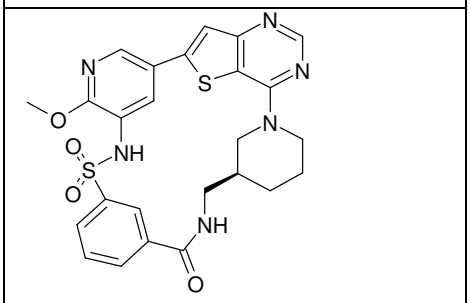


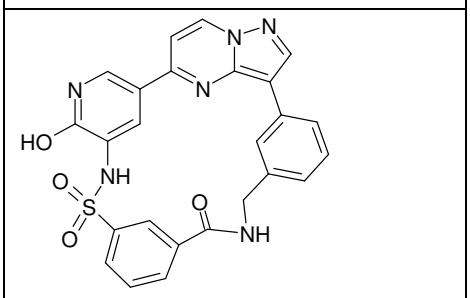


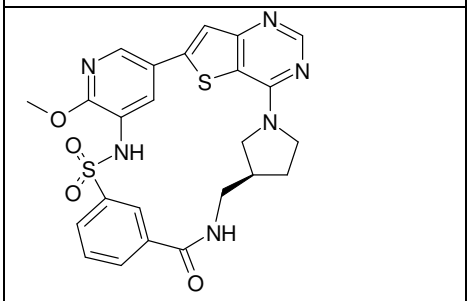


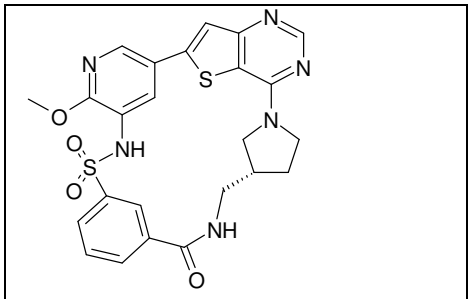


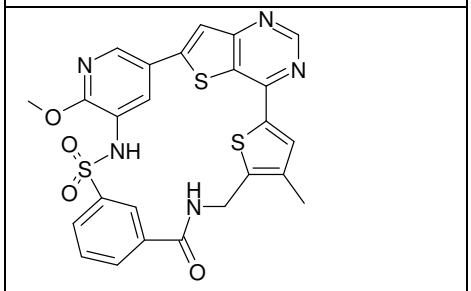


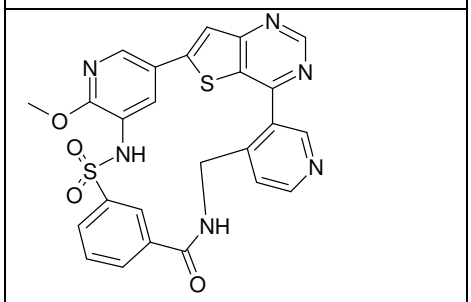


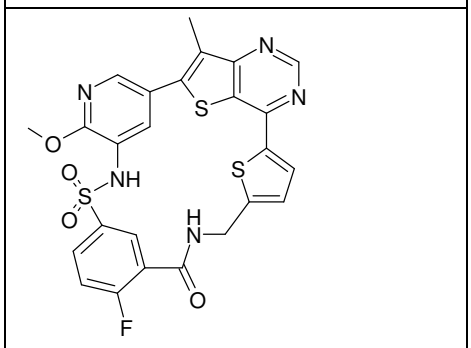


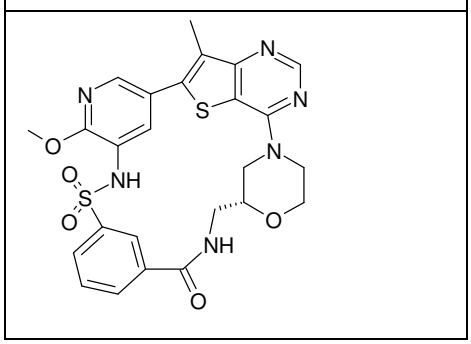


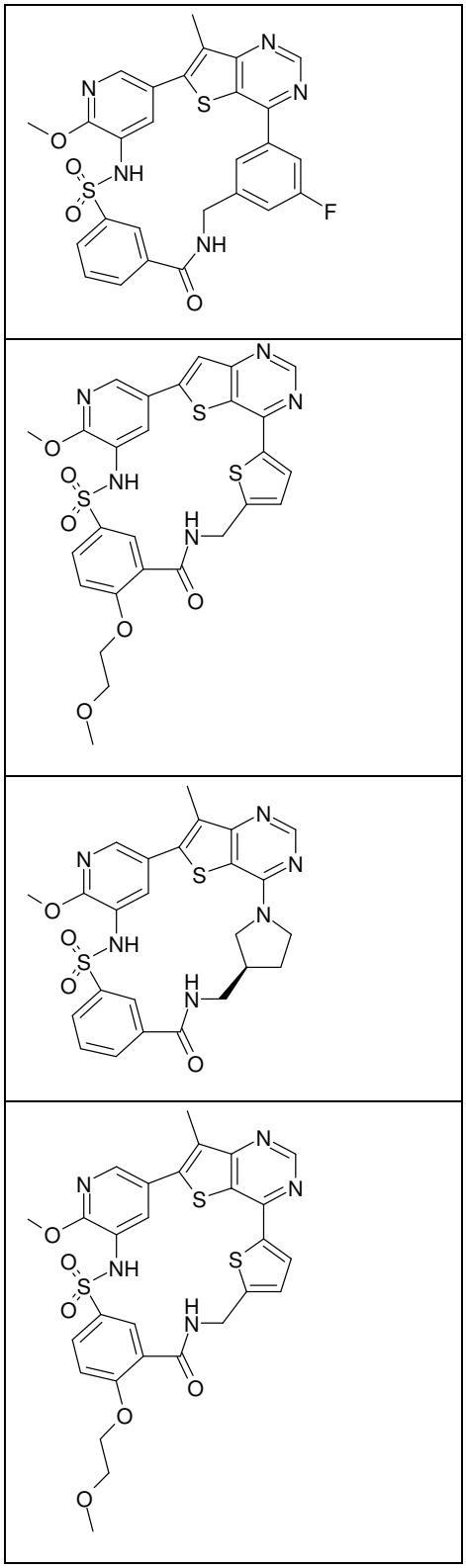


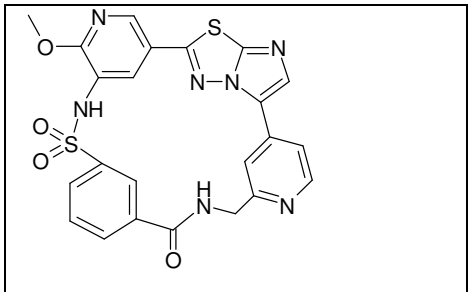


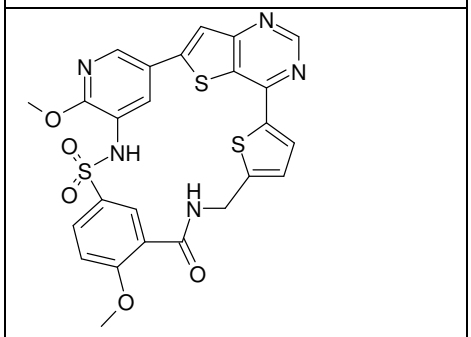


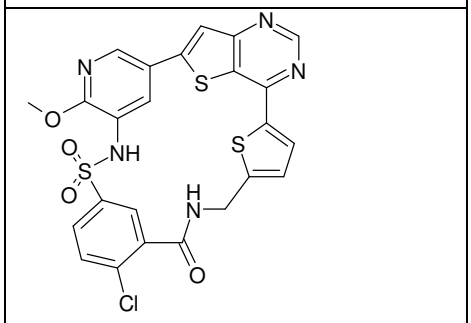


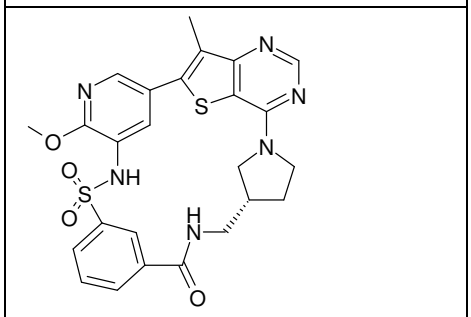


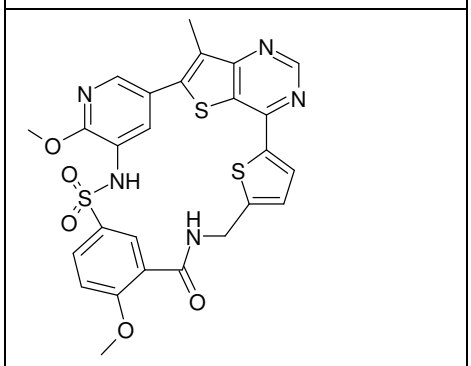


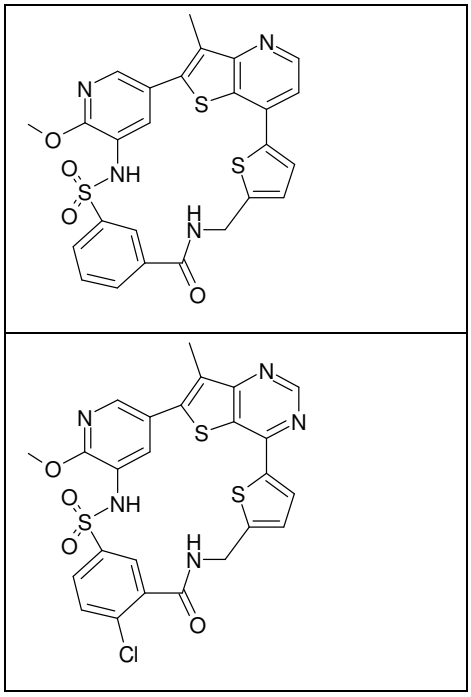












6. A compound of formula I as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable ester, amide, solvate or salt thereof, for use as a pharmaceutical.

7. A pharmaceutical formulation including a compound of formula I, as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable ester, amide, solvate or salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

8. A compound, as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable ester, amide, solvate or salt thereof, for use in the treatment of a disease in which inhibition of a PI3-K, a PIM family kinase and/or mTOR is desired and/or required.

9. Use of a compound of formula I, as defined in any one of Claims 1 to 5, or a pharmaceutically acceptable ester, amide, solvate or salt thereof, for the manufacture of a medicament for the treatment of a disease in which inhibition of a PI3-K, a PIM family kinase and/or mTOR is desired and/or required.

10. A compound for use as claimed in Claim 8 or a use as claimed in Claim 9, wherein the disease is cancer, an immune disorder, a cardiovascular disease, a viral infection, inflammation, a metabolism/endocrine function disorder, a neurological

disorder, an obstructive airways disease, an allergic disease, an inflammatory disease, immunosuppression, a disorder commonly connected with organ transplantation, an AIDS-related disease, benign prostate hyperplasia, familial adenomatosis, polyposis, neuro-fibromatosis, psoriasis, a bone disorder, atherosclerosis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis glomerulonephritis and post-surgical stenosis, restenosis, stroke, diabetes, hepatomegaly, Alzheimer's disease, cystic fibrosis, a hormone-related disease, an immunodeficiency disorder, a destructive bone disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, chronic myelogenous leukaemia, liver disease, a pathologic immune condition involving T cell activation, CNS disorders, pulmonary artery hypertension (PAH), and other associated diseases.

11. A compound for use as claimed in Claim 8 or a use as claimed in Claim 9, wherein the disease is cancer selected from carcinoma such as cancer of the bladder, breast, colon, kidney, liver, lung (including non-small cell cancer and small cell lung cancer), esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, skin, squamous cell carcinoma, testis, genitourinary tract, larynx, glioblastoma, neuroblastoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma, small cell lung carcinoma, lung adenocarcinoma, bone, adenoma, adenocarcinoma, follicular carcinoma, undifferentiated carcinoma, papilliary carcinoma, seminona, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's and leukaemia; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocitic leukemia, acute lymphoblastic leukemia, 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 leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; and other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid follicular cancer and Kaposi's sarcoma.

12. ~~A method of treatment of a disease in which inhibition of a PI3-K is desired and/or required, which method comprises administration of a therapeutically effective amount of a compound of formula I as defined in any one of Claims 1 to 5, or a pharmaceutically-acceptable ester, amide, solvate or salt thereof, to a patient suffering from, or susceptible to, such a condition.~~

12~~3~~. A combination product comprising:

(A) a compound of formula I as defined in any one of Claims 1 to 5, or a pharmaceutically-acceptable ester, amide, solvate or salt thereof; and

(B) another therapeutic agent that is useful in the treatment of in the treatment of cancer and/or a proliferative disease,

wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

13~~4~~. A combination product as claimed in Claim 13 which comprises a pharmaceutical formulation including a compound of formula I as defined in any one of Claims 1 to 5, or a pharmaceutically-acceptable ester, amide, solvate or salt thereof, another therapeutic agent that is useful in the treatment of cancer and/or a proliferative disease, and a pharmaceutically-acceptable adjuvant, diluent or carrier.

14~~5~~. A combination product as claimed in Claim 13 which comprises a kit of parts comprising components:

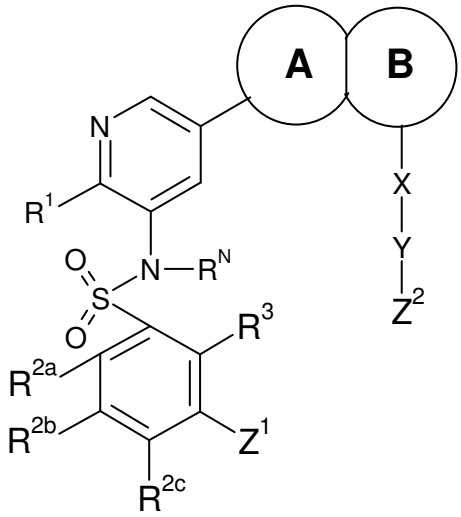
(a) a pharmaceutical formulation including a compound of formula I as defined in any one of Claims 1 to 5, or a pharmaceutically-acceptable ester, amide, solvate or salt thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including another therapeutic agent that is useful in the treatment of cancer and/or a proliferative disease in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

15~~6~~. A process for the preparation of a compound of formula I as defined in Claim 1, which process comprises:

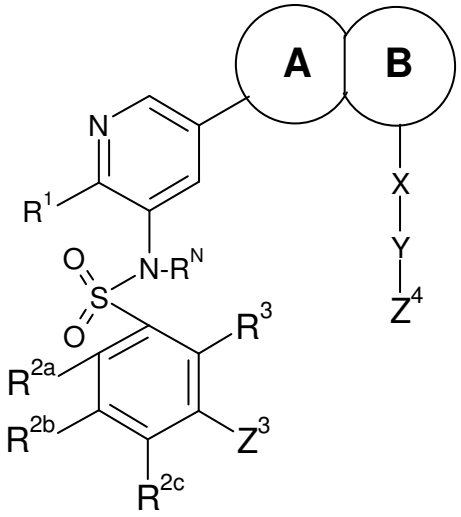
(i) for compounds of formula I in which Z contains a -C(O)N(R^{x3})- or -N(R^{x3})C(O)- moiety, intramolecular reaction of a compound of formula II,



II

wherein Z^1 and Z^2 independently represents -C(O)OH, -N(R^{x3})H or a partial Z moiety with a terminal -C(O)OH group or terminal -N(R^{x3})H group (or derivatives thereof, such as carboxylic acid ester derivatives), wherein one of Z^1 and Z^2 contains the -C(O)OH group (or derivative) and the other contains the -N(R^{x3})H group (or derivative) and ring A/ring B, R^1, R^{2a}, R^{2b}, R^{2c}, R^3, X and Y are as defined in Claim 1;

(ii) compounds of formula I in which Z contains -O-, -S- or -N(R^{x3})-, may be prepared by reaction of a compound of formula III,



III

wherein Z^3 represents -OH, -N(R^{x3})H or -L^x (in which L^x is a suitable leaving group), or Z^3 contains a partial Z moiety with a terminal -OH, -N(R^{x3})H or -L^x group and Z^4 represents L^y-, HO- or H(R^{x3})N- (as appropriate) or a partial Z moiety with a terminal L^y-, HO- or H(R^{x3})N-, L^y is a suitable leaving group (and wherein one of Z^3 and Z^4 contains a -OH, -SH or -N(R^{x3})H moiety and the other contains the L^x or L^y moiety), and ring A/ring B, R^1, R^{2a}, R^{2b}, R^{2c}, R^3, X and Y are as defined in Claim 1;

(iii) compounds of formula I in which R^{x3}, R^{y2}, R^{y3} and/or R^{y4} represent optionally substituted C_{1-6} or C_{1-3} alkyl, may be prepared by reaction of a corresponding compound of formula I in which R^{x3}, R^{y2}, R^{y3} and/or R^{y4} represent hydrogen, with a compound of formula IV,

$$L^1\text{-}R^{12\text{-}14} \qquad \text{IV}$$

wherein $R^{12\text{-}14}$ represents R^{x3}, R^{y2}, R^{y3} or R^{y4} (as appropriate/required) and L^1 represents a suitable leaving group as defined for L^x, or with a compound of formula V,

$$H(O)C\text{-}R^{12a\text{-}14a} \qquad \text{V}$$

wherein $R^{12a\text{-}14a}$ represents C_{1-5} or C_{1-2} alkyl optionally substituted by one or more halo atoms;

(iv) for compounds of formula I containing a $-N(R^{x3})\text{-}CH_2\text{-}$ moiety, reduction of a corresponding compound of formula I containing a $-N(R^{x3})C(O)-$ moiety.

16~~7~~. A process for the preparation of:

(I) a pharmaceutical formulation as defined in Claim 7, which process comprises bringing into association a compound of formula I, as defined in any one of one of Claims 1 to 4, or a pharmaceutically acceptable ester, amide, solvate or salt thereof with a pharmaceutically-acceptable adjuvant, diluent or carrier; and/or

(II) a combination product as defined in Claim 12, 13 or 14, which process comprises bringing into association a compound of formula I, as defined in any one of Claims 1 to 4, or a pharmaceutically acceptable ester, amide, solvate or salt thereof with the other therapeutic agent that is useful in the treatment of cancer and/or a proliferative disease, and at least one pharmaceutically-acceptable adjuvant, diluent or carrier.