[0008] An aim of the present invention is to provide alternative or improved compounds for inhibiting RAS proteins. For example, an aim of the present invention is to provide alternative or improved compounds for inhibiting KRAS proteins.

[0009] Furthermore, it is an aim of certain embodiments of this invention to provide new compounds for use in treatment of conditions modulated by RAS proteins. For example, it is an aim of certain embodiments of this invention to provide compounds for use in the treatment of cancer. Said compounds may be more selective for KRAS proteins having the G12D mutation over alternative KRAS proteins than prior art compounds. Alternatively, said compounds may have broad spectrum activity across a range of KRAS proteins.

[0010] It is an aim of certain embodiments of this invention to provide new cancer treatments. In particular, it is an aim of certain embodiments of this invention to provide compounds which have comparable activity to existing treatments, optionally they should have better activity.

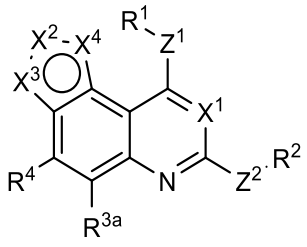
[0011] It is an aim of certain embodiments of this invention to provide compounds which exhibit reduced cytotoxicity relative to prior art compounds and existing therapies.

[0012] Another aim of certain embodiments of this invention is to provide compounds having a convenient pharmacokinetic profile and a suitable duration of action following dosing. A further aim of certain embodiments of this invention is to provide compounds in which the metabolised fragment or fragments of the drug after absorption are GRAS (Generally Regarded As Safe).

[0013] Certain embodiments of the present invention satisfy some or all of the above aims.

BRIEF SUMMARY OF THE DISCLOSURE

[0014] In accordance with the present disclosures there is provided a compound of formula (**Ia**), or a pharmaceutically acceptable salt thereof:



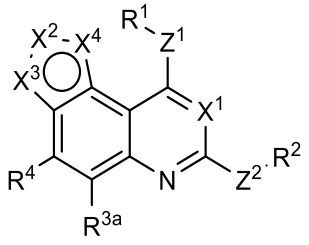
(**Ia**)

wherein

Z^1 is independently selected from -O- and -NR^{5a}-;

Z^2 is independently absent or is selected from -O- and -NR^{5b}-;

[0015] In accordance with the present disclosures there is provided, in an aspect, a compound of formula (**I**), or a pharmaceutically acceptable salt thereof:



(**I**)

Z^1 is independently selected from -O- and -NR^{5a}-;

Z^2 is independently absent or is selected from -O- and -NR^{5b}-;

X^1 is independently selected from N and CR^{3b};

X^2 is selected from N, NR^6, O and S;

X^3 is selected from N and NR^6;

X^4 is CR^{3c};

R^1 is independently selected from C_0-C_3-alkylene-R^{1a} and C_2-C_6-alkylene-R^{1b}; wherein R^{1a} is independently selected from an oxygen containing 4- to 7- membered heterocycloalkyl ring, a 4- to 7- membered heterocycloalkyl ring; and a C_3-C_7-cycloalkyl ring substituted with an NR^7R^8 group; wherein said heterocycloalkyl ring or said cycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups; R^{1b} is independently selected from: NR^7R^8, OR^8, SR^8, SOR^8, SO_2R^8 and $SO(NH)R^8$;

or R^1 and R^{5a} together with the nitrogen to which they are attached form a ring system selected from: a monocyclic 4- to 7-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups; a fused, spirofused or bridged bicyclic 6- to 11-membered heterocyclyl group, optionally substituted with from 1 to 4 R^9 groups;

R^2 is independently C_1-C_6-alkyl, C_1-C_4-haloalkyl, C_0-C_4-alkylene-R^{2a}, C_1-C_4-alkylene-R^{2b}, C_2-C_4-alkylene-R^{2c};

R^{2a} is independently selected from monocyclic 4- to 7-membered heterocycloalkyl group, a fused, spirofused or bridged bicyclic 6- to 11-membered heterocycloalkyl group; a 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl group; phenyl; C_3-C_7-cycloalkyl; wherein any heterocycloalkyl or cycloalkyl R^{2a} group is optionally substituted with from 1 to 6 R^{10} groups and any heteroaryl or phenyl R^{2a} group is optionally substituted with from 1 to 6 R^{11} groups;

wherein R^{2b} is independently selected from $CONR^{12}R^{12}$ and CO_2R^{12};

wherein R^{2c} is independently selected from $NR^{12}R^{13}$ and OR^{12};

or R^2 and R^{5b} together with the nitrogen to which they are attached form a ring system selected from: monocyclic 4- to 7-membered heterocycloalkyl group, a fused, spirofused or bridged

bicyclic 6- to 11-membered heterocycloalkyl group, said heterocycloalkyl group being optionally substituted with from 1 to 6 R^{10} groups;

R^{3a} , R^{3b} and R^{3c} are each independently selected from: H, halo, C_1-C_4-alkyl, O-C_1-C_4-alkyl, C_1-C_4-haloalkyl, O-C_1-C_4-haloalkyl, cyclopropyl, nitro and cyano;

R^4 is independently selected from phenyl, said phenyl being optionally fused to a C_5-C_7-cycloalkyl ring; naphthyl; monocyclic 4- to 7-membered cycloalkyl or heterocycloalkyl; and 5-, to 10-membered monocyclic or bicyclic heterocyclyl, wherein R^4 is optionally substituted with from 1 to 4 R^{14} groups;

R^{5a}, R^{5b}, R^8 and R^{12} are each independently selected at each occurrence from H, C_1-C_4-haloalkyl, and C_1-C_4-alkyl;

R^6 is independently selected from H, C_1-C_4-haloalkyl, C_1-C_4-alkyl and C_3-C_4-cycloalkyl;

R^7 and R^{13} are each independently at each occurrence selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl and C(O)-C_1-C_4-alkyl;

or R^{12} and R^{13} together with the nitrogen to which they are attached form a ring system selected from: monocyclic 4- to 7-membered heterocycloalkyl group, a fused, spirofused or bridged bicyclic 6- to 11-membered heterocycloalkyl group, said heterocycloalkyl group being optionally substituted with from 1 to 6 R^{10} groups;

R^9 and R^{10} are each independently at each occurrence selected from oxo, halo, cyano, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_1-C_4-alkyl substituted with cyano, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

R^{11} is independently selected from halo, cyano, nitro, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, monocyclic 4- to 7-membered cycloalkyl or heterocycloalkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

R^{14} is independently at each occurrence selected from halo, cyano, nitro, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

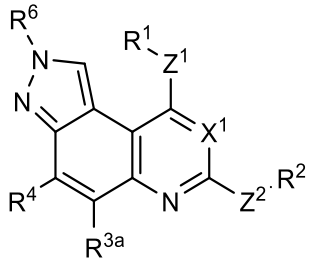
wherein any of the aforementioned alkyl, alkylene or cycloalkyl (e.g. cyclopropyl) groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: C_1-C_4-alkyl, halo, nitro, cyano, NR^aR^b, OR^a, SR^a, CO_2R^a, $C(O)R^a$, $CONR^aR^a$; wherein R^a is independently at each occurrence selected from H, C_1-C_4-alkyl and C_1-C_4-haloalkyl; and R^b is independently at each occurrence selected from H, C_1-C_4-alkyl, C(O)-C_1-C_4-alkyl and $S(O)_2$-C_1-C_4-alkyl.

[0016] In accordance with the present disclosures there is provided a compound of formula (**Ib**), or a pharmaceutically acceptable salt thereof:

R^{14} is independently at each occurrence selected from halo, cyano, nitro, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl, phenyl and cyclopropyl;
wherein any of the aforementioned alkyl, alkylene, phenyl or cycloalkyl (e.g. cyclopropyl) groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: C_1-C_4-alkyl, C_1-C_4-alkyl substituted with OR^a, halo, nitro, cyano, NR^aR^b, OR^a, SR^a, CO_2R^a, $C(O)R^a$, $CONR^aR^a$; wherein R^a is independently at each occurrence selected from H, C_1-C_4-alkyl and C_1-C_4-haloalkyl; and R^b is independently at each occurrence selected from H, C_1-C_4-alkyl, $C(O)$-C_1-C_4-alkyl and $S(O)_2$-C_1-C_4-alkyl.

[0017] For the absence of doubt, the ring comprising X^2 and X^3 is selected from pyrazole, isoxazole and isothiazole. Thus, either X^2 is N and X^3 is NR^6 or X^3 is N and X^2 is selected from NR^6, O and S.

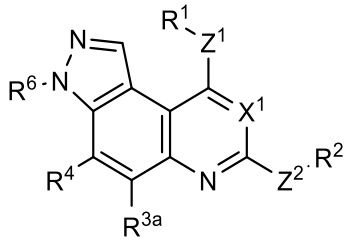
[0018] In an example, the compound of formula (**I**) is a compound of formula (**II**):



(**II**)

wherein R^1, R^2, R^{3a}, R^4, R^6, X^1, Z^1 and Z^2 are as described above for compounds of formula (**I**).

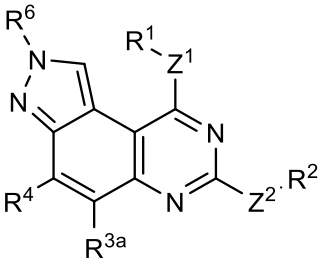
[0019] In an example, the compound of formula (**I**) is a compound of formula (**III**):



(**III**)

wherein R^1, R^2, R^{3a}, R^4, R^6, X^1, Z^1 and Z^2 are as described above for compounds of formula (**I**).

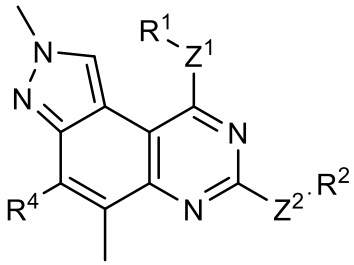
[0020] In an example, the compound of formula (**I**) is a compound of formula (**IV**)



(**IV**)

wherein R^1, R^2, R^{3a}, R^4, R^6, Z^1 and Z^2 are as described above for compounds of formula (**I**).

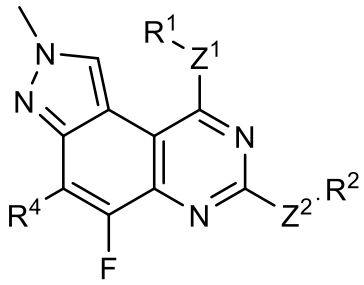
[0021] In an example, the compound of formula (I) is a compound of formula **(IVa**):



(**IVa**)

wherein R^1, R^2, R^4, Z^1, and Z^2 are as described above for compounds of formula (**I**).

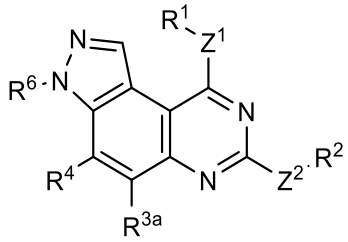
[0022] In an example, the compound of formula (**I**) is a compound of formula (**IVb**):



(**IVb**)

wherein R^1, R^2, R^4, Z^1, and Z^2 are as described above for compounds of formula (**I**).

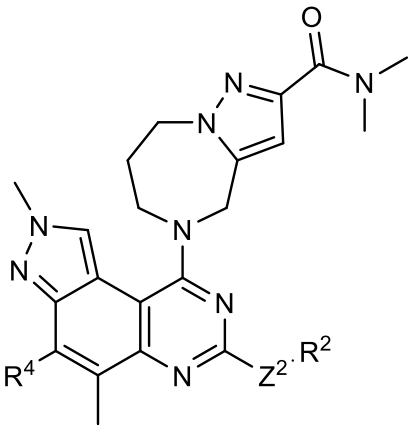
[0023] In an example, the compound of formula (**I**) is a compound of formula (**V**):



(**V**)

wherein R^1, R^2, R^{3a}, R^4, R^6, Z^1 and Z^2 are as described above for compounds of formula (**I**).

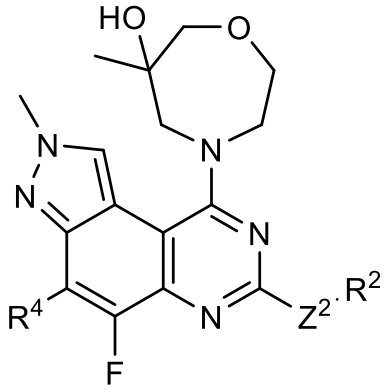
[0024] In an example, the compound of formula (**I**) is a compound of formula (**Va**):



(**Va**)

wherein R^2, R^4, Z^2 are as described above for compounds of formula (**I**).

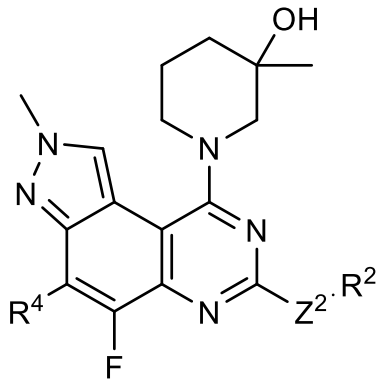
[0025] In an example, the compound of formula (**I**) is a compound of formula (**Vb**):



(**Vb**)

wherein R^2, R^4, Z^2 are as described above for compounds of formula (**I**).

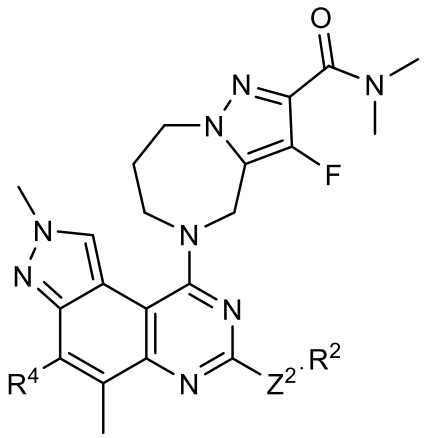
[0026] In an example, the compound of formula (**I**) is a compound of formula (**Vc**):



(**Vc**)

wherein R^2, R^4, Z^2 are as described above for compounds of formula (**I**).

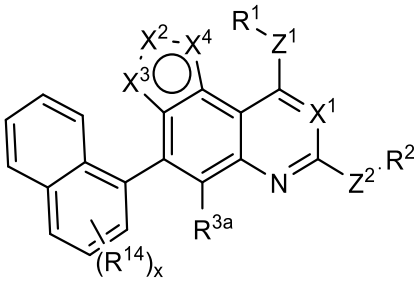
[0027] In an example, the compound of formula (**I**) is a compound of formula (**Vd**):



(**Vd**)

wherein R^2, R^4, Z^2 are as described above for compounds of formula (**I**).

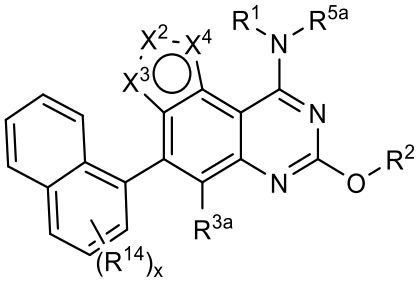
[0028] In an example, the compound of formula (**I**) is a compound of formula (**VI**):



(**VI**)

wherein R^1, R^2, R^{3a}, R^{14}, X^1, X^2, X^3, X^4, Z^1 and Z^2 are as described above for compounds of formula (**I**); and x is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the x R^{14} groups may be attached to either ring of the naphthyl group.

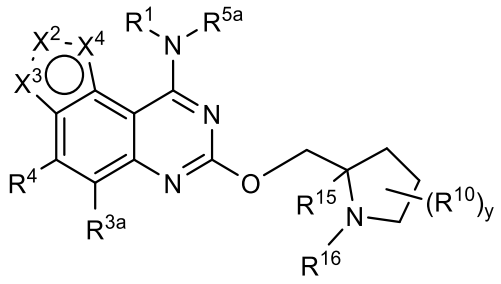
[0029] In an example, the compound of formula (**I**) is a compound of formula (**VII**):



(**VII**)

wherein R^1, R^2, R^{3a}, R^{5a}, R^{14}, X^2, X^3 and X^4 are as described above for compounds of formula (**I**); and x is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the x R^{14} groups may be attached to either ring of the naphthyl group.

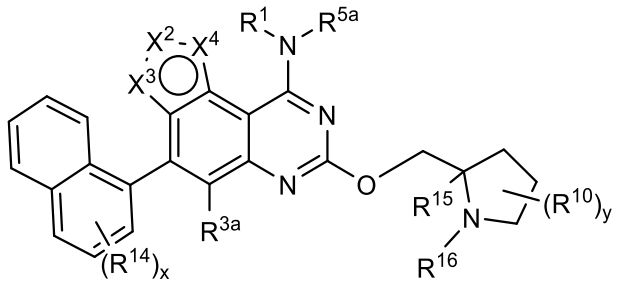
[0030] In an example, the compound of formula (**I**) is a compound of formula (**VIII**):



(**VIII**)

wherein R^1, R^{3a}, R^4, R^{5a}, R^{10}, X^2, X^3 and X^4 are as described above for compounds of formula (**I**); and wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to which they are attached form a 5- or 6-membered heterocycloalkyl ring, optionally substituted with 1 or 2 R^{10} groups; and y is independently selected from 0, 1, 2, 3, and 4.

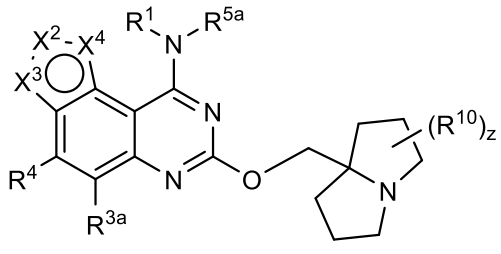
[0031] In an example, the compound of formula (**I**) is a compound of formula (**IX**):



(**IX**)

wherein R^1, R^{3a}, R^{5a}, R^{10}, R^{14}, X^2, X^3 and X^4 are as described above for compounds of formula (**I**); wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to which they are attached form a 5- or 6-membered heterocycloalkyl ring, optionally substituted with 1 or 2 R^{10} groups; x is independently selected from 0, 1, 2, 3, and 4; and y is independently selected from 0, 1, 2, 3, and 4.

[0032] In an example, the compound of formula (**I**) is a compound of formula (**X**):

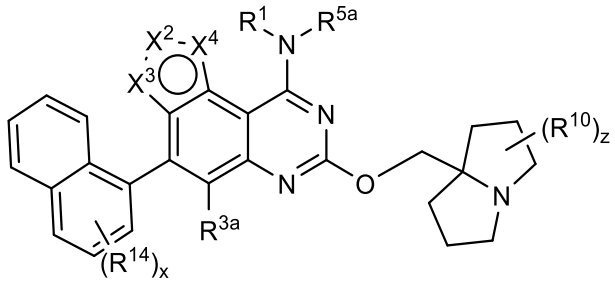


(**X**)

wherein R^1, R^{3a}, R^4, R^{5a}, R^{10}, X^2, X^3 and X^4 are as described above for compounds of formula (**I**); and wherein z is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt,

throughout this specification, the z R^{10} groups may be attached to either ring of the pyrrolizidinyl group.

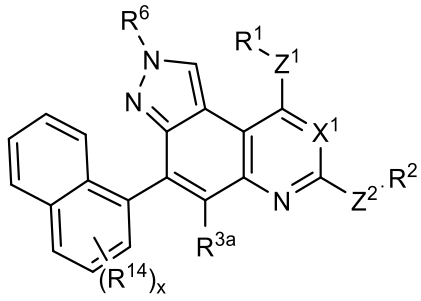
[0033] In an example, the compound of formula (**I**) is a compound of formula (**XI**):



(**XI**)

wherein R^1, R^{3a}, R^{5a}, R^{10}, R^{14}, X^2, X^3 and X^4 are as described above for compounds of formula (**I**); wherein x is independently selected from 0, 1, 2, 3, and 4; and wherein z is independently selected from 0, 1, 2, 3, and 4.

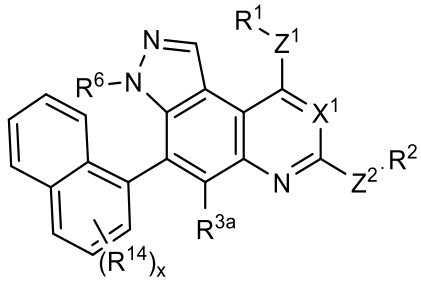
[0034] In an example, the compound of formula (**I**) is a compound of formula (**XII**):



(**XII**)

wherein R^1, R^2, R^{3a}, R^6, R^{14}, X^1, Z^1 and Z^2 are as described above for compounds of formula (**I**); and x is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the x R^{14} groups may be attached to either ring of the naphthyl group.

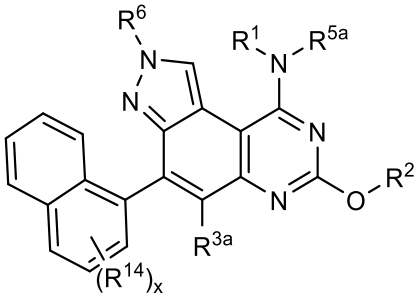
[0035] In an example, the compound of formula (**I**) is a compound of formula (**XIII**):



(**XIII**)

wherein R^1, R^2, R^{3a}, R^6, R^{14}, X^1, Z^1 and Z^2 are as described above for compounds of formula (**I**); and x is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the x R^{14} groups may be attached to either ring of the naphthyl group.

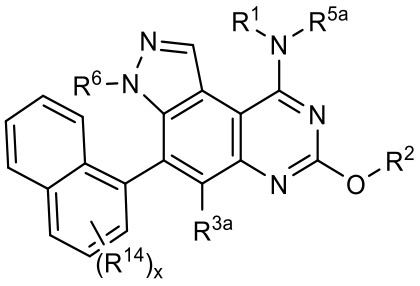
[0036] In an example, the compound of formula (**I**) is a compound of formula (**XIV**):



(**XIV**)

wherein R^1, R^2, R^{3a}, R^6, R^{5a}, and R^{14} are as described above for compounds of formula (**I**); and x is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the x R^{14} groups may be attached to either ring of the naphthyl group.

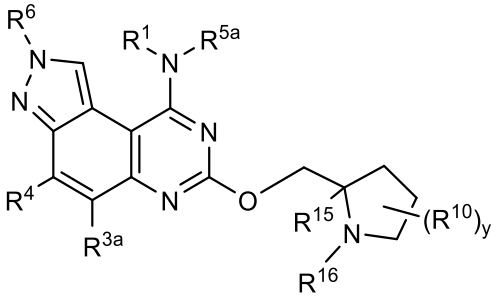
[0037] In an example, the compound of formula (**I**) is a compound of formula (**XV**):



(**XV**)

wherein R^1, R^2, R^{3a}, R^6, R^{5a}, and R^{14} are as described above for compounds of formula (**I**); and x is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the x R^{14} groups may be attached to either ring of the naphthyl group.

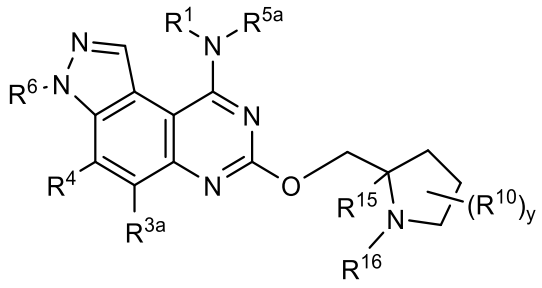
[0038] In an example, the compound of formula (**I**) is a compound of formula (**XVI**):



(**XVI**)

wherein R^1, R^{3a}, R^4, R^{5a}, R^6 andR^{10} are as described above for compounds of formula (**I**); and wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to which they are attached form a 5- or 6-membered heterocycloalkyl ring, optionally substituted with 1 or 2 R^{10} groups; and y is independently selected from 0, 1, 2, 3, and 4.

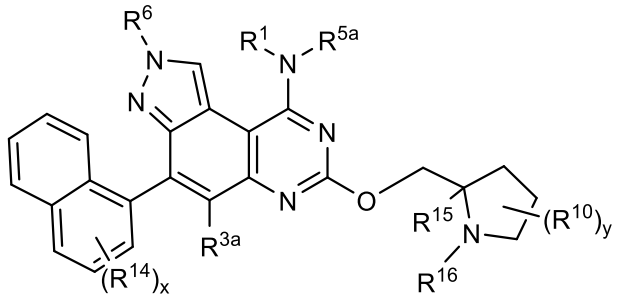
[0039] In an example, the compound of formula (**I**) is a compound of formula (**XVII**):



(**XVII**)

wherein R^1, R^{3a}, R^4, R^{5a}, R^6 and R^{10} are as described above for compounds of formula (**I**); and wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to which they are attached form a 5- or 6-membered heterocycloalkyl ring, optionally substituted with 1 or 2 R^{10} groups; and y is independently selected from 0, 1, 2, 3, and 4.

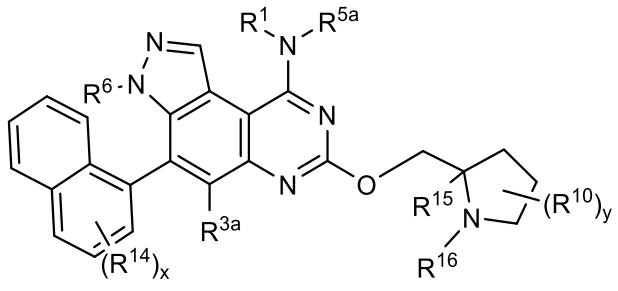
[0040] In an example, the compound of formula (**I**) is a compound of formula (**XVIII**):



(**XVIII**)

wherein R^1, R^{3a}, R^{5a}, R^6, R^{10}, and R^{14} are as described above for compounds of formula (**I**); wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to which they are attached form a 5- or 6-membered heterocycloalkyl ring, optionally substituted with 1 or 2 R^{10} groups; x is independently selected from 0, 1, 2, 3, and 4; and y is independently selected from 0, 1, 2, 3, and 4.

[0041] In an example, the compound of formula (**I**) is a compound of formula (**XIX**):

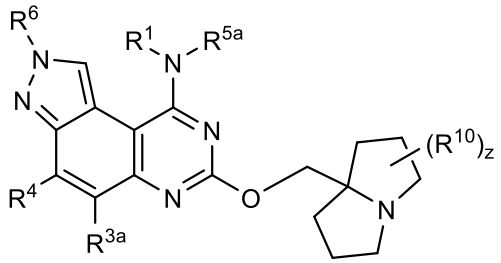


(**XIX**)

wherein R^1, R^{3a}, R^{5a}, R^6, R^{10}, and R^{14} are as described above for compounds of formula (**I**); wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently

selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to which they are attached form a 5- or 6-membered heterocycloalkyl ring, optionally substituted with 1 or 2 R^{10} groups; x is independently selected from 0, 1, 2, 3, and 4; and y is independently selected from 0, 1, 2, 3, and 4.

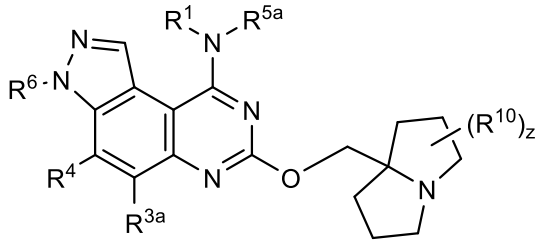
[0042] In an example, the compound of formula (**I**) is a compound of formula (**XX**):



(**XX**)

wherein R^1, R^{3a}, R^4, R^{5a}, R^6 and R^{10} are as described above for compounds of formula (**I**); and wherein z is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the z R^{10} groups may be attached to either ring of the pyrrolizidinyl group.

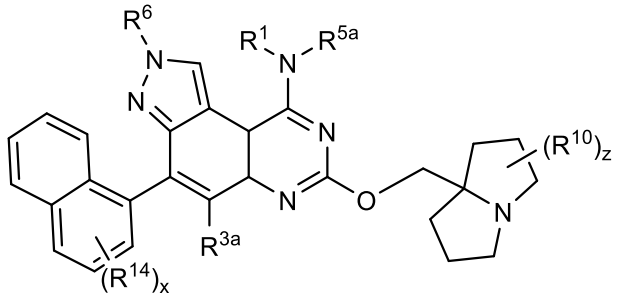
[0043] In an example, the compound of formula (**I**) is a compound of formula (**XXI**):



(**XXI**)

wherein R^1, R^{3a}, R^4, R^{5a}, R^6 and R^{10} are as described above for compounds of formula (**I**); and wherein z is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the z R^{10} groups may be attached to either ring of the pyrrolizidinyl group.

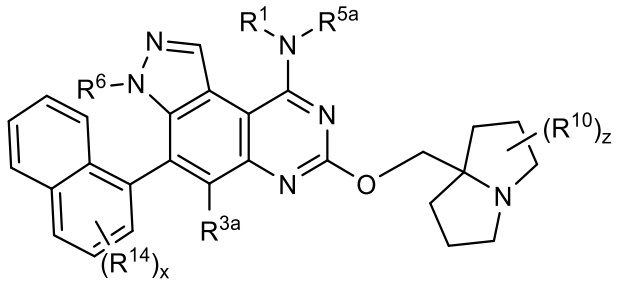
[0044] In an example, the compound of formula (**I**) is a compound of formula (**XXII**):



(**XXII**)

wherein R^1, R^{3a}, R^{5a}, R^6, R^{10}, and R^{14} are as described above for compounds of formula (**I**); wherein x is independently selected from 0, 1, 2, 3, and 4; and wherein z is independently selected from 0, 1, 2, 3, and 4.

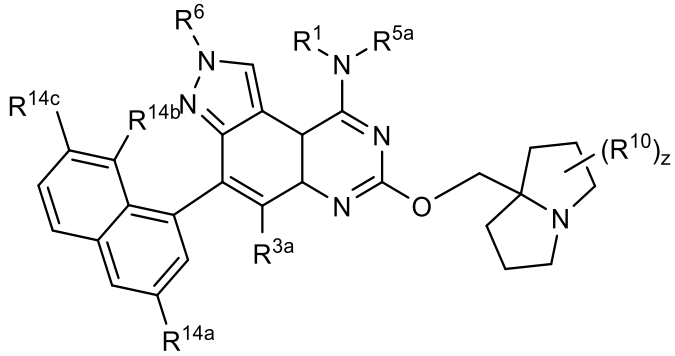
[0045] In an example, the compound of formula (**I**) is a compound of formula (**XXIII**):



(**XXIII**)

wherein R^1, R^{3a}, R^{5a}, R^6, R^{10}, and R^{14} are as described above for compounds of formula (**I**); wherein x is independently selected from 0, 1, 2, 3, and 4; and wherein z is independently selected from 0, 1, 2, 3, and 4.

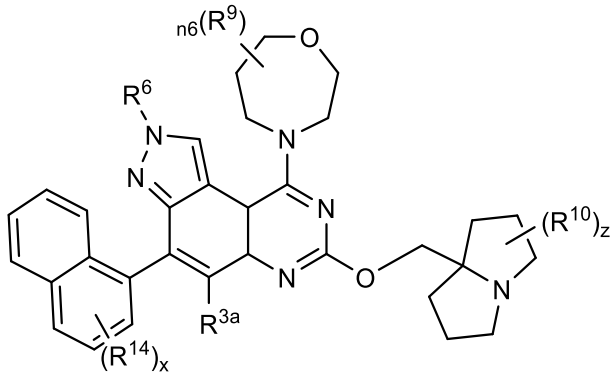
[0046] In an example, the compound of formula (**I**) is a compound of formula (**XXIV**):



(**XXIV**)

wherein R^1, R^{3a}, R^{5a}, R^6, and R^{10} are as described above for compounds of formula (**I**); wherein z is independently selected from 0, 1, 2, 3, and 4; and wherein R^{14a} is OR^{12} e.g., OH; R^{14b} is C_1-C_4-alkyl e.g., methyl or ethyl; and R^{14c} is halo e.g, F.

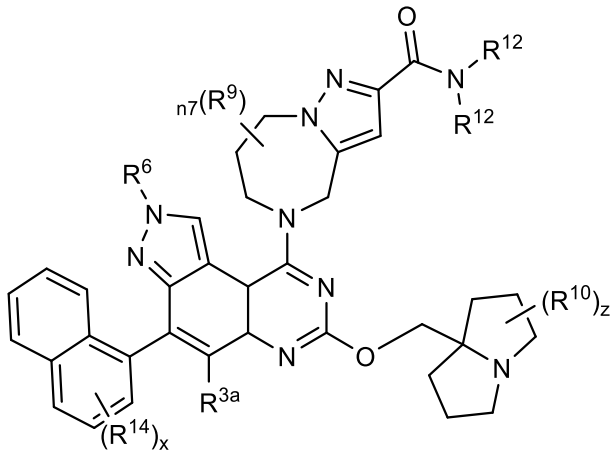
[0047] In an example, the compound of formula (**I**) is a compound of formula (**XXV**):



(**XXV**)

wherein R^{3a}, R^6, R^{10}, R^9 and R^{14} are as described above for compounds of formula (**I**); wherein x is independently selected from 0, 1, 2, 3, and 4; wherein n10 is independently selected from 0, 1 and 2; and wherein z is independently selected from 0, 1, 2, 3, and 4. n6 may be 0. n6 may be 1. n6 may be 2.

[0048] In an example, the compound of formula (**I**) is a compound of formula (**XXVI**):



(**XXVI**)

wherein R^{3a}, R^6, R^9, R^{10} and R^{14} are as described above for compounds of formula (**I**); wherein R^{12} is independently at each occurrence selected from H, and C_1-C_4-alkyl, e.g., methyl; wherein x is independently selected from 0, 1, 2, 3, and 4; wherein n7 is independently selected from 0 and 1; and wherein z is independently selected from 0, 1, 2, 3, and 4. n7 may be 0.

[0049] The following examples apply to compounds of any of formulae (**I**)-(**XXIII**). These examples are independent and interchangeable. Any one example may be combined with any other example, where chemically allowed. In other words, any of the features described in the following examples may (where chemically allowable) be combined with the features described in one or more other examples. In particular, where a compound is exemplified or illustrated in this specification, any two or more of the examples listed below, expressed at any level of generality,

which encompass that compound may be combined to provide a further example which forms part of the present disclosure.

[0050] X^1 may be N. X^1 may be CR^{3b}.

[0051] The ring comprising X^2 and X^3 may be pyrazole, The ring comprising X^2 and X^3 may be selected from isoxazole and isothiazole. It may be that X^2 is N and X^3 is NR^6 . It may be that X^3 is N and X^2 is selected from NR^6, O and S. It may be that X^3 is N and X^2 is NR^6. It may be that X^3 is N and X^2 is selected from O and S.

[0052] Z^1 may be -O-. Z^1 may be $-NR^{5a}-$.

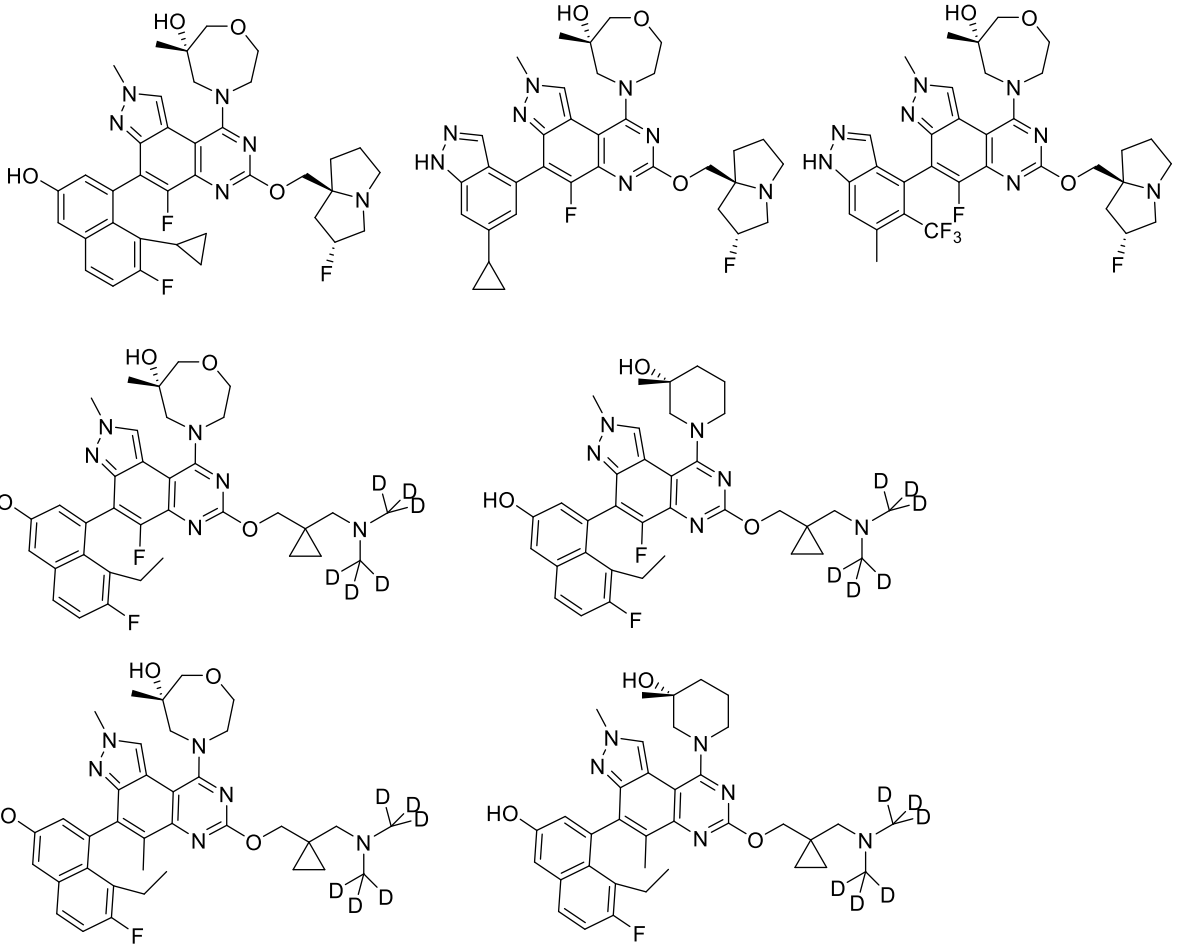
[0053] Z^2 may be -O-. Z^2 may be $-NR^{5b}-$.

[0054] R^1 is independently C_0-C_3-alkylene-R^{1a} wherein R^{1a} is independently selected from a 4- to 7- membered heterocycloalkyl ring; a phenyl ring; and a C_3-C_7-cycloalkyl ring optionally substituted with an NR^7R^8 group; wherein said heterocycloalkyl ring, said phenyl ring or said cycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups.

[0055] R^1 is independently C_0-C_3-alkylene-R^{1a} wherein R^{1a} is independently selected from a 4- to 7- membered heterocycloalkyl ring; and a C_3-C_7-cycloalkyl ring optionally substituted with an NR^7R^8 group; wherein said heterocycloalkyl ring or said cycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups.

[0056] R^1 may be C_0-C_3-alkylene-R^{1a}. R^1 may be C_0-C_3-alkylene-R^{1a} wherein R^{1a} is independently selected from an oxygen containing 4- to 7- membered heterocycloalkyl ring, a 4- to 7- membered heterocycloalkyl ring; and a C_3-C_7-cycloalkyl ring optionally substituted with an NR^7R^8 group; wherein said heterocycloalkyl ring or said cycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups. R^1 may be CH_2-R^{1a} wherein R^{1a} is independently selected from a 4- to 7- membered heterocycloalkyl ring; and a C_3-C_7-cycloalkyl ring optionally substituted with an NR^7R^8 group; wherein said heterocycloalkyl ring or said cycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups.

[0057] R^1 may be C_0-C_3-alkylene-R^{1a} wherein R^{1a} is independently selected from an oxygen containing 4- to 7- membered heterocycloalkyl ring, a nitrogen containing 4- to 7- membered heterocycloalkyl ring; and a C_3-C_7-cycloalkyl ring optionally substituted with an NR^7R^8 group; wherein said heterocycloalkyl ring or said cycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups. R^1 may be CH_2-R^{1a} wherein R^{1a} is independently selected from a nitrogen containing 4- to 7- membered heterocycloalkyl ring; and a C_3-C_7-cycloalkyl ring optionally substituted with an NR^7R^8 group; wherein said



[00161a] In an aspect of the present disclosure, there is provided a compound as disclosed herein for use in therapy.

[00161b] In another aspect of the present disclosure, there is provided use of a compound as disclosed herein in the manufacture of a medicament for treating cancer in a subject; optionally wherein the cancer is selected from: pancreatic carcinoma, colorectal carcinoma, rectal carcinoma, endometrial carcinoma, non-small cell lung carcinoma, gastric carcinoma, ovarian carcinoma and small cell lung carcinoma.

[00161c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein and a pharmaceutically acceptable excipient.

DETAILED DESCRIPTION

[00162] In an aspect of the invention there is provided the compounds of the present invention for use as a medicament.

[00163] In accordance with another aspect, the present invention provides a method of treating a condition which can be modulated by inhibition of KRAS proteins having the

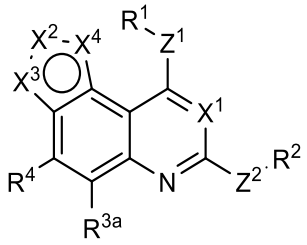
G12D mutation, the method comprising administering a therapeutically effective amount of a compound of the invention to a subject in need thereof.

[00164] In accordance with another aspect, the present invention provides a pharmaceutical formulation comprising a compound of the present invention and a pharmaceutically acceptable excipient.

[00165] In an embodiment, the pharmaceutical composition may be a combination product comprising an additional pharmaceutically active agent. The additional pharmaceutically active agent may be, for example anti-inflammatory agents, anti-fibrotic agents, chemotherapeutics, anti-cancer agents, immunosuppressants, anti-tumour vaccines, cytokine therapy, or tyrosine kinase inhibitors.

CLAIMS

1. A compound of formula (**I**), or a pharmaceutically acceptable salt thereof:



(**I**)

Z^1 is independently selected from -O- and -NR^{5a}-;

Z^2 is independently absent or is selected from -O- and -NR^{5b}-;

X^1 is independently selected from N and CR^{3b};

X^2 is selected from N, NR^6, O and S;

X^3 is selected from N and NR^6;

X^4 is CR^{3c};

R^1 is independently selected from C_0-C_3-alkylene-R^{1a} and C_2-C_6-alkylene-R^{1b}; wherein R^{1a} is independently selected from: a 4- to 7- membered heterocycloalkyl ring; a phenyl ring; and a C_3-C_7-cycloalkyl ring optionally substituted with an NR^7R^8 group; wherein said heterocycloalkyl ring, said phenyl ring or said cycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups;

R^{1b} is independently selected from: NR^7R^8, OR^8, SR^8, SOR^8, SO_2R^8 and $SO(NH)R^8$;

or R^1 and R^{5a} together with the nitrogen to which they are attached form a ring system selected from: a monocyclic 4- to 7-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups; and a fused, spirofused or bridged bicyclic 6- to 11-membered heterocyclyl group, optionally substituted with from 1 to 4 R^9 groups;

R^2 is independently C_1-C_6-alkyl, C_1-C_4-haloalkyl, C_0-C_4-alkylene-R^{2a}, C_1-C_4-alkylene-R^{2b}, C_2-C_4-alkylene-R^{2c};

R^{2a} is independently selected from monocyclic 4- to 7-membered heterocycloalkyl group; a fused, spirofused or bridged bicyclic 6- to 11-membered heterocycloalkyl group; a 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl group; phenyl; and C_3-C_7-cycloalkyl; wherein any heterocycloalkyl or cycloalkyl R^{2a} group is optionally substituted with from 1 to 6 R^{10} groups and any heteroaryl or phenyl R^{2a} group is optionally substituted with from 1 to 6 R^{11} groups;

wherein R^{2b} is independently selected from $CONR^{12}R^{12}$ and CO_2R^{12};

wherein R^{2c} is independently selected from $NR^{12}R^{13}$ and OR^{12};

or R^2 and R^{5b} together with the nitrogen to which they are attached form a ring system selected from: monocyclic 4- to 7-membered heterocycloalkyl group; and a fused, spirofused or bridged

bicyclic 6- to 11-membered heterocycloalkyl group, said heterocycloalkyl group being optionally substituted with from 1 to 6 R^{10} groups;

R^{3a} , R^{3b} and R^{3c} are each independently selected from: H, halo, C_1-C_4-alkyl, O-C_1-C_4-alkyl, C_1-C_4-haloalkyl, O-C_1-C_4-haloalkyl, cyclopropyl, nitro and cyano;

R^4 is independently selected from phenyl, said phenyl being optionally fused to a C_5-C_7-cycloalkyl ring; naphthyl; monocyclic 4- to 7-membered cycloalkyl or heterocycloalkyl; and 5-, to 10-membered monocyclic or bicyclic heterocyclyl; wherein R^4 is optionally substituted with from 1 to 4 R^{14} groups;

R^{5a}, R^{5b}, R^8 and R^{12} are each independently selected at each occurrence from H, C_1-C_4-haloalkyl, cyclopropyl and C_1-C_4-alkyl;

R^6 is independently selected from H, C_1-C_4-haloalkyl, C_1-C_4-alkyl and C_3-C_4-cycloalkyl;

R^7 and R^{13} are each independently at each occurrence selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl and C(O)-C_1-C_4-alkyl;

or R^{12} and R^{13} together with the nitrogen to which they are attached form a ring system selected from: monocyclic 4- to 7-membered heterocycloalkyl group; and a fused, spirofused or bridged bicyclic 6- to 11-membered heterocycloalkyl group; said heterocycloalkyl group being optionally substituted with from 1 to 6 R^{10a} groups;R^9 is independently at each occurrence selected from oxo, halo, cyano, $NR^{12}R^{13}$, OR^{12}, COR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, $CONR^{12}R^{13}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_1-C_4-alkyl substituted with cyano, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

R^{10} is independently at each occurrence selected from oxo, halo, cyano, $NR^{12}R^{13}$, OR^{12}, COR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_1-C_4-alkyl substituted with cyano, C_1-C_4-alkyl substituted with phenyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

R^{10a} is independently at each occurrence selected from oxo, halo, cyano, $NR^{12}R^{13a}$, OR^{12}, COR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, $CONR^{12}R^{13a}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13a}$, C_1-C_4-alkyl substituted with OR^{12}, C_1-C_4-alkyl substituted with cyano, C_1-C_4-alkyl substituted with phenyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

R^{13a} is independently at each occurrence selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl and C(O)-C_1-C_4-alkyl;

R^{11} is independently selected from halo, cyano, nitro, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, monocyclic 4-

to 7-membered cycloalkyl or heterocycloalkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl and cyclopropyl;

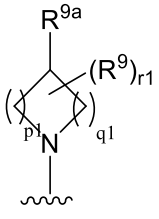
R^{14} is independently at each occurrence selected from halo, cyano, nitro, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_2-C_4-alkenyl, C_2-C_4-alkynyl, C_1-C_4-haloalkyl, phenyl and cyclopropyl;
wherein any of the aforementioned alkyl, alkylene, phenyl or cycloalkyl (e.g. cyclopropyl) groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: C_1-C_4-alkyl, C_1-C_4-alkyl substituted with OR^a, halo, nitro, cyano, NR^aR^b, OR^a, SR^a, CO_2R^a, $C(O)R^a$, $CONR^aR^a$; wherein R^a is independently at each occurrence selected from H, C_1-C_4-alkyl and C_1-C_4-haloalkyl; and R^b is independently at each occurrence selected from H, C_1-C_4-alkyl, $C(O)$-C_1-C_4-alkyl and $S(O)_2$-C_1-C_4-alkyl.

2. A compound of claim 1, wherein R^1 and R^{5a} are selected such that NR^1R^5 comprises no more than a single amine, wherein said single amine may be a primary, secondary or tertiary amine.

3. A compound of claim 1 or claim 2, wherein R^1 and R^{5a} together with the nitrogen to which they are attached form a ring system selected from: a monocyclic 4- to 7-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups; a fused or spirofused bicyclic 6- to 11-membered heterocyclyl group, optionally substituted with from 1 to 4 R^9 groups; and a bridged bicyclic 6- to 11-membered heterocyclyl group, optionally substituted with from 1 to 4 R^9 groups; wherein the nitrogen to which R^1 and R^{5a} are attached is the only nitrogen in the ring system.

4. A compound of any one of claims 1 to 3, wherein R^1 and R^{5a} together with the nitrogen to which they are attached form a ring system selected from: a monocyclic 4- to 7-membered group heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups; a fused or spirofused bicyclic 6- to 11-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups.

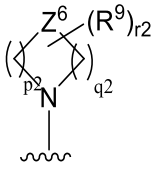
5. A compound of claim 4, wherein R^1 and R^5 together with the nitrogen to which they are attached form a ring system having the structure:



wherein R^{9a} is selected from $NR^{12}R^{13}$ and C_1-C_4-alkyl substituted with $NR^{12}R^{13}$;

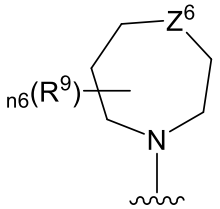
p1 is selected from 0, 1, 2 and 3, q1 is selected from 0, 1 and 2; and r1 is selected from 0, 1, 2 and 3.

6. A compound of claim 4, wherein R^1 and R^{5a} together with the nitrogen to which they are attached form a ring system having the structure:



wherein Z^6 is independently selected from $C(O)NR^{9b}$, NR^{9b}, O, S, $S(O)_2$, S(O), $S(O)(NR^{9b})$ and S(O)(NH); R^{9b} is selected from H and C_1-C_4-alkyl; p2 is selected from 2 and 3, q2 is 2; and r2 is selected from 0, 1, 2 and 3.

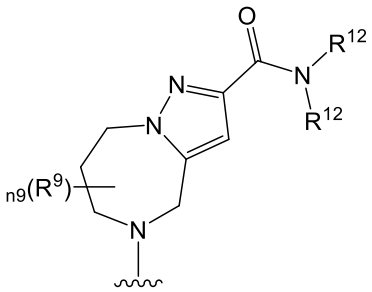
7. A compound of claim 5, wherein R^1 and R^{5a} together with the nitrogen to which they are attached form a ring system having the structure:



wherein Z^6 is independently selected from $C(O)NR^{9b}$, O, S, $S(O)_2$, S(O), $S(O)(NR^{9b})$, S(O)(NH) and NR^{9b}; R^{9b} is independently at each occurrence selected from H and C_1-C_4-alkyl; and n6 is an integer selected from 0, 1, 2, 3 and 4.

8. A compound of claim 6, wherein Z^6 may be O.

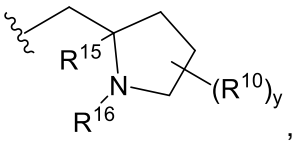
9. A compound of claim 6, wherein R^1 and R^{5a} together with the nitrogen to which they are attached form a ring system having the structure:



;

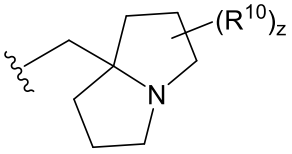
wherein R^{12} is independently at each occurrence selected from H, C_1-C_4-haloalkyl, and C_1-C_4-alkyl; and n9 is an integer selected from 0, 1, 2 and 3.

10. A compound of any one of claims 1 to 9, wherein R^2 has the structure:



, wherein R^{15} is independently selected from H, C_1-C_4-alkyl and R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to which they are attached form a 5- or 6-membered heterocycloalkyl ring, optionally substituted with 1 or 2 R^{10} groups; and y is independently selected from 0, 1, 2, 3, and 4.

11. A compound of claim 10, wherein R^2 has the structure:



, wherein z is independently selected from 0, 1, 2, 3, and 4.

12. A compound of any one of claims 1 to 11, wherein X^1 is N.

13. A compound of any one of claims 1 to 12, wherein X^2 is N and X^3 is NR^6 .

14. A compound of any one of claims 1 to 12, wherein X^3 is N and X^2 is NR^6.

15. A compound of claim 13 or claim 14, wherein R^6 is selected from C_1-C_4-haloalkyl, C_1-C_4-alkyl and C_3-C_4-cycloalkyl.

16. A compound of any one of claims 1 to 15, wherein R^{3c} is H.

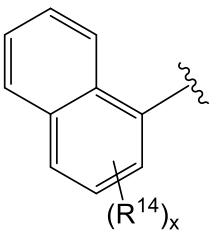
17. A compound of any one of claims 1 to 15, wherein R^{3a} is H.

18. A compound of any one of claims 1 to 15, wherein R^{3a} is F.

19. A compound of any one of claims 1 to 15, wherein R^{3a} is methyl.

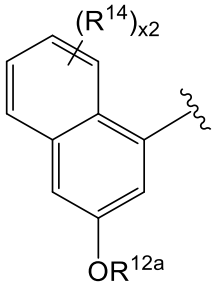
20. A compound of any one of claims 1 to 19, wherein R^4 is phenyl, said phenyl being optionally fused to a C_5-C_7-cycloalkyl ring, wherein R^4 is optionally substituted with from 1 to 4 R^{14} groups.

21. A compound of any one of claims 1 to 19, wherein R^4 has the structure:



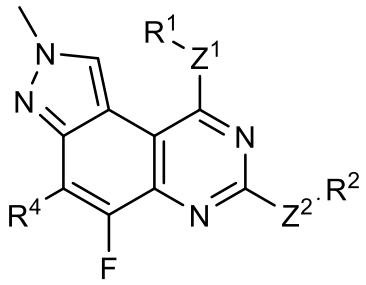
wherein x is independently selected from 0, 1, 2, 3, and 4.

22. A compound of claim 21, wherein R^4 has the structure:



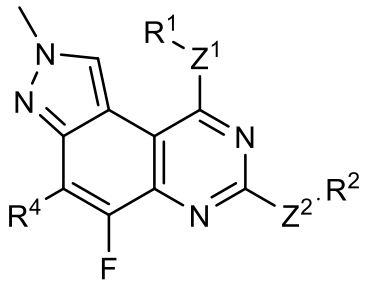
wherein R^{12a} is independently H or C_1-C_4-alkyl; x2 is independently selected from 0, 1, 2 and 3.

23. A compound of any one of claims 1-22 having the structure:



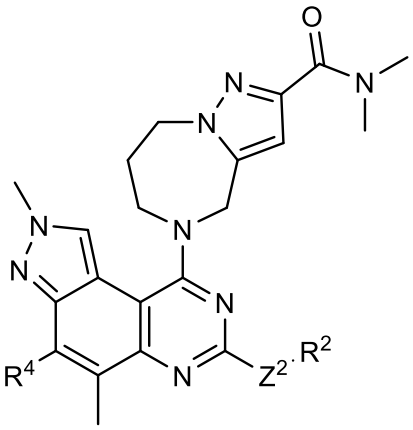
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24. A compound of any one of claims 1-23 having the structure:



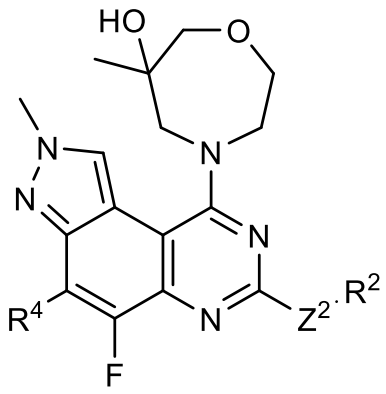
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25. A compound of any one of claims 1-24 having the structure:



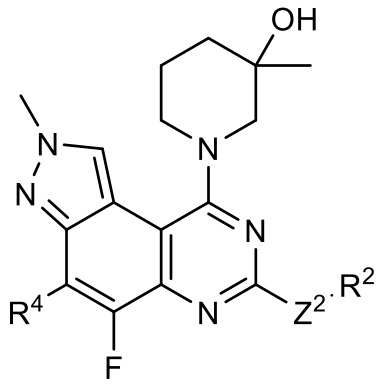
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26. A compound of any one of claims 1-25 having the structure:



.

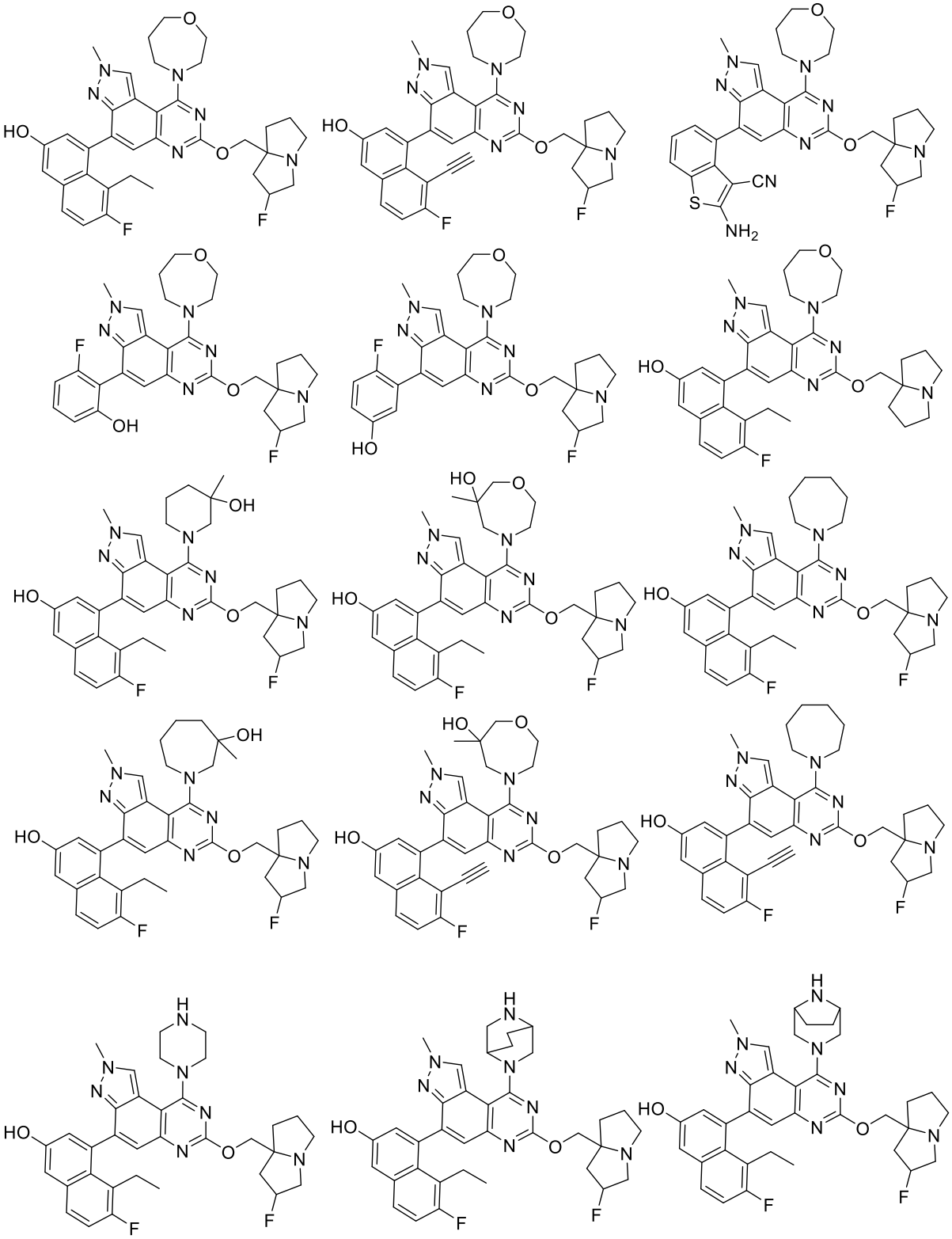
27. A compound of any one of claims 1-26 having the structure

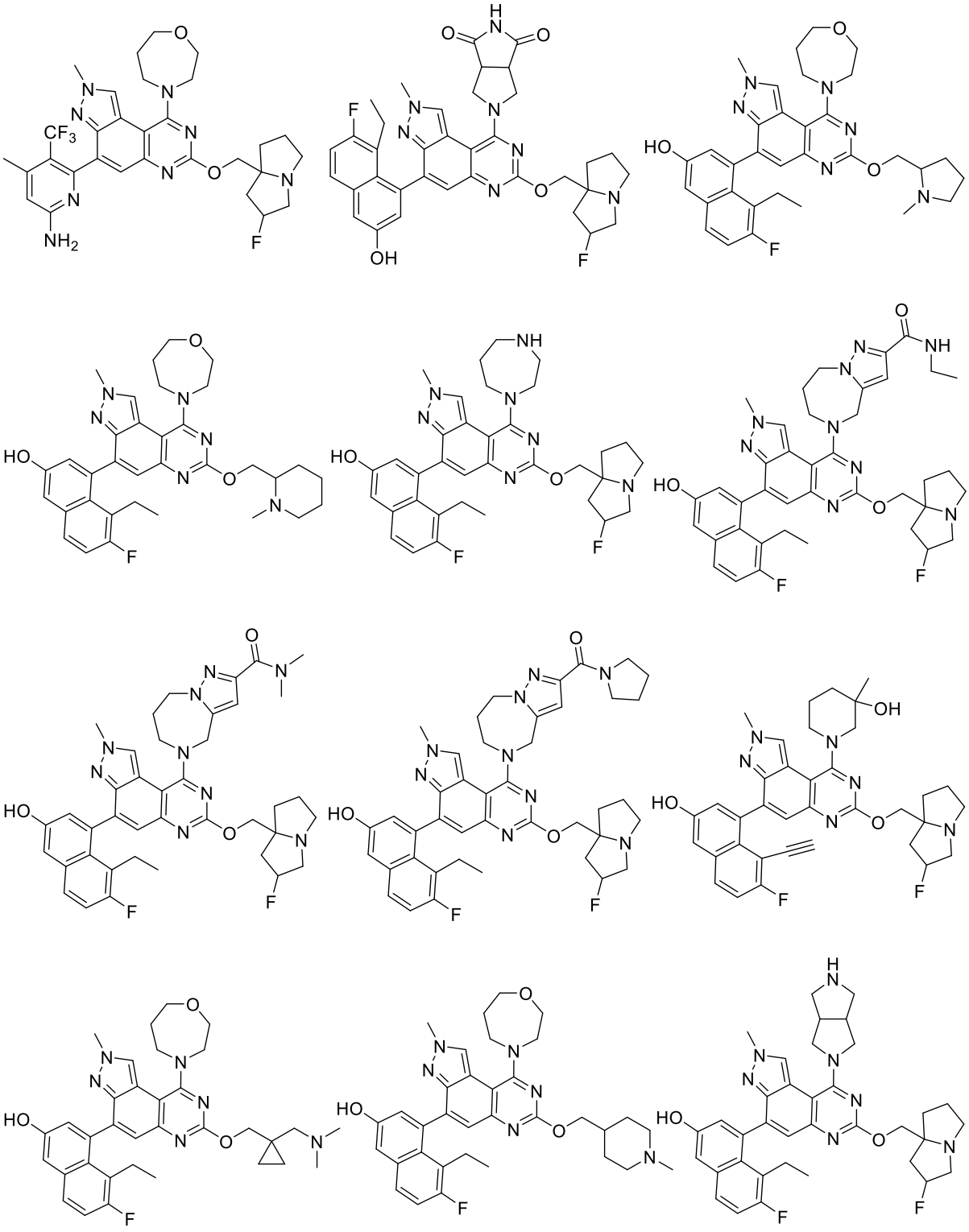


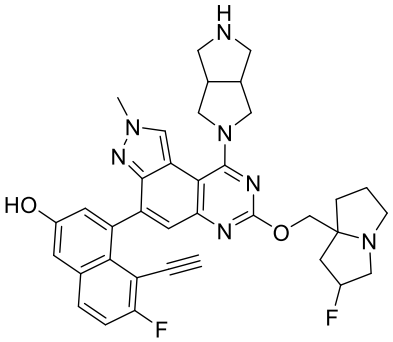
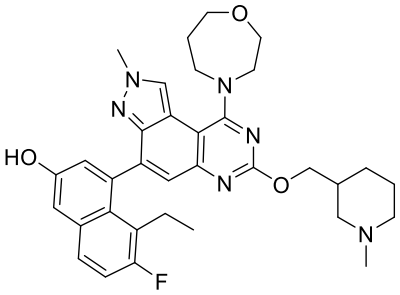
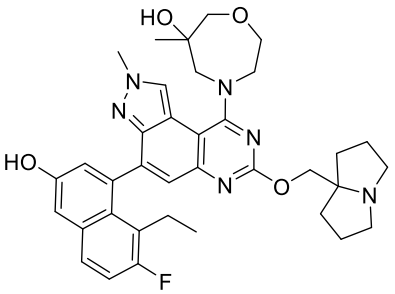
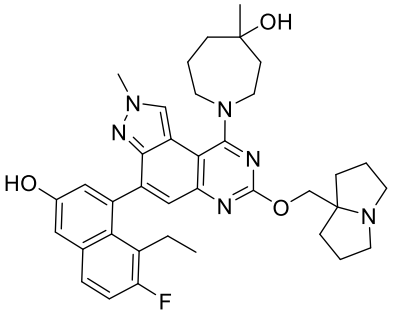
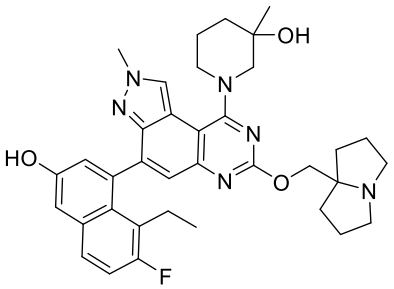
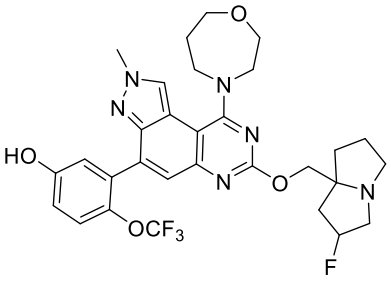
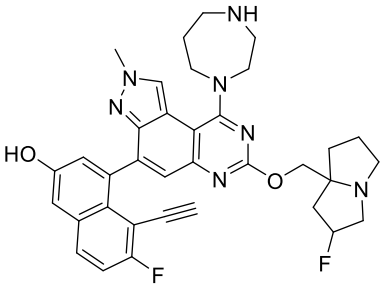
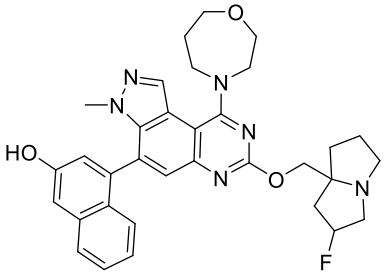
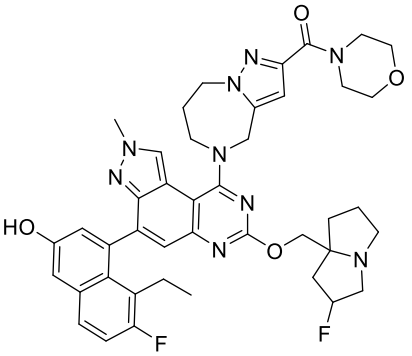
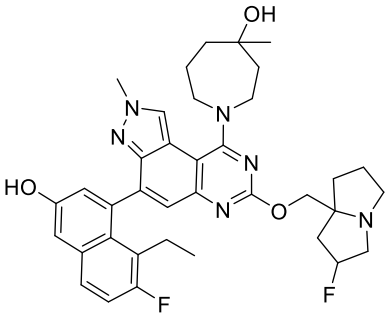
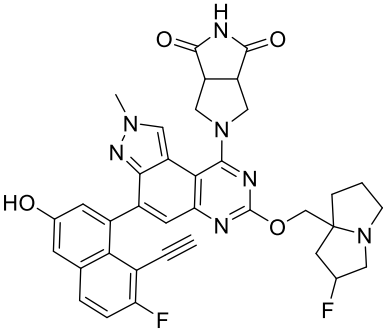
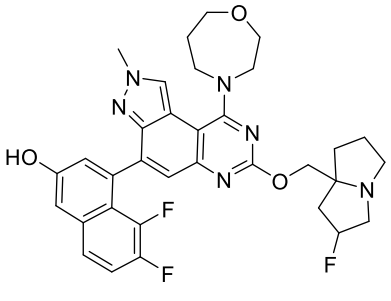
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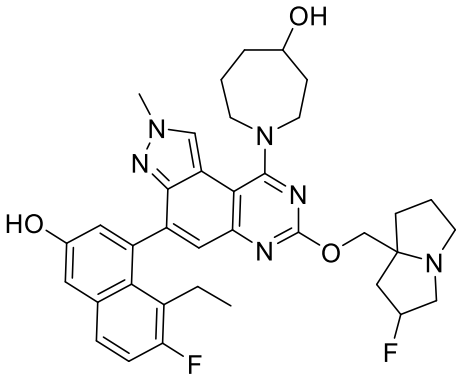
28. A compound of any one of claims 1 to 27, wherein R^4 is 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl, optionally substituted with from 1 to 4 R^{14} groups.

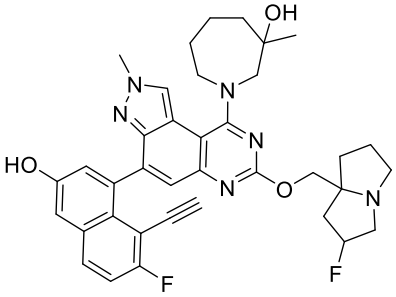
29. A compound of any one of claims 1 to 28, wherein the compound of formula (**I**) is selected from:

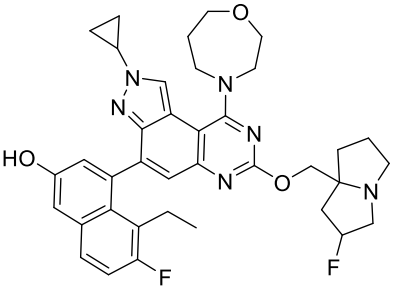


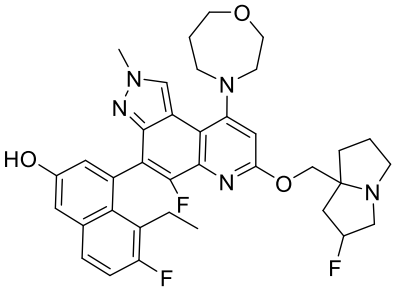


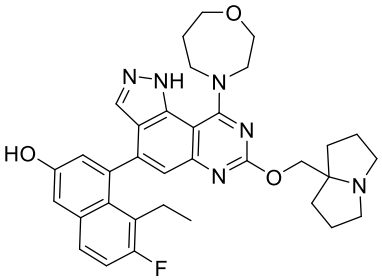













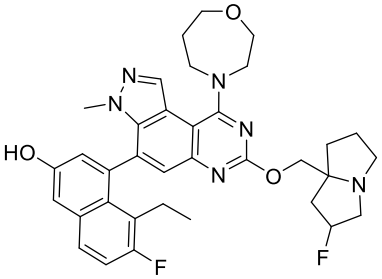


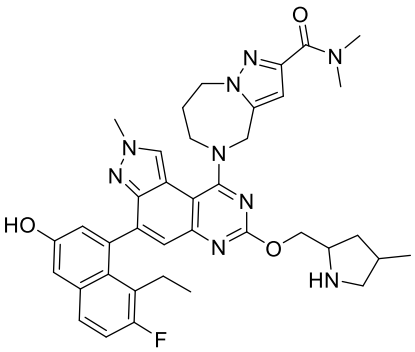


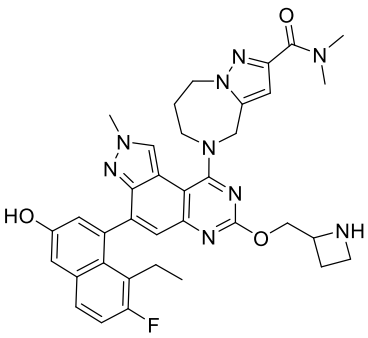


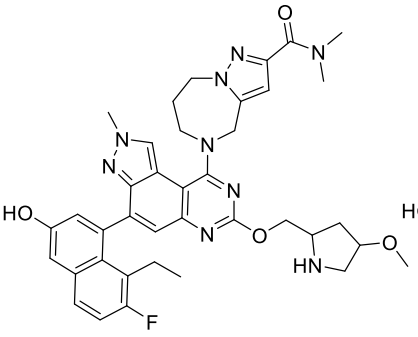


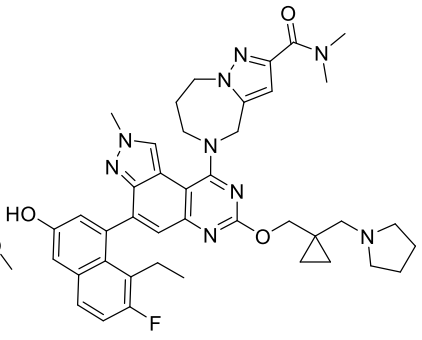


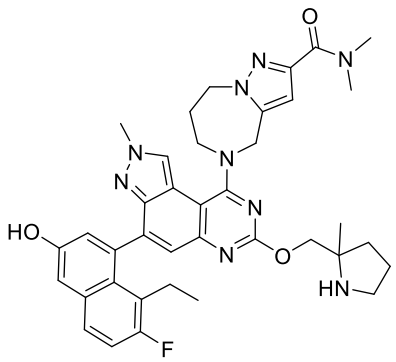
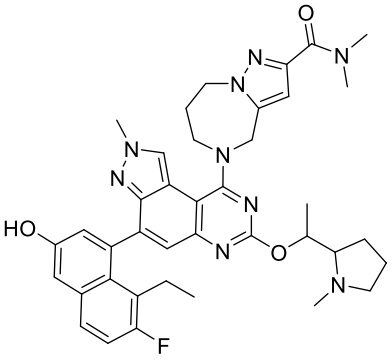
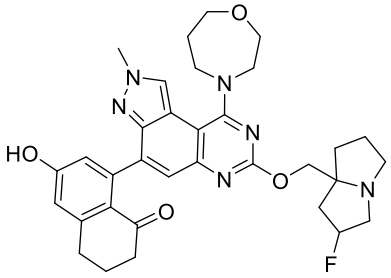
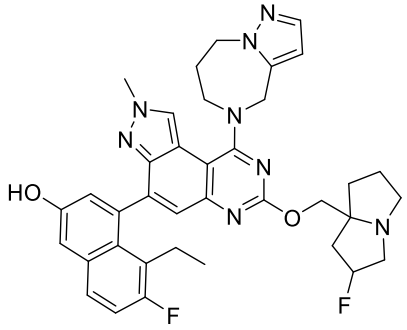
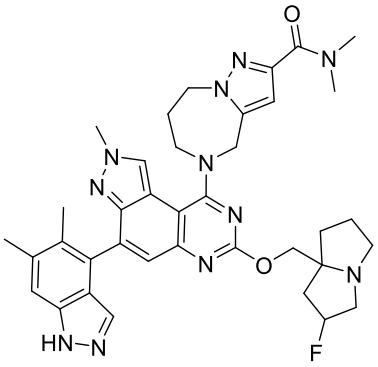
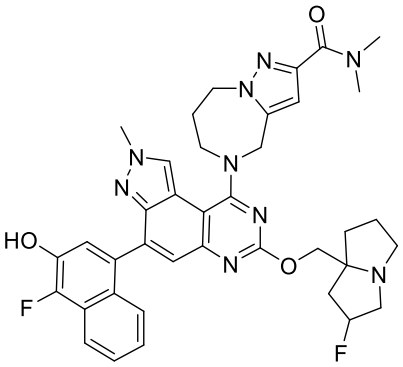
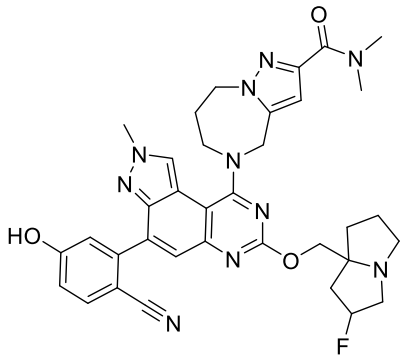
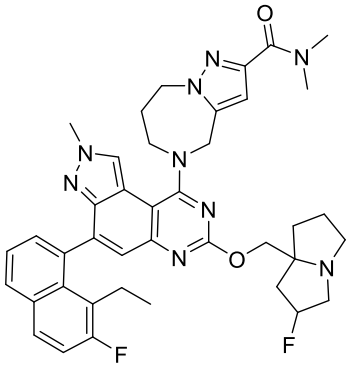
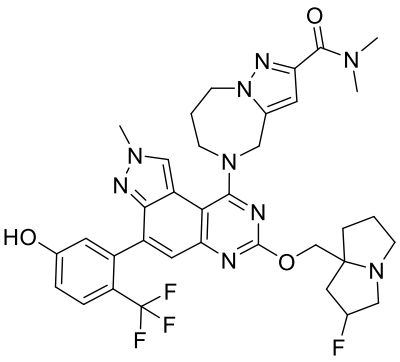
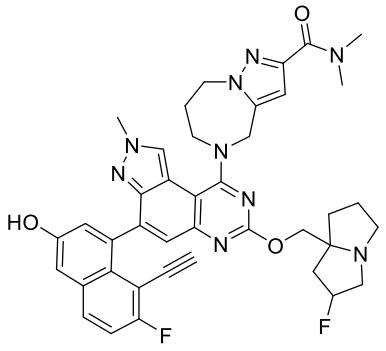
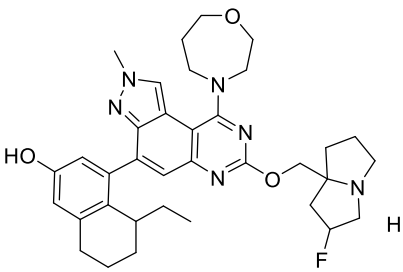


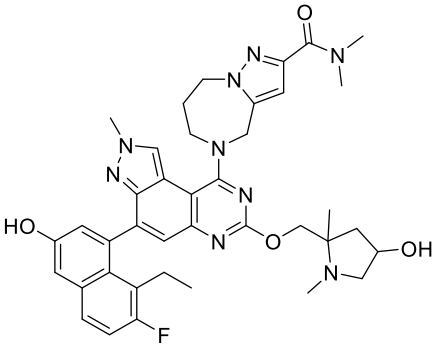


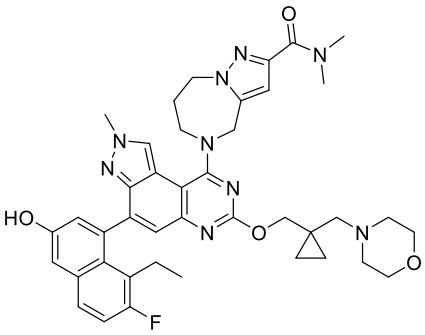
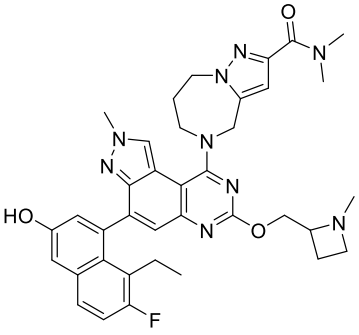
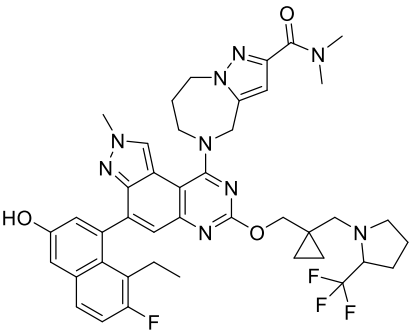
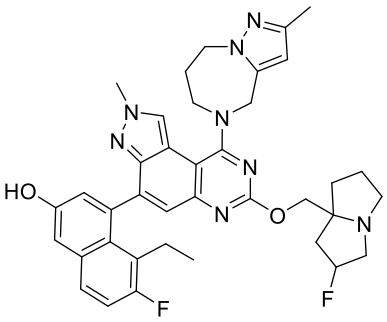
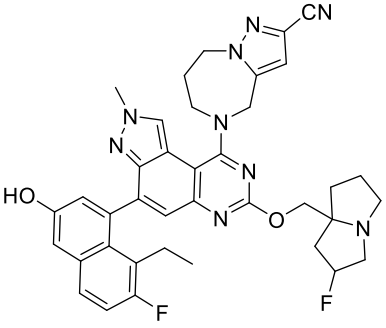
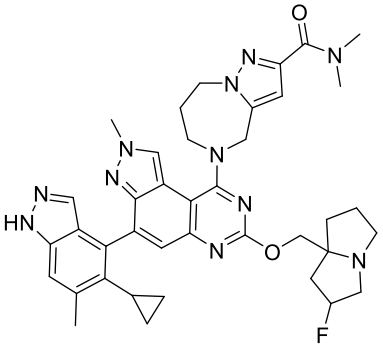
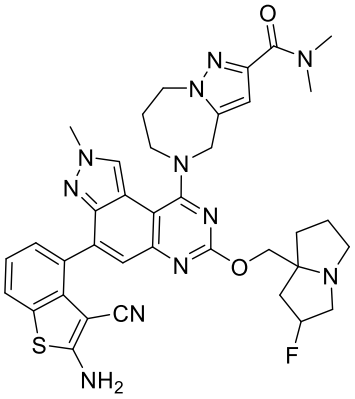
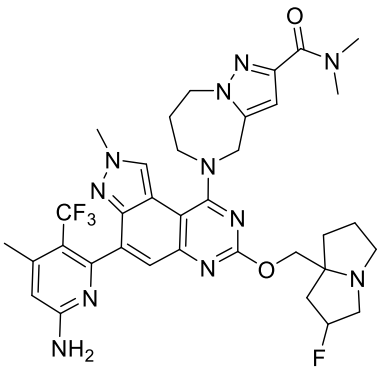
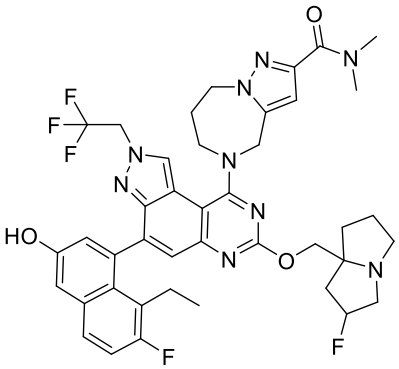
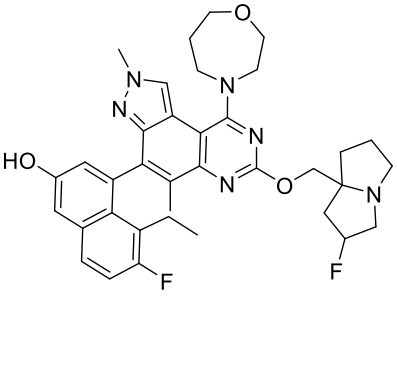
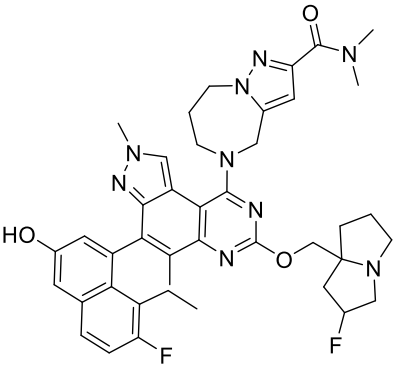


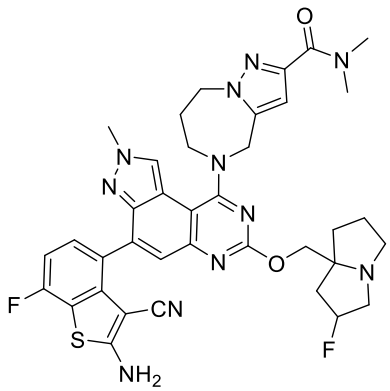
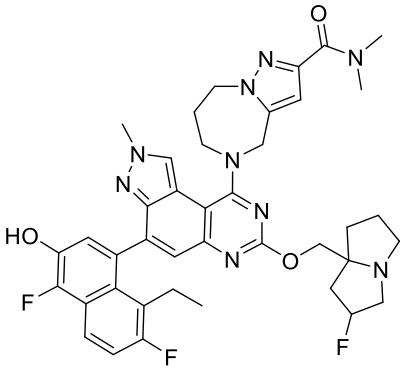
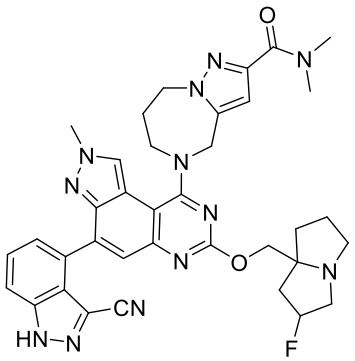
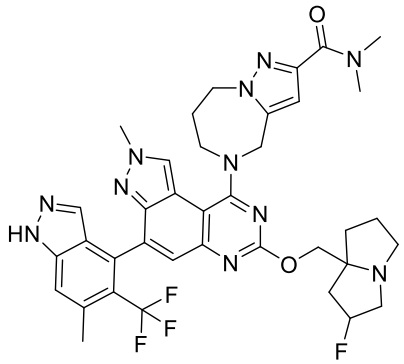
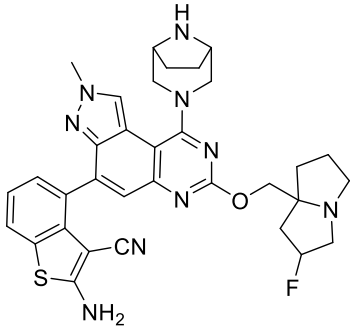
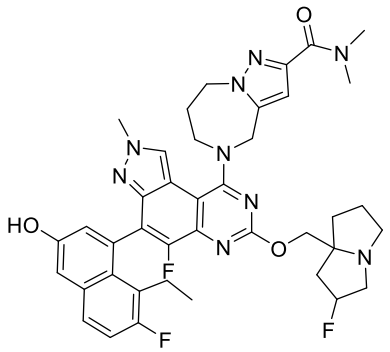
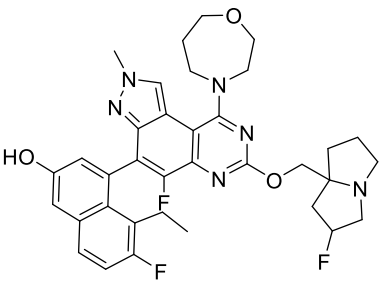
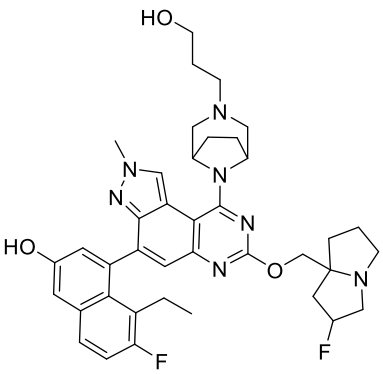
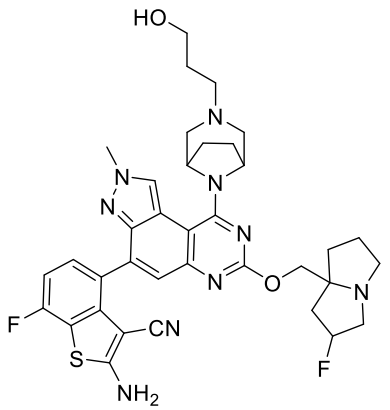
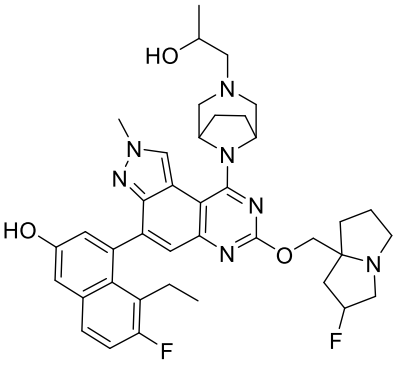
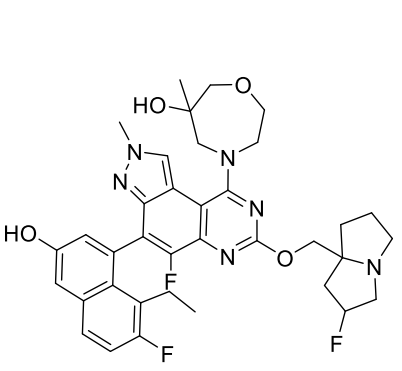


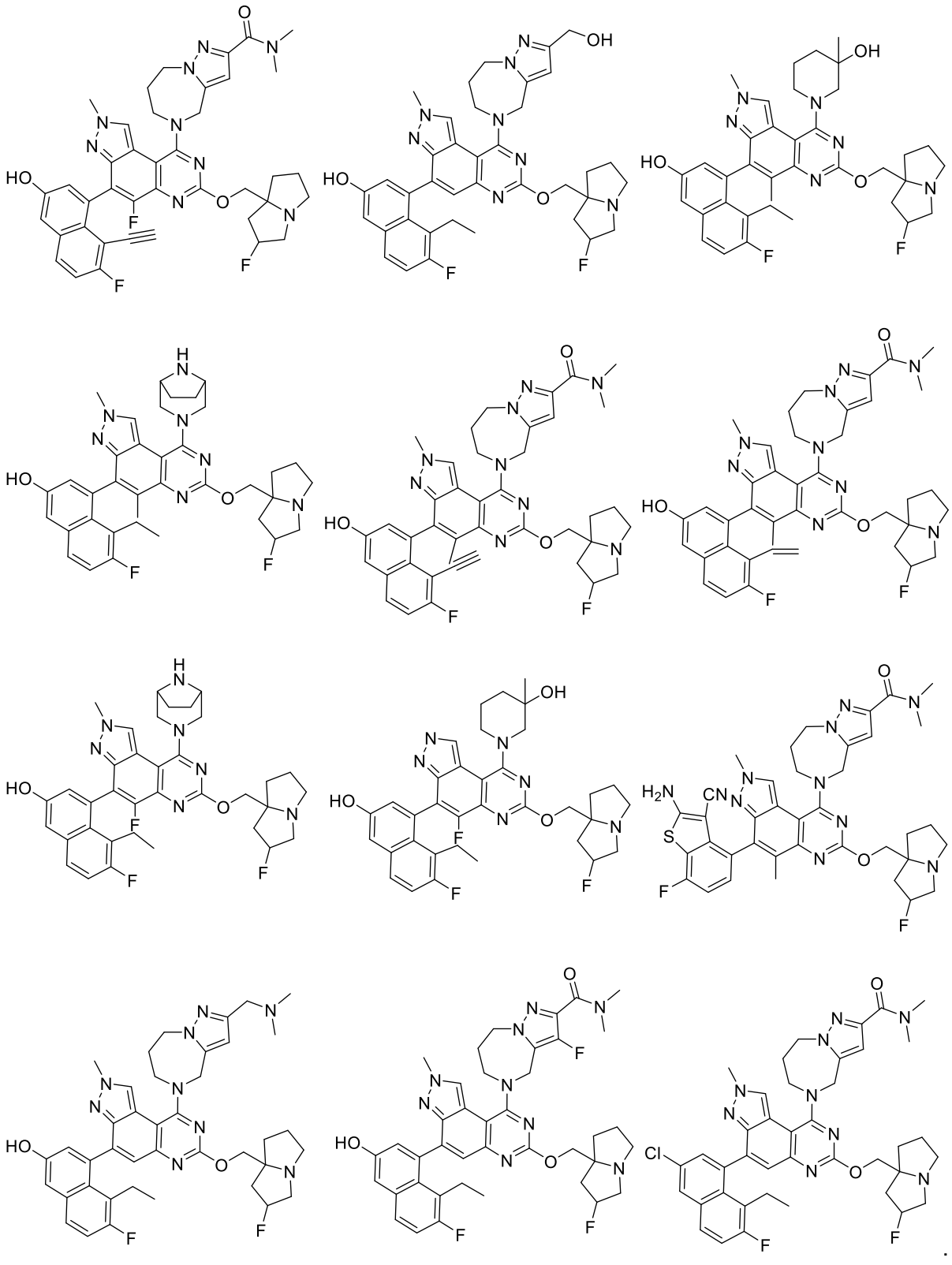


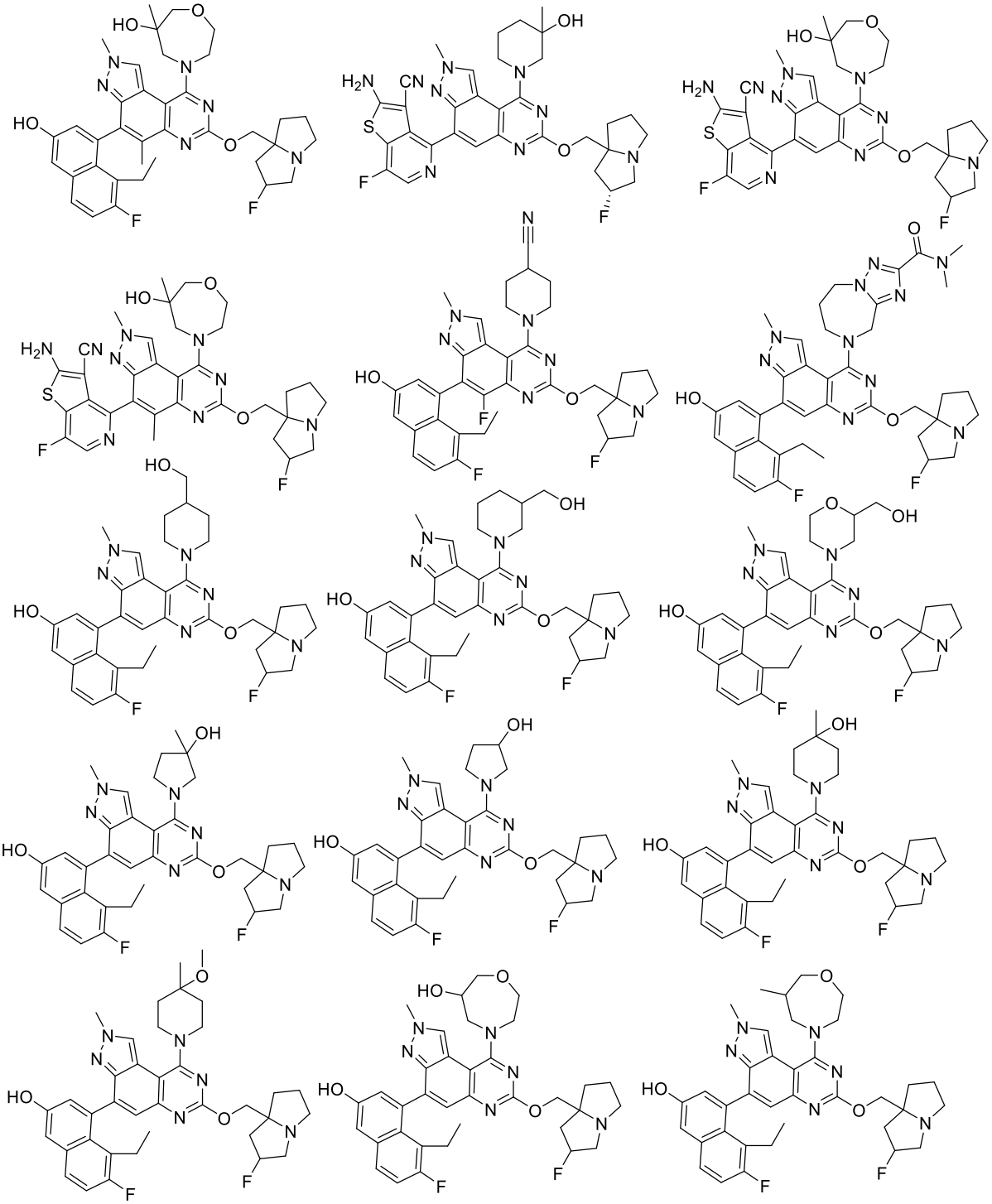












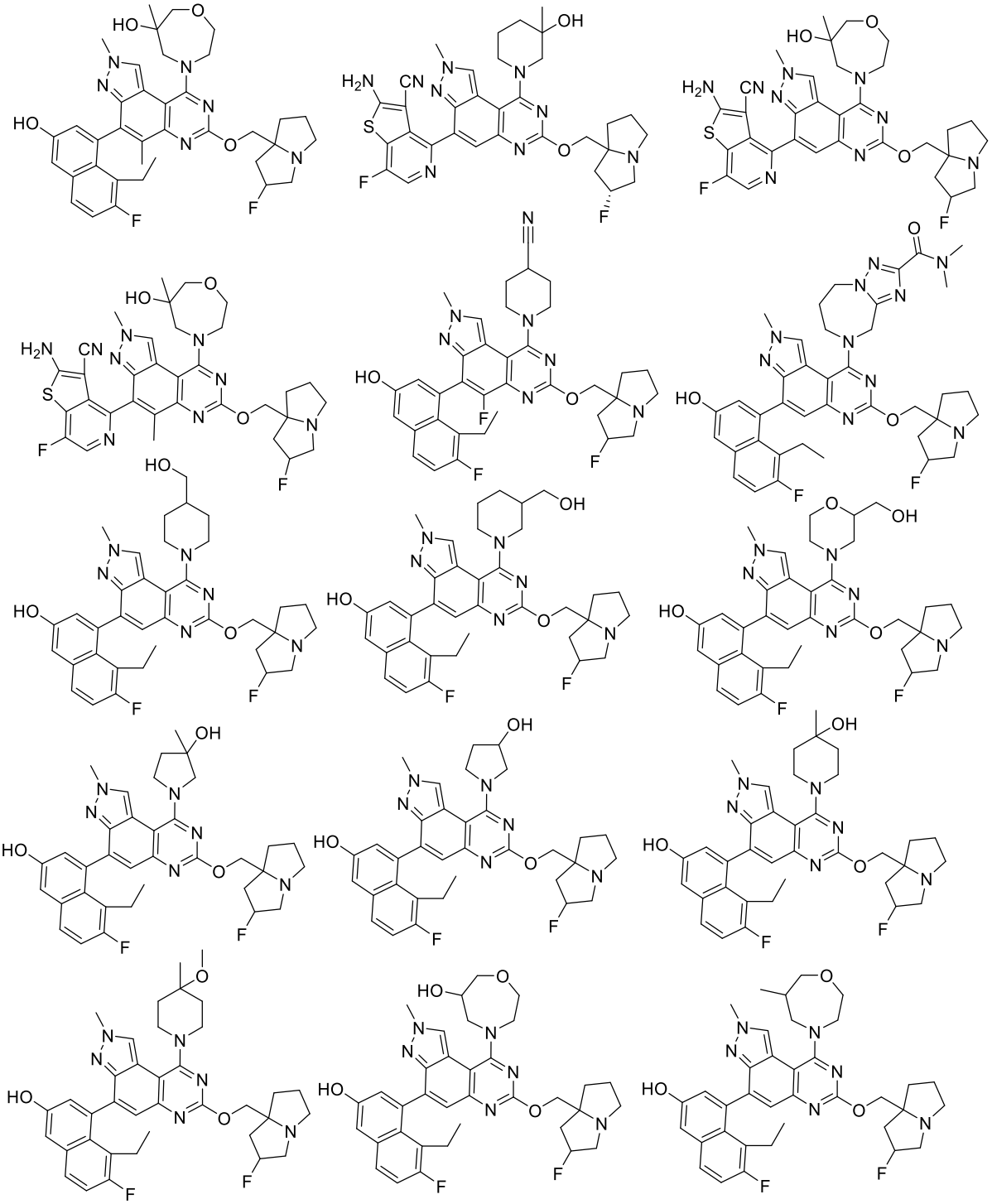


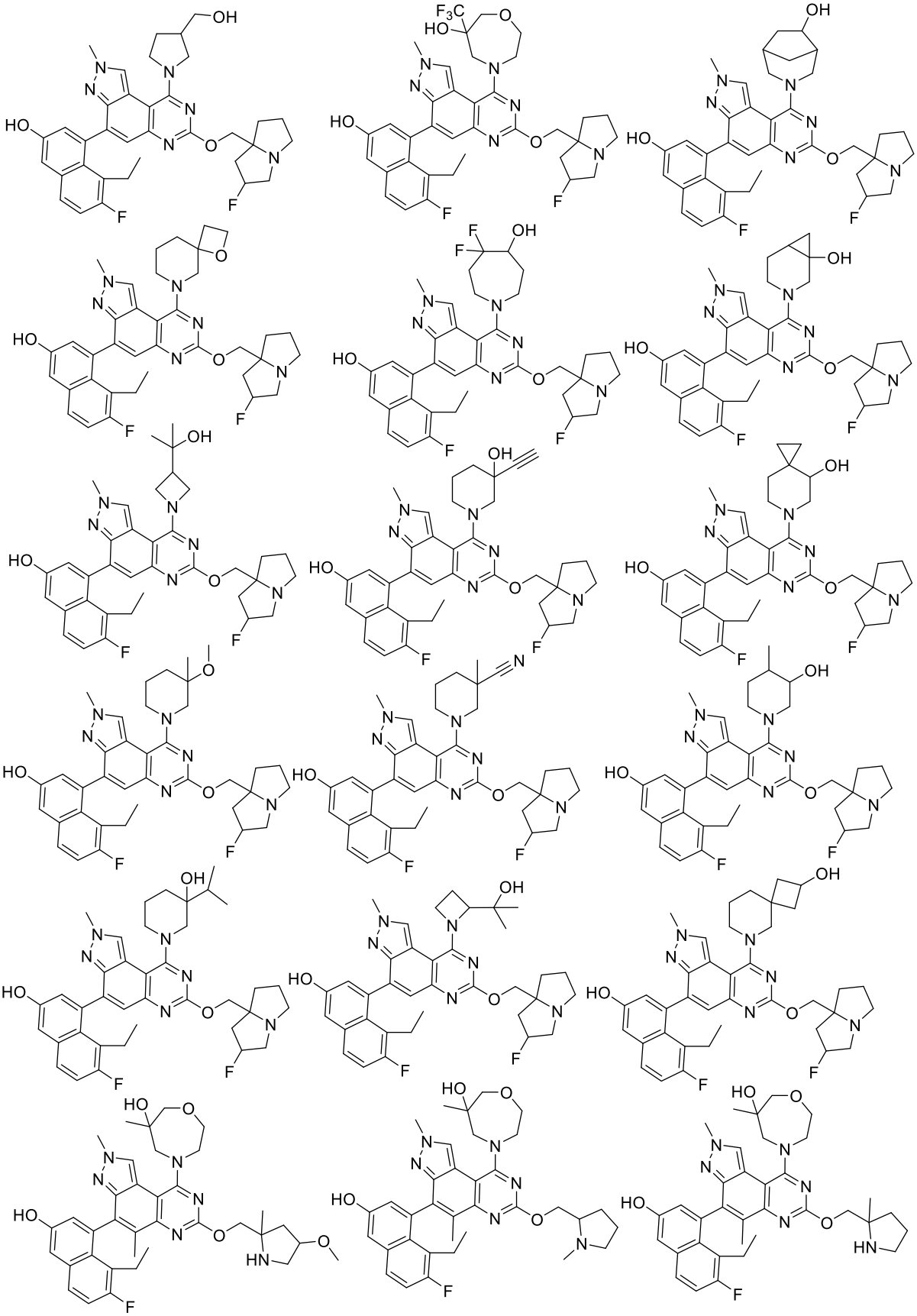












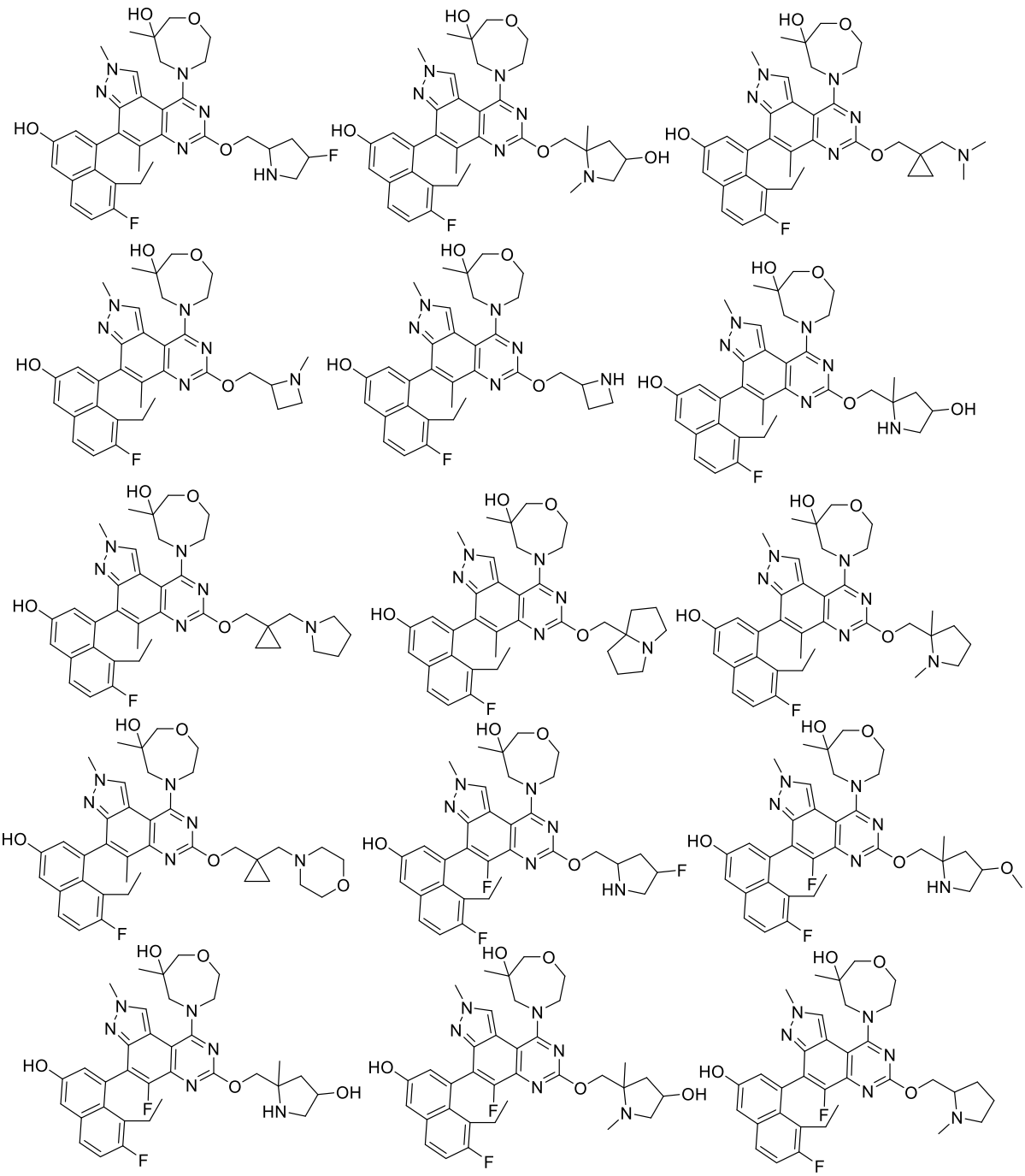












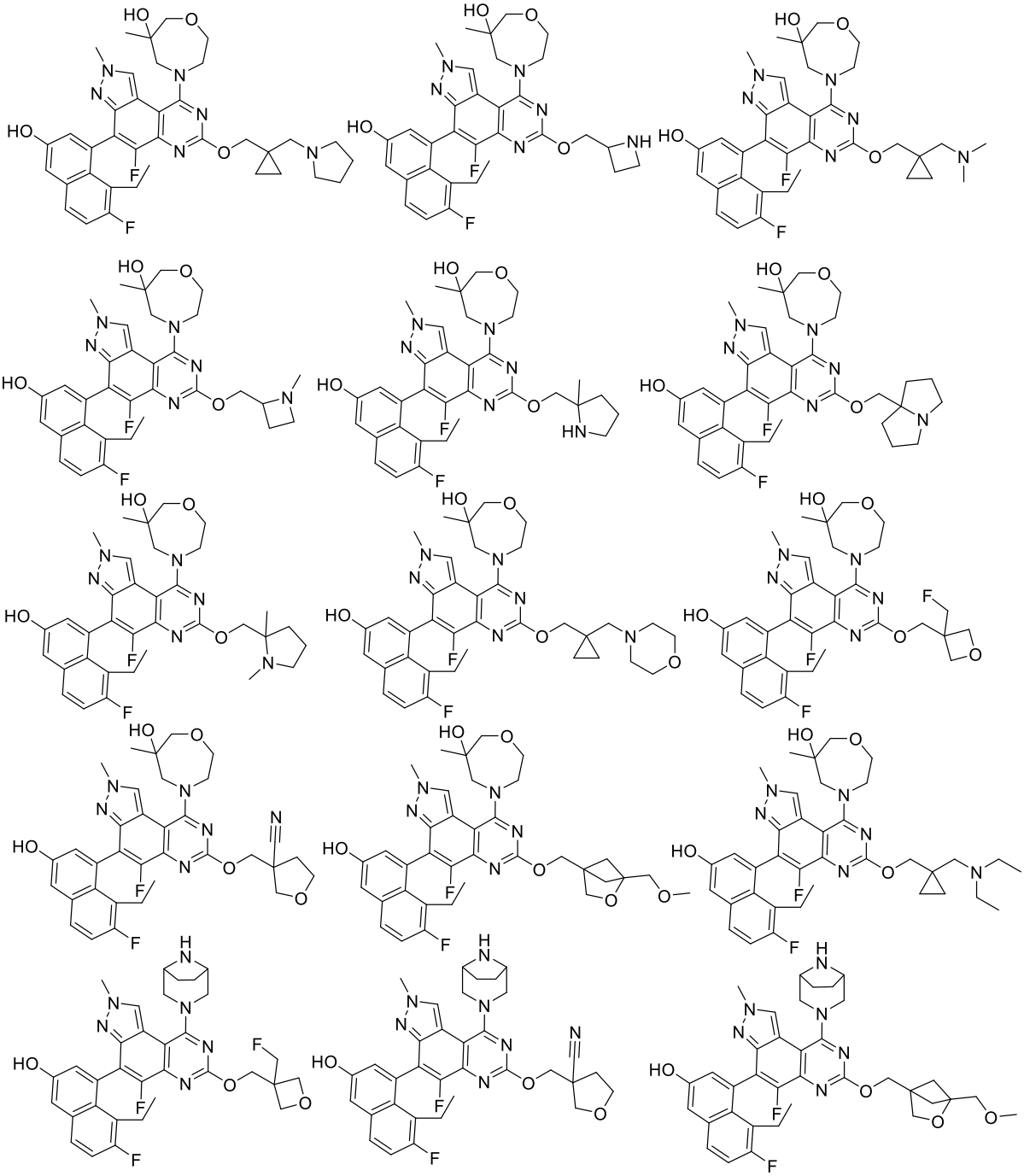


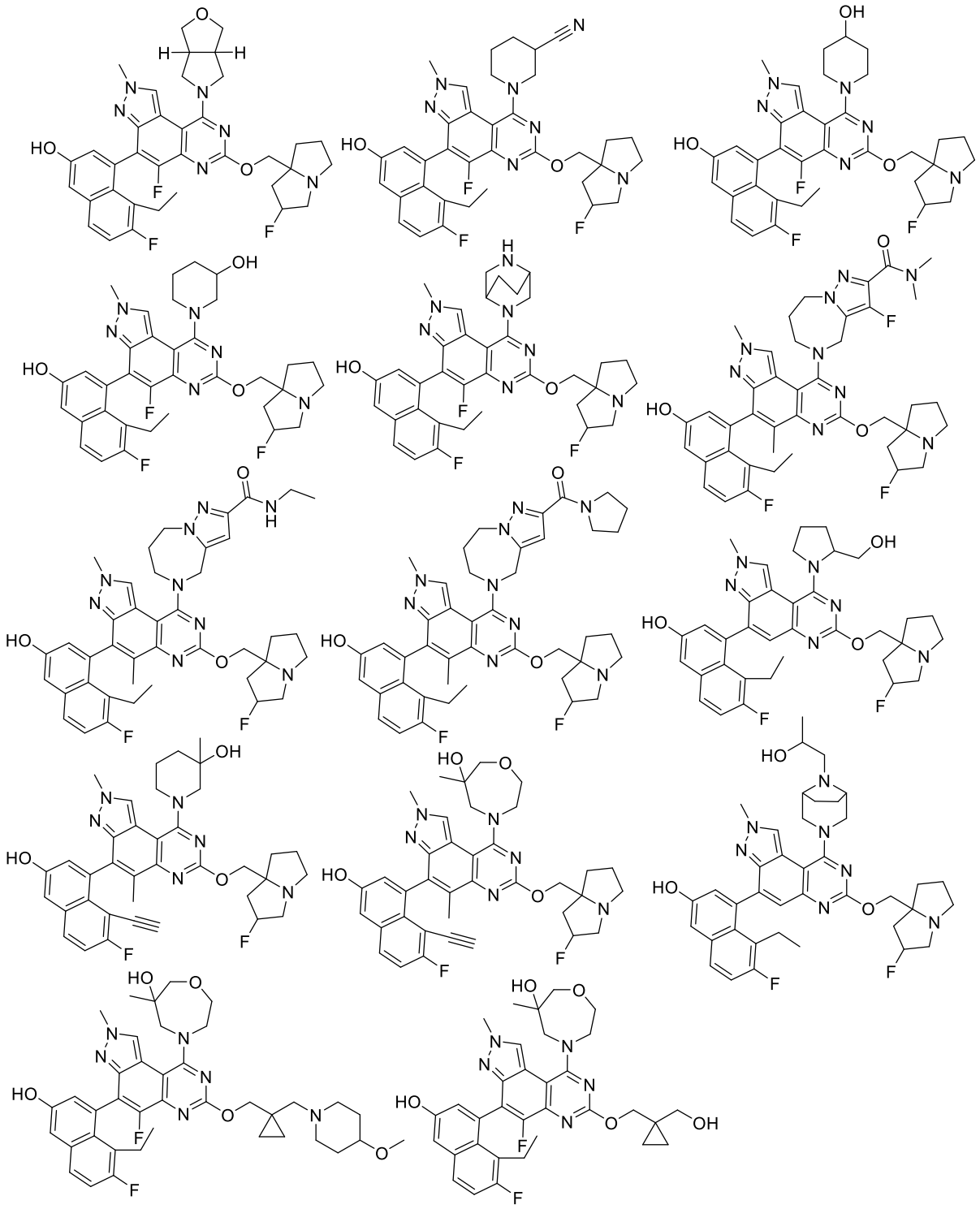


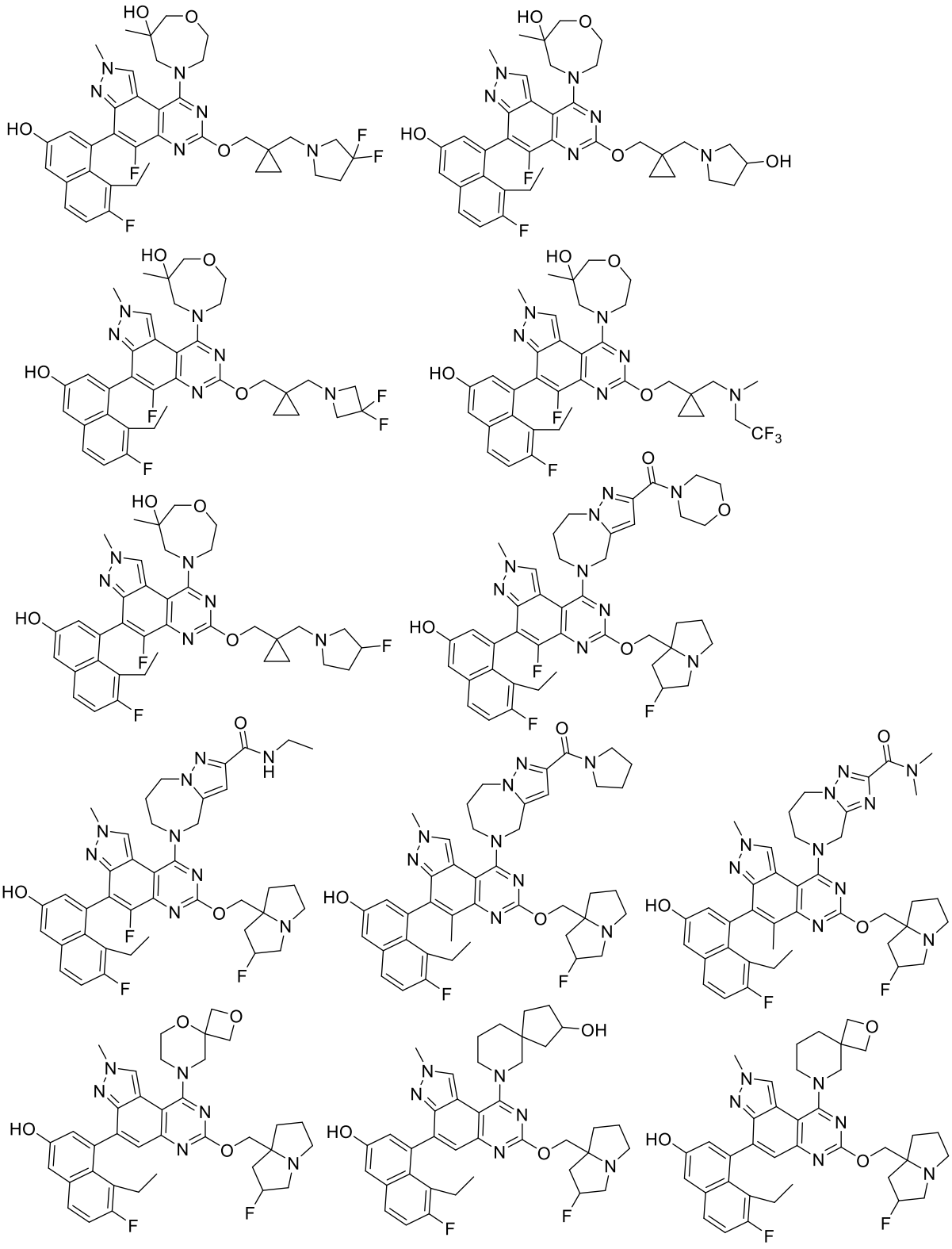


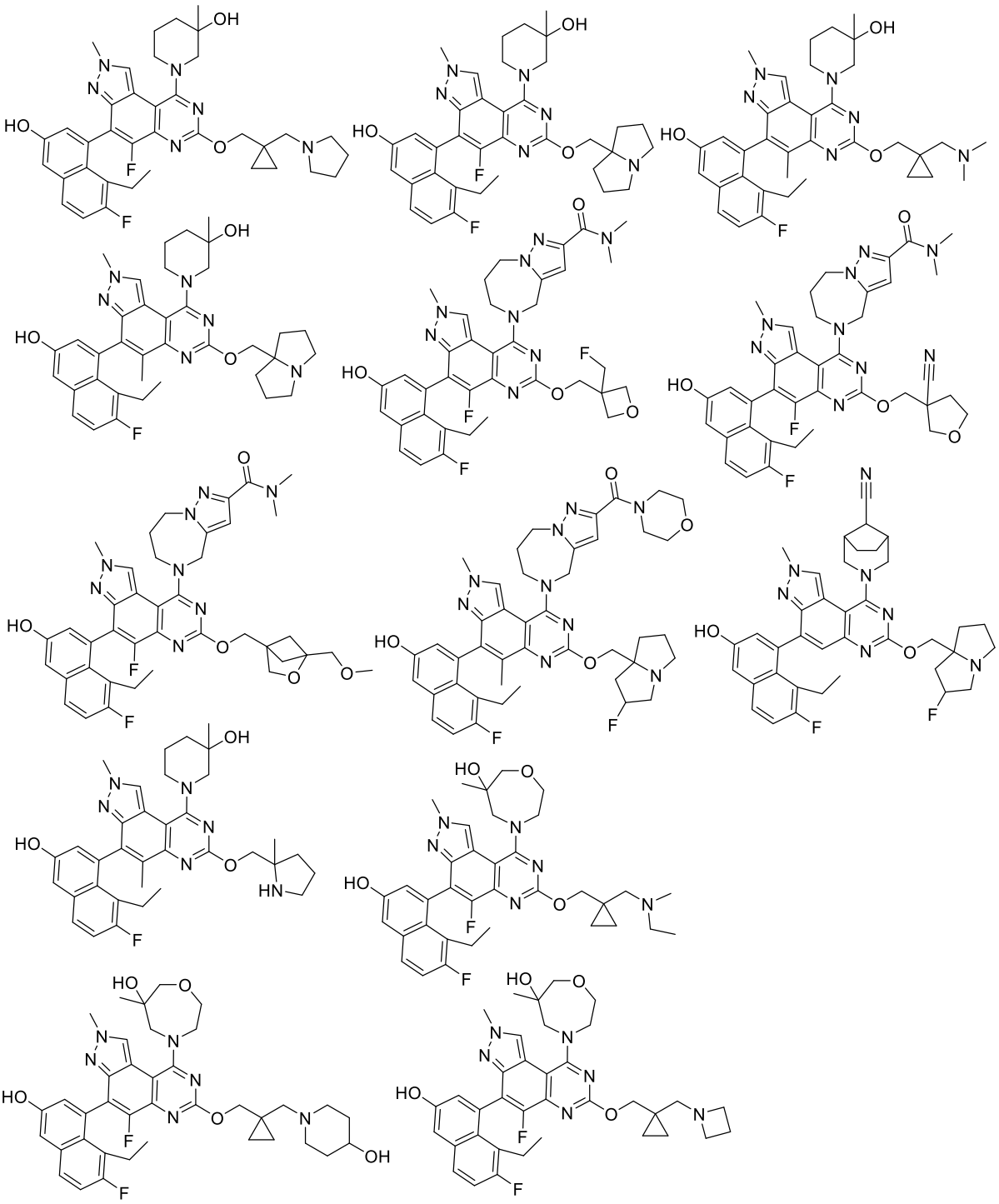


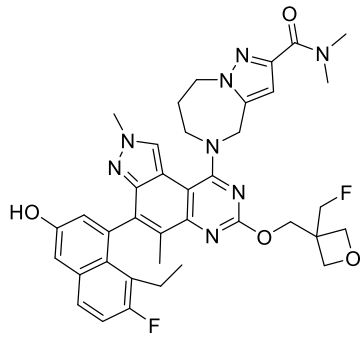
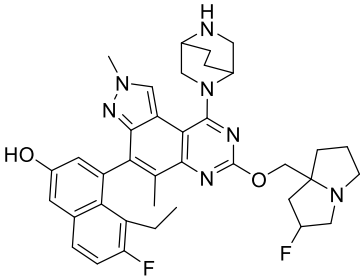
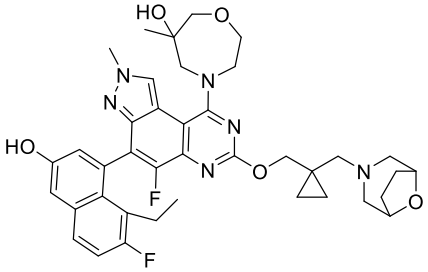
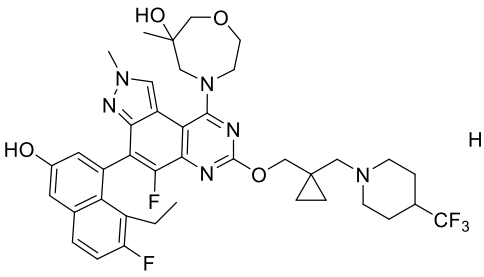
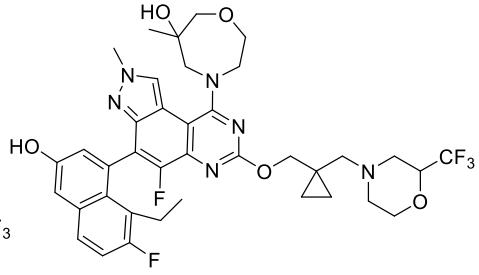
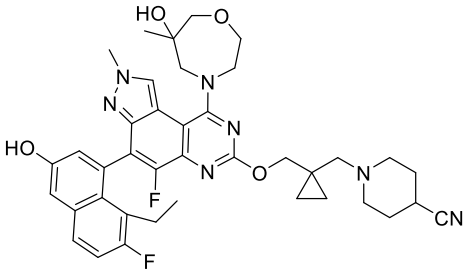
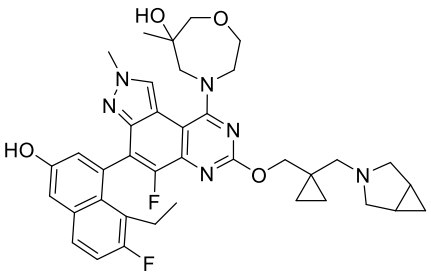
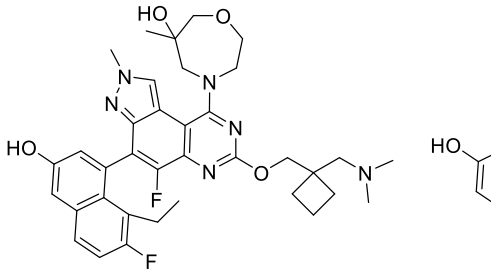
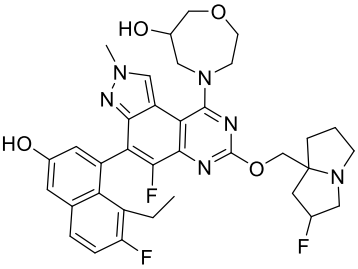
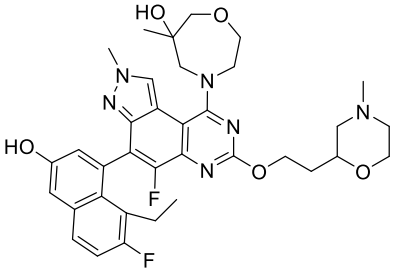
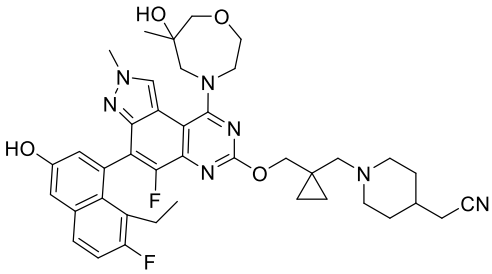


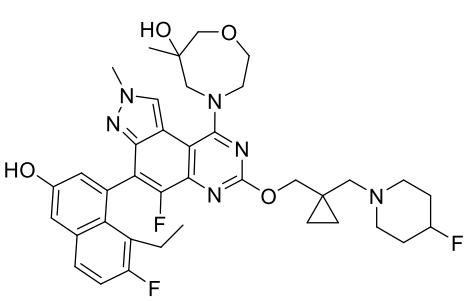


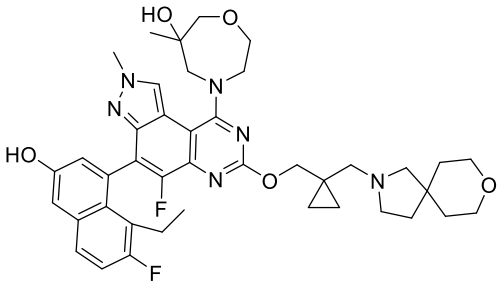


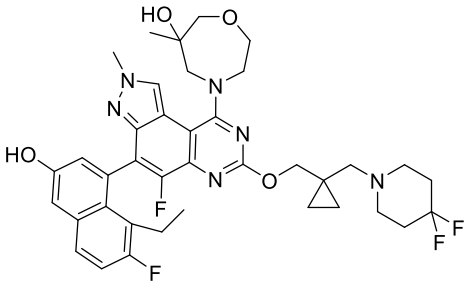


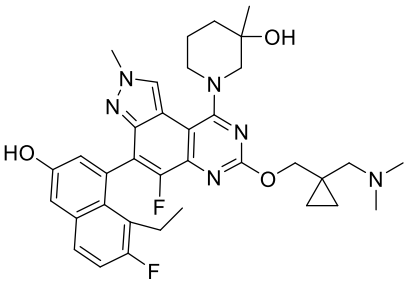


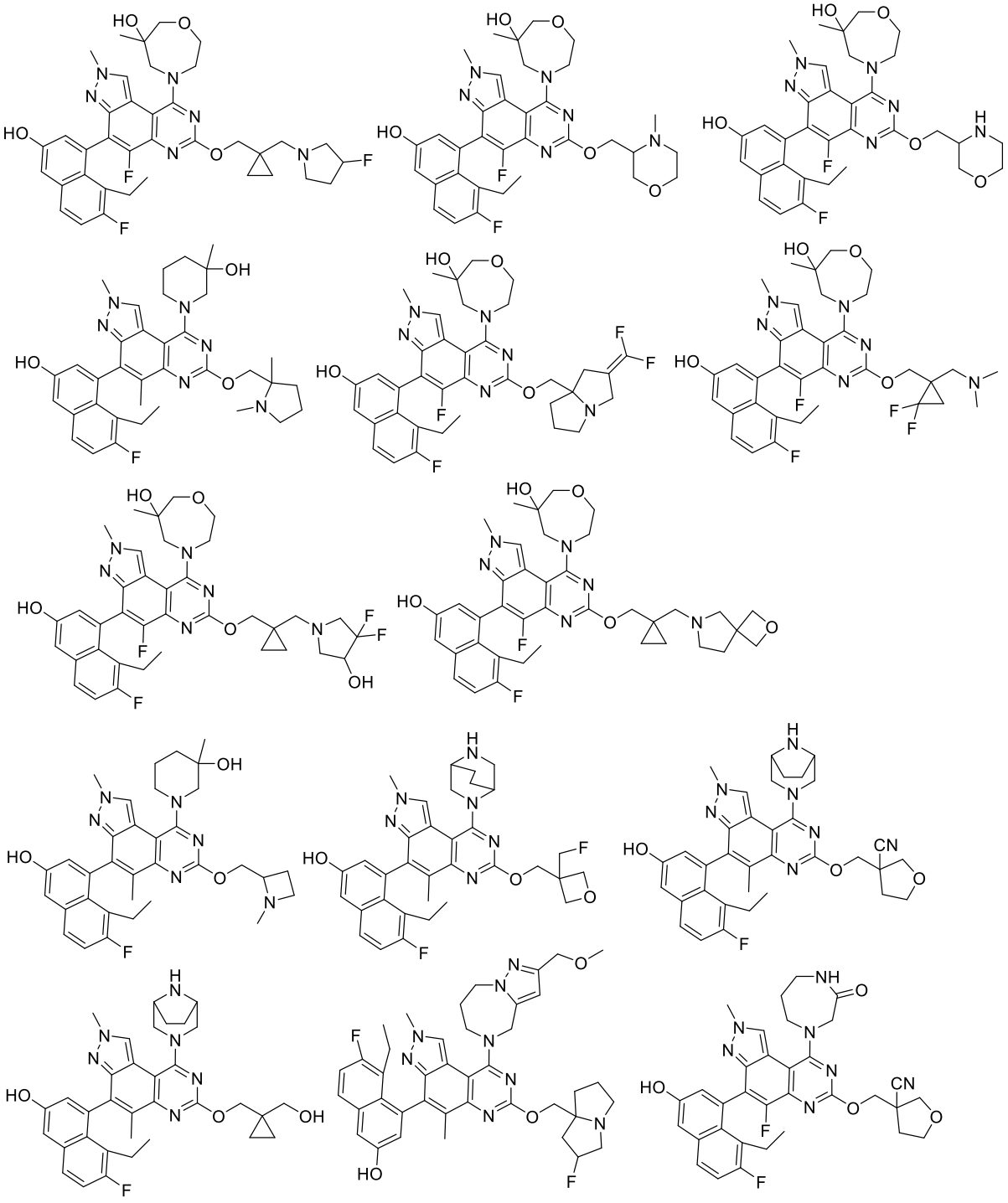












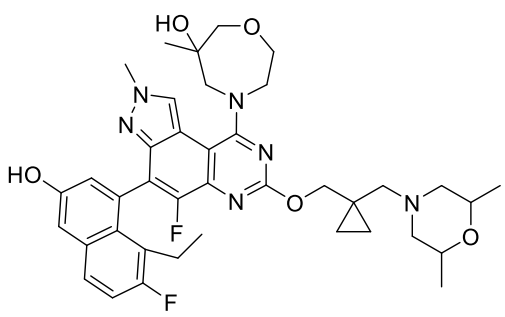


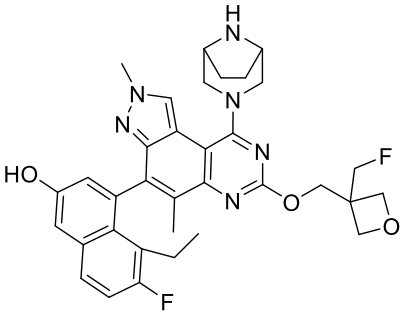


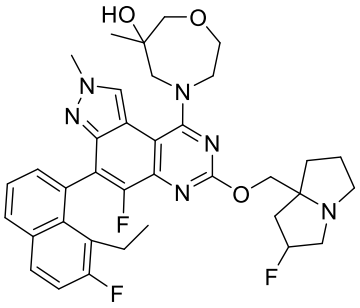


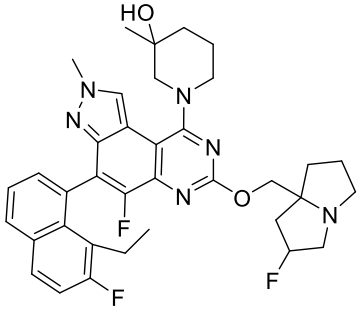


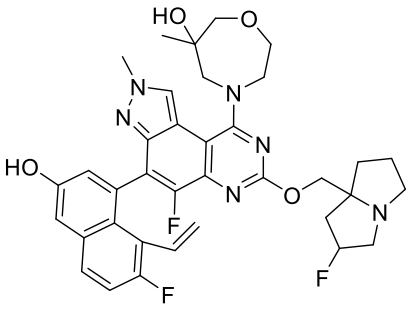


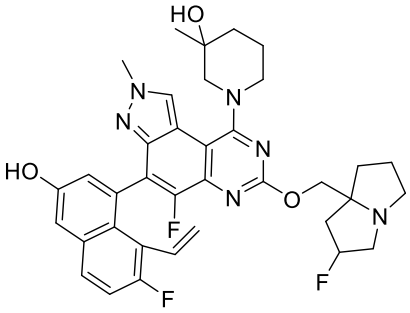


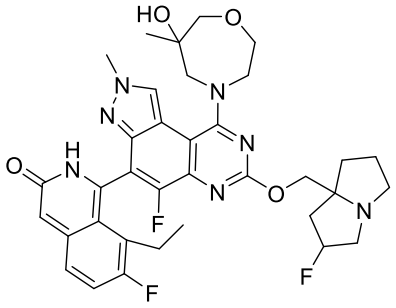


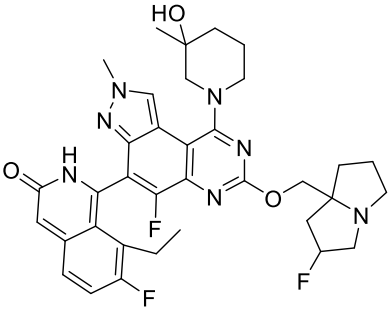


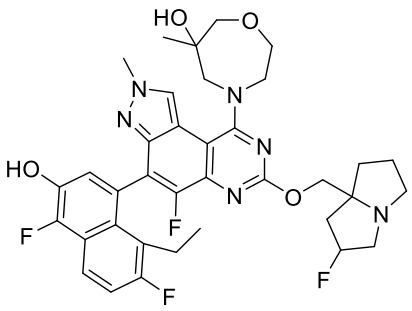


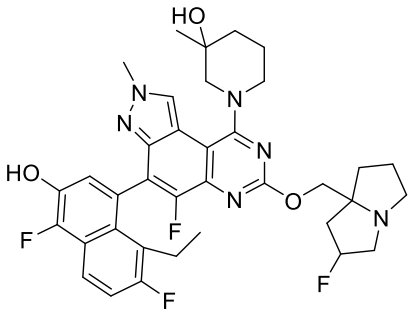


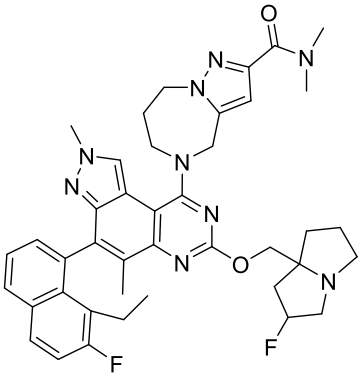


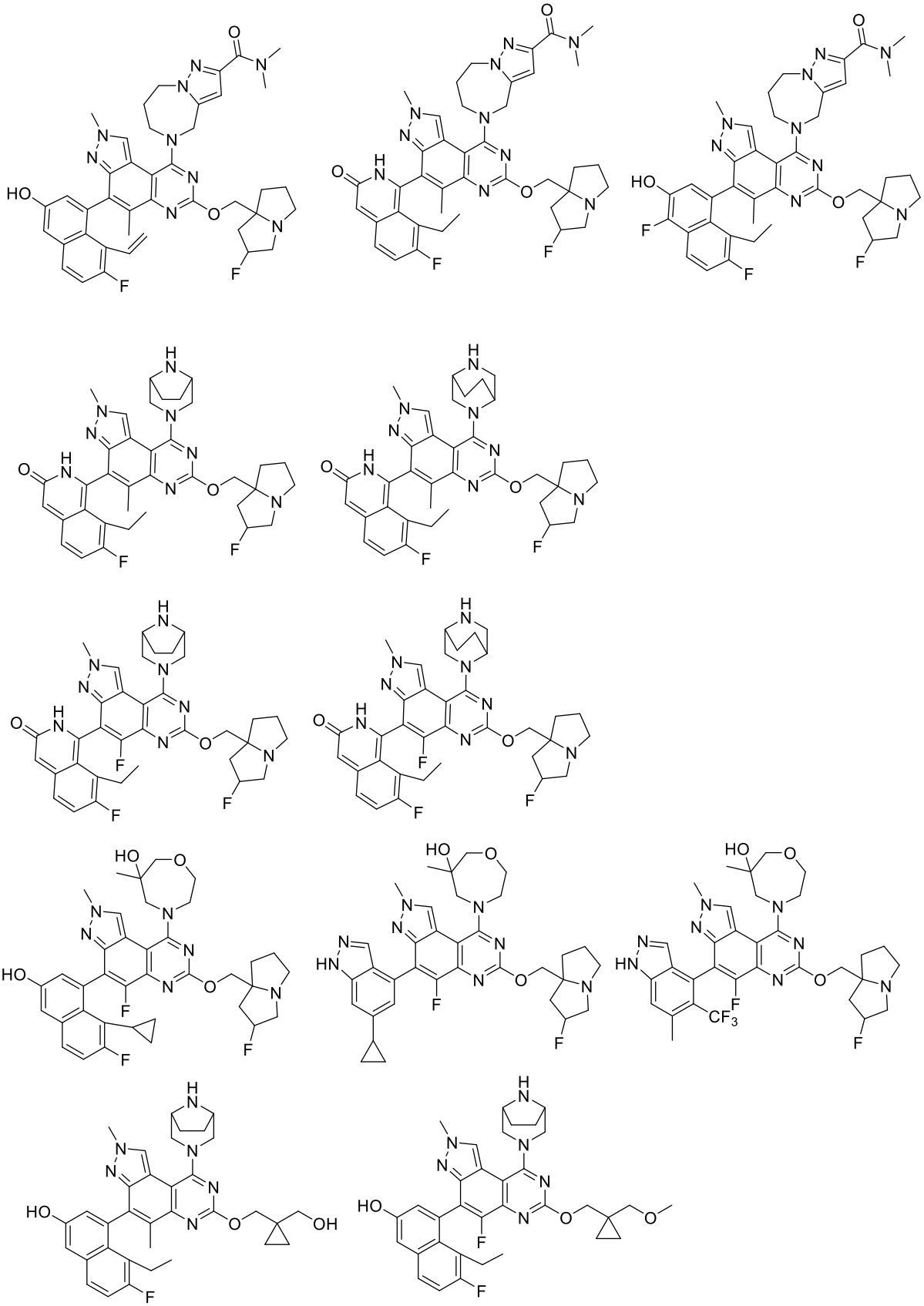


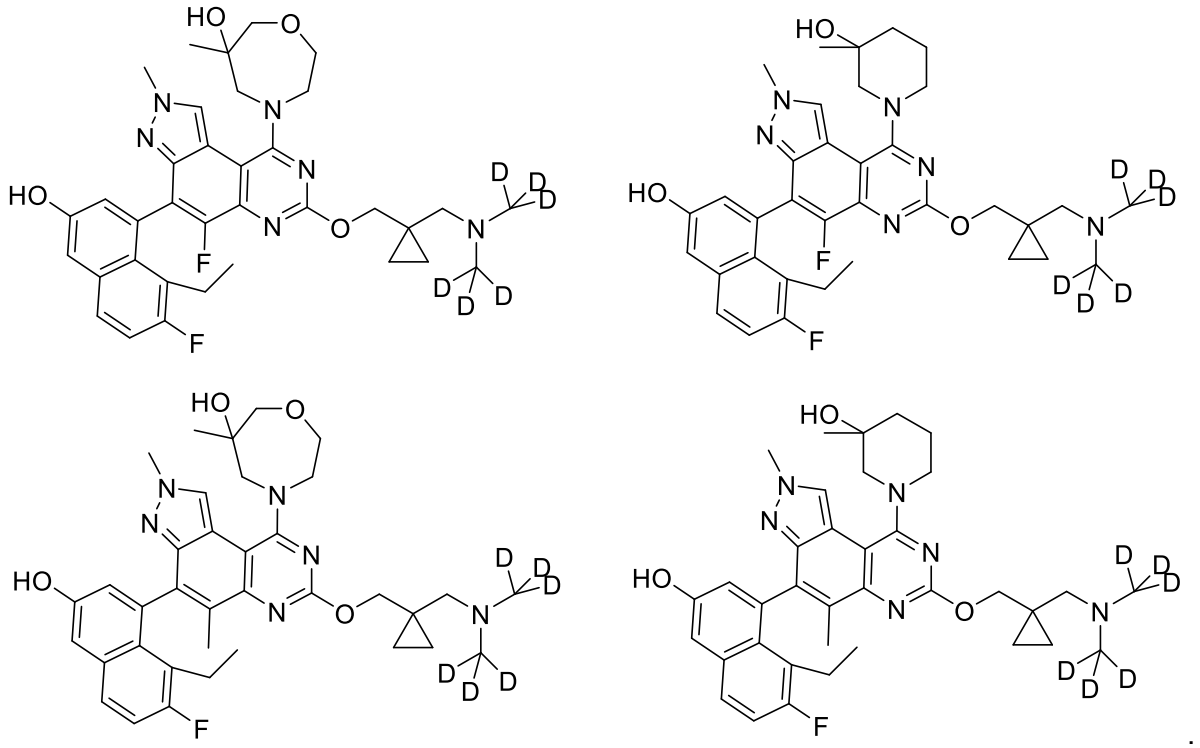












30. A compound of any one of claims 1 to 29 for use in therapy.

31. Use of a compound of any one of claims 1 to 30 in the manufacture of a medicament for treating cancer in a subject; optionally wherein the cancer is selected from: pancreatic carcinoma, colorectal carcinoma, rectal carcinoma, endometrial carcinoma, non-small cell lung carcinoma, gastric carcinoma, ovarian carcinoma and small cell lung carcinoma.

32. The use of claim 31, wherein the subject being treated has a cancer having wild-type KRAS.

33. The use of claim 32, wherein the subject being treated has a cancer having a KRAS mutation selected from: KRAS G12D, KRAS G12C, KRAS G12V, KRAS G12A, KRAS G12D, KRAS G12S, KRAS G13D and KRAS Q61H.

34. A pharmaceutical composition comprising a compound of any one of claims 1 to 29 and a pharmaceutically acceptable excipient.