Compounds

[0001] This invention relates to compounds and their methods of use. In particular, the compounds of the present invention may be useful for inhibiting RAS proteins. More specifically, this invention relates to compounds for inhibiting a broad spectrum of KRAS proteins, including mutant strains and wild-type KRAS. The compounds of the invention may therefore be used in treating conditions mediated by KRAS proteins. For example, the compounds may be used in treating cancer.

BACKGROUND

[0002] RAS (HRAS, KRAS4A and 4B, and NRAS) proteins are a group of closely related monomeric globular proteins that act as molecular switches, cycling between inactive (GDP-bound) and active (GTP-bound) states to transduce upstream cellular signals to downstream effectors to regulate a wide variety of processes, including cellular proliferation. RAS is the most frequently mutated oncogene in cancer (~30%), with KRAS the most commonly mutated isoform accounting for ~85% of RAS mutations (Hobbs et al, Journal of Cell Science (2016) 129, 1287-1292 doi:10.1242/jcs.182873).

[0003] KRAS G12D is a missense gain of function mutation that results in an amino acid substitution of the glycine (G) at codon 12 with aspartic acid and is the most prevalent accounting for ~26% of all KRAS mutations in cancer. KRAS G12D mutations are present in 36% pancreatic carcinoma patients, 13% colorectal carcinoma patients,10% rectal carcinoma patients, 6% endometrial carcinoma patients, 4% of non-small cell lung carcinoma patients, 4% gastric carcinoma patients, 3% ovarian carcinoma patients and 2% small cell lung carcinoma patients (e.g. The AACR Project GENIE Consortium, (2017) Cancer Discovery; 7(8):818-831. Dataset version 8). Many of these patients with G12D mutations have high unmet need with little option of efficacious targeted therapy. The mainstay of treatment for many of these patients remains chemotherapy combinations with an associated high degree of side effects and lack of efficacy.

[0004] Other KRAS missense gain of functions mutations that result in amino acid substitutions at codon 12, codon 13 and codon 61, as well as amplification of KRAS wildtype protein also drive carcinogenesis. Alterations in KRAS are found in approximately one in seven cancers (Hoffman et al, Cancer Discovery (2022) 12, 924-937). Activating mutations in KRAS are highly prevalent in solid tumours and are predominately found in 35% lung, 45% colorectal and up to 90% pancreatic cancers. G12D, G12V and G12C are the most frequently occurring KRAS mutations and are found more than half of all KRAS driven cancers. Other KRAS mutations include KRAS G12V, KRAS G12A, KRAS G13D and KRAS Q61H. KRAS

amplifications are found in approximately 7% of cancers with KRAS alterations and are commonly occurring in ovarian carcinoma, breast carcinoma, lung adenocarcinoma, gastric adenocarcinoma, uterine cancers and esophagogastric cancers (Hoffman reviews). Pan KRAS inhibitors have the potential to treat a broader patient population including cancers harbouring KRAS mutations, KRAS wildtype amplifications and cancers driven by loss of the tumour suppressor NF1. In addition, pan KRAS inhibitors can potentially be used to treat cancers with acquired resistance to allele specific inhibitors such as KRAS G12C inhibitors.

[0005] Due to this frequency of KRAS mutations in multiple different tumour types and the established role of KRAS as an oncogenic driver mutation in cancer, modulating the activity of KRAS is a highly attractive therapeutic goal and has been the subject of significant research efforts for greater than 30 years. However, it has proven extremely challenging to affect KRAS activity directly and research efforts have focussed on other targets in the signalling cascade that are either upstream or downstream from KRAS. Other approaches to inhibit KRAS activity have included affecting other points on the MAPK pathway (English et al., 2002; Adjei 2014; Chin et al., 2020), many of which have shown MAPK pathway inhibition to be clinically effective. Recently, mutant KRAS G12C selective inhibitors have been reported (Kettle and Cassar 2020)., which bind covalently to an allosteric pocket and have progressed into clinical trials and shown responses in selected patients.

[0006] Compounds which are capable of modulating G12D mutant KRAS are described in WO2021/041671. Compounds capable of modulating multiple RAS isoforms and mutants have also been described (Kessler *et al*. 2019), however these compounds are believed to be of limited therapeutic benefit owing to a lack of sufficient potency as well as little selectivity for KRAS over HRAS and NRAS isoforms.

[0007] 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.

[0008] 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.

[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.

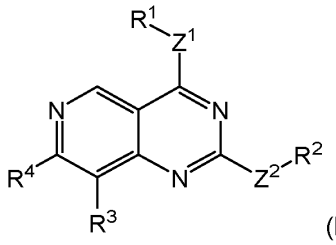
[0010] It is an aim of certain embodiments of this invention to provide compounds which exhibit reduced cytotoxicity relative to prior art compounds and existing therapies.

[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

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



(I)

wherein

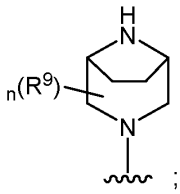
Z^1 is independently selected from -O- and -NR^5-;

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 nitrogen containing 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 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 bridged bicyclic 6- to 11-membered heterocycloalkyl group is not:



;

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^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^3 is 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;

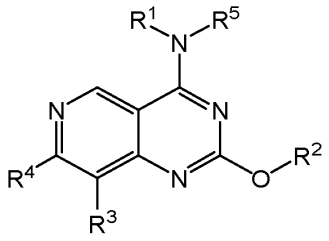
R^9 and R^{10} are each independently at each occurrence selected from oxo, halo, cyano, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_1-C_4-alkyl substituted with cyano, C_2-C_4-alkenyl,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

n is an integer selected from 0, 1, 2, 3 and 4;

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.

[0014] In an embodiment, 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 an oxygen containing 4- to 7- membered heterocycloalkyl ring, a nitrogen containing 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; $C(O)NR^7R^8$;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 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 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^3 is 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;

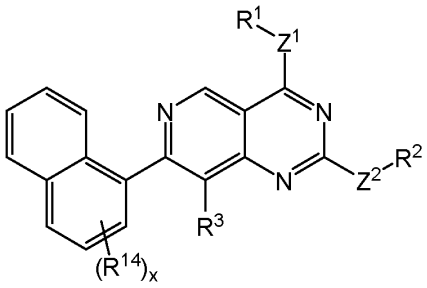
R^9 and R^{10} are each independently at each occurrence selected from oxo, halo, cyano, $NR^{12}R^{13}$, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_1-C_4-alkyl substituted with cyano, C_2-C_4-alkenyl,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

n is an integer selected from 0, 1, 2, 3 and 4;

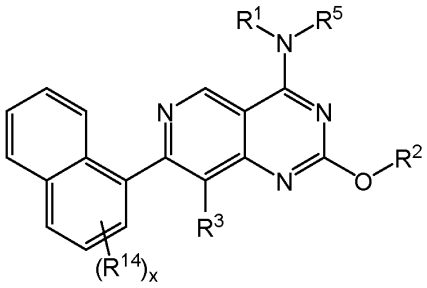
wherein any of the aforementioned alkyl, alkylene or cyclopropyl groups is optionally substituted, where chemically possible, by 1 to 5 substituents which are each independently at each occurrence selected from the group consisting of: C_1-C_4-alkyl, halo, nitro, cyano, NR^aR^b, OR^a, SR^a, CO_2R^a,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



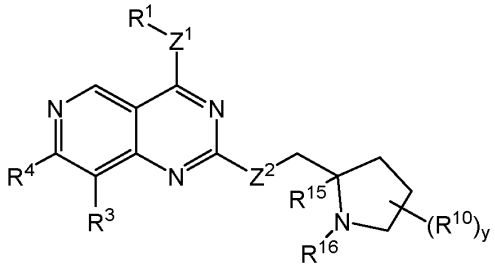
wherein R^1, R^2, R^3, R^{14}, Z^1 and Z^2 are as described above for compounds of formula (**I**); and x is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the x R^{14} groups may be attached to either ring of the naphthyl group.

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



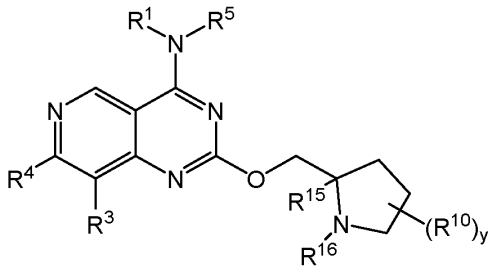
wherein R^1, R^2, R^3, R^{14} are as described above for compounds of formula (**Ia**); and x is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the x R^{14} groups may be attached to either ring of the naphthyl group.

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



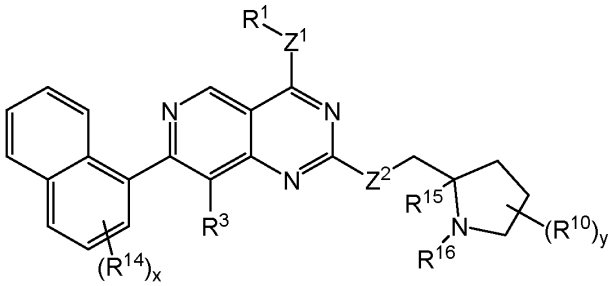
wherein R^1, R^3, R^4, R^{10}, Z^1 and Z^2 are as described above for compounds of formula (**I**); and wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms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



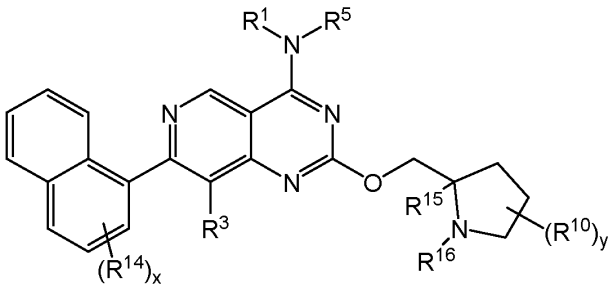
wherein R^1, R^3, R^4, R^{10} are as described above for compounds of formula (**Ia**); and wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to which they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

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



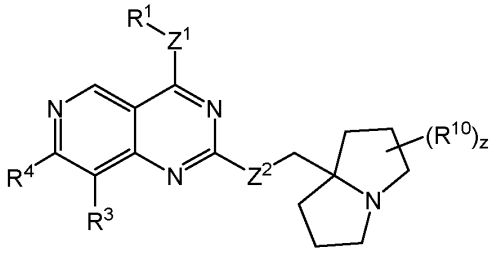
wherein R^1, R^3, R^{10}, R^{14}, Z^1 and Z^2 are as described above for compounds of formula (**I**); wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to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



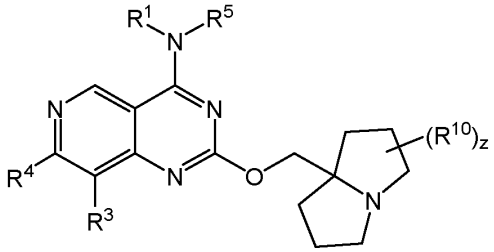
wherein R^1, R^3, R^{10}, R^{14} are as described above for compounds of formula (**Ia**); wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to which they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

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



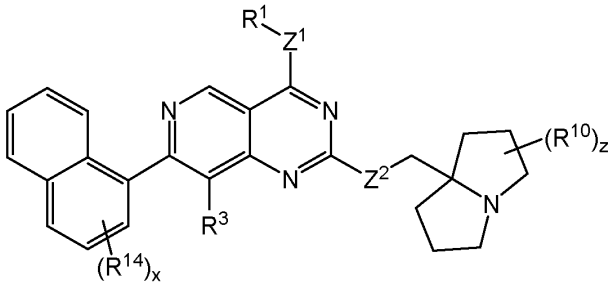
wherein R^1, R^3, R^4, R^{10}, Z^1 and Z^2 are as described above for compounds of formula (**I**); and wherein z is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the z R^{10} groups may be attached to either ring of the pyrrolizidinyl group.

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



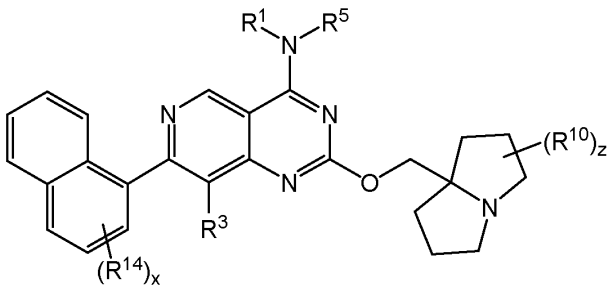
wherein R^1, R^3, R^4, R^{10} are as described above for compounds of formula (**Ia**); and wherein z is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the z R^{10} groups may be attached to either ring of the pyrrolizidinyl group.

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



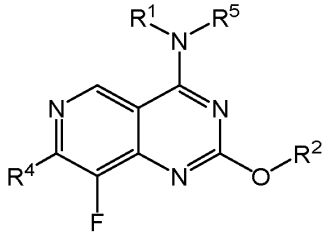
wherein R^1, R^3, R^{10}, R^{14}, Z^1 and Z^2 are as described above for compounds of formula (**I**); wherein x is independently selected from 0, 1, 2, 3, and 4; and z is independently selected from 0, 1, 2, 3 and 4.

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



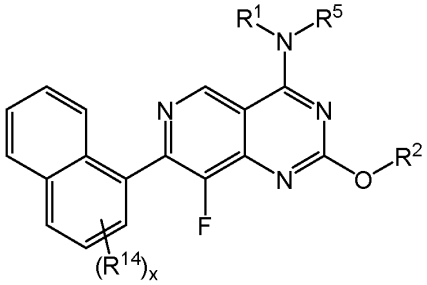
wherein R^1, R^3, R^{10}, R^{14}, are as described above for compounds of formula (**Ia**); wherein x is independently selected from 0, 1, 2, 3, and 4; and z is independently selected from 0, 1, 2, 3 and 4.

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



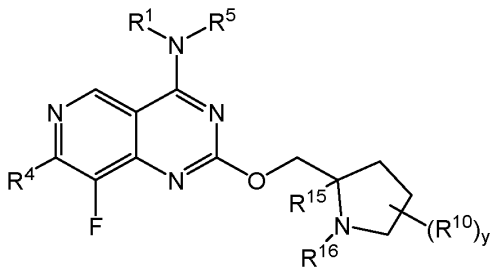
wherein R^1, R^2, R^4 and R^5 are as described above for compounds of formula (**I**) or (**Ia**).

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



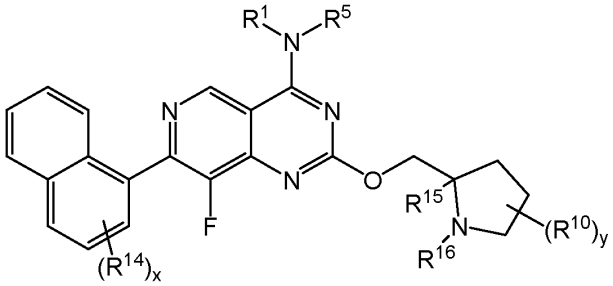
wherein R^1, R^2, R^5 and R^{14} are as described above for compounds of formula (**I**) or (**Ia**); and x is independently selected from 0, 1, 2, 3, and 4.

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



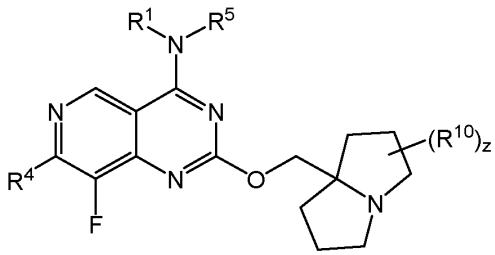
wherein R^1, R^4, R^5 and R^{10} are as described above for compounds of formula (**I**) or (**Ia**); and wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms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



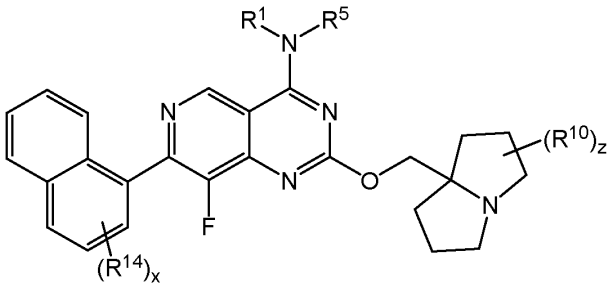
wherein R^1, R^3, R^5, R^{10} and R^{14} are as described above for compounds of formula (**I**) or (**Ia**); wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the 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 embodiment, the compound of formula (**I**) or (**Ia**) is a compound of formula (**XI**):



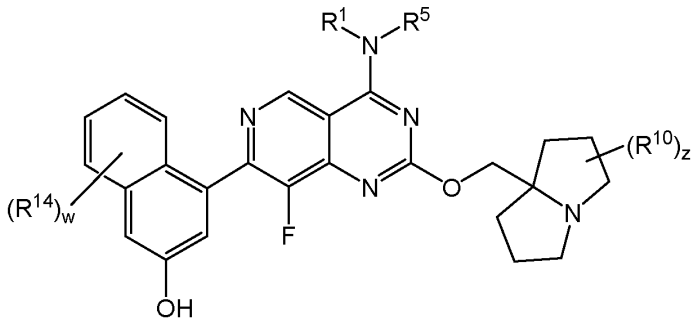
wherein R^1, R^3, R^4, R^{10}, Z^1 and Z^2 are as described above for compounds of formula (**I**) or (**Ia**); and wherein z is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the z R^{10} groups may be attached to either ring of the pyrrolizidinyl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

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



wherein R^1, R^5, R^{10} and 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] In an embodiment, the compound of formula (**I**) or (**Ia**) is a compound of formula (**XIII**):



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

[0032] The following embodiments apply to compounds of any of formulae (**I**)-(**XII**). These embodiments are independent and interchangeable. Any one embodiment may be combined with any other embodiment, where chemically allowed. In other words, any of the features described in the following embodiments may (where chemically allowable) be combined with the features described in one or more other embodiments. In particular, where

a compound is exemplified or illustrated in this specification, any two or more of the embodiments listed below, expressed at any level of generality, which encompass that compound may be combined to provide a further embodiment which forms part of the present disclosure.

[0033] Z^1 may be -O-. Z^1 may be -NR^5-.

[0034] Z^2 may be -O-. Z^2 may be -NR^6-.

[0035] R^1 may be independently C_0-C_3-alkylene-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 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.

[0036] 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 nitrogen containing 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 nitrogen containing 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.

[0037] R^1 may be 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 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.

[0038] R^1 may be C_0-C_3-alkylene-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 CH_2-alkylene-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.

[0039] 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 an oxygen 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 an oxygen containing 4- to 7- membered heterocycloalkyl ring e.g. a tetrahydropyranyl ring.

[0040] 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.

[0041] 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.

[0042] 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.

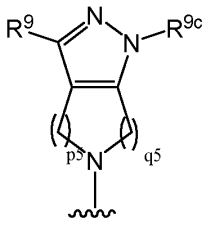
[0043] It may be that R^1 and R^5 are selected such that NR^1R^5 comprises no more than a single amine, wherein said single amine may be a primary, secondary or tertiary amine. Compounds having no more than a single amine at this position surprisingly exhibit broad spectrum inhibition at similar concentrations across a range of mutant KRAS forms as well as wild type KRAS rather than inhibition of the specific KRAS G12C and G12D proteins. Certain compounds of the invention 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.

[0044] 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.

[0045] 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 nitrogen in the ring system.

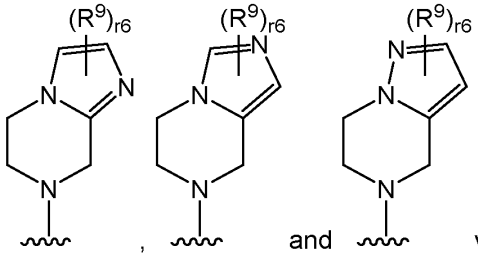
[0046] It may be that R^1 and R^5 are selected such that the nitrogen of NR^1R^5 is the nitrogen of the single amine. It may be that R^1 and R^5 are selected such that NR^1R^5 is the single amine. For the avoidance of doubt, the term "amine" as used herein encompasses primary amines, e.g., methylamine; secondary amines, e.g., dimethylamine; tertiary amines, e.g., trimethylamine; cyclic amines, e.g., piperidine. For the avoidance of doubt, the term "amine" as used herein excludes amides and lactams, e.g., piperazinonyl.

[0047] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a ring system having the structure:



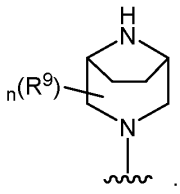
wherein R^{9c} is selected from H and C_1-C_4-alkyl, p5 and q5 and are each selected from 0, 1, 2 and 3; providing that the sum of p5 and q5 is 1 or greater.

[0048] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a ring system having a structure selected from:



wherein r6 is selected from 0, 1 and 2.

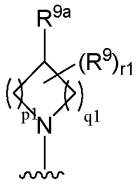
[0049] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a ring system selected from: a monocyclic 4- to 7-membered group heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups; a fused or spirofused bicyclic 6- to 11-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups; and a bridged bicyclic 6- to 11-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups, wherein the bridged bicyclic 6- to 11-membered heterocycloalkyl group is not:



[0050] 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 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.

[0051] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a 6 or 7-membered group heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups. It may be that R^1 and R^5 together with the nitrogen to which they are attached form a 6 or 7-membered group heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups, wherein the total number of heteroatoms in the 6 or 7-membered group heterocycloalkyl group is 1 or 2. The total number of heteroatoms may be 2. It may be that R^1 and R^5 together with the nitrogen to which they are attached form a 6 or 7-membered group heterocycloalkyl group, optionally substituted with 1 R^9 group.

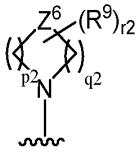
[0052] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a monocyclic 4- to 7-membered group heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups. It may be that R^1 and R^5 together with the nitrogen to which they are attached form a monocyclic unsubstituted 4- to 7-membered group heterocycloalkyl group. It may be that there is at least one R^9 group and that at least one of said R^9 groups is selected from $NR^{12}R^{13}$ and C_1-C_4-alkyl substituted with $NR^{12}R^{13}$. It may be that 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. r1 may be 0. R^9 may independently at each occurrence be methyl. R^{9a} may be selected from NHR^{12} and C_1-C_4-alkyl substituted with NHR^{12}.

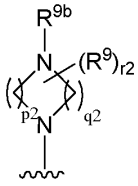
[0053] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a monocyclic 4- to 7-membered group heterocycloalkyl group comprising two nitrogen atoms in the ring, optionally substituted with from 1 to 4 R^9 groups.

[0054] It may be that 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. Z^6 may be selected from NR^{9b}, O, S, $S(O)_2$, S(O) and S(O)(NH). Z^6 may be selected from $C(O)NR^{9b}$, O, S, $S(O)_2$, S(O), $S(O)(NR^{9b})$ and S(O)(NH). Z^6 may be selected from O, S, $S(O)_2$, S(O) and S(O)(NH). Z^6 may be selected from NR^{9b}, O and S. Z^6 may be selected from O and S. Z^6 may be O.

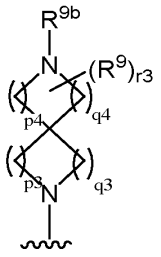
[0055] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a ring system having the structure:



wherein 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. r2 may be 0. R^9 may independently at each occurrence be methyl. R^{9b} may be H. R^{9b} may be C_1-C_4-alkyl.

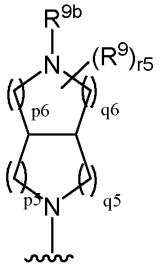
[0056] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a fused or spirofused bicyclic 6- to 11-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups. It may be that R^1 and R^5 together with the nitrogen to which they are attached form a fused or spirofused bicyclic 6- to 11-membered heterocycloalkyl group comprising two nitrogen atoms in the ring system, optionally substituted with from 1 to 4 R^9 groups.

[0057] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a spirofused bicyclic 6- to 11-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups. It may be that R^1 and R^5 together with the nitrogen to which they are attached form a spirofused bicyclic 6- to 11-membered heterocycloalkyl group comprising two nitrogen atoms in the ring system, optionally substituted with from 1 to 4 R^9 groups. It may be that R^1 and R^5 together with the nitrogen to which they are attached form a ring system having the structure:



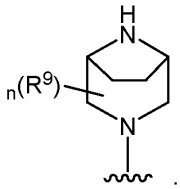
wherein R^{9b} is selected from H and C_1-C_4-alkyl; p3, p4, q3 and q4 are each independently selected from 0, 1, 2 and 3; providing that the sum of p3, p4, q3 and q4 is from 3 to 8, the sum of p3 and q3 is 2 or greater, and the sum of p4 and q4 is 2 or greater; and r3 is selected from 0, 1, 2 and 3. For the absence of doubt, throughout this specification, the r3 R^9 groups may be attached to either ring of the spirofused bicyclic ring system. r3 may be 0. R^9 may independently at each occurrence be methyl. R^{9b} may be H.

[0058] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a fused bicyclic 6- to 11-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups. It may be that R^1 and R^5 together with the nitrogen to which they are attached form a fused bicyclic 6- to 11-membered heterocycloalkyl group comprising two nitrogen atoms in the ring system, optionally substituted with from 1 to 4 R^9 groups. It may be that R^1 and R^5 together with the nitrogen to which they are attached form a ring system having the structure:

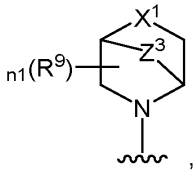


wherein R^{9b} is selected from H and C_1-C_4-alkyl; p5, p6, q5 and are each selected from 0, 1, 2 and 3; providing that the sum of p3, p4, q3 and q4 is from 2 to 7, the sum of p5 and q5 is 1 or greater, and the sum of p6 and q6 is 1 or greater; and r5 is selected from 0, 1, 2 and 3. For the absence of doubt, throughout this specification, the r5 R^9 groups may be attached to either ring of the fused bicyclic ring system. r5 may be 0. R^9 may independently at each occurrence be methyl. R^{9b} may be H.

[0059] It may be that 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, wherein the bridged bicyclic 6- to 11-membered heterocycloalkyl group is not:

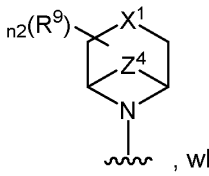


[0060] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a ring system having the structure:



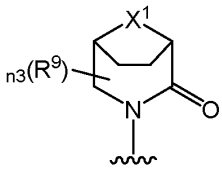
, wherein X^1 is independently selected from $C(O)NR^{9d}$, O and NR^{17}; Z^3 is independently selected from: CH_2, CH_2CH_2, CH_2-O-CH_2CH_2, CH_2-O-CH_2, CH_2-NR^{17}-CH_2CH_2 and CH_2-NR^{17}-CH_2; R^{17} is independently at each occurrence selected from H, C_1-C_4-haloalkyl, and C_1-C_4-alkyl; R^{9d} is independently selected from H and C_1-C_4-alkyl; and n1 is an integer selected from 0, 1, 2, 3 and 4. For the absence of doubt, throughout this specification, the n1 R^9 groups may be attached to either ring of the bridged bicyclic ring system. Z^3 may be independently selected from: CH_2, CH_2CH_2, CH_2-O-CH_2CH_2, CH_2-O-CH_2, X^1 may be independently selected from O and NR^{17}. X^1 may be NR^{17}. X^1 may be NH. n1 may be 0. R^9 may independently at each occurrence be methyl.

[0061] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a ring system having the structure:



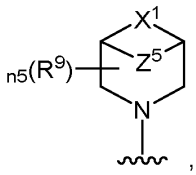
, wherein X^1 is independently selected from $C(O)NR^{9d}$, O and NR^{17}; Z^4 is independently selected from: CH_2, CH_2CH_2, CH_2-O-CH_2CH_2, CH_2-O-CH_2, CH_2-NR^{17}-CH_2CH_2 and CH_2-NR^{17}-CH_2; R^{17} is independently at each occurrence selected from H, C_1-C_4-haloalkyl, and C_1-C_4-alkyl; R^{9d} is independently selected from H and C_1-C_4-alkyl; and n2 is an integer selected from 0, 1, 2, 3 and 4. For the absence of doubt, throughout this specification, the n2 R^9 groups may be attached to either ring of the bridged bicyclic ring system. Z^4 may be independently selected from: CH_2, CH_2CH_2, CH_2-O-CH_2CH_2, CH_2-O-CH_2. X^1 may be independently selected from O and NR^{17}. X^1 may be NR^{17}. X^1 may be NH. n2 may be 0. R^9 may independently at each occurrence be methyl.

[0062] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a ring system having the structure:



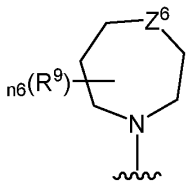
, wherein X^1 is independently selected from $C(O)NR^{9d}$, O and NR^{17}; Z^4 is independently selected from: CH_2, CH_2CH_2, CH_2-O-CH_2CH_2, CH_2-O-CH_2, CH_2-NR^{17}-CH_2CH_2 and CH_2-NR^{17}-CH_2; R^{17} is independently at each occurrence selected from H, C_1-C_4-haloalkyl, and C_1-C_4-alkyl; R^{9d} is independently selected from H and C_1-C_4-alkyl; and n3 is an integer selected from 0, 1, 2, 3 and 4. For the absence of doubt, throughout this specification, the n3 R^9 groups may be attached to either ring of the bridged bicyclic ring system. X^1 may be independently selected from O and NR^{17}. X^1 may be NR^{17}. X^1 may be NH. n3 may be 0. R^9 may independently at each occurrence be methyl.

[0063] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a ring system having the structure:



, wherein X^1 is independently selected from $C(O)NR^{9d}$, O and NR^{17}; Z^5 is independently selected from: CH_2, CH_2CH_2, CH_2-O-CH_2CH_2, CH_2-O-CH_2, CH_2-NR^{17}-CH_2CH_2 and CH_2-NR^{17}-CH_2; R^{17} is independently at each occurrence selected from H, C_1-C_4-haloalkyl, and C_1-C_4-alkyl; R^{9d} is independently selected from H and C_1-C_4-alkyl; and n5 is an integer selected from 0, 1, 2, 3 and 4. For the absence of doubt, throughout this specification, the n5 R^9 groups may be attached to either ring of the bridged bicyclic ring system. Z^5 is independently selected from: CH_2, CH_2CH_2, CH_2-O-CH_2CH_2, CH_2-O-CH_2. X^1 may be independently selected from O and NR^{17}. X^1 may be NR^{17}. X^1 may be NH. n5 may be 0. R^9 may independently at each occurrence be methyl.

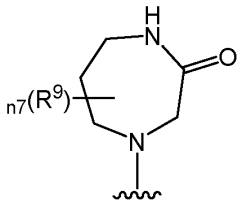
[0064] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a ring system having the structure:



wherein Z^6 is independently selected from $C(O)NR^{9b}$, 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-

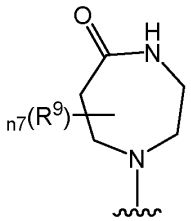
alkyl; and n6 is an integer selected from 0, 1, 2, 3 and 4. Z^6 may be selected from NR^{9b}, O, S, $S(O)_2$, S(O), and S(O)(NH). Z^6 may be selected from $C(O)NR^{9b}$, O, S, $S(O)_2$, S(O), $S(O)(NR^{9b})$ and S(O)(NH). Z^6 may be selected from O, S, $S(O)_2$, S(O) and S(O)(NH). Z^6 may be selected from NR^{9b}, O and S. Z^6 may be selected from O and S. Z^6 may be O.

[0065] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a ring system having the structure:



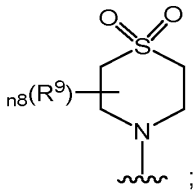
wherein n7 is an integer selected from 0, 1, 2 and 3.

[0066] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a ring system having the structure:



wherein n7 is an integer selected from 0, 1, 2 and 3.

[0067] It may be that R^1 and R^5 together with the nitrogen to which they are attached form a ring system having the structure:



;

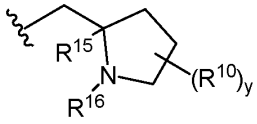
wherein n8 is an integer selected from 0, 1, 2 and 3.

[0068] n7 may be 0.

[0069] R^2 may be C_0-C_4-alkylene-R^{2a}. R^2 may be CH_2-R^{2a}. R^{2a} may be selected from monocyclic 4- to 7-membered heterocycloalkyl group, a fused, spirofused or bridged bicyclic 6- to 11-membered heterocycloalkyl group; wherein said R^{2a} group is optionally substituted with from 1 to 6 R^{10} groups. R^{2a} may comprise at least one nitrogen in the ring system. R^{2a}

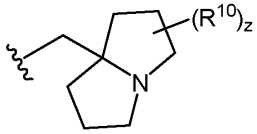
may comprise a single nitrogen in the ring system. R^{2a} may be selected from monocyclic 4- to 7-membered heterocycloalkyl group, a fused, spirofused or bridged bicyclic 6- to 11-membered heterocycloalkyl group; wherein said R^{2a} group is optionally substituted with from 1 to 6 R^{10} groups and wherein R^{2a} comprises at least one nitrogen in the ring system. R^{2a} may be monocyclic 4- to 7-membered heterocycloalkyl group; wherein said R^{2a} group is optionally substituted with from 1 to 6 R^{10} groups and wherein R^{2a} comprises at least one nitrogen in the ring system. R^{2a} may be a fused, spirofused or bridged bicyclic 6- to 11-membered heterocycloalkyl group; wherein said R^{2a} group is optionally substituted with from 1 to 6 R^{10} groups and wherein R^{2a} comprises at least one nitrogen in the ring system.

[0070] R^2 may have the structure:



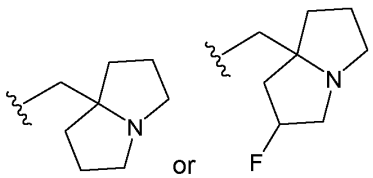
, wherein R^{15} is independently selected from H, C_1-C_4-alkyl; wherein R^{16} is independently selected from H, C_1-C_4-alkyl and cyclopropyl; or wherein R^{15} and R^{16} together with the atoms to which they are attached form a 5- or 6-membered heterocycloalkyl ring, optionally substituted with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

[0071] R^2 may have the structure:



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

[0072] R^2 may have the structure:

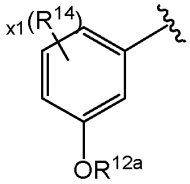


.

[0073] R^3 may be selected from 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^3 may be F. R^3 may be C_1-C_4-alkyl, e.g. Me.

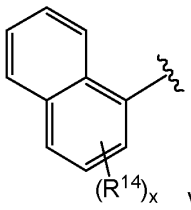
[0074] R^4 may be phenyl, said phenyl being optionally fused to a C_5-C_7-cycloalkyl ring, wherein R^4 is optionally substituted with from 1 to 4 R^{14} groups. R^4 may be phenyl, optionally substituted with from 1 to 4 R^{14} groups.

[0075] R^4 may have the structure:



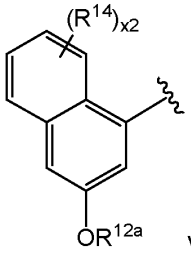
wherein R^{12a} is independently H or C_1-C_4-alkyl; x1 is independently selected from 0, 1, 2 and 3. R^{12a} may be H.

[0076] R^4 may be naphthyl, optionally substituted with from 1 to 4 R^{14} groups. R^4 may have the structure:



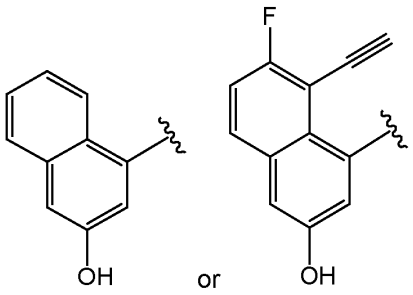
wherein x is independently selected from 0, 1, 2, 3, and 4. For the absence of doubt, throughout this specification, the x R^{14} groups may be attached to either ring of the naphthyl group.

[0077] R^4 may have the structure:



wherein R^{12a} is independently H or C_1-C_4-alkyl; x2 is independently selected from 0, 1, 2 and 3. For the absence of doubt, throughout this specification, the x2 R^{14} groups may be attached to either ring of the naphthyl group. R^{12a} may be H.

[0078] R^4 may have the structure:



.

[0079] R^4 may be 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl, optionally substituted with from 1 to 4 R^{14} groups. R^4 may be 9- or 10-membered bicyclic heteroaryl, optionally substituted with from 1 to 4 R^{14} groups.

[0080] R^5 may be H. R^5 may be C_1-C_4-alkyl, e.g. methyl.

[0081] R^6 may be H. R^6 may be C_1-C_4-alkyl, e.g. methyl.

[0082] R^7 may be selected from H and C_1-C_4-alkyl. R^7 may be H. R^7 may be C_1-C_4-alkyl, e.g. methyl.

[0083] R^8 may be selected from H and C_1-C_4-alkyl. R^8 may be H. R^8 may be C_1-C_4-alkyl, e.g. methyl.

[0084] R^9 may be independently at each occurrence selected from oxo, fluoro, cyano, $NR^{12}R^{13}$, OR^{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. R^9 may be independently at each occurrence selected from oxo, fluoro, $NR^{12}R^{13}$, OR^{12}, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$ and C_1-C_4-alkyl substituted with OR^{12}.

[0085] R^9 may be independently at each occurrence selected from oxo, halo, cyano, $NR^{12}R^{13}$ provided that R^{12} is not H and R^{13} is not H, OR^{12}, CO_2R^{12}, $CONR^{12}R^{12}$, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$ provided that R^{12} is not H and R^{13} is not H, 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.

[0086] R^{10} may be 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.

[0087] R^{10} may be independently at each occurrence selected from oxo, fluoro, $NR^{12}R^{13}$, OR^{12}, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$ and C_1-C_4-alkyl substituted with OR^{12}.

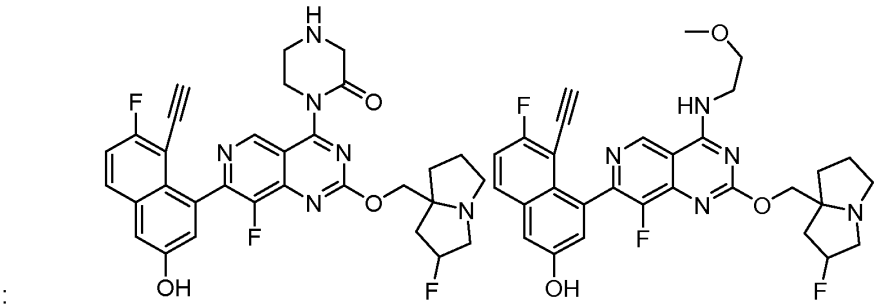
[0088] R^{11} may be each independently at each occurrence selected from halo, cyano, nitro, $NR^{12}R^{13}$, OR^{12}, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_1-C_4-haloalkyl and cyclopropyl. R^{11} may be each independently at each occurrence selected from OR^{12}, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyclopropyl.

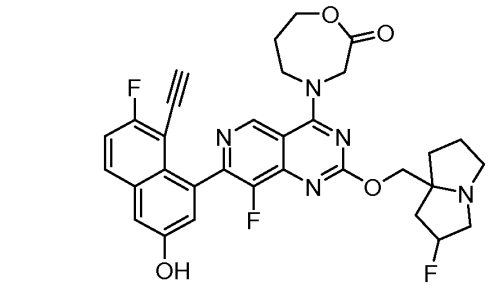
[0089] R^{12} may independently at each occurrence be selected from H and C_1-C_4-alkyl.

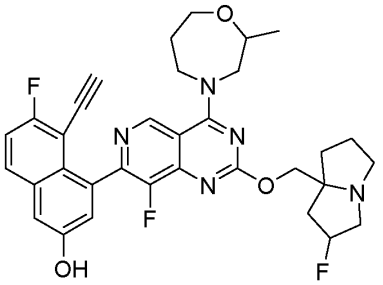
[0090] R^{13} may independently at each occurrence be selected from H and C_1-C_4-alkyl.

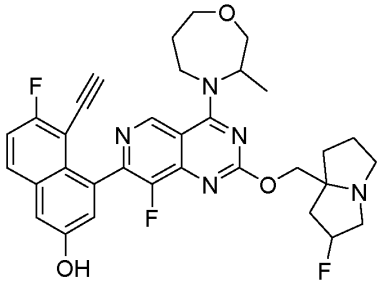
[0091] R^{14} may be each independently at each occurrence selected from halo, cyano, nitro, $NR^{12}R^{13}$, OR^{12}, C_1-C_4-alkyl, C_1-C_4-alkyl substituted with $NR^{12}R^{13}$, C_1-C_4-alkyl substituted with OR^{12}, C_1-C_4-haloalkyl and cyclopropyl. R^{14} may be each independently at each occurrence selected from OR^{12}, C_1-C_4-alkyl, C_1-C_4-haloalkyl and cyclopropyl.

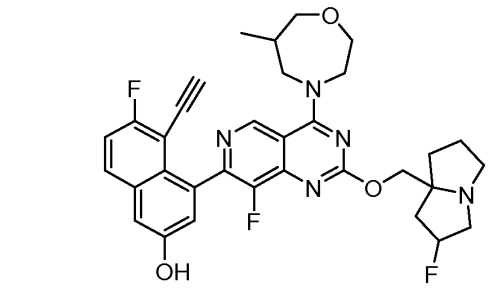
[0092] The compound of formula (**I**) may be selected from:

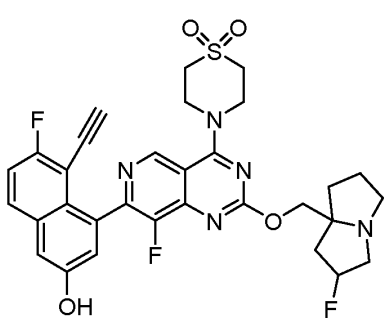


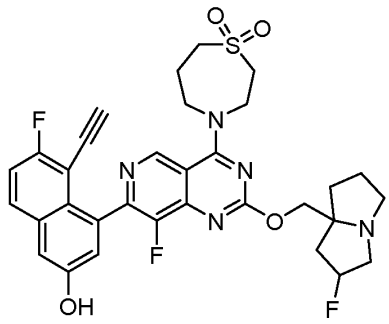


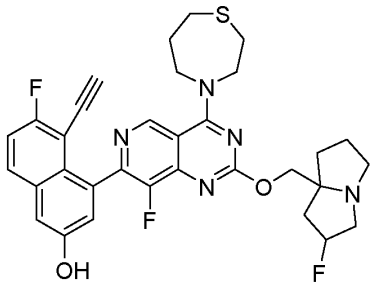


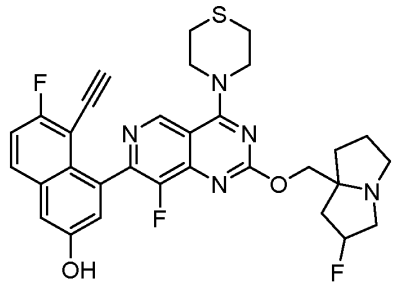


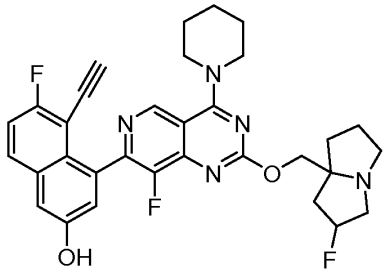


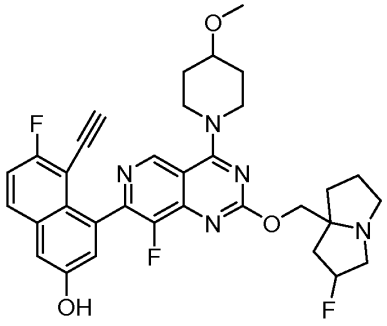


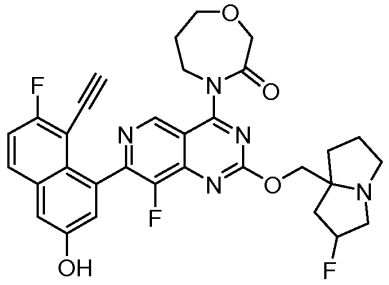


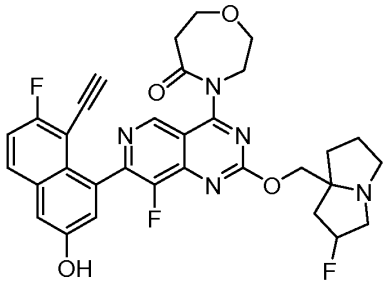


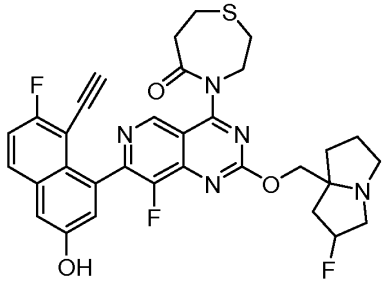


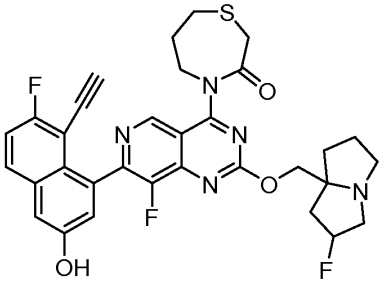












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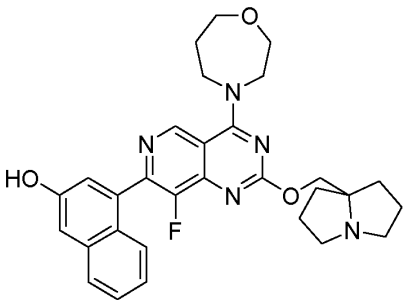
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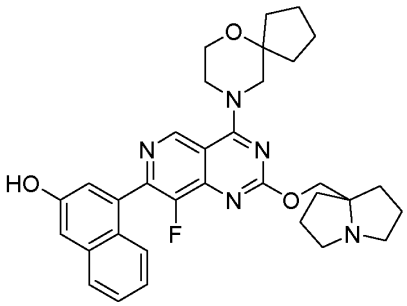
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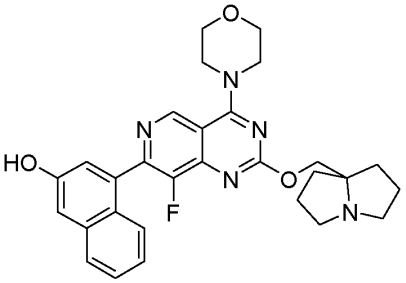
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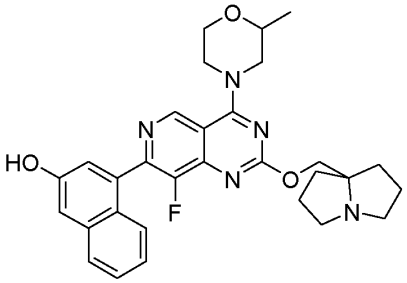
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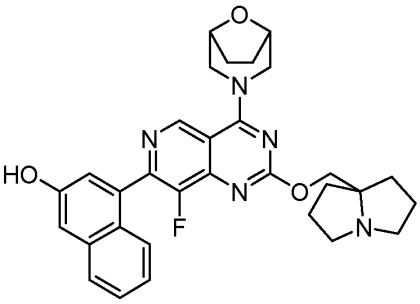
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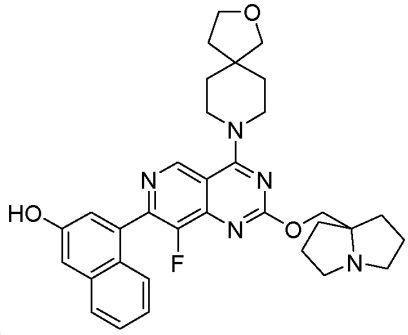
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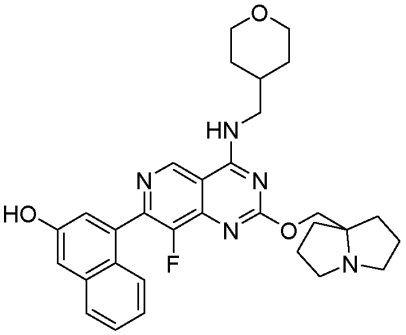
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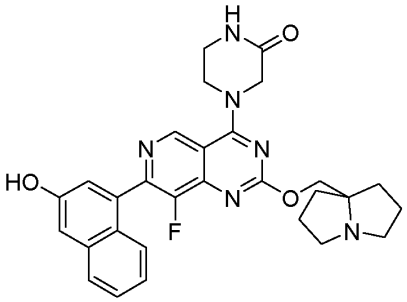
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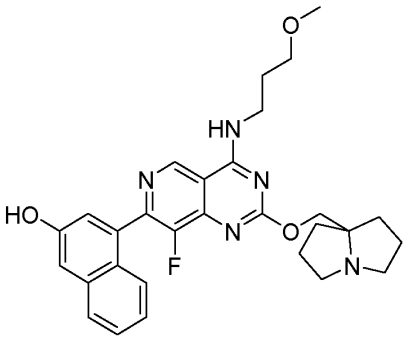
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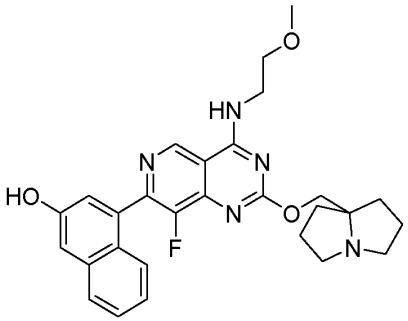
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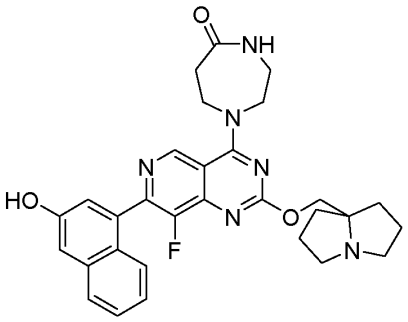
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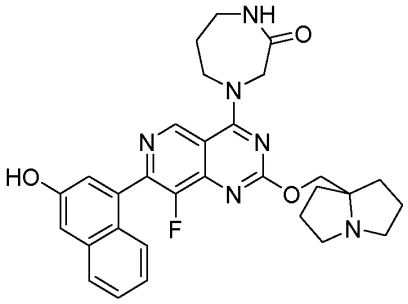
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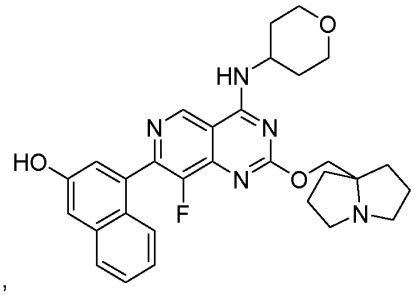
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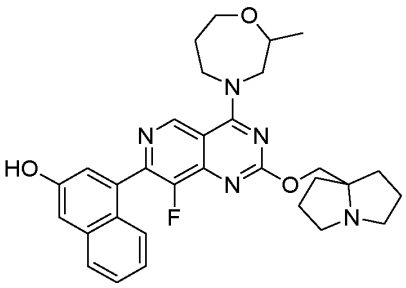
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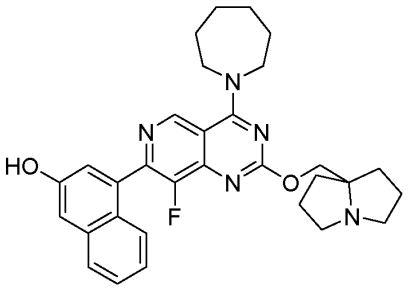
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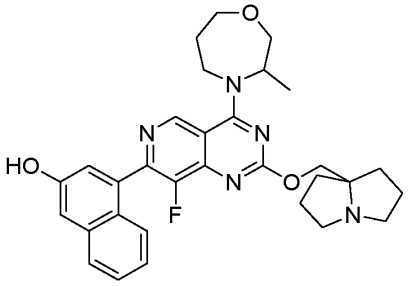
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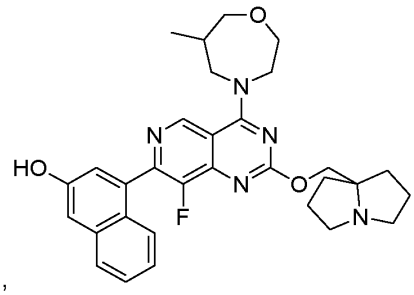
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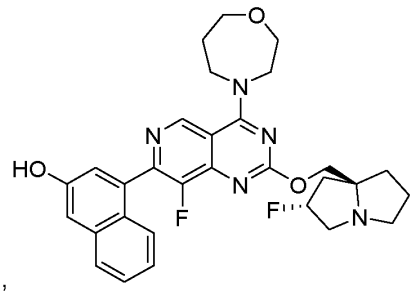
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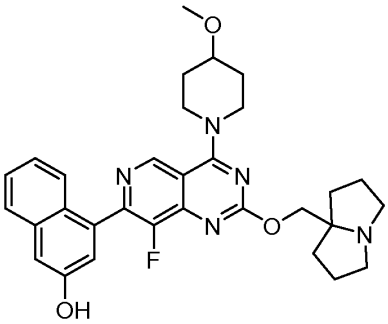
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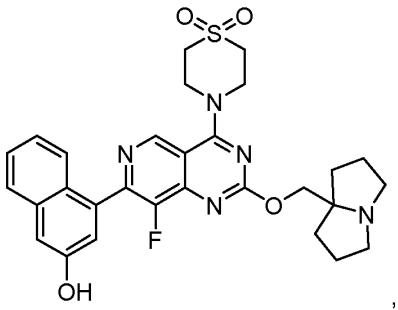
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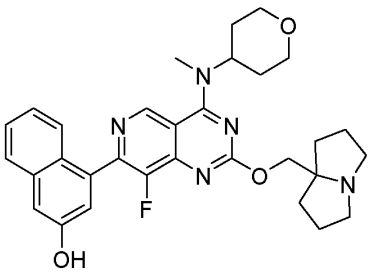
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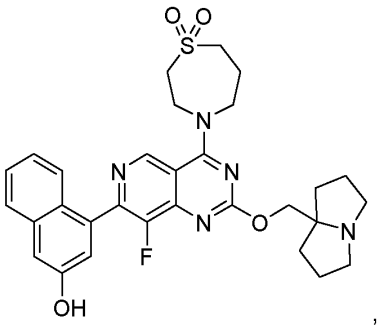
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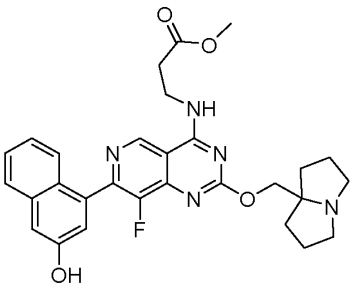
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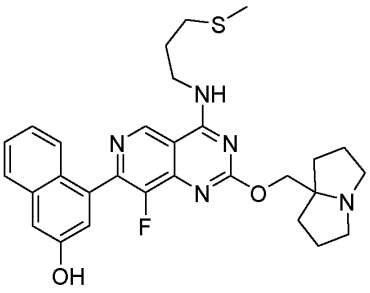
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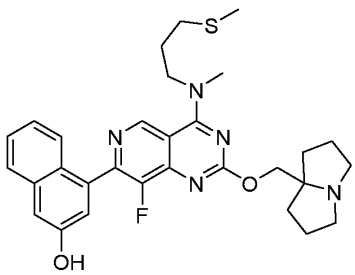
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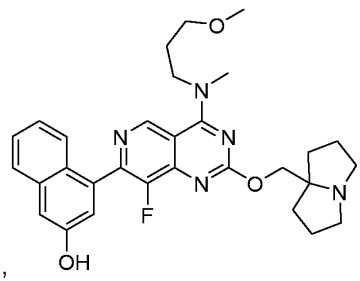
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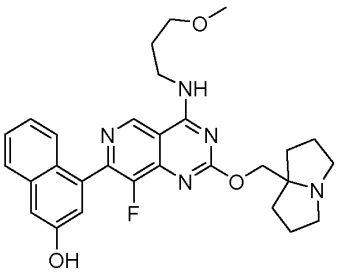
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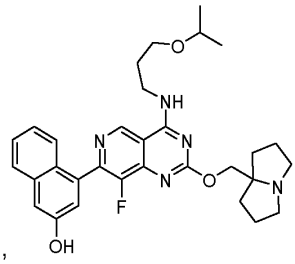
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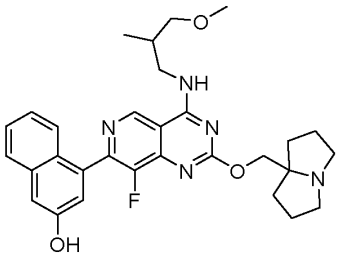
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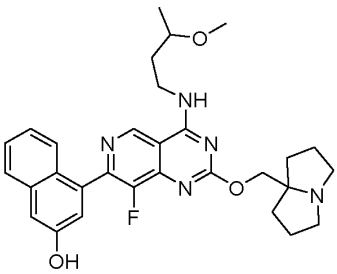
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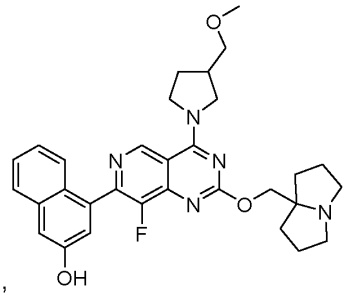
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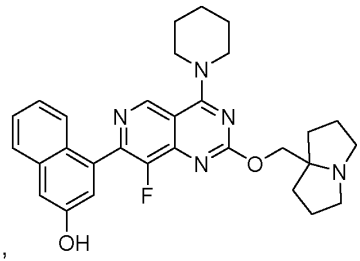
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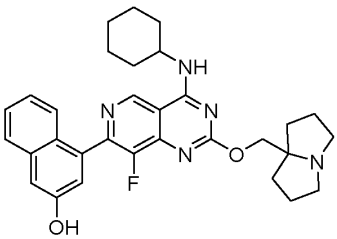
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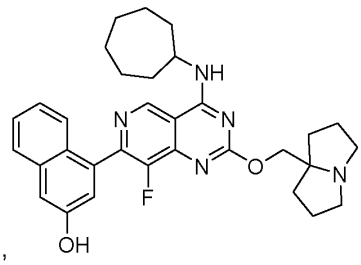
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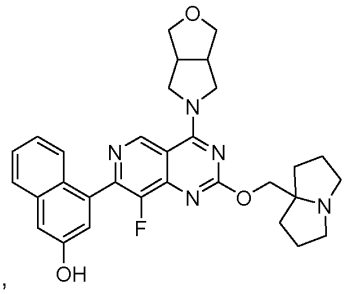
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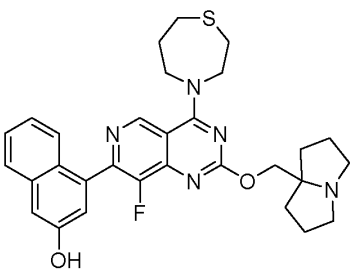
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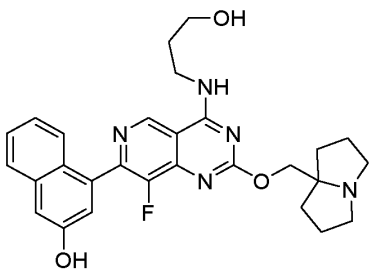
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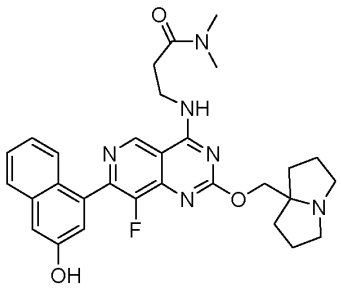
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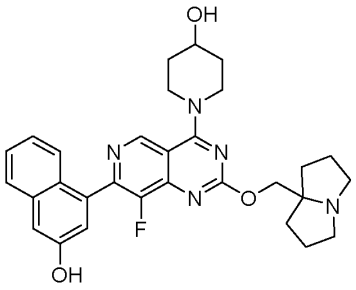
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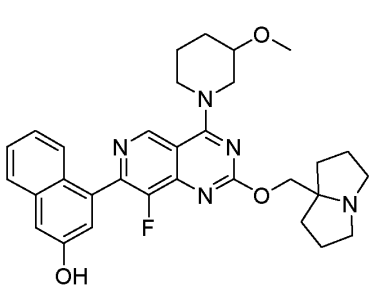
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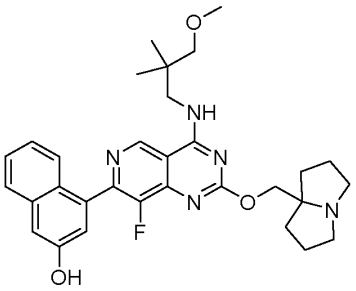
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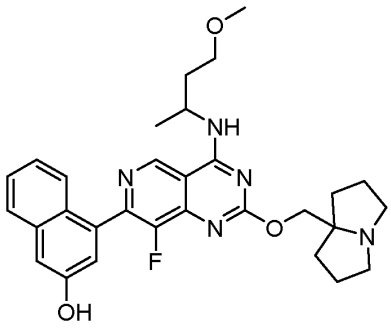
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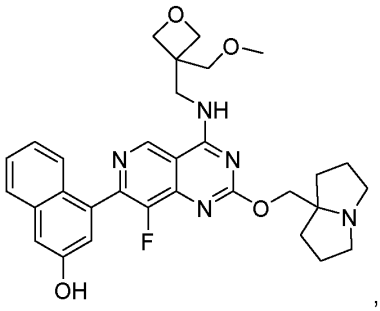
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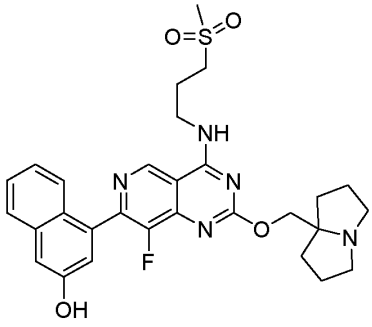
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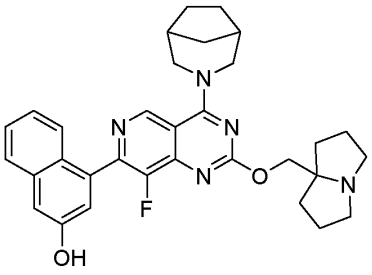
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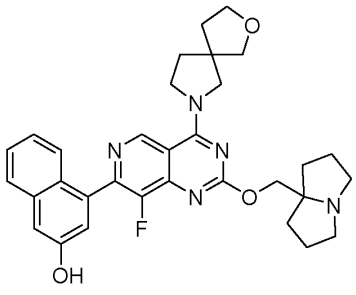
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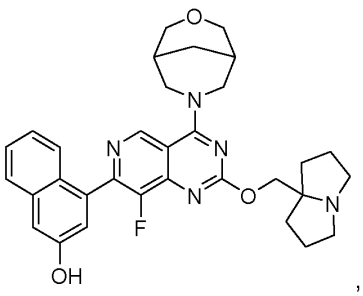
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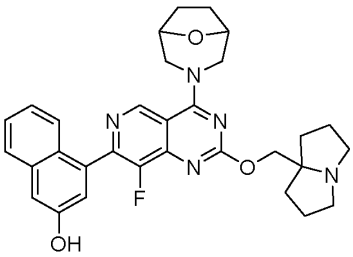
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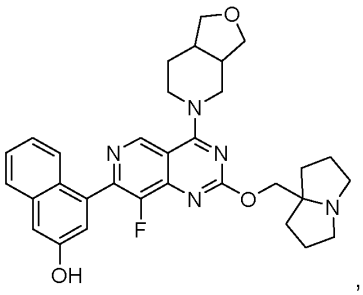
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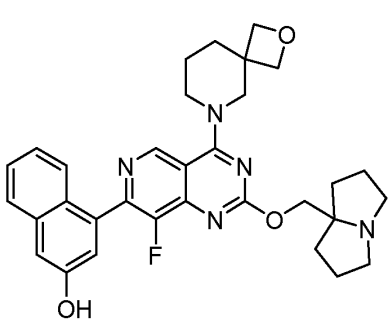
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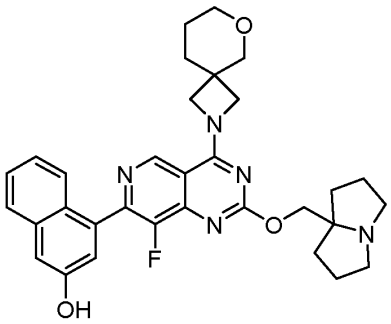
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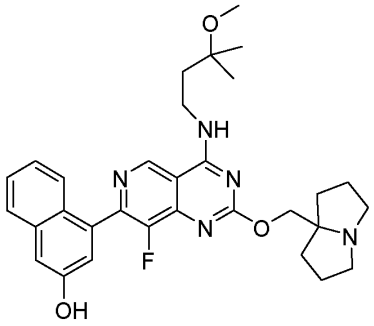
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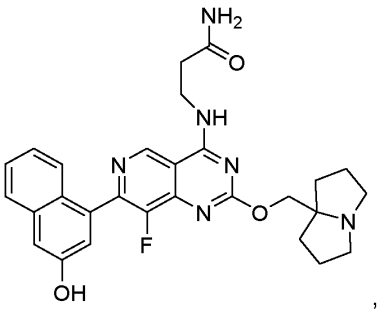
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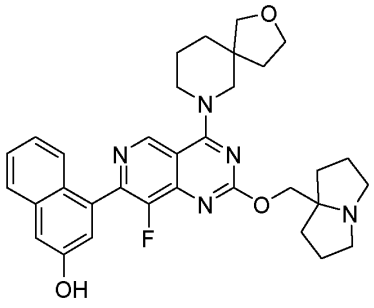
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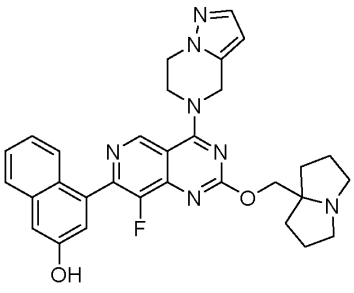
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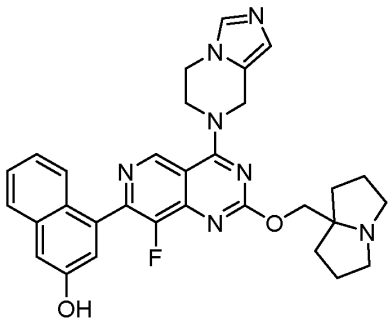
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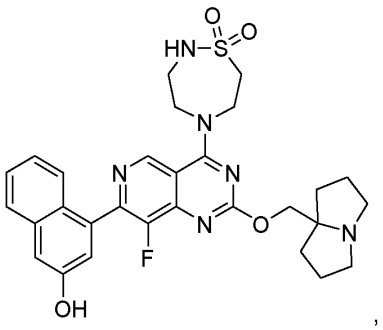
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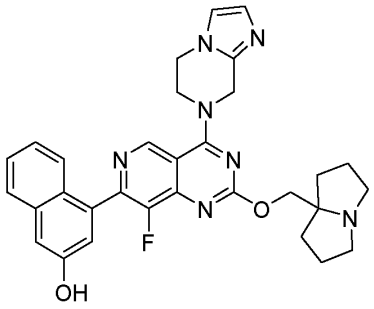
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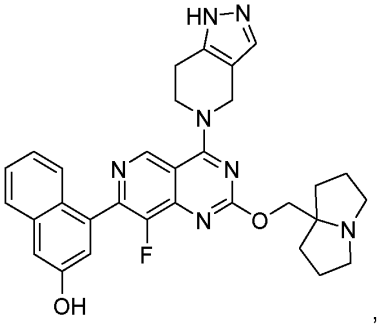
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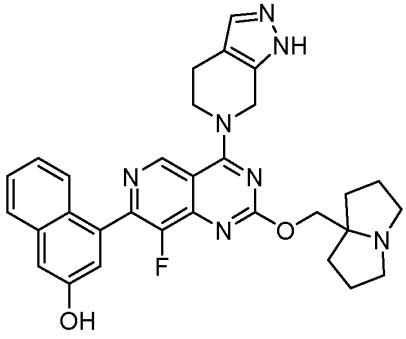
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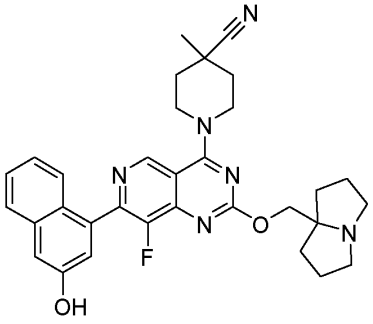
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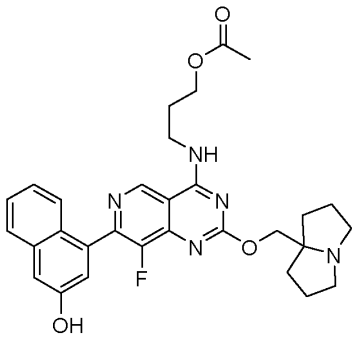
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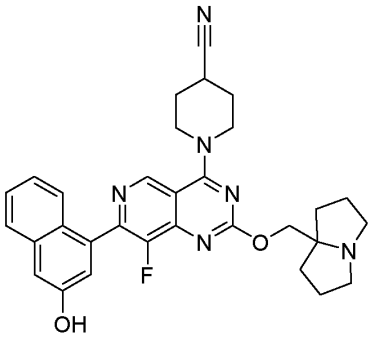
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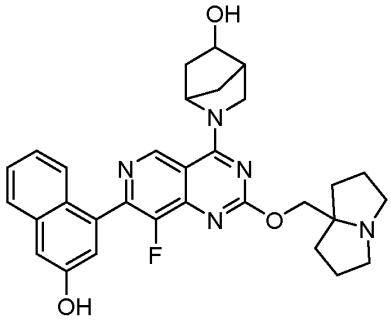
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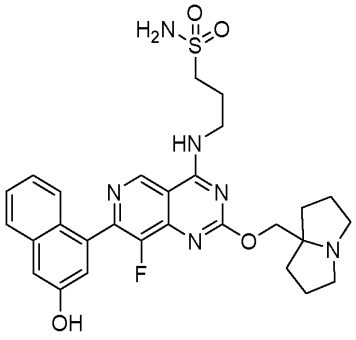
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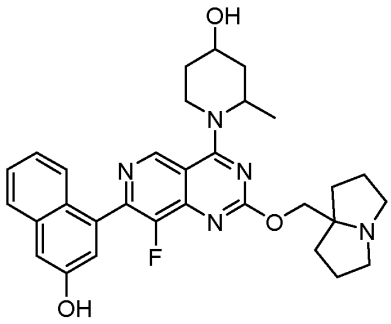
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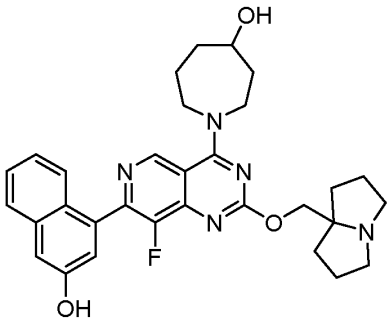
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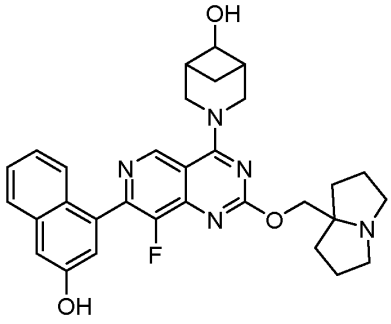
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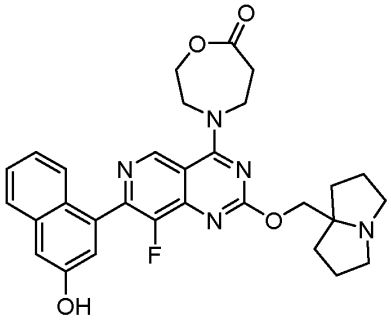
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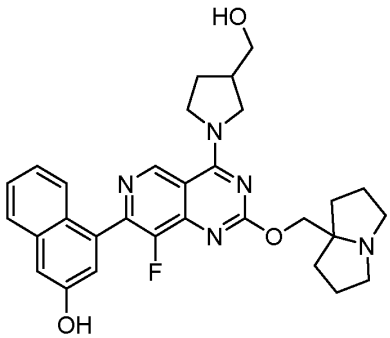
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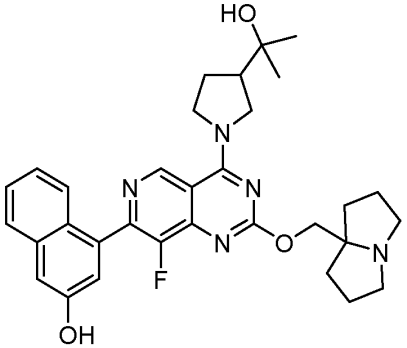
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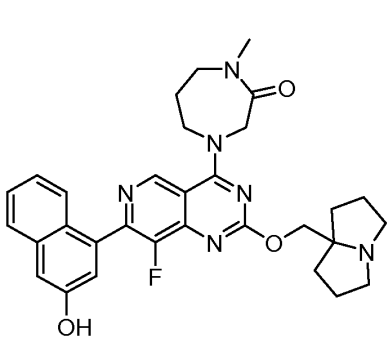
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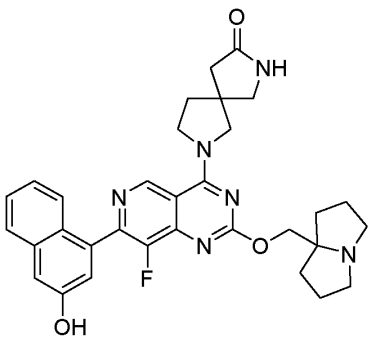
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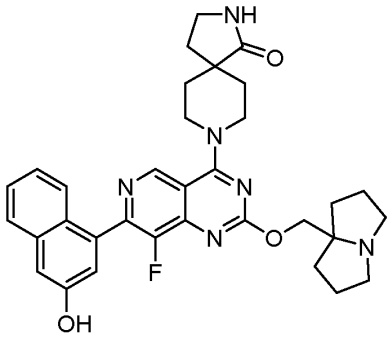
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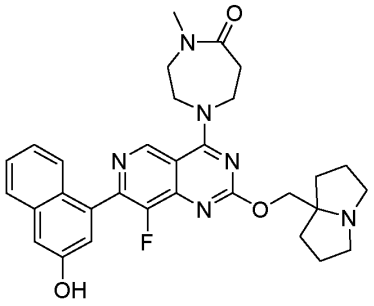
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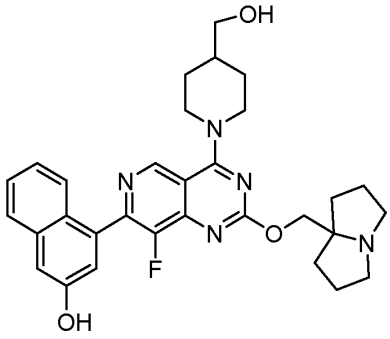
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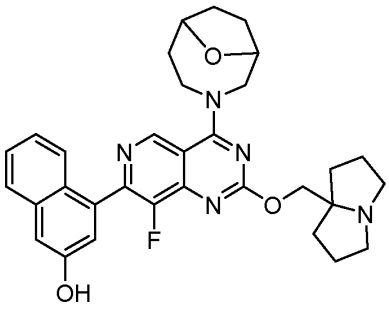
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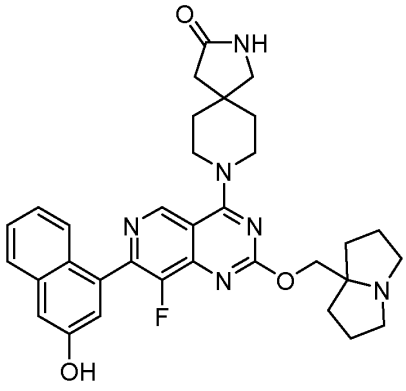
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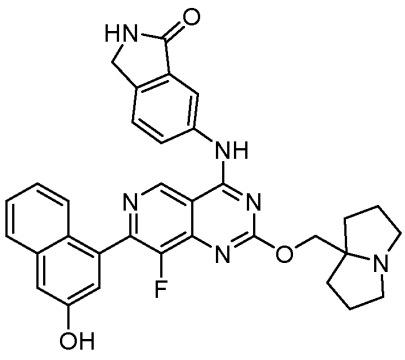
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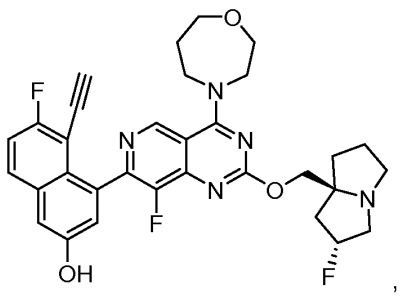
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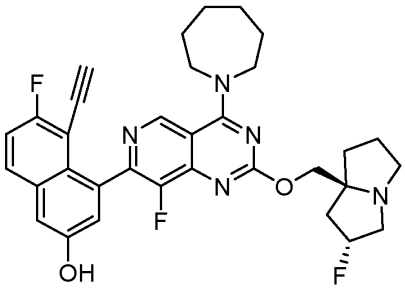
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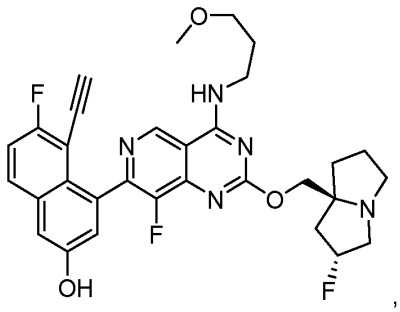
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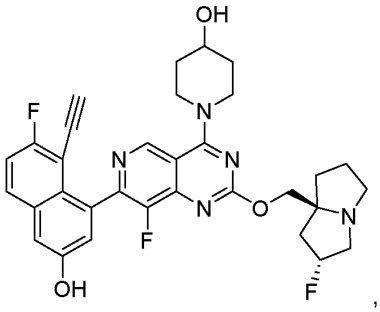
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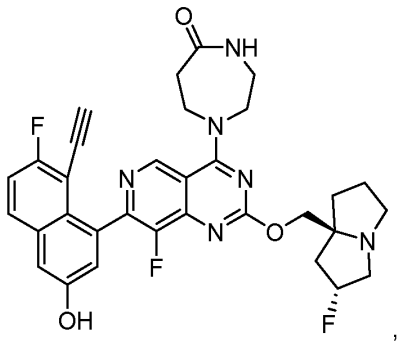
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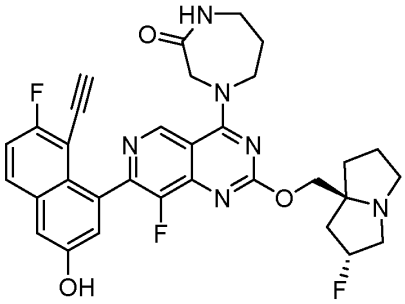
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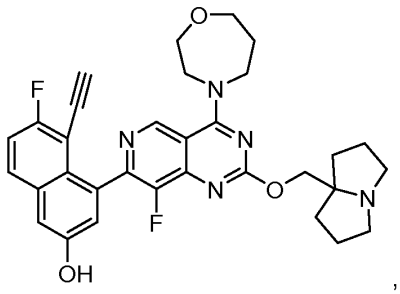
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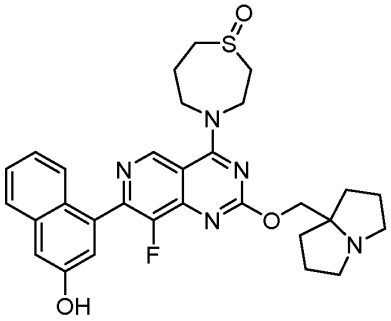
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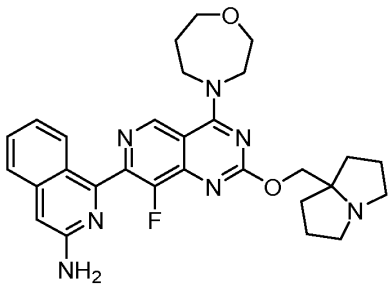
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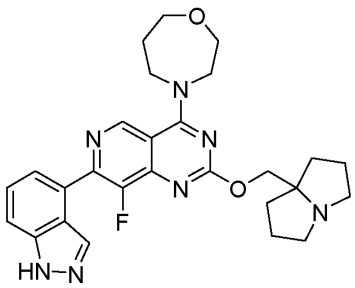
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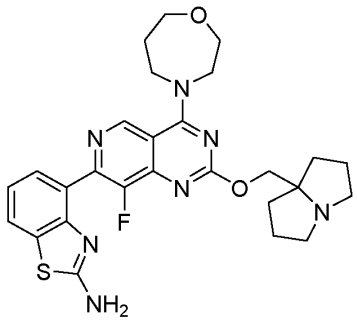
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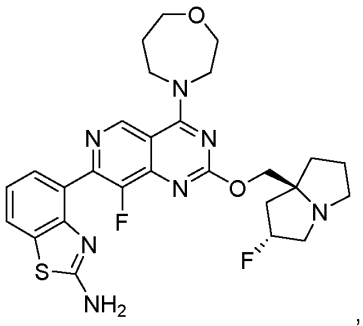
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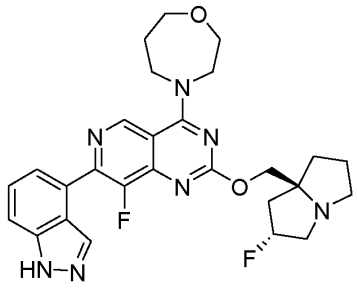
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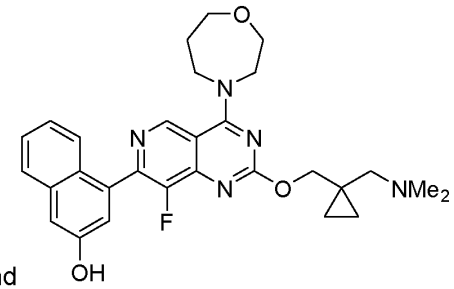
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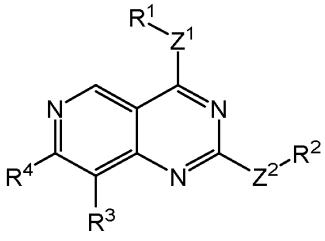
The invention also encompasses the subject matter of the following numbered clauses:

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


(**I**)

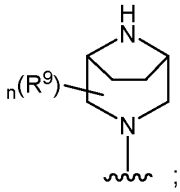
wherein

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 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 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 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 bridged bicyclic 6- to 11-membered heterocycloalkyl group is not:



;

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^3 is 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;

n is an integer selected from 0, 1, 2, 3 and 4;

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.

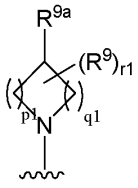
2. A compound of clause 1, wherein Z^1 is -NR^5-.

3. A compound of clause 1 or clause 2, wherein Z^2 is -O-.

4. A compound of any one of clauses 1 to 3, wherein R^1 is C_0-C_3-alkylene-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 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.

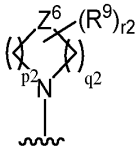
5. A compound of any one of clauses 1 to 3, wherein R^1 and R^5 together with the nitrogen to which they are attached form a ring system selected from: a monocyclic 4- to 7-membered group heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups; a fused or spirofused bicyclic 6- to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

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



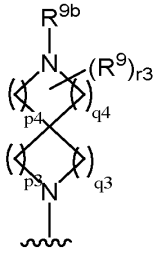
wherein R^{9a} is selected from $NR^{12}R^{13}$ and C_1-C_4-alkyl substituted with $NR^{12}R^{13}$; p1 is selected from 0, 1, 2 and 3, q1 is selected from 0, 1 and 2; and r1 is selected from 0, 1, 2 and 3.

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



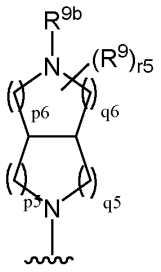
wherein Z^6 is independently selected from NR^{9b}, O, S, $S(O)_2$, S(O) and S(O)(NH); R^{9b} is selected from H and C_1-C_4-alkyl; p2 is selected from 2 and 3, q2 is 2; and r2 is selected from 0, 1, 2 and 3.

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



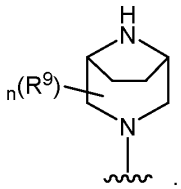
wherein R^{9b} is selected from H and C_1-C_4-alkyl; p3, p4, q3 and q4 are each independently selected from 0, 1, 2 and 3; providing that the sum of p3, p4, q3 and q4 is from 3 to 8, the sum of p3 and q3 is 2 or greater, and the sum of p4 and q4 is 2 or greater; and r3 is selected from 0, 1, 2 and 3.

9. A compound of clause 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^{9b} is selected from H and C_1-C_4-alkyl; p5, p6, q5 and are each selected from 0, 1, 2 and 3; providing that the sum of p3, p4, q3 and q4 is from 2 to 7, the sum of p5 and q5 is 1 or greater, and the sum of p6 and q6 is 1 or greater; and r5 is selected from 0, 1, 2 and 3.

10. A compound of clause 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, wherein the bridged bicyclic 6- to 11-membered heterocycloalkyl group is not:



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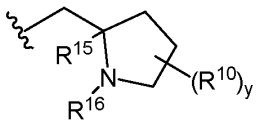
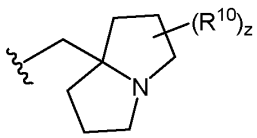
11. A compound of any one of clauses 1 to 10, wherein R^2 has the structure:



, 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.

12. A compound of clause 11, wherein R^2 has the structure:

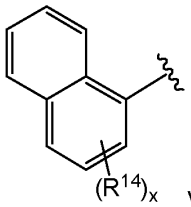


, wherein z is independently selected from 0, 1, 2, 3, and 4. z may be selected from 0 and 1. z may be 0. z may be 1.

13. A compound of any one of clauses 1 to 12, wherein R^3 is F.

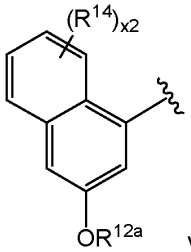
14. A compound of any one of clauses 1 to 13, wherein R^4 is phenyl, said phenyl being optionally fused to a C_5-C_7-cycloalkyl ring, wherein R^4 is optionally substituted with from 1 to 4 R^{14} groups.

15. A compound of any one of clauses 1 to 13, wherein R^4 has the structure:



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

16. A compound of clause 15, 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.

17. A compound of any one of clauses 1 to 13, wherein R^4 is 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl, optionally substituted with from 1 to 4 R^{14} groups.

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

19. A compound of any one of clauses 1 to 17 for use in treating cancer.

20. A compound for use of clause 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. A compound for use of clause 19 or clause 20, wherein the subject being treated has a cancer having the KRAS G12D mutation.

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

DETAILED DESCRIPTION

[0093] In an aspect of the invention there is provided the compounds of the present invention for use as a medicament.

[0094] 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.

[0095] In accordance with another aspect, the present invention provides a method of treating a condition which can be modulated by inhibition of wild-type KRAS proteins, or KRAS proteins having a mutation, the method comprising administering a therapeutically effective amount of a compound of the invention to a subject in need thereof.

[0096] In accordance with another aspect, the present invention provides a pharmaceutical formulation comprising a compound of the present invention and a pharmaceutically acceptable excipient.

[0097] 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.

[0098] In an aspect of the invention there is provided the compounds of the present invention for use in treating cancer.

[0099] In an aspect of the invention there is provided a method of treating cancer, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the invention.

[00100] In an aspect of the invention there is provided the use of a compound of the invention for manufacture of a medicament for the treatment of cancer.

[00101] The cancer may be a solid tumour. The cancer may be a carcinoma.

[00102] The cancer may be a liquid cancer, e.g. leukaemia.

[00103] The cancer may be selected from cervical cancer, endometrial cancer, multiple myeloma, stomach cancer, bladder cancer, uterine cancer, esophageal squamous cell carcinoma, gastric cancer, glioblastomas, astrocytomas; retinoblastoma, osteosarcoma, chondosarcoma, Ewing's sarcoma, rabdomysarcoma, Wilm's tumor, basal cell carcinoma, non-small cell lung cancer, brain tumour, hormone refractory prostate cancer, prostate cancer, metastatic breast cancer, breast cancer, metastatic pancreatic cancer, pancreatic cancer, colorectal cancer, head and neck squamous cell carcinoma, cancer of the head and neck, appendix cancer, cholangiocarcinoma, cancer of unknown primary, ampulla of Vater

cancer, ovarian cancer, acute myeloid leukaemia, small cell lung carcinoma, germ cell tumour, small bowel cancer, melanoma, soft tissue sarcoma, gastrointestinal stromal tumour, thyroid cancer, gastrointestinal neuroendocrine tumour, renal cell carcinoma and histiocytosis.

[00104] The cancer may be selected from pancreatic carcinoma, colorectal carcinoma, rectal carcinoma, endometrial carcinoma, non-small cell lung carcinoma, gastric carcinoma, ovarian carcinoma and small cell lung carcinoma.

[00105] The cancer may have wild-type KRAS. The cancer may have a KRAS mutation. The cancer may have a KRAS mutation selected from: KRAS G12D, KRAS G12C, KRAS G12V, KRAS G12A, KRAS G13D and KRAS Q61H. The cancer may have a KRAS G12D mutation. The cancer may have a KRAS G12D mutation, said cancer being selected from pancreatic carcinoma, colorectal carcinoma, rectal carcinoma, endometrial carcinoma, non-small cell lung carcinoma, gastric carcinoma, ovarian carcinoma and small cell lung carcinoma.

[00106] The cancer may have a confirmed KRAS G12D mutation. The cancer may have a confirmed KRAS G12D mutation, said cancer being selected from pancreatic carcinoma, colorectal carcinoma, rectal carcinoma, endometrial carcinoma, non-small cell lung carcinoma, gastric carcinoma, ovarian carcinoma and small cell lung carcinoma.

[00107] The subject may be human.

[00108] The subject may have a cancer with a KRAS G12D mutation. The subject may have a cancer with a KRAS G12D mutation, said cancer being selected from pancreatic carcinoma, colorectal carcinoma, rectal carcinoma, endometrial carcinoma, non-small cell lung carcinoma, gastric carcinoma, ovarian carcinoma and small cell lung carcinoma.

[00109] The subject may have a cancer with a confirmed KRAS G12D mutation. The subject may have a cancer with a confirmed KRAS G12D mutation, said cancer being selected from pancreatic carcinoma, colorectal carcinoma, rectal carcinoma, endometrial carcinoma, non-small cell lung carcinoma, gastric carcinoma, ovarian carcinoma and small cell lung carcinoma.

[00110] The subject may have a confirmed G12D mutation in their tumour. To be confirmed, the test for G12D presence in the tumour must have >95% analytical specificity for the detection of mutations in the KRAS gene. Such validated tests would include already commercially available tests i.e. Foundation One CDx and CARIS DNA sequencing.

[00111] As mentioned above, the invention includes a method of treating cancer. The method may comprise:

a) confirming that the subject has a cancer with a G12D mutation; and

b) administering to a subject in need thereof a therapeutically effective amount of a compound of the invention.

[00112] The term "halo" refers to one of the halogens, group 17 of the periodic table. In particular the term refers to fluorine, chlorine, bromine and iodine. Preferably, the term refers to fluorine or chlorine.

[00113] The term "alkyl" refers to a linear or branched hydrocarbon chain. For example, the term "C_{1-6} alkyl" or "C_{1-4}-alkyl" refers to a linear or branched hydrocarbon chain containing 1, 2, 3, 4, 5, or 6 carbon atoms, for example methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, n-pentyl and n-hexyl. Where an alkyl group is indicated as being C_{0-4}alkyl, then it should be appreciated that this represents the possibility for the alkyl unit to be absent or 1, 2, 3, or 4 carbon atoms in length. Alkylene groups may likewise be linear or branched and may have two places of attachment to the remainder of the molecule. Furthermore, an alkylene group may, for example, correspond to one of those alkyl groups listed in this paragraph. The alkyl and alkylene groups may be unsubstituted or substituted by one or more substituents. Possible substituents are described below. Substituents for the alkyl group may be halogen, e.g. fluorine, chlorine, bromine and iodine, OH, C_{1-6} alkoxy.

[00114] The term "alkoxy" refers to an alkyl group which is attached to a molecule *via* oxygen. For example, the term "C_{1-6} alkoxy" refers to an alkyl group which is attached to a molecule via oxygen. This includes moieties where the alkyl part may be linear or branched and may contain 1, 2, 3, 4, 5, or 6 carbon atoms, for example methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, n-pentyl and n-hexyl. Therefore, the alkoxy group may be methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, sec-butoxy, tert-butoxy, n-pentoxy and n-hexoxy. The alkyl part of the alkoxy group may be unsubstituted or substituted by one or more substituents. Possible substituents are described below. Substituents for the alkyl group may be halogen, e.g. fluorine, chlorine, bromine and iodine, OH, C_{1-6} alkoxy.

[00115] The term "haloalkyl" refers to a hydrocarbon chain substituted with at least one halogen atom independently chosen at each occurrence, for example fluorine, chlorine, bromine and iodine. For example, the term "C_{1-6} haloalkyl" refers to a linear or branched hydrocarbon chain containing 1, 2, 3, 4, 5 or 6 carbon atoms substituted with at least one halogen. The halogen atom may be present at any position on the hydrocarbon chain. For example, C_{1-6} haloalkyl may refer to chloromethyl, fluoromethyl, trifluoromethyl, chloroethyl e.g. 1-chloromethyl and 2-chloroethyl, trichloroethyl e.g. 1,2,2-trichloroethyl, 2,2,2-trichloroethyl, fluoroethyl e.g. 1-fluoromethyl and 2-fluoroethyl, trifluoroethyl e.g. 1,2,2-trifluoroethyl and 2,2,2-trifluoroethyl, chloropropyl, trichloropropyl, fluoropropyl, trifluoropropyl.

[00116] The term "alkenyl" refers to a branched or linear hydrocarbon chain containing at least one double bond. For example, the term "C_{2-6} alkenyl" refers to a branched or linear hydrocarbon chain containing at least one double bond and having 2, 3, 4, 5 or 6 carbon atoms. The double bond(s) may be present as the *E* or *Z* isomer. The double bond may be at any possible position of the hydrocarbon chain. For example, the "C_{2-6} alkenyl" may be ethenyl, propenyl, butenyl, butadienyl, pentenyl, pentadienyl, hexenyl and hexadienyl.

[00117] The term "alkynyl" refers to a branched or linear hydrocarbon chain containing at least one triple bond. For example, the term "C_{2-6} alkynyl" refers to a branched or linear hydrocarbon chain containing at least one triple bond and having 2, 3, 4, 5 or 6 carbon atoms. The triple bond may be at any possible position of the hydrocarbon chain. For example, the "C_{2-6} alkynyl" may be ethynyl, propynyl, butynyl, pentynyl and hexynyl.

[00118] The term "heteroalkyl" refers to a branched or linear hydrocarbon chain containing at least one heteroatom selected from N, O and S positioned between any carbon in the chain or at an end of the chain. For example, the term "C_{1-6} heteroalkyl" refers to a branched or linear hydrocarbon chain containing 1, 2, 3, 4, 5, or 6 carbon atoms and at least one heteroatom selected from N, O and S positioned between any carbon in the chain or at an end of the chain. For example, the hydrocarbon chain may contain one or two heteroatoms. The C_{1-6} heteroalkyl may be bonded to the rest of the molecule through a carbon or a heteroatom. For example, the "C_{1-6} heteroalkyl" may be C_{1-6} *N*-alkyl, C_{1-6} *N,N*-alkyl, or C_{1-6} *O*-alkyl.

[00119] The term "cycloalkyl" refers to a saturated hydrocarbon ring system. For example, "C_{3-8} cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[00120] The term "cycloalkenyl" refers to an unsaturated hydrocarbon ring system that is not aromatic. The ring may contain more than one double bond provided that the ring system is not aromatic. For example, the "C_{3-8} cycloalkyl" may be cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadiene, cyclooctenyl and cycloatadienyl.

[00121] The term "heterocycloalkyl" refers to a saturated hydrocarbon ring system containing carbon atoms and at least one heteroatom within the ring selected from N, O and S. For example, there may be 1, 2 or 3 heteroatoms, optionally 1 or 2. The "heterocycloalkyl" may be bonded to the rest of the molecule through any carbon atom or heteroatom. The "heterocycloalkyl" may have one or more, e.g. one or two, bonds to the rest of the molecule: these bonds may be through any of the atoms in the ring. For example, the "heterocycloalkyl" may be a "C_{3-8} heterocycloalkyl". The term "C_{3-8} heterocycloalkyl" refers to a saturated

hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 carbon atoms and at least one heteroatom within the ring selected from N, O and S. For example, there may be 1, 2 or 3 heteroatoms, optionally 1 or 2. The "C_{3-8} heterocycloalkyl" may be bonded to the rest of the molecule through any carbon atom or heteroatom. The "C_{3-8} heterocycloalkyl" may have one or more, e.g. one or two, bonds to the rest of the molecule: these bonds may be through any of the atoms in the ring. For example, the "C_{3-8} heterocycloalkyl" may be oxirane, aziridine, azetidine, oxetane, tetrahydrofuran, pyrrolidine, imidazolidine, succinimide, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, piperidine, morpholine, thiomorpholine, piperazine, and tetrahydropyran.

[00122] The term "heterocycloalkenyl" refers to an unsaturated hydrocarbon ring system that is not aromatic, containing carbon atoms and at least one heteroatom within the ring selected from N, O and S. For example, there may be 1, 2 or 3 heteroatoms, optionally 1 or 2. The "heterocycloalkenyl" may be bonded to the rest of the molecule through any carbon atom or heteroatom. The "heterocycloalkenyl" may have one or more, e.g. one or two, bonds to the rest of the molecule: these bonds may be through any of the atoms in the ring. For example, the "heterocycloalkenyl" may be a "C_{3-8} heterocycloalkenyl". The term "C_{3-8} heterocycloalkenyl" refers to a saturated hydrocarbon ring system containing 3, 4, 5, 6, 7 or 8 atoms at least one of the atoms being a heteroatom within the ring selected from N, O and S. The "heterocycloalkenyl" may be tetrahydropyridine, dihydropyran, dihydrofuran, pyrroline.

[00123] The term "fused" refers to a bicyclic ring system in which the two rings are attached via two atoms that are situated adjacent to each other on each ring.

[00124] The term "spirofused" refers to a bicyclic ring system in which the two rings are attached via a single atom.

[00125] The term "bridged" refers to a bicyclic ring system in which the two rings are attached via two atoms that are not situated adjacent to each other on either ring.

[00126] The term "aromatic" when applied to a substituent as a whole means a single ring or polycyclic ring system with 4n + 2 electrons in a conjugated π system within the ring or ring system where all atoms contributing to the conjugated π system are in the same plane.

[00127] The term "aryl" refers to an aromatic hydrocarbon ring system. The ring system has 4n +2 electrons in a conjugated π system within a ring where all atoms contributing to the conjugated π system are in the same plane. For example, the "aryl" may be phenyl and naphthyl. The aryl system itself may be substituted with other groups.

[00128] The term "heteroaryl" refers to an aromatic hydrocarbon ring system with at least one heteroatom within a single ring or within a fused ring system, selected from O, N and S. The

ring or ring system has 4n +2 electrons in a conjugated π system where all atoms contributing to the conjugated π system are in the same plane. For example, the "heteroaryl" may be imidazole, thiene, furane, thianthrene, pyrrole, benzimidazole, pyrazole, pyrazine, pyridine, pyrimidine and indole.

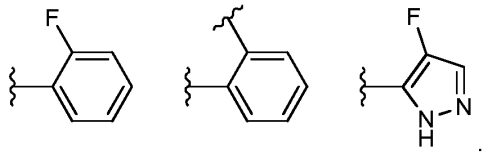
[00129] The term "halogen" herein includes reference to F, Cl, Br and I. Halogen may be Br. Halogen may be I.

[00130] A bond terminating in a "~" represents that the bond is connected to another atom that is not shown in the structure. A bond terminating inside a cyclic structure and not terminating at an atom of the ring structure represents that the bond may be connected to any of the atoms in the ring structure where allowed by valency.

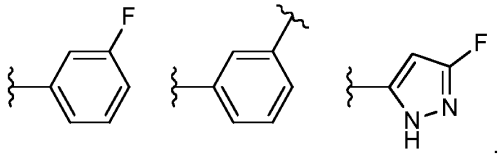
[00131] Where a moiety is substituted, it may be substituted at any point on the moiety where chemically possible and consistent with atomic valency requirements. The moiety may be substituted by one or more substituents, e.g. 1, 2, 3 or 4 substituents; optionally there are 1 or 2 substituents on a group. Where there are two or more substituents, the substituents may be the same or different.

[00132] Substituents are only present at positions where they are chemically possible, the person skilled in the art being able to decide (either experimentally or theoretically) without inappropriate effort which substitutions are chemically possible, and which are not.

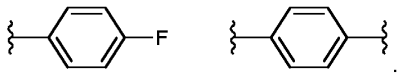
[00133] Ortho, meta and para substitution are well understood terms in the art. For the absence of doubt, "ortho" substitution is a substitution pattern where adjacent carbons possess a substituent, whether a simple group, for example the fluoro group in the example below, or other portions of the molecule, as indicated by the bond ending in "~".



[00134] "Meta" substitution is a substitution pattern where two substituents are on carbons one carbon removed from each other, i.e. with a single carbon atom between the substituted carbons. In other words, there is a substituent on the second atom away from the atom with another substituent. For example, the groups below are meta substituted.



[00135] "Para" substitution is a substitution pattern where two substituents are on carbons two carbons removed from each other, i.e with two carbon atoms between the substituted carbons. In other words, there is a substituent on the third atom away from the atom with another substituent. For example, the groups below are para substituted.



[00136] Throughout the description the disclosure of a compound also encompasses pharmaceutically acceptable salts, solvates and stereoisomers thereof. Where a compound has a stereocentre, both (*R*) and (*S*) stereoisomers are contemplated by the invention, equally mixtures of stereoisomers or a racemic mixture are completed by the present application. Where a compound of the invention has two or more stereocentres any combination of (*R*) and (*S*) stereoisomers is contemplated. The combination of (*R*) and (*S*) stereoisomers may result in a diastereomeric mixture or a single diastereoisomer. The compounds of the invention may be present as a single stereoisomer or may be mixtures of stereoisomers, for example racemic mixtures and other enantiomeric mixtures, and diastereomeric mixtures. Where the mixture is a mixture of enantiomers the enantiomeric excess may be any of those disclosed above. Where the compound is a single stereoisomer the compounds may still contain other diastereomers or enantiomers as impurities. Hence a single stereoisomer does not necessarily have an enantiomeric excess (e.e.) or diastereomeric excess (d.e.) of 100% but could have an e.e. or d.e. of about at least 85%, at least 60% or less. For example, the e.e. or d.e. may be 90% or more, 90% or more, 80% or more, 70% or more, 60% or more, 50% or more, 40% or more, 30% or more, 20% or more, or 10% or more.

[00137] The invention contemplates pharmaceutically acceptable salts of the compounds of the invention. These may include the acid addition and base salts of the compounds. These may be acid addition and base salts of the compounds. In addition, the invention contemplates solvates of the compounds. These may be hydrates or other solvated forms of the compound.

[00138] Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulfate/sulfate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 1,5-naphthalenedisulfonate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

[00139] Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. Hemisalts of acids and bases may also be formed, for example, hemisulfate and hemicalcium salts. For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

[00140] Pharmaceutically acceptable salts of compounds of formula (I) may be prepared by one or more of three methods:

(i) by reacting the compound of the invention with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of the invention or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the compound of the invention to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

[00141] All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

[00142] The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

[00143] Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non- ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

[00144] Hereinafter all references to compounds of any formula include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

[00145] The compounds of the invention include compounds of a number of formulae as herein defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labelled compounds of the invention.

[00146] The present invention also includes all pharmaceutically acceptable isotopically-labelled compounds of the invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number most commonly found in nature.

[00147] Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

[00148] Certain isotopically-labelled compounds, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

[00149] Substitution with heavier isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

[00150] Before purification, the compounds of the present invention may exist as a mixture of enantiomers depending on the synthetic procedure used. The enantiomers can be separated by conventional techniques known in the art. Thus the invention covers individual enantiomers as well as mixtures thereof.

[00151] For some of the steps of the process of preparation of the compounds of the invention, it may be necessary to protect potential reactive functions that are not wished to react, and to cleave said protecting groups in consequence. In such a case, any compatible protecting radical can be used. In particular methods of protection and deprotection such as those described by T.W. GREENE (Protective Groups in Organic Synthesis, A. Wiley- Interscience Publication, 1981) or by P. J. Kocienski (Protecting groups, Georg Thieme Verlag, 1994), can be used. All of the above reactions and the preparations of novel starting materials used in the preceding methods are conventional and appropriate reagents and reaction conditions for their performance or preparation as well as procedures for isolating the desired products will be

well-known to those skilled in the art with reference to literature precedents and the examples and preparations hereto.

[00152] Also, the compounds of the present invention as well as intermediates for the preparation thereof can be purified according to various well-known methods, such as for example crystallization or chromatography.

[00153] One or more compounds of the invention may be combined with one or more pharmaceutical agents, for example anti-inflammatory agents, anti-fibrotic agents, chemotherapeutics, anti-cancer agents, immunosuppressants, anti-tumour vaccines, cytokine therapy, or tyrosine kinase inhibitors, for the treatment of conditions modulated by the inhibition of RAS proteins, for example cancer, sarcoma, melanoma, skin cancer, haematological tumors, lymphoma, carcinoma, and leukemia.

[00154] The method of treatment or the compound for use in the treatment of cancer, sarcoma, melanoma, skin cancer, haematological tumors, lymphoma, carcinoma, and leukemia as defined hereinbefore may be applied as a sole therapy or be a combination therapy with an additional active agent.

[00155] The method of treatment or the compound for use in the treatment of cancer, sarcoma, melanoma, skin cancer, haematological tumors, lymphoma, carcinoma, and leukemiamay involve, in addition to the compound of the invention, additional active agents. The additional active agents may be one or more active agents used to treat the condition being treated by the compound of the invention and additional active agent. The additional active agents may include one or more of the following active agents:-

(i) steroids such as corticosteroids, including glucocorticoids and mineralocorticoids, for example aclometasone, aclometasone dipropionate, aldosterone, amcinonide, beclomethasone, beclomethasone dipropionate, betamethasone, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, budesonide, clobetasone, clobetasone butyrate, clobetasol propionate, cloprednol, cortisone, cortisone acetate, cortivazol, deoxycortone, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, dexamethasone isonicotinate, difluorocortolone, fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluocortolone caproate, fluocortolone pivalate, fluorometholone, fluprednidene, fluprednidene acetate, flurandrenolone, fluticasone, fluticasone propionate, halcinonide, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone valerate, icomethasone, icomethasone enbutate, meprednisone, methylprednisolone, mometasone paramethasone, mometasone furoate monohydrate, prednicarbate, prednisolone, prednisone,

tixocortol, tixocortol pivalate, triamcinolone, triamcinolone acetonide, triamcinolone alcohol and their respective pharmaceutically acceptable derivatives. A combination of steroids may be used, for example a combination of two or more steroids mentioned in this paragraph;

(ii) TNF inhibitors for example etanercept; monoclonal antibodies (e.g. infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi)); fusion proteins (e.g. etanercept (Enbrel)); and 5-HT2A agonists (e.g. 2,5-dimethoxy-4-iodoamphetamine, TCB-2, lysergic acid diethylamide (LSD), lysergic acid dimethylazetidide);

(iii) anti-inflammatory drugs, for example non-steroidal anti-inflammatory drugs;

(iv) dihydrofolate reductase inhibitors/antifolates, for example methotrexate, trimethoprim, brodimoprim, tetroxoprim, iclaprim, pemetrexed, ralitrexed and pralatrexate; and

(v) immunosuppressants for example cyclosporins, tacrolimus, sirolimus pimecrolimus, angiotensin II inhibitors (e.g. Valsartan, Telmisartan, Losartan, Irbesatan, Azilsartan, Olmesartan, Candesartan, Eprosartan) and ACE inhibitors e.g. sulfhydryl-containing agents (e.g. Captopril, Zofenopril), dicarboxylate-containing agents (e.g. Enalapril, Ramipril, Quinapril, Perindopril, Lisinopril, Benazepril, Imidapril, Zofenopril, Trandolapril), phosphate-containing agents (e.g. Fosinopril), casokinins, lactokinins and lactotripeptides.

(vi) Anti-fibrotic agents for example: Pirfenidone, Nintedanib, Anti-IL-13 monoclonal antibodies (e.g. Tralokinumab, QAX576, Lebrikizumab), simtuzumab, FG-3019, lysophosphatidic acid receptor antagonists (e.g. BMS-986020, AM966), LOXL2 inhibitors, BET bromodomain inhibitors (e.g. JQ1), HDAC inhibitors (e.g. Vorinostat), thrombin inhibitors (e.g. Dabigatran), FactorXa inhibitors (e.g. Apixban, Rivaroxaban) 15PGDH inhibitors, anti-αvβ6 monoclonal antibodies (e.g. BG00011), Anti-CTGF monoclonal antibodies (e.g. FG-3019), PAR1 inhibitors, Nox4 inhibitors and PAI-1 inhibitors.

(vii) CNS therapies, for example: Levodopa, Dopamine agonists, Apomorphine, Glutamate antagonist, Anticholinergics, COMT inhibitors, MAO-B inhibitors, riluzole (Rilutek), Tetrabenazine (Xenazine), haloperidol (Haldol), chlorpromazine, risperidone (Risperdal), quetiapine (Seroquel), amantadine, levetiracetam (Keppra), clonazepam (Klonopin), Donepezil (Aricept), Galantamine (Razadyne), Rivastigmine (Exelon)), Memantine (Ebixa, Axura), Aducanumab, Ocrelizumab, interferon beta-1a (Avonex, Rebif), peginterferon beta-1a (Plegridy), teriflunomide (Aubagio), fingolimod (Gilenya), mitoxantrone (Novantrone), dimethyl fumarate (Tecfidera), natalizumab (Tysabri)

[00156] The method of treatment or the compound for use in the treatment of cancer, sarcoma, melanoma, skin cancer, haematological tumors, lymphoma, carcinoma, leukemia, and central nervous system disorders may involve, in addition to the compound of the

invention, conventional surgery or radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumor agents:

(i) antiproliferative/antineoplastic drugs and combinations thereof, such as alkylating agents (for example cis platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, uracil mustard, bendamustin, melphalan, chlorambucil, chlormethine, busulphan, temozolamide, nitrosoureas, ifosamide, melphalan, pipobroman, triethylene-melamine, triethylenethiophoporamine, carmustine, lomustine, stroptozocin and dacarbazine); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5 fluorouracil and tegafur, raltitrexed, methotrexate, pemetrexed, cytosine arabinoside, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, pentostatine, and gemcitabine and hydroxyurea); antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinase inhibitors); proteasome inhibitors, for example carfilzomib and bortezomib; interferon therapy; and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, mitoxantrone and camptothecin); bleomcin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, ara-C, paclitaxel (Taxol™), nabpaclitaxel, docetaxel, mithramycin, deoxyco-formycin, mitomycin-C, L-asparaginase, interferons (especially IFN-a), etoposide, and teniposide;

(ii) cytostatic agents such as antiestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5*-reductase such as finasteride; and navelbene, CPT-ll, anastrazole, letrazole, capecitabine, reloxafme, cyclophosphamide, ifosamide, and droloxafine;

(iii) anti-invasion agents, for example dasatinib and bosutinib (SKI-606), and metalloproteinase inhibitors, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase;

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies, for example the anti erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti erbB1 antibody cetuximab, tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as gefitinib, erlotinib, 6-

acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib) and antibodies to costimulatory molecules such as CTLA-4, 4-IBB and PD-I, or antibodies to cytokines (IL-I0, TGF-beta); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; modulators of protein regulators of cell apoptosis (for example Bcl-2 inhibitors); inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib , tipifarnib and lonafarnib), inhibitors of cell signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor, kinase inhibitors; aurora kinase inhibitors and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors; and CCR2, CCR4 or CCR6 modulator;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, for example the anti vascular endothelial cell growth factor antibody bevacizumab (Avastin™); thalidomide; lenalidomide; and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib, vatalanib, sunitinib, axitinib and pazopanib;

(vi) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2;

(vii) immunotherapy approaches, including for example antibody therapy such as alemtuzumab, rituximab, ibritumomab tiuxetan (Zevalin®) and ofatumumab; interferons such as interferon α; interleukins such as IL-2 (aldesleukin); interleukin inhibitors for example IRAK4 inhibitors; cancer vaccines including prophylactic and treatment vaccines such as HPV vaccines, for example Gardasil, Cervarix, Oncophage and Sipuleucel-T (Provenge); gp100;dendritic cell-based vaccines (such as Ad.p53 DC); and toll-like receptor modulators for example TLR-7 or TLR-9 agonists; and

(viii) cytotoxic agents for example fludaribine (fludara), cladribine, pentostatin (NipentTM);

(ix) steroids such as corticosteroids, including glucocorticoids and mineralocorticoids, for example aclometasone, aclometasone dipropionate, aldosterone, amcinonide, beclomethasone, beclomethasone dipropionate, betamethasone, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, budesonide, clobetasone, clobetasone butyrate, clobetasol propionate, cloprednol, cortisone, cortisone acetate, cortivazol, deoxycortone, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, dexamethasone isonicotinate, difluorocortolone,

fluclorolone, flumethasone, flunisolide, fluocinolone, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluorocortisone, fluorocortolone, fluocortolone caproate, fluocortolone pivalate, fluorometholone, fluprednidene, fluprednidene acetate, flurandrenolone, fluticasone, fluticasone propionate, halcinonide, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone aceponate, hydrocortisone buteprate, hydrocortisone valerate, icomethasone, icomethasone enbutate, meprednisone, methylprednisolone, mometasone paramethasone, mometasone furoate monohydrate, prednicarbate, prednisolone, prednisone, tixocortol, tixocortol pivalate, triamcinolone, triamcinolone acetonide, triamcinolone alcohol and their respective pharmaceutically acceptable derivatives. A combination of steroids may be used, for example a combination of two or more steroids mentioned in this paragraph;

(x) targeted therapies, for example PI3Kd inhibitors, for example idelalisib and perifosine; PD-1, PD-L1, PD-L2 and CTL4-A modulators, antibodies and vaccines; other IDO inhibitors (such as indoximod); anti-PD-1 monoclonal antibodies (such as MK-3475 and nivolumab); anti-PD-L1 monoclonal antibodies (such as MEDI-4736 and RG-7446); anti-PD-L2 monoclonal antibodies; and anti-CTLA-4 antibodies (such as ipilimumab);

(xii) chimeric antigen receptors, anticancer vaccines and arginase inhibitors.

[00157] Such combination treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention within a therapeutically effective dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

[00158] Compounds of the invention may exist in a single crystal form or in a mixture of crystal forms or they may be amorphous. Thus, compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, or spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

[00159] For the above-mentioned compounds of the invention the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. For example, if the compound of the invention is administered orally, then the daily dosage of the compound of the invention may be in the range from 0.01 micrograms per kilogram body weight (µg/kg) to 100 milligrams per kilogram body weight (mg/kg).

[00160] A compound of the invention, or pharmaceutically acceptable salt thereof, may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the compounds of the invention, or pharmaceutically acceptable salt thereof, is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

[00161] Depending on the mode of administration of the compounds of the invention, the pharmaceutical composition which is used to administer the compounds of the invention will preferably comprise from 0.05 to 99 %w (per cent by weight) compounds of the invention, more preferably from 0.05 to 80 %w compounds of the invention, still more preferably from 0.10 to 70 %w compounds of the invention, and even more preferably from 0.10 to 50 %w compounds of the invention, all percentages by weight being based on total composition.

[00162] The pharmaceutical compositions may be administered topically (e.g. to the skin) in the form, e.g., of creams, gels, lotions, solutions, suspensions, or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of a sterile solution, suspension or emulsion for injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion); by rectal administration in the form of suppositories; or by inhalation in the form of an aerosol.

[00163] For oral administration the compounds of the invention may be admixed with an adjuvant or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch, corn starch or amylopectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum and titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

[00164] For the preparation of soft gelatine capsules, the compounds of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above-mentioned excipients for tablets. Also, liquid or semisolid formulations of the compound of the invention may be filled into hard gelatine capsules. Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such

liquid preparations may contain colouring agents, flavouring agents, sweetening agents (such as saccharine), preservative agents and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

[00165] For intravenous (parenteral) administration the compounds of the invention may be administered as a sterile aqueous or oily solution.

[00166] The size of the dose for therapeutic purposes of compounds of the invention will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well-known principles of medicine.

[00167] Dosage levels, dose frequency, and treatment durations of compounds of the invention are expected to differ depending on the formulation and clinical indication, age, and co-morbid medical conditions of the patient.

[00168] Throughout the description and claims of this specification, the words “comprise” and “contain” and variations of them mean “including but not limited to”, and they are not intended to (and do not) exclude other moieties, additives, components, integers or steps. Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

[00169] Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any foregoing embodiments. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

[00170] The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

EXAMPLES

As used herein the following terms have the meanings given: “Boc” refers to tert-butyloxycarbonyl; “Cbz” refers to carboxybenzyl; “dba” refers to dibenzylideneacetone; “DCM” refers to dichloromethane; “DIPEA” refers to N,N-diisopropylethylamine; “DMA” refers to dimethylacetamide; “DMF” refers to *N*,*N*-dimethylformamide; “DMSO” refers to dimethyl sulfoxide; “dppf’ refers to 1,1’- bis(diphenylphosphino)ferrocene; “EtOAc” refers to ethyl acetate; “EtOH” refers to ethanol; “Et_2O” refers to diethyl ether; “IPA” refers to isopropyl alcohol; “LiHMDS” refers to lithium bis(trimethylsilyl)amide; “mCPBA” refers to meta-chloroperoxybenzoic acid; “MeCN” refers to acetonitrile; “MeOH” refers to methanol; “min” refers to minutes; “NMR” refers to nuclear magnetic resonance; “PhMe” refers to toluene; “pTsOH” refers to p-toluenesulfonic acid; “py” refers to pyridine; “r.t.” refers to room temperature; “SCX” refers to strong cation exchange; “T3P” refers to propylphosphonic anhydride; “Tf_2O” refers to trifluoromethanesulfonic anhydride; “THF” refers to tetrahydrofuran; “THP” refers to 2-tetrahydropyranyl; “(UP)LC-MS” refers to (ultra performance) liquid chromatography/mass spectrometry. Solvents, reagents and starting materials were purchased from commercial vendors and used as received unless otherwise described. All reactions were performed at room temperature unless otherwise stated. Compound identity and purity confirmations were performed by LCMS UV using a Waters Acquity SQ Detector 2 (ACQ-SQD2#LCA081). The diode array detector wavelength was 254nM and the MS was in positive and negative electrospray mode (*m/z*: 150-800). A 2µL aliquot was injected onto a guard column (0.2µm x 2mm filters) and UPLC column (C18, 50 x 2.1mm, < 2µm) in sequence maintained at 40°C. The samples were eluted at a flow rate of 0.6mL/min with a mobile phase system composed of A (0.1% (v/v) Formic Acid in Water) and B (0.1% (v/v) Formic Acid in Acetonitrile) according to the gradients outlined in Table 1 below. Method 3 utilised a Shimadzu 2020 series spectrometer equipped with a binary pump and diode array detector (acquisition wavelength 214 and 254 nm) and the MS was in positive and negative electrospray mode (*m/z*: 100-900). 2µL Aliquot were injected onto an Agilent Poroshell 120 EC-C18 column (2.7 µm, 4.6×50 mm) maintained at 35°C and eluted at 1.0ml/min using mobile phase consisting of : A: 0.05% Formic acid in water (v/v), B: 0.05% Formic acid in ACN(v/v). Method 4 utilised a Agilent Technologies 1290 series spectrometer equipped with a binary pump and diode array detector (acquisition wavelength 214 and 254 nm) and the MS was in positive electrospray mode (*m/z*: 70-1000). 2µL Aliquots were injected onto an Agilent Eclipse Plus RRHD C18, (1.8µm, 3.0×50 mm) column maintained at 40°C and eluted at 0.8ml/min using mobile phase consisting of : A: 0.05% Formic acid in water (v/v), B: 0.05% Formic acid in ACN(v/v). Retention times RT are reported in minutes.

Method 1 (Long acidic)		
Time (min)	%A	%B
0	95	5
1.1	95	5
6.1	5	95
7	5	95
7.5	95	5
8	95	5
Method 2 (Short acidic)		
Time (min)	%A	%B
0	95	5
0.3	95	5
2	5	95
2.6	95	5
3	95	5
Method 3		
Time (min)	%A	%B
0.01	85	15
1.0	85	15
4.0	0	100
4.5	0	100
4.51	85	15
5.0	85	15
Method 4		
Time (min)	%A	%B
0.00	80	20
2.65	20	80
3.00	20	80

Table 1

NMR was also used to characterise final compounds. NMR spectra were obtained on a Bruker AVIII 400 Nanobay with 5mm BBFO probe. Optionally, compound Rf values on silica thin layer chromatography (TLC) plates were measured.

Compound purification was performed by flash column chromatography on silica or by preparative LCMS. LCMS purification was performed using a Waters 3100 Mass detector in positive and negative electrospray mode (*m/z*: 150-800) with a Waters 2489 UV/Vis detector.

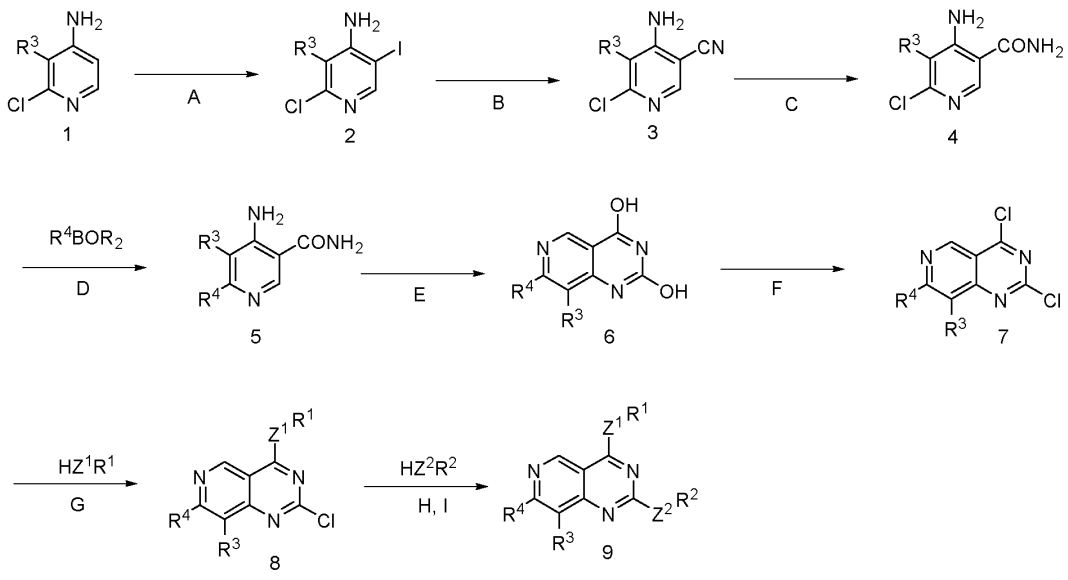
Samples were eluted at a flow rate of 20mL/min on a XBridge™ prep C18 5µM OBD 19x100mm column with a mobile phase system composed of A (0.1% (v/v) Formic Acid in Water) and B (0.1% (v/v) Formic Acid in Acetonitrile) according to the gradient outlined in Table 2 below.

Time (min)	%A	%B
0	90	10
1.5	90	10
11.7	5	95
13.7	5	95
14	90	90
15	90	90

Table 2

GENERAL REACTION SCHEMES

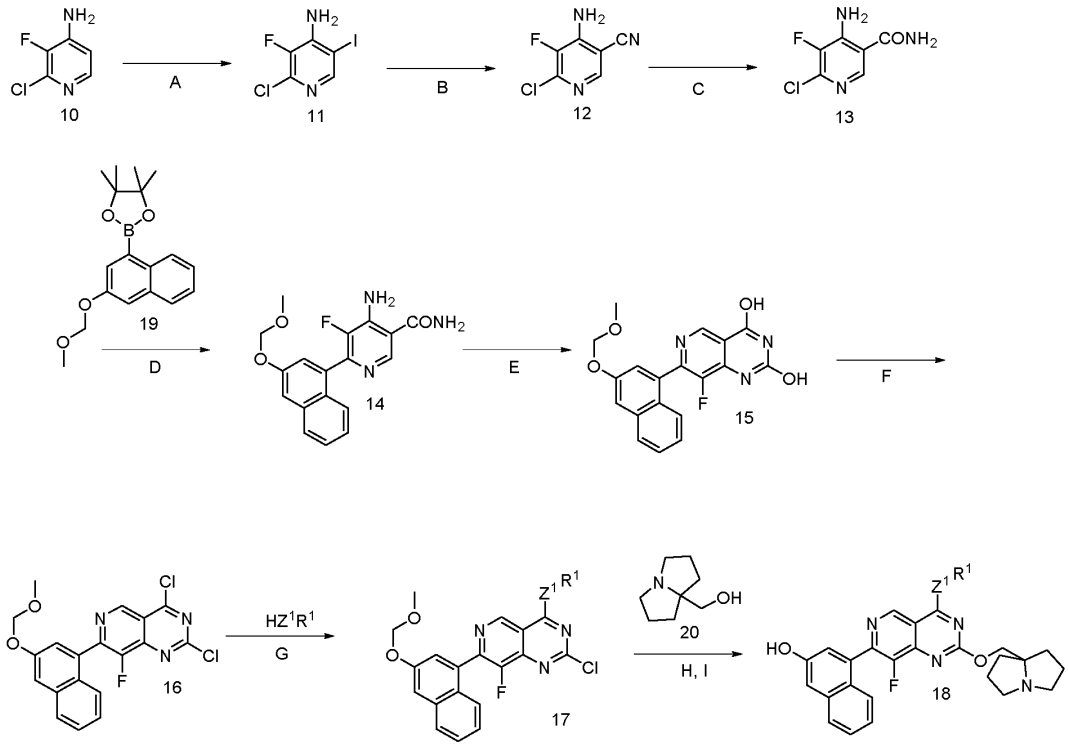
Certain compounds of the invention can be made using the following general reaction schemes. Certain compounds of the invention may be made according to or analogously to the synthetic examples described below.



Scheme 1

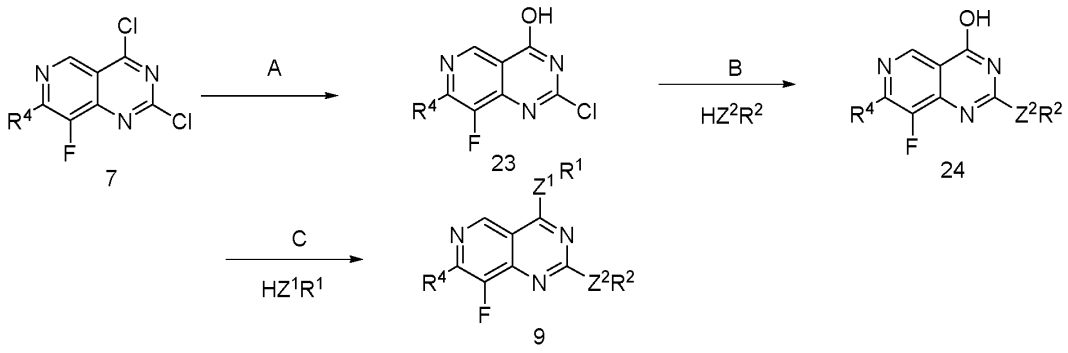
Compounds of the invention can be prepared according to Scheme 1. In step A compound 1 is iodinated with a reagent such as N-iodosuccinimide. In step B iodide 2 is converted to nitrile 3 with a source of cyanide such as zinc (II) cyanide in the presence of a palladium catalyst such as $Pd(P(Ph_3)_{4)}$. In step C treatment of nitrile 3 with a strong acid such as concentrated H_2SO_4 results in hydrolysis to primary amide 4 which undergoes Suzuki coupling in step D with the appropriate boronic acid or ester of R_4. In step E reaction of amide

5 with a carbonyl equivalent such as carbonyldiimidazole (CDI) to cyclise between the amino and carboxamide groups resulting dihydroxy compound 6. Treatment with $POCl_3$ in step F generates dichloro compound 7 which can undergo sequential nucleophilic aromatic substitution reactions in steps G and H with the appropriate HZ^1R^1 and HZ^2R^2 reagents. Step I may or may not be required and represents a deprotection step to remove protecting groups from reactive atoms present on the R_4, Z_1R_1 and Z_2R_2 groups.



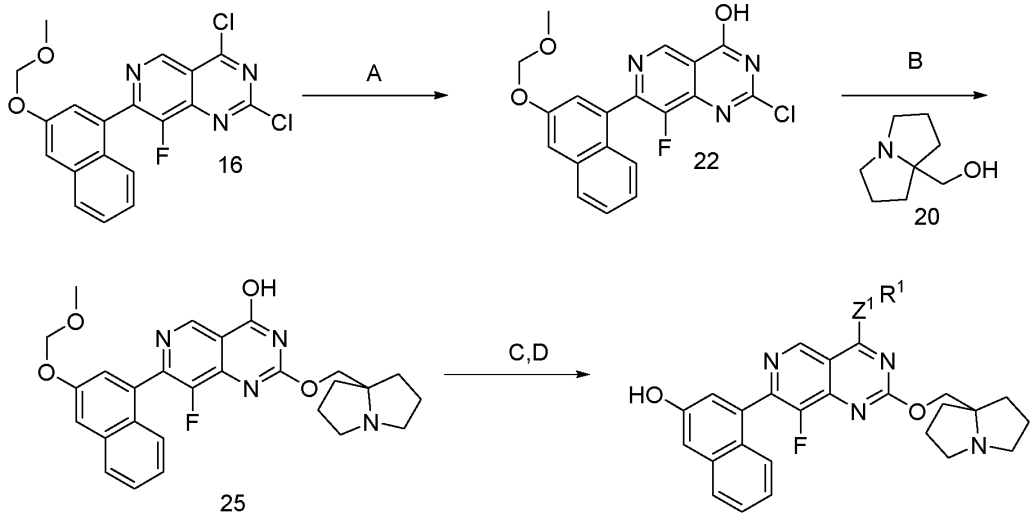
Scheme 2

Certain examples were prepared according to Scheme 2 from common intermediate 16, in addition these examples all required intermediates 19 and 20. Step I was required as a final step to remove the methoxymethyl protecting group introduced in intermediate 19 as well as any acid labile protecting groups present on the Z^1R^1 substituent.



Scheme 3

Compounds of formula 9 may also be prepared according to scheme 3 in which the appropriate dichloro species is hydrolysed to a compound of formula 23. Compounds of formula 23 can then undergo substitution with a nucleophile of general formula HZ^2R^2 whereby Z is a nucleophilic atom to afford compounds of formula 24. The hydroxy group ca be displaced following activation with a reagent such as HATU, with an appropriate nucleophile of formula HZ^1R^1.

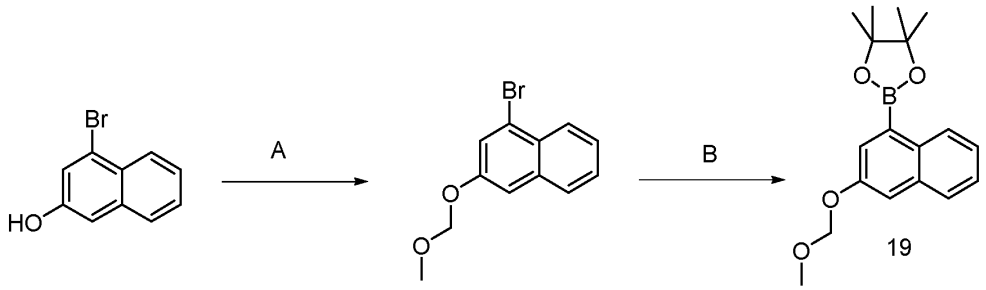


Scheme 4

Certain examples were prepared according to Scheme 4 from common intermediate 16. Step D was required as a final step to remove the methoxymethyl protecting group introduced in intermediate 19 as well as any acid labile protecting groups present on the Z^1R^1 substituent.

Intermediate 19

2-[3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



STEP A: 3-(methoxymethoxy)naphthalene: To a suspension of 4-bromonaphthalen-2-ol (3g, 13.45mmol) and *N,N*-diisopropylethylamine (7.03mL, 40.35mmol) in DCM (30mL) at 0°C was added chloromethyl methyl ether (1.53mL, 20.17mmol). The resulting mixture was stirred for 30 min. The reaction was then diluted with distilled water, extracted with DCM (x2), organics were combined and washed with brine (x2), dried over Na_2SO_4, filtered and the filtrate evaporated in vacuo to afford a reddish/pink oil. This was purified by flash column chromatography eluting 0-60% EtOAc in pet. ether (40g SiO_2, dry loaded with DCM). The desired fractions were combined and evaporated in vacuo to afford a pink oil analysed as 1-bromo-3-(methoxymethoxy)naphthalene (3.2g, 11.9mmol, 89% yield).

UPLC-MS (ES^+, short acidic): 2.06 min, m/z 266.9, 268.9 $[M+H]^+$

^1H NMR (400MHz, $CDCl_3$) δ/ppm: 8.19-8.15 (1H, m), 7.77-7.73 (1H, m), 7.60 (1H, d, J = 2.4Hz), 7.53-7.46 (2H, m), 7.42-7.40 (1H, m), 5.31 (2H, s), 3.55 (3H, s).

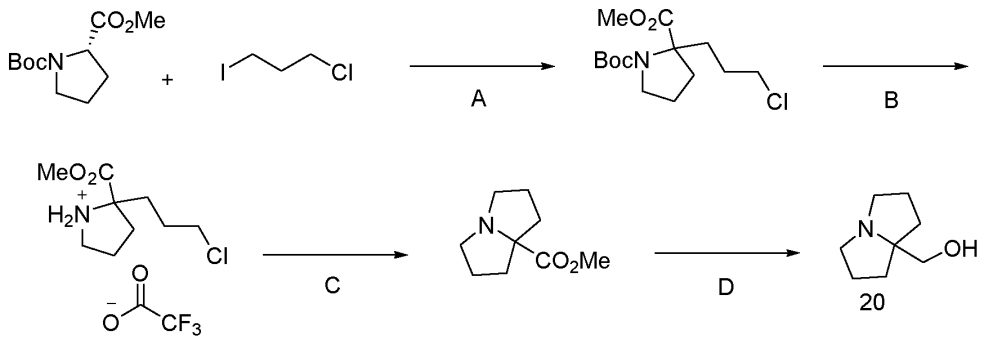
STEP B: 2-[3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: To a nitrogen purged suspension of 1-bromo-3-(methoxymethoxy)naphthalene (5.2g, 19.4mmol), bis(pinacolato)diboron (9.9g, 38.9mmol) and potassium acetate (6.7g, 68mmol) in toluene (50mL) was added [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II) (1.4g, 1.9mmol). The mixture was stirred at 110°C for 2.5 hrs. The reaction mixture was then filtered over celite, washing with EtOAc and the filtrate evaporated in vacuo to afford a black oil. This was taken up in distilled water and EtOAc, extracted aqueous (x2) with EtOAc, combined organics were washed with brine, dried over Na_2SO_4, filtered and evaporated in vacuo to afford a black oil. This was purified by flash column chromatography (40g SiO2, dry loaded with DCM) eluting with 0-20% EtOAc in petrol ether, desired fractions were combined and evaporated in vacuo to afford waxy colourless residue. Analysed as 2-[3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6g, 98% yield).

UPLC-MS (ES^+, short acidic): 2.16 min, m/z 315 $[M+H]^+$

^{1}H NMR (400MHz, D_6-DMSO) δ/ppm: 8.56-8.59 (1H, d, *J*=7.1Hz), 7.86-7.89 (1H, d, *J*=7.1Hz), 7.63-7.65 (1H, d, *J*=2.4Hz), 7.58-7.60 (1H, d, *J*=2.4Hz), 7.40-7.50 (2H, m), 5.31 (2H, s), 3.55 (3H, s), 1.2 (s, 12H).

Intermediate 20

1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol



STEP A: O1-tert-butyl O2-methyl 2-(3-chloropropyl)pyrrolidine-1,2-dicarboxylate: A 1M solution of lithium bis(trimethylsilyl)amide (43.6mL, 43.6mmol) in THF was added to a solution of N-boc-Proline methylester (10g, 43.6mmol) in THF (100mL) at -78°C. Afterwards, the mixture allowed to stir at that temperature for 30 min. 3-chloropropyl iodide (5.6mL, 52.3mmol) was added and reaction mixture was allowed to gradually warm up to 0°C. After 2 hrs in ice bath TLC (3:1 pet. ether:EtOAc) shows complete consumption of starting material (vis. with I_2). Reaction mixture was quenched with a saturated solution of aqueous ammonium chloride (50 mL), partitioned between a layer of ethyl acetate (100mL) and water (50mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (100mL), organic extracts were combined, washed with a saturated solution of brine (100mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford a pale yellow oil analysed as O1-tert-butyl O2-methyl 2-(3-chloropropyl)pyrrolidine-1,2-dicarboxylate (13g, 42.5mmol, 97% yield).

^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 3.50-3.62 (4H, m), 3.35-3.45 (2H, m), 3.19-3.23 (1H, m), 2.11-2.20 m, 1H), 1.50-2.05 (m, 6H), 1.25-1.29 (9H, d).

STEP B: methyl 2-(3-chloropropyl)pyrrolidin-1-ium-2-carboxylate; 2,2,2-trifluoroacetate: Trifluoroacetic acid (10mL, 130.2mmol) was added to a solution of O1-tert-butyl O2-methyl 2-(3-chloropropyl)pyrrolidine-1,2-dicarboxylate (13g, 42.5mmol) in DCM (22mL). The resulting solution was allowed to stir at room temp overnight. All volatiles removed under reduced pressure and dark oil re-dissolved in DCM and evaporated again to remove TFA. The

resulting dark oil was analysed as methyl 2-(3-chloropropyl)pyrrolidin-1-ium-2-carboxylate; 2,2,2-trifluoroacetate (19g, 59.4mmol, 140% yield). NMR indicates product is TFA salt and contains approximately 1 equiv. of TFA remains, used without further purification.

^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 10.20-10.45 (1H, bs), 7.70-8-02 (1H, bs), 3.91 (s, 3H), 3.45-3.70 (m, 4H), 2.45-2.55 (1H, m), 2.26-2.31 (1H, m), 2.15-2.25 (3H, m), 1.95-2.04 (2H, m), 1.55-1.65 (1H, m).

STEP C: methyl 1,2,3,5,6,7-hexahydropyrrolizine-8-carboxylate: Potassium carbonate (27g, 195.4mmol) was added to a mixture of potassium iodide (1g, 6.02mmol) and methyl 2-(3-chloropropyl)pyrrolidin-1-ium-2-carboxylate; 2,2,2-trifluoroacetate (13.5g, 42.2mmol) in methanol (200mL). The mixture was allowed to stir at 35°C for 90 mins before concentrating under reduced pressure. Then the reaction mixture was partitioned between a layer of DCM (150mL) and water (150mL). The organic layer was separated. The aqueous layer was extracted with DCM (100mL). The organic extracts were combined, washed with brine (100ml) dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford methyl 1,2,3,5,6,7-hexahydropyrrolizine-8-carboxylate (6.5g, 38.4mmol, 91% yield) as a clear oil.

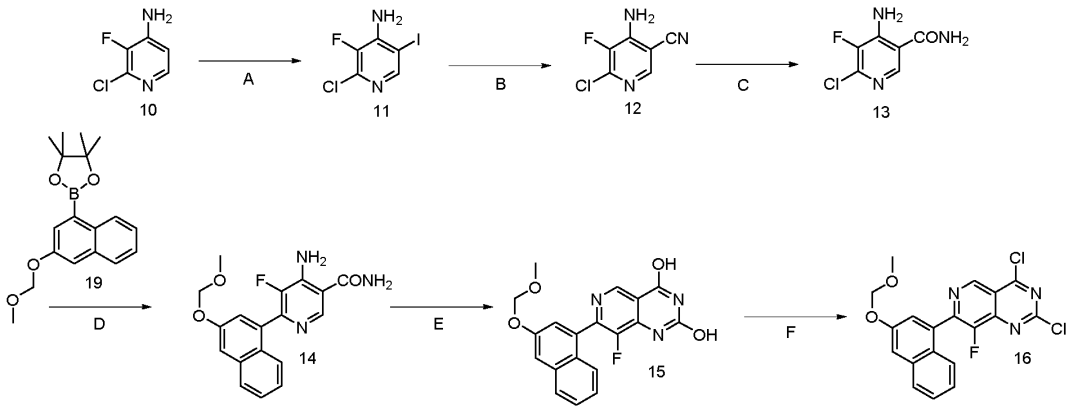
^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 3.73 (3H, s), 3.12-3.20 (2H, m), 2.62-2.70 (2H, m), 2.25-2.31 (2H, m), 1.78-1.85 (4H, m), 1.62-1.74 (2H, m).

STEP D: 1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol: At 0 °C, under an N_2 atmosphere a 1M solution of lithium aluminium hydride (19.5mL, 19.5mmol) in THF was added dropwise to a solution of methyl 1,2,3,5,6,7-hexahydropyrrolizine-8-carboxylate (1.1g, 6.5mmol) in THF (10mL). The mixture was allowed to stir at that temperature for 30 mins. Maintaining temp of 0°C, inert atmosphere and using vigorous stirring, the reaction was quenched with dropwise addition of water (0.7 mL) then dropwise addition of a 15% aq. NaOH (0.7 mL) followed by more water (2ml). The mixture was allowed to stir and warm up to room temperature until the precipitated salts dispersed into a freely moving suspension, before filtering, washing the filter cake with THF (2 x 10mL). The filtrate was collected and concentrated under reduced pressure to afford 1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol (1.0g, 7.1mmol, 100% yield) as a yellow oil.

^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 43.75-3.79 (1H, m), 3.30 (2H, s), 2.98-3.03 (2H, m), 2.59-2.65 (2H, m), 1.51-1.92 (8H, m).

INTERMEDIATE 16

2,4-dichloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine



STEP A: 2-chloro-3-fluoro-5-iodo-pyridin-4-amine: A suspension of 2-hloro-3-fluoropyridin-4-amine (7g, 47.8mmol), N-iodosuccinimide (12.9g, 57.3mmol) and p-toluenesulfonic acid monohydrate (909mg, 4.8mmol) in MeCN (50mL) was allowed to stir at 70°C overnight. LCMS shows complete conversion to desired product. The mixture was cooled, partitioned between water (100mL) and EtOAc (200mL) and the aqueous re-extracted with EtOAc (100mL). Combined organics were washed with saturated aqueous $NaHCO_3$ (100mL), saturated aqueous Na_2SO_3 (100mL) and brine (100mL) before drying (Na_2SO_4), filtering and concentrating to afford a pink solid analysed as 2-chloro-3-fluoro-5-iodo-pyridin-4-amine (12.2g, 44.8mmol, 94% yield).

UPLC-MS (ES+, Short acidic): 1.44 min, m/z 273.2, 274.1, 275.1 $[M+H]^+$

^1H NMR (400 MHz, D_6-DMSO) δ/ppm: 8.10 (s, 1H), 6.70-6.79 (bs, 2H).

STEP B: 4-amino-6-chloro-5-fluoro-pyridine-3-carbonitrile: 2-Chloro-3-fluoro-5-iodo-pyridin-4-amine (6g, 22.02mmol) was dissolved in DMF (30mL) and degassed by bubbling through N_2 for 5 mins. Under an N_2 atmosphere at room temperature tetrakis(triphenylphosphine)palladium(0) (1.27g, 1.1mmol) and zinc (II) cyanide (3.4g, 28.6mmol) were added and the mixture heated to 90°C with stirring. After 2 hr TLC (2:1 pet. ether:EtOAc) indicated the reaction was complete. The mixture was cooled to room temp and quenched with saturated aqueous $NaHCO_3$. The mixture was partitioned between water (50mL) and EtOAc (100mL). The aqueous phase was aqueous re-extracted with EtOAc (2 x 100mL). Combined organics were washed with brine (2 x 100mL), dried (Na_2SO_4), filtered and concentrated to a cream waxy solid. This was re-dissolved and evaporated from DCM to afford a less waxy cream solid analysed as desired product 4-amino-6-chloro-5-fluoro-pyridine-3-carbonitrile (2.7g, 15.7mmol, 71% yield) with residual DMF and catalyst by-products.

UPLC-MS (ES+, Short acidic): 1.18 min, m/z 172.2 $[M+H]^+$

^{1}H NMR (400 MHz, D_6-DMSO) δ/ppm: 8.19 (s, 1H), 7.55-7.59 (bs, 2H).

STEP C: 4-amino-6-chloro-5-fluoro-pyridine-3-carboxamide: To 4-amino-6-chloro-5-fluoro-pyridine-3-carbonitrile (2.7g, 15.7mmol) was carefully added conc. H_2SO_4 (5mL) and the resulting suspension was stirred at 60°C for 1 hr. The reaction was cooled to room temperature and diluted with ice/water (20mL) and the resulting suspension basified to approximately pH 9 by addition of solid sodium carbonate. The resulting precipitated solod was collected by vacuum filtration and dried on the filter for 2 hrs affording 4-amino-6-chloro-5-fluoro-pyridine-3-carboxamide (1.3g, 6.7mmol, 45% yield).

UPLC-MS (ES$^+$, Short acidic): 1.00 min, m/z 190.3 $[M+H]^+$

^{1}H NMR (400 MHz, D_6-DMSO) δ/ppm: 8.32 (s, 1H), 8.05-8-14 (bs, 1H), 7.60-7.67 (bs, 2H), 5.55-7.65 (bs, 1H).

STEP D: 4-amino-5-fluoro-6-[3-(methoxymethoxy)-1-naphthyl]pyridine-3-carboxamide: A solution of 4-amino-6-chloro-5-fluoro-pyridine-3-carboxamide (600mg, 3.17mmol), 2-[3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1491.6mg, 4.75mmol) and cesium carbonate (2.1g, 6.33mmol) in 1,4-dioxane (12mL) and water (4mL) was degassed with nitrogen for 2 min. [1,1'-bis(di-tert-butylphosphino)ferrocene]dichloropalladium (II) (206mg, 0.32mmol) was added and the mixture was stirred at 90°C for 2hrs. The reaction mixture was allowed to cool back down to room temperature and partitioned between a layer of ethyl acetate (40mL) and water (40mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (40mL), organic extracts combined, washed with a saturated solution of brine (40mL) and dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with 50-100% ethyl acetate in petrol afforded 4-amino-5-fluoro-6-[3-(methoxymethoxy)-1-naphthyl]pyridine-3-carboxamide (639mg, 1.87mmol, 59% yield) as a brown solid.

UPLC-MS (ES$^+$, Short acidic, KH-N202973-06-01_UPLCMS): 1.28 min, m/z 342.4 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.50 (s, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.71-7.30 (m, 5H), 6.53 (s, 2H), 5.84 (br s, 2H), 5.33 (s, 2H), 3.53 (s, 3H).

STEP E: 8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine-2,4-diol: At 0°C, sodium hydride, (60% dispersed in mineral oil) (187mg, 4.68mmol) was added to a solution of 4-amino-5-fluoro-6-[3-(methoxymethoxy)-1-naphthyl]pyridine-3-carboxamide (639mg, 1.87mmol) in DMF (9mL). Afterwards, the mixture was allowed to stir at that temperature for 30 min. 1,1'-carbonyldiimidazole (531mg, 3.28mmol) was added and reaction mixture was

allowed to stir at 50°C for 1hr. Reaction mixture allowed to cool back down to room temperature. Water (50 mL) was added and acidified to ~pH2 with 2M HCl (aq) and the mixture allowed to stir at room temperature for 10 mins. The resulting solid precipitate was collected by vacuum filtration, washed with water (2 x 10 mL). and taken up in ethyl acetate and dried under vacuum to afford 8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine-2,4-diol (605mg, 1.65mmol, 88% yield) as an off-white solid.

UPLC-MS (ES$^+$, Short acidic): 1.45 min, m/z 368.2 $[M+H]^+$

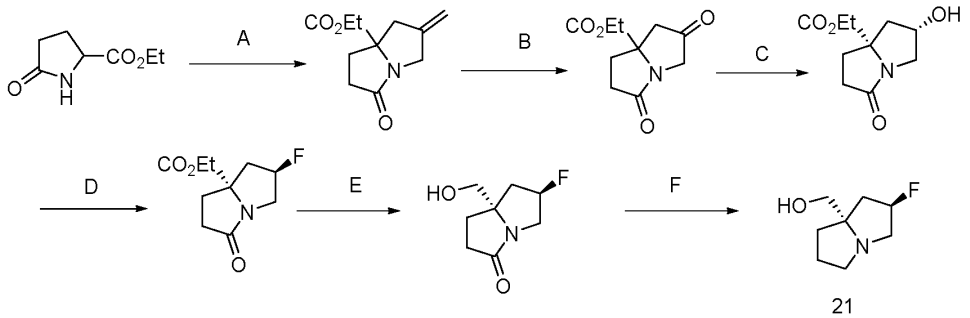
^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 11.95 (s, 1H), 11.73 (s, 1H), 8.93 (s, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.68-7.35 (m, 5H), 5.38 (s, 2H), 3.45 (s, 3H)

STEP F: 2,4-dichloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine: Phosphorus oxychloride (0.91mL, 9.8mmol) was added to a suspension of 8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine-2,4-diol (200mg, 0.5400mmol) and N,N-diisopropylethylamine (0.47mL, 2.72mmol). The mixture was allowed to stir at 100°C for 30 mins before cooling back down to room temperature. All volatiles were removed under reduced pressure to afford 2,4-dichloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine (220mg, 0.54mmol, 100% yield) as a brown oil.

UPLC-MS (ES$^+$, Short acidic): 1.97 min, m/z 400.2 $[M-Cl+MeOH]^+$

Intermediate 21

[trans2-Fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol



21

STEP A: Ethyl 6-methylene-3-oxo-1,2,5,7-tetrahydropyrrolizine-8-carboxylate. At -40°C, LiHMDS (1.34L, 1.34mol, 2.1eq) was added dropwise into a solution of ethyl 5-oxo-2-pyrrolidinecarboxylate (100g, 637mmol, 1.0eq) and 3-chloro-2-chloromethyl-1-propene (239g, 1.91mol, 3.0eq) in THF (2000mL). The mixture was allowed to warm to room temperature and stir over night. The mixture was cooled to -60°C and adjusted to pH 7 with 2M HCl, poured into water (10L), extracted with EtOAc (2L x 3), washed with brine (5L) and dried over Na_2SO_4. The filtered mixture was concentrated and purified by silica gel column

(5:1 Pet.ether/EtOAc to 3:1 Pet.ether/EtOAc) to afford ethyl 6-methylene-3-oxo-1,2,5,7-tetrahydropyrrolizine-8-carboxylate as a colourless oil (40g, 30% yield).

^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 5.01-5.06 (2H, d), 4.16-4.30 (3H, m), 3.69-3.73 (1H, d), 3.02-3.06 (1H, d), 2.30-2.75 (4H, m), 2.07-2.16 (1H, m), 1.23-1.27 (3H, t).

STEP B: Ethyl 3,6-dioxo-1,2,5,7-tetrahydropyrrolizine-8-carboxylate. At -78°C, O_2 was bubbled through a solution of ethyl 6-methylene-3-oxo-1,2,5,7-tetrahydropyrrolizine-8-carboxylate (115.1g, 550mmol, 1.0eq) in DCM (1L) and MeOH (100mL) for 30 minutes. Ozone was then bubbled through the solution with stirring at -78°C until the solution became blue. O_2 was then bubbled through the solution at the same temperature for a further 30 min. Dimethyl sulfide (68.35g, 1.1mol, 2.0eq) was added at -78°C and the solution was allowed to reach room temperature and stir over night. The mixture was concentrated and purified by silica gel column (5:1 Pet.ether/EtOAc to 3:1 Pet.ether/EtOAc) to give ethyl 3,6-dioxo-1,2,5,7-tetrahydropyrrolizine-8-carboxylate (108g, 93% yield) as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 4.20-4.24 (2H, q), 4.08-4.14 (1H, d), 3.52-3.56 (1H, d), 2.95-3.00 (2H, m), 2.81-2.86 (1H, m), 2.39-2.48 (2H, m), 2.19-2.24 (1H, m), 1.26-1.29 (3H, t).

STEP C: cis-Ethyl 2-hydroxy-5-oxo-2,3,6,7-tetrahydro-1H-pyrrolizine-8-carboxylate. At 0°C, $NaBH_4$ (5.81g, 153mmol, 0.3eq) was added to a solution of ethyl 3,6-dioxo-1,2,5,7-tetrahydropyrrolizine-8-carboxylate (108g, 512mmol, 1.0eq) in EtOH (550mL) and stirred for 10 min. To the mixture was added aqueous NH_4Cl (50mL) before stirring for a further 20 min at 0°C. The mixture was concentrated *in vacuo* and the crude was purified by silica gel column (30:1 DCM/MeOH) to afford ethyl trans-ethyl 2-hydroxy-5-oxo-2,3,6,7-tetrahydro-1H-pyrrolizine-8-carboxylate as a yellow oil and apparent mixture of sterioisomers (88g, 81% yield).

LC-MS (ES^+, Method 4): 0.40min, 214.10 $[M+H]^+$.

STEP D: trans-Ethyl 2-fluoro-5-oxo-2,3,6,7-tetrahydro-1H-pyrrolizine-8-carboxylate. At -78°C, DAST (99.8g, 619mmol, 1.5eq) was added dropwise into a solution of ethyl (2S,8S)-2-hydroxy-5-oxo-2,3,6,7-tetrahydro-1H-pyrrolizine-8-carboxylate (88g, 413mmol, 1.0eq) in DCM (1.5L) and stirred at room temperature overnight. The mixture was cooled to 0°C before adding MeOH (60mL) and diluting with brine (2000mL). The phases were separated and the organics dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by silica gel column (8:1 to 5:1 pet. Ether/EtOAc) to give trans-ethyl 2-fluoro-5-oxo-2,3,6,7-tetrahydro-1H-pyrrolizine-8-carboxylate as a yellow oil (42g, 47% yield).

^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 5.21-5.36 (1H, d), 4.20-4.47 (3H, m), 3.19-3.41 (1H, dd), 2.10-2.60 (6H, m), 1.24-1.28 (3H, t).

STEP E: trans-6-Fluoro-8-(hydroxymethyl)-2,5,6,7-tetrahydro-1H-pyrrolizin-3-one. At 0°C, $LiBH_4$ (81mL, 163mmol, 1.0eq) was added dropwise into ethyl (2R,8S)-2-fluoro-5-oxo-2,3,6,7-tetrahydro-1H-pyrrolizine-8-carboxylate (35g, 163mmol, 1.0eq) in THF (350mL) and stirred at room temperature for 2hrs. The mixture was cooled to 0°C, before adding aqueous NH_4Cl (100mL) and stirring for 30 mins at 0°C, the mixture was concentrated and the crude was purified by silica gel column (30:1 DCM/MeOH) to give trans-6-fluoro-8-(hydroxymethyl)-2,5,6,7-tetrahydro-1H-pyrrolizin-3-one (28g, 99% yield).

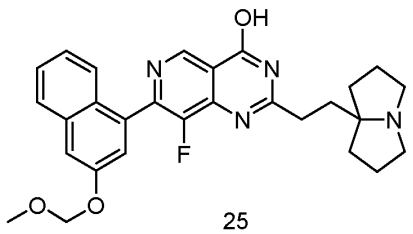
^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 5.21-5.35 (1H, d), 4.05-4.16 (1H, m), 3.51-3.55 (1H, d), 3.42-3.46 (1H, d) 2.52-3.11 (3H, m), 1.94-2.41 (5H, m).

STEP F: [trans-2-Fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol. At 0°C, BH_3.DMS (10M, 75.1mL, 751mmol, 5.0eq) was added dropwise into (6R,8S)-6-fluoro-8-(hydroxymethyl)-2,5,6,7-tetrahydro-1H-pyrrolizin-3-one (26g, 150mmol, 1.0eq) in THF (1300mL) and stirred at room temperature overnight. The mixture was cooled to 0°C, MeOH (300mL) was added and stirring continued for 1hr at 0°C. The mixture was concentrated and the crude was dissolved in MeOH (300mL) and stirred at 50°C overnight. The mixture was concentrated to give (21g, 87.9% yield) of [trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol, intermediate 21 as a colourless oil.

^{1}H NMR (400MHz, $CDCl_3$) δ/ppm: 5.11-525 (1H, d), 2.80-3.31 (6H, m), 1.74-2.11 (6H, m).

Intermediate 25

8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-ol



25

Intermediate 25 was prepared according to the route in Scheme 4.

STEP A: 2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-ol. A solution of 2,4-dichloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine

(1.88mmol, 1.0eq) in DMF (10ml) was added DIEA (4.1g, 31.75mmol, 6.8eq) and NaOH (1.9g, 46.68mmol, 10.0eq). The reaction mixture was stirred at room tempperature for 1hr. The reaction mixture was poured into water and extracted with DCM. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (DCM/MeOH, 20:1) to afford 2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-ol as a white solid (890mg, 50% yield).

LC-MS (ES^+, Method 4): 1.59min, 386.0 $[M+H]^+$.

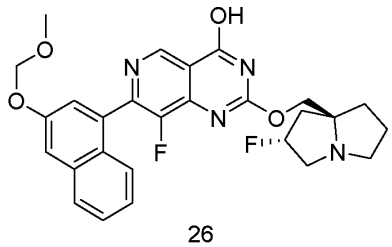
STEP B: 8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-ol. A solution of 2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-ol (885mg, 2.29mmol, 1.0eq) and 1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol (972mg, 6.88mmol, 3.0eq) in THF(10ml) under N_2 at 0°C was added 60% NaH (734mg, 18.352 mol, 8.0eq). The reaction mixture was stirred at 25°C for 16hrs.The reaction mixture was quenched with MeOH and concentrated *in vacuo*. The residue was purified by RP-column chromatography (MeCN, 55%, water, 45% and formic acid 0.1%) to give 8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-ol (1g, 89% yield) as an off-white solid.

LC-MS (ES^+, Method 4): 1.53min, 491.1 $[M+H]^+$.

^1H NMR (400MHz, D6-DMSO) δ/ppm: 8.85 (1H, s), 8.39-8.42 (1H, bs), 7.85-7.91 (1H, m), 7.30-7.57 (5H, m), 5.37 (2H, s), 3.98 (2H, s), 3.45 (3H, s), 2.99-3.12 (2H, m), 2.40-2.51 (2H, m), 1.46-1.88 (6H, m), 1.51-1.63 (2H, m).

Intermediate 26

8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-ol



26

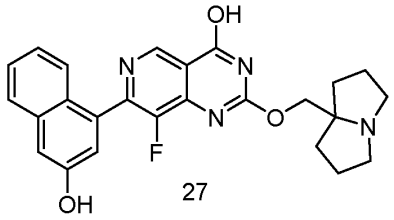
Intermediate 26 was made in an analogous manner to intermediate 25 following the steps in Scheme 4, replacing intermediate 20 in step B with intermediate 21.

LC-MS (ES$^+$, Method 4): 1.15min, 509.15 $[M+H]^+$.

^{1}H NMR (400MHz, D6-DMSO) δ/ppm: 9.04 (1H, s), 8.84-8.88 (1H, d), 7.30-7.64 (6H, m), 5.37 (2H, s), 4.11-4.25 (2H, m), 2.74-3.51 (4H, m), 1.72-2.09 (10H, m).

Intermediate 27

8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-ol



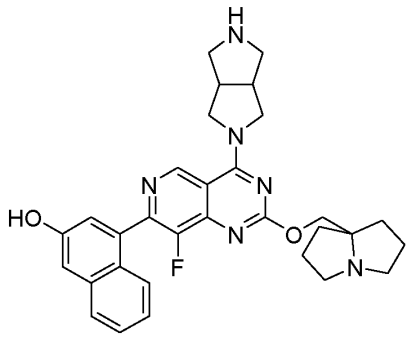
27

8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-ol (Intermediate 25) (0.3g, 0.6mmol) was dissolved in 4N HCl in dioxane (5mL) and stirred at room temperature for 30 mins. Concentration of the reaction mixture afforded a crude solid containing 8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-ol (280mg, ~100% yield) which was used without further purification.

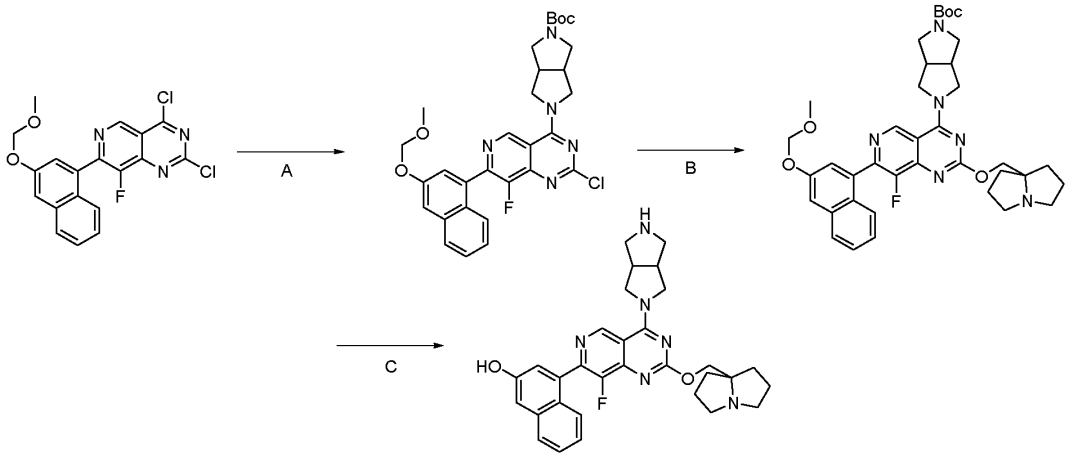
LC-MS (ES$^+$, Method 4): 0.73min, 447.1 $[M+H]^+$.

EXAMPLE COMPOUNDS

EXAMPLE 1



4-[4-(2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrol-5-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



STEP A: tert-butyl 2-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-carboxylate: At -40°C, a solution of tert-butyl hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (77.6mg, 0.37mmol) in DCM (1.5mL) was added to a solution of N,N-diisopropylethylamine (0.36mL, 2.04mmol) and 2,4-dichloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine (123mg, 0.30mmol) in DCM (1.5mL). The resulting mixture was allowed to stir at -40°C for 30mins. Water (20mL) was added. Then reaction mixture partitioned between a layer of DCM (20mL) and water (10mL). The organic layer was separated. The aqueous layer was extracted with DCM (2 x 20mL), organic extracts combined, filtered over a hydrophobic frit and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with 20-100% ethyl acetate in pet. ether afforded tert-butyl 2-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-carboxylate (108mg, 0.19mmol, 61.7% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 2.05 min, m/z 580.3 $[M]^+$

^1H NMR (400 MHz, $CDCl_3$) δ/ppm: 9.41 (s, 1H), 7.83 (d, *J*=8.2 Hz, 1H), 7.72-7.63 (m, 2H), 7.56 (d, *J*=2.4 Hz, 1H), 7.51-7.43 (m, 1H), 7.33 (ddd, *J*=8.4, 6.9, 1.4 Hz, 1H), 5.34 (s, 2H), 4.40-4.24 (m, 2H), 4.05-3.95 (m, 2H), 3.81-3.66 (m, 2H), 3.54 (s, 3H), 3.49-3.33 (m, 2H), 3.21-3.07 (m, 2H), 1.48 (s, 9H).

STEP B: tert-butyl 2-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-carboxylate: A solution of 1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol (79mg, 0.56mmol) in 1,4-Dioxane (0.9284mL) was added to tert-butyl 2-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-1,3,3a,4,6,6a-

hexahydropyrrolo[3,4-c]pyrrole-5-carboxylate (108mg, 0.19mmol) . N,N-diisopropylethylamine (0.1mL, 0.56mmol) was added and the reaction mixture was allowed to stir at 90°C overnight. The reaction mixture allowed to cool back down to room temperature. And partitioned between a layer of ethyl acetate (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (20mL), organic extracts combined, washed with a saturated solution of brine (20mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with 0-20% 1M NH_3- MeOH in DCM afforded tert-butyl 2-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-carboxylate (91mg, 0.1329mmol, 72% yield) as an off-white solid.

UPLC-MS (ES^+, Short acidic): 1.76 min, m/z 685.5 $[M+H]^+$

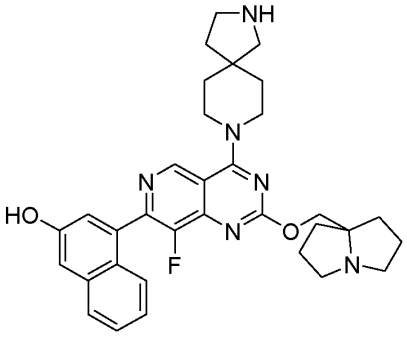
^1H NMR (400 MHz, $CDCl_3$) δ/ppm: 9.29 (s, 1H), 7.82 (d, *J*=8.3 Hz, 1H), 7.71-7.66 (m, 1H), 7.53 (d, *J*=2.4 Hz, 1H), 7.49-7.41 (m, 2H), 7.35-7.29 (m, 1H), 5.34 (s, 2H), 4.35-4.19 (m, 4H), 4.01-3.91 (m, 2H), 3.79-3.63 (m, 2H), 3.54 (s, 3H), 3.46-3.33 (m, 2H), 3.19-3.03 (m, 4H), 2.72-2.58 (m, 2H), 2.20-2.05 (m, 2H), 1.96-1.80 (m, 4H), 1.75-1.53 (m, 2H), 1.48 (s, 9H)

STEP C: 4-[4-(2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrol-5-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol: At 0°C, trifluoroacetic acid (0.31mL, 3.99mmol) was added to a solution of tert-butyl 2-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-carboxylate (91.mg, 0.13mmol) in DCM (1.3mL) . The mixture was allowed to stir at room temperature for 90 mins before concentrating under reduced pressure and dry loading onto celite. Purification by reverse phase chromatography eluting with 5-40% MeCN in water with fractions containing the desire product isolated by SCX (MeCN (x2) followed by 1 M NH_3 in MeOH (x2)) and purification by flash column chromatography on silica gel eluting with 20-100% 1M NH_3 - MeOH in DCM afforded 4-[4-(2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrol-5-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol (8.1mg, 0.015mmol, 11% yield) as a yellow solid.

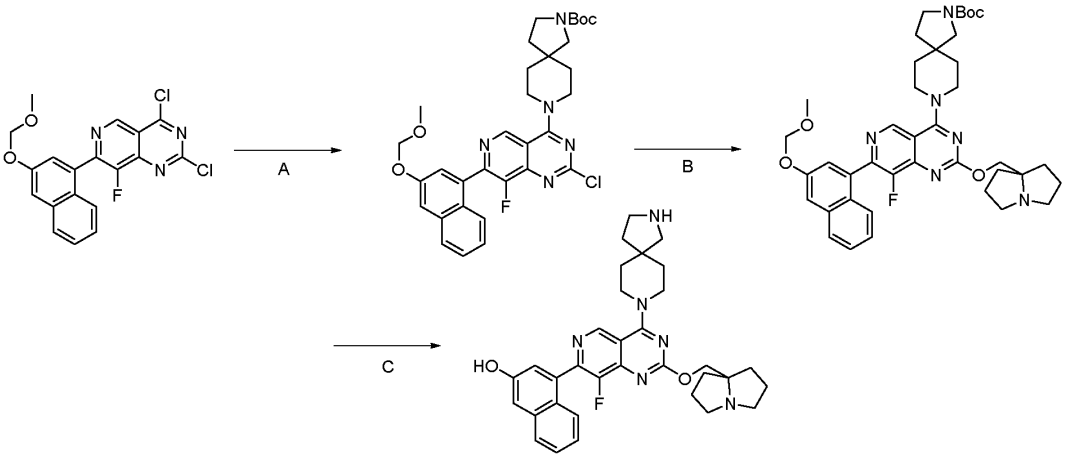
UPLC-MS (ES+, Short acidic): 1.33 min, m/z 541.3 $[M+H]^+$

^1H NMR (400 MHz, MeOH-d_4) δ/ppm: 9.34 (s, 1H), 7.78 (d, *J*=8.3 Hz, 1H), 7.55-7.50 (m, 1H), 7.47-7.41 (m, 1H), 7.30 (d, *J*=2.4 Hz, 1H), 7.28-7.22 (m, 2H), 4.42-4.30 (m, 4H), 4.09-4.00 (m, 2H), 3.23-3.07 (m, 6H), 2.98-2.90 (m, 2H), 2.82-2.72 (m, 2H), 2.17-2.06 (m, 2H), 2.03-1.85 (m, 4H), 1.85-1.74 (m, 2H).

EXAMPLE 2



4-[4-(2,8-diazaspiro[4.5]decan-8-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



STEP A: tert-butyl 8-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decane-2-carboxylate: At -40°C, tert-butyl 2,8-diazaspiro[4.5]decane-2-carboxylate, 2-(tert-butoxycarbonyl)-2,8-diazaspiro[4.5]decane (78 mg, 0.33mmol) was added to a solution of N,N-Diisopropylethylamine (0.32mL, 1.82mmol) and 2,4-dichloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine (110mg, 0.27mmol) in DCM (1.36mL) Afterwards, the mixture was allowed to stir at -40°C for 45 mins. Water (10 mL) was added, the reaction mixture partitioned between a layer of DCM (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with DCM (2 x 20mL), organic extracts combined, filtered over a hydrophobic frit and concentrated under reduced pressure. Purification by flash column chromatography on silica gel, eluting with 0-100% ethyl acetate in pet. ether afforded tert-butyl 8-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decane-2-carboxylate (60mg, 0.098mmol, 36% yield) as an orange gum.

UPLC-MS (ES^+, Short acidic): 2.16 min, m/z 608.5 $[M]^+$

^1H NMR (400 MHz, $CDCl_3$) δ/ppm: 9.20 (s, 1H), 7.84 (d, *J*=8.2 Hz, 1H), 7.71-7.65 (m, 1H), 7.56 (d, *J*=2.4 Hz, 1H), 7.51-7.42 (m, 2H), 7.37-7.30 (m, 1H), 5.34 (s, 2H), 4.30-4.20 (m, 1H), 4.17-4.07 (m, 1H), 4.07-3.96 (m, 1H), 3.96-3.83 (m, 1H), 3.58-3.42 (m, 5H), 3.40 (s, 1H), 3.31 (s, 1H), 1.92-1.78 (m, 6H), 1.48 (s, 9H).

STEP B: tert-butyl 8-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decane-2-carboxylate: A solution of 1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol (41 mg, 0.29mmol) in 1,4-dioxane (0.49mL) was added to tert-butyl 8-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decane-2-carboxylate (60mg, 0.10mmol). N,N-Diisopropylethylamine (0.05mL, 0.29mmol) was added and reaction mixture was allowed to stir at 90°C overnight. Reaction mixture allowed to cool back down to room temperature. Partitioned between a layer of ethyl acetate (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (20mL), organic extracts combined, washed with a saturated solution of brine (20mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with 0-10% 1M NH_3- MeOH in DCM afforded tert-butyl 8-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decane-2-carboxylate (40.2mg, 0.0564mmol, 57.662% yield) as an orange gum.

UPLC-MS (ES^+, Short acidic): 1.85 min, m/z 713.5 $[M+H]^+$

^1H NMR (400 MHz, $CDCl_3$) δ/ppm:9.08 (s, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.74-7.67 (m, 1H), 7.54 (d, *J*=2.3 Hz, 1H), 7.50-7.41 (m, 2H), 7.36-7.29 (m, 1H), 5.34 (s, 2H), 4.42-3.99 (m, 4H), 3.99-3.74 (m, 2H), 3.57-3.41 (m, 5H), 3.37 (s, 1H), 3.28 (s, 1H), 3.25-3.01 (m, 2H), 2.79-2.54 (m, 2H), 2.26-2.04 (m, 2H). 2.04-1.63 (m, 12H), 1.48 (s, 9H).

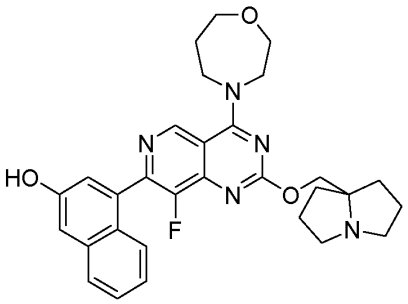
STEP C: 4-[4-(2,8-diazaspiro[4.5]decan-8-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol: At 0C, triethylsilane (0.09mL, 0.56mmol) was added to a solution of tert-butyl 8-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decane-2-carboxylate (40.2mg, 0.06mmol) in DCM (0.6mL) .Trifluoroacetic acid (0.86mL, 11.28mmol) was added and reaction mixture allowed to stir at room temperature for 2h. Reaction mixture was concentrated under reduced pressure and dry loaded onto celite. Purification by reverse phase chromatography eluting with 5-40% MeCN in water with fractions containing the desired product isolated by SCX (MeCN (x2)

followed by 1 M NH_3 in MeOH (x2)) afforded 4-[4-(2,8-diazaspiro[4.5]decan-8-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol (18.5mg, 0.033mmol, 58% yield) as a yellow solid.

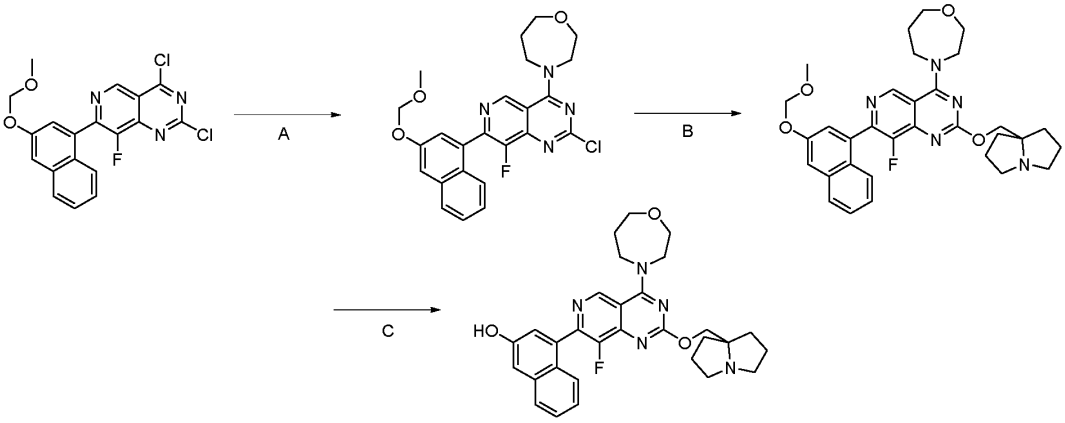
UPLC-MS (ES^+, Long acidic): 2.30 min, m/z 569.4 $[M+H]^+$

^1H NMR (400 MHz, MeOH-d_4,) δ/ppm: 9.12 (s, 1H), 7.77 (d, *J*=8.3 Hz, 1H), 7.58-7.52 (m, 1H), 7.47-7.41 (m, 1H), 7.32-7.78 (m, 1H), 7.28-7.22 (m, 2H), 4.31 (s, 2H), 4.23-4.12 (m, 2H), 4.12-4.01 (m, 2H), 3.17-3.03 (m, 4H), 2.88 (s, 2H), 2.79-2.70 (m, 2H), 2.15-2.05 (m, 2H), 2.01-1.73 (m, 12H).

EXAMPLE 3



4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



STEP A, 4-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane: At -40 °C, [1,4]-Oxazepane (28 mg, 0.27 mmol) was added to a solution of N,N-Diisopropylethylamine (0.32mL, 1.82mmol) and 2,4-dichloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine (110mg, 0.27mmol) in DCM (1.36mL) Afterwards, the mixture was allowed to stir at -40°C for 45 mins. Water (10 mL) was added.

And the reaction mixture partitioned between a layer of DCM (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with DCM (2 x 20mL), organic extracts combined, filtered over a hydrophobic frit and concentrated under reduced pressure. Purification by flash column chromatography on silica gel, eluting with 0-100% ethyl acetate in pet. ether afforded 4-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (68 mg, 0.14 mmol, 53% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 1.89 min, m/z 469.2 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.40 (s, 1H), 7.96 (d, J=8.2 Hz, 1H), 7.66 (d, J=2.7 Hz, 1H), 7.63 (d, J=9.2 Hz, 1H), 7.55 (ddd, J=1.3, 6.9, 8.2 Hz, 1H), 7.44 (d, J=2.4 Hz, 1H), 7.38 (ddd, J=1.3, 6.9, 8.3 Hz, 1H), 5.39 (s, 2H), 4.25 - 4.20 (m, 4H), 3.97 - 3.93 (m, 2H), 3.78 - 3.74 (m, 2H), 3.46 (s, 3H), 2.13 - 2.08 (m, 2H).

STEP B, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane: A solution of 1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol (61 mg, 0.43mmol) in 1,4-dioxane (0.72mL) was added to 4-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (68mg, 0.14mmol). N,N-Diisopropylethylamine (0.07mL, 0.43mmol) was added and reaction mixture was allowed to stir at 90°C overnight. Reaction mixture allowed to cool back down to room temperature. Partitioned between a layer of ethyl acetate (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (20mL), organic extracts combined, washed with a saturated solution of brine (20mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with 0-10% 1M NH_3- MeOH in DCM afforded 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (42 mg, 0.07 mmol, 51% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 1.52 min, m/z 574.5 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.26 (s, 1H), 7.95 (d, J=8.3 Hz, 1H), 7.65 - 7.60 (m, 2H), 7.55 - 7.51 (m, 1H), 7.41 (d, J=2.3 Hz, 1H), 7.37 (ddd, J=1.4, 7.0, 8.4 Hz, 1H), 5.39 (s, 2H), 4.21 - 4.15 (m, 6H), 3.97 - 3.93 (m, 2H), 3.77 - 3.73 (m, 2H), 3.46 (s, 3H), 3.05 - 2.93 (m, 2H), 1.92 - 1.80 (m, 8H), 1.64 - 1.58 (m, 2H).

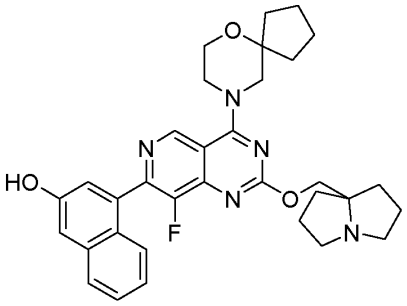
STEP C, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido [4,3-d]pyrimidin-7-yl]naphthalen-2-ol: At 0 °C, triethylsilane (0.12 mL, 0.74 mmol)

was added to a solution of 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (42 mg, 0.07 mmol) in DCM (0.7 mL) .Trifluoroacetic acid (1.1 mL, 14.7 mmol) was added and reaction mixture allowed to stir at room temperature for 2h. Reaction mixture was concentrated under reduced pressure and dry loaded onto celite. Purification by reverse phase chromatography eluting with 5-40% MeCN in water with fractions containing the desired product isolated by SCX (MeCN (x2) followed by 1 M NH_3 in MeOH (x2)) afforded 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido [4,3-d]pyrimidin-7-yl]naphthalen-2-ol (22 mg, 0.04 mmol, 57% yield) as a yellow solid.

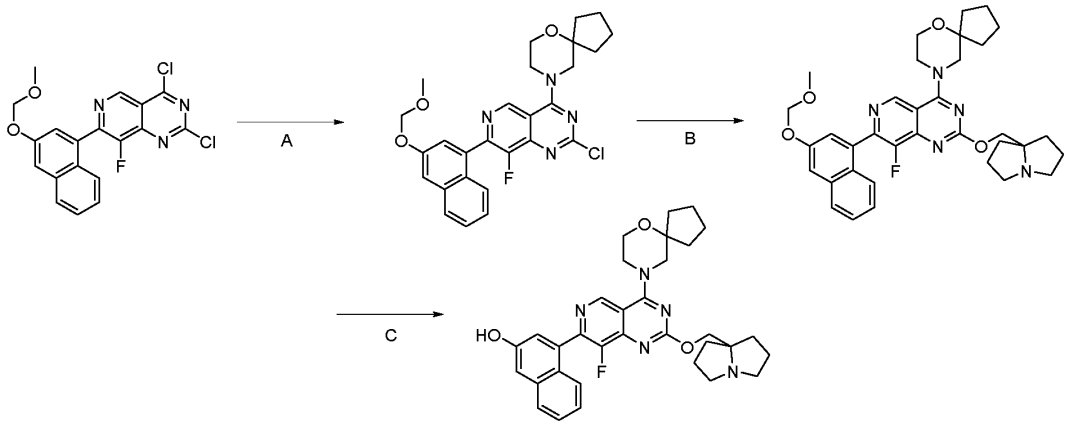
UPLC-MS (ES^+, Long acidic): 2.79 min, m/z 530.4 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.97 (s, 1H), 9.24 (s, 1H), 7.81 (d, J=8.2 Hz, 1H), 7.55 (d, J=8.3 Hz, 1H), 7.45 (ddd, J=1.2, 6.9, 8.1 Hz, 1H), 7.30 (d, J=2.3 Hz, 1H), 7.28 - 7.22 (m, 2H), 4.21 - 4.14 (m, 4H), 4.08 (s, 2H), 3.96 - 3.92 (m, 2H), 3.77 - 3.73 (m, 2H), 2.93 (td, J=5.4, 10.1 Hz, 2H), 2.13 - 2.07 (m, 2H), 1.94 - 1.86 (m, 8H), 1.85 - 1.71 (m, 8H), 1.62 - 1.54 (m, 2H).

EXAMPLE 4



4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(6-oxa-9-azaspiro[4.5]-decan-9-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



STEP A, 9-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-6-oxa-9-azaspiro[4.5]decane: At -40 °C, 6-oxa-9-azaspiro[4.5]decane (38 mg, 0.27 mmol) was added to a solution of N,N-Diisopropylethylamine (0.32mL, 1.82mmol) and 2,4-dichloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine (110mg, 0.27mmol) in DCM (1.36mL) Afterwards, the mixture was allowed to stir at -40°C for 45 mins. A second portion of 6-oxa-9-azaspiro[4.5]decane (38 mg, 0.27 mmol) was added and the mixture was stirred for 1 h at -40°C. Water (10 mL) was added. And the reaction mixture partitioned between a layer of DCM (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with DCM (2 x 20mL), organic extracts combined, filtered over a hydrophobic frit and concentrated under reduced pressure. Purification by flash column chromatography on silica gel, eluting with 0-100% ethyl acetate in pet. ether afforded 9-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-6-oxa-9-azaspiro[4.5]decane (74 mg, 0.15 mmol, 54% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 2.10 min, m/z 509.3 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.38 (s, 1H), 7.96 (d, J=8.2 Hz, 1H), 7.66 (d, J=2.6 Hz, 1H), 7.63 (d, J=8.4 Hz, 1H), 7.55 (ddd, J=1.2, 6.9, 8.1 Hz, 1H), 7.44 (d, J=2.4 Hz, 1H), 7.38 (ddd, J=1.4, 6.9, 8.4 Hz, 1H), 5.39 (s, 2H), 4.14 - 4.12 (m, 2H), 4.02 (s, 2H), 3.85 - 3.81 (m, 2H), 3.46 (s, 3H), 1.75 - 1.64 (m, 8H).

STEP B, 9-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-6-oxa-9-azaspiro[4.5]decane: A solution of 1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol (61 mg, 0.43mmol) in 1,4-dioxane (0.72mL) was added to 9-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-6-oxa-9-azaspiro [4.5]decane (74 mg, 0.15 mmol). N,N-Diisopropylethylamine (0.07mL, 0.43mmol) was added and reaction mixture was allowed to stir at 90°C overnight. Reaction mixture

allowed to cool back down to room temperature. Partitioned between a layer of ethyl acetate (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (20mL), organic extracts combined, washed with a saturated solution of brine (20mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with 0-10% 1M NH_3- MeOH in DCM afforded 9-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-6-oxa-9-azaspiro[4.5] decane (36 mg, 0.06 mmol, 40% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 1.70 min, m/z 614.4 $[M]^+$

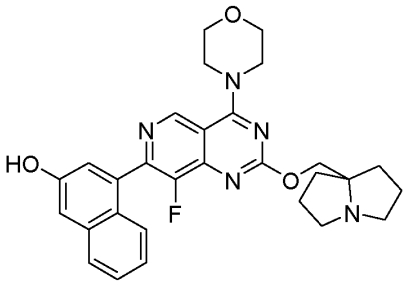
^1H NMR (400 MHz, $CDCl_3$) δ/ppm: 9.11 (s, 1H), 7.82 (d, J=8.2 Hz, 1H), 7.70 (d, J=9.5 Hz, 1H), 7.54 (d, J=2.0 Hz, 1H), 7.48 - 7.43 (m, 2H), 7.35 - 7.30 (m, 1H), 5.34 (s, 2H), 4.25 - 4.24 (m, 2H), 3.99 - 3.92 (m, 6H), 3.54 (s, 3H), 3.12 - 3.12 (m, 2H), 2.66 - 2.65 (m, 2H), 1.89 - 1.65 (m, 12H), 1.29 - 1.29 (m, 2H), 0.88 - 0.87 (m, 2H).

STEP C, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(6-oxa-9-azaspiro[4.5]-decan-9-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol: At 0 °C, triethylsilane (0.12 mL, 0.74 mmol) was added to a solution of 9-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-6-oxa-9-azaspiro[4.5] decane (36 mg, 0.06 mmol) in DCM (0.7 mL) .Trifluoroacetic acid (1.1 mL, 14.7 mmol) was added and reaction mixture allowed to stir at room temperature for 2h. Reaction mixture was concentrated under reduced pressure and dry loaded onto celite. Purification by reverse phase chromatography eluting with 5-40% MeCN in water with fractions containing the desired product isolated by SCX (MeCN (x2) followed by 1 M NH_3 in MeOH (x2)) afforded 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(6-oxa-9-azaspiro[4.5]-decan-9-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol (27 mg, 0.05 mmol, 80% yield) as a yellow solid.

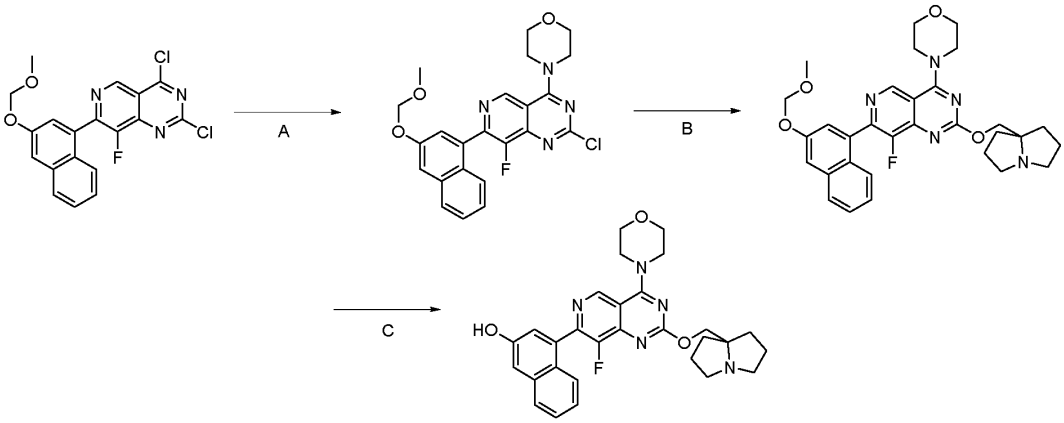
UPLC-MS (ES^+, Long acidic): 3.11 min, m/z 570.5 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.99 (s, 1H), 9.21 (s, 1H), 7.81 (d, J=8.1 Hz, 1H), 7.56 (d, J=8.2 Hz, 1H), 7.45 (ddd, J=1.2, 6.9, 8.2 Hz, 1H), 7.31 - 7.23 (m, 3H), 4.09 (s, 2H), 4.03 - 3.99 (m, 2H), 3.93 (s, 2H), 3.83 (t, J=5.0 Hz, 2H), 3.38 - 3.37 (m, 2H), 2.94 - 2.94 (m, 2H), 1.93 - 1.86 (m, 2H), 1.82 - 1.69 (m, 10H), 1.63 - 1.57 (m, 4H).

EXAMPLE 5



4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(morpholin-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



STEP A, 4-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]morpholine: At -40 °C, morpholine (24 mg, 0.27 mmol) was added to a solution of N,N-Diisopropylethylamine (0.32mL, 1.82mmol) and 2,4-dichloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine (110mg, 0.27mmol) in DCM (1.36mL) Afterwards, the mixture was allowed to stir at -40°C for 45 mins. Water (10 mL) was added. And the reaction mixture partitioned between a layer of DCM (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with DCM (2 x 20mL), organic extracts combined, filtered over a hydrophobic frit and concentrated under reduced pressure. Purification by flash column chromatography on silica gel, eluting with 0-100% ethyl acetate in pet. ether afforded 4-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-1,4-morpholine (61 mg, 0.14 mmol, 50% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 1.85 min, m/z 455.3 $[M]^+$

STEP B, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]morpholine: A solution of 1,2,3,5,6,7-

hexahydropyrrolizin-8-ylmethanol (57 mg, 0.41 mmol) in 1,4-dioxane (0.67 mL) was added to 4-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]morpholine (61 mg, 0.14 mmol). N,N-Diisopropylethylamine (0.07 mL, 0.41 mmol) was added and reaction mixture was allowed to stir at 90 °C overnight. Reaction mixture allowed to cool back down to room temperature. Partitioned between a layer of ethyl acetate (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (20mL), organic extracts combined, washed with a saturated solution of brine (20mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with 0-10% 1M NH_3- MeOH in DCM afforded 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]morpholine (23 mg, 0.04 mmol, 30% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 1.51 min, m/z 560.5 $[M]^+$

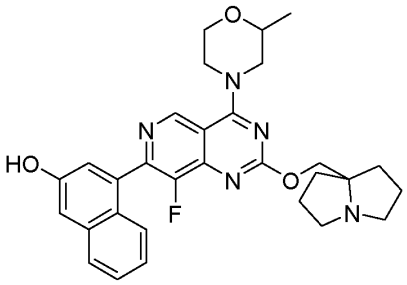
^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.25 (s, 1H), 7.95 (d, J=8.3 Hz, 1H), 7.65 - 7.61 (m, 2H), 7.54 (ddd, J=1.2, 6.9, 8.1 Hz, 1H), 7.41 (d, J=2.4 Hz, 1H), 7.37 (ddd, J=1.3, 7.0, 8.4 Hz, 1H), 5.39 (s, 2H), 4.15 - 4.14 (m, 2H), 4.05 - 4.03 (m, 4H), 3.82 - 3.81 (m, 4H), 3.46 (s, 3H), 2.98 - 2.98 (m, 2H), 1.96 - 1.84 (m, 8H).One CH_2 under solvent peak.

STEP C, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(morpholin-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol: At 0 °C, triethylsilane (0.06 mL, 0.40 mmol) was added to a solution of 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl] pyrido[4,3-d]pyrimidin-4-yl]morpholine (23 mg, 0.04 mmol) in DCM (0.4 mL) .Trifluoroacetic acid (0.6 mL, 8.1 mmol) was added and reaction mixture allowed to stir at room temperature for 2h. Reaction mixture was concentrated under reduced pressure and dry loaded onto celite. Purification by reverse phase chromatography eluting with 5-40% MeCN in water with fractions containing the desired product isolated by SCX (MeCN (x2) followed by 1 M NH_3 in MeOH (x2)) afforded 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(morpholin-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol (17 mg, 0.03 mmol, 80% yield) as a yellow solid.

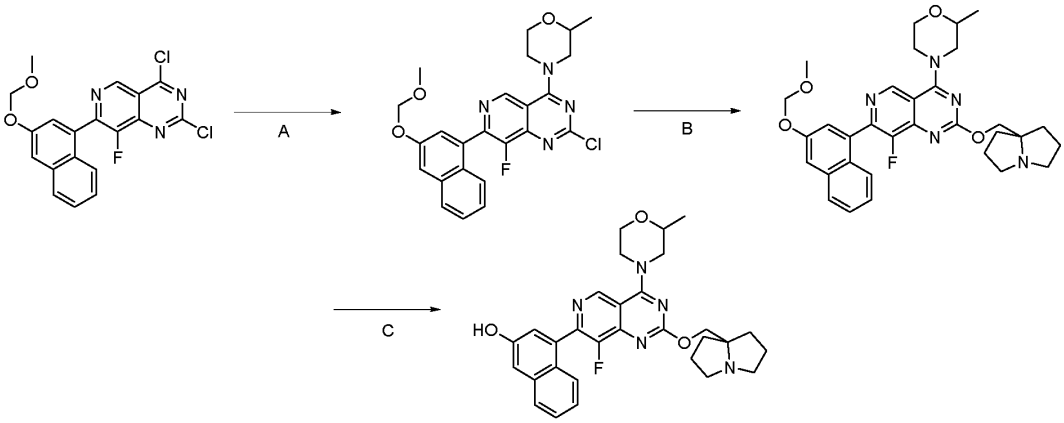
UPLC-MS (ES^+, Long acidic): 2.72 min, m/z 516.5 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.98 (s, 1H), 9.23 (s, 1H), 7.81 (d, J=8.2 Hz, 1H), 7.55 (d, J=8.7 Hz, 1H), 7.45 (ddd, J=1.2, 6.9, 8.2 Hz, 1H), 7.30 (d, J=2.7 Hz, 3H), 7.28 - 7.23 (m, 3H), 4.08 (s, 2H), 4.02 (t, J=4.7 Hz, 4H), 3.81 (t, J=4.7 Hz, 4H), 2.97 - 2.90 (m, 2H), 2.58 - 2.54 (m, 2H), 1.94 - 1.72 (m, 6H), 1.63 - 1.54 (m, 2H).

EXAMPLE 6



4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(2-methylmorpholin-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



STEP A, 4-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2-methyl-morpholine: At -40 °C, 2-methylmorpholine hydrochloride (37 mg, 0.27 mmol) was added to a solution of N,N-Diisopropylethylamine (0.41 mL, 2.37 mmol) and 2,4-dichloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine (110 mg, 0.27 mmol) in DCM (1.36mL) Afterwards, the mixture was allowed to stir at -40°C for 45 mins. Water (10 mL) was added. And the reaction mixture partitioned between a layer of DCM (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with DCM (2 x 20mL), organic extracts combined, filtered over a hydrophobic frit and concentrated under reduced pressure. Purification by flash column chromatography on silica gel, eluting with 0-100% ethyl acetate in pet. ether afforded 4-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2-methyl-morpholine (77 mg, 0.16 mmol, 60% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 1.95 min, m/z 469.2 $[M]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.39 (s, 1H), 7.96 (d, J=8.3 Hz, 1H), 7.67 (d, J=2.6 Hz, 1H), 7.63 (d, J=9.4 Hz, 1H), 7.55 (ddd, J=1.4, 6.8, 8.3 Hz, 1H), 7.44 (d, J=2.4 Hz, 1H), 7.38 (ddd, J=6.3, 6.3, 2.8 Hz, 1H), 5.39 (s, 2H), 4.56 (t, J=12.0 Hz, 2H), 4.01 - 3.97 (m, 1H), 3.79 - 3.59 (m, 4H), 3.46 (s, 3H), 1.21 (d, J=6.2 Hz, 3H).

STEP B, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2-methylmorpholine: A solution of 1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol (75 mg, 0.53 mmol) in 1,4-dioxane (0.89 mL) was added to 4-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2-methyl morpholine (83 mg, 0.17 mmol). N,N-Diisopropylethylamine (0.09 mL, 0.53 mmol) was added and reaction mixture was allowed to stir at 90 °C overnight. Reaction mixture allowed to cool back down to room temperature. Partitioned between a layer of ethyl acetate (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (20mL), organic extracts combined, washed with a saturated solution of brine (20mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with 0-10% 1M NH_3- MeOH in DCM afforded 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2-methylmorpholine (52 mg, 0.09 mmol, 51% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 1.58 min, m/z 574.5 $[M]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.25 (s, 1H), 7.95 (d, J=8.5 Hz, 1H), 7.65 - 7.61 (m, 2H), 7.54 (ddd, J=1.1, 6.9, 8.2 Hz, 1H), 7.41 (d, J=2.4 Hz, 1H), 7.37 (ddd, J=1.3, 6.9, 8.3 Hz, 1H), 5.39 (s, 2H), 4.51 - 4.45 (m, 2H), 4.16 - 4.15 (m, 2H), 3.99 - 3.95 (m, 1H), 3.77 - 3.68 (m, 2H), 3.53 - 3.50 (m, 1H), 3.46 (s, 3H), 3.25 - 3.20 (m, 1H), 3.01 - 3.01 (m, 2H), 1.94 - 1.81 (m, 6H), 1.64 - 1.64 (m, 2H), 1.20 (d, J=6.2 Hz, 3H). One CH_2 under solvent peak.

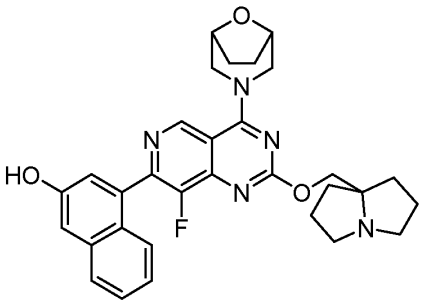
STEP C, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(2-methylmorpholin-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol: At 0 °C, triethylsilane (0.14 mL, 0.90 mmol) was added to a solution of 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl] pyrido[4,3-d]pyrimidin-4-yl]-2-methylmorpholine (52 mg, 0.09 mmol) in DCM (0.9 mL) .Trifluoroacetic acid (1.37 mL, 18 mmol) was added and reaction mixture allowed to stir at room temperature for 2h. Reaction mixture was concentrated under reduced pressure and dry loaded onto celite. Purification by reverse phase chromatography eluting with 5-40% MeCN in water with fractions containing the desired product isolated by SCX (MeCN (x2) followed by 1 M NH_3 in MeOH (x2)) afforded 4-[8-fluoro-2-(1,2,3,5,6,7-

hexahydropyrrolizin-8-ylmethoxy)-4-(2-methylmorpholin-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol (36 mg, 0.07 mmol, 75% yield) as a yellow solid.

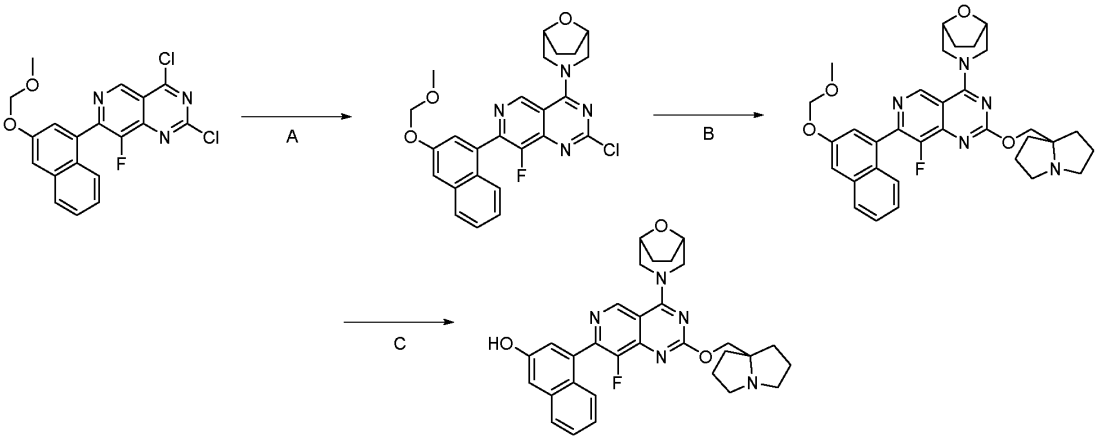
UPLC-MS (ES^+, Long acidic): 2.89 min, m/z 530.5 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.98 (s, 1H), 9.22 (s, 1H), 7.81 (d, J=8.3 Hz, 1H), 7.56 (d, J=8.6 Hz, 1H), 7.45 (ddd, J=1.3, 6.9, 8.3 Hz, 1H), 7.30 (d, J=2.7 Hz, 1H), 7.28 - 7.23 (m, 2H), 4.49 - 4.45 (m, 2H), 4.09 (s, 2H), 3.99 - 3.95 (m, 1H), 3.75 - 3.68 (m, 2H), 3.52 - 3.45 (m, 1H), 3.24 - 3.16 (m, 1H), 2.96 - 2.91 (m, 2H), 2.59 - 2.56 (m, 2H), 1.94 - 1.88 (m, 2H), 1.81 - 1.73 (m, 4H), 1.61 - 1.55 (m, 2H), 1.20 (d, J=6.2 Hz, 3H)

EXAMPLE 7



4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



STEP A, 3-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-8-oxa-3-azabicyclo[3.2.1]octane: At -40 °C, 8-oxa-3-azabicyclo[3,2,1]octane hydrochloride (41 mg, 0.27 mmol) was added to a solution of N,N-Diisopropylethylamine (0.41 mL, 2.37 mmol) and 2,4-dichloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine (110 mg, 0.27 mmol) in DCM (1.36mL) Afterwards, the mixture was allowed to stir at -40°C

for 45 mins. Water (10 mL) was added. And the reaction mixture partitioned between a layer of DCM (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with DCM (2 x 20mL), organic extracts combined, filtered over a hydrophobic frit and concentrated under reduced pressure. Purification by flash column chromatography on silica gel, eluting with 0-100% ethyl acetate in pet. ether afforded 3-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-8-oxa-3-azabicyclo[3.2.1]octane (96 mg, 0.2 mmol, 73% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 1.94 min, m/z 481.2 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.35 (s, 1H), 7.96 (d, J=8.4 Hz, 1H), 7.67 - 7.61 (m, 2H), 7.56 - 7.52 (m, 1H), 7.43 (d, J=2.3 Hz, 1H), 7.40 - 7.35 (m, 1H), 5.39 (s, 2H), 4.50 - 4.45 (m, 4H), 3.82 - 3.78 (m, 2H), 3.46 (s, 3H), 1.86 - 1.75 (m, 4H).

STEP B, 3-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-8-oxa-3-azabicyclo[3.2.1]octane: A solution of 1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol (84 mg, 0.60 mmol) in 1,4-dioxane (1.0 mL) was added to 3-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-8-oxa-3-azabicyclo[3.2.1]octane (96 mg, 0.2 mmol). N,N-Diisopropylethylamine (0.1 mL, 0.60 mmol) was added and reaction mixture was allowed to stir at 90 °C overnight. Reaction mixture allowed to cool back down to room temperature. Partitioned between a layer of ethyl acetate (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (20mL), organic extracts combined, washed with a saturated solution of brine (20mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with 0-10% 1M NH_3- MeOH in DCM afforded 3-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-8-oxa-3-azabicyclo[3.2.1]octane (61 mg, 0.10 mmol, 52% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 1.56 min, m/z 586.5 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.21 (s, 1H), 7.94 (d, J=8.0 Hz, 1H), 7.65 - 7.62 (m, 2H), 7.53 (ddd, J=1.2, 6.9, 8.1 Hz, 1H), 7.40 (d, J=2.3 Hz, 1H), 7.37 (ddd, J=1.4, 6.9, 8.3 Hz, 1H), 5.39 (s, 2H), 4.48 - 4.42 (m, 4H), 4.11 - 4.10 (m, 2H), 3.75 - 3.71 (m, 2H), 3.46 (s, 3H), 2.98 - 2.97 (m, 2H), 1.95 - 1.91 (m, 2H), 1.87 - 1.76 (m, 8H), 1.65 - 1.59 (m, 2H). One CH_2 under solvent peak.

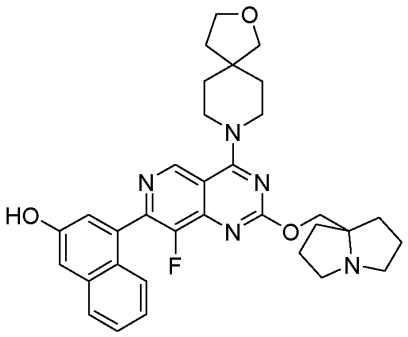
STEP C, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol: At 0 °C, triethylsilane (0.17 mL,

1.03 mmol) was added to a solution of 3-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-8-oxa-3-azabicyclo[3.2.1]octane (61 mg, 0.10 mmol) in DCM (1.0 mL) .Trifluoroacetic acid (1.58 mL, 21 mmol) was added and reaction mixture allowed to stir at room temperature for 2h. Reaction mixture was concentrated under reduced pressure and dry loaded onto celite. Purification by reverse phase chromatography eluting with 5-40% MeCN in water with fractions containing the desired product isolated by SCX (MeCN (x2) followed by 1 M NH_3 in MeOH (x2)) afforded 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol (28 mg, 0.05 mmol, 50% yield) as a yellow solid.

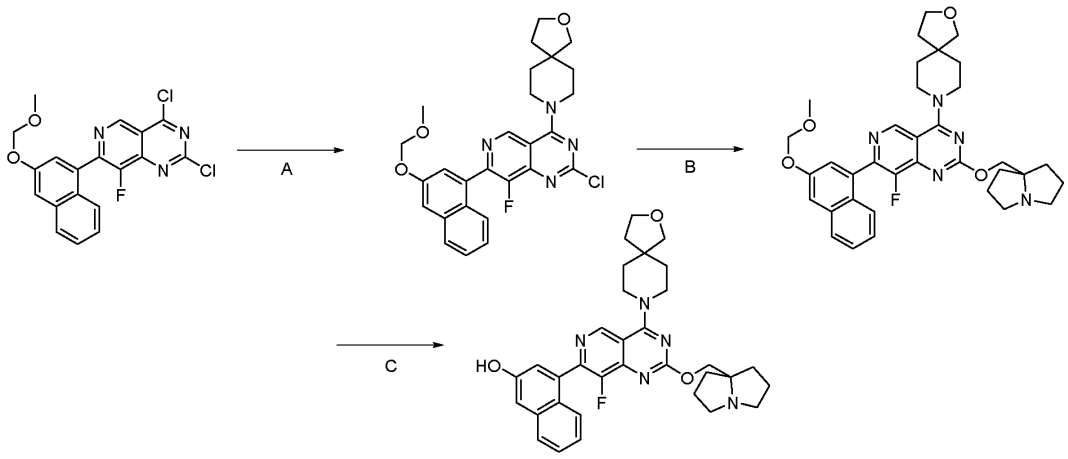
UPLC-MS (ES^+, Long acidic): 2.84 min, m/z 542.5 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.98 (s, 1H), 9.19 (s, 1H), 7.81 (d, J=8.1 Hz, 1H), 7.55 (d, J=8.5 Hz, 1H), 7.47 - 7.42 (m, 1H), 7.30 (d, J=2.3 Hz, 1H), 7.28 - 7.22 (m, 2H), 4.50 - 4.42 (m, 4H), 4.08 (s, 2H), 3.73 (d, J=11.6 Hz, 2H), 2.98 - 2.90 (m, 2H), 2.59 - 2.54 (m, 2H), 1.94 - 1.88 (m, 2H), 1.83 - 1.75 (m, 8H), 1.63 - 1.56 (m, 2H).

EXAMPLE 8



4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(2-oxa-8-azaspiro[4.5]decan-8-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



STEP A, 8-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2-oxa-8-azaspiro[4.5]decane: At -40 °C, 2-Oxa-8-azaspiro[4.5]decane (38 mg, 0.27 mmol) was added to a solution of N,N-Diisopropylethylamine (0.32 mL, 1.82 mmol) and 2,4-dichloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine (110 mg, 0.27 mmol) in DCM (1.36mL) Afterwards, the mixture was allowed to stir at -40°C for 45 mins. Water (10 mL) was added. And the reaction mixture partitioned between a layer of DCM (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with DCM (2 x 20mL), organic extracts combined, filtered over a hydrophobic frit and concentrated under reduced pressure. Purification by flash column chromatography on silica gel, eluting with 0-100% ethyl acetate in pet. ether afforded 8-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2-oxa-8-azaspiro [4.5]decane (78 mg, 0.15 mmol, 56% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 1.95 min, m/z 509.3 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.31 (s, 1H), 7.95 (d, J=8.2 Hz, 1H), 7.67 - 7.61 (m, 2H), 7.54 (ddd, J=1.1, 6.9, 8.2 Hz, 1H), 7.44 (d, J=2.4 Hz, 1H), 7.38 (ddd, J=1.3, 6.9, 8.3 Hz, 1H), 5.39 (s, 2H), 4.16 - 4.09 (m, 2H), 4.06 - 4.00 (m, 2H), 3.82 (t, J=7.1 Hz, 2H), 3.57 (s, 2H), 3.46 (s, 3H), 1.86 (t, J=7.1 Hz, 2H), 1.80 - 1.76 (m, 4H).

STEP B, 8-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2-oxa-8-azaspiro[4.5]decane: A solution of 1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol (65 mg, 0.46 mmol) in 1,4-dioxane (0.76 mL) was added to 8-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2-oxa-8-azaspiro [4.5]decane (78 mg, 0.15 mmol). N,N-Diisopropylethylamine (0.08 mL, 0.46 mmol) was added and reaction mixture was allowed to stir at 90 °C overnight. Reaction mixture allowed to cool back down to room temperature. Partitioned between a layer of ethyl acetate

(20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (20mL), organic extracts combined, washed with a saturated solution of brine (20mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with 0-10% 1M NH_3- MeOH in DCM afforded 8-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2-oxa-8-azaspiro [4.5]decane (50 mg, 0.08 mmol, 53% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 1.61 min, m/z 614.5 $[M]^+$

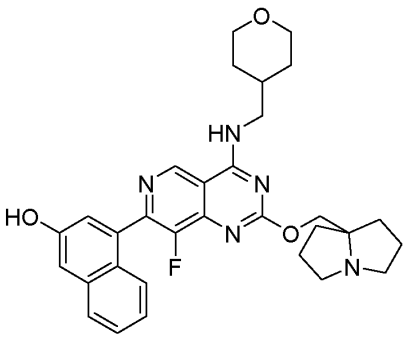
^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.17 (s, 1H), 7.97 - 7.93 (m, 2H), 7.65 - 7.61 (m, 2H), 7.56 - 7.51 (m, 1H), 7.41 (d, J=2.5 Hz, 1H), 7.37 (ddd, J=1.2, 6.9, 8.3 Hz, 1H), 5.39 (s, 2H), 4.07 - 4.02 (m, 2H), 3.97 - 3.91 (m, 2H), 3.82 (t, J=7.0 Hz, 2H), 3.57 (s, 3H), 3.46 (s, 4H), 1.88 - 1.76 (m, 14H).

STEP C, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(2-oxa-8-azaspiro[4.5]decan-8-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol: At 0 °C, triethylsilane (0.13 mL, 0.81 mmol) was added to a solution of 8-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-2-oxa-8-azaspiro [4.5]decane (50 mg, 0.08 mmol) in DCM (0.81 mL) .Trifluoroacetic acid (1.24 mL, 16 mmol) was added and reaction mixture allowed to stir at room temperature for 2h. Reaction mixture was concentrated under reduced pressure and dry loaded onto celite. Purification by reverse phase chromatography eluting with 5-40% MeCN in water with fractions containing the desired product isolated by SCX (MeCN (x2) followed by 1 M NH_3 in MeOH (x2)) afforded 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(2-oxa-8-azaspiro[4.5]decan-8-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol (34 mg, 0.06 mmol, 74% yield) as a yellow solid.

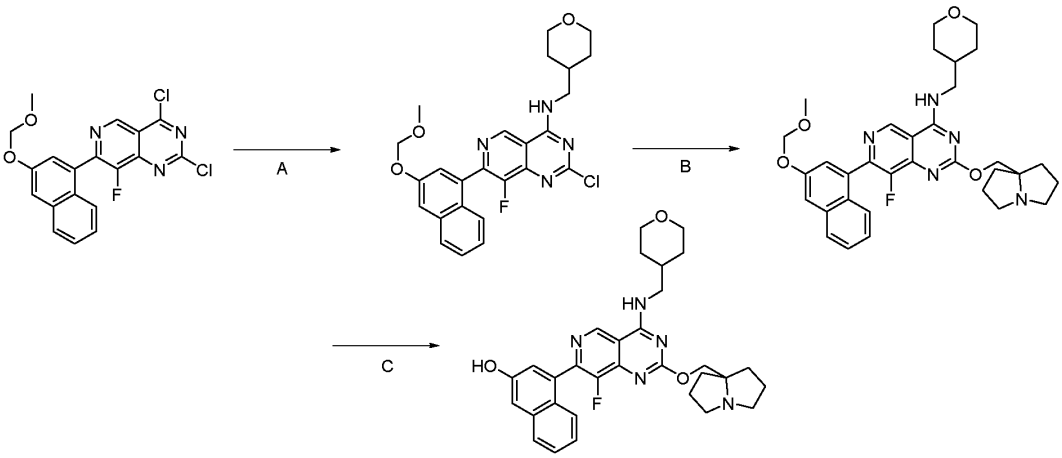
UPLC-MS (ES^+, Long acidic): 2.95 min, m/z 570.5 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.98 (s, 1H), 9.15 (s, 1H), 7.81 (d, J=8.2 Hz, 1H), 7.55 (d, J=10.1 Hz, 1H), 7.45 (ddd, J=1.5, 6.9, 8.3 Hz, 1H), 7.30 (d, J=2.3 Hz, 1H), 7.28 - 7.23 (m, 2H), 4.08 (s, 2H), 4.06 - 3.99 (m, 2H), 3.97 - 3.88 (m, 2H), 3.81 (t, J=7.1 Hz, 2H), 3.57 (s, 2H), 2.98 - 2.91 (m, 2H), 2.60 - 2.55 (m, 2H), 1.95 - 1.72 (m, 12H), 1.63 - 1.56 (m, 2H).

EXAMPLE 9



4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(tetrahydropyran-4-ylmethylamino)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



STEP A, 2-Chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]-N-(tetrahydropyran-4-ylmethyl) pyrido[4,3-d]pyrimidin-4-amine: At -40 °C, 4-(aminomethyl)tetrahydro-2H-pyran (93 mg, 0.81 mmol) was added to a solution of N,N-Diisopropylethylamine (0.32 mL, 1.82 mmol) and 2,4-dichloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine (110 mg, 0.27 mmol) in DCM (1.36mL) Afterwards, the mixture was allowed to stir at -40°C for 45 mins. Water (10 mL) was added. And the reaction mixture partitioned between a layer of DCM (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with DCM (2 x 20mL), organic extracts combined, filtered over a hydrophobic frit and concentrated under reduced pressure. Purification by flash column chromatography on silica gel, eluting with 0-100% ethyl acetate in pet. ether afforded 2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]-N-(tetrahydropyran-4-ylmethyl) pyrido[4,3-d] pyrimidin-4-amine (41 mg, 0.08 mmol, 31% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 1.90 min, m/z 483.3 $[M]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.57 (s, 1H), 9.51 (t, J=5.4 Hz, 1H), 7.97 - 7.93 (m, 1H), 7.65 (d, J=2.5 Hz, 1H), 7.57 - 7.52 (m, 2H), 7.40 (d, J=2.4 Hz, 1H), 7.36 (ddd, J=1.2, 7.0, 8.2 Hz, 1H), 5.39 (s, 2H), 3.92 - 3.86 (m, 2H), 3.55 - 3.50 (m, 2H), 3.46 (s, 3H), 2.06 - 2.02 (m, 1H), 1.72 - 1.68 (m, 2H), 1.37 - 1.29 (m, 2H). One CH_2 under solvent peak.

STEP B, 8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]-N-(tetrahydropyran-4-ylmethyl)pyrido[4,3-d]pyrimidin-4-amine: A solution of 1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol (36 mg, 0.25 mmol) in 1,4-dioxane (0.42 mL) was added to 2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]-N-(tetrahydropyran-4-ylmethyl) pyrido[4,3-d] pyrimidin-4-amine (41 mg, 0.08 mmol). N,N-Diisopropylethylamine (0.04 mL, 0.25 mmol) was added and reaction mixture was allowed to stir at 90 °C overnight. Reaction mixture allowed to cool back down to room temperature. Partitioned between a layer of ethyl acetate (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (20mL), organic extracts combined, washed with a saturated solution of brine (20mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with 0-10% 1M NH_3- MeOH in DCM afforded 8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]-N-(tetrahydropyran-4-ylmethyl)pyrido[4,3-d]pyrimidin-4-amine (33 mg, 0.06 mmol, 67% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 1.56 min, m/z 588.6 $[M]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.42 (s, 1H), 9.04 - 9.00 (m, 1H), 7.96 - 7.93 (m, 1H), 7.63 (d, J=2.6 Hz, 1H), 7.54 - 7.51 (m, 2H), 7.38 - 7.33 (m, 2H), 5.39 (s, 2H), 4.16 - 4.15 (m, 2H), 3.92 - 3.88 (m, 2H), 3.53 - 3.49 (m, 2H), 3.46 (s, 3H), 2.98 - 2.97 (m, 2H), 1.92 - 1.62 (m, 11H), 1.36 - 1.30 (m, 2H). 2 x CH_2 under solvent peaks.

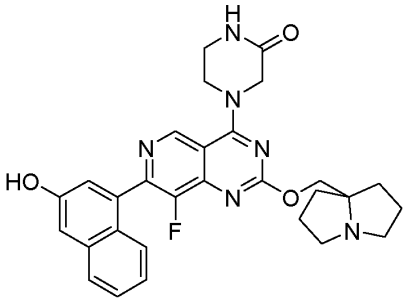
STEP C, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(tetrahydropyran-4-ylmethylamino)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol: At 0 °C, triethylsilane (0.13 mL, 0.81 mmol) was added to a solution of 8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]-N-(tetrahydropyran-4-ylmethyl)pyrido[4,3-d]pyrimidin-4-amine (33 mg, 0.06 mmol) in DCM (0.57 mL) .Trifluoroacetic acid (0.87 mL, 11 mmol) was added and reaction mixture allowed to stir at room temperature for 2h. Reaction mixture was concentrated under reduced pressure and dry loaded onto celite. Purification by reverse phase chromatography eluting with 5-40% MeCN in water with fractions containing the desired product isolated by SCX (MeCN (x2) followed by 1 M NH_3 in MeOH (x2)) afforded 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(tetrahydropyran-4-

ylmethylamino)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol (16 mg, 0.03 mmol, 52% yield) as a yellow solid.

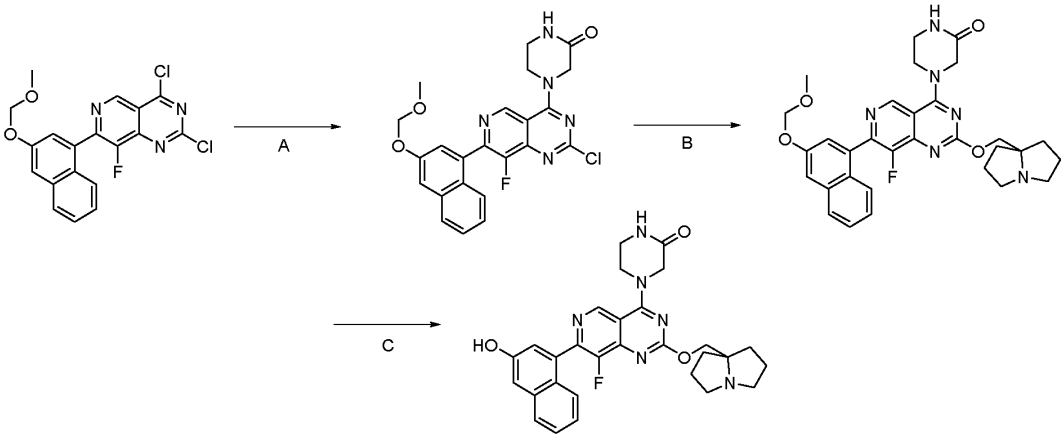
UPLC-MS (ES^+, Long acidic): 2.89 min, m/z 544.5 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.97 (s, 1H), 9.40 (s, 1H), 8.99 (t, J=5.6 Hz, 1H), 7.81 (d, J=8.2 Hz, 1H), 7.48 - 7.42 (m, 2H), 7.29 (d, J=2.4 Hz, 1H), 7.24 (ddd, J=1.4, 6.9, 8.3 Hz, 1H), 7.19 (d, J=2.7 Hz, 1H), 4.10 (s, 2H), 3.91 - 3.87 (m, 2H), 3.53 - 3.48 (m, 2H), 3.32 - 3.28 (m, 2H), 2.97 - 2.91 (m, 2H), 2.59 - 2.56 (m, 2H), 2.01 - 2.01 (m, 1H), 1.91 - 1.87 (m, 2H), 1.84 - 1.75 (m, 4H), 1.72 - 1.68 (m, 2H), 1.62 - 1.54 (m, 2H), 1.37 - 1.28 (m, 2H).

EXAMPLE 10



4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]piperazin-2-one



STEP A, 4-[2-Chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]piperazin-2-one: At -40 °C, 2-piprazinone (327 mg, 3.264 mmol) was added to a solution of N,N-Diisopropylethylamine (2.4 mL, 19 mmol) and 2,4-dichloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidine (3.3 g, 2.72 mmol) in DCM (40 mL) Afterwards, the mixture was allowed to stir at -40°C for 45 mins. Water (10 mL) was added.

And the reaction mixture partitioned between a layer of DCM (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with DCM (2 x 20mL), organic extracts combined, filtered over a hydrophobic frit and concentrated under reduced pressure. Purification by flash column chromatography on silica gel, eluting with 0-100% ethyl acetate in pet. ether afforded 4-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]piperazin-2-one (777 mg, 1.66 mmol, 61% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 2.03 min, m/z 468.2 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.46 (s, 1H), 8.45 - 8.41 (m, 1H), 7.97 (d, J=8.2 Hz, 1H), 7.68 (d, J=2.1 Hz, 1H), 7.63 (d, J=8.3 Hz, 1H), 7.59 - 7.54 (m, 1H), 7.46 (d, J=2.3 Hz, 1H), 7.41 - 7.37 (m, 1H), 5.41 (s, 2H), 4.61 (s, 2H), 4.27 - 4.22 (m, 2H), 3.51 - 3.47 (m, 5H).

STEP B, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]piperazin-2-one: A solution of 1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol (272 mg, 1.92 mmol) in 1,4-dioxane (15 mL) was added to 4-[2-chloro-8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]piperazin-2-one (300 mg, 0.64 mmol). N,N-Diisopropylethylamine (0.24 mL, 1.92 mmol) was added and reaction mixture was allowed to stir at 90 °C overnight. Reaction mixture allowed to cool back down to room temperature. Partitioned between a layer of ethyl acetate (20mL) and water (20mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (20mL), organic extracts combined, washed with a saturated solution of brine (20mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with 0-10% 1M NH_3- MeOH in DCM afforded 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]piperazin-2-one (206 mg, 0.36 mmol, 56% yield) as a yellow solid.

UPLC-MS (ES^+, Short acidic): 1.23 min, m/z 573.3 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.30 (s, 1H), 8.38 - 8.34 (m, 1H), 7.96 (d, J=8.1 Hz, 1H), 7.65 - 7.61 (m, 2H), 7.55 (t, J=7.5 Hz, 1H), 7.45 - 7.35 (m, 2H), 5.40 (s, 2H), 4.53 (s, 2H), 4.20 - 4.20 (m, 2H), 4.12 (s, 2H), 3.51 - 3.46 (m, 5H), 2.98 - 2.93 (m, 2H), 2.58 - 2.58 (m, 2H), 1.96 - 1.90 (m, 2H), 1.84 - 1.75 (m, 4H), 1.63 - 1.57 (m, 2H).

STEP C, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]piperazin-2-one: A solution of 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-

4-yl]piperazin-2-one (179 mg, 0.31 mmol) in 4M HCl in 1,4-dioxane (10 mL) was stirred at room temperature for 16 h. Reaction mixture was concentrated under reduced pressure and purified by prep HPLC to give 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]piperazin-2-one (49 mg, 0.09 mmol, 30% yield) as a yellow solid.

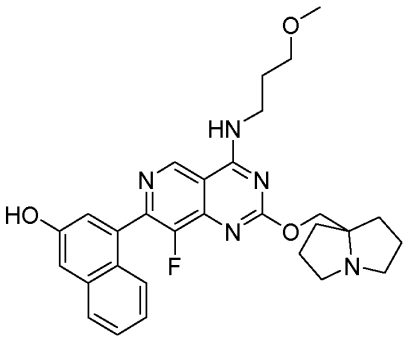
UPLC-MS (ES^+, Long acidic): 1.65 min, m/z 529.3 $[M]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm: 9.96 (br s, 1H), 9.26 (s, 1H), 8.32 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz,1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.30 - 7.22 (m, 3H), 4.51 (s, 2H), 4.17 (br s, 2H), 4.10 (s, 2H), 3.47 (br s, 2H), 2.96 - 2.91 (m, 2H), 2.57 - 2.53 (m, 2H), 1.93 - 1.87 (m, 2H), 1.83 - 1.73 (m, 4H), 1.61 - 1.55 (m, 2H).

The following examples were prepared according to scheme 4 from intermediate 25 or intermediate 26.

EXAMPLE 11

4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(3-methoxypropylamino)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



STEP C, 8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]-N-(3-methoxypropyl)pyrido[4,3-d]pyrimidin-4-amine. A mixture of 8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-ol (115mg, 0.23mmol, 1.0 eq), DIEA (151.2mg, 1.17mmol, 5.0eq) and HATU (355.9mg, 0.93mmol, 4.0eq) in DMA (10mL) was stirred at room temperature for 30 mins. Then 3-methoxypropan-1-amine (20.9mg, 0.2mmol, 1.0eq) was added to the mixture at 0°C and slowly warmed to room temperature under N_2 overnight. The mixture was diluted with water (50mL) and extracted with DCM (20mL x3). The combined organic layers were washed with water (100mL x2), brine (100mL), dried over Na_2SO_4, filtered and concentrated under vacuum to give the crude which was purified by silica gel column (DCM/MeOH, 30:1) to give

8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]-N-(3-methoxypropyl)pyrido[4,3-d]pyrimidin-4-amine (47mg, 36% yield).

LC-MS (ES^+, Method 4): 2.21min, 562.4 $[M+H]^+$.

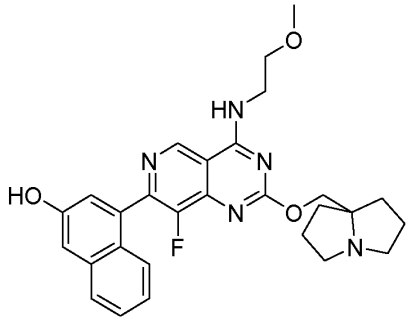
STEP D, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(3-methoxypropylamino)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol. A solution of 8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-[3-(methoxymethoxy)-1-naphthyl]-N-(3-methoxypropyl)pyrido[4,3-d]pyrimidin-4-amine (47 mg, 0.084mmol, 1.0eq) in 4N HCl in dioxane (2mL) was stirred at room temperature for 1hr. The mixture was adjusted pH to 8 with aqueous $NaHCO_3$ (30mL) and extracted with DCM (15mL x3). The combined organic layers were washed with brine (50mL), dried over Na_2SO_4, filtered and concentrated to give the crude which was purified by prep-TLC (DCM/MeOH, 10:1) to give 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(3-methoxypropylamino)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol (20mg, 46% yield) as a pale yellow solid.

LC-MS (ES^+, Method 3): 2.66min, 518.35 $[M+H]^+$.

^1H NMR (400MHz, D6-DMSO) δ/ppm: 9.37 (1H, s), 9.01-9.06 (1H, bs), 8.30 (1H, s), 7.70-7.75 (1H, m), 7.19-7.49 (5H, m), 4.13-4.17 (2H, m), 3.60-3.66 (2H, m), 3.44-3.50 (2H, m), 3.27 (s, 3H), 3.00-3.006 (2H, m), 2.59-2.63 (2H, m), 1.45-2.01 (8H, m).

EXAMPLE 12

8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-N-(2-methoxyethyl)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-amine



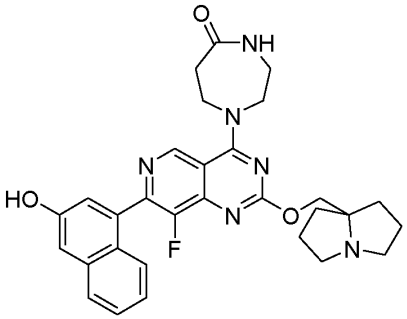
8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-N-(2-methoxyethyl)-7-[3-(methoxymethoxy)-1-naphthyl]pyrido[4,3-d]pyrimidin-4-amine was prepared in an analogous fashion to example 11, replacing 3-methoxypropan-1-amine in step c with 2-methoxyethylamine.

LC-MS (ES^+, Method 4): 0.96min, 504.15 $[M+H]^+$.

^{1}H NMR (400MHz, D6-DMSO) δ/ppm: 9.39 (1H, s), 9.10 (1H, d), 8.24 (1H, s), 7.80 (1H, d), 7.44 (2H, q), 7.28 (1H, s), 7.25 – 7.18 (2H, m), 4.11 (2H, s), 3.76 (2H, d), 3.63 (2H, s), 3.54 (3H, s), 2.96 (2H, s), 2.63 – 2.56 (2H, m), 1.92-2.01 (2H, m), 1.80 (4H, m), 1.61 (2H, d).

EXAMPLE 13

4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]-1,4-diazepan-5-one

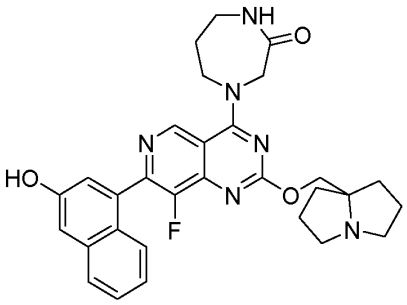


4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]-1,4-diazepan-5-one was prepared in an analogous fashion to example 11, replacing 3-methoxypropan-1-amine in step C with 1,4-diazepan-5-one.

LC-MS (ES$^+$, Method 4): 0.57min, 543.2 [M+H]$^+$.

EXAMPLE 14

4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]-1,4-diazepan-2-one



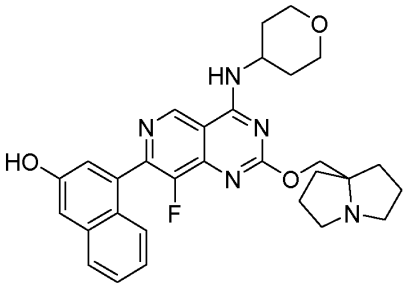
4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]-1,4-diazepan-2-one was prepared in an analogous fashion to example 11, replacing 3-methoxypropan-1-amine in step C with 1,4-diazepan-2-one

LC-MS (ES^+, Method 4): 0.72min, 543.2 $[M+H]^+$.

^1H NMR (400MHz, D6-DMSO) δ/ppm:10.01-10.04 (1H, bs), 9.47 (1H, s), 7.80-7.91 (2H, m), 7.44-7.55 (2H, m), 7.30-7/50 (3H, m), 4.55 (2H, s), 4.41 (2H, s), 4.21 (2H, s), 2.95-3.26 (6H, m), 1.55-2.12 (10H, m).

EXAMPLE 15

4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(tetrahydropyran-4-ylamino)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



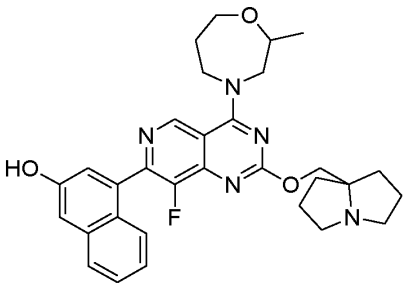
4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(tetrahydropyran-4-ylamino)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol was prepared in an analogous fashion to example 11, replacing 3-methoxypropan-1-amine in step C with 4-aminotetrahydropyran.

LC-MS (ES^+, Method 3): 3.24min, 530.3 $[M+H]^+$.

^1H NMR (400MHz, D6-DMSO) δ/ppm: 9.45 (s, 1H), 8.72 (d, J = 7.6 Hz, 1H), 8.23 (s, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.44 (q, J = 8.1, 7.6 Hz, 2H), 7.35 – 7.10 (m, 3H), 4.50 – 4.40 (m, 1H), 4.21 (s, 2H), 3.96 (d, J = 9.1 Hz, 2H), 3.47 (s, 2H), 3.07 (dt, J = 10.9, 5.8 Hz, 2H), 2.69 (dt, J = 10.3, 6.6 Hz, 2H), 1.90 (dtd, J = 40.8, 14.4, 13.3, 6.4 Hz, 8H), 1.69 (tt, J = 14.4, 5.6 Hz, 4H).

EXAMPLE 16

4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(2-methyl-1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



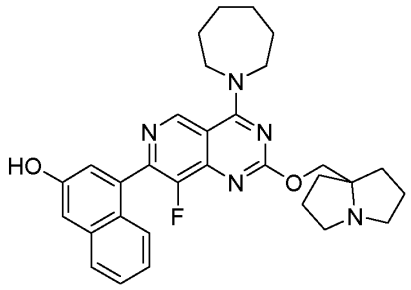
4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(2-methyl-1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol was prepared in an analogous fashion to example 11, replacing 3-methoxypropan-1-amine in step C with 2-methyl-1,4-oxazepane.

LC-MS (ES^+, Method 3): 0.75min, 544.3 $[M+H]^+$.

^1H NMR (400MHz, D6-DMSO) δ/ppm: 9.17 (1H, s), 7.74-7.76 (1H, d), 7.39-7.48 (2H, m). 7.15-7.27 (3H, m), 4.30-4.35 (1H, d), 4.15-4.25 (4H, m), 3.79-3.83 (2H, m), 3.35-3.50 (2H, m), 3.10.3.19 (2H, m), 2.70-2.81 (2H, m), 1.15-2.15 (8H, m), 1.19-1.23 (3H, m).

EXAMPLE 17

4-[4-(azepan-1-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



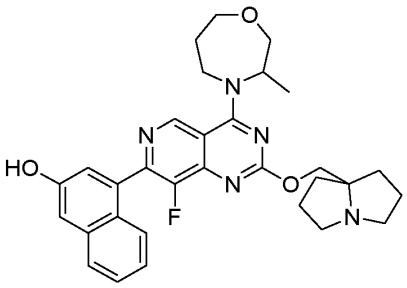
4-[4-(azepan-1-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol was prepared in an analogous fashion to example 11, replacing 3-methoxypropan-1-amine in step C with azepane.

LC-MS (ES^+, Method 4): 1.11min, 528.2 $[M+H]^+$.

^1H NMR (400MHz, D6-DMSO) δ/ppm: 9.29 (s, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.31 – 7.22 (m, 3H), 4.58 (s, 2H), 4.06 (t, J = 5.6 Hz, 4H), 3.51 (dt, J = 12.9, 6.4 Hz, 2H), 3.23 (dt, J = 11.9, 6.2 Hz, 2H), 2.14 (ddd, J = 22.4, 12.3, 6.2 Hz, 4H), 1.99 (dq, J = 22.6, 5.4, 4.8 Hz, 8H), 1.61 (q, J = 3.4, 2.9 Hz, 4H).

EXAMPLE 18

4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(3-methyl-1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



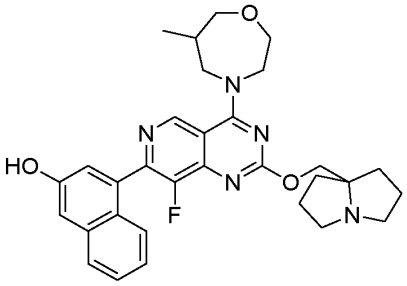
4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(3-methyl-1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol was prepared in an analogous fashion to example 11, replacing 3-methoxypropan-1-amine in step C with 3-methyl-1,4-oxazepane.

LC-MS (ES^+, Method 3): 3.34min, 544.2 $[M+H]^+$.

^1H NMR (400MHz, D6-DMSO) δ/ppm: 9.13 (s, 1H), 8.23 (s, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.33 – 7.18 (m, 3H), 4.85 (q, J = 7.0 Hz, 1H), 4.42 – 4.35 (m, 1H), 4.21 (s, 2H), 4.10 (dd, J = 13.5, 5.4 Hz, 1H), 3.97 (dd, J = 12.2, 5.3 Hz, 1H), 3.85 – 3.75 (m, 1H), 3.60 (dd, J = 13.3, 9.9 Hz, 2H), 3.07 (dt, J = 11.1, 5.9 Hz, 2H), 2.69 (dt, J = 10.2, 6.6 Hz, 2H), 2.26 – 2.12 (m, 1H), 1.90 (dtt, J = 46.0, 13.6, 6.2 Hz, 7H), 1.68 (dd, J = 12.2, 7.2 Hz, 2H), 1.30 (d, J = 6.3 Hz, 3H).

EXAMPLE 19

4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(6-methyl-1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(6-methyl-1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol was prepared in an analogous fashion to example 11, replacing 3-methoxypropan-1-amine in step C with 6-methyl-1,4-oxazepane.

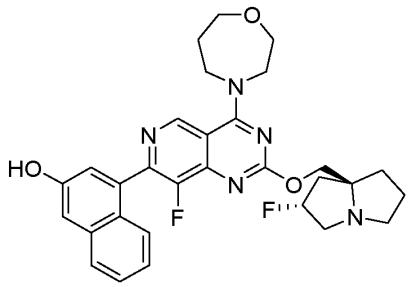
LC-MS (ES^+, Method 4): 0.89min, 544.2 $[M+H]^+$.

^1H NMR (400MHz, D6-DMSO) δ/ppm: 9.23 (s, 1H), 8.22 (s, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.27 – 7.21 (m,

2H), 4.35 (dd, J = 13.9, 3.3 Hz, 1H), 4.29 – 4.23 (m, 1H), 4.19 (s, 2H), 4.06 (td, J = 10.0, 4.2 Hz, 2H), 3.92 (q, J = 5.2 Hz, 1H), 3.81 (d, J = 8.0 Hz, 1H), 3.63 (d, J = 3.9 Hz, 1H), 3.34 (d, J = 3.1 Hz, 1H), 3.04 (dt, J = 10.9, 5.8 Hz, 2H), 2.66 (dt, J = 10.0, 6.6 Hz, 2H), 2.35 – 2.28 (m, 1H), 1.94 (ddd, J = 15.3, 6.3, 2.9 Hz, 2H), 1.83 (ddq, J = 19.5, 12.7, 6.2 Hz, 4H), 1.65 (dt, J = 11.8, 7.2 Hz, 2H), 0.93 (d, J = 6.9 Hz, 3H).

EXAMPLE 20

4-[8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol

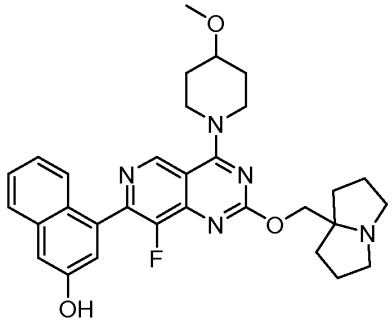


4-[8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol was prepared in an analogous fashion to example 11, from intermediate 26 replacing 3-methoxypropan-1-amine in step C with 1,4-oxazepane.

LC-MS (ES^+, Method 4): 1.26min, 548.3 $[M+H]^+$.

^1H NMR (400MHz, D6-DMSO) δ/ppm: 9.70-10.19 (1H, bs), 9.24 (1H, s), 7.77-7.81 (1H, d), 7.22-7.55 (4H, m), 5.15-5.31 (1H, d), 4.07-4.20 (6H, m), 3.90-3.96 (2H, m), 3.70-3.79 (2H, m), 3.05-3.11 (3H, m), 2.82-2.86 (1H, m), 1.76-2.19 (8H, m).

EXAMPLE 21



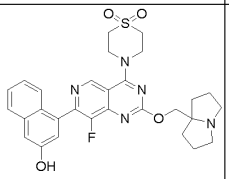
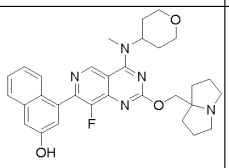
4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(4-methoxy-1-piperidyl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol

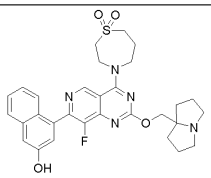
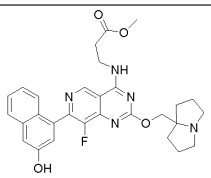
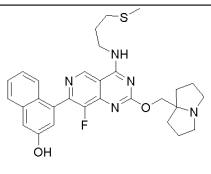
4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(4-methoxy-1-piperidyl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol was prepared in an analogous fashion to example 11, replacing 3-methoxypropan-1-amine in step C with 4-methoxypiperidine.

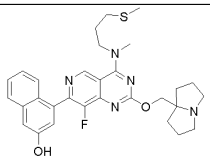
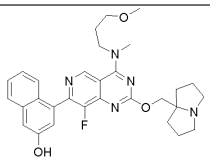
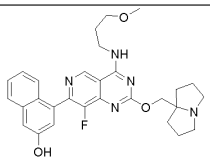
LC-MS (ES^+, Method 4): 1.11min, 544.15 $[M+H]^+$.

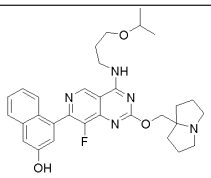
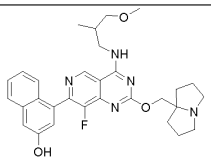
^1H NMR (400MHz, D6-DMSO) δ/ppm: 10.01 (s, 1H), 9.20 (s, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.45 (m, 1H), 7.30 – 7.22 (m, 3H), 4.43 (s, 2H), 4.21 (m, 2H), 3.80 (m, 2H), 3.60 (m, 1H), 3.50 (s, 2H), 3.03 (s, 2H), 2.11 – 1.99 (m, 6H), 1.97 – 1.84 (m, 4H), 1.71 (m, 2H).

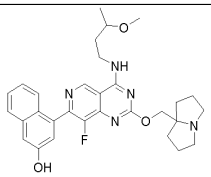
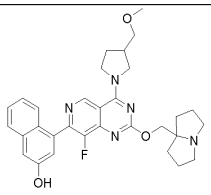
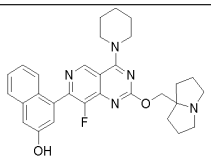
Further examples (Table 3) were prepared in an analogous fashion to example 11, from intermediate 26 replacing 3-methoxypropan-1-amine in step C with the appropriate building block or directly from intermediate 27 under the same conditions without the requirement for acidic deprotection step D.

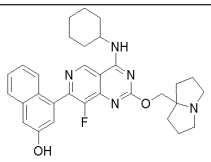
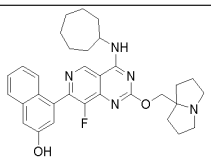
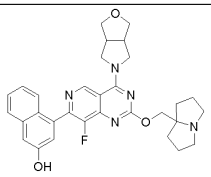
Building block	Example	Structure	^{1}HNMR	LC-MS
1lambda6-thiomorpholine-1,1-dione	**22** 4-[4-(1,1-dioxo-1,4-thiazinan-4-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d6) δ/ppm 9.22 (s, 1H), 8.19 (s, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.31 – 7.22 (m, 3H), 4.38 – 4.30 (m, 4H), 4.17 (s, 2H), 3.48 – 3.47 (m, 4H), 3.04 – 2.99 (m, 2H), 2.66 – 2.60 (m, 2H), 1.94 (dt, J = 12.1, 6.1 Hz, 2H), 1.82 (m, 4H), 1.64 (m, Hz, 2H)	ES^+, (Method 4): 0.83min, 564.10 $[M+H]^+$
N-methyloxan-4-amine	**23** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-[methyl(tetrahydropyran-4-yl)amino]pyrido[4,3-		(400 MHz, DMSO-d_6) δ/ppm 9.28 (s, 1H), 8.23 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.49 – 7.39 (m, 1H), 7.32 – 7.20 (m, 3H), 4.85 (m, 1H), 4.22 (s, 2H), 4.00 (dd, *J* = 11.2, 4.3 Hz, 2H), 3.52 – 3.45	ES^+, (Method 4): 1.73min, 544.2 $[M+H]^+$

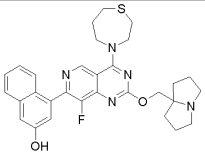
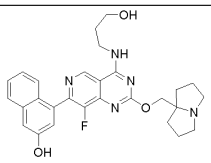
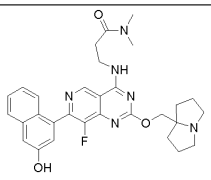
	d]pyrimidin-7-yl]naphthalen-2-ol		(m, 2H), 3.39 (s, 3H), 3.07 (dt, *J* = 11.1, 5.9 Hz, 2H), 2.69 (dt, *J* = 10.2, 6.6 Hz, 2H), 1.90 (m, 10H), 1.67 (dt, *J* = 12.0, 7.2 Hz, 2H)	
1lambda6,4-thiazepane-1,1-dione	**24** 4-[4-(1,1-dioxo-1,4-thiazepan-4-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d6) δ/ppm 9.25 (s, 1H), 8.23 (s, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.32 – 7.20 (m, 3H), 4.25 (m, 4H), 4.20 (s, 2H), 3.71 (t, J = 5.2 Hz, 2H), 3.38 (t, J = 5.6 Hz, 2H), 3.06 (dt, J = 11.0, 5.8 Hz, 2H), 2.68 (dt, J = 10.2, 6.6 Hz, 2H), 2.31 (dd, J = 11.5, 5.8 Hz, 2H), 1.89 (m, 6H), 1.67 (m, 2H)	ES$^+$, (Method 3): 3.16min, 577.7 $[M+H]^+$
3-aminopropanoic acid	**25** methyl 3-[[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]amino]propanoate		(400 MHz, DMSO-d_6) δ/ppm 9.08 (s, 1H), 8.85 (t, *J* = 5.4 Hz, 1H), 7.92 (s, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.15 (q, *J* = 7.8 Hz, 2H), 7.01 – 6.90 (m, 3H), 3.99 (s, 2H), 3.53 (t, *J* = 6.3 Hz, 2H), 3.35 (s, 3H), 2.87 (dt, *J* = 11.5, 6.1 Hz, 2H), 2.52 (m, 2H), 2.21 (m, 2H), 1.71 m, 2H), 1.60 (m, 4H), 1.44 (m, 2H)	ES$^+$, (Method 4): 1.7min, 532.2 $[M+H]^+$
3-(methylsulfanyl)propan-1-amine	**26** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-		(400 MHz, DMSO-d_6) δ/ppm 9.37 (s, 1H), 9.02 (t, *J* = 5.6 Hz, 1H), 8.24 (s, 1H), 7.79 (d, *J* = 8.2	ES$^+$, (Method 4): 0.97min

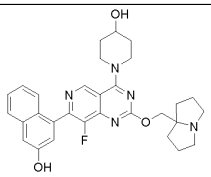
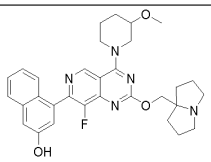
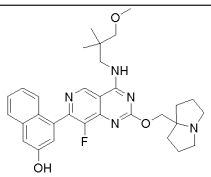
	8-ylmethoxy)-4-(3-methylsulfanylpropylamino)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		Hz, 1H), 7.44 (q, *J* = 7.8 Hz, 2H), 7.29 – 7.18 (m, 3H), 4.16 (s, 2H), 3.67 (m, 2H), 3.01 (m, 2H), 2.62 (m, 4H), 2.09 (s, 3H), 1.94 (m, 4H), 1.81 (m, 4H), 1.63 (m, 2H)	, 534.1 $[M+H]^+$
methyl[3-(methylsulfanyl)propyl]amine	**27** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-[methyl(3-methylsulfanylpropyl)amino]pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d6) δ/ppm 9.34 (s, 1H), 8.23 (s, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.30 – 7.21 (m, 3H), 4.23 (s, 2H), 3.93 (m, 2H), 3.57 (s, 3H), 3.10 (m, 2H), 2.73 (m, 2H), 2.59 (t, J = 7.1 Hz, 2H), 2.10 (s, 3H), 2.04 (t, J = 7.3 Hz, 2H), 1.96 (m, 2H), 1.85 (m, 4H), 1.69 (m, 2H).	ES^+, (Method 4): 1.03min , 548.2 $[M+H]^+$
(3-methoxypropyl)(methyl)amine	**28** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-[3-methoxypropyl(methyl)amino]pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		400 MHz, DMSO-d6) δ/ppm 9.37 (m, 1H), 9.01 (m, 1H), 8.30 (m, 1H), 7.79 (m, 1H), 7.45 (m, 2H), 7.20 (m, 3H), 4.19 (m, 2H), 3.60 (m, 2H), 3.46 (m, 2H), 3.27 (s, 3H), 3.01 (m, 2H), 2.59 (m, 2H), 1.60-1.95 (m, 10H).	ES^+, (Method 3): 3.4min, 532.2 $[M+H]^+$
3-methoxypropylamine	**29** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(3-methoxypropylamino)pyrido[4,3-		400 MHz, DMSO-d6) δ/ppm 9.37 (m, 1H), 9.01 (m, 1H), 8.30 (m, 1H), 7.79 (m, 1H), 7.45 (m, 2H), 7.20 (m, 3H), 4.19 (m, 2H), 3.92 (m, 2H) 3.66 (s, 3H), 3.54 (m,	ES^+, (Method 3): 2.7min, 518.4 $[M+H]^+$

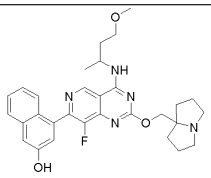
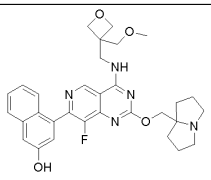
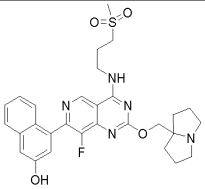
	d]pyrimidin-7-yl]naphthalen-2-ol		2H), 3.46 (s, 3H), 3.11 (m, 2H), 2.67 (m, 2H), 1.65-2.05 (m, 10H).	
3-isopropoxypropylamine	**30** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(3-isopropoxypropylamino)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 9.97 (s, 1H), 9.39 (s, 1H), 9.04 (t, *J* = 6.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.29 (d, *J* = 2.4 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 4.38 (s, 2H), 3.66 (q, *J* = 4.0 Hz, 2H), 3.58 – 3.54 (m, 1H), 3.50 (t, *J* = 4.0 Hz, 2H), 3.29 – 3.25 (m, 2H), 2.98-2.92 (m, 2H), 2.09 – 1.79 (m, 10H), 1.11 – 1.09 (d, *J* = 8.0 Hz, 6H).	ES^+, (Method 4): 1.1min, 546.2 $[M+H]^+$
3-methoxy-2-methylpropylamine	**31** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-[(3-methoxy-2-methyl-propyl)amino]pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d6) δ/ppm 9.40 (s, 1H), 8.97 (s, 1H), 8.23 (s, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.44 (q, J = 7.6 Hz, 2H), 7.29 – 7.19 (m, 3H), 4.15 (s, 2H), 3.62 (m, 2H), 3.28 (s, 3H), 3.02 – 2.98 (m, 2H), 2.65 (m, 2H), 2.60 (m, 2H), 2.23 (m, 1H), 1.89-1.95 (m, 2H), 1.74-1.85(m, 4H), 1.58-1.65 (m, 2H), 0.97 (d, J = 6.8 Hz, 3H).	ES^+, (Method 4): 1.1min, 532.2 $[M+H]^+$

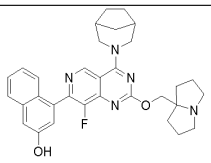
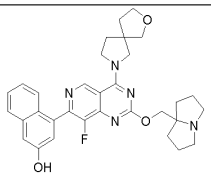
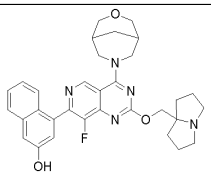
3-methoxy-3-methylpropylamine	**32** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(3-methoxybutylamino)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 10.19 (s, 1H), 9.42 (s, 1H), 9.13 (m, 1H), 7.81 (m, 1H), 7.46 – 7.42 (m, 2H), 7.30 (m, 1H), 7.24 (m, 1H), 7.20 (m, 1H), 4.59 (s, 2H), 3.66 (m, 2H), 3.54 – 3.52 (m, 1H), 3.50 – 3.44 (m, 2H), 3.27 (s, 3H), 3.26 – 3.19 (m, 2H), 2.21 – 2.07 (m, 4H), 2.04 – 1.95 (m, 4H), 1.84 (m, 2H), 1.17 (m, 3H).	ES^+, (Method 4): 1.0min, 532.2 $[M+H]^+$
3-(methoxymethyl)pyrrolidine	**33** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-[3-(methoxymethyl)pyrrolidin-1-yl]pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		400 MHz, DMSO-d_6) δ/ppm 10.20 (s, 1H), 9.41 (s, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.31 – 7.22 (m, 3H), 4.58 (s, 2H), 4.18 – 3.98 (m, 4H), 3.56 – 3.49 (m, 2H), 3.45 – 3.44 (m, 2H), 3.31 (s, 3H), 3.26 – 3.21 (m, 2H), 2.66 (s, 1H), 2.21 – 1.97 (m, 10H).	ES^+, (Method 4): 1.0min, 544.2 $[M+H]^+$
piperidine	**34** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1-piperidyl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 9.12 (s, 1H), 8.22 (s, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.30 – 7.22 (m, 3H), 4.16 (s, 2H), 3.95 (s, 4H), 3.01-3.07 (m, 2H), 2.63-2.69 (m, 2H), 1.98 – 1.92 (m, 2H), 1.79-1.83	ES^+, (Method 3): 2.8min, 513.6 $[M+H]^+$

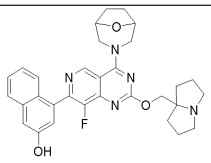
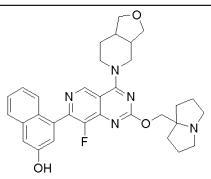
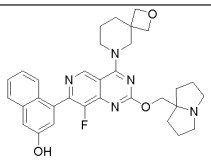
			(m,4H), 1.75 (s, 6H), 1.68 – 1.61 (m, 2H).	
cyclohexylamine	**35** 4-[4-(cyclohexylamino)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 10.23 (s, 1H) 9.51 (s, 1H), 8.81 (m, 1H), 7.80 (m, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.44 - 7.22 (m, 5H), 4.61 (s, 2H), 4.25 (m, 1H) 3.52 (m, 2H), 3.24 (m, 2H), 2.47-1.31 (m, 14H),.	ES^+, (Method 4): 1.2min, 528.2 $[M+H]^+$
cycoheptylamine	**36** 4-[4-(cycloheptylamino)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 9.45 (s, 1H), 8.66 (d, *J* = 7.7 Hz, 1H), 8.20 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 6.4 Hz, 2H), 7.29 – 7.18 (m, 3H), 4.38 (m, 1H), 4.13 (s, 2H), 2.99 – 2.96 (m, 2H), 2.59 (m, 2H), 2.02 – 1.97 (m, 2H), 1.89-1.95 (m, 2H), 1.76 (m, 8H), 1.63 – 1.49 (m, 8H).	ES^+, (Method 4): 1.2min, 542.2 $[M+H]^+$
hexahydro-1H-furo[3,4-c]pyrrole	**37** 4-[4-(1,3,3a,4,6,6a-hexahydrofuro[3,4-c]pyrrol-5-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d6) δ/ppm 9.40 (s, 1H), 8.26 (s, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.32 – 7.24 (m, 3H), 4.34 – 4.26 (m, 2H), 4.23 (s, 2H), 4.00 (d, J = 12.7 Hz, 2H), 3.89 – 3.85 (m, 2H), 3.77 (d, J = 6.2 Hz, 2H), 3.16 (s, 2H), 3.13 – 3.07 (m, 2H), 2.75 – 2.69 (m, 2H), 2.02 – 1.96 (m, 2H), 1.93 – 1.79	ES^+, (Method 3): 2.6min, 542.2 $[M+H]^+$

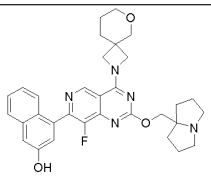
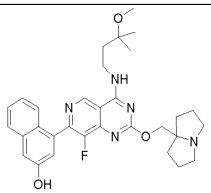
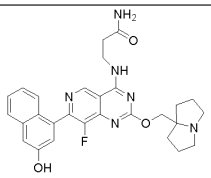
			(m, 4H), 1.73 – 1.66 (m, 2H).	
1,4-thiazepane	**38** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-thiazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d6) δ/ppm 10.17 (s, 1H), 9.99 (s, 1H), 9.29 (s, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.30 – 7.23 (m, 3H), 4.58 (s, 2H), 4.32 (s, 2H), 4.19 (s, 2H), 3.54 – 3.48 (m, 2H), 3.23 (m, 2H), 3.15 (t, J = 5.8 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 2.22 (s, 2H), 2.17 (m, 2H), 1.97-2.03 (m, 2H), 2.01 (s, 4H).	ES^+, (Method 4): 1.0min, 546.1 $[M+H]^+$
3-hydroxyprop-1-ylamine	**39** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(3-hydroxypropylamino)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d6) δ/ppm 9.37 (s, 1H), 8.97 (m, 1H), 8.22 (s, 1H), 7.81 (m, 1H), 7.47-7.41 (m, 2H), 7.19-7.28 (m, 3H), 4.12 (s, 2H), 3.5303.66 (m, 4H), 2.98 (m, 2H), 2.61 (m, 2H), 1.57-2.01 (m, 10H).	ES^+, (Method 4): 0.82min, 504.2 $[M+H]^+$
3-amino-N,N-dimethylpropanamide	**40** 3-[[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]amino]-N,N-dimethyl-propanamide		(400 MHz, DMSO-d_6) δ/ppm 9.35 (d, *J* = 3.8 Hz, 1H), 9.04 (t, *J* = 5.5 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.29 – 7.18 (m, 3H), 4.14 (s, 2H), 3.78 (m, 2H), 3.00 (s, 6H), 2.85 (s, 3H), 2.76 (m, 2H), 2.65 – 2.60 (m, 2H), 1.95 – 1.90 (m, 2H), 1.84 – 1.78 (m, 4H), 1.64 – 1.61 (m, 2H).	ES^+, (Method 4): 0.90min, 545.2 $[M+H]^+$

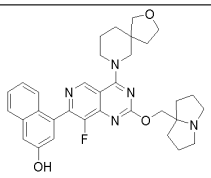
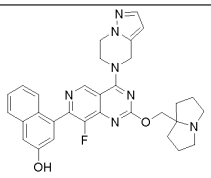
4-hydroxypiperidine	**41** 1-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]piperidin-4-ol		(400 MHz, DMSO-d_6) δ/ppm 9.15 (s, 1H), 7.81 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.32 – 7.19 (m, 3H), 4.28 – 4.23 (m, 2H), 4.20 (s, 2H), 3.91 – 3.88 (m, 1H), 3.75 – 3.69 (m, 2H), 3.12 – 3.06 (m, 2H), 2.74 – 2.69 (m, 2H), 2.00 – 1.94 (m, 4H), 1.88 – 1.81 (m, 4H), 1.72 – 1.56 (m, 4H).	ES$^+$, (Method 4): 0.83min, 530.1 $[M+H]^+$
3-methoxypiperidine	**42** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(3-methoxy-1-piperidyl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 9.21 (s, 1H), 8.21 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 21.8 Hz, 3H), 4.16 (s, 2H), 4.10 (d, *J* = 13.6 Hz, 1H), 3.93 (t, *J* = 6.44 Hz, 2H), 3.85 (t, *J* = 12.8 Hz, 2H), 3.29 (s, 3H), 3.04 – 3.00 (m, 2H), 2.64 (t, *J* = 9.2 Hz, 2H), 2.01 – 1.90 (m, 4H), 1.86 – 1.76 (m, 4H), 1.61-1.67 (m, 4H).	ES$^+$, (Method 4): 1.0min, 544.2 $[M+H]^+$
2,2-dimethyl-3-methoxy-prop-1-ylamine	**43** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-[(3-methoxy-2,2-dimethyl-propyl)amino]pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 9.46 (s, 1H), 8.75 (t, *J* = 6.2 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.29 – 7.20 (m, 3H), 4.20 (s, 2H), 3.58 (d, *J* = 6.1 Hz, 2H), 3.28 (s, 3H), 3.19 (s, 2H), 3.08 – 3.03 (m, 2H), 2.70 – 2.65 (m, 2H), 1.97 –	ES$^+$, (Method 3): 3.5min, 546.3 $[M+H]^+$

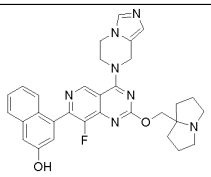
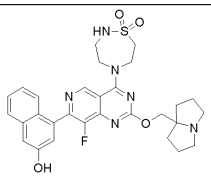
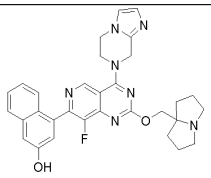
			1.75 (m, 6H), 1.69 – 1.62 (m, 2H), 0.97 (s, 6H)	
1-methyl-3-methoxyprop-1-ylamine	**44** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-[(3-methoxy-1-methyl-propyl)amino]pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 9.97 (s, 1H), 9.47 (s, 1H), 8.77 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.44 (t, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 2.4 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 4.55-4.62 (m, 1H), 4.48 (s, 2H), 3.43 (m, 2H), 3.40 (m, 2H), 3.24 (s, 3H), 3.09 (m, 2H), 2.15 – 2.03 (m, 4H), 1.99 – 1.92 (m, 4H), 1.90 – 1.79 (m, 2H), 1.30 (d, *J* = 6.6 Hz, 3H).	ES^+, (Method 3): 3.5min, 532.1 $[M+H]^+$
[3-(methoxymethyl)oxetan-3-yl]methanamine	**45** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-[[3-(methoxymethyl)oxetan-3-yl]methylamino]pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 9.99 (s, 1H), 9.51 (s, 1H), 9.13-9.16 (m, 1H), 7.81 (m, 1H), 7.20-7.45 (m, 5H), 4.50-4.60 (m, 4H), 4.39 (m, 2H), 3.93 (m, 2H), 3.62 (s, 2H), 3.50-3.57 (m, 2H), 3.41 (s, 3H), 3.21-3.29 (m, 2H), 1.97-2.20 (m, 8H).	ES^+, (Method 4): 0.93min, 560.1 $[M+H]^+$
3-methylsulfonylpropylamine	**46** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(3-methylsulfonylpropylamino)pyrido[4,3-		(400 MHz, DMSO-d_6) δ/ppm 9.37 (s, 1H), 9.08-9.05 (m, 1H), 8.20 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.47-7.42 (m, 2H), 7.29 (s, 1H), 7.25-7.22 m, 1H), 7.19 (s, 1H), 4.19 (s, 2H), 3.73 – 3.70 (m, 4H), 3.08 – 3.04 (m, 2H), 3.01	ES^+, (Method 4): 1.0min, 566.3 $[M+H]^+$

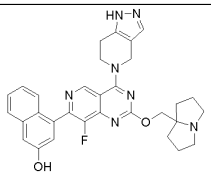
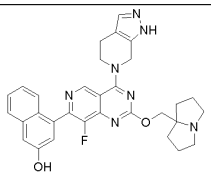
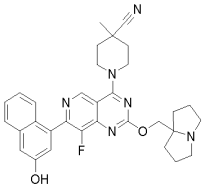
	d]pyrimidin-7-yl]naphthalen-2-ol		(s, 3H), 2.71-2.65 (m, 2H), 2.13 (p, *J* = 7.1 Hz, 2H), 2.03-1.92 (m, 2H), 1.90-1.77(m, 4H), 1.69-1.62(m, 2H).	
3-azabicyclo[3.2.1]octane	**47** 4-[4-(3-azabicyclo[3.2.1]octan-3-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 9.17 (s, 1H), 8.23 (s, 1H), 7.80 (m, 1H), 7.55 (m, 1H), 7.43 (m, 1H), 7.29 (m, 1H), 7.22 – 7.22 (m, 2H), 4.54 (m, 2H), 4.12 (s, 2H),3.57(d, 2H) 3.03 – 2.98 (m, 2H), 2.67 – 2.59 (m, 2H), 2.36 (m, 2H), 1.92 (m, 2H), 1.80 (m, 5H), 1.62 (m, 5H), 1.52 (m, 2H).	ES^+, (Method 4): 1.2min, 540.2 $[M+H]^+$
2-oxa-7-azaspiro[4.4]nonane	**48** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(2-oxa-7-azaspiro[4.4]nonan-7-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 9.99 (s, 1H), 9.42 (s, 1H), 7.81 (m, 1H), 7.51 (m, 1H), 7.45 (m, 1H), 7.31 – 7.22 (m, 3H), 4.56 (s, 2H), 4.15 (s, 3H), 3.85 (m, 3H), 3.71 (m, 1H), 3.64 (m, 1H), 3.52-3.46 (m, 2H), 3.23-3.17 (m, 2H), 2.20 – 1.94 (m, 12H).	ES^+, (Method 4): 1.2min, 556.3 $[M+H]^+$
3-oxa-7-azabicyclo[3.3.1]nonane	**49** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(3-oxa-7-azabicyclo[3.3.1]nonan-7-yl)pyrido[4,3-		(400 MHz, DMSO-d_6) δ/ppm 10.02 (s, 1H), 9.22 (s, 1H), 7.80 (m, 1H), 7.56 (m, 1H), 7.44 m, 1H), 7.30 – 7.21 (m, 3H), 4.90 (m, 2H), 4.10 (s, 2H), 3.91 (m, 2H), 3.79 (m, 2H), 3.63 (m, 2H), 3.00 – 2.94 (m, 2H), 2.61 – 2.56 (m, 2H) , 2.02 –	ES^+, (Method 3): 2.6min, 556.3 $[M+H]^+$

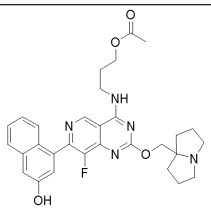
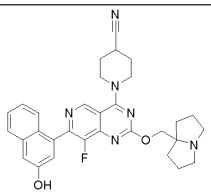
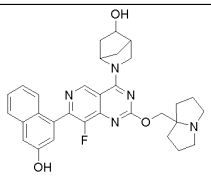
	d]pyrimidin-7-yl]naphthalen-2-ol		1.99 (m, 2H), 1.93 – 1.88 (m, 4H), 1.83 – 1.71 (m, 4H), 1.63 – 1.56 (m, 2H).	
8-oxa-3-azabicyclo[3.2.1]octane	**50** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 10.00 (s, 1H), 9.24 (s, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 2.5 Hz, 1H), 7.27 – 7.20 (m, 2H), 4.50 (m, 6H), 3.75 (m, 2H), 3.49 – 3.45 (m, 2H), 3.20 – 3.14 (m, 2H), 2.15 (m, 2H), 2.08 (m, 2H), 1.98 (m, 4H), 1.86 – 1.74 (m, 4H).	ES^+, (Method 4): 0.97min, 542.2 $[M+H]^+$
octahydrofuro[3,4-c]pyridine	**51** 4-[4-(3,3a,4,6,7,7a-hexahydro-1H-furo[3,4-c]pyridin-5-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 10.01 (s, 1H), 9.28 (m, 1H), 7.22-7.83 (m, 6H), 4.40 (m, 2H), 4.26 (m, 2H), 4.09 (m, 1H), 3.78-3.89 (m, 4H), 3.53-3.63 (m, 2H), 2.98-.3.11 (m, 2H), 2.67 (m, 1H), 1.73-2.67 (m, 11H).	ES^+, (Method 3): 2.6min, 556.3 $[M+H]^+$
2-oxa-8-azaspiro[3.5]nonane	**52** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(2-oxa-8-azaspiro[3.5]nonan-8-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 10.00 (s, 1H), 9.22 (s, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.31 – 7.24 (m, 3H), 4.59 (s, 2H), 4.35 (s, 4H), 4.24 (s, 2H), 3.94 – 3.91 (m, 2H), 3.52 – 3.50 (m, 2H), 3.24 – 3.21 (m, 2H),	ES^+, (Method 3): 3.4min, 556.2 $[M+H]^+$

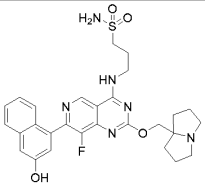
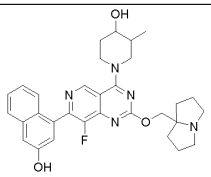
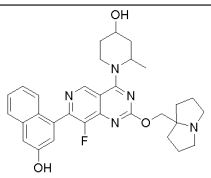
			2.20 – 1.98 (m, 10H), 1.75 (s, 2H).	
6-oxa-2-azaspiro[3.5]nonane	**53** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(6-oxa-2-azaspiro[3.5]nonan-2-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 9.99 (s, 1H), 9.11 (s, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.49 (q, *J* = 3.7 Hz 2H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 4.61 (s, 2H), 4.56 (s, 2H), 4.12 – 3.98 (m, 2H), 3.71 (m, 2H), 3.56 (s, 2H), 3.52-3.46 (m, 2H), 3.23-3.17 (m, 2H), 2.15 (m, 2H), 2.09 (m, 2H), 2.03 – 1.95 (m, 4H), 1.93-1.88 (m, 2H), 1.59 (s, 2H).	ES^+, (Method 3): 2.7min, 556.3 $[M+H]^+$
3-methoxy-3-methyl-butan-1-amine	**54** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-[(3-methoxy-3-methyl-butyl)amino]pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 10.01 (s, 1H), 9.41 (s, 1H), 9.21 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 2.4 Hz, 1H), 7.24 (m, 1H), 7.21 (m, 1H), 4.54 (s, 2H), 3.64-3.59 (m, 2H), 3.44 (s, 2H), 3.19 (s, 3H), 2.09 (m, 4H), 2.02 – 1.97 (m, 4H), 1.95 – 1.85 (m, 4H), 1.24 (s, 6H).	ES^+, (Method 3): 2.7min, 546.3 $[M+H]^+$
3-aminopropanamide	**55** 3-[[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-		400 MHz, DMSO-d6) δ/ppm 10.46 (s, 1H), 10.02 (d, J = 1.8 Hz, 1H), 9.47 (s, 1H), 9.31 (d, J = 5.5 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.49 – 7.40 (m, 3H), 7.34 – 7.16 (m,	ES^+, (Method 3): 3.1min, 517.2 $[M+H]^+$

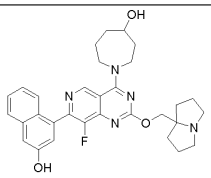
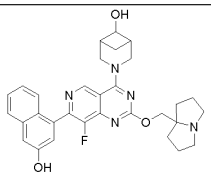
	d]pyrimidin-4-yl]amino]propanamide		4H), 6.92 (s, 1H), 4.60 (s, 2H), 3.79 (m, 2H), 3.52 (m, 2H), 3.21 m, 2H), 2.56 (m, 2H), 2.20 – 2.06 (m, 4H), 2.05 – 1.97 (m, 4H).	
2-oxa-9-azaspiro[4.5]decane	**56** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(2-oxa-9-azaspiro[4.5]decan-9-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 9.16 (s, 1H), 8.21 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.30 – 7.21 (m, 3H), 4.11 (m 2H), 3.86 (m, 2H), 3.82 (m, 2H), 3.74 (m, 2H), 4.05-3.99 (s, 1H), 3.38 (s, 1H), 2.99-2.94 (m, 2H), 2.61 – 2.55 (m, 2H), 1.92 – 1.58 (m, 14H).	ES^+, (Method 4): 0.97min, 570.2 $[M+H]^+$
4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine	**57** 4-[4-(6,7-dihydro-4H-pyrazolo[1,5-a]pyrazin-5-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 10.16 (s, 1H), 9.38 (s, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.50 (d, *J* = 1.8 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.28 – 7. 24 (m, 2H), 6.25 (d, *J* = 1.9 Hz, 1H), 5.29 (s, 2H), 4.63 (s, 2H), 4.48 (s, 4H), 3.55-3.49 (m, 2H), 3.27-3.22 (m, 2H), 2.24-2.17 (m, 2H), 2.15-2.07 (m, 2H), 2.06-1.97 (m, 4H).	ES^+, (Method 4): 1.1min, 552.2 $[M-H]^+$

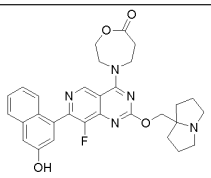
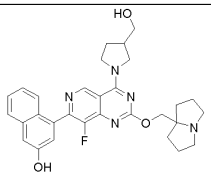
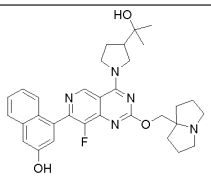
5,6,7,8-Tetrahydroimidazo[1,5-a]pyrazine	**58** 4-[4-(6,8-dihydro-5H-imidazo[1,5-a]pyrazin-7-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		400 MHz, DMSO-d_6) δ/ppm 10.03 (s, 1H), 9.37 (s, 1H), 8.14 (s, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.75 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.32 – 7.24 (m, 3H), 6.90 (s, 1H), 5.21 (s, 2H), 4.59 (s, 2H), 4.40 (m, 4H), 3.50 – 3.45 (m, 2H), 3.20 – 3.16 (m, 2H), 2.21-2.15 (m, 2H), 2.13-2.06 (m, 2H), 2.04-1.96 (m, 4H).	ES^+, (Method 4): 1.2min, 552.2 $[M-H]^+$
1,2,5-thiadiazepane-1,1-dioxide	**59** 4-[4-(1,1-dioxo-1,2,5-thiadiazepan-5-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 10.15 (s, 1H), 9.34 (s, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.32– 7.24 (m, 4H), 4.59 (s, 2H), 4.35-4.32 (m, 4H), 3.72– 3.69 (m, 2H), 3.54 – 3.51 (m, 4H), 3.27 – 3.22 (m, 2H), 2.22-2.08 (m, 4H), 2.05 – 1.97 (m, 4H).	ES^+, (Method 4): 1.0min, 579.3 $[M+H]^+$
5,6,7,8-Tetrahydroimidazo[1,2-a]pyrazine	**60** 4-[4-(6,8-dihydro-5H-imidazo[1,2-a]pyrazin-7-yl)-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 9.33 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.31 – 7.22 (m, 4H), 6.95 (s, 1H), 5.16 (s, 2H), 4.42-4.34 (m, 4H), 4.27 (s, 2H), 3.13-3.06 (m, 2H), 2.76-2.70 m, 2H), 2.00-1.96 (m, 2H), 1.93-1.80 (m, 4H), 1.74-1.67 (m, 2H).	ES^+, (Method 4): 1.3min, 552.3 $[M+H]^+$

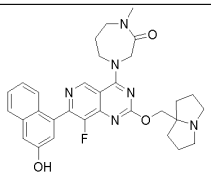
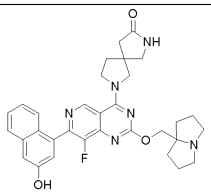
4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine	**61** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4,6,7-tetrahydropyrazolo[4,3-c]pyridin-5-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 12.37 (s, 1H), 10.00 (s, 1H), 9.30 (s, 1H), 7.83-7.80 (d, *J* = 8.2 Hz, 1H), 7.56-7.54 (d, *J* = 9.0 Hz, 2H), 7.47-7.43 (m, *J* = 7.5 Hz, 1H), 7.31-7.30 (d, *J* = 2.4 Hz, 1H), 7.27– 7.23 (m, 2H), 5.06 (s, 2H), 4.58 (s, 2H), 4.25-4.23 (m, *J* = 6.2 Hz, 2H), 3.48 (m, 2H), 3.20-3.16 (m, 2H), 2.54 (s, 2H), 2.19 – 1.99 (m, 8H).	ES$^+$, (Method 4): 0.87min, 552.3 $[M+H]^+$
4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine	**62** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4,5,7-tetrahydropyrazolo[3,4-c]pyridin-6-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d6) δ/ppm 11.99 (s, 1H), 9.98 (s, 1H), 9.25 (s, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.55 (t, J = 3.7 Hz, 2H), 7.44 (t, J = 7.5 Hz, 1H), 7.29 (s, 1H), 7.28 – 7.20 (m, 2H), 4.95 (s, 2H), 4.22 (t, J = 5.4 Hz, 2H), 4.18 (s, 2H), 3.00 (s, 4H), 2.65 (d, J = 13.3 Hz, 2H), 1.99 – 1.90 (m, 2H), 1.88 – 1.77 (m, 4H), 1.69 – 1.59 (m, 2H).	ES$^+$, (Method 4): 0.76min, 552.3 $[M+H]^+$
4-methylpiperidine-4-carbonitrile	**63** 1-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]-4-methyl-piperidine-4-carbonitrile		(400 MHz, DMSO-d_6) δ/ppm 10.14 (s, 1H), 10.00 (s, 1H), 9.26 (s, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.54 (m d, *J* = 8.2 Hz,, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.32 – 7.22 (m, 3H), 4.61 (m,, 4H), 3.60 – 3.48 (m, 4H), 3.25 – 3.19 (m, 2H), 2.17 – 1.97 (m,	ES$^+$, (Method 4): 1.0min, 553.2 $[M+H]^+$

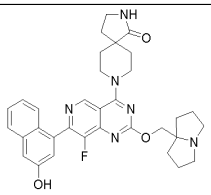
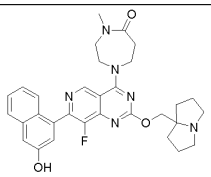
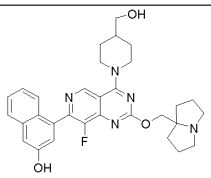
			10H), 1.86 – 1.78 (m, 2H), 1.45 (s, 3H).	
3-aminopropyl acetate	**64** 3-[[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]amino]propyl acetate		400 MHz, DMSO-d_6) δ/ppm 9.37 (s, 1H), 9.06 – 9.03 (m, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.29 – 7.19 (m, 3H), 4.16 – 4.12 (m, 4H), 3.68 – 3.65 (m, 2H), 3.06 – 3.00 (m, 2H), 2.68 – 2.62 (m, 2H), 2.03 (s, 3H), 2.01 – 1.91 (m, 4H), 1.89 – 1.76 (m, 4H), 1.68 – 1.61 (m, 2H).	ES^+, (Method 4): 0.9min, 546.2 $[M+H]^+$
4-Cyanopiperidine	**65** 1-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]piperidine-4-carbonitrile		(400 MHz, DMSO-d_6) δ/ppm 9.17 (s, 1H), 8.23 (s, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.31 – 7.21 (m, 3H), 4.21 – 4.15 (m, 4H), 3.83-3.77 (m, 2H), 3.31 – 3.28 (m, 1H), 3.08 – 3.03 (m, 2H), 2.71 – 2.64 (m, 2H), 2.54 (s, 2H) 2.16 – 2.08 (m, 2H), 2.02-1.92 (m, 4H), 1.90-1.76 (m, 4H), 1.70 – 1.62 (m, 2H).	ES^+, (Method 4): 0.69min , 539.2 $[M+H]^+$
2-azabicyclo[2.2.1]heptan-5-ol	**66** 2-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]-2-		(400 MHz, DMSO-d_6) δ/ppm 9.96 (s, 1H), 9.26 (s, 1H), 7.79-7.81 (m, 1H), 7.19-7.51 (m, 5H), 5.00-5.11 (m, 2H), 3.89-4.09 (m, 4H), 3.39-3.48 (m, 1H), 2.99-3.06 (m, 2H), 2.59-2.66 (m, 3H), 1.53-2.11 (m, 12H).	ES^+, (Method 4): 1.0min, 542.3 $[M+H]^+$

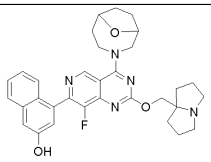
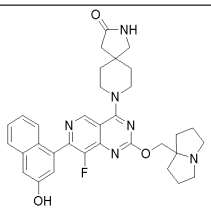
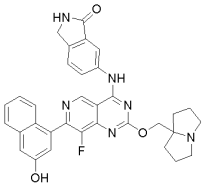
	azabicyclo[2.2.1]heptan-5-ol			
3-aminopropane-1-sulfonamide	**67** 3-[[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]amino]propane-1-sulfonamide		(400 MHz, DMSO-d_6) δ/ppm 9.37 (s, 1H), 9.11 (t, *J* = 5.6 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.30 – 7.15 (m, 3H), 6.84 (s, 2H), 4.20 (s, 2H), 3.72 (d, *J* = 6.2 Hz, 2H), 3.15 – 3.05 (m, 4H), 2.73 – 2.66 (m, 2H), 2.12 (m, 2H), 1.98 – 1.93 (m, 2H), 1.87 – 1.81 (m, 4H), 1.68 – 1.65 (m, 2H).	ES^+, (Method 4): 1.5min, 567.1 $[M+H]^+$
3-methylpiperidin-4-ol	**68** 1-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-4-ol		(400 MHz, DMSO-d_6) δ/ppm 9.14 (s, 1H), 8.20 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.30 – 7.22 (m, 3H), 4.49 (d, *J* = 13.8 Hz, 1H), 4.38 (d, *J* = 12.3 Hz, 1H), 4.18 (s, 2H), 3.37 – 3.35 (m, 2H), 3.15 (q, *J* = 13.3 Hz, 2H), 3.07-3.01 (m, 2H), 2.69 – 2.64 (m, 2H), 2.03-1.74 (m, 8H), 1.68 – 1.63 (m, 2H), 1.62 – 1.53 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 3H).	ES^+, (Method 4): 0.80min, 544.2 $[M+H]^+$
2-methylpiperidin-4-ol	**69** 1-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-		(400 MHz, DMSO-d_6) δ/ppm 9.06 (s, 1H), 8.24 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.31 – 7.20 (m, 3H), 5.08 – 5.00 (m, 1H),	ES^+, (Method 3): 3.2min, 544.3 $[M+H]^+$

	d]pyrimidin-4-yl]-2-methyl-piperidin-4-ol		4.44 (d, *J* = 13.8 Hz, 1H), 4.18 (d, *J* = 3.0 Hz, 2H), 4.02 (td, *J* = 11.6, 6.0 Hz, 2H), 3.53 (t, *J* = 13.3 Hz, 1H), 3.09-303 (m, 2H), 2.71-2.65 (m, 2H), 2.02-1.75 (m, 8H), 1.71 – 1.50 (m, 4H), 1.45 (d, *J* = 7.0 Hz, 3H).	
azepan-4-ol	**70** 1-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]azepan-4-ol		(400 MHz, DMSO-d6) δ/ppm 9.29 (s, 1H),7.99 (s, 1H),7.81 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.28 – 7.21 (m, 2H), 4.58 (s, 2H), 4.13 – 4.00 (m, 3H), 3.99 – 3.88 (m, 1H), 3.88 – 3.78 (m, 1H), 3.59 – 3.41 (m, 2H), 3.28 – 3.14 (m, 2H), 2.72 (d, J = 6.6 Hz, 1H), 2.22 – 2.06 (m, 6H), 2.05 – 1.94 (m, 5H), 1.92 – 1.79 (m,1H), 1.74 (t, J = 11.1 Hz, 1H), 1.67 – 1.55 (m, 1H).	ES^+, (Method 4): 0.90min, 544.3 $[M+H]^+$
3-azabicyclo[3.1.1]heptan-6-ol	**71** 3-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]-3-azabicyclo[3.1.1]heptan-6-ol		(400 MHz, DMSO-d_6) δ/ppm 9.59 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.29 – 7.22 (m, 3H), 4.17 (s, 2H), 4.10 – 4.07 (m, 1H), 3.52 – 3.35 (m, 3H), 3.06 – 3.30 (m, 2H), 2.68 – 2.62 (m, 4H), 1.98 – 1.76 (m, 6H), 1.68 – 1.61 (m, 3H),	ES^+, (Method 3): 3.3min, 542.3 $[M+H]^+$

			1.48 – 1.28 (m, 2H), 0.89 – 0.85 (m, 1H).	
1,4-oxazepan-7-one	**72** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepan-7-one		400 MHz, DMSO-d_6) δ/ppm 9.12 (s, 1H), 8.19 (s, 1H), 7.81-7.79 (d, *J* = 8.3 Hz, 1H), 7.55-7.53 (d, *J* = 8.5 Hz, 1H), 7.46-7.42 (t, *J* = 7.6 Hz, 1H), 7.30 (s, 1H), 7.26-7.24 (m, 2H), 4.60-4.59 (m, 2H), 4.29-4.27 (m, 2H), 4.18 (s, 2H), 4.16-4.13 (m, 2H), 3.21 (m, 2H), 3.04–3.01 (m, 2H), 2.68-2.64 (m, 2H), 1.97-1.91 (m, 2H), 1.87-1.76 (m, 4H), 1.68-1.61 (m, 2H)	ES$^+$, (Method 4): 0.63min, 542.3 $[M+H]^+$
pyrrolidin-3-ylmethanol	**73** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-[3-(hydroxymethyl)pyrrolidin-1-yl]pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 10.28 (s, 1H), 10.00 (s, 1H), 9.42 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.27 – 7.22 (m, 2H), 4.82 (t, *J* = 5.3 Hz, 1H), 4.58 (s, 2H), 4.19 – 3.96 (m, 4H), 3.66 – 3.48 (m, 4H), 3.41 (s, 1H), 3.25 – 3.19 (m, 2H), 2.20 – 1.97 (m, 10H).	ES$^+$, (Method 4): 1.5min, 530.2 $[M+H]^+$
2-pyrrolidin-3-ylpropan-2-ol	**74** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-[3-(1-hydroxy-1-methyl-		(400 MHz, DMSO-d_6) δ/ppm 10.71 (s, 1H), 9.93 (s, 1H), 8.39 – 8.25 (d, *J* = 8 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.94 (t, *J* = 7.5 Hz, 1H), 7.80	ES$^+$, (Method 4): 0.78min, 558.2 $[M+H]^+$

	ethyl)pyrrolidin-1-yl]pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(s, 1H), 7.78 – 7.69 (m, 2H), 5.08 (s, 2H), 4.49-4.31 (m, 7H), 4.03-3.97 (m, 2H), 3.76-3.69 (m, 2H), 2.68-2.62 (m, 2H), 2.62 – 2.55 (m, 2H), 2.54 – 2.43 (m, 5H), 1.70 (d, *J* = 9.5 Hz, 6H).	
1-methyl-1,4-diazepan-2-one	**75** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]-1-methyl-1,4-diazepan-2-one		(400 MHz, DMSO-d_6) δ/ppm 10.29 (s, 1H), 9.47 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.31 – 7.23 (m, 3H), 4.61 (d, *J* = 8.0 Hz, 4H), 4.17 (t, *J* = 6.0 Hz, 2H), 3.44 (d, *J* = 7.9 Hz, 2H), 3.25 – 3.20 (m, 2H), 2.91 (s, 3H), 2.24 – 1.99 (m, 12H).	ES^+, (Method 4): 0.77min, 583.2 $[M+H]^+$
2,7-diazaspiro[4.4]nonan-3-one	**76** 2-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.4]nonan-8-one		(400 MHz, DMSO-d_6) δ/ppm 9.38 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.71 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.32 – 7.23 (m, 3H), 4.17 (s, 2H), 3.39 (d, *J* = 9.9 Hz, 4H), 3.28 (s, 2H), 3.07 – 3.02 (m, 2H), 2.69 – 2.65 (m, 2H), 2.44 (d, *J* = 16.7 Hz, 2H), 2.12 (s, 2H), 1.99 – 1.93 (m, 2H), 1.89-1.77 (m, 4H), 1.69-1.62 (m, 2H).	ES^+, (Method 4): 0.70min, 569.2 $[M+H]^+$

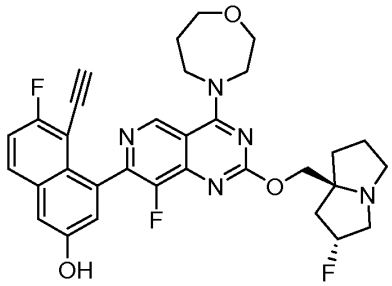
2,8-diazaspiro[4.5]decan-1-one	**77** 8-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decan-1-one		(400 MHz, DMSO-d_6) δ/ppm 10.17 (s, 1H), 9.99 (s, 1H), 9.23 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.69 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.48 – 7.42 (m, 1H), 7.32 – 7.22 (m, 3H), 4.58 (s, 2H), 4.49 (d, *J* = 13.2 Hz, 2H), 3.70 (t, *J* = 12.0 Hz, 2H), 3.53 – 3.49 (m, 2H), 3.24 (t, *J* = 4.68 Hz, 2H), 2.21 – 1.87 (m, 14H), 1.63 (d, *J* = 13.5 Hz, 2H).	ES^+, (Method 4): 0.28min, 583.2 $[M+H]^+$
4-methyl-1,4-diazepan-5-one	**78** 1-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]-4-methyl-1,4-diazepan-5-one		(400 MHz, DMSO-d_6) δ/ppm 10.21 (s, 1H), 9.19 (s, 1H), 7.83 (m, 1H), 7.24-7.55 (m, 5H), 4.60 (s, 2H), 4.10-4.20 (m, 4H), 3.81 (m, 2H), 3.50 (m, 2H), 3.22 (m, 2H), 2.87 (s, 3H), 1.98-2.20 (m, 8H).	ES^+, (Method 4): 0.77min, 557.2 $[M+H]^+$
4-Piperidinemethanol	**79** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-[4-(hydroxymethyl)-1-piperidyl]pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 10.15 (s, 1H), 9.98 (s, 1H), 9.19 (s, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.33 – 7.20 (m, 3H), 4.64 (d, *J* = 13.2 Hz, 2H), 4.57 (s, 2H), 3.54 – 3.48 (m, 2H), 3.46 – 3.41 (m, 2H), 3.25 – 3.21 (m, 2H), 2.14 (m, 4H), 2.00 (m, 5H), 1.90 (m, 3H), 1.39 (m, 3H).	ES^+, (Method 4): 1.0min, 544.4 $[M+H]^+$

9-oxa-3-azabicyclo[4.2.1]nonane	**80** 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(9-oxa-3-azabicyclo[4.2.1]nonan-3-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 9.98 (s, 1H), 9.22 (s, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 2.1 Hz, 1H), 7.26 (d, J = 7.4 Hz, 1H), 7.24 (d, J = 2.1 Hz, 1H), 4.74 (d, J = 13.3 Hz, 1H), 4.58 (t, J = 7.4 Hz, 2H), 4.24 - 4.05 (m, 3H), 3.85 (m, 1H), 3.58 (m, 1H), 2.98 (m, 2H), 2.65 - 2.58 (m, 1H), 2.32 - 2.23 (m, 1H), 2.14 - 1.54 (m, 14H)	ES^+, (Method 2): 1.3min, 556.4 $[M+H]^+$
2,8-diazaspiro[4.5]decan-3-one	**81** 8-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-yl]-2,8-diazaspiro[4.5]decan-3-one		(400 MHz, DMSO-d_6) δ/ppm 9.97 (s, 1H), 9.14 (s, 1H), 7.81-7.79 (d, *J* = 8.3 Hz, 1H), 7.60 (s, 1H), 7.55-7.53 (d, *J* = 8.5 Hz, 1H), 7.46-7.42 (t, *J* = 7.4 Hz, 1H), 7.29 – 7.22 (m, 3H), 4.08 (s, 2H), 4.04 (m, 2H), 3.92-3.85 (m, 2H), 3.17 (s, 2H), 2.94 (m, 2H), 2.54 (m, 2H), 2.21 (s, 2H), 1.93-1.87(m, 2H), 1.83-1.75 (m, 8H), 1.62-1.57 (m, 2H).	ES^+, (Method 4): 0.83min, 583.2 $[M+H]^+$
6-aminoisoindolin-1-one	**82** 6-[[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(3-hydroxy-1-naphthyl)pyrido[4,3-d]pyrimidin-4-		(400 MHz, DMSO-d_6) δ/ppm 10.77 (s, 1H), 10.20 (s, 1H), 10.02 (s, 1H), 9.75 (s, 1H), 8.65 (s, 1H), 8.37 (s, 1H), 7.99-7.95 (m, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.54 – 7.43	ES^+, (Method 3): 2.1min, 583.2 $[M+H]^+$

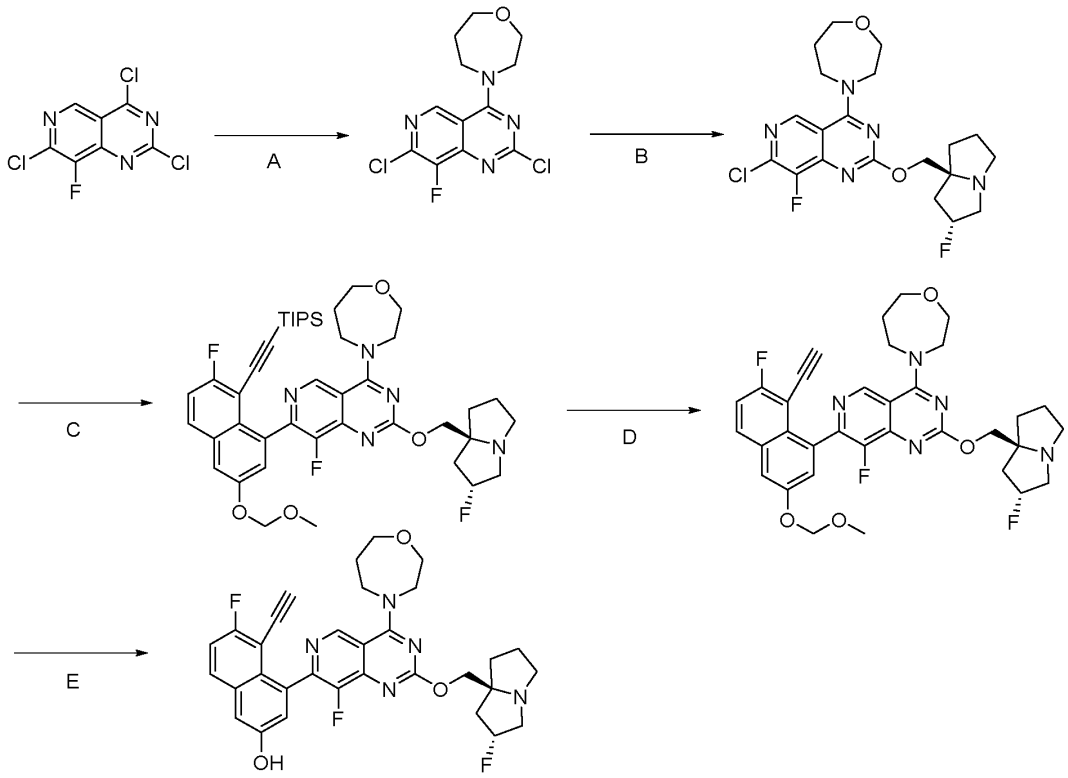
	yl]amino]isoindolin-1-one		(m, 2H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.30 – 7.23 (m, 2H), 4.63 (s, 2H), 4.42 (s, 2H), 3.57 – 3.45 (m, 2H), 3.25 – 3.21 (m, 2H), 2.24 – 2.14 (m, 2H), 2.14 – 2.06 (m, 2H), 2.06 – 1.96 (m, 4H).	

Table 3

EXAMPLE 83



5-ethynyl-6-fluoro-4-[8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



STEP A, 4-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane. At -40°C, 1,4-oxazepane (563 mg, 5.57 mmol) in DCM (2 mL) was added dropwise into a solution of 2,4,7-trichloro-8-fluoro-pyrido[4,3-d]pyrimidine (4.98 g, 4.64 mmol) and DIEA (4.02 g, 31.1 mmol) in DCM (20 mL) and stirred at -40°C for 30 mins. The mixture was added water (15 mL) and washed with brine (10 mL), dried over Na_2SO_4. The organic layer was concentrated and the crude was purified by silica gel column (PE/EA=10/1-2/1, v/v) to afford 4-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane (700 mg, 47%) as a yellow solid.
LC-MS (ES^+, Method 3): 3.78min, 317.1 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ/ppm 9.19 (s, 1H), 3.83-3.88 (m, 2H), 3.44-3.49 (m, 2H), 2.09-2.18 (m, 2H).

STEP B, 4-[7-chloro-8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane. A solution of 4-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane (400 mg, 1.26 mmol), [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (1.6 g, 10.09 mmol), DIEA (1.3 g, 10.09 mmol) in dioxane (20 mL) was stirred at 90°C under an N_2 atmosphere overnight. The mixture was concentrated and purified by silica gel column (DCM to DCM/MeOH=30/1, v/v) to give 4-[7-

chloro-8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (300 mg, 54%) as a colourless oil.
LC-MS (ES^+, Method 3): 2.38min, 440.2 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d_6) δ/ppm 8.91 (1H, s), 5.15-5.35 (d, 1H), 4.01-4.19 (m, 4H), 3.70-3.75 (m, 2H), 3.25-3.31 (m, 2H), 3.01-3.13 (m, 3H), 2.76-2.80 (m, 1H), 1.69-2.07 (m, 8H).

STEP C, 2-[2-fluoro-8-[8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]-6-(methoxymethoxy)-1-naphthyl]ethynyl-triisopropyl-silane.
4-[7-chloro-8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (260 mg, 0.591 mmol, 1.0 eq), 2-[2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]ethynyl-triisopropyl-silane (454 mg, 0.887 mmol), $Pd(dtpbf)Cl_2$ (38 mg, 0.059 mmol) and Cs_2CO_3 (385 mg, 1.18 mmol) in dioxane (12 mL) and water (4 mL) was stirred at 90°C under N_2 protection over night. The mixture was concentrated and purified by silica gel column (DCM/MeOH=50/1, v/v) to give the step C product as a colourless oil (260 mg, 54%).
LC-MS (ES^+, Method 3): 3.38min, 790.3 $[M+H]^+$.

STEP D, 4-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane. A solution of methyl 2-[2-fluoro-8-[8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]-6-(methoxymethoxy)-1-naphthyl]ethynyl-triisopropyl-silane (255 mg, 0.323 mmol,) and CsF (245 mg, 1.61 mmol) in DMF (10 mL) was stirred at r.t. for 1h. The mixture was poured into water (100 mL), extracted with EtOAc (20 mL x 3), washed with brine (60 mL x 3), dried over Na_2SO_4. The organic layer was concentrated to give crude step D product (230mg, 100%) as a yellow oil.

LC-MS (ES^+, Method 3): 2.78min, 634.2 $[M+H]^+$.

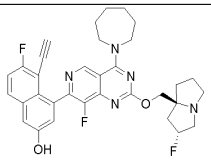
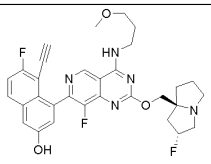
STEP E, 5-ethynyl-6-fluoro-4-[8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol. 4 M HCl-dioxane (10 mL) was added dropwise into a solution of 4-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (209 mg, 0.316 mmol,) in dioxane (5 mL) and stirred at r.t. for 2h. The mixture was concentrated and purified by preparative-HPLC to give 5-ethynyl-6-fluoro-4-[8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-

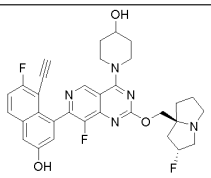
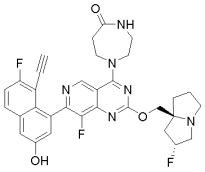
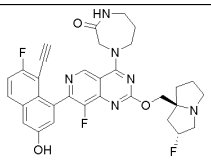
yl]methoxy]-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol (110 mg, 59.1%) as a yellow solid.

LC-MS (ES^+, Method 3): 3.36min, 590.3 $[M+H]^+$.

^1H NMR (400 MHz, DMSO-d6) δ/ppm 10.18 (s, 1H), 9.11 (s, 1H), 7.97 (m, 1H), 7.46 (t, J = 9.0 Hz, 1H), 7.39 (d, J = 2.6 Hz, 1H), 5.33 (d, J = 53.9 Hz, 1H), 4.15 (m, 6H), 3.99 (s, 1H), 3.94 (t, J = 4.7 Hz, 2H), 3.76 (t, J = 5.2 Hz, 2H), 3.22 (m, 2H), 3.15 (s, 1H), 2.91 (m, 1H), 2.12 (m, 5H), 1.85 (m, 3H).

The following examples (Table 4) were prepared using the same synthetic scheme and procedures as described for example 83, replacing 1,4-oxazepane in step A with the building block shown in the corresponding table entry.

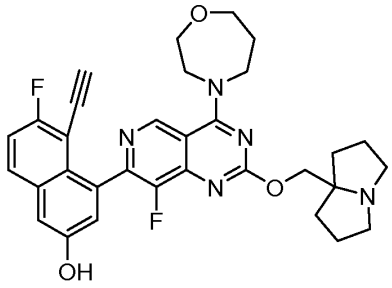
Building block	Example	Structure	^{1}HNMR	LC-MS
azepane	**84** 4-[4-(azepan-1-yl)-8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-7-yl]-5-ethynyl-6-fluoro-naphthalen-2-ol		(400 MHz, DMSO-d_6) δ/ppm 9.08 (s, 1H), 7.99 – 7.95 (m, 1H), 7.46 (t, *J* = 9.0 Hz, 1H), 7.38 (d, *J* = 2.5 Hz, 1H), 7.17 (d, *J* = 2.5 Hz, 1H), 5.29 (d, *J* = 54.2 Hz, 1H), 4.17 - 4.12 (m, 1H), 4.08 – 3.97 (m, 6H), 3.14 – 3.11 (m, 2H), 3.05 (s, 1H), 2.88 – 2.82 (m, 1H), 2.16 – 1.76 (m, 10H), 1.66-1.57 (m, 4H).	ES^+, (Method 3): 3.47min, 588.1 $[M+H]^+$
3-methoxyprop-1-ylamine	**85** 5-ethynyl-6-fluoro-4-[8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-4-(3-methoxypropylamino)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol		(400 MHz, DMSO-d6) δ/ppm 9.25 (s, 1H), 8.92 (t, J = 5.4 Hz, 1H), 8.14 (s, 1H), 7.97 (t, J = 7.6 Hz, 1H), 7.46 (t, J = 9.0 Hz, 1H), 7.38 (s, 1H), 7.15 (s, 1H), 5.29 (d, J = 54.2 Hz, 1H), 4.17 – 4.04 (m, 2H), 3.96 (s, 1H), 3.70 – 3.63 (m, 2H), 3.46 (s, 2H), 3.28 (s, 3H), 3.14	ES^+, (Method 4): 1.73min, 544.2 $[M+H]^+$

			(d, J = 10.1 Hz, 2H), 3.06 (s, 1H), 2.86 (t, J = 7.9 Hz, 1H), 2.16 – 1.78 (m, 8H).	
4-hydroxypiperidine	**86** 1-[7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]piperidin-4-ol		400 MHz, DMSO-d_6) δ/ppm 8.99 (s, 1H), 7.97 (dd, *J* = 9.2, 5.9 Hz, 1H), 7.46 (t, *J* = 9.0 Hz, 1H), 7.39 (d, *J* = 2.6 Hz, 1H), 7.19 (d, *J* = 2.5 Hz, 1H), 5.35-5.22 (m, 1H), 5.01 – 4.76 (m, 1H), 4.23 – 4.17 (m, 2H), 4.15 – 4.11(m, 1H), 4.05 – 4.01 (m, 1H), 3.98 (s, 1H), 3.91-3.87 (m, 1H), 3.70-3.64(m, 2H), 3.16-3.09 (m, 2H), 3.03 (s, 1H), 2.87-2.83 (m, 1H), 2.15 – 1.95 (m, 6H), 1.80-1.75 (m, 2H), 1.67-1.60 (m, 2H).	ES^+, (Method 4): 1.1min, 590.3 $[M+H]^+$
1,4-diazepan-5-one	**87** 1-[7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-1,4-diazepan-5-one		(400 MHz, DMSO-d_6) δ/ppm 8.99 (s, 1H), 7.99 – 7.96 (m, 1H), 7.71 – 7.68 (m, 1H), 7.48 – 7.39 (m, 2H), 7.19 (s, 1H), 5.30 (d, *J* = 54.4 Hz, 1H), 4.19 – 4.00 (m, 6H), 3.95 (s, 1H), 3.43 – 3.35 (m, 2H), 3.16 – 3.13 (m, 2H), 3.07 (s, 1H), 2.88 – 2.83 (m, 3H), 2.20 – 1.99 (m, 3H), 1.88 – 1.75 (m, 3H).	ES^+, (Method 3): 3.2min, 603.1 $[M+H]^+$
1,4-diazepan-2-one	**88** 4-[7-(8-ethynyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-2-[[trans-2-fluoro-		(400 MHz, DMSO-d6) δ/ppm 10.16 (s, 1H), 9.29 (s, 1H), 7.99-9.95 (m, 1H), 7.93-7.90 (m, 1H), 7.46 (t, J = 9.0 Hz, 1H),	ES^+, (Method 3): 2.5min,

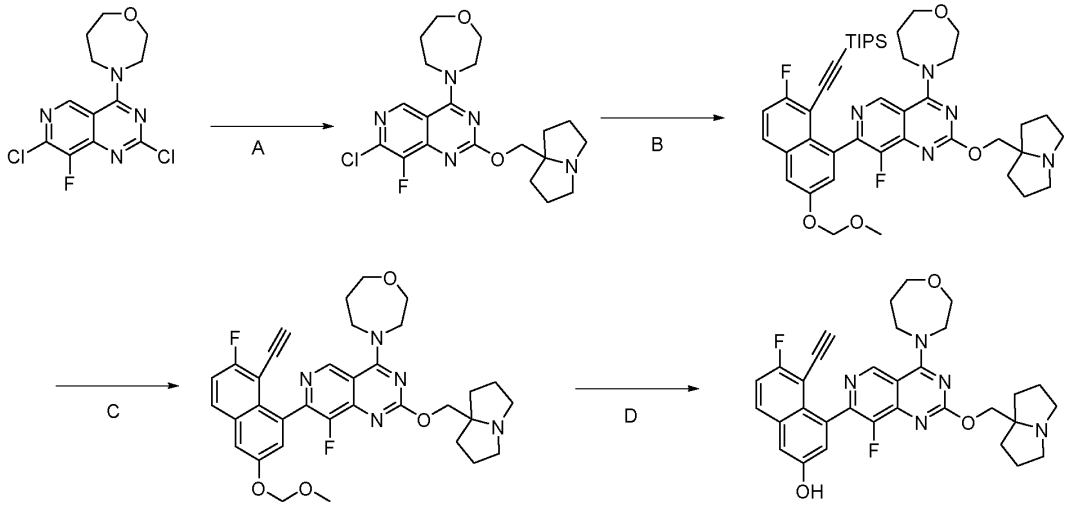
	1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-1,4-diazepan-2-one		7.40 (d, J = 2.6 Hz, 1H), 7.19 (d, J = 2.5 Hz, 1H), 5.40 (s, 1H), 5.36-5.20 (m, 1H), 4.56 – 4.43 (m, 2H), 4.25-4.17 (m, 1H), 4.17 –4.00(m, 4H), 3.26-3.22 (m, 2H), 3.13 – 3.03 (m, 3H), 2.86-2.80 (m, 1H), 2.18 – 1.96 (m, 5H), 1.88-1.75 (m, 3H).	603.1 $[M+H]^+$

Table 4

EXAMPLE 89



5-ethynyl-6-fluoro-4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



STEP A, 4-[7-chloro-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane. A mixture of 4-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-

4-yl)-1,4-oxazepane (200 mg, 0.63 mmol),(tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (89mg, 0.636 mmol) and DIEA (244.5 mg, 1.89 mmol) in dioxane (5 ml) was stirred at 90°C under N_2 overnight.The reaction solution was purified by column chromatography (DCM/MeOH=50/1 to DCM/MeOH=10/1). Ion of the product containing fractions afforded 4-[7-chloro-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (125mg, 45%) as a yellow solid.

LC-MS ES^+, (Method 3): 2.3 min, 422.2 $[M+H]^+$

^1H NMR (400 MHz, DMSO-d6) δ/ppm 9.02 (s, 1H), 4.55 (m, 2H), 4.11-4.16 (m, 4H), 3.89 - 3.92 (m, 2H), 3.68-3.74 (m, 2H), 3.51-3.55 (m, 2H), 3.15-3.22 (m, 2H), 1.96-2.18 (m, 11H).

STEP B, 2-[2-fluoro-8-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]-6-(methoxymethoxy)-1-naphthyl]ethynyl-triisopropyl-silane. A solution of 4-[7-chloro-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (100 mg, 0.237 mmol), 2-[2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]ethynyl-triisopropyl-silane (182 mg, 0.35 mmol), $Pd(dtpbf)Cl_2$(15 mg, 0.024 mmol) and Cs_2CO_3 (154 mg, 0.474 mmol) in 3:1 1,4-dioxane/water ml) was stirred under N_2 at 90°C for 2 h.The reaction mixture was cooled to room temperature, diluted with EtOAc and filtered through celite before concentrating and purifying by RP-column chromatography (MeCN 55%, HCOOH 0.1% and water 45%) to afford 2-[2-fluoro-8-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]-6-(methoxymethoxy)-1-naphthyl]ethynyl-triisopropyl-silane as a colourless oil (86mg, 45%).

LC-MS ES^+, (Method 3): 3.8 min, 790.3 $[M+H]^+$

STEP C, 4-[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane. To 2-[2-fluoro-8-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]-6-(methoxymethoxy)-1-naphthyl]ethynyl-triisopropyl-silane (5 mg, 0.007 mmol) in DMF(1 ml) was added CsF(5 mg, 0.032 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction was diluted with EtOAc and washed with water. The organic layer was concentated in vacuo and used crude in the next step without analysis.

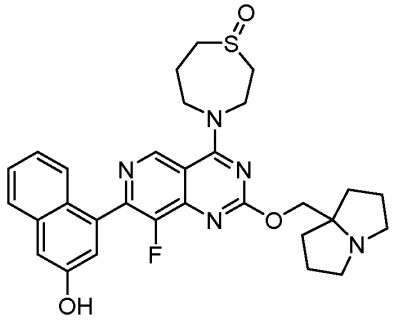
STEP D, 5-ethynyl-6-fluoro-4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol. A solution of -[7-[8-ethynyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (5mg, 0.008mmol) was dissolved in 4M HCl in dioxane (3mL) and stirred at room temperature for 30 mins. The mixture was then

concentrated in vacuo and purified by preparative HPLC to afford 5-ethynyl-6-fluoro-4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol as a white solid (3mg, 62%).

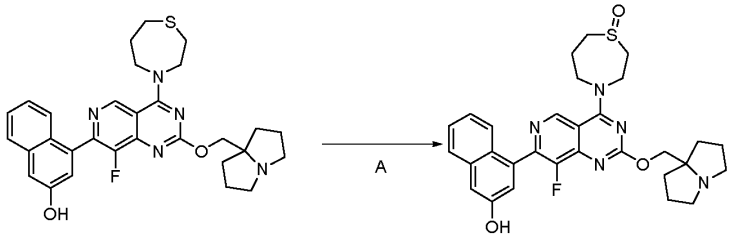
LC-MS ES$^+$, (Method 3): 3.3 min, 572.2 $[M+H]^+$

1H NMR (400 MHz, DMSO-d6) δ/ppm 9.11 (s, 1H), 8.18 (s, 1H), 7.97 (m, 1H), 7.46 (t, J = 9.0 Hz, 1H), 7.39 (s, 1H), 7.18 (s, 1H), 4.19 (s, 2H), 4.15 (m, 4H), 3.99 (s, 1H), 3.95 (t, J = 5.2 Hz, 2H), 3.76 (t, J = 5.2 Hz, 2H), 3.09 (m, 2H), 2.73 (m, 2H), 2.10 (m, 2H), 1.96 (m, 2H), 1.84 (m, 4H), 1.69 (m, 2H).

EXAMPLE 90



4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1-oxo-1,4-thiazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



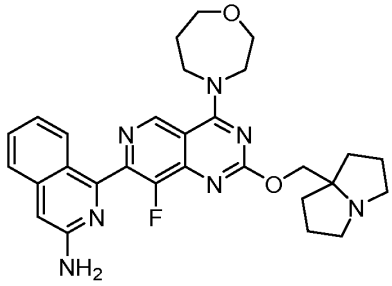
4-[8-Fluoro-2-(tetrahydro-pyrrolizin-7a-ylmethoxy)-4-[1,4]thiazepan-4-yl-pyrido[4,3-d]pyrimidin-7-yl]-naphthalen-2-ol (170 mg, 0.311 mmol) was added to a mixture of sodium metaperiodate (70.62 mg, 0.32 mmol) and water (8.5 mL) at 0°C with stirring. Then to this mixture was added dioxane (5.1 mL) and MeOH (6.8 mL). The reaction mixture was stirred at 0°C. for 5.5 hours. It was then filtered under suction, the white solid was washed with $CHCl_3$ (3 x 5 mL), and the resulting water-chloroform filtrate was transferred into a separation funnel. The chloroform was removed and the aqueous layer was extracted with $CHCl_3$/IPA=3/1 (3x10 mL), The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The crude was purified by preparative TLC to give 4-[8-

fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1-oxo-1,4-thiazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol (30mg, 17%) as a yellow solid.

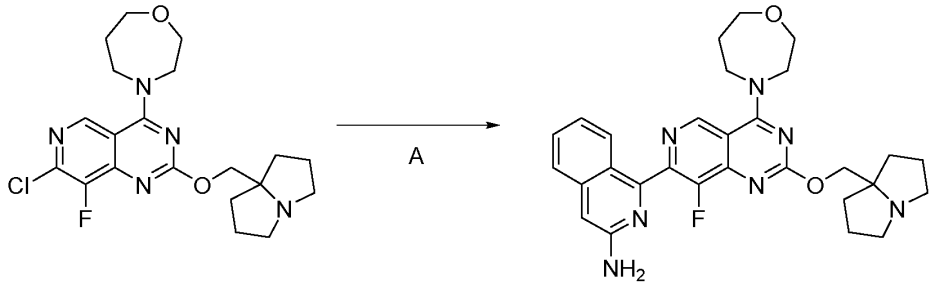
LC-MS ES$^+$, (Method 4): 1.5 min, 562.1 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d6) δ/ppm 9.30 (s, 1H) , 7.82 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.34 – 7.22 (m, 3H), 4.47 – 4.37 (m, 1H), 4.17 (d, J = 9.6 Hz, 4H), 3.26 (d, J = 11.1 Hz, 2H), 3.21 – 3.17 (m, 2H), 3.06 – 3.02 (m, 2H), 2.69 – 2.65 (m, 1H), 2.73 – 2.63 (m, 3H), 2.14 – 2.05 (m, 1H), 1.97 – 1.94 (m, 2H), 1.89 – 1.81 (m, 4H), 1.70 – 1.65 (m, 2H).

EXAMPLE 91



1-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]isoquinolin-3-amine

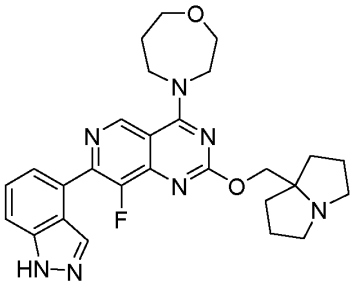


A mixture of 4-[7-chloro-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (150 mg, 0.35 mmol), 1-tributylstannylisoquinolin-3-amine (169 mg, 0.39 mmol), $Pd(PPh_3)_4$ (82 mg, 0.071 mmol), LiCl (30 mg, 0.71 mmol) and CuCl (70 mg, 0.71 mmol) in dry DMF (10 ml) was stirred under N_2 at 90°C for 3 h. The reaction mixture was diluted with EtOAc (50 ml), washed with brine (100 ml x 6). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (DCM:MeOH=20:1, 0.5% $NH_3.H_2O$) to afford 1-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]isoquinolin-3-amine (39.3 mg, 21% yield) as a yellow solid.

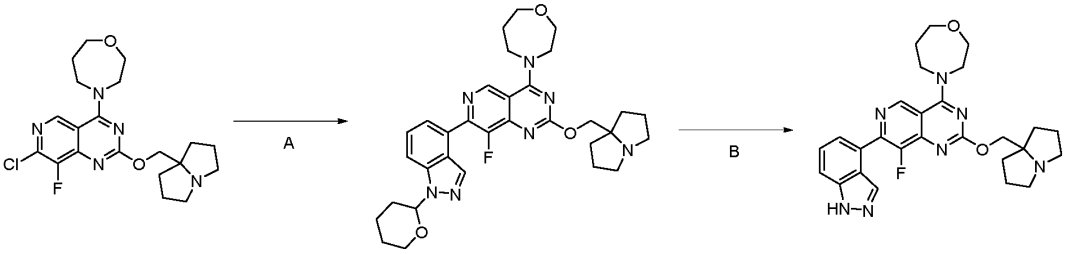
LC-MS ES+, (Method 3): 2.6 min, 530.2 [M+H]+

1H NMR (400 MHz, DMSO-d6) δ/ppm 9.20 (s, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.11 – 7.05 (m, 1H), 6.78 (s, 1H), 6.08 (d, J = 6.7 Hz, 2H), 4.20 – 4.13 (m, 4H), 4.09 (s, 2H), 3.94 (t, J = 4.6 Hz, 2H), 3.74 (t, J = 5.1 Hz, 2H), 2.97 – 2.91 (m, 2H), 2.60 – 2.53 (m, 2H), 2.10 – 2.07 (m, 2H), 1.93 – 1.87 (m, 2H), 1.83 – 1.70 (m, 4H), 1.61 – 1.55 (m, 2H).

EXAMPLE 92



4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(1H-indazol-4-yl)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane



STEP A, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(1-tetrahydropyran-2-ylindazol-4-yl)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane. A mixture of 4-[7-chloro-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (200 mg, 0.47 mmol), 1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (311 mg, 0.95 mmol,), Pd(dtbpf)Cl_2 (30. mg, 0.047 mmol) and Cs_2CO_3 (308mg, 0.95 mmol) in 1,4-dioxane/H_2O=3/1 (18 mL) was stirred at 90°C under N_2 for 2h. The mixture was diluted with water (100 mL) and extracted with EtOAc (50 mL x 3). The combined organic layer was washed with brine (50 mL x 2), dried over Na_2SO_4 and concentrated under vacuum to give the crude product which was purified by silica gel column chromatography (DCM/MeOH/$NH_3.H_2O$= 10/1/0.05, v/v) to give 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(1H-indazol-4-yl)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane(180 mg, 64%) as a brown solid.

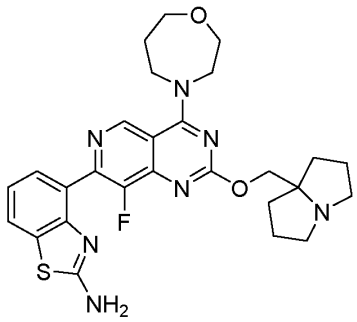
LC-MS ES+, (Method 3): 2.7 min, 588.3 [M+H]+

STEP B, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(1H-indazol-4-yl)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane. To a mixture of 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(1-tetrahydropyran-2-ylindazol-4-yl)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (150 mg, 0.25 mmol) in ethanol (15 mL) was added HCl-dioxane(4M, 15 mL) dropwise. The mixture was stirred at rt for 3h. The mixture was concentrated to give a residue and adjusted to pH = 7 with aq.$NaHCO_3$ (30 mL). It was then extracted with EtOAc (30 mL x 3). The combined organic layer was washed with brine (30 mL x 2), dried over Na_2SO_4 and concentrated in vacuo to give crude product which was purified by preparative-HPLC (MeCN/TFA in water) to give , 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-7-(1H-indazol-4-yl)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane 4.7 mg 3.63%) as a white solid.

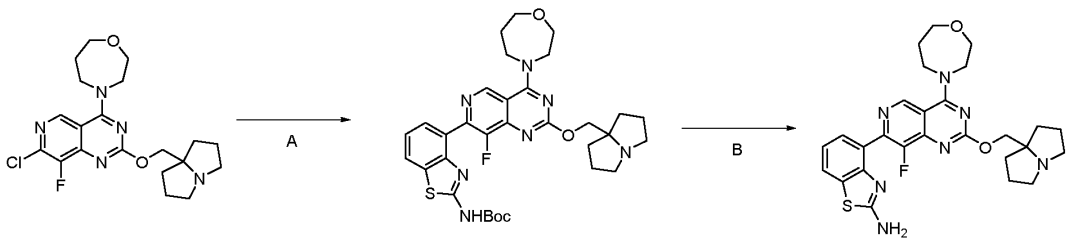
LC-MS ES^+, (Method 4): 0.73 min, 504.2 $[M+H]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm 13.27 (s, 1H), 9.27 (s, 1H), 8.30 (s, 1H), 8.22 (s, 1H), 7.71-7.69 (d, *J* = 8.3 Hz, 1H), 7.65-7.63 (d, *J* = 7.1 Hz, 1H), 7.54-7.50 (t, *J* = 7.7 Hz, 1H), 4.18 (m, 2H), 4.17 (s, 2H), 4.15 – 4.13 (m, 2H), 3.94-3.92 (m, 2H), 3.75-3.72 (m, 2H), 3.06-3.00 (m, 2H), 2.68-2.62 (m, 2H), 2.11-2.06 (m, 2H), 1.97-1.91 (m, 2H), 1.87-1.78 (m, 4H), 1.68-1.61 (m, 2H).

EXAMPLE 93



4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]-1,3-benzothiazol-2-amine



STEP A, tert-butyl N-[4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]-1,3-benzothiazol-2-yl]carbamate. A mixture of 4-(7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane (20 mg, 0.04 mmol), tert-butyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazol-2-yl)carbamate (35.6 mg, 0.094 mmol), Pd(dtpbf)Cl_2 (3.06 mg, 0.0047 mmol) and Cs_2CO_3 (30.8 mg, 0.098 mmol) in dioxane (1.5mL) and H_2O (0.5 mL) stirred at 90°C under N_2 for 2 hours. The mixture concentrated under vacuum and purified by silica gel chromatography (eluting with 20/1 DCM/MeOH) to afford a yellow solid analysed as tert-butyl N-[4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]-1,3-benzothiazol-2-yl]carbamate (180 mg, 59 % yield).

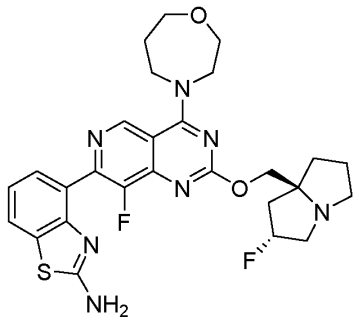
LC-MS ES^+, (Method 3): 2.9 min, 636.2 $[M+H]^+$

STEP B, 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]-1,3-benzothiazol-2-amine. A mixture of tert-butyl (4-(8-fluoro-4-(1,4-oxazepan-4-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)benzo[d]thiazol-2-yl)carbamate (160 mg, 0.25 mmol) and HCl.dioxane (3 mL) in MeOH (3 mL) was stirred at 50°C under N_2 for 2 hours. The pH of the resulting mixture was adjusted to 8 with saturated Na_2CO_3 solution, extracted with EtOAc (20 mL x 3), dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 140 mg crude, purified by silica gel column chromatography (eluting with 1/20 MeOH/DCM) to give a brown solid analysed as , 4-[8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]-1,3-benzothiazol-2-amine (80 mg, 59%).

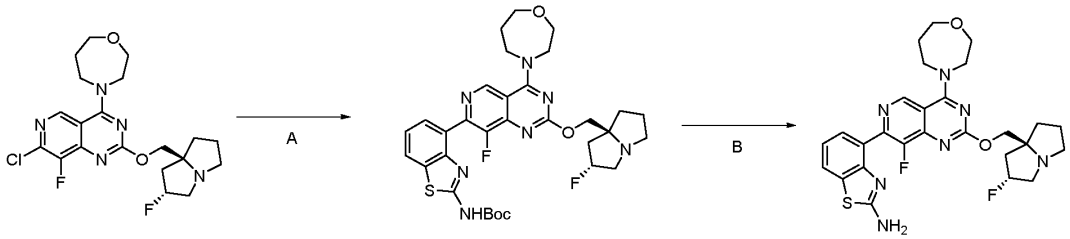
LC-MS ES^+, (Method 4): 0.63 min, 536.1 $[M+H]^+$

^1H NMR (400 MHz, DMSO-d6) δ/ppm 9.15 (s, 1H), 7.79 (dd, J = 7.8, 1.3 Hz, 1H), 7.60 (s, 2H), 7.37 (dd, J = 7.6, 1.3 Hz, 1H), 7.16 (t, J = 7.7 Hz, 1H), 4.16 – 4.10 (m, 4H), 4.07 (s, 2H), 3.91 (t, J = 4.5 Hz, 2H), 3.73 (t, J = 5.2 Hz, 2H), 2.97 – 2.90 (m, 2H), 2.59 – 2.53 (m, 2H), 2.11 – 2.03 (m, 2H), 1.92 – 1.85 (m, 2H), 1.83 – 1.71 (m, 4H), 1.62 – 1.53 (m, 2H).

EXAMPLE 94



4-[8-fluoro-4-(1,4-oxazepan-4-yl)-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-7-yl]-1,3-benzothiazol-2-amine



STEP A, tert-butyl N-[4-[8-fluoro-4-(1,4-oxazepan-4-yl)-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-7-yl]-1,3-benzothiazol-2-yl]carbamate. A solution of 4-[7-chloro-8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (200 mg, 0.45 mmol), tert-butyl N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzothiazol-2-yl]carbamate (342 mg, 0.91 mmol), Pd(dtpbf)Cl_2 (29 mg, 0.045 mmol) and Cs_2CO_3 (296 mg, 0.91 mmol) in dioxane (9 mL) and water (3 mL) was stirred at 90°C for 2 h under N_2 protection. The mixture was concentrated under vacuum and the crude was purified by silica gel column column (DCM/MeOH =100/1 to DCM/MeOH =30/1, v/v) to give tert-butyl N-[4-[8-fluoro-4-(1,4-oxazepan-4-yl)-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-7-yl]-1,3-benzothiazol-2-yl]carbamate (250 mg, 84%) as a yellow solid.

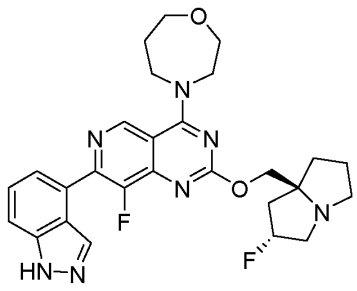
LC-MS ES^+, (Method 3): 2.8 min, 654.2 $[M+H]^+$

STEP B, 4-[8-fluoro-4-(1,4-oxazepan-4-yl)-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-7-yl]-1,3-benzothiazol-2-amine. 4 M HCl-dioxane (5 mL) was added dropwise into a solution of tert-butyl N-[4-[8-fluoro-4-(1,4-oxazepan-4-yl)-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-7-yl]-1,3-benzothiazol-2-yl]carbamate (120 mg, 0.184 mmol) in MeOH (5 mL) and stirred at 50°C for 2 h. The mixture was concentrated and purified by preparatve-HPLC to give 4-[8-fluoro-4-(1,4-oxazepan-4-yl)-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-7-yl]-1,3-benzothiazol-2-amine (21 mg 21%).

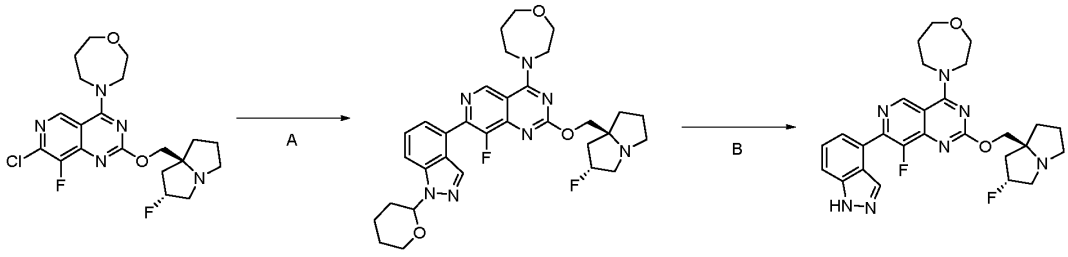
LC-MS ES^+, (Method 4): 0.73 min, 554.3 $[M+H]^+$

^1H NMR (400 MHz, DMSO-d_6) δ/ppm 9.15 (s, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.59 (s, 2H), 7.37 (d, J = 7.4 Hz, 1H), 7.17 – 7.14 (m, 1H), 5.29 (d, J = 54.5 Hz, 1H), 4.17 – 4.08 (m, 6H), 3.93 – 3.90 (m, 2H), 3.74 -3.72 (m, 2H), 3.17 – 3.04 (m, 3H), 2.87 – 2.82 (m, 1H), 2.19 – 1.97 (m, 5H), 1.90 – 1.74 (m, 3H).

EXAMPLE 95



4-[8-fluoro-7-(1H-indazol-4-yl)-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane



STEP A, 4-[8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-(1-tetrahydropyran-2-ylindazol-4-yl)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane. A solution of 4-[7-chloro-8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (200 mg, 0.45 mmol), 1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (373 mg, 1.13 mmol), $Pd(dtpbf)Cl_2$ (29 mg, 0.045 mmol) and Cs_2CO_3 (296 mg, 0.91 mmol) in dioxane (9 mL) and water (3 mL) was stirred at 90°C for 2 h under N_2 protection. The mixture was concentrated under vacuum and the crude was purified by silica gel column (DCM/MeOH =100/1to DCM/MEOH =30/1, v/v) to give 4-[8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-(1-tetrahydropyran-2-ylindazol-4-yl)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (200 mg, 73%) as a yellow solid.

LC-MS ES^+, (Method 3): 2.7 min, 606.3 $[M+H]^+$

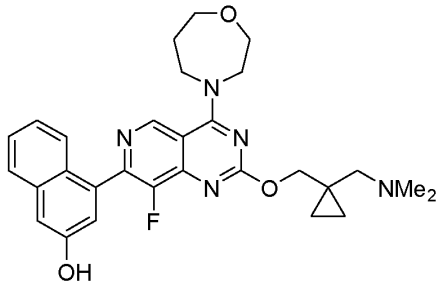
STEP B, 4-[8-fluoro-7-(1H-indazol-4-yl)-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane. 4 M HCl-dioxane (4 mL) was added dropwise into a solution of 4-[8-fluoro-2-[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-7-(1-tetrahydropyran-2-ylindazol-4-yl)pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (100 mg, 0.165 mmol) in MeOH (4 mL) and stirred at r.t. for 1 h. The mixture was concentrated and purified by preparative-HPLC to give 4-[8-fluoro-7-(1H-indazol-4-yl)-2-

[[trans-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-1,4-oxazepane (40 mg, 47%).

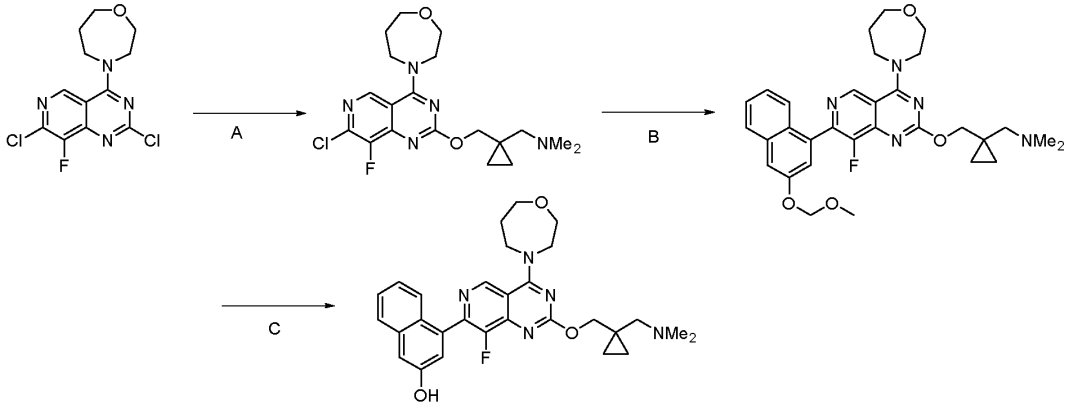
LC-MS ES$^+$, (Method 4): 1.6 min, 522.2 $[M+H]^+$

^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm 13.29 (s, 1H), 9.24 (s, 1H), 8.30 (s, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.63 (d, J = 7.1 Hz, 1H), 7.53 – 7.49 (m, 1H), 5.37 – 5.22 (m, 1H), 4.18 – 4.07 (m, 6H), 3.93 – 3.90 (m, 2H), 3.74 – 3.71 (m, 2H), 3.18 – 3.05 (m, 3H), 2.88 – 2.82 (m, 1H), 2.21 – 1.98 (m, 5H), 1.91 – 1.75 (m, 3H).

EXAMPLE 96



4-[2-[[1-[(dimethylamino)methyl]cyclopropyl]methoxy]-8-fluoro-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol



STEP A, 1-[1-[[7-chloro-8-fluoro-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]-N,N-dimethyl-methanamine. To a solution of 4-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane (111 mg, 0.35 mmol) and (1-((dimethylamino)methyl)cyclopropyl)methanol (136 mg, 1.05 mmol) in dioxane (10 ml) was added DIEA (137 mg, 1.05 mmol) , the mixture was stirred at 90°C under N^2 overnight. The mixture was concentrated and purified by column (DCM/MeOH=20/1, v/v) to give -[1-[[7-chloro-8-fluoro-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]-N,N-dimethyl-methanamine (80 mg, 65%) as a yellow solid.

LC-MS ES$^+$, (Method 4): 0.95 min, 410.2 [M+H]

^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm 8.92 (s, 1H), 4.25 (s, 2H), 4.06-4.19 (m, 4H), 3.78-3.88 (m, 2H), 3.68-3.72 (m, 2H), 2.00-2.56 (m, 10H, 3.20-3.30 (m, 4H)

STEP B, 1-[1-[[8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]-N,N-dimethyl-methanamine. To a solution of 1-[1-[[7-chloro-8-fluoro-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]-N,N-dimethyl-methanamine (150 mg, 0.37 mmol), 2-(3-(2-methoxymethoxy)naphthalene-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (230 mg, 0.74 mmol) and Pd(dtpbf)Cl_2 (23.6 mg, 0.037 mmol) in dioxane (9 ml) and water (3 ml) was added Cs_2CO_3 (239 mg, 0.74 mmol), the mixture was stirred at 90°C under nitrogen for 3 h. The mixture was concentrated and purified by silica gel flash column chromatography (DCM/MeOH=10/1, v/v) to give 1-[1-[[8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]-N,N-dimethyl-methanamine (210 mg, 100%) as a brown oil.

LC-MS ES$^+$, (Method 4): 0.59 min, 562.2 [M+H]

STEP C, 4-[2-[[1-[(dimethylamino)methyl]cyclopropyl]methoxy]-8-fluoro-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol. To a solution of 1-[1-[[8-fluoro-7-[3-(methoxymethoxy)-1-naphthyl]-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]cyclopropyl]-N,N-dimethyl-methanamine (190 mg, 0.34 mmol) in DCM (3 ml) was added HCl/dioxane (3 ml), the mixture was stirred at rt overnight. The mixture was adjusted to pH=8 with sat.$NaHCO_3$ and extracted with $CHCl_3$/IPA=3/1 (20 ml x 3), the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated and purified by preparative-HPLC to give 4-[2-[[1-[(dimethylamino)methyl]cyclopropyl]methoxy]-8-fluoro-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol (32 mg, 19%) as a light yellow solid.

LC-MS ES$^+$, (Method 3): 2.1 min, 518.2 [M+H]

^{1}HNMR (400 MHz, DMSO-d6) δ/ppm 9.23 (s, 1H), 8.16 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 14.8 Hz, 1H), 7.29-7.22 (m, 3H), 4.28 (s, 2H), 4.19-4.14 (m, 4H), 3.93 (t, J = 8.8 Hz, 2H), 3.74 (t, J = 10.4 Hz, 2H), 2.31 (s, 2H), 2.22 (s, 6H), 2.09 (t, J = 9.6 Hz, 2H), 0.65 (t, J = 10.0 Hz, 2H), 0.44 (t, J = 10.0 Hz, 2H).

Biological results

HTRF Nucleotide exchange assay method

The capacity of compounds to bind KRAS G12D, other KRAS mutants and wildtype RAS isoforms was quantified using a HTRF nucleotide exchange assay. Recombinant human

RAS protein (2nM; aa1-188 KRAS WT, HRAS WT, NRAS WT, or KRAS containing the containing the G12D, G13D or Q61H amino acid substitutions, or 4nM KRAS; aa1-188 containing the G12V, G12C, G12A or G12S amino acid substitution, an N-terminal 6xHis-tag and leader sequence), and 2nM Europium-labeled anti-6xHis antibody were mixed in assay buffer (10mM HEPES pH7.3, 150mM NaCl, 5mM $MgCl_2$, 0.05% BSA, 0.0025% NP-40 and 100mM KF) with various concentrations of compound in a 384-well plate and a volume of 5uL. After a 60-minute incubation at room temperature, 5ul of 200nM EDA-GTP-DY647P1 (diluted in assay buffer) was added to the plate. Following 30-minute incubation at room temperature, time-resolved fluorescence was measured on a PerkinElmer Envision plate reader. DMSO (0.3%) and unlabeled GDP (1μM) or equivalent tool compound were used to generate the Max and Min assay signals, respectively. Data was analysed using a four-parameter logistic model to calculate IC_{50} values, with at least two independent replicates were performed for each compound. The results are presented in Table 5 where "A" corresponds to an IC_{50} ≤ 10nM, "B" to an IC_{50} >10nM up to 100nM, "C" is >100nM up to 10μM, "D" represents >10% up to 49% inhibition at 10μM and ND = not determined:

Example	$KRAS^{G12D}$ NEA	$KRAS^{WT}$ NEA	$KRAS^{G12C}$ NEA	$KRAS^{G12V}$ NEA	$KRAS^{G12S}$ NEA	$KRAS^{G12A}$ NEA	$KRAS^{G13D}$ NEA	$KRAS^{Q61H}$ NEA
1	B	C	C	C	ND	ND	C	C
2	C	C	C	ND	ND	ND	ND	ND
3	A	B	A	A	B	A	C	B
4	C	C	C	C	D	C	D	ND
5	C	C	C	C	ND	ND	ND	ND
6	C	C	C	C	ND	ND	ND	ND
7	C	C	C	C	ND	ND	ND	ND
8	C	C	C	C	ND	ND	C	C
9	C	C	C	C	C	C	D	ND
10	C	C	C	C	C	C	D	ND
11	B	C	C	C	ND	ND	ND	ND
12	C	C	ND	ND	ND	ND	ND	ND
13	B	C	C	C	C	C	D	ND
14	B	C	B	B	C	C	D	ND
15	C	C	ND	ND	ND	ND	ND	ND
16	B	B	B	B	C	B	ND	ND
17	B	B	B	B	B	B	ND	ND
18	B	B	B	ND	ND	ND	ND	ND
19	B	B	B	B	C	B	D	C
20	A	B	A	A	B	B	ND	ND
21	C	C	ND	ND	ND	ND	ND	ND
22	C	C	ND	ND	C	C	D	ND

23	C	C	ND	ND	ND	ND	ND	ND
24	C	C	B	ND	ND	ND	ND	ND
25	C	C	C	ND	ND	ND	ND	ND
26	C	C	C	ND	ND	ND	ND	ND
27	C	C	C	ND	C	C	D	ND
28	C	C	C	ND	ND	ND	ND	ND
29	C	C	ND	ND	ND	ND	ND	ND
30	C	C	ND	ND	ND	ND	ND	ND
31	C	C	ND	ND	C	C	D	ND
32	C	C	ND	ND	C	C	D	ND
33	C	C	ND	ND	D	C	D	ND
34	B	B	B	B	C	B	D	6.4
35	C	C	ND	ND	ND	ND	ND	ND
36	C	C	ND	ND	D	C	D	ND
37	C	C	ND	ND	ND	ND	ND	ND
38	B	B	A	A	B	A	D	B
39	C	C	ND	ND	ND	ND	ND	ND
40	C	C	ND	ND	ND	ND	ND	ND
41	B	B	B	B	C	B	ND	ND
42	C	C	ND	ND	ND	ND	ND	ND
43	C	C	ND	ND	ND	ND	ND	ND
44	C	C	ND	ND	ND	ND	ND	ND
45	C	C	C	C	C	ND	ND	ND
46	C	C	ND	ND	C	ND	ND	ND
47	C	B	B	B	C	B	ND	ND
48	C	C	ND	ND	ND	ND	ND	ND
49	C	C	ND	ND	ND	ND	ND	ND
50	C	C	ND	ND	ND	ND	ND	ND
51	C	C	C	C	ND	ND	ND	ND
52	B	B	B	B	C	B	ND	ND
53	C	C	ND	ND	ND	ND	ND	ND
54	C	C	ND	ND	ND	ND	ND	ND
55	ND	ND	ND	ND	ND	ND	ND	ND
56	C	C	C	C	C	C	D	C
57	C	C	ND	ND	ND	ND	ND	ND
58	C	C	ND	ND	ND	ND	ND	ND
59	C	C	C	C	C	C	ND	ND
60	C	C	ND	ND	ND	ND	ND	ND
61	C	C	ND	ND	ND	ND	ND	ND
62	C	C	ND	ND	ND	ND	ND	ND
63	C	C	ND	ND	ND	ND	ND	ND
64	C	C	ND	ND	ND	ND	ND	ND
65	C	C	B	B	C	B	ND	ND
66	C	C	ND	ND	ND	ND	ND	ND
67	C	C	ND	ND	ND	ND	ND	ND

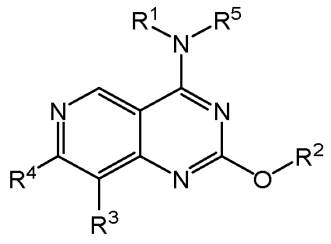
68	C	C	ND	ND	ND	ND	ND	ND
69	B	C	ND	ND	ND	ND	ND	ND
70	A	B	B	B	C	B	ND	ND
71	C	C	ND	ND	ND	ND	ND	ND
72	C	C	C	C	ND	ND	ND	ND
73	C	C	C	C	ND	ND	ND	ND
74	D	C	D	D	ND	ND	ND	ND
75	C	C	C	C	ND	ND	ND	ND
76	D	C	C	C	ND	ND	ND	ND
77	C	C	C	C	ND	ND	ND	ND
78	C	C	C	C	ND	ND	ND	ND
79	B	B	B	B	ND	ND	ND	ND
80	C	C	ND	ND	ND	ND	ND	ND
81	C	C	C	B	ND	ND	ND	ND
82	C	C	C	B	ND	ND	ND	ND
83	A	A	A	A	A	A	D	A
84	A	A	A	A	A	A	C	A
85	A	A	A	A	B	A	D	B
86	A	A	A	A	ND	ND	ND	ND
87	A	A	ND	ND	ND	ND	ND	ND
88	A	A	A	A	A	A	ND	ND
89	A	A	A	A	A	A	D	A
90	A	B	B	B	C	B	ND	ND
91	C	C	C	C	ND	ND	ND	ND
92	C	D	ND	ND	ND	ND	ND	ND
93	C	C	ND	ND	ND	ND	ND	ND
94	C	C	ND	ND	ND	ND	ND	ND
95	C	D	ND	ND	ND	ND	ND	ND
96	B	B	B	B	ND	ND	ND	ND

Table 5

As can be seen from Table 5, compounds of the invention exhibit KRAS inhibition across a broad spectrum of KRAS proteins, including wild-type KRAS and KRAS having a range of mutations.

CLAIMS

1. A compound of formula (**I**), 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 an oxygen containing 4- to 7- membered heterocycloalkyl ring, a nitrogen containing 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; $C(O)NR^7R^8$;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 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 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^3 is 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;

n is an integer selected from 0, 1, 2, 3 and 4;

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.

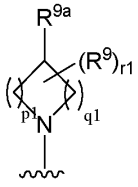
2. A compound of claim 1, wherein R^1 and R^5 together with the nitrogen to which they are attached form a ring system selected from: a monocyclic 4- to 7-membered heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups; a fused or spirofused bicyclic 6- to 11-membered heterocycloalkyl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

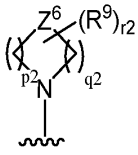
5. A compound of any one of claims 1 to 3, wherein R^1 and R^5 together with the nitrogen to which they are attached form a ring system selected from: a monocyclic 4- to 7-membered group heterocycloalkyl group, optionally substituted with from 1 to 4 R^9 groups; a fused or spirofused bicyclic 6- to 11-membered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



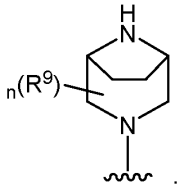
wherein R^{9a} is selected from $NR^{12}R^{13}$ and C_1-C_4-alkyl substituted with $NR^{12}R^{13}$; p1 is selected from 0, 1, 2 and 3, q1 is selected from 0, 1 and 2; and r1 is selected from 0, 1, 2 and 3.

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 $C(O)NR^{9b}$, 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, wherein the bridged bicyclic 6- to 11-membered heterocycloalkyl group is not:



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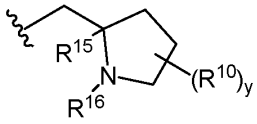
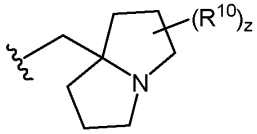
9. A compound of any one of claims 1 to 8, wherein R^2 has the structure:



, 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:

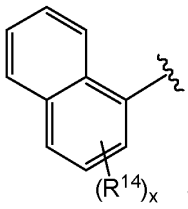


, wherein z is independently selected from 0, 1, 2, 3, and 4. z may be selected from 0 and 1. z may be 0. z may be 1.

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

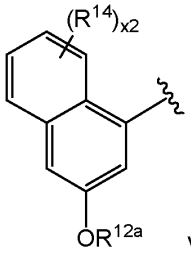
12. A compound of any one of claims 1 to 11, wherein R^4 is phenyl, said phenyl being optionally fused to a C_5-C_7-cycloalkyl ring, wherein R^4 is optionally substituted with from 1 to 4 R^{14} groups.

13. A compound of any one of claims 1 to 11, wherein R^4 has the structure:



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

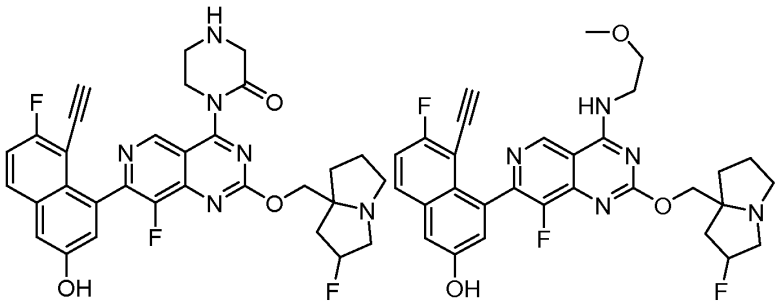
14. A compound of claim 13, wherein R^4 has the structure:

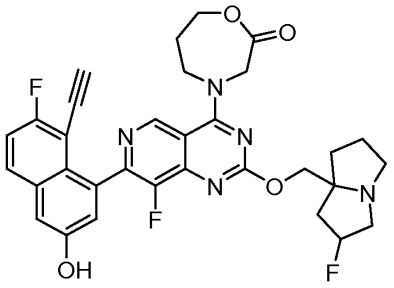


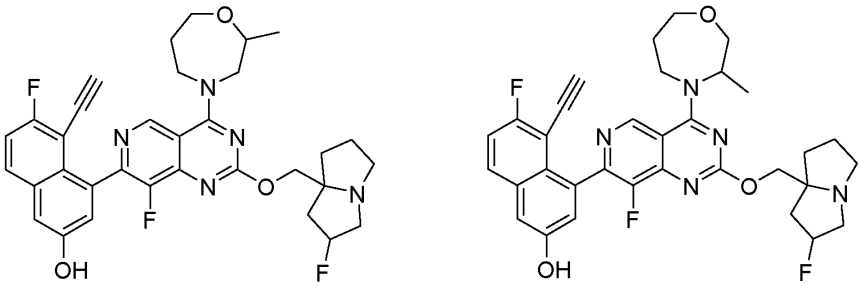
wherein R^{12a} is independently H or C_1-C_4-alkyl; x2 is independently selected from 0, 1, 2 and 3.

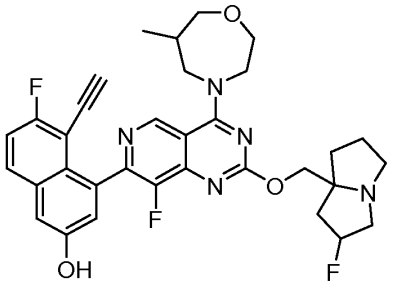
15. A compound of any one of claims 1 to 11, wherein R^4 is 5-, 6-, 9- or 10-membered monocyclic or bicyclic heteroaryl, optionally substituted with from 1 to 4 R^{14} groups.

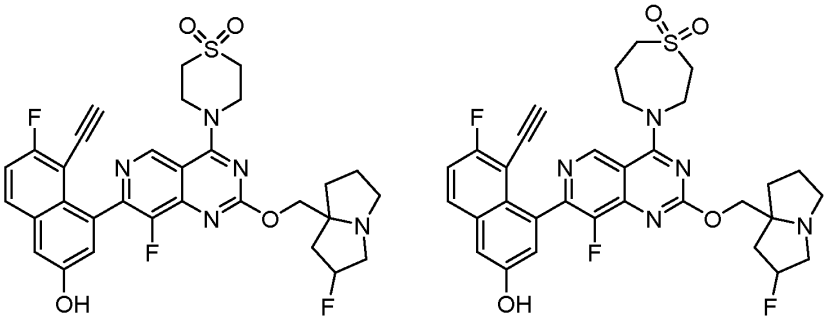
16. A compound of claim 1, wherein the compound of formula (I) is selected from

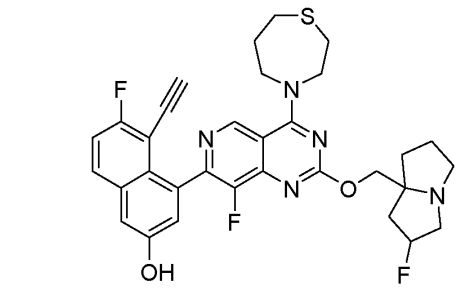


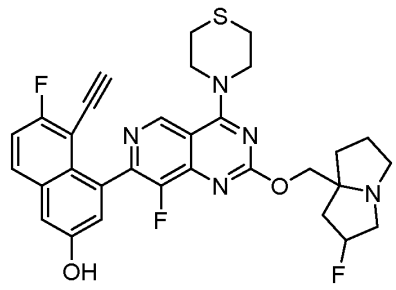


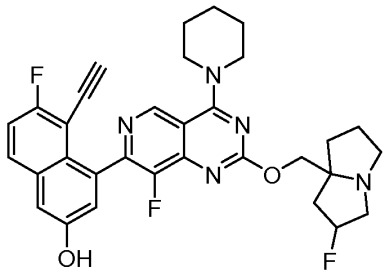


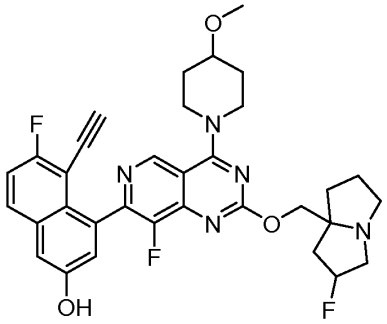


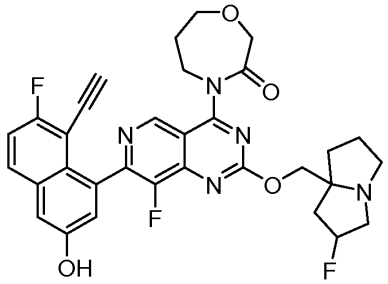


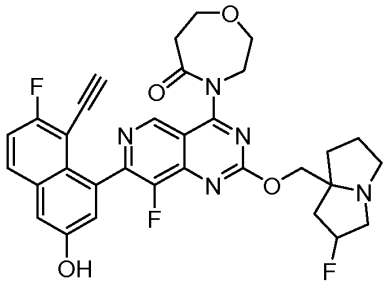


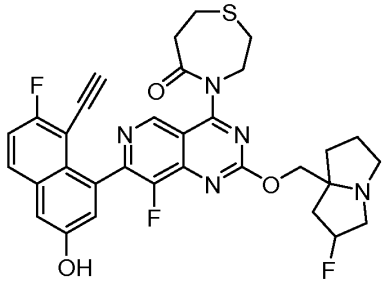


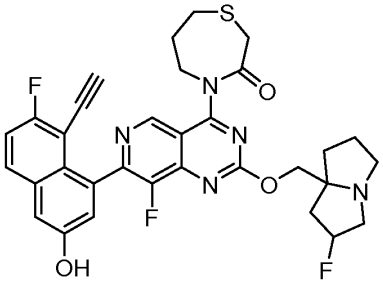












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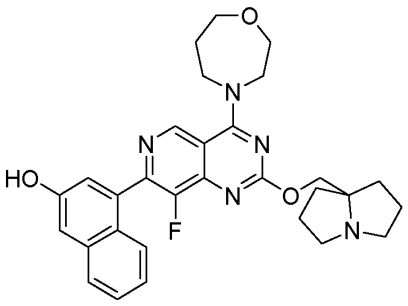
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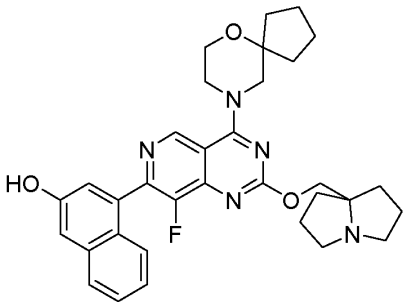
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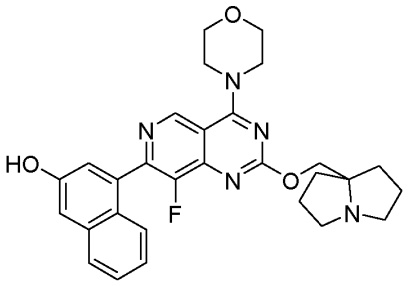
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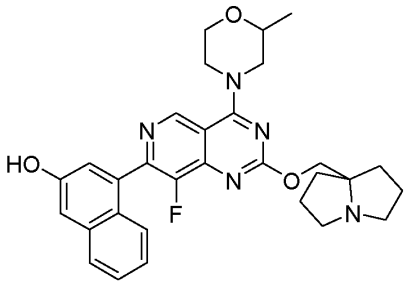
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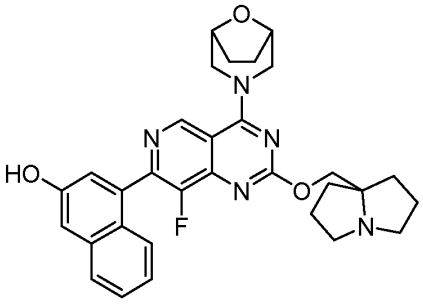
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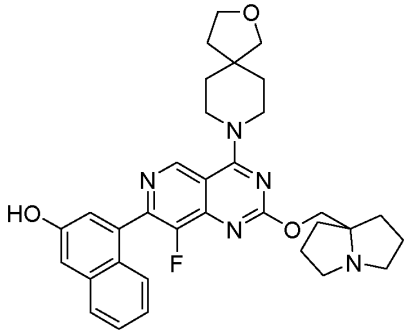
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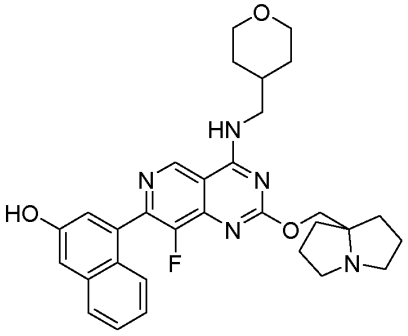
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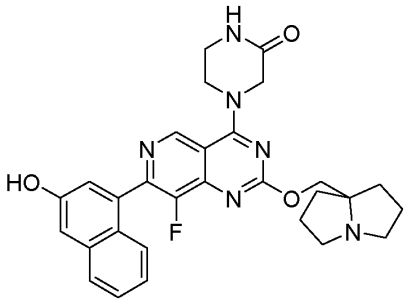
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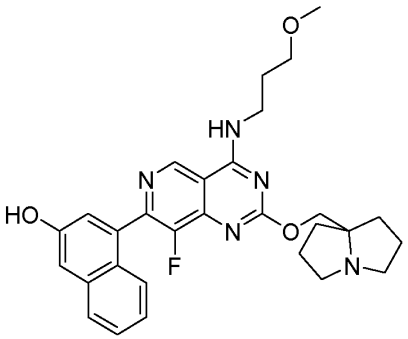
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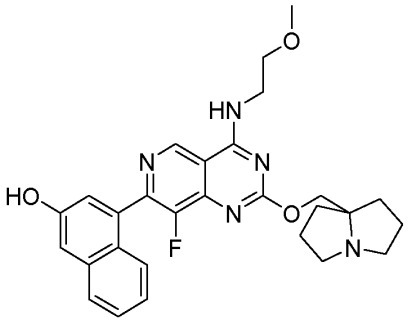
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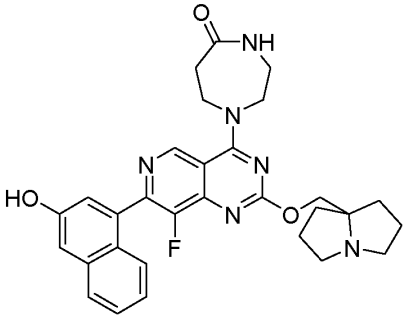
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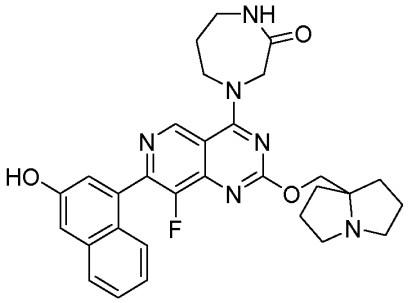
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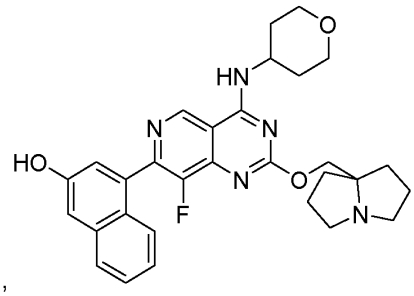
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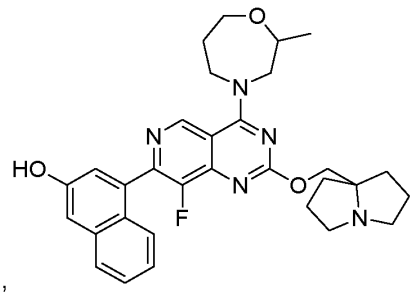
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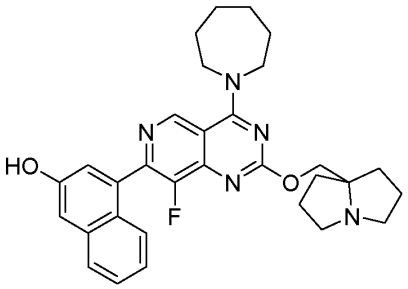
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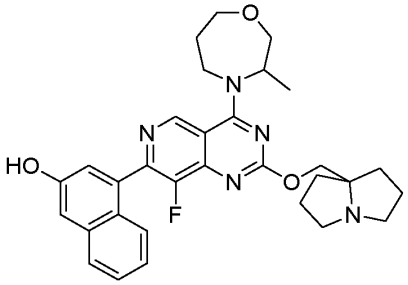
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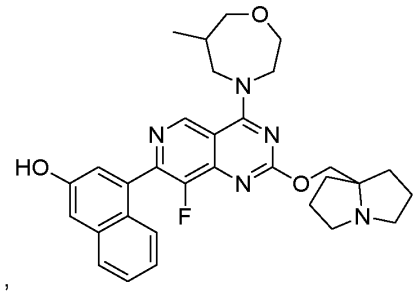
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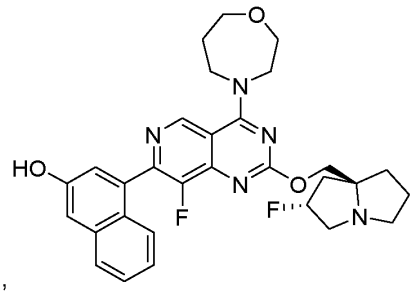
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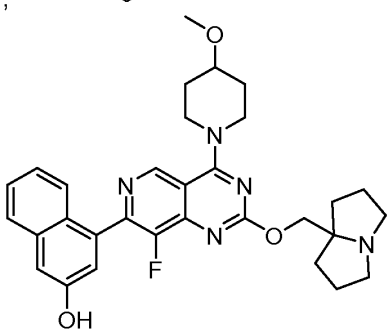
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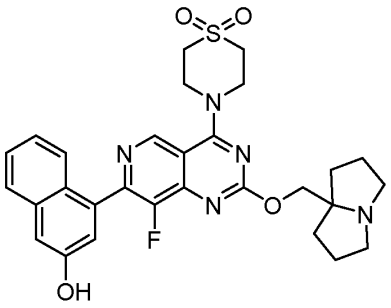
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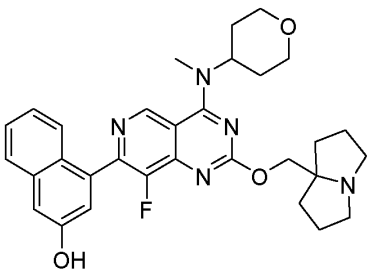
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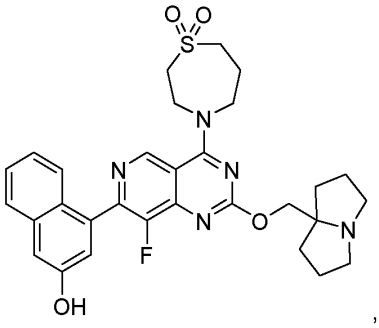
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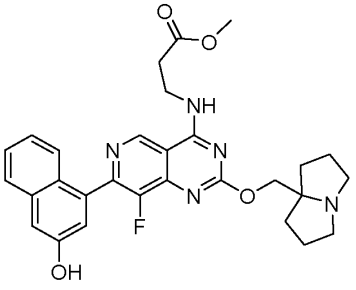
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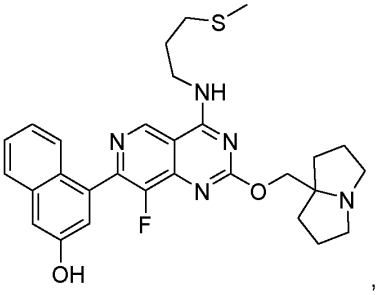
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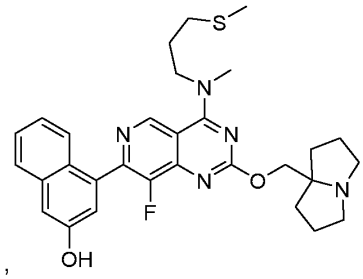
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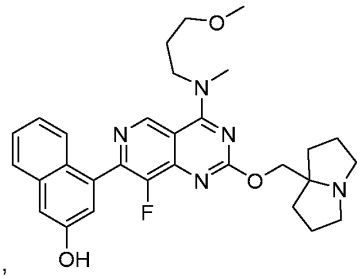
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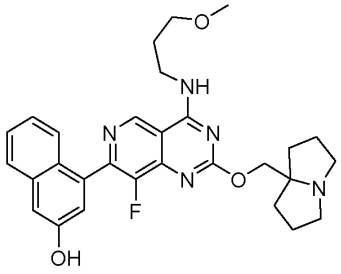
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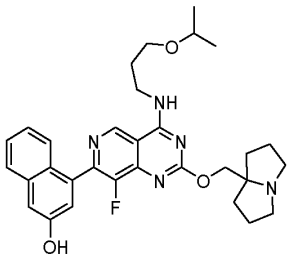
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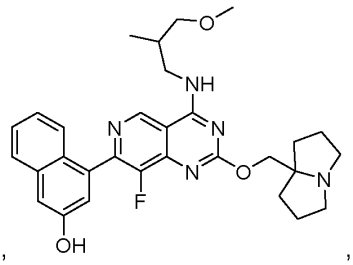
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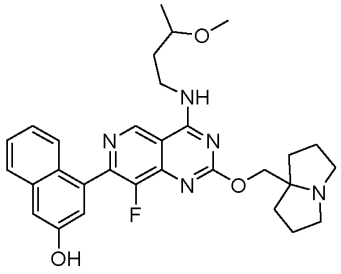
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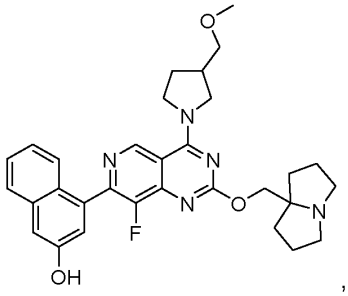
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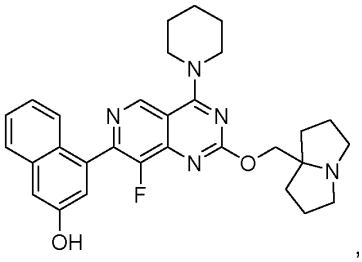
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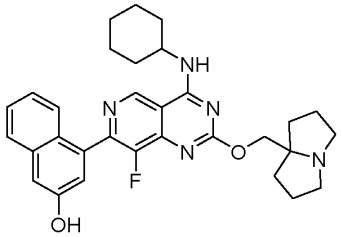
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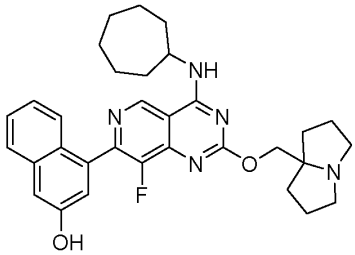
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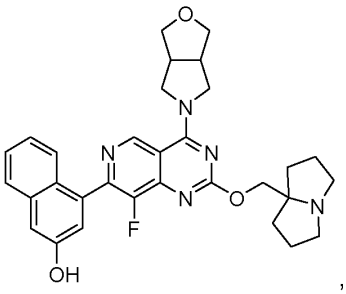
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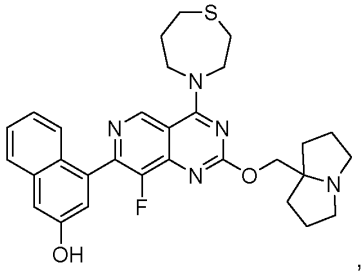
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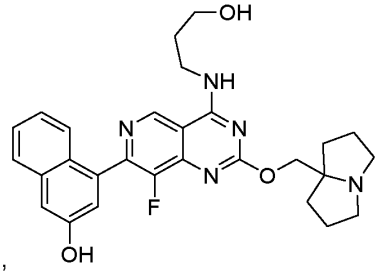
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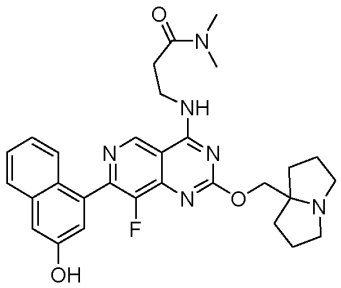
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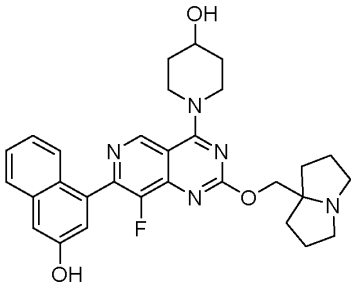
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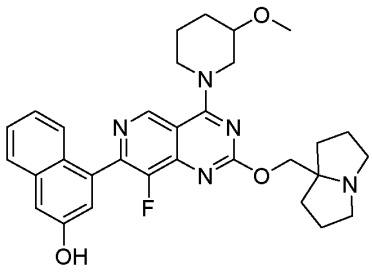
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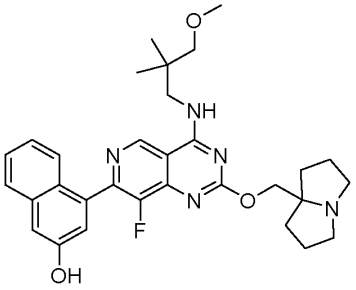
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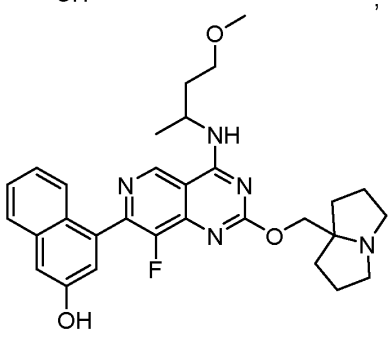
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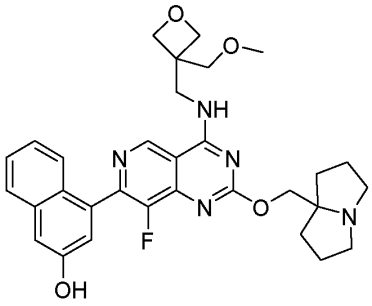
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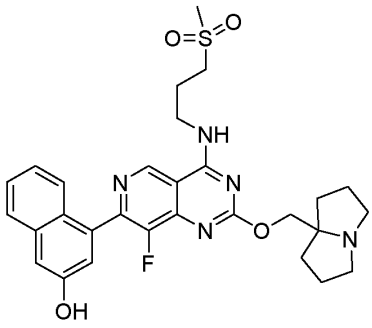
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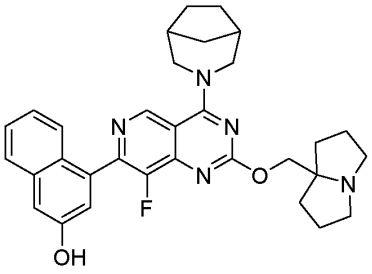
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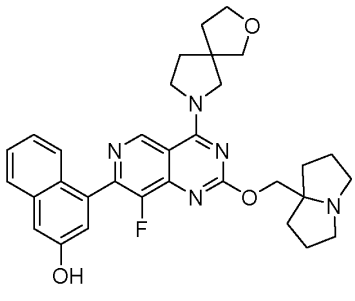
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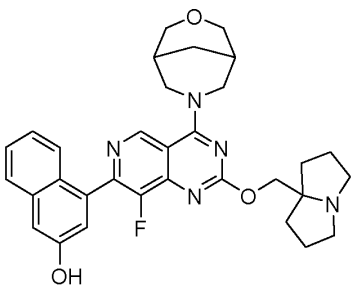
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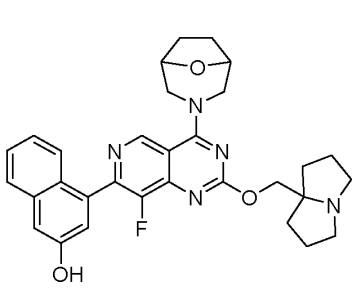
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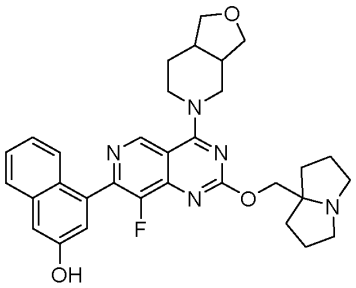
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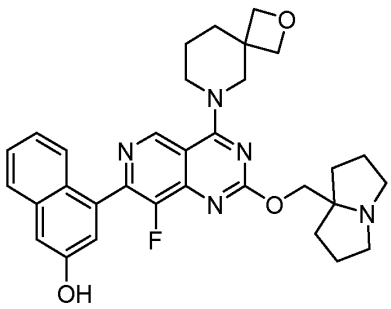
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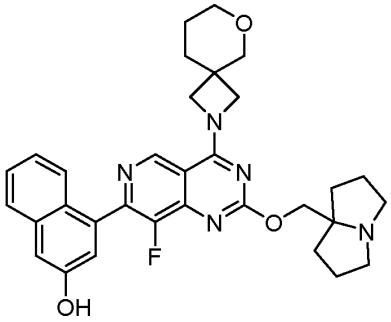
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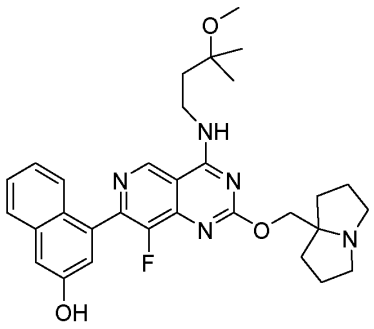
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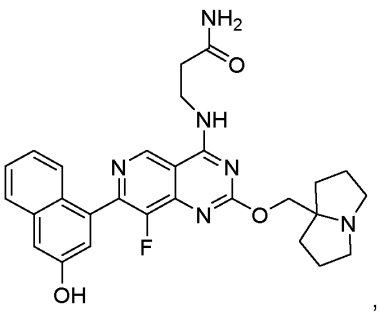
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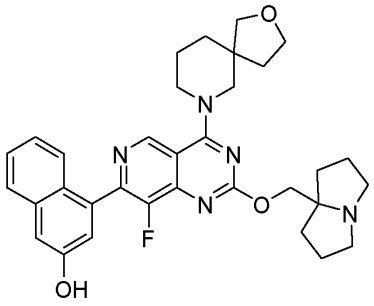
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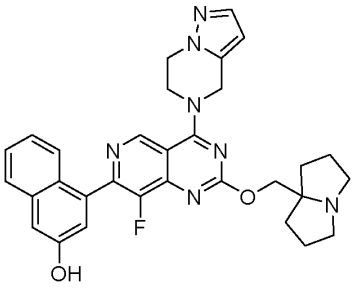
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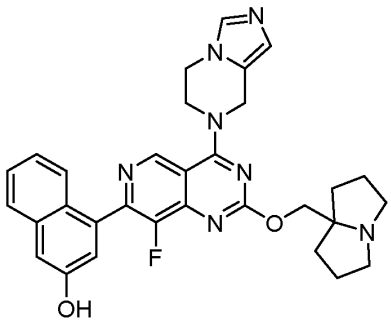
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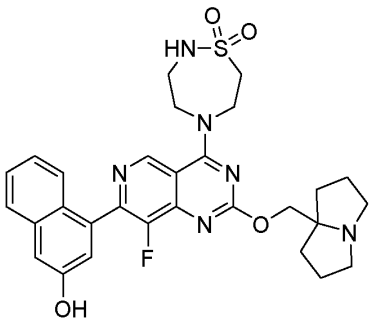
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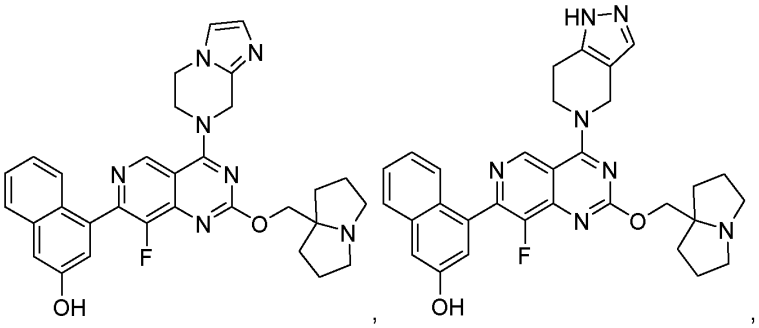

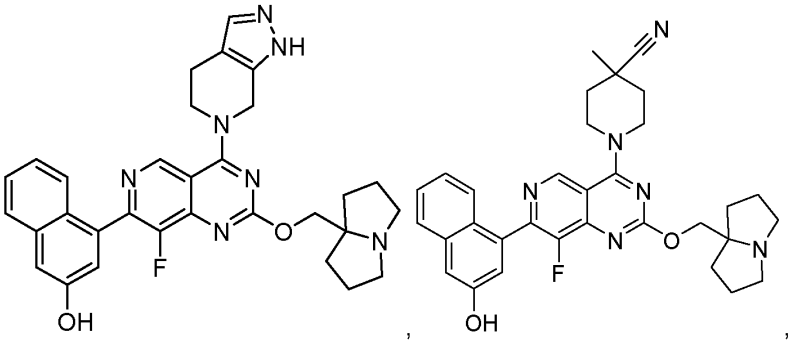

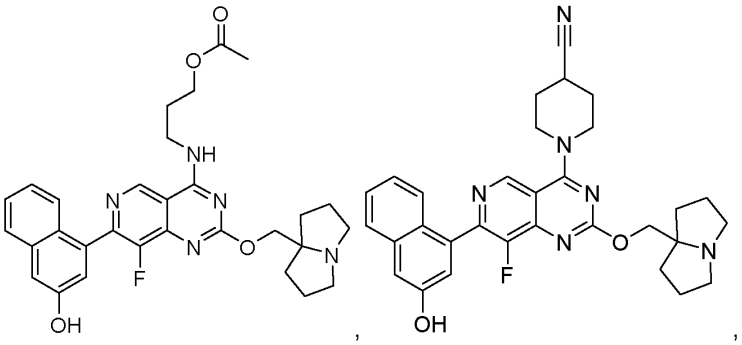

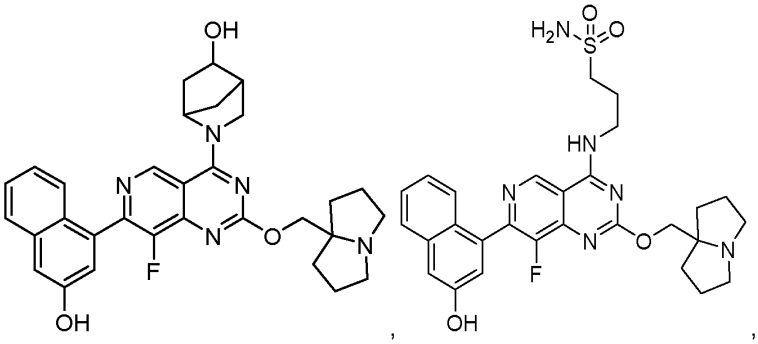

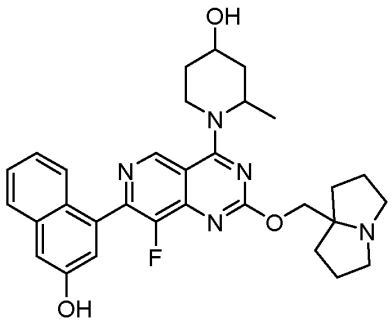
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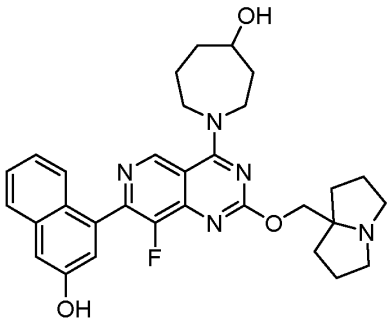
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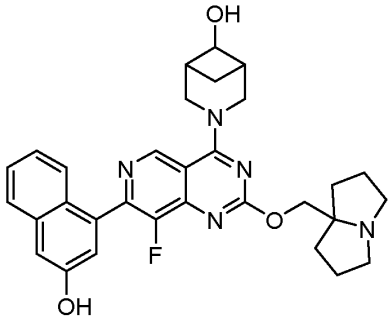
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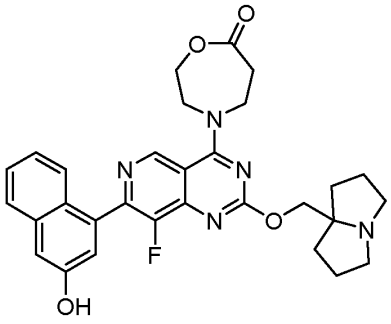
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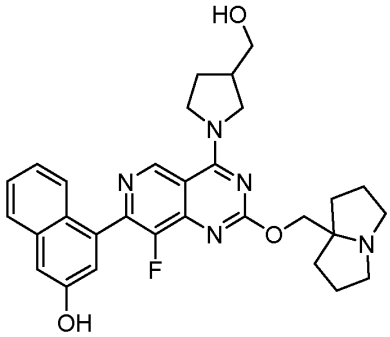
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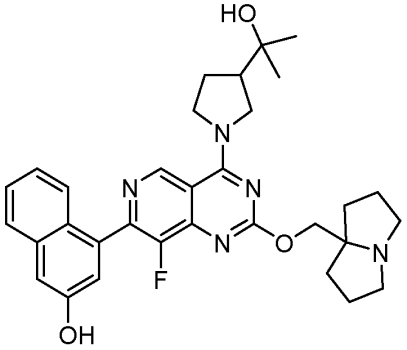
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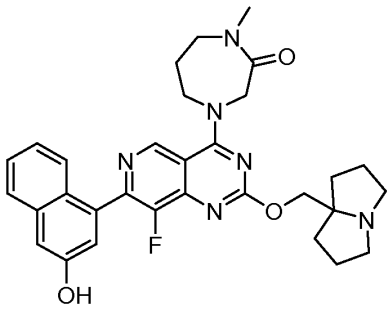
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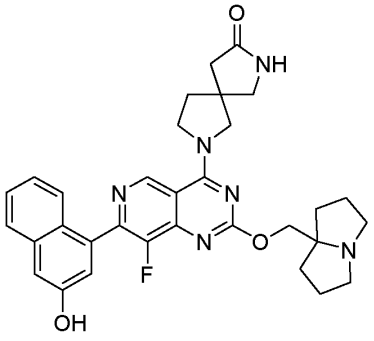
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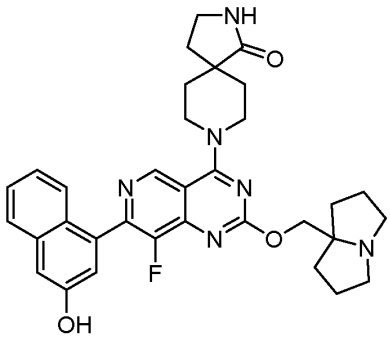
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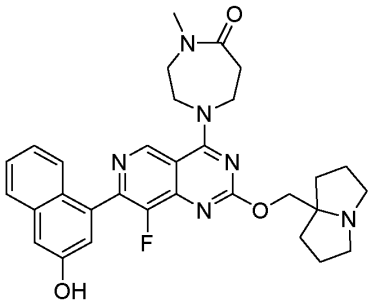
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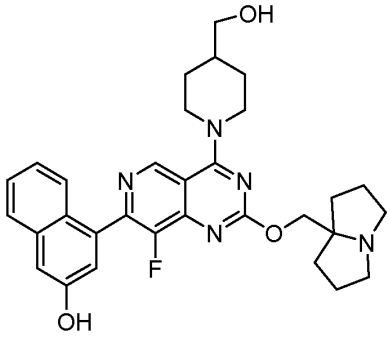
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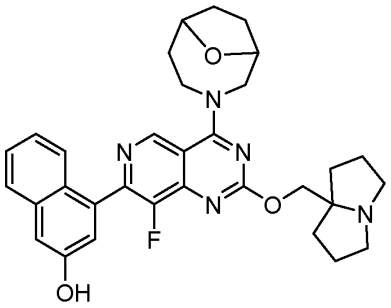
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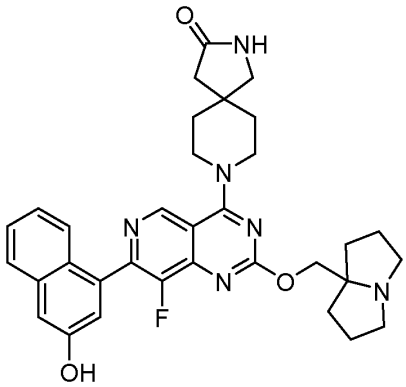
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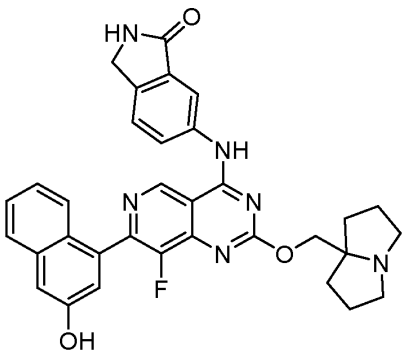
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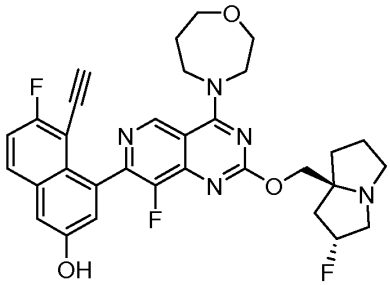
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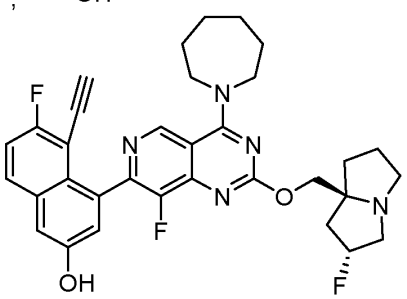
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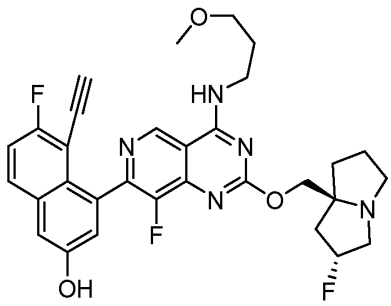
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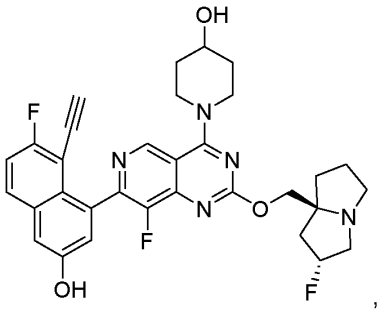
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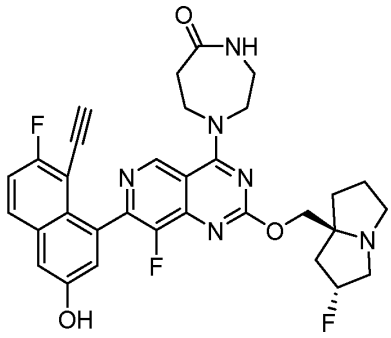
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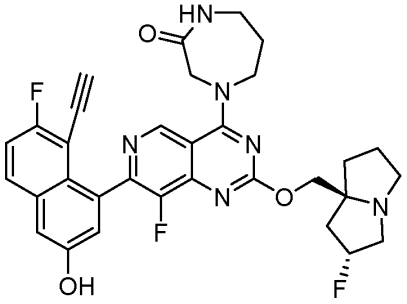
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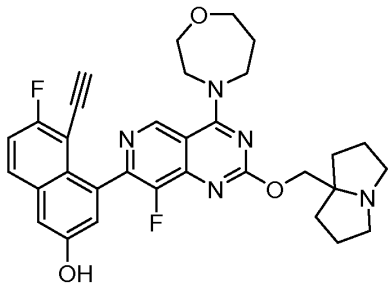
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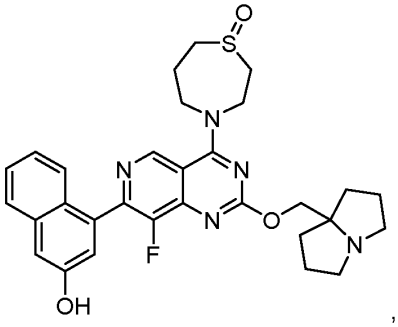
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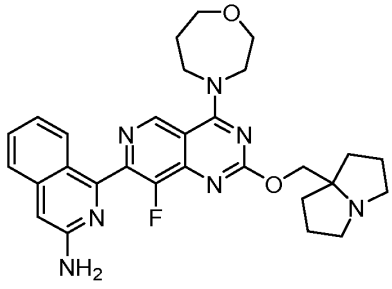
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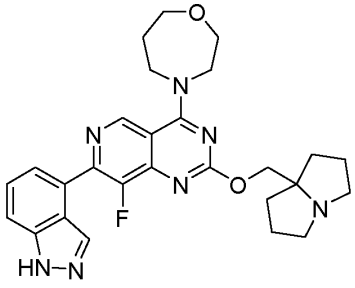
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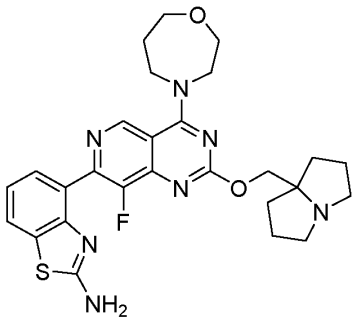
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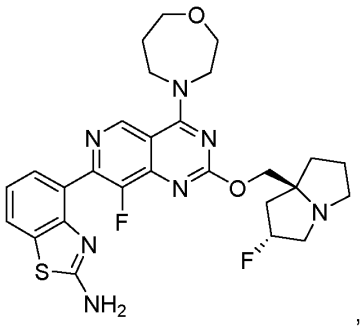
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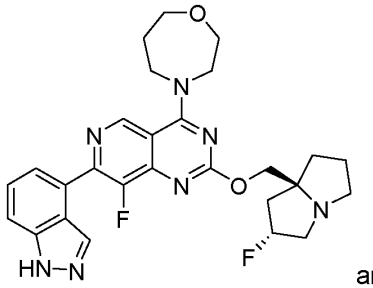
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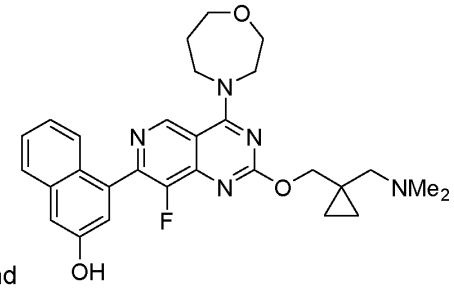
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17. A compound of any one of claims 1 to 16 for medical use.

18. A compound of any one of claims 1 to 16 for use in treating cancer.

19. A compound for use of claim 18, 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.

20. A compound for use of claim 18 or 19, wherein the subject being treated has a cancer having wild-type KRAS.

21. A compound for use of claim 18 or 19, 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.

22. A pharmaceutical composition comprising a compound of any one of claims 1 to 16 and a pharmaceutically acceptable excipient.