[0009] 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.

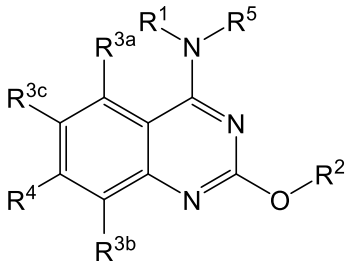
[0010] It is an aim of certain embodiments of this invention to provide compounds which exhibit reduced cytotoxicity relative to prior art compounds and existing therapies.

[0011] 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).

[0012] Certain embodiments of the present invention satisfy some or all of the above aims.

BRIEF SUMMARY OF THE DISCLOSURE

[0012a] In a first aspect of the present disclosure, there is provided a compound of formula (**Ia**), or a pharmaceutically acceptable salt thereof:



(**Ia**)

wherein

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 fused or spirofused bicyclic 6- to 11-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups and a C_3-C_7-cycloalkyl ring; 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: OR^8, SR^8, SOR^8, SO_2R^8, $SO(NH)R^8$, $OC(O)R^8$, and $SO_2NR^7R^8$;

or R^1 and R^5 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 heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups;

wherein R^1 and R^5 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;

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;

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

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

or R^2 and R^6 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; and 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl, wherein R^4 is optionally substituted with from 1 to 4 R^{14} groups;

R^5, R^6, 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^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;

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} and R^{14} are each 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 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.

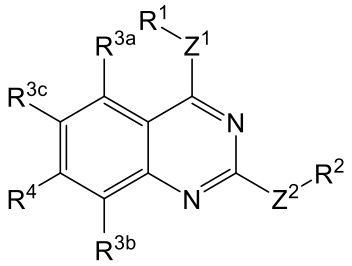
[0012b] In another aspect of the present disclosure, there is provided a compound as disclosed herein for medical use.

[0012c] In yet another aspect of the present disclosure, there is provided a use of a compound as disclosed herein in the manufacture of a medicament for treating cancer in a subject in need thereof.

[0012d] 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.

[0012e] In another aspect of the present disclosure, there is provided a compound as disclosed herein for use in therapy.

[0013] In accordance with the present disclosures there is provided a compound of formula (**I**), or a pharmaceutically acceptable salt thereof:



(**I**)

wherein

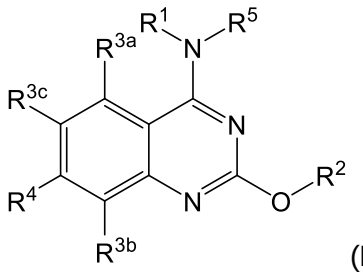
Z^1 is independently selected from -O- and -NR^5-;

Z^2 is independently absent or is selected from -O- and -NR^6-;

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^5 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 heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups;

[0014] In an example, the compound of formula (**I**) is a compound of formula (**Ia**):



(**Ia**);

wherein

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 fused or spirofused bicyclic 6- to 11-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups and a C_3-C_7-cycloalkyl ring; 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: OR^8, SR^8, SOR^8, SO_2R^8, $SO(NH)R^8$, $OC(O)R^8$, and $SO_2NR^7R^8$;

or R^1 and R^5 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 heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups;

wherein R^1 and R^5 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;

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;

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

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

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; and 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl, wherein R^4 is optionally substituted with from 1 to 4 R^{14} groups;

R^5, 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;

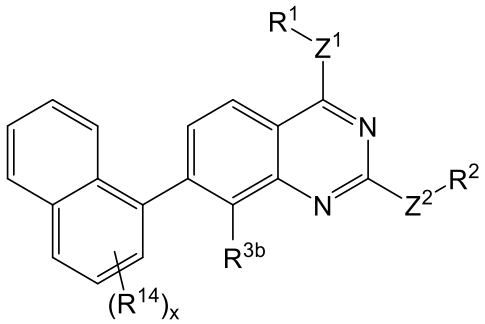
R^7 and R^{13} are each independently at each occurrence selected from H, C_1-C_4-alkyl, C_1-C_4-haloalkyl and C(O)-C_1-C_4-alkyl;

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} and R^{14} are each 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;

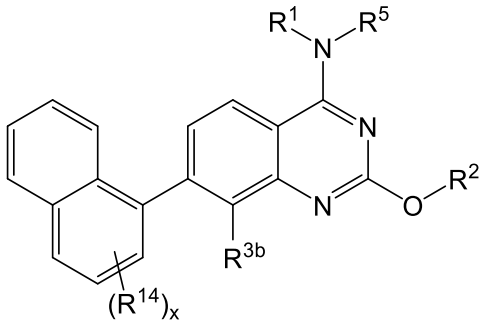
wherein any of the aforementioned alkyl, alkylene or cyclopropyl groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: C_1-C_4-alkyl, halo, nitro, cyano, NR^aR^b, OR^a, SR^a, CO_2R^a,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

[0015] In an example, the compound of formula (**I**) is a compound of formula (**II**):



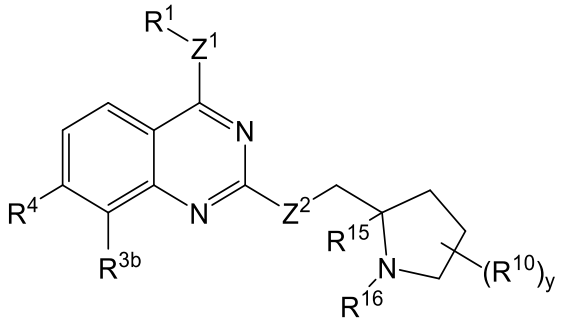
wherein R^1, R^2, R^{3b}, R^{14}, Z^1 and Z^2 are as described above for compounds of formula (**I**); and x is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the x R^{14} groups may be attached to either ring of the naphthyl group.

[0016] In an example, the compound of formula (**I**) is a compound of formula (**IIa**):



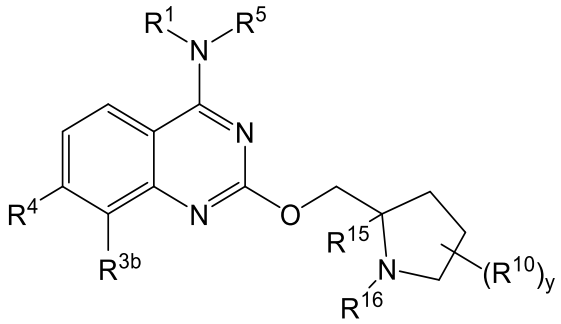
wherein R^1, R^2, R^5, R^{3b}, R^{14} are as described above for compounds of formula (**I**); and x is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the x R^{14} groups may be attached to either ring of the naphthyl group.

[0017] In an example, the compound of formula (**I**) is a compound of formula (**III**):



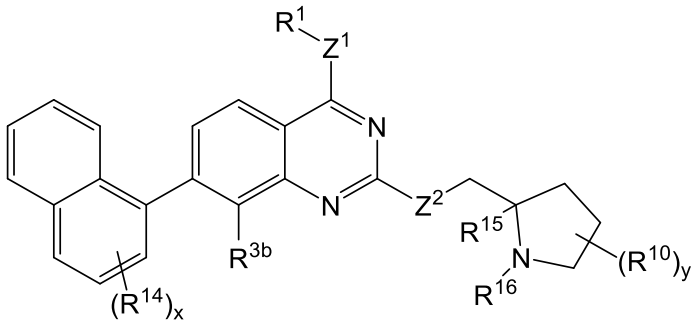
wherein R^1, R^{3b}, R^4, R^{10}, Z^1 and Z^2 are as described above for compounds of formula (**I**); and wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms 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.

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



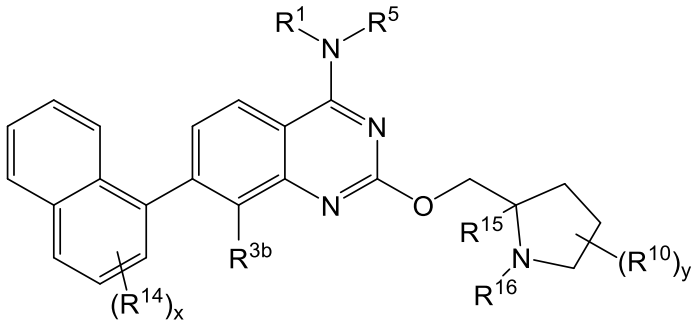
wherein R^1, R^{3b}, R^4, R^5, R^{10} are as described above for compounds of formula (**I**); and wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to which 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.

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



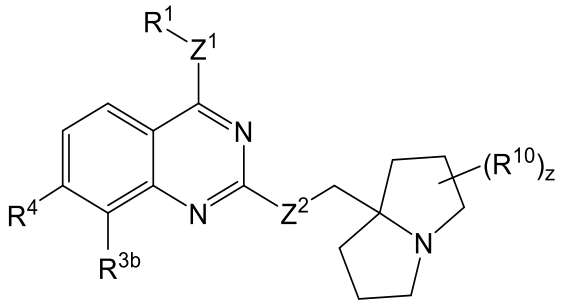
wherein R^1, R^{3b}, R^{10}, R^{14}, Z^1 and Z^2 are as described above for compounds of formula (**I**); wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms 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.

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



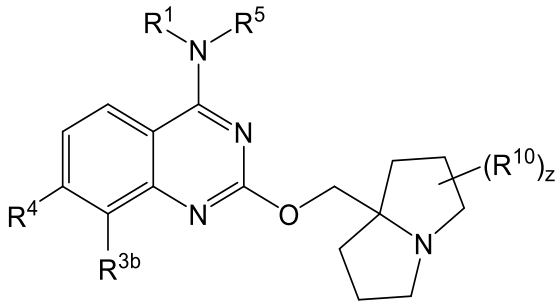
wherein R^1, R^{3b}, R^5, R^{10}, R^{14} are as described above for compounds of formula (**I**); wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to which 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.

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



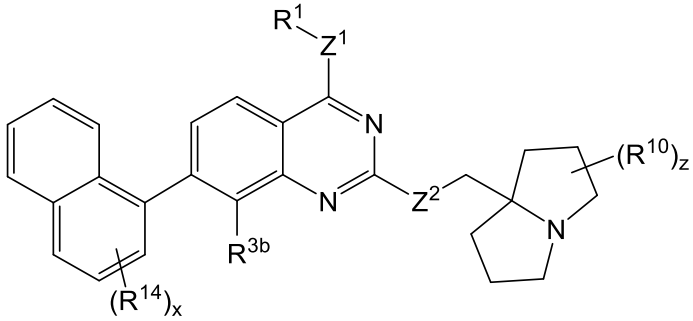
wherein R^1, R^{3b}, R^4, R^{10}, Z^1 and Z^2 are as described above for compounds of formula (**I**); and wherein z is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the z R^{10} groups may be attached to either ring of the pyrrolizidinyl group.

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



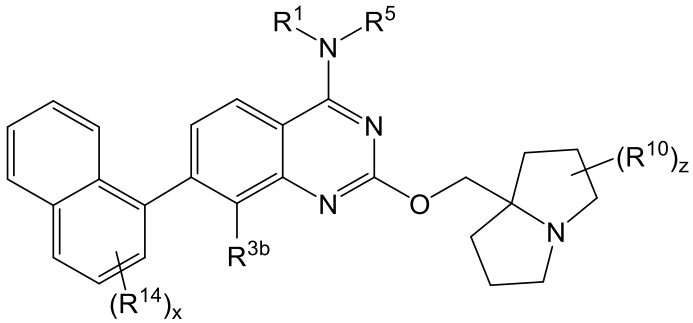
wherein R^1, R^{3b}, R^4, R^5, R^{10} are as described above for compounds of formula (**I**); and wherein z is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the z R^{10} groups may be attached to either ring of the pyrrolizidinyl group.

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



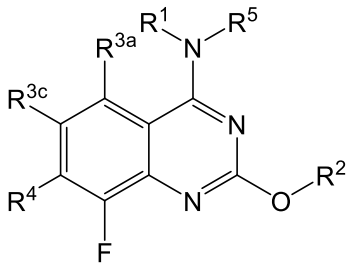
wherein R^1, R^{3b}, R^{10}, R^{14}, Z^1 and Z^2 are as described above for compounds of formula (**I**); wherein x is independently selected from 0, 1, 2, 3, and 4; and z is independently selected from 0, 1, 2, 3 and 4.

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



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

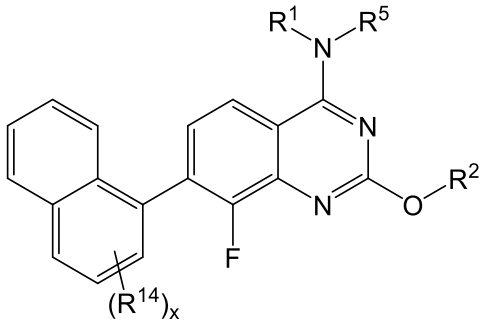
[0025] In an example, the compound of formula (**I**) or (**Ia**) is a compound of formula (**VII**):



;

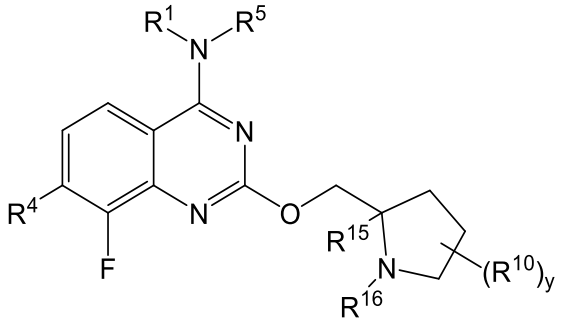
wherein R^1, R^2, R^{3a}, R^{3c}, R^4, and R^5 are as described above for compounds of formula (**I**) or (**Ia**).

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



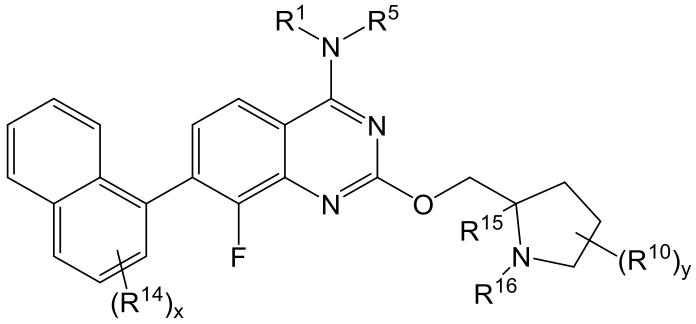
wherein R^1, R^2, R^5 and R^{14} are as described above for compounds of formula (**I**) or (**Ia**); and x is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the x R^{14} groups may be attached to either ring of the naphthyl group.

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



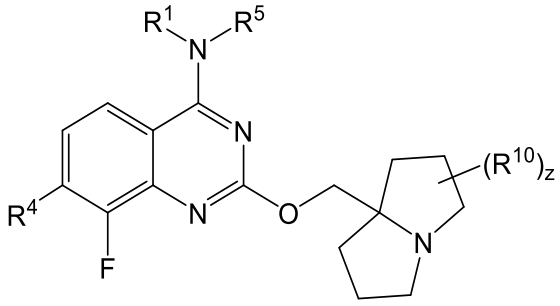
wherein R^1, R^4, R^5, R^{10} are as described above for compounds of formula (**I**) or (**Ia**); and wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to 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.

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



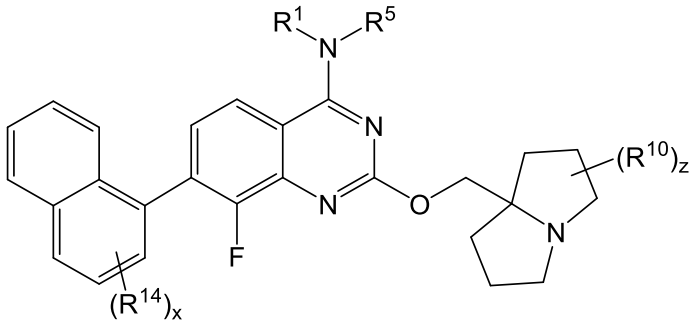
wherein R^1, R^{10}, R^5, R^{14} are as described above for compounds of formula (**I**) or (**Ia**); wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to 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.

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



wherein R^1, R^4, R^5, R^{10} are as described above for compounds of formula (**I**) or (**Ia**); 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.

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



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

[0031] The following examples apply to compounds of any of formulae (**I**)-(**XII**). 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.

[0032] Z^1 may be -O-. Z^1 may be -NR^5-.

[0033] Z^2 may be -O-. Z^2 may be -NR^6-.

[0034] 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 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.

[0035] 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 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 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.

[0042] R^1 may be R^{1a} wherein R^{1a} is a 4- to 7- membered heterocycloalkyl ring; wherein said heterocycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups. R^1 may be R^{1a} wherein R^{1a} is a nitrogen containing 4- to 7- membered heterocycloalkyl ring; wherein said heterocycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups. R^1 may be R^{1a} wherein R^{1a} is a 4- to 7- membered heterocycloalkyl ring; wherein said heterocycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups wherein the ring does not comprise any nitrogen atoms.

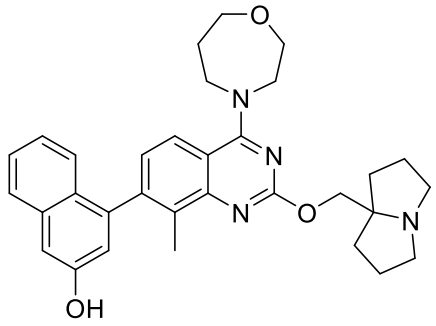
[0043] R^1 may be C_0-C_3-alkylene-R^{1a} wherein R^{1a} is a C_3-C_7-cycloalkyl ring substituted with an NR^7R^8 group; wherein said cycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups. R^1 may be CH_2-alkylene-R^{1a} wherein R^{1a} is a C_3-C_7-cycloalkyl ring substituted with an NR^7R^8 group; wherein said cycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups.

[0044] R^1 may be R^{1a} wherein R^{1a} is a C_3-C_7-cycloalkyl ring substituted with an NR^7R^8 group; wherein said cycloalkyl ring is optionally substituted with from 1 to 4 R^9 groups.

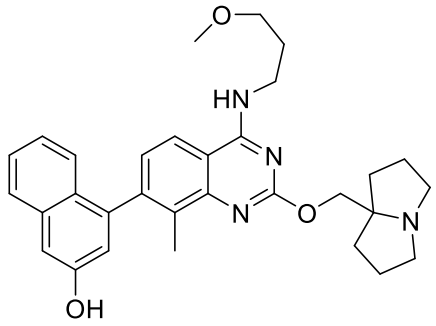
[0045] R^1 may be C_2-C_6-alkylene-R^{1b}. R^1 may be C_2-C_3-alkylene-R^{1b}. R^1 may be C^3-alkylene-R^{1b}. R^{1b} may be independently selected from: NR^7R^8, OR^8 and SR^8. R^{1b} may be OR^8. R^{1b} may be SR^8. R^{1b} may be NR^7R^8. R^8 may be C_1-C_4-alkyl, e.g. Me.

[0046] It may be that R^1 and R^5 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. Compounds having no more than a single amine at this position surprisingly exhibit broad spectrum inhibition at similar concentrations across a range of mutant KRAS forms as well as wild type KRAS rather than inhibition of the specific KRAS G12C and G12D proteins. The compounds of the present disclosure exhibit broad spectrum inhibition at similar concentrations of KRAS mutants including KRAS G12D, KRAS G12C, KRAS G12V, KRAS G12A, KRAS G13D and KRAS Q61H as well as wild-type KRAS. As such these compounds may be of therapeutic benefit in treating cancers bearing KRAS mutations beyond G12D and G12C, as well as cancers dependant on wild type KRAS.

[0047] It may be that R^1 and R^5 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 heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups; and a bridged bicyclic 6- to 11-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups; wherein the nitrogen to which R^1 and R^5 are attached is the only heteroatom in the ring system.

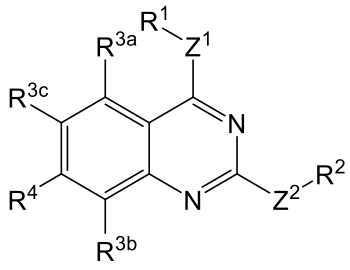


[00103] The compound of formula (**I**) may be:



The present disclosure also encompasses the subject matter of the following numbered clauses:

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



(**I**)

wherein

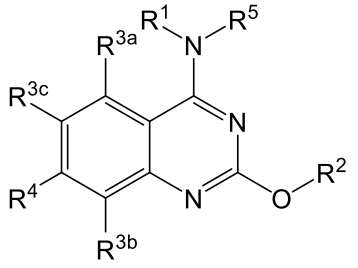
Z^1 is independently selected from -O- and -NR^5-;

Z^2 is independently absent or is selected from -O- and -NR^6-;

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; 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 $SO(NH)R^8$;

CLAIMS

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



(**Ia**)

wherein

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 fused or spirofused bicyclic 6- to 11-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups and a C_3-C_7-cycloalkyl ring; 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: OR^8, SR^8, SOR^8, SO_2R^8, $SO(NH)R^8$, $OC(O)R^8$, and $SO_2NR^7R^8$;

or R^1 and R^5 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 heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups;

wherein R^1 and R^5 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;

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;

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

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

or R^2 and R^6 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; and 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl, wherein R^4 is optionally substituted with from 1 to 4 R^{14} groups;

R^5, R^6, 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^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;

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} and R^{14} are each 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 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.

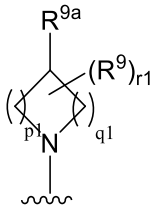
2. A compound of claim 1, wherein R^1 and R^5 together with the nitrogen to which they are attached form a ring system selected from: a monocyclic 4- to 7-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups; a fused or spirofused bicyclic 6- to 11-membered heterocycloalkyl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

3. A compound of claim 1, wherein R^1 and R^5 are selected such that the nitrogen of NR^1R^5 is the nitrogen single amine.

4. A compound of any one of claims 1 to 3, wherein R^1 is 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 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.

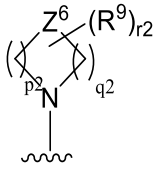
5. A compound of any one of claims 1 to 3, wherein R^1 and R^5 together with the nitrogen to which they are attached form a ring system selected from: a monocyclic 4- to 7-membered group heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups; a fused or spirofused bicyclic 6- to 11-membered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

6. A compound of claim 5, 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.

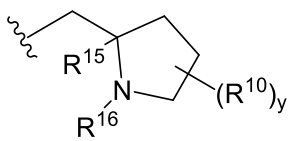
7. A compound of claim 5, wherein R^1 and R^5 together with the nitrogen to which they are attached form a ring system having the structure:



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.

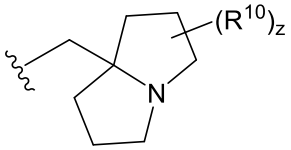
8. A compound of claim 5, wherein R^1 and R^5 together with the nitrogen to which they are attached form a bridged bicyclic 6- to 11-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups.

9. A compound of any one of claims 1 to 8, wherein R^2 has the structure:



, 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.

10. A compound of claim 9, wherein R^2 has the structure:



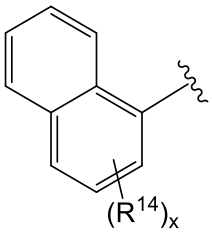
, wherein z is independently selected from 0, 1, 2, 3, and 4..

11. A compound of any one of claims 1 to 10, wherein R^{3b} is F.

12. A compound of any one of claims 1 to 11, wherein both R^{3a} and R^{3c} are H.

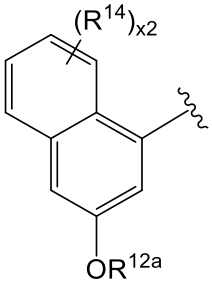
13. A compound of any one of claims 1 to 12, wherein R^4 is phenyl, said phenyl being optionally fused to a C_5-C_7-cycloalkyl ring, wherein R^4 is optionally substituted with from 1 to 4 R^{14} groups.

14. A compound of any one of claims 1 to 12, wherein R^4 has the structure:



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

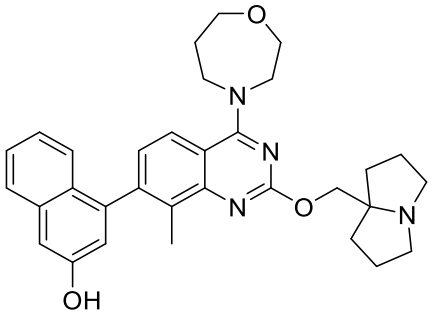
15. A compound of claim 14, wherein R^4 has the structure:

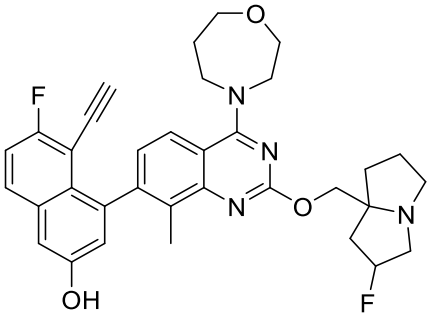


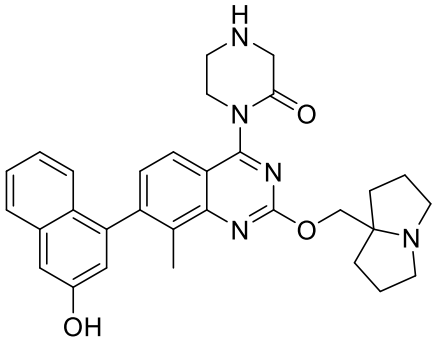
wherein R^{12a} is independently H or C_1-C_4-alkyl; x2 is independently selected from 0, 1, 2 and 3.

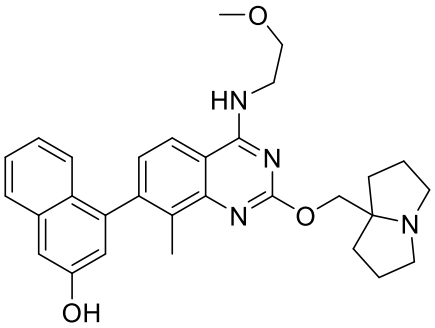
16. A compound of any one of claims 1 to 12, wherein R^4 is 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl, optionally substituted with from 1 to 4 R^{14} groups.

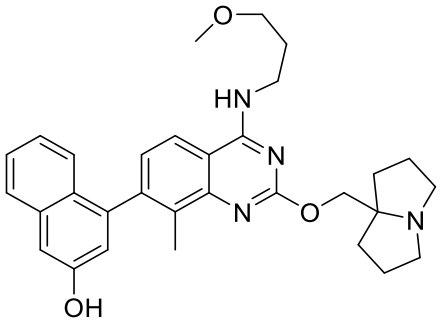
17. A compound of claim 1, wherein the compound of formula (**I**) is selected from:

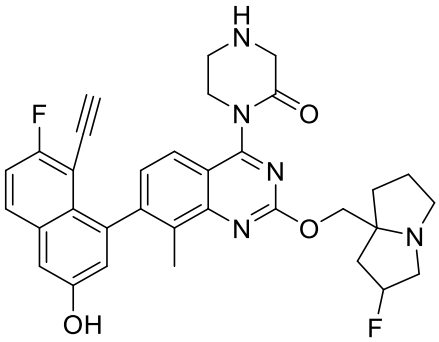


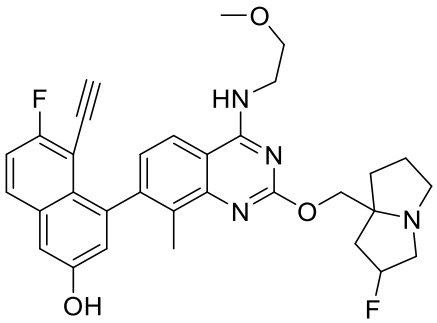


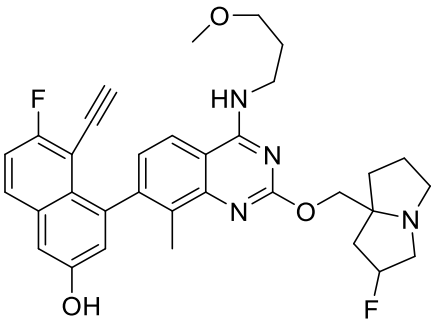


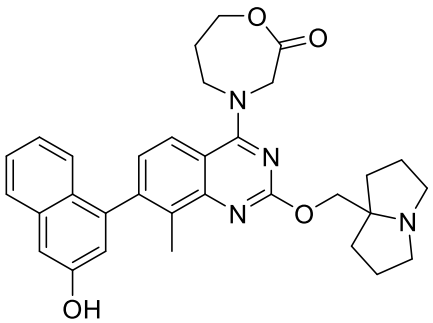


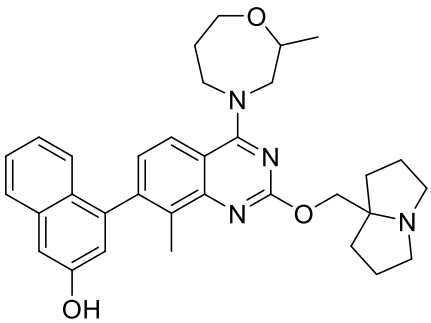


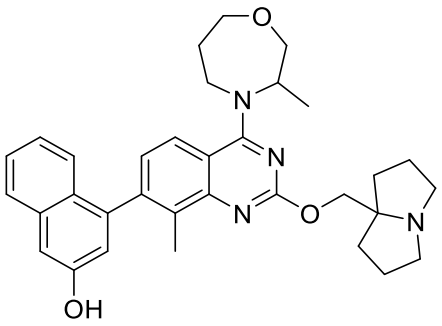


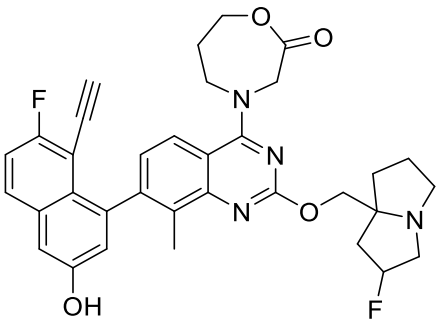


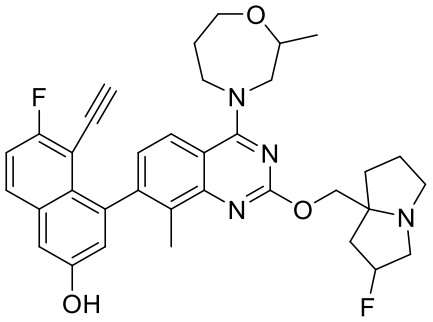


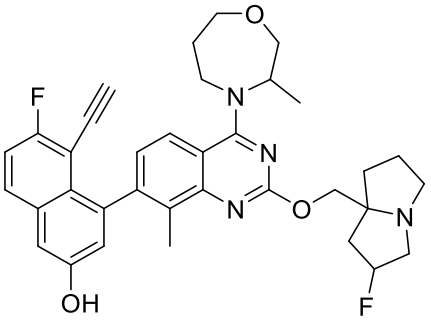


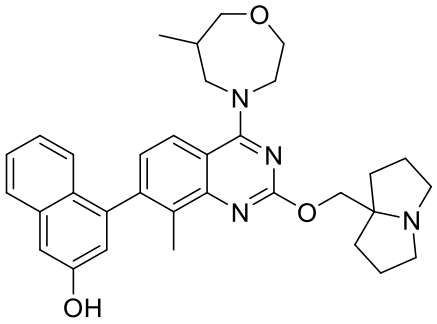


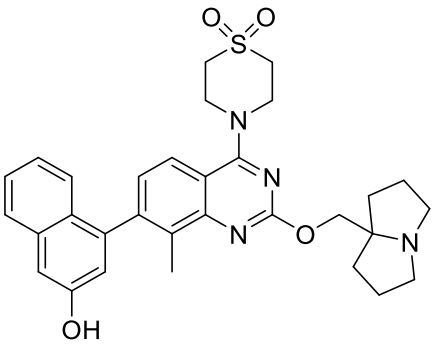


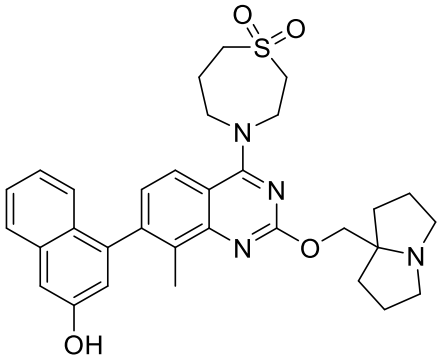


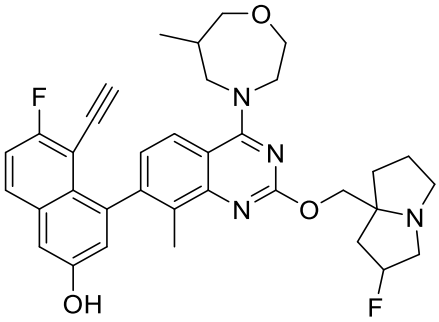


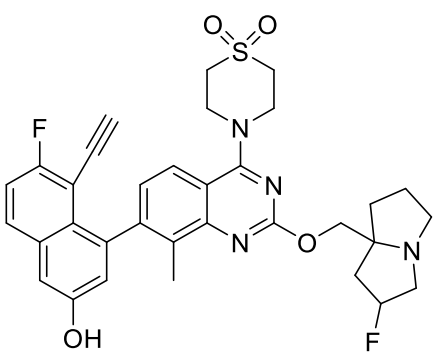


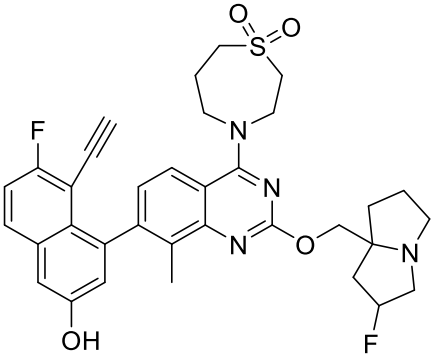


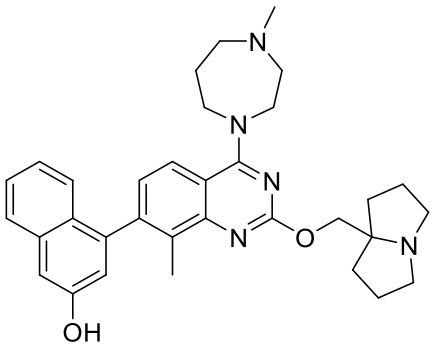


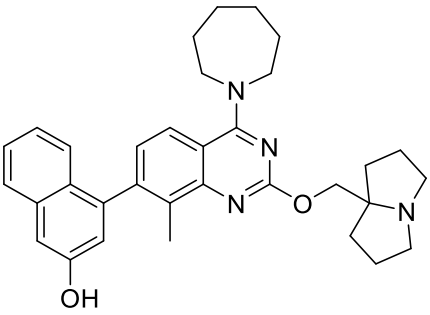


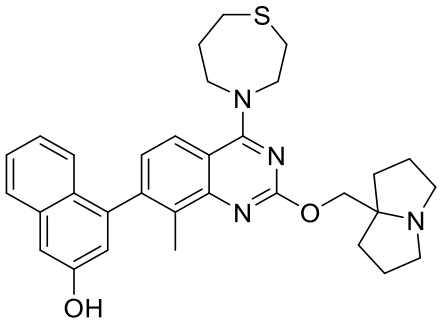


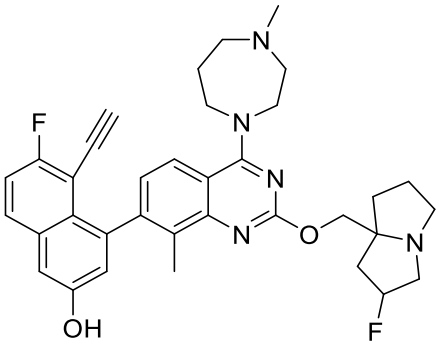


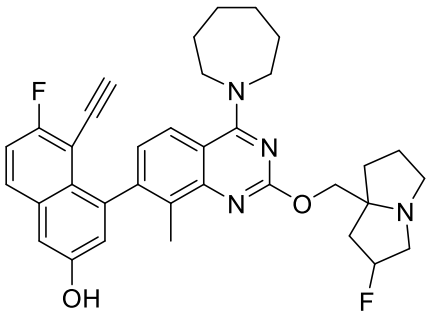


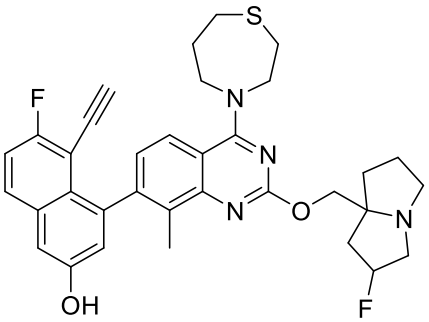


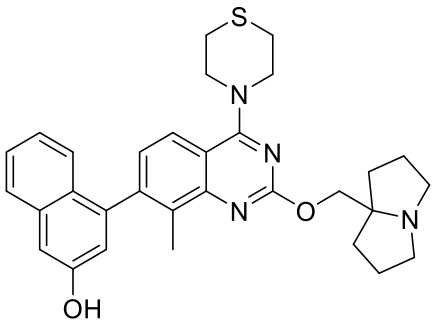


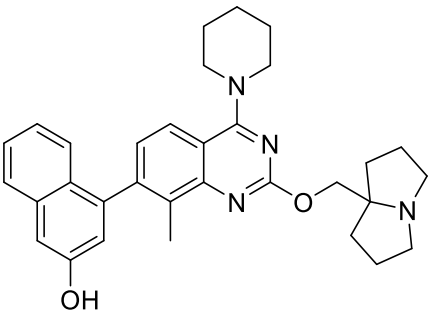


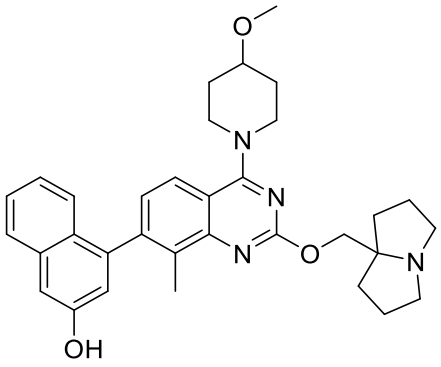


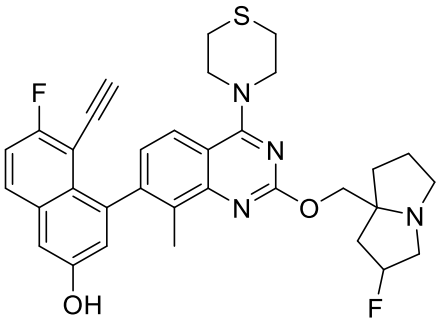


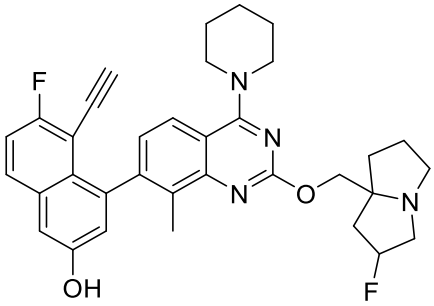
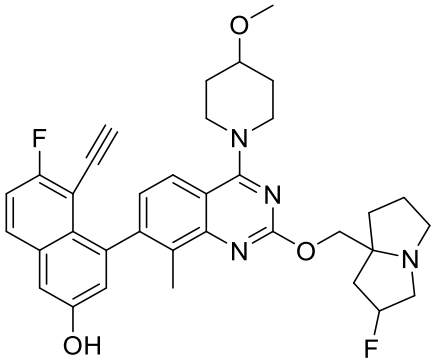
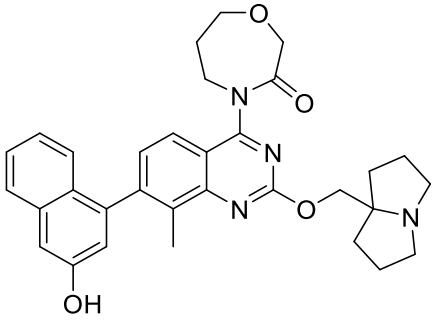
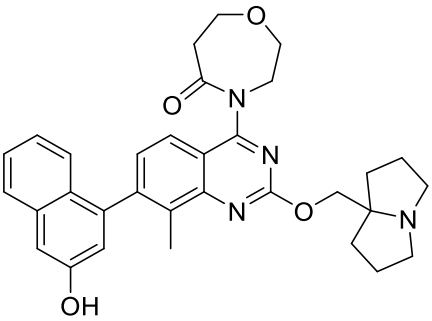
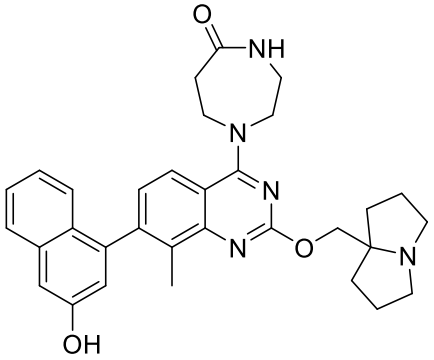
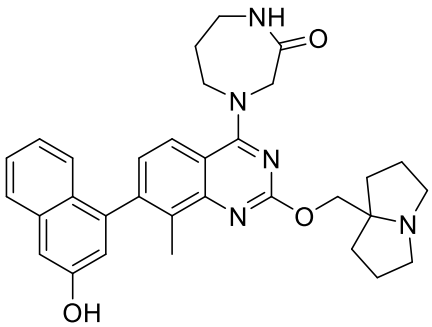
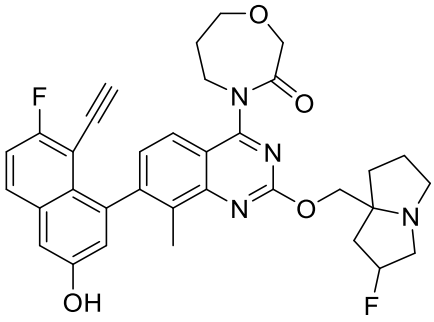
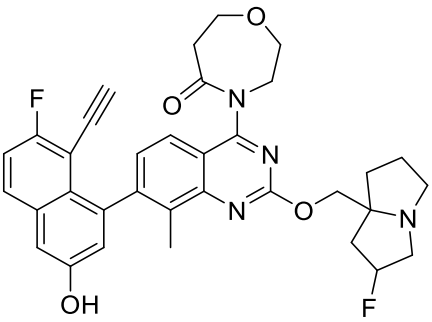
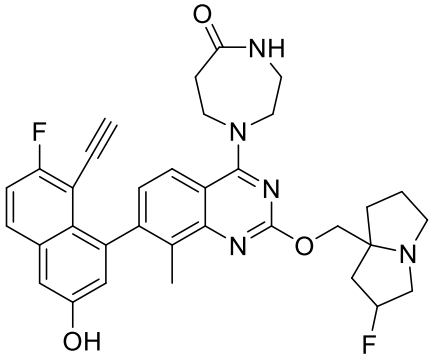
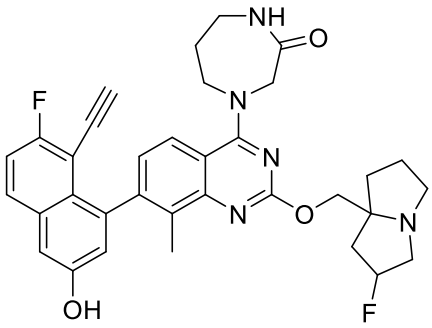


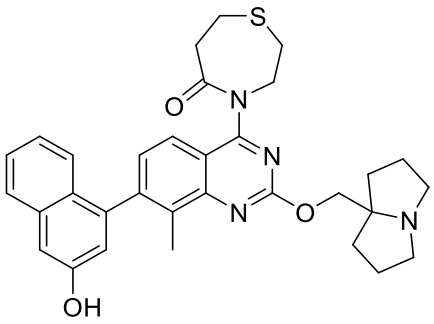


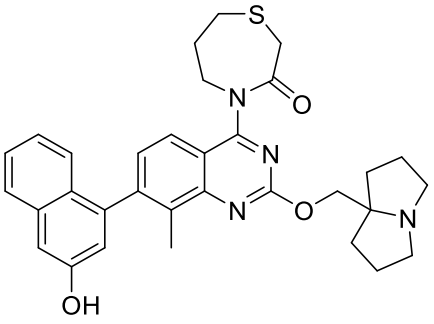


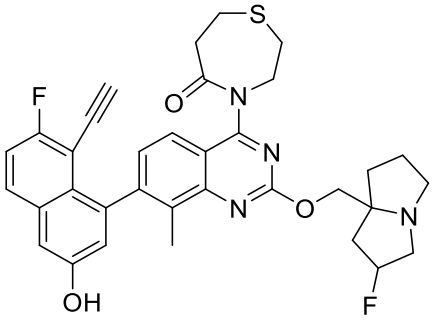


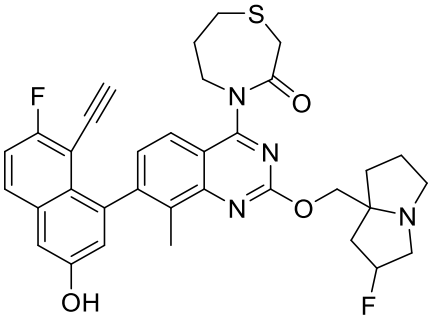


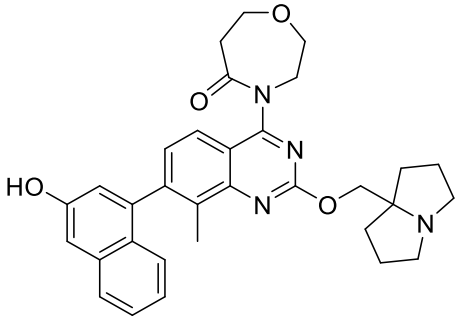













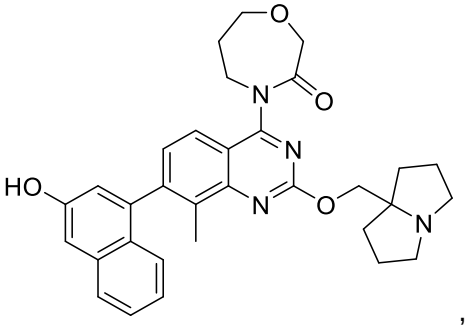




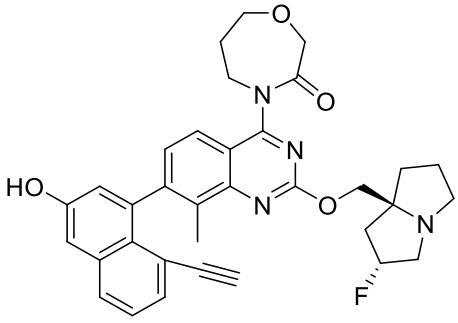


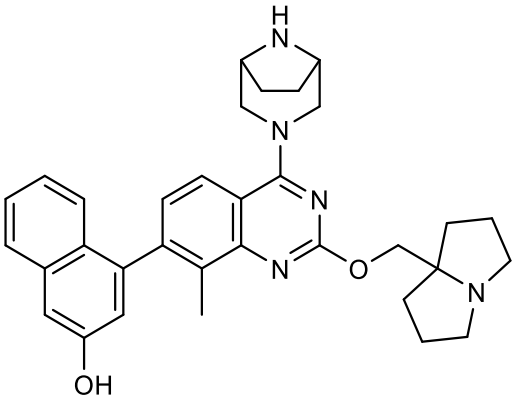


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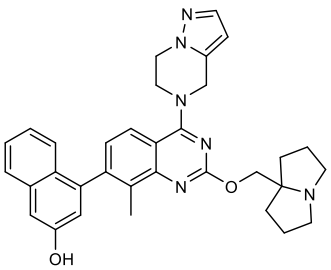
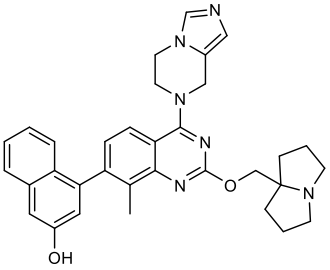
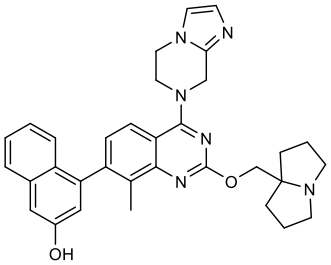
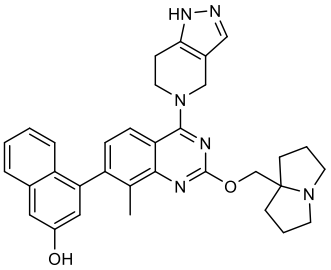
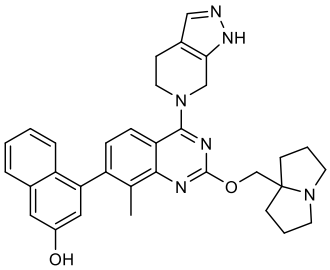
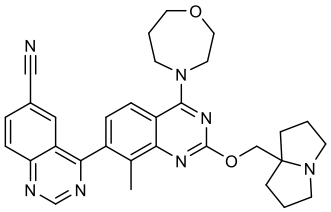
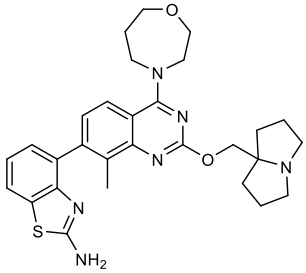
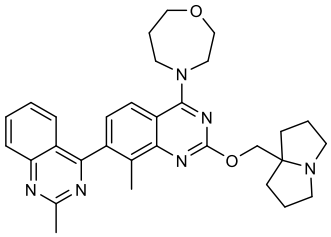
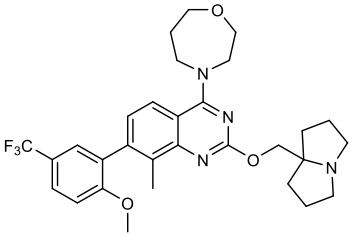
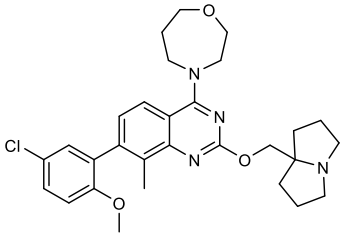
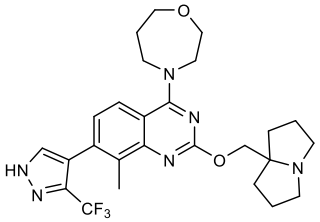
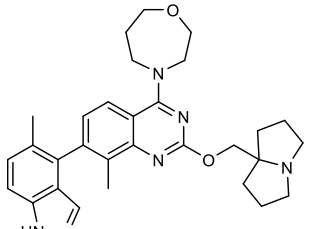
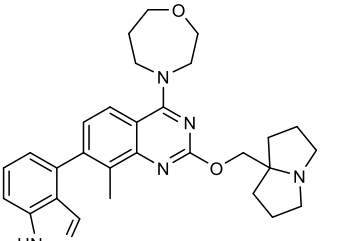
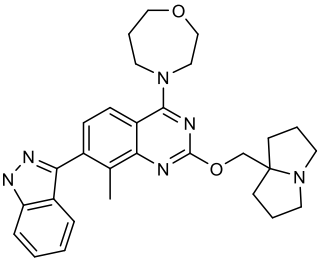
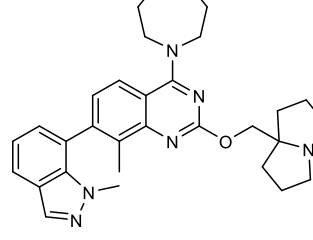


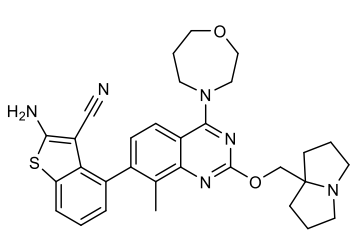
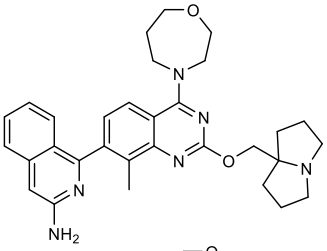
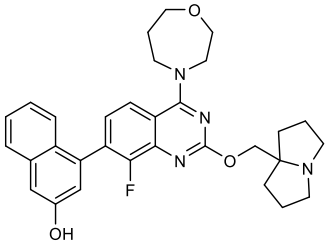
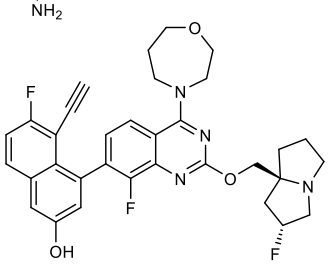
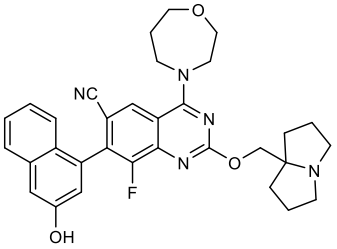
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and

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18. A compound of any one of claims 1 to 17 for medical use.

19. Use of a compound of any one of claims 1 to 17 in the manufacture of a medicament for treating cancer in a subject in need thereof.

20. The use of claim 19, 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.

21. The use of claim 19 or 20, wherein the subject being treated has a cancer having wild-type KRAS.

22. The use of claim 19 or 20, wherein the subject being treated has a cancer having a KRAS mutation selected from: KRAS G12D, KRAS G12C, KRAS G12V, KRAS G12A, KRAS G13D and KRAS Q61H.

23. A pharmaceutical composition comprising a compound of any one of claims 1 to 17 and a pharmaceutically acceptable excipient.

24. A compound of any one of claims 1 to 17 for use in therapy.