

PHARMACEUTICAL COMPOUND

The present invention relates to PARP1 inhibitor compounds, and in particular to PARP1 inhibitor compounds for use in medicine. The inhibitors of the invention may be used in pharmaceutical compositions, and in particular pharmaceutical compositions for treating a cancer. The invention also relates to methods of manufacture of such inhibitors, and methods of treatment using such inhibitors.

Background to the Invention

The family of poly(ADP-ribose) polymerases (PARPs) consists of 17 PARP proteins that catalyse the transfer of ADP-ribose to target proteins, a posttranslational process termed PARylation. Target protein modification by PARylation causes significant changes to function and as such PARPs play an important role in many cellular processes such as chromatin remodelling, transcription, replication, recombination, cell cycle progression and DNA damage repair (Kamaletdinova, T. *et al. Cell.* 2019; 8: 1625). PARP1 and 2 are the most widely studied PARP enzymes, primarily due to their role in DNA damage repair, in particular in the base excision repair (BER) process of DNA single-strand breaks (Ngoi, YL. *et al. Cancer J.* 2021; 27: 521-528). PARP1 is activated by DNA damage breaks, and the subsequent PARylation of target proteins leads to recruitment of additional factors that initiate repair of DNA lesions. Auto-PARylation of PARP triggers the release of bound PARP from the DNA allowing other DNA repair proteins access to complete lesion repair. This highlights the critical role PARP plays in enabling a cancer cell to repair DNA damage caused by exogenous agents such as radiation therapy and chemotherapeutic agents. Hence, inhibition of PARP enzymes has been utilised as a strategy to selectively kill cancer cells that harbour genetic defects in complementary DNA damage repair pathways (Farmer, H. *et al. Nature.* 2005; 434: 917–921). This synthetic lethality approach has been demonstrated successfully in tumours with epigenetic modifications or deleterious mutations in BRCA1 and BRCA2, two functionally redundant tumour suppressor proteins involved in DNA double-strand break (DSB) repair by homologous recombination (HR) (Lord, CJ. and Ashworth, A. *Science.* 2017; 355: 1152–1158). Such tumours with HR deficiency (HRD) are dependent on PARP function for survival – following PARP inhibition in these tumours, DSB breaks will be processed by alternative error-prone repair pathways leading to genomic instability and cancer cell death.

The inhibition of PARP can trap the inactivated PARP at the sites of DNA damage. This leads to replication fork stalling and subsequent collapse in S-phase when the fork reaches the site of the trapped PARP, resulting in the generation of genotoxic DNA double-strand breaks. It is believed that this PARP1-DNA trapping can lead to the selective death of cancer cells harbouring HRD (Farmer, H. *et al. Nature*. 2005; 434: 917–921).

This strategy has led to the successful approval of several PARP inhibitors for the treatment of cancers with HRD, such as in BRCA1/2-mutated breast, ovarian and prostate cancer, as well as in ovarian and prostate cancer harbouring genomic consequences of HRD, and ovarian cancer in the maintenance setting where platinum sensitivity acts as a surrogate for HRD (Fong, PC. *et al. N. Engl. J. Med.* 2009; 361: 123–134).

It has recently been shown that genomic instability, in the form of unrepaired DNA double-strand breaks or micronuclei disruption can trigger innate immune system activation via the cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS), leading to generation of cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) and induction of dimerization of Stimulator of interferon genes (STING). STING subsequently translocates from the endoplasmic reticulum to the Golgi where it recruits and activates TANK-binding kinase 1 (TBK1). TBK1 phosphorylates interferon regulatory transcription factor 3 (IRF3) which drives the production of type I interferons and supports the induction of an adaptive immune response (Zhu, Y. *et al. Mol. Cancer*. 2019, 18: 152).

For example, PARP inhibitor-induced STING pathway activation and anti-tumour immune responses have been demonstrated in multiple tumour models, providing rationale for exploiting combinations of PARP inhibitors with immunotherapies for improved therapeutic efficacy (Sen, T. *et al. Cancer Discov.* 2019; 9: 646–661). For example, the PARP inhibitor Olaparib was also recently shown to induce synthetic lethal effects in combination with a synthetic cyclic dinucleotide STING agonist in DNA damage repair deficient cancer cells and a BRCA-deficient breast cancer model (Pantelidou, C. *et al.* 2021: bioRxiv).

Overall, modulation of nucleic acid sensing pathways via multiple mechanisms has been shown to promote anti-tumour efficacy in a variety of cell and animal models thus demonstrating therapeutic potential for augmenting efficacy of immunotherapies and overcoming resistance to immune checkpoint blockade through use of PARP inhibitors. There are numerous clinical

trials ongoing combining PARP inhibitors with immunotherapies (reviewed in Chabanon, RM, *et al. Nat. Rev. Cancer.* 2021; 21: 701-717).

Recently, PARP1 has also been shown to bind the Epstein Barr Virus (EBV) genome and that PARP1 inhibition can alter EBV chromatin structure and latent gene expression (Morgan, SM. *et al. Nat. Commun.* 2022; 13: 187). Hence, PARP1 inhibitors may play a role in cancers where EBV plays a contributing role such as Burkitt's lymphoma, Hodgkin's lymphoma, nasopharyngeal and gastrointestinal cancers. Interestingly, EBV has also been shown to be a causative factor in multiple sclerosis (MS) whereby EBV infection greatly increases the risk of subsequent MS (Bjornevik, K. *et al. Science* (2021); 375: 296-301).

First-generation PARP inhibitors generally demonstrate non-selective activity at PARP1 and 2. Haematological toxicities such as anaemia, neutropenia and thrombocytopenia are associated with clinical use of these molecules which restricts their use in combination with cytotoxic chemotherapies and other targeted agents due to dose-limiting cytopenias (LaFargue, CJ. *et al. Lancet Oncol.* 2019, 20, e15–e28). Evidence from pre-clinical mouse studies strongly suggests that PARP2 inhibition is a major driver of these haematological toxicities, with PARP2 being particularly linked to erythropoiesis in mice (Farrés, J. *et al. Blood.* 2013; 122: 44-54). In addition, PARP2 function has been shown to be dispensable for anti-tumour activity in HRD mouse cancer models (Ronson, G E. *et al. Nat. Commun.* 2018, 9: 746). Taken together, these data suggest an unmet medical need for the development of inhibitors with improved selectivity for PARP1 over PARP2 and other PARPs, thus providing expanded therapeutic utility (1) as single agents and (2) in combination with other anti-cancer agents.

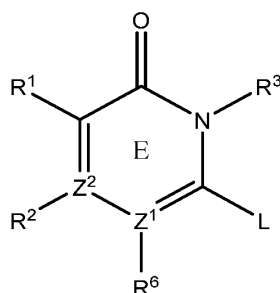
To date, two PARP1-selective inhibitors, AZD5305 and AZD9574, have entered clinical development. AZD5305 was described as a potent PARP1 inhibitor and trapper with 500-fold selectivity over PARP2 and less off-target activity against secondary pharmacology targets than first-generation PARP inhibitors (Johannes, JW. *et al. J. Med. Chem.* 2021; 64: 14498-14512). Importantly, significantly less haematotoxicity was observed for AZD5305 in rodent models than with first-generation PARP inhibitors, confirming the reported pathogenic role of PARP2 in haematologic toxicity (Illuzzi, G. *et al. Clin. Cancer Res.* 2022; CCR-22-0301).

Having regard to the above, it is an aim of the present invention to provide PARP1 inhibitors, and in particular PARP1 inhibitors for use in medicine. It is a further aim to provide

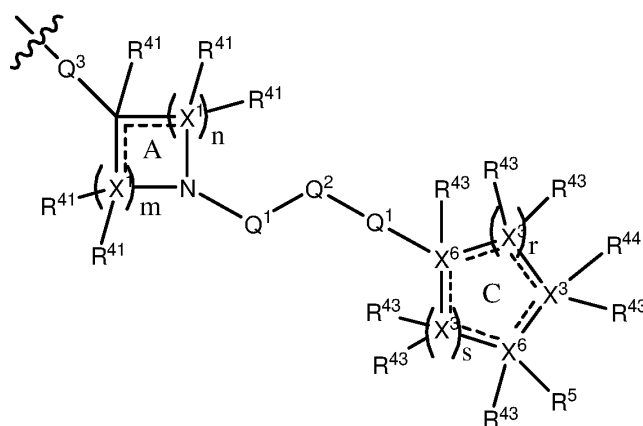
pharmaceutical compositions comprising such inhibitors, and in particular to provide compounds and pharmaceutical compositions for treating a cancer. It is also an aim to provide methods of synthesis of the compounds.

Summary of the Invention

Accordingly, the present invention provides a PARP1 inhibitor compound for use in medicine, which compound comprises the following structure:



wherein R¹ is selected from H and a substituted or unsubstituted organic group; R² may be present or absent and is independently selected from H and a substituted or unsubstituted organic group; R¹ and R² may together form a ring; R³ is independently selected from H and a substituted or unsubstituted organic group; R⁶ may be present or absent and is independently selected from H and a substituted or unsubstituted organic group; Z¹ and Z² are independently selected from C and N; and L comprises a group having the following structure:



wherein, n is a number independently selected from 0, 1, 2, 3, 4, 5 and 6; m is a number independently selected from 0, 1, 2, 3, 4, 5 and 6; and $m + n$ is a number selected from 2, 3, 4, 5, and 6; preferably wherein both n and m are at least 1;

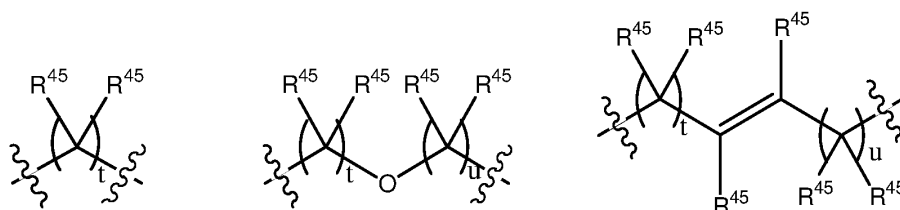
wherein, r is a number independently selected from 0, 1, 2, 3, 4, and 5; s is a number independently selected from 0, 1, 2, 3, 4, and 5, preferably from 1, 2, 3, 4 and 5; and $r + s$ is a number selected from 1, 2, 3, 4, and 5; preferably wherein both r and s are at least 1;

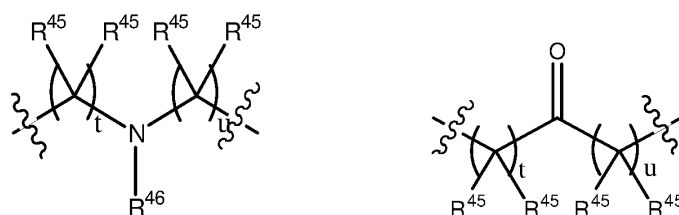
and wherein, each X^1 may be the same or different and is independently selected from C, N, O and S; each X^3 may be the same or different and is independently selected from C, N, O and S, preferably wherein at least one X^3 is independently N; each X^6 may be the same or different and is independently selected from C and N; each R^{41} may be the same or different, and may be present or absent, and is selected from H and a substituted or unsubstituted organic group; each R^{43} may be the same or different, and may be present or absent, and is selected from H and a substituted or unsubstituted organic group; and R^{44} may be present or absent, and is selected from H and a substituted or unsubstituted organic group;

and wherein, the dotted lines indicate that: the ring A may comprise single bonds, or a combination of both single and double bonds, and may be aliphatic or aromatic; and independently the ring C may comprise single bonds, or a combination of both single and double bonds, and may be aliphatic or aromatic;

and wherein, R^5 is selected from H and a substituted or unsubstituted organic group and is preferably a substituted or unsubstituted organic group;

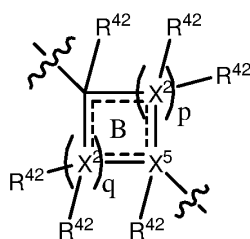
and wherein each Q^1 may be the same or different, and may be present or absent, and comprises a group independently selected from the following structures:





wherein t is independently a number selected from 0, 1, 2, 3, 4 and 5; u is independently a number selected from 0, 1, 2, 3, 4 and 5; and $t + u$ is a number selected from 0, 1, 2, 3, 4, 5 and 6 (preferably a number selected from 0, 1, 2, and 3); each R^{45} may be the same or different and is independently selected from H and a substituted or unsubstituted organic group; and R^{46} is selected from H and a substituted or unsubstituted organic group;

and wherein Q^2 may be present or absent and is a group having the following structure:

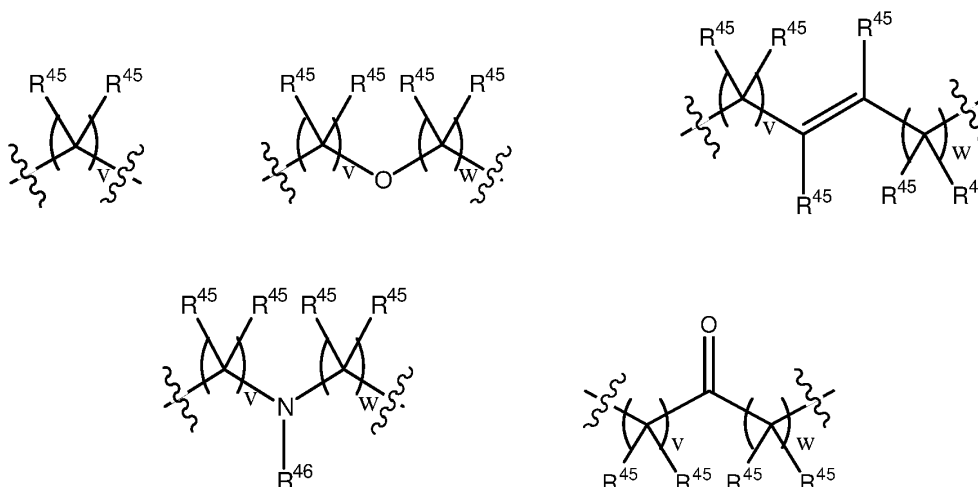


wherein, p is a number independently selected from 0, 1, 2, 3, 4, 5 and 6; q is a number independently selected from 0, 1, 2, 3, 4, 5 and 6; and $p + q$ is a number selected from 2, 3, 4, 5, and 6;

and wherein, each X^2 may be the same or different and is independently selected from C, N, O and S; X^5 is independently selected from C and N; each R^{42} may be the same or different, and may be present or absent, and is selected from H and a substituted or unsubstituted organic group;

and wherein, the dotted lines indicate that: the ring B may comprise single bonds, or a combination of both single and double bonds, and may be aliphatic or aromatic;

and wherein Q^3 may be present or absent and comprises a group independently selected from the following structures:



wherein v is independently a number selected from 0, 1, 2, 3, 4 and 5; w is independently a number selected from 0, 1, 2, 3, 4 and 5; and $v + w$ is a number selected from 0, 1, 2, 3, 4, 5 and 6 (preferably a number selected from 0, 1, and 2).

In the context of the present invention, the Z^1 , Z^2 , X^1 , X^2 , X^3 , X^4 , X^5 and X^6 atoms maintain their normal valency and the number of substituents attached to these will depend on their nature and the number of other bonds they possess. Maintaining the valency means ensuring that an atom has its normal (typically most common) valency in organic compounds (i.e. 2 for oxygen and divalent sulphur, 3 for nitrogen and 4 for carbon). Nitrogen atoms may, in some instances, have 4 bonds, but in such cases they are typically positively charged such that the compound may have a counter-ion. Such compounds are also considered to be part of the invention, and in these cases, due to the positive charge, it will be clear that the nitrogen atom still maintains its normal valency of 3. For the avoidance of doubt, where the number of R groups may vary according to the choice of X group, it may vary as follows.

R^6 is absent when Z^1 is N. R^2 is absent when Z^2 is N. Each R^{41} may be the same or different, provided that for each X^1 : R^{41} is absent when X^1 is O or divalent S; R^{41} is absent when X^1 is N and is double bonded to an adjacent atom; one R^{41} is present when X^1 is N and is not double bonded to an adjacent atom; one R^{41} is present when X^1 is C and is double bonded to an adjacent atom; and two R^{41} are present when X^1 is C and is not double bonded to an adjacent atom. Each

R^{43} may be the same or different, provided that for each X^3 : R^{43} is absent when X^3 is O or divalent S; R^{43} is absent when X^3 is N and is double bonded to an adjacent atom; one R^{43} is present when X^3 is N and is not double bonded to an adjacent atom; one R^{43} is present when X^3 is C and is double bonded to an adjacent atom; and two R^{43} are present when X^3 is C and is not double bonded to an adjacent atom. For each X^6 : R^{43} is absent when X^6 is N or is C and is double bonded to an adjacent atom; and one R^{43} is present when X^6 is C and not double bonded to an adjacent atom. For the X^3 with which it is associated: R^{44} is absent when X^3 is O or divalent S; R^{44} is absent when X^3 is N and is double bonded to an adjacent atom; one R^{44} is present when X^3 is N and is not double bonded to an adjacent atom; one R^{44} is present when X^3 is C and is double bonded to an adjacent atom; and one R^{44} is present when X^3 is C and the C is attached to R^{43} and not double bonded to an adjacent atom. Each R^{42} may be the same or different, provided that for each X^2 : R^{42} is absent when X^2 is O or divalent S; R^{42} is absent when X^2 is N and is double bonded to an adjacent atom; one R^{42} is present when X^2 is N and is not double bonded to an adjacent atom; one R^{42} is present when X^2 is C and is double bonded to an adjacent atom; and two R^{42} are present when X^2 is C and is not double bonded to an adjacent atom. For X^5 : R^{42} is absent when X^5 is N or is C and is double bonded to an adjacent atom; and one R^{42} is present when X^5 is C and not double bonded to an adjacent atom. Each R^{11} may be the same or different, provided that for each X^4 : R^{11} is absent when X^4 is O or divalent S; R^{11} is absent when X^4 is N and is double bonded to an adjacent atom; one R^{11} is present when X^4 is N and is not double bonded to an adjacent atom; one R^{11} is present when X^4 is C and is double bonded to an adjacent atom; and two R^{11} are present when X^4 is C and is not double bonded to an adjacent atom. Each R^{14} bonded to N may be the same or different, provided that R^{14} is absent when the N is double bonded to an adjacent atom.

In these compounds, and elsewhere herein, in some embodiments any R group may form a ring with any other R group on an adjacent and/or proximal atom, although in most embodiments this is not preferred, except where explicitly stated. Thus, in some embodiments the following substituents may together form a ring: R^5 with R^{44} ; R^{11} with another R^{11} ; R^{13} with another R^{13} ; R^{41} with another R^{41} ; R^{42} with another R^{42} ; R^{43} with another R^{43} ; R^{45} with another R^{45} . In the context of the present invention, an adjacent and/or proximal atom may mean another atom directly bonded to an atom (adjacent) or may be two atoms with only a single atom in between (proximal), or may mean two atoms close enough sterically to be capable of forming a ring

(proximal). Preferably R groups attached to the same atom do not together form a ring, although this is not excluded.

In the present context the invention includes compounds in which a single R group on an atom, or two R groups on the same atom, form a group which is double bonded to that atom. Accordingly, an R group, or two R groups attached to the same atom, may together form a =O group, or a =C(R')₂ group (wherein each R' group is the same or different and is H or an organic group, preferably H or a straight or branched C₁-C₆ alkyl group). This is more typical in cases where the R groups are attached to a C atom, such that together they form a C=O group or a C=C(R')₂ group. Thus in some cases a C ring atom in a ring may comprise a =O group, as may an X, and/or one or more of R¹¹, R⁴¹, R⁴², R⁴³, R⁴⁴, and R⁴⁵.

In the present context a part of any structure present in brackets may be repeated the number of times given by the numbers next to the brackets (whether regular brackets or square brackets). For example, in the case of (C(R))_{0,1,2} or [C(R)]_{0,1,2} the C-R group may be absent, present once i.e. -C(R)-; or present twice i.e. -C(R)-C(R)-.

In the context of the present invention, a compound is considered to be a PARP1 inhibitor if its presence is capable of preventing or reducing the ability of immobilised PARP1 to undergo auto-poly-ADP ribosylation (AutoPARylation) following incubation with biotinylated-NAD⁺ as compared to the same process in its absence. Typically, the compound is considered to be a PARP1 inhibitor if it has an IC₅₀ < 10 μM in a suitable assay. A suitable assay may be conducted using 2 nM PARP1, 2 μM biotin-NAD⁺ assay solution in 20 mM HEPES (pH 7.5), 100 mM NaCl, 2 mM DTT, 0.1 % BSA (w/v), 0.02 % Tween (v/v) assay buffer. PARylation may take place for 2 h at room temperature and may be detected using a dissociation-enhanced lanthanide fluorescence immunoassay (DELFI) readout. A particularly suitable assay is described in the Examples below. Preferably, the compound has an IC₅₀ < 1 μM, more preferably < 100 nM and most preferably < 10 nM in the PARP1 inhibitor assay.

A compound is also considered to be a selective PARP1 inhibitor if its presence is capable of displacing or reducing the ability of a high affinity Cy5 fluorescent dye-labelled chemical probe to bind to PARP1 whilst displacing the same chemical probe at PARP2 with at least 10-fold weaker activity. Typically, the compound is considered to be a selective PARP1 inhibitor if it

has an $IC_{50} < 10 \mu M$ in this assay at PARP1 with at least 10-fold selectivity preference over PARP2. A suitable such assay may be conducted for 1 h at room temperature using 10 nM PARP1 or PARP2, Tb-cryptate antibody and PARP1/2 binding probe in 20 mM HEPES (pH 7.5), 100 mM NaCl, 2 mM DTT, 0.1 % BSA (w/v), 0.02 % Tween (v/v) assay buffer. Probe binding displacement may be detected using homogeneous time-resolved fluorescence. A particularly suitable assay is described in the Examples below. Preferably the selectivity preference of PARP1 over PARP2 is at least 50-fold, more preferably at least 100-fold.

The compound is also considered to be a selective PARP1 inhibitor if it has an $IC_{50} < 10 \mu M$ at PARP1 with at least 10-fold selectivity preference over PARP2 in NanoBRET assays demonstrating cellular target engagement. These assays are based on bioluminescence resonance energy transfer (BRET) between a Nano-luc-tagged protein (eg PARP1 or PARP2) and a fluorescent group on a high affinity NAD^+ competitive binding probe. Such cellular probe displacement assays can be utilised to measure inhibitor affinities and selectivity ratios at PARP1 and 2. A particularly suitable assay is described in the Examples below. Preferably the selectivity preference of PARP1 over PARP2 is at least 50-fold, more preferably at least 100-fold.

In all of the embodiments of this invention (both above and below herein), the substituents (each of the R groups) are not especially limited, provided that they do not prevent the PARP1 inhibitory function from occurring. In all of the embodiments mentioned in connection with this invention, both above and in the following, the substituents are selected from H and an organic group. Thus, both above and in the following, the terms 'substituent' and 'organic group' are not especially limited and may be any functional group or any atom, especially any functional group or atom common in organic chemistry. Thus, 'substituent' and 'organic group' may have any of the following meanings.

The organic group may comprise any one or more atoms from any of groups IIIA, IVA, VA, VIA or VIIA of the Periodic Table, such as a B, Si, N, P, O, or S atom (e.g. OH, OR, NH_2 , NHR , NR_2 , SH, SR, SO_2R , SO_3H , PO_4H_2) or a halogen atom (e.g. F, Cl, Br or I) where R is a linear or branched lower hydrocarbon (1-6 C atoms) or a linear or branched higher hydrocarbon (7 C atoms or more, e.g. 7-40 C atoms).

The organic group preferably comprises a hydrocarbon group. The hydrocarbon group may comprise a straight chain, a branched chain or a cyclic group. Independently, the hydrocarbon group may comprise an aliphatic or an aromatic group. Also independently, the hydrocarbon group may comprise a saturated or unsaturated group.

When the hydrocarbon comprises an unsaturated group, it may comprise one or more alkene functionalities and/or one or more alkyne functionalities. When the hydrocarbon comprises a straight or branched chain group, it may comprise one or more primary, secondary and/or tertiary alkyl groups.

When the hydrocarbon comprises a cyclic group it may comprise an aromatic ring, a non-aromatic ring, an aliphatic ring, a heterocyclic group, and/or fused ring derivatives of these groups. The ring may be fully saturated, partially saturated, or fully unsaturated. The cyclic group may thus comprise a benzene, naphthalene, anthracene, phenanthrene, phenalene, biphenylene, pentalene, indene, *as*-indacene, *s*-indacene, acenaphthylene, fluorene, fluoranthene, acephenanthrylene, azulene, heptalene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyrrolidine, furan, oxetane, tetrahydrofuran, 2-azatetrahydrofuran, 3-aza-tetrahydrofuran, oxazole, isoxazole, furazan, 1,2,4-oxadiazol, 1,3,4-oxadiazole, thiophene, isothiazole, thiazole, thiolane, pyridine, pyridazine, pyrimidine, pyrazine, piperidine, 2-azapiperidine, 3-azapiperidine, piperazine, pyran, tetrahydropyran, 2-azapyran, 3-azapyran, 4-azapyran, 2-aza-tetrahydropyran, 3-aza-tetrahydropyran, morpholine, thiopyran, 2-azathiopyran, 3-azathiopyran, 4-azathiopyran, thiane, indole, indazole, benzimidazole, 4-azaindole, 5-azaindole, 6-azaindole, 7-azaindole, isoindole, 4-azaisoindole, 5-azaisoindole, 6-azaisoindole, 7-azaisoindole, indolizine, 1-azaindolizine, 2-azaindolizine, 3-azaindolizine, 5-azaindolizine, 6-azaindolizine, 7-azaindolizine, 8-azaindolizine, 9-azaindolizine, purine, carbazole, carboline, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, quinoline, cinnoline, quinazoline, quinoxaline, 5-azaquinoline, 6-azaquinoline, 7-azaquinoline, isoquinoline, phthalazine, 6-azaisoquinoline, 7-azaisoquinoline, pteridine, chromene, isochromene, acridine, phenanthridine, perimidine, phenanthroline, phenoxazine, xanthene, phenoxanthiin, and/or thianthrene, as well as regioisomers of the above groups. These groups may generally be attached at any point in the group, and also may be attached at a hetero-atom or at a carbon atom. In some instances particular attachment points are preferred, such as at 1-yl, 2-yl and the like, and these are specified explicitly where

appropriate. All tautomeric ring forms are included in these definitions. For example pyrrole is intended to include 1*H*-pyrrole, 2*H*-pyrrole and 3*H*-pyrrole.

The number of carbon atoms in the hydrocarbon group is not especially limited, but preferably the hydrocarbon group comprises from 1-40 C atoms. The hydrocarbon group may thus be a lower hydrocarbon (1-6 C atoms) or a higher hydrocarbon (7 C atoms or more, e.g. 7-40 C atoms). The lower hydrocarbon group may be a methyl, ethyl, propyl, butyl, pentyl or hexyl group or regioisomers of these, such as isopropyl, isobutyl, tert-butyl, etc. The number of atoms in the ring of the cyclic group is not especially limited, but preferably the ring of the cyclic group comprises from 3-10 atoms, such as 3, 4, 5, 6, 7, 8, 9 or 10 atoms.

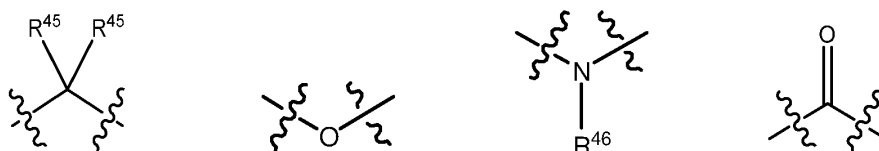
The groups comprising heteroatoms described above, as well as any of the other groups defined above, may comprise one or more heteroatoms from any of groups IIIA, IVA, VA, VIA or VIIA of the Periodic Table, such as a B, Si, N, P, O, or S atom or a halogen atom (e.g. F, Cl, Br or I). Thus, the substituent may comprise one or more of any of the common functional groups in organic chemistry, such as hydroxy groups, carboxylic acid groups, ester groups, ether groups, aldehyde groups, ketone groups, amine groups, amide groups, imine groups, thiol groups, thioether groups, sulphate groups, sulphonic acid groups, sulphonyl groups, and phosphate groups etc. The substituent may also comprise derivatives of these groups, such as carboxylic acid anhydrides and carboxylic acid halides.

In addition, any substituent may comprise a combination of two or more of the substituents and/or functional groups defined above.

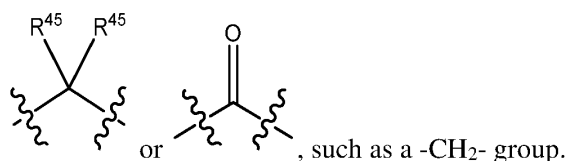
The rings A, B (when present) and C of the compounds of the present invention form a bicyclic or tricyclic ring structure (which may comprise further fused rings when the substituents on either ring themselves form a ring). Each of rings A, B, C and D are not necessarily limited, provided that they do not prevent the PARP1 inhibitory function from occurring. Rings A, B, C and D may independently be comprised of an aromatic ring, a non-aromatic ring, an aliphatic ring, and/or a heterocyclic group. The rings may be fully saturated, partially saturated, or fully unsaturated. Each ring may thus independently comprise a benzene, naphthalene, anthracene, phenanthrene, phenalene, biphenylene, pentalene, indene, *as*-indacene, *s*-indacene, acenaphthylene, fluorene, fluoranthene, acephenanthrylene, azulene, heptalene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pyrrolidine, oxetane, furan,

tetrahydrofuran, 2-aza-tetrahydrofuran, 3-aza-tetrahydrofuran, oxazole, isoxazole, furazan, 1,2,4-oxadiazol, 1,3,4-oxadiazole, thiophene, isothiazole, thiazole, thiolane, pyridine, pyridazine, pyrimidine, pyrazine, piperidine, 2-azapiperidine, 3-azapiperidine, piperazine, pyran, tetrahydropyran, 2-azapyran, 3-azapyran, 4-azapyran, 2-aza-tetrahydropyran, 3-aza-tetrahydropyran, morpholine, thiopyran, 2-azathiopyran, 3-azathiopyran, 4-azathiopyran, thiane, indole, indazole, benzimidazole, 4-azaindole, 5-azaindole, 6-azaindole, 7-azaindole, isoindole, 4-azaisoindole, 5-azaisoindole, 6-azaisoindole, 7-azaisoindole, indolizine, 1-azaindolizine, 2-azaindolizine, 3-azaindolizine, 5-azaindolizine, 6-azaindolizine, 7-azaindolizine, 8-azaindolizine, 9-azaindolizine, purine, carbazole, carboline, benzofuran, isobenzofuran, benzothiophene, isobenzothiophene, quinoline, cinnoline, quinazoline, quinoxaline, 5-azaquinoline, 6-azaquinoline, 7-azaquinoline, isoquinoline, phthalazine, 6-azaisoquinoline, 7-azaisoquinoline, pteridine, chromene, isochromene, acridine, phenanthridine, perimidine, phenanthroline, phenoxazine, xanthene, phenoxanthiin, and/or thianthrene, as well as regioisomers of the above groups. These rings may generally be substituted at any point in the group, and also may be substituted at a hetero-atom or at a carbon atom. All tautomeric ring forms are included in these definitions. For example, pyrrole is intended to include 1*H*-pyrrole, 2*H*-pyrrole and 3*H*-pyrrole.

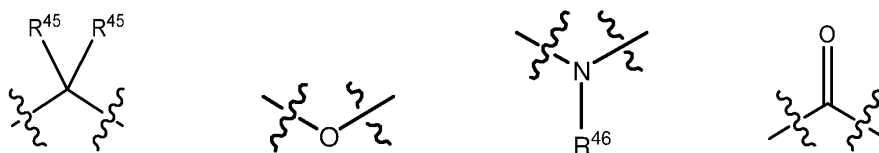
In typical embodiments, the invention provides a compound as defined above, wherein Q³ is absent or is a group independently selected from the following structures:



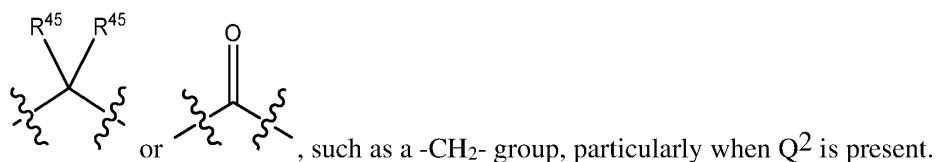
wherein each R⁴⁵ may be the same or different and is independently selected from H and a substituted or unsubstituted organic group; and R⁴⁶ is selected from H and a substituted or unsubstituted organic group. It is preferred that Q³ is absent or is



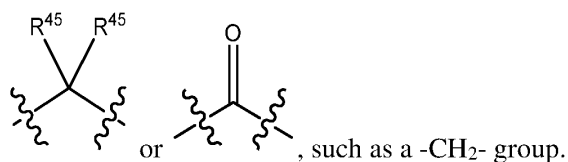
In typical embodiments, the invention provides a compound as defined above, wherein Q^2 is present and each Q^1 is independently absent or is a group independently selected from the following structures:



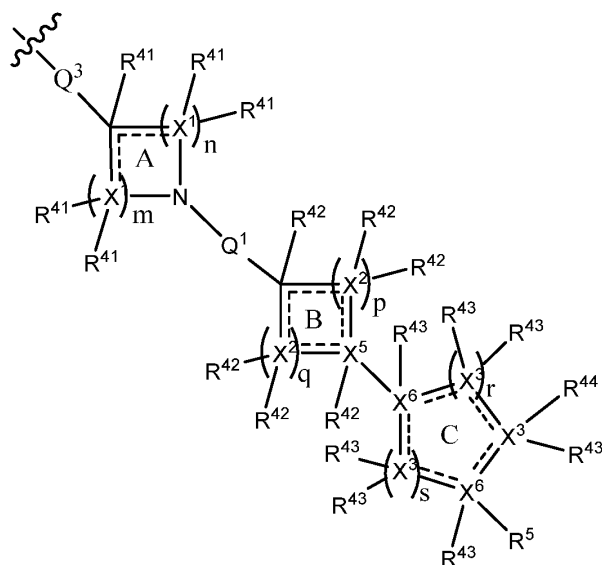
wherein each R^{45} may be the same or different and is independently selected from H and a substituted or unsubstituted organic group; and R^{46} is selected from H and a substituted or unsubstituted organic group. It is preferred that Q^1 is absent or is



The Q^1 group bound to ring A is preferably

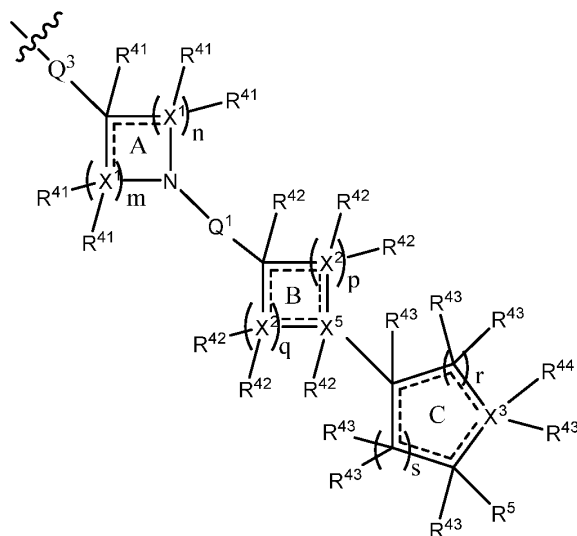


In some embodiments, the invention provides a compound as defined above, wherein the group L comprises a group having the following structure:



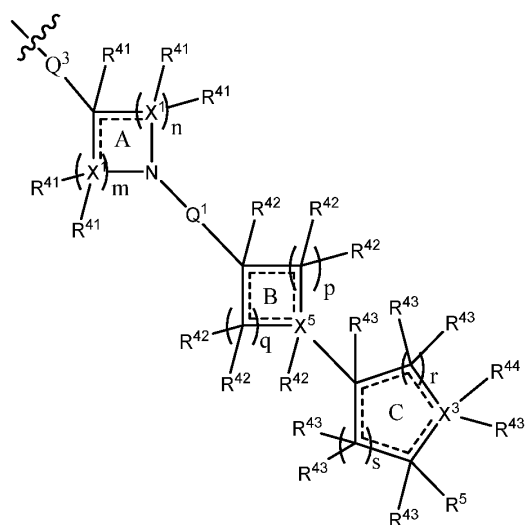
wherein Q^1 is absent or is a group as defined above, Q^3 is absent or is a group as defined above, and n , m , p , q , r , s , X^1 , X^2 , X^3 , X^5 , X^6 , R^{41} , R^{42} , R^{43} , R^{44} , R^5 , and rings A, B, and C are as defined above. It is preferred that X^5 is N with no R^{42} substituent.

In some embodiments, the group L comprises a group having the following structure:



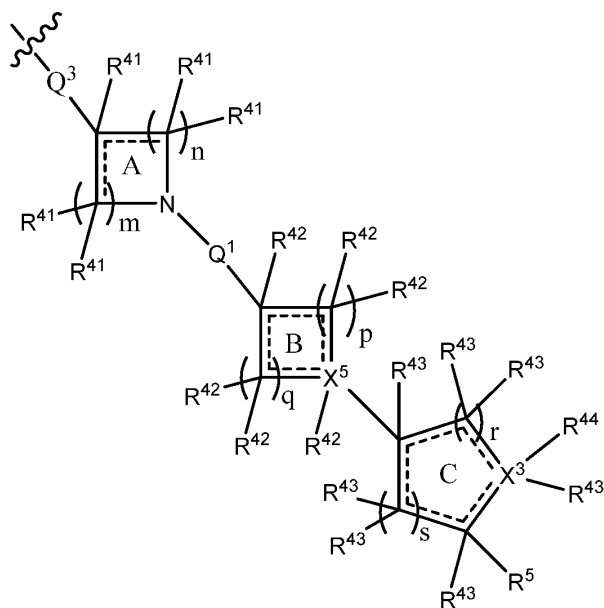
wherein n , m , p , q , r , s , X^1 , X^2 , X^3 , X^5 , R^{41} , R^{42} , R^{43} , R^{44} , R^5 , Q^1 , Q^3 and rings A, B, and C are as defined above. It is preferred that X^5 is N with no R^{42} substituent.

In some embodiments, the group L comprises a group having the following structure:



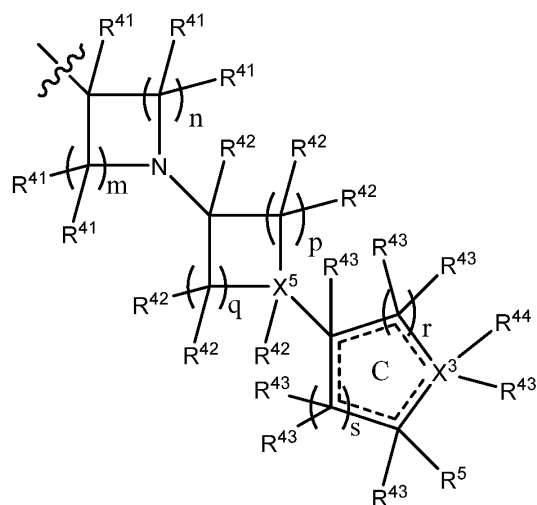
wherein n , m , p , q , r , s , X^1 , X^3 , X^5 , R^{41} , R^{42} , R^{43} , R^{44} , R^5 , Q^1 , Q^3 and rings A, B, and C are as defined above. It is preferred that X^5 is N with no R^{42} substituent.

In some embodiments, the group L comprises a group having the following structure:



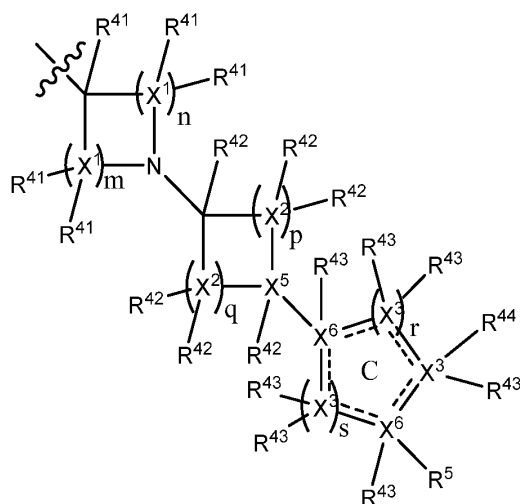
wherein n , m , p , q , r , s , X^3 , X^5 , R^{41} , R^{42} , R^{43} , R^{44} , R^5 , and rings A, B, and C are as defined above. It is preferred that X^5 is N with no R^{42} substituent.

In some embodiments, the group L comprises a group having the following structure:



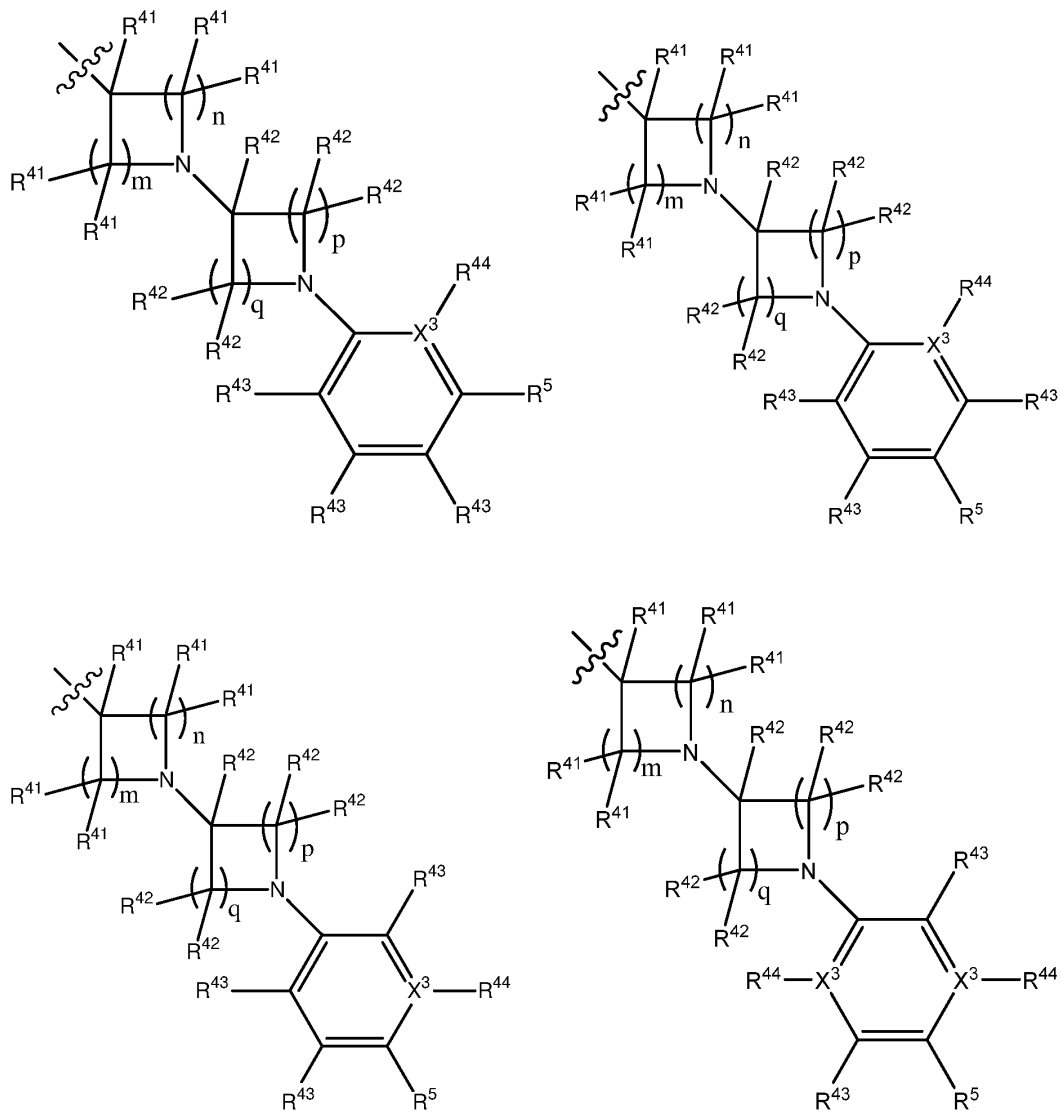
wherein n , m , p , q , r , s , X^3 , X^5 , R^{41} , R^{42} , R^{43} , R^{44} , R^5 , and ring C, are as defined above. It is preferred that X^5 is N with no R^{42} substituent.

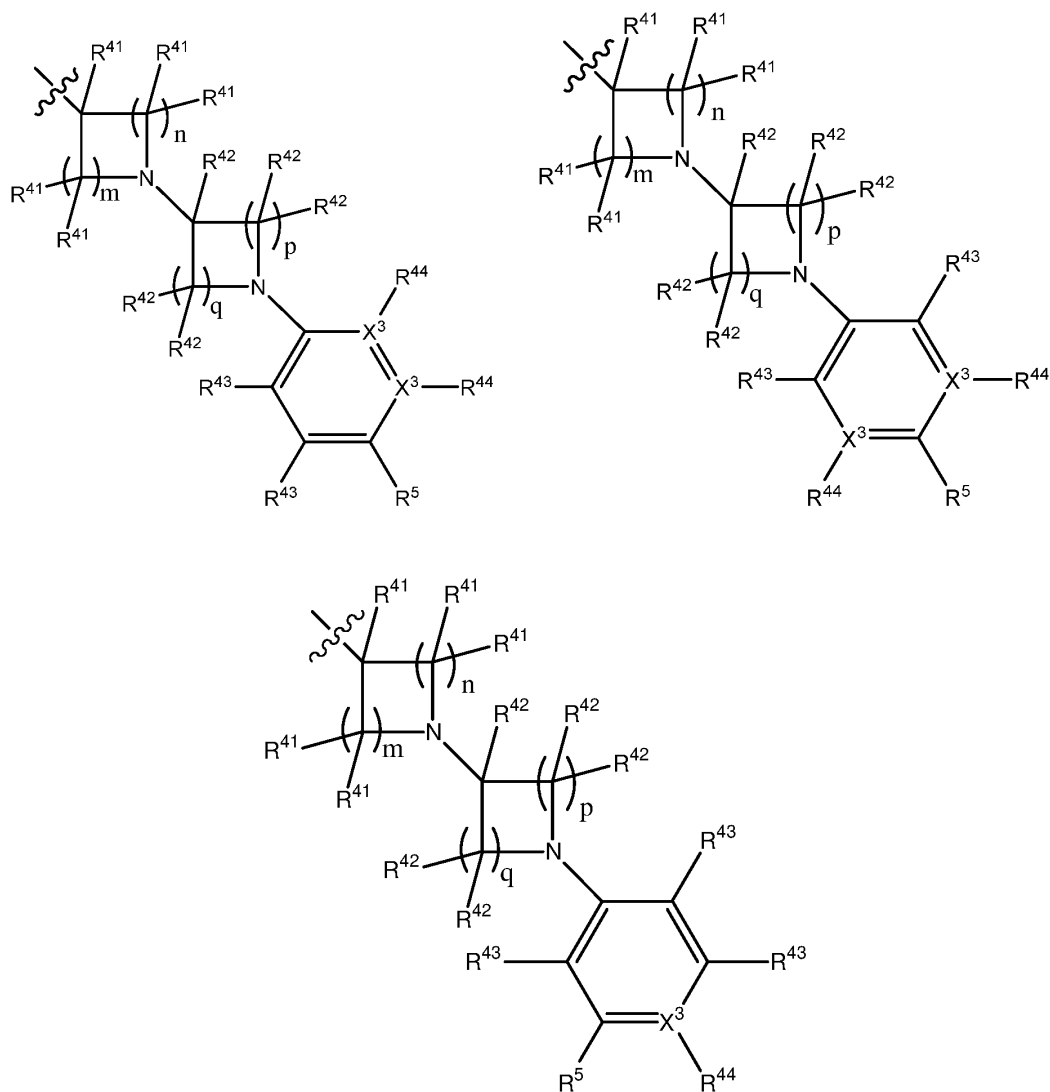
In some embodiments, the group L comprises a group having the following structure:



wherein n , m , p , q , r , s , X^1 , X^2 , X^3 , X^5 , X^6 , R^{41} , R^{42} , R^{43} , R^{44} , R^5 , and ring C, are as defined above. It is preferred that X^5 is N with no R^{42} substituent.

In some embodiments, the group L comprises a group selected from the following structures:

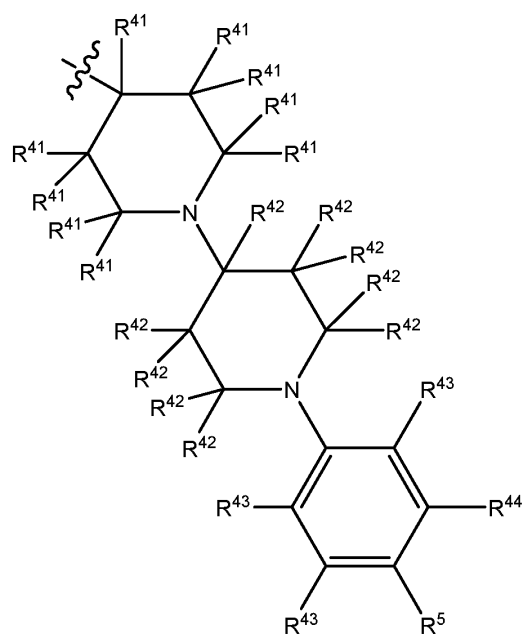
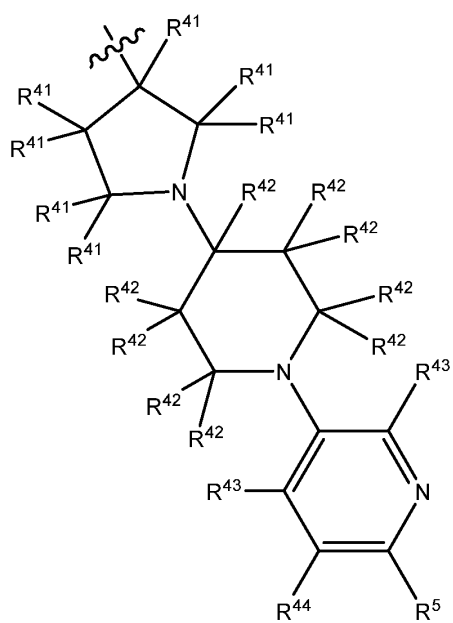
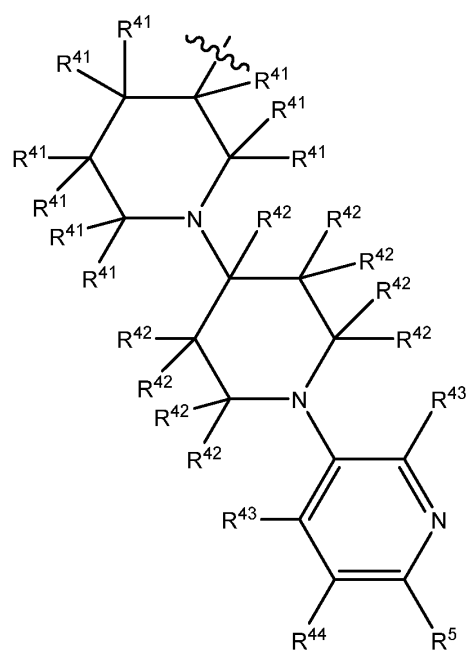
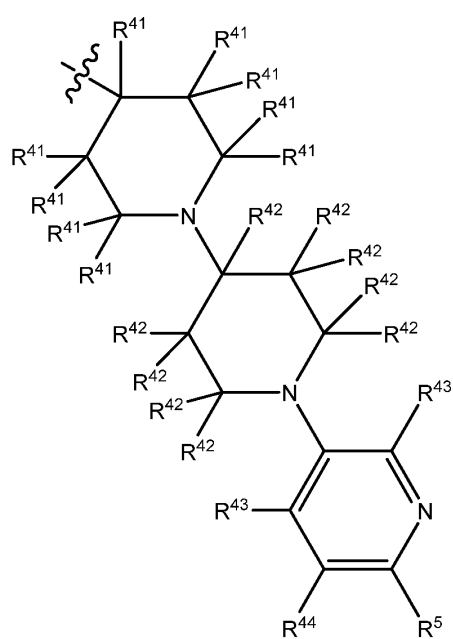


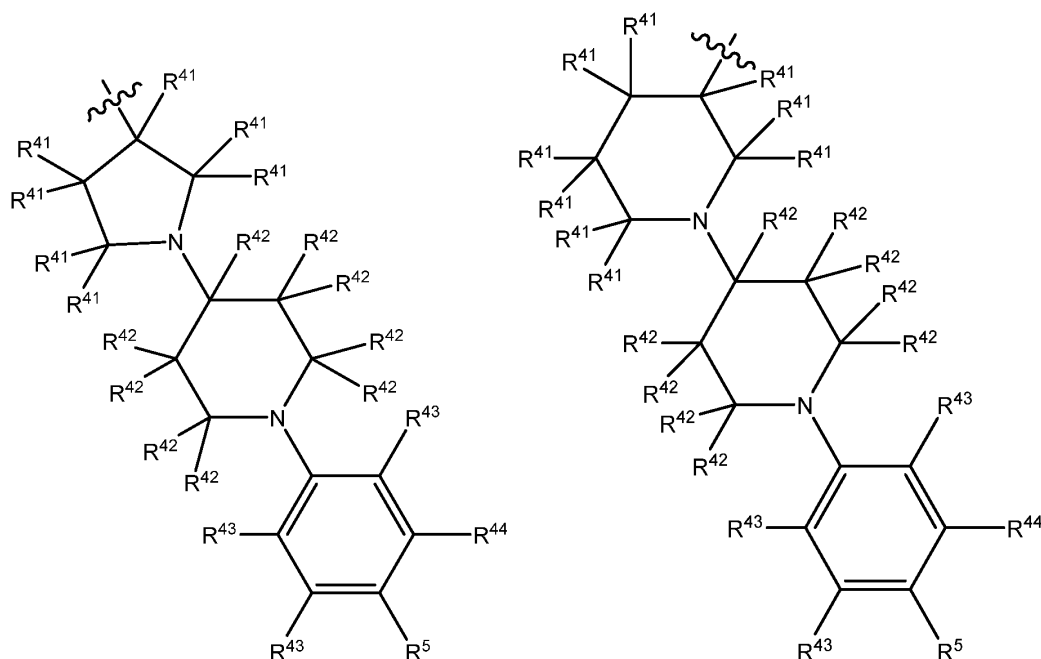


wherein n , m , p , q , X^3 , R^{41} , R^{42} , R^{43} , R^{44} , and R^5 , are as defined above.

In these structures for the L group it is preferred that m is selected from 1 or 2, n is selected from 2 or 3, p is selected from 1, 2 or 3 (more preferably for 2 or 3) and q is selected from 1 or 2.

In some embodiments, group L comprises a group having any the following structures:





wherein, R^{41} , R^{42} , R^{43} , R^{44} , and R^5 are as defined above.

Typically, R^{41} , R^{42} , R^{43} , R^{44} and R^5 are each independently selected from H and a group selected from the following groups:

- deuterium;
- a halogen (such as -F, -Cl, -Br and -I);
- a nitrile group;
- a substituted or unsubstituted linear or branched C_1 - C_6 alkyl group (such as Me, Et, Pr, i-Pr, n-Bu, i-Bu, t-Bu, pentyl and hexyl);
- a substituted or unsubstituted linear or branched C_1 - C_6 alkyl-aryl group (such as $-CH_2Ph$, $-CH_2(2,3 \text{ or } 4)F-Ph$, $-CH_2(2,3 \text{ or } 4)Cl-Ph$, $-CH_2(2,3 \text{ or } 4)Br-Ph$, $-CH_2(2,3 \text{ or } 4)I-Ph$, $-CH_2CH_2Ph$, $-CH_2CH_2CH_2Ph$, $-CH_2CH_2CH_2CH_2Ph$, $-CH_2CH_2CH_2CH_2CH_2Ph$, and $-CH_2CH_2CH_2CH_2CH_2CH_2Ph$);
- a substituted or unsubstituted linear or branched C_1 - C_6 halogenated alkyl group (such as $-CH_2F$, $-CH_2Cl$, $-CH_2Br$, $-CH_2I$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CH_2CF_3$, $-CH_2CCl_3$, $-CH_2CBr_3$, and $-CH_2Cl_3$);

- -NH_2 or a substituted or unsubstituted linear or branched primary secondary or tertiary $\text{C}_1\text{-C}_6$ amine group (such as -NMeH , -NMe_2 , -NEtH , -NEtMe , -NEt_2 , -NPrH , -NPrMe , -NPrEt , -NPr_2 , -NBuH , -NBuMe , -NBuEt , $\text{-CH}_2\text{-NH}_2$, $\text{-CH}_2\text{-NMeH}$, $\text{-CH}_2\text{-NMe}_2$, $\text{-CH}_2\text{-NEtH}$, $\text{-CH}_2\text{-NEtMe}$, $\text{-CH}_2\text{-NEt}_2$, $\text{-CH}_2\text{-NPrH}$, $\text{-CH}_2\text{-NPrMe}$, and $\text{-CH}_2\text{-NPrEt}$);
- a substituted or unsubstituted amino-aryl group (such as -NH-Ph , $\text{-NH-(2,3 or 4)F-Ph}$, $\text{-NH-(2,3 or 4)Cl-Ph}$, $\text{-NH-(2,3 or 4)Br-Ph}$, $\text{-NH-(2,3 or 4)I-Ph}$, $\text{-NH-(2,3 or 4)Me-Ph}$, $\text{-NH-(2,3 or 4)Et-Ph}$, $\text{-NH-(2,3 or 4)Pr-Ph}$, $\text{-NH-(2,3 or 4)Bu-Ph}$, $\text{-NH-(2,3 or 4)OMe-Ph}$, $\text{-NH-(2,3 or 4)OEt-Ph}$, $\text{-NH-(2,3 or 4)OPr-Ph}$, $\text{-NH-(2,3 or 4)OBu-Ph}$, $\text{-NH-2,(3,4,5 or 6)F}_2\text{-Ph}$, $\text{-NH-2,(3,4,5 or 6)Cl}_2\text{-Ph}$, $\text{-NH-2,(3,4,5 or 6)Br}_2\text{-Ph}$, $\text{-NH-2,(3,4,5 or 6)I}_2\text{-Ph}$, $\text{-NH-2,(3,4,5 or 6)Me}_2\text{-Ph}$, $\text{-NH-2,(3,4,5 or 6)Et}_2\text{-Ph}$, $\text{-NH-2,(3,4,5 or 6)Pr}_2\text{-Ph}$, $\text{-NH-2,(3,4,5 or 6)Bu}_2\text{-Ph}$,
- a substituted or unsubstituted cyclic amine or amido group (such as pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, 2-keto-pyrrolidinyl, 3-keto-pyrrolidinyl, 2-keto-piperidinyl, 3-keto-piperidinyl, and 4-keto-piperidinyl);
- a substituted or unsubstituted cyclic $\text{C}_3\text{-C}_8$ alkyl group (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl);
- an -OH group or a substituted or unsubstituted linear or branched $\text{C}_1\text{-C}_6$ alcohol group (such as $\text{-CH}_2\text{OH}$, $\text{-CH}_2\text{CH}_2\text{OH}$, $\text{-CH(CH}_3\text{)CH}_2\text{OH}$, $\text{-C(CH}_3\text{)}_2\text{OH}$, $\text{-CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $\text{-CH(CH}_3\text{)CH}_2\text{CH}_2\text{OH}$, $\text{-CH(CH}_3\text{)CH(CH}_3\text{)OH}$, $\text{-CH(CH}_2\text{CH}_3\text{)CH}_2\text{OH}$, $\text{-C(CH}_3\text{)}_2\text{CH}_2\text{OH}$, $\text{-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, and $\text{-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$);
- a substituted or unsubstituted linear or branched $\text{C}_1\text{-C}_6$ carboxylic acid group (such as -COOH , $\text{-CH}_2\text{COOH}$, $\text{-CH}_2\text{CH}_2\text{COOH}$, $\text{-CH}_2\text{CH}_2\text{CH}_2\text{COOH}$, $\text{-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$, and $\text{-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$);
- a substituted or unsubstituted linear or branched carbonyl group (such as -(CO)Me , -(CO)Et , -(CO)Pr , -(CO)iPr , -(CO)nBu , -(CO)iBu , -(CO)tBu , -(CO)Ph , $\text{-(CO)CH}_2\text{Ph}$, $\text{-(CO)CH}_2\text{OH}$, $\text{-(CO)CH}_2\text{OCH}_3$, $\text{-(CO)CH}_2\text{NH}_2$, $\text{-(CO)CH}_2\text{NHMe}$, $\text{-(CO)CH}_2\text{NMe}_2$, -(CO)-cyclopropyl , $\text{-(CO)-1,3-epoxypropan-2-yl}$, -(CO)NH_2 , -(CO)NHMe , -(CO)NMe_2 , -(CO)NHEt , -(CO)NEt_2 , $\text{-(CO)-pyrrolidine-N-yl}$, $\text{-(CO)-morpholine-N-yl}$, $\text{-(CO)-piperazine-N-yl}$, $\text{-(CO)-N-methyl-piperazine-N-yl}$, $\text{-(CO)NHCH}_2\text{CH}_2\text{OH}$, $\text{-(CO)NHCH}_2\text{CH}_2\text{OMe}$, $\text{-(CO)NHCH}_2\text{CH}_2\text{NH}_2$, $\text{-(CO)NHCH}_2\text{CH}_2\text{NHMe}$, and $\text{-(CO)NHCH}_2\text{CH}_2\text{NMe}_2$);
- a substituted or unsubstituted linear or branched $\text{C}_1\text{-C}_6$ carboxylic acid ester group (such as -COOMe , -COOEt , -COOPr , -COO-i-Pr , -COO-n-Bu , -COO-i-Bu , -COO-t-Bu , $\text{-CH}_2\text{COOMe}$, $\text{-CH}_2\text{CH}_2\text{COOMe}$, $\text{-CH}_2\text{CH}_2\text{CH}_2\text{COOMe}$, and $\text{-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOMe}$);

- a substituted or unsubstituted linear or branched C₁-C₆ amide group (such as -CO-NH₂, -CO-NMeH, -CO-NMe₂, -CO-NEtH, -CO-NEtMe, -CO-NEt₂, -CO-NPrH, -CO-NPrMe, and -CO-NPrEt);
- a substituted or unsubstituted linear or branched C₁-C₇ amino carbonyl group (such as -NH-CO-Me, -NH-CO-Et, -NH-CO-Pr, -NH-CO-Bu, -NH-CO-pentyl, -NH-CO-hexyl, -NH-CO-Ph, -NMe-CO-Me, -NMe-CO-Et, -NMe-CO-Pr, -NMe-CO-Bu, -NMe-CO-pentyl, -NMe-CO-hexyl, -NMe-CO-Ph);
- a substituted or unsubstituted linear or branched C₁-C₇ alkoxy or aryloxy group (such as -OMe, -OEt, -OPr, -O-i-Pr, -O-n-Bu, -O-i-Bu, -O-t-Bu, -O-pentyl, -O-hexyl, -OCH₂F, -OCHF₂, -OCF₃, -OCH₂Cl, -OCHCl₂, -OCCl₃, -O-Ph, -O-CH₂-Ph, -O-CH₂-(2,3 or 4)-F-Ph, -O-CH₂-(2,3 or 4)-Cl-Ph, -CH₂OMe, -CH₂OEt, -CH₂OPr, -CH₂OBu, -CH₂CH₂OMe, -CH₂CH₂CH₂OMe, -CH₂CH₂CH₂CH₂OMe, and -CH₂CH₂CH₂CH₂CH₂OMe);
- a substituted or unsubstituted linear or branched aminoalkoxy group (such as -OCH₂NH₂, -OCH₂NHMe, -OCH₂NMe₂, -OCH₂NHEt, -OCH₂NEt₂, -OCH₂CH₂NH₂, -OCH₂CH₂NHMe, -OCH₂CH₂NMe₂, -OCH₂CH₂NHEt, and -OCH₂CH₂NEt₂);
- a substituted or unsubstituted sulphonyl group (such as -SO₂Me, -SO₂Et, -SO₂Pr, -SO₂iPr, -SO₂Ph, -SO₂-(2,3 or 4)-F-Ph, -SO₂-cyclopropyl, -SO₂CH₂CH₂OCH₃, -SO₂NH₂, -SO₂NHMe, -SO₂NMe₂, -SO₂NHEt, -SO₂NEt₂, -SO₂-pyrrolidine-N-yl, -SO₂-morpholine-N-yl, -SO₂NHCH₂OMe, and -SO₂NHCH₂CH₂OMe);
- a substituted or unsubstituted aminosulphonyl group (such as -NHSO₂Me, -NHSO₂Et, -NHSO₂Pr, -NHSO₂iPr, -NHSO₂Ph, -NHSO₂-(2,3 or 4)-F-Ph, -NHSO₂-cyclopropyl, -NHSO₂CH₂CH₂OCH₃);
- a substituted or unsubstituted aromatic group (such as Ph-, 2-F-Ph-, 3-F-Ph-, 4-F-Ph-, 2-Cl-Ph-, 3-Cl-Ph-, 4-Cl-Ph-, 2-Br-Ph-, 3-Br-Ph-, 4-Br-Ph-, 2-I-Ph-, 3-I-Ph-, 4-I-Ph-, 2,(3,4,5 or 6)-F₂-Ph-, 2,(3,4,5 or 6)-Cl₂-Ph-, 2,(3,4,5 or 6)-Br₂-Ph-, 2,(3,4,5 or 6)-I₂-Ph-, 2,(3,4,5 or 6)-Me₂-Ph-, 2,(3,4,5 or 6)-Et₂-Ph-, 2,(3,4,5 or 6)-Pr₂-Ph-, 2,(3,4,5 or 6)-Bu₂-Ph-, 2,(3,4,5 or 6)-(CN)₂-Ph-, 2,(3,4,5 or 6)-(NO₂)₂-Ph-, 2,(3,4,5 or 6)-(NH₂)₂-Ph-, 2,(3,4,5 or 6)-(MeO)₂-Ph-, 2,(3,4,5 or 6)-(CF₃)₂-Ph-, 3,(4 or 5)-F₂-Ph-, 3,(4 or 5)-Cl₂-Ph-, 3,(4 or 5)-Br₂-Ph-, 3,(4 or 5)-I₂-Ph-, 3,(4 or 5)-Me₂-Ph-, 3,(4 or 5)-Et₂-Ph-, 3,(4 or 5)-Pr₂-Ph-, 3,(4 or 5)-Bu₂-Ph-, 3,(4 or 5)-(CN)₂-Ph-, 3,(4 or 5)-(NO₂)₂-Ph-, 3,(4 or 5)-(NH₂)₂-Ph-, 3,(4 or 5)-(MeO)₂-Ph-, 3,(4 or 5)-(CF₃)₂-Ph-, 2-Me-Ph-, 3-Me-Ph-, 4-Me-Ph-, 2-Et-Ph-, 3-Et-Ph-, 4-Et-Ph-, 2-Pr-Ph-, 3-Pr-Ph-, 4-Pr-Ph-, 2-Bu-Ph-, 3-Bu-Ph-, 4-Bu-Ph-, 2-(CN)-Ph-, 3-(CN)-Ph-, 4-(CN)-Ph-, 2-(NO₂)-Ph-, 3-(NO₂)-Ph-, 4-(NO₂)-Ph-, 2-(NH₂)-Ph-, 3-(NH₂)-Ph-, 4-(NH₂)-Ph-, 2-MeO-Ph-, 3-MeO-Ph-, 4-MeO-Ph-,

2-(NH₂-CO)-Ph-, 3-(NH₂-CO)-Ph-, 4-(NH₂-CO)-Ph-, 2-CF₃-Ph-, 3-CF₃-Ph-, 4-CF₃-Ph-, 2-CF₃O-Ph-, 3-CF₃O-Ph-, and 4-CF₃O-Ph-);

- a saturated or unsaturated, substituted or unsubstituted, heterocyclic group including an aromatic heterocyclic group and/or a non-aromatic heterocyclic group (such as pyrrole-1-yl, pyrrole-2-yl, pyrrole-3-yl, pyrazole-1-yl, pyrazole-3-yl, pyrazole-4-yl, pyrazole-5-yl, imidazole-1-yl, imidazole-2-yl, imidazole-4-yl, imidazole-5-yl, 1,2,3-triazole-1-yl, 1,2,3-triazole-4-yl, 1,2,3-triazole-5-yl, 1,2,4-triazole-1-yl, 1,2,4-triazole-3-yl, 1,2,4-triazole-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazine-3-yl, pyridazine-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-6-yl, pyrazine-2-yl, pyrrolidine-1-yl, pyrrolidine-2-yl, pyrrolidine-3-yl, piperidine-1-yl, piperidine-2-yl, piperidine-3-yl, piperidine-4-yl, 2-azapiperidine-1-yl, 2-azapiperidine-3-yl, 2-azapiperidine-4-yl, 3-azapiperidine-1-yl, 3-azapiperidine-2-yl, 3-azapiperidine-4-yl, 3-azapiperidine-5-yl, piperazine-1-yl, piperazine-2-yl, furan-2-yl, furan-3-yl, pyran-2-yl, pyran-3-yl, pyran-4-yl, 2-azapyran-2-yl, 2-azapyran-3-yl, 2-azapyran-4-yl, 2-azapyran-5-yl, 2-azapyran-6-yl, 3-azapyran-2-yl, 3-azapyran-4-yl, 3-azapyran-5-yl, 3-azapyran-6-yl, 4-azapyran-2-yl, 4-azapyran-3-yl, 4-azapyran-4-yl, 4-azapyran-5-yl, 4-azapyran-6-yl, oxetan-2-yl, oxetan-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-2-yl, 2-aza-tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-4-yl, 2-aza-tetrahydrofuran-5-yl, 3-aza-tetrahydrofuran-2-yl, 3-aza-tetrahydrofuran-3-yl, 3-aza-tetrahydrofuran-4-yl, 3-aza-tetrahydrofuran-5-yl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, 2-aza-tetrahydropyran-2-yl, 2-aza-tetrahydropyran-3-yl, 2-aza-tetrahydropyran-4-yl, 2-aza-tetrahydropyran-5-yl, 2-aza-tetrahydropyran-6-yl, 3-aza-tetrahydropyran-2-yl, 3-aza-tetrahydropyran-3-yl, 3-aza-tetrahydropyran-4-yl, 3-aza-tetrahydropyran-5-yl, 3-aza-tetrahydropyran-6-yl, morpholine-2-yl, morpholine-3-yl, morpholine-4-yl, thiophen-2-yl, thiophen-3-yl, isothiazole-3-yl, isothiazole-4-yl, isothiazole-5-yl, thiazole-2-yl, thiazole-4-yl, thiazole-5-yl, thiopyran-2-yl, thiopyran-3-yl, thiopyran-4-yl, 2-azathiopyran-2-yl, 2-azathiopyran-3-yl, 2-azathiopyran-4-yl, 2-azathiopyran-5-yl, 2-azathiopyran-6-yl, 3-azathiopyran-2-yl, 3-azathiopyran-4-yl, 3-azathiopyran-5-yl, 3-azathiopyran-6-yl, 4-azathiopyran-2-yl, 4-azathiopyran-3-yl, 4-azathiopyran-4-yl, 4-azathiopyran-5-yl, 4-azathiopyran-6-yl, thiolane-2-yl, thiolane-3-yl, thiane-2-yl, thiane-3-yl, thiane-4-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, furazan-3-yl, (1,3,4-oxadiazol)-2-yl, (1,3,4-oxadiazol)-5-yl, (1,2,4-oxadiazol)-3-yl, (1,2,4-oxadiazol)-5-yl; and tetrazole-1-yl, tetrazole-2-yl, tetrazole-5-yl);

- where there are two R groups attached to the same atom, they may together form a group which is double bonded to that atom, (such as a carbonyl group (=O) or an alkene group (=C(R')₂) wherein each R' group is the same or different and is H or an organic group, preferably H or a straight or branched C₁-C₆ alkyl group).

In some arrangements, a pair of R⁴¹ groups attached to different atoms may together form a ring with ring A atoms, and/or a pair of R⁴² groups attached to different atoms may together form a ring with ring B atoms, optionally wherein each of the pair of R⁴¹ groups and/or pair of R⁴² groups independently comprises (X⁷)_{1 or 2}, wherein each X⁷ may be the same or different and is independently selected from C, N, O and S; and wherein each X⁷ is independently unsubstituted or (i) independently substituted with H or an organic group selected from a C₁-C₆ alkyl group, a C₁-C₆ halogenated alkyl group, a halogen such as F, or hydroxyl, when X⁷ is C; and (ii) independently substituted with H or an organic group selected from a C₁-C₆ alkyl group or a C₁-C₆ amide group, when X⁷ is N.

In some arrangements, groups R⁵ and R⁴⁴ may together form a ring with atoms X⁶ and X³ of ring C to which they are attached, optionally wherein the R⁵ and R⁴⁴ groups together comprise (X⁸)_{3, 4 or 5}, wherein each X⁸ may be the same or different and is independently selected from C, N, O and S; and wherein each X⁸ is independently unsubstituted or (i) independently substituted with H or an organic group selected from a C₁-C₆ alkyl group, a C₁-C₆ halogenated alkyl group, a halogen such as F, or hydroxyl, when X⁸ is C; and (ii) independently substituted with H or an organic group selected from a C₁-C₆ alkyl group, a C₁-C₆ halogenated alkyl group, or a C₁-C₆ amide group, when X⁸ is N.

It is preferred that R⁴¹, R⁴², R⁴³ and R⁴⁴ are each independently selected from H, deuterium, a halogen (such as -F, -Cl, -Br, and -I, preferably F or Cl), a nitrile group, a substituted or unsubstituted C₁-C₆ alkyl group, a substituted or unsubstituted linear or branched C₁-C₆ halogenated alkyl group, (preferably CF₃ or CHF₂), a cyclopropyl group, an -OH group or a substituted or unsubstituted linear or branched C₁-C₆ alcohol group, a substituted or unsubstituted linear or branched C₁-C₇ amino carbonyl group (such as -NH-CO-Me), an -NH₂ group or a substituted or unsubstituted C₁-C₆ amino group and a substituted or unsubstituted

C₁-C₆ alkoxy group; wherein, when a pair of R⁴¹ groups attached to different atoms together forms a ring with ring A atoms, and/or a pair of R⁴² groups attached to different atoms together forms a ring with ring B atoms, each of the pair of R⁴¹ groups and/or pair of R⁴² groups independently comprises -CH₂- or -CH₂CH₂-; and wherein, when groups R⁵ and R⁴⁴ together form a ring with atoms of ring C, R⁵ and R⁴⁴ together comprise -CH=CH-CH=CH- or -NH-CO-NH-.

It is preferred that R⁴⁵ is selected from H, a halogen (such as -F, -Cl, -Br, and -I, preferably -F), a substituted or unsubstituted C₁-C₆ alkyl group, a substituted or unsubstituted linear or branched C₁-C₆ halogenated alkyl group (preferably CF₃), an -NH₂ group or a substituted or unsubstituted C₁-C₆ amino group, an -OH group or a substituted or unsubstituted linear or branched C₁-C₆ alcohol group and a substituted or unsubstituted C₁-C₆ alkoxy group.

Typically, R⁴⁶ is selected from H and a group selected from the following groups:

- a substituted or unsubstituted linear or branched C₁-C₆ alkyl group (such as Me, Et, Pr, i-Pr, n-Bu, i-Bu, t-Bu, pentyl and hexyl);
- a substituted or unsubstituted linear or branched C₁-C₆ alkyl-aryl group (such as -CH₂Ph, -CH₂(2,3 or 4)F-Ph, -CH₂(2,3 or 4)Cl-Ph, -CH₂(2,3 or 4)Br-Ph, -CH₂(2,3 or 4)I-Ph, -CH₂CH₂Ph, -CH₂CH₂CH₂Ph, -CH₂CH₂CH₂CH₂Ph, -CH₂CH₂CH₂CH₂CH₂Ph, and -CH₂CH₂CH₂CH₂CH₂CH₂Ph);
- a substituted or unsubstituted linear or branched C₁-C₆ halogenated alkyl group (such as -CH₂F, and -CH₂CF₃);
- a substituted or unsubstituted cyclic amine or amido group (such as pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, 2-keto-pyrrolidinyl, 3-keto-pyrrolidinyl, 2-keto-piperidinyl, 3-keto-piperidinyl, and 4-keto-piperidinyl);
- a substituted or unsubstituted cyclic C₃-C₈ alkyl group (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl);
- a substituted or unsubstituted linear or branched C₂-C₆ alcohol group (such as -CH₂CH₂OH, -CH(CH₃)CH₂OH, -C(CH₃)₂OH, -CH₂CH₂CH₂OH, -CH₂CH₂CH₂CH₂OH, -CH(CH₃)CH₂CH₂OH, -CH(CH₃)CH(CH₃)OH, -CH(CH₂CH₃)CH₂OH, -C(CH₃)₂CH₂OH, -CH₂CH₂CH₂CH₂CH₂OH, and -CH₂CH₂CH₂CH₂CH₂CH₂OH);

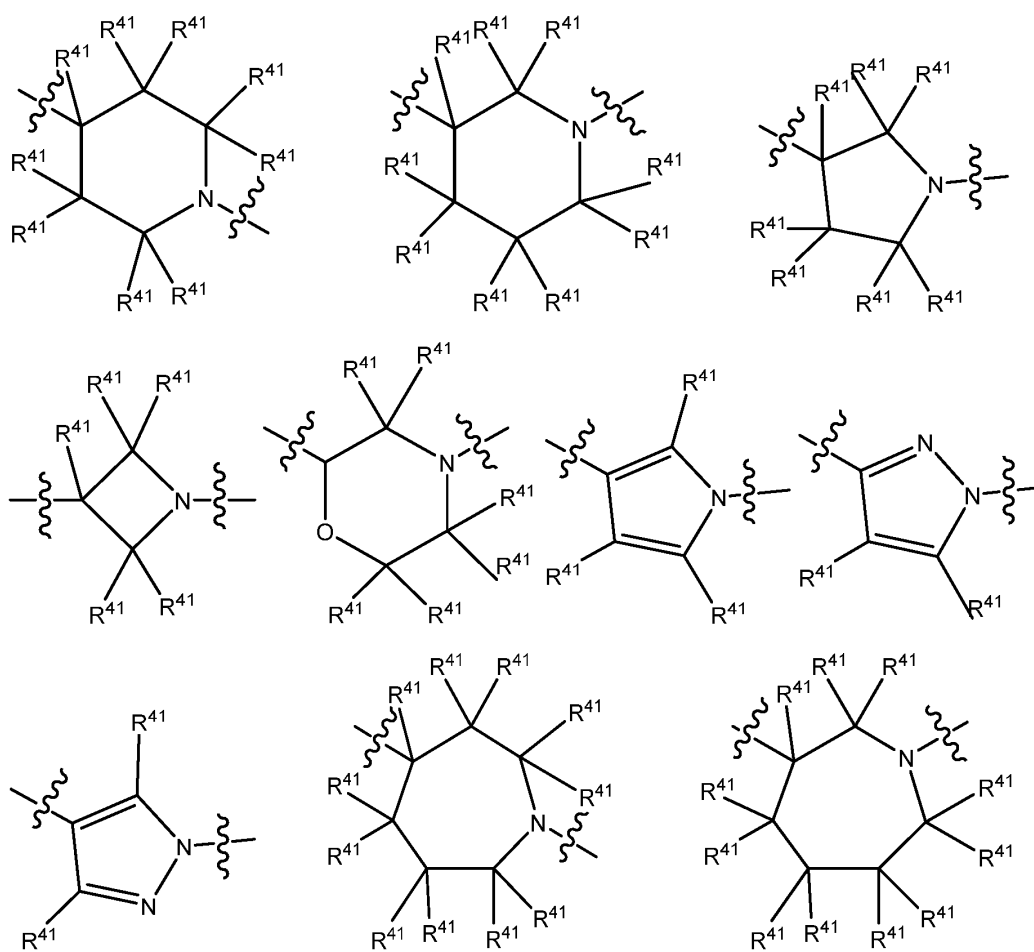
- a substituted or unsubstituted linear or branched C₂-C₆ carboxylic acid group (such as -CH₂COOH, -CH₂CH₂COOH, -CH₂CH₂CH₂COOH, -CH₂CH₂CH₂CH₂COOH, and -CH₂CH₂CH₂CH₂CH₂COOH);
- a substituted or unsubstituted linear or branched carbonyl group (such as -(CO)Me, -(CO)Et, -(CO)Pr, -(CO)-i-Pr, -(CO)-n-Bu, -(CO)-i-Bu, -(CO)-t-Bu, -(CO)Ph, -(CO)CH₂Ph, -(CO)CH₂OH, -(CO)CH₂OCH₃, -(CO)CH₂NH₂, -(CO)CH₂NHMe, -(CO)CH₂NMe₂, -(CO)-cyclopropyl, -(CO)-1,3-epoxypropan-2-yl; -(CO)NH₂, -(CO)NHMe, -(CO)NMe₂, -(CO)NH₂Et, -(CO)NEt₂, -(CO)-pyrrolidine-N-yl, -(CO)-morpholine-N-yl, -(CO)-piperazine-N-yl, -(CO)-N-methyl-piperazine-N-yl, -(CO)NHCH₂CH₂OH, -(CO)NHCH₂CH₂OMe, -(CO)NHCH₂CH₂NH₂, -(CO)NHCH₂CH₂NHMe, and -(CO)NHCH₂CH₂NMe₂;
- a substituted or unsubstituted linear or branched C₁-C₆ carboxylic acid ester group (such as -COOMe, -COOEt, -COOPr, -COO-i-Pr, -COO-n-Bu, -COO-i-Bu, -COO-t-Bu, -CH₂COOMe, -CH₂CH₂COOMe, -CH₂CH₂CH₂COOMe, and -CH₂CH₂CH₂CH₂COOMe);
- a substituted or unsubstituted linear or branched C₁-C₆ amide group (such as -CO-NH₂, -CO-NMeH, -CO-NMe₂, -CO-NEtH, -CO-NEtMe, -CO-NEt₂, -CO-NPrH, -CO-NPrMe, and -CO-NPrEt);
- a substituted or unsubstituted sulphonyl group (such as -SO₂Me, -SO₂Et, -SO₂Pr, -SO₂iPr, -SO₂Ph, -SO₂-(2,3 or 4)-F-Ph, -SO₂-cyclopropyl, -SO₂CH₂CH₂OCH₃, -SO₂NH₂, -SO₂NHMe, -SO₂NMe₂, -SO₂NH₂Et, -SO₂NEt₂, -SO₂-pyrrolidine-N-yl, -SO₂-morpholine-N-yl, -SO₂NHCH₂OMe, and -SO₂NHCH₂CH₂OMe;
- a substituted or unsubstituted aromatic group (such as Ph-, 2-F-Ph-, 3-F-Ph-, 4-F-Ph-, 2-Cl-Ph-, 3-Cl-Ph-, 4-Cl-Ph-, 2-Br-Ph-, 3-Br-Ph-, 4-Br-Ph-, 2-I-Ph-, 3-I-Ph-, 4-I-Ph-, 2,(3,4,5 or 6)-F₂-Ph-, 2,(3,4,5 or 6)-Cl₂-Ph-, 2,(3,4,5 or 6)-Br₂-Ph-, 2,(3,4,5 or 6)-I₂-Ph-, 2,(3,4,5 or 6)-Me₂-Ph-, 2,(3,4,5 or 6)-Et₂-Ph-, 2,(3,4,5 or 6)-Pr₂-Ph-, 2,(3,4,5 or 6)-Bu₂-Ph-, 2,(3,4,5 or 6)-(CN)₂-Ph-, 2,(3,4,5 or 6)-(NO₂)₂-Ph-, 2,(3,4,5 or 6)-(NH₂)₂-Ph-, 2,(3,4,5 or 6)-(MeO)₂-Ph-, 2,(3,4,5 or 6)-(CF₃)₂-Ph-, 3,(4 or 5)-F₂-Ph-, 3,(4 or 5)-Cl₂-Ph-, 3,(4 or 5)-Br₂-Ph-, 3,(4 or 5)-I₂-Ph-, 3,(4 or 5)-Me₂-Ph-, 3,(4 or 5)-Et₂-Ph-, 3,(4 or 5)-Pr₂-Ph-, 3,(4 or 5)-Bu₂-Ph-, 3,(4 or 5)-(CN)₂-Ph-, 3,(4 or 5)-(NO₂)₂-Ph-, 3,(4 or 5)-(NH₂)₂-Ph-, 3,(4 or 5)-(MeO)₂-Ph-, 3,(4 or 5)-(CF₃)₂-Ph-, 2-Me-Ph-, 3-Me-Ph-, 4-Me-Ph-, 2-Et-Ph-, 3-Et-Ph-, 4-Et-Ph-, 2-Pr-Ph-, 3-Pr-Ph-, 4-Pr-Ph-, 2-Bu-Ph-, 3-Bu-Ph-, 4-Bu-Ph-, 2-(CN)-Ph-, 3-(CN)-Ph-, 4-(CN)-Ph-, 2-(NO₂)-Ph-, 3-(NO₂)-Ph-, 4-(NO₂)-Ph-, 2-(NH₂)-Ph-, 3-(NH₂)-Ph-, 4-(NH₂)-Ph-, 2-MeO-Ph-, 3-MeO-Ph-, 4-MeO-Ph-,

2-(NH₂-CO)-Ph-, 3-(NH₂-CO)-Ph-, 4-(NH₂-CO)-Ph-, 2-CF₃-Ph-, 3-CF₃-Ph-, 4-CF₃-Ph-, 2-CF₃O-Ph-, 3-CF₃O-Ph-, and 4-CF₃O-Ph-); and

- a substituted or unsubstituted saturated or unsaturated, substituted or unsubstituted, heterocyclic group including an aromatic heterocyclic group and/or a non-aromatic heterocyclic group (such as pyrrole-2-yl, pyrrole-3-yl, pyrazole-3-yl, pyrazole-4-yl, pyrazole-5-yl, imidazole-2-yl, imidazole-4-yl, imidazole-5-yl, 1,2,3-triazole-4-yl, 1,2,3-triazole-5-yl, 1,2,4-triazole-3-yl, 1,2,4-triazole-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazine-3-yl, pyridazine-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-6-yl, pyrazine-2-yl, pyrrolidine-2-yl, pyrrolidine-3-yl, piperidine-2-yl, piperidine-3-yl, piperidine-4-yl, 2-azapiperidine-3-yl, 2-azapiperidine-4-yl, 3-azapiperidine-2-yl, 3-azapiperidine-4-yl, 3-azapiperidine-5-yl, piperazine-2-yl, furan-2-yl, furan-3-yl, pyran-2-yl, pyran-3-yl, pyran-4-yl, 2-azapyran-3-yl, 2-azapyran-4-yl, 2-azapyran-5-yl, 2-azapyran-6-yl, 3-azapyran-2-yl, 3-azapyran-4-yl, 3-azapyran-5-yl, 3-azapyran-6-yl, 4-azapyran-2-yl, 4-azapyran-3-yl, 4-azapyran-5-yl, 4-azapyran-6-yl, oxetan-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-4-yl, 2-aza-tetrahydrofuran-5-yl, 3-aza-tetrahydrofuran-2-yl, 3-aza-tetrahydrofuran-4-yl, 3-aza-tetrahydrofuran-5-yl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, 2-aza-tetrahydropyran-3-yl, 2-aza-tetrahydropyran-4-yl, 2-aza-tetrahydropyran-5-yl, 2-aza-tetrahydropyran-6-yl, 3-aza-tetrahydropyran-2-yl, 3-aza-tetrahydropyran-4-yl, 3-aza-tetrahydropyran-5-yl, 3-aza-tetrahydropyran-6-yl, morpholine-2-yl, morpholine-3-yl, thiophen-2-yl, thiophen-3-yl, isothiazole-3-yl, isothiazole-4-yl, isothiazole-5-yl, thiazole-2-yl, thiazole-4-yl, thiazole-5-yl, thiopyran-2-yl, thiopyran-3-yl, thiopyran-4-yl, 2-azathiopyran-3-yl, 2-azathiopyran-4-yl, 2-azathiopyran-5-yl, 2-azathiopyran-6-yl, 3-azathiopyran-2-yl, 3-azathiopyran-4-yl, 3-azathiopyran-5-yl, 3-azathiopyran-6-yl, 4-azathiopyran-2-yl, 4-azathiopyran-3-yl, 4-azathiopyran-5-yl, 4-azathiopyran-6-yl, thiolane-2-yl, thiolane-3-yl, thiane-2-yl, thiane-3-yl, thiane-4-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, furazan-3-yl, (1,3,4-oxadiazol)-2-yl, (1,3,4-oxadiazol)-5-yl, (1,2,4-oxadiazol)-3-yl, (1,2,4-oxadiazol)-5-yl; and tetrazole-5-yl).

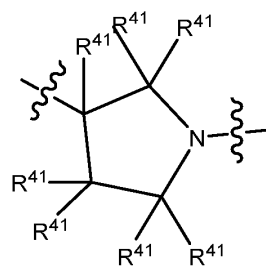
It is preferred that R⁴⁶ is selected from H, a substituted or unsubstituted C₁-C₆ alkyl group or a substituted or unsubstituted linear or branched C₁-C₆ halogenated alkyl group.

Ring A of the group L preferably comprises any of the following structures:

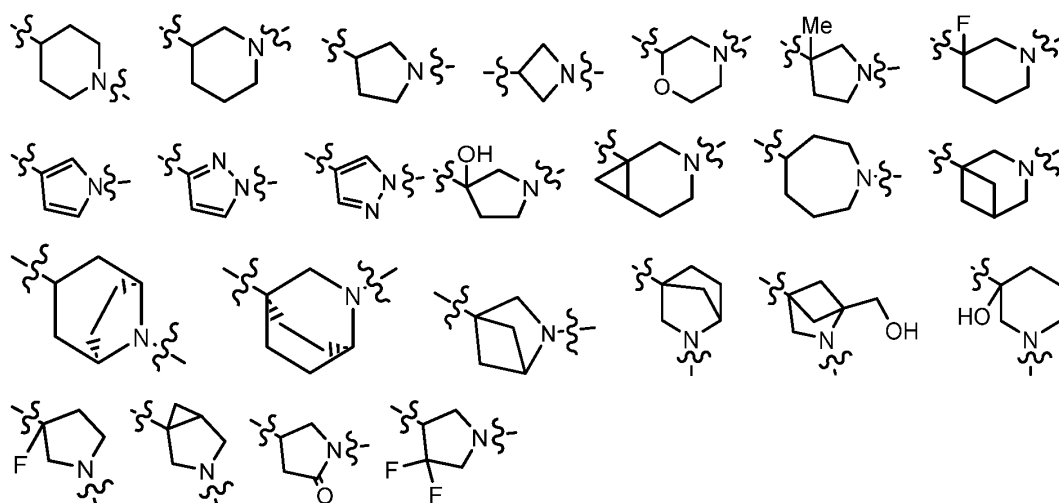


wherein R^{41} is as defined herein.

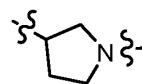
More preferably, ring A of the group L comprises



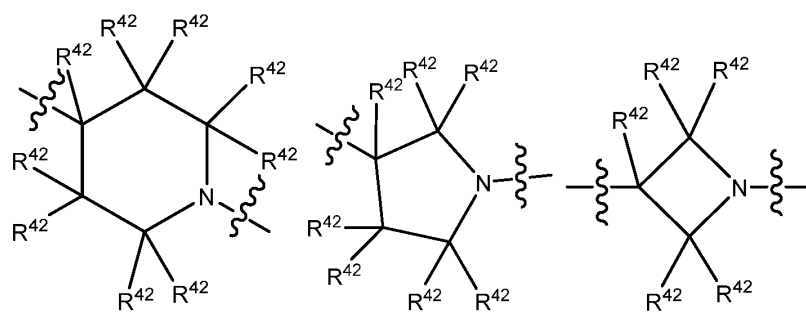
Still more preferably, ring A of the group L comprises any of the following structures:



Particularly preferably, ring A of the group L comprises

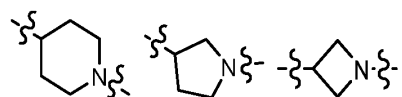


In one arrangement, Q² of the group L is present and comprises any of the following structures:

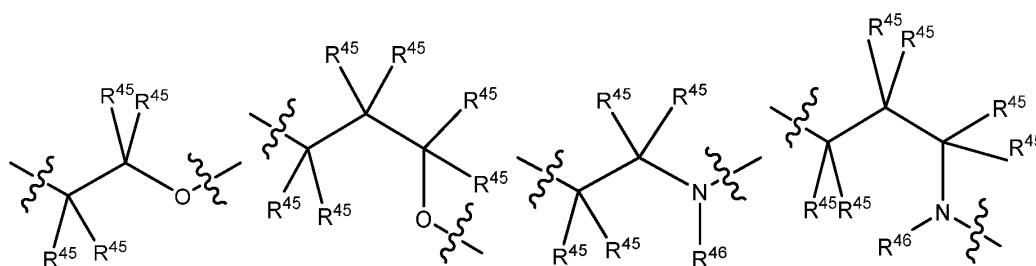


wherein R⁴² is as defined herein.

More preferably, Q² of the group L comprises any of the following structures:

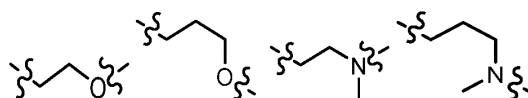


Alternatively, group Q^2 of the group L is absent and only one Q^1 group is present. In this arrangement the Q^1 group typically separates ring A from ring C by 3 or 4 atoms in the linear direction and may comprise any of the following structures:

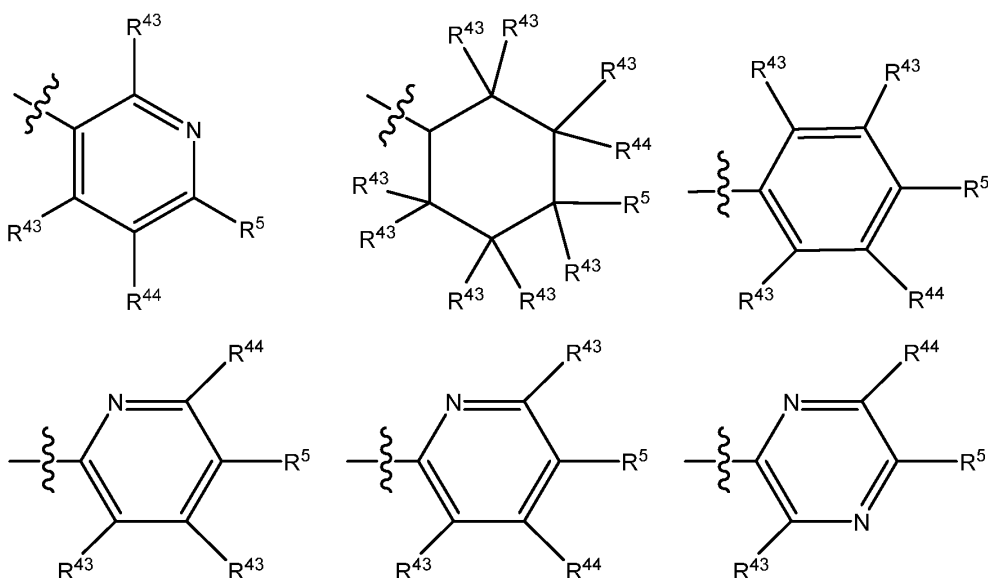


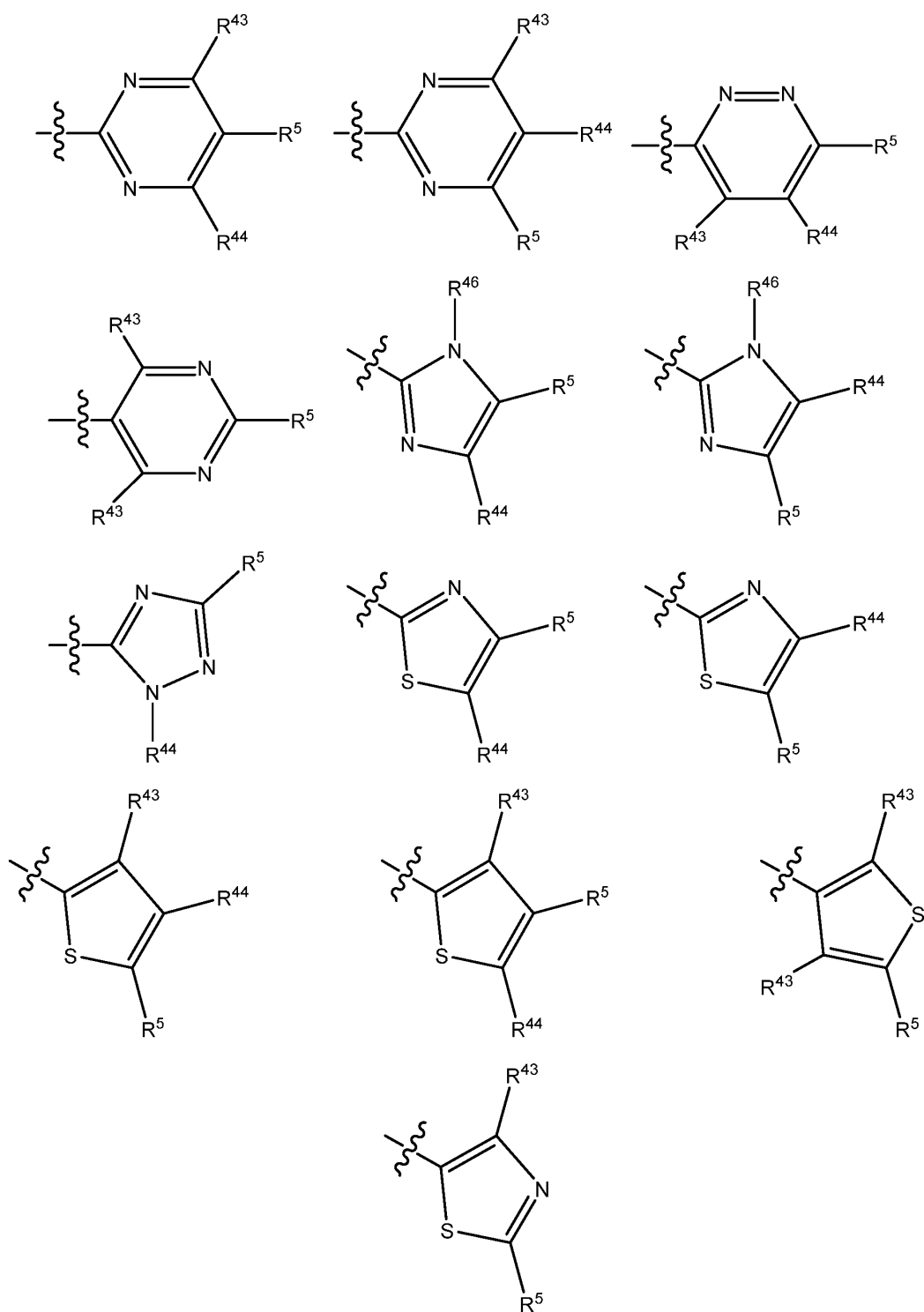
wherein R^{45} and R^{46} are as defined herein.

In this arrangement, the Q^1 group preferably comprises any of the following structures:



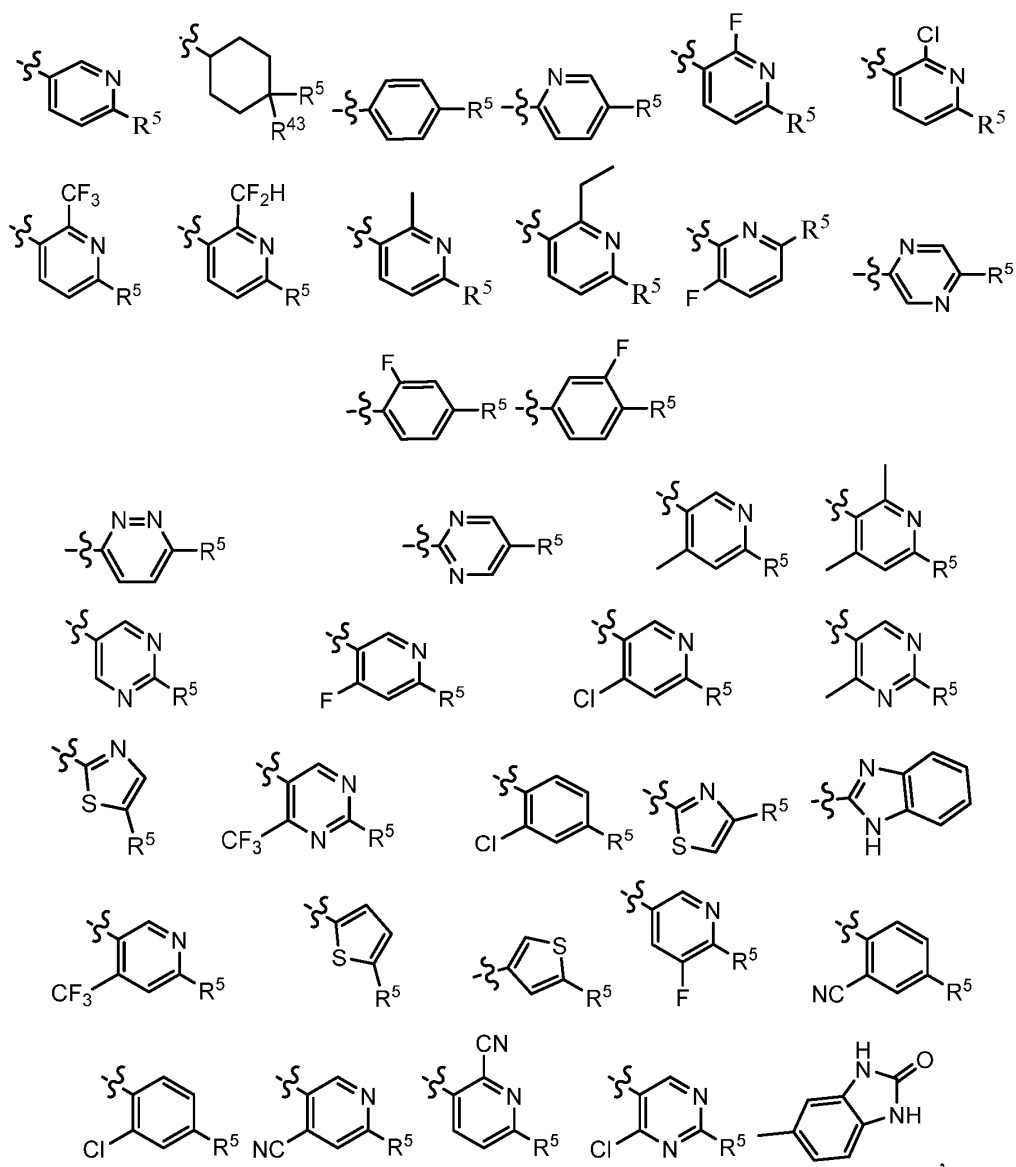
Preferably, ring C of the group L comprises any of the following structures:





wherein R^5 , R^{43} , R^{44} and R^{46} are as defined herein.

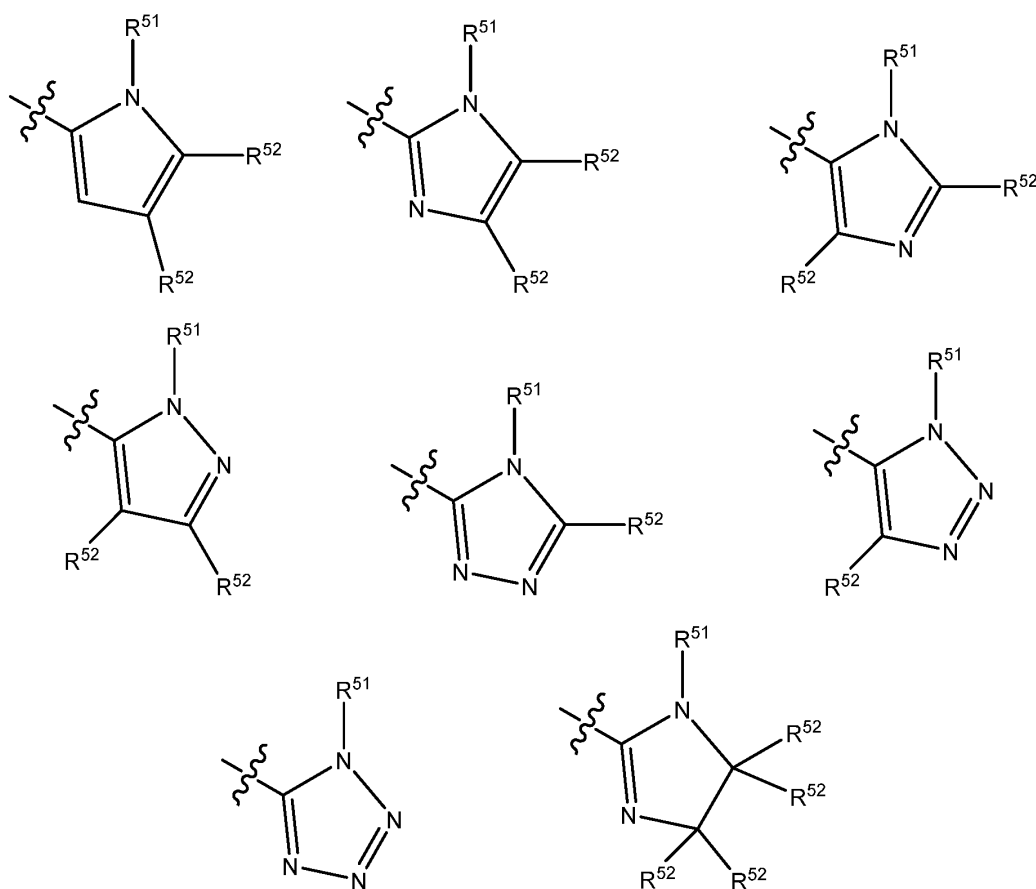
More preferably, ring C of the group L comprises any of the following structures:



wherein R^5 and R^{43} are as defined herein.

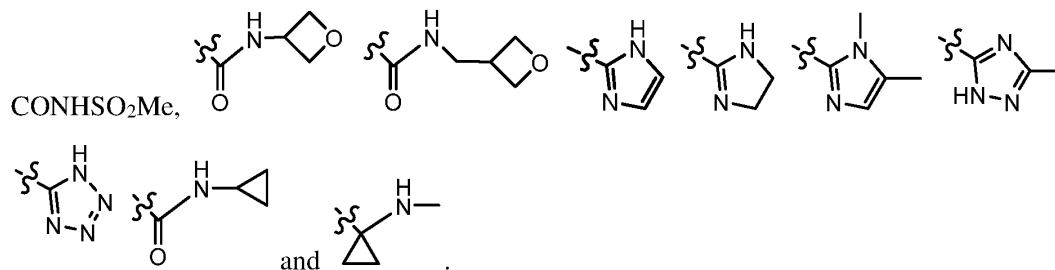
In some arrangements, R^5 is a substituted or unsubstituted organic group.

Preferably, the group R^5 is not MeO, and is more preferably selected from H, -F, -Cl, -Br, -I, -CN, $-\text{CONR}^{51}\text{R}^{51}$, $-\text{NR}^{51}\text{COR}^{52}$, $-\text{SO}_2\text{NR}^{51}\text{R}^{51}$, $-\text{NR}^{51}\text{SO}_2\text{R}^{53}$, $-\text{O}-\text{CR}^{52}\text{R}^{52}\text{R}^{52}$, $-\text{CR}^{52}\text{R}^{52}\text{NR}^{51}\text{R}^{51}$ and any of the following structures:

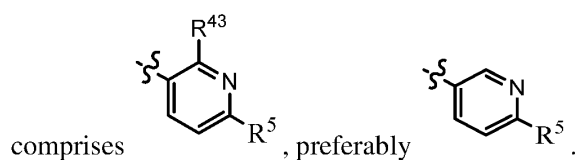


wherein, each of R^{51} , R^{52} and R^{53} may be the same or different and are independently selected from H and a substituted or unsubstituted organic group. More preferably, the group R^5 is $-\text{CONR}^{51}\text{R}^{51}$.

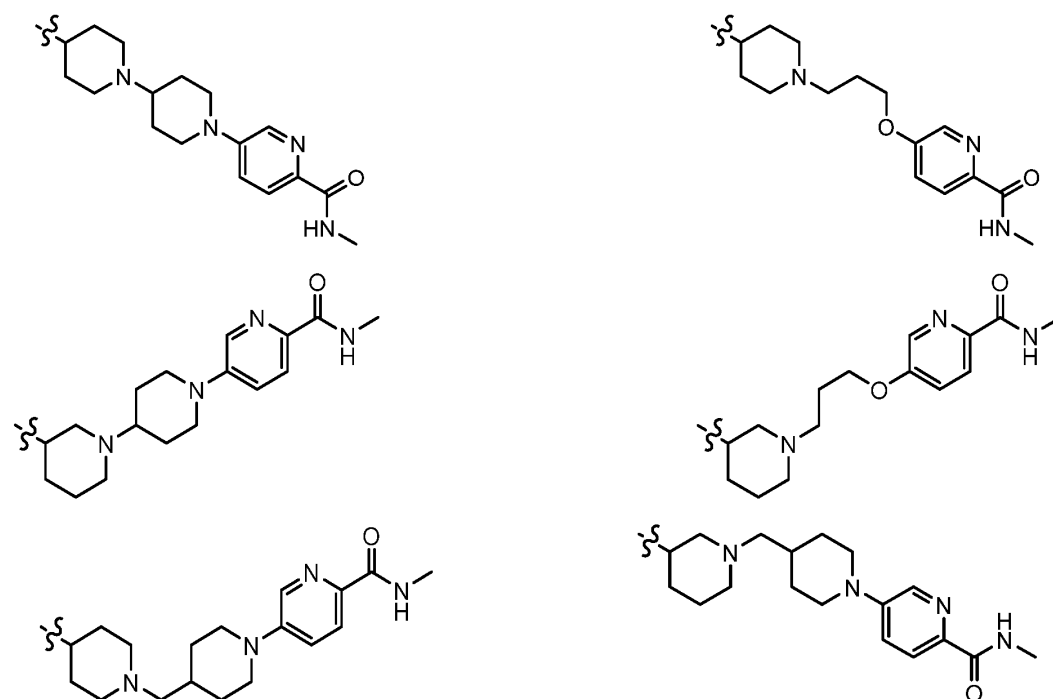
Still more preferably, the group R^5 is selected from -F, -Cl, -CN, -CONH₂, -CONHMe, -CONHEt, -CONMe₂, -CONHCOMe, -CONHCH₂-CH₂OMe, -CONH-CH₂-CH₂F, -CONH-CH₂-CF₃, -CONH-CH₂-CHF₂, -OCHF₂, -NHCOMe, -NHSO₂Me, -SO₂NHMe, -

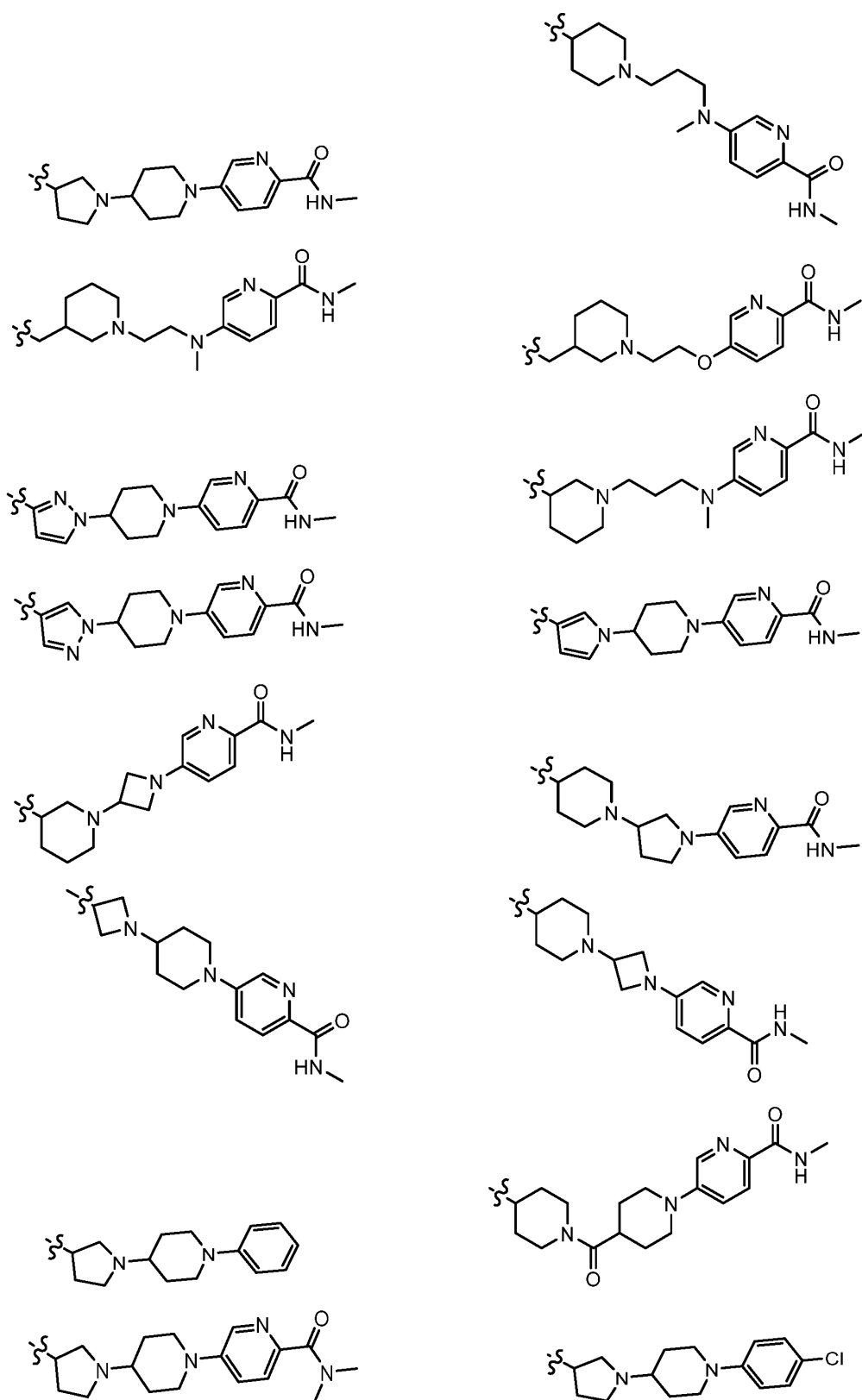


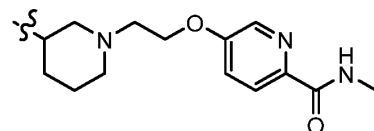
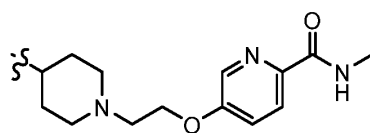
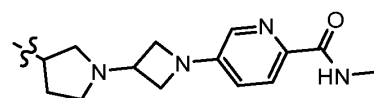
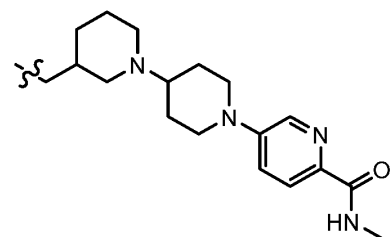
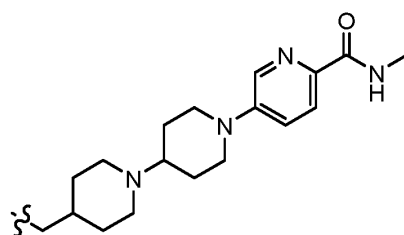
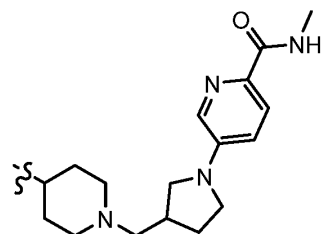
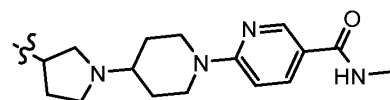
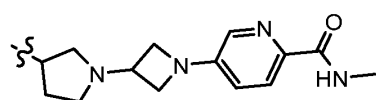
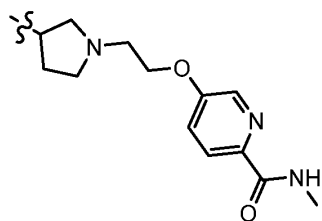
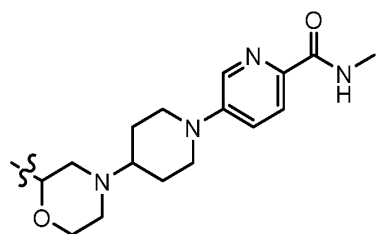
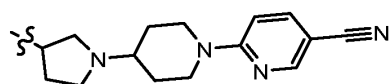
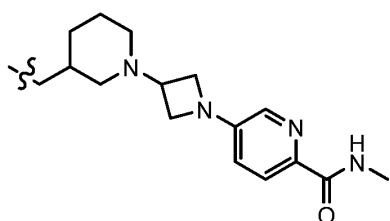
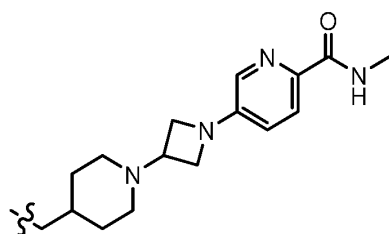
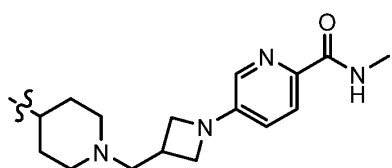
A particularly preferred group R^5 is -CONHMe, especially where ring C of the group L

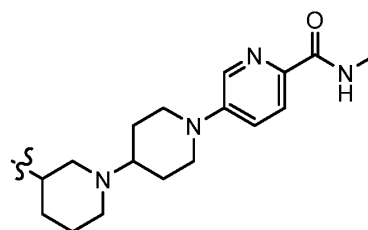
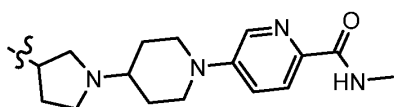
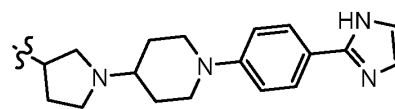
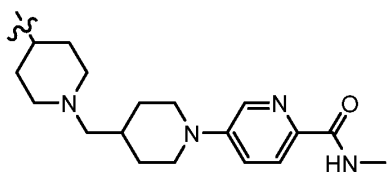
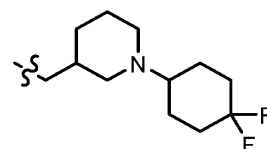
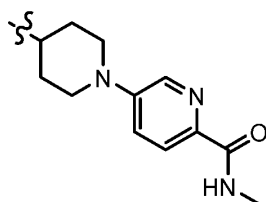
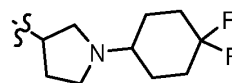
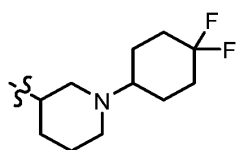
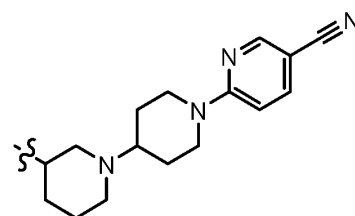
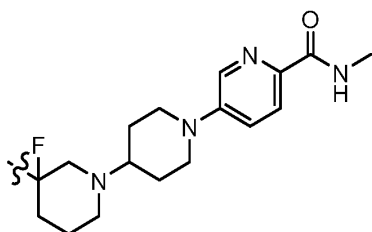
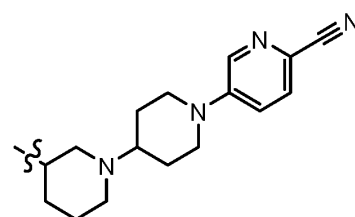
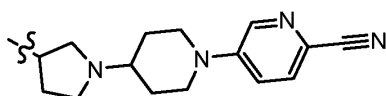
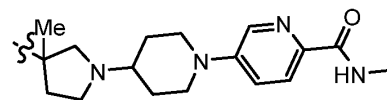
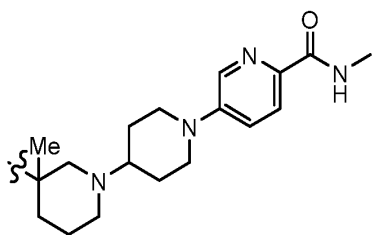


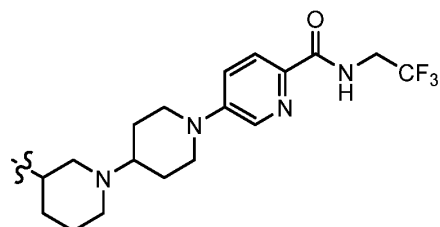
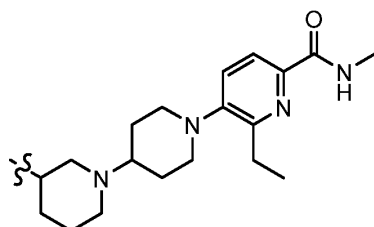
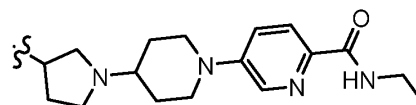
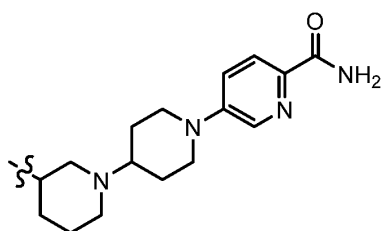
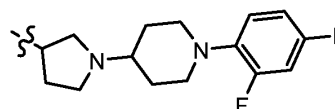
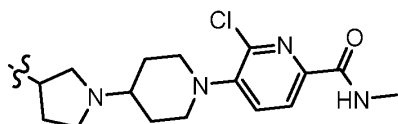
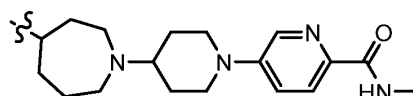
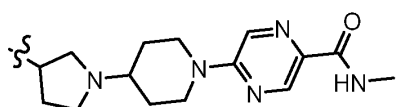
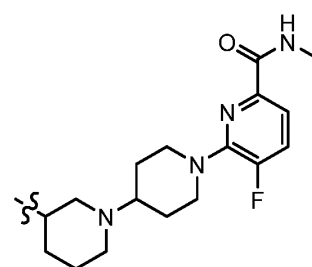
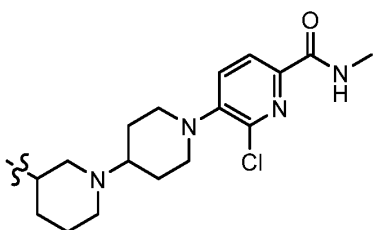
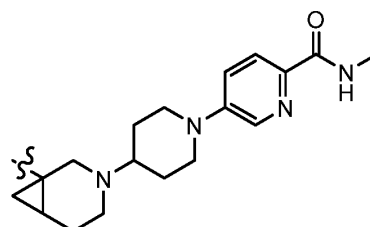
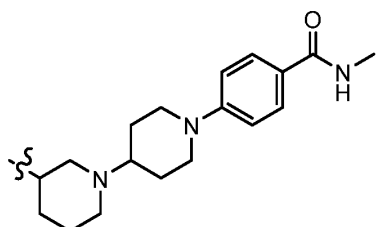
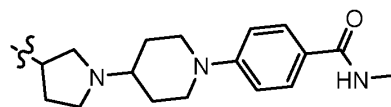
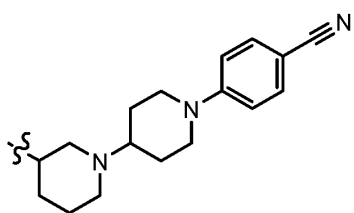
In some embodiments, the group L of the compound according to the invention comprises a group having any the following structures:

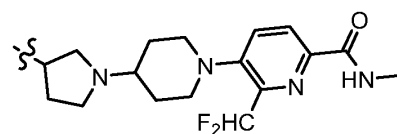
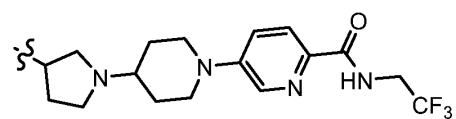
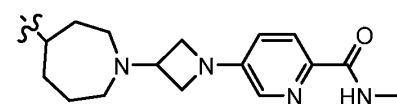
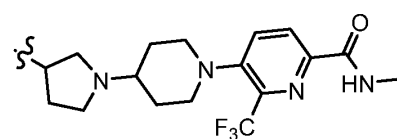
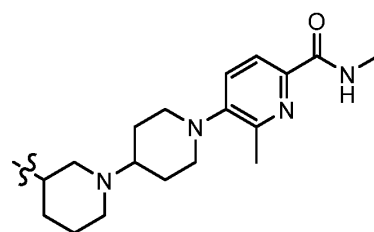
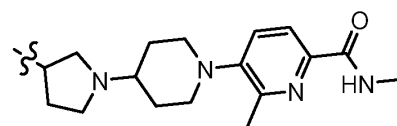
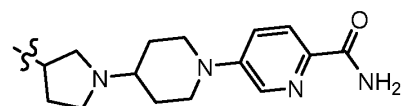
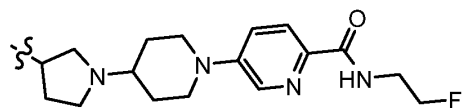
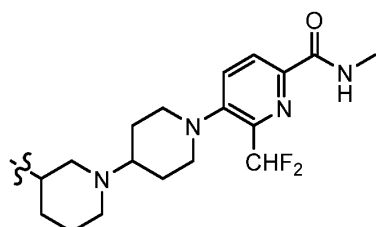
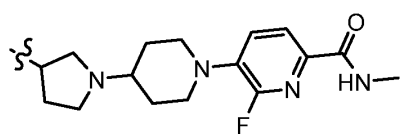
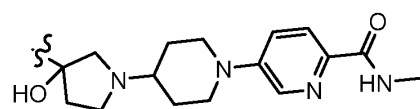
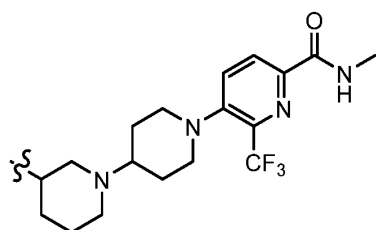
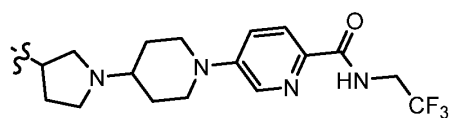
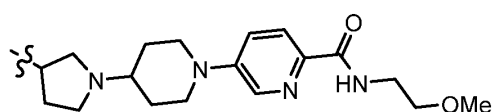
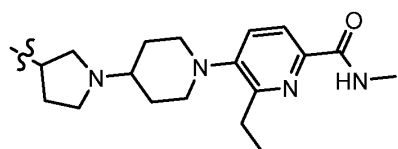
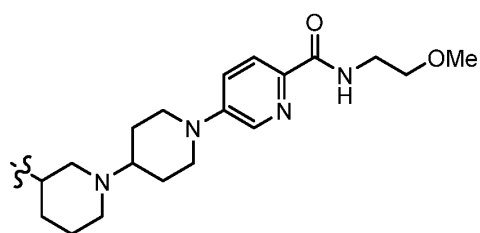


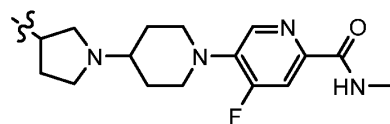
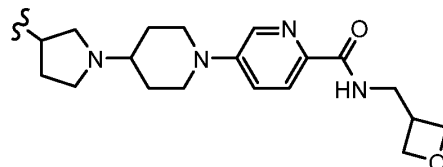
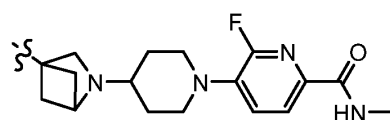
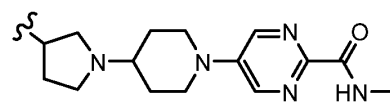
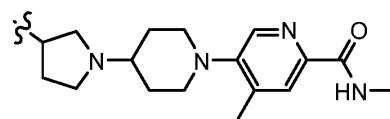
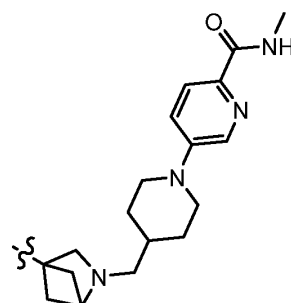
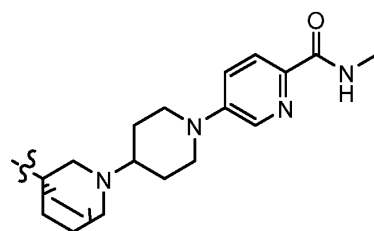
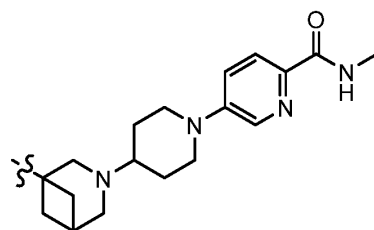
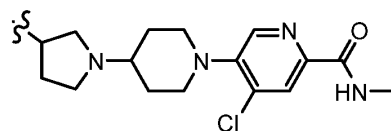
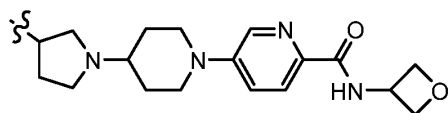
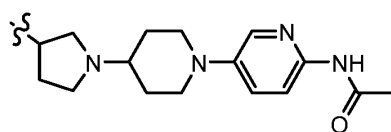
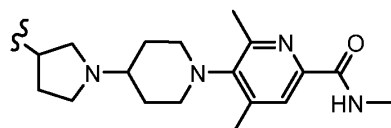
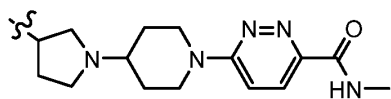
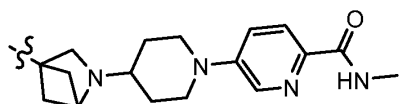
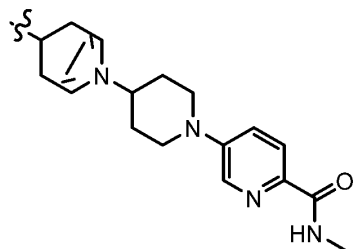
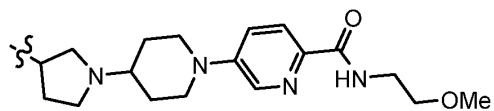


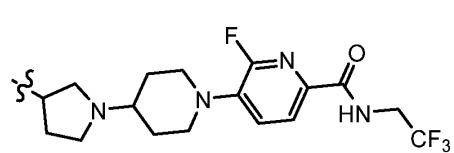
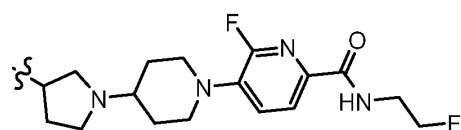
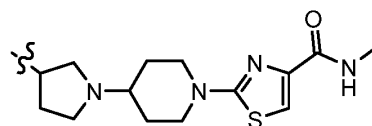
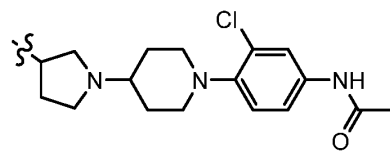
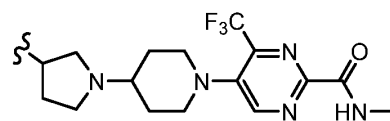
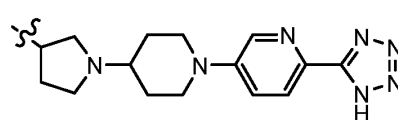
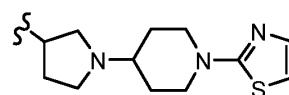
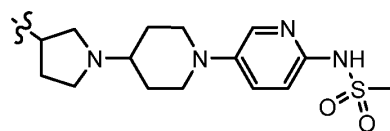
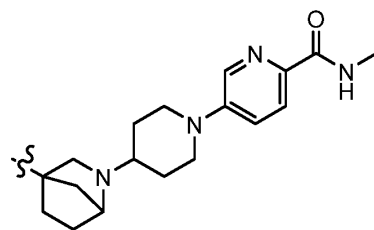
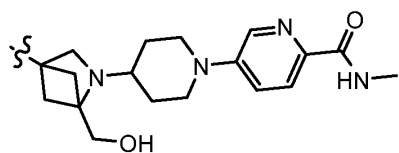
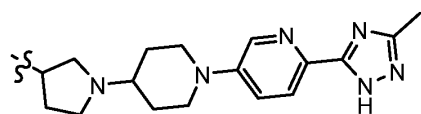
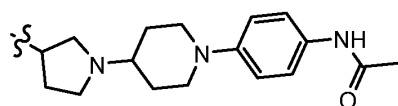
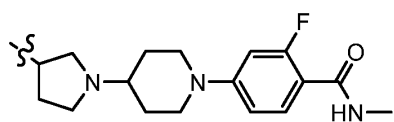
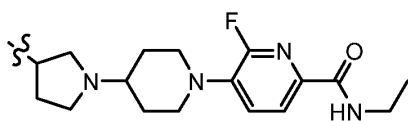
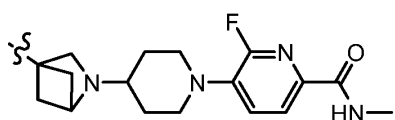
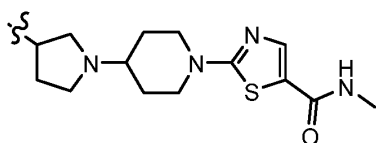
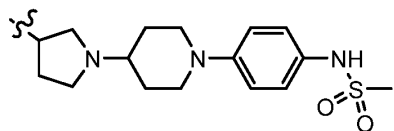
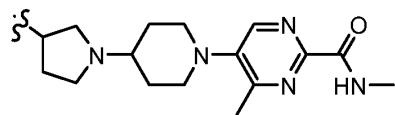


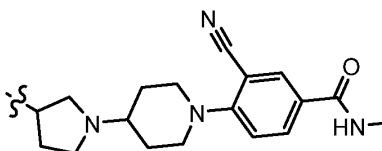
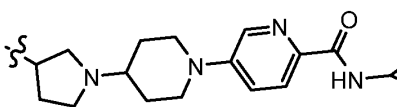
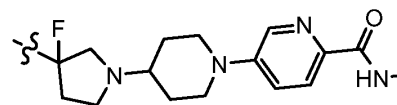
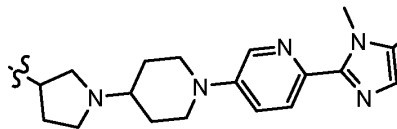
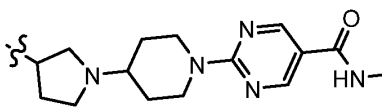
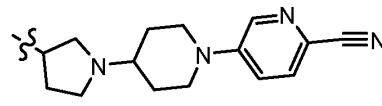
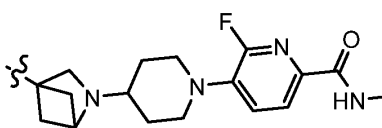
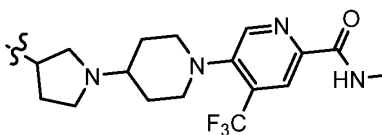
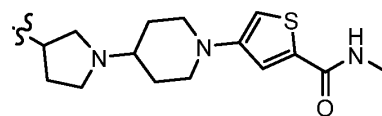
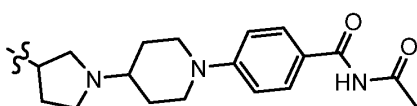
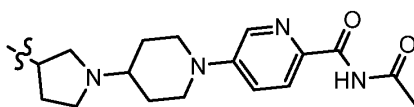
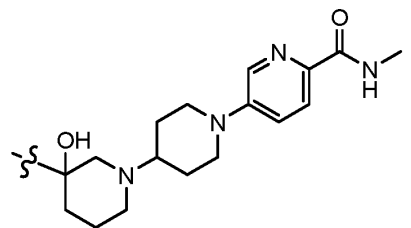
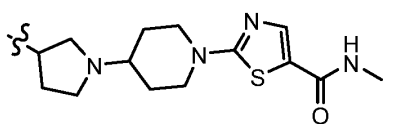
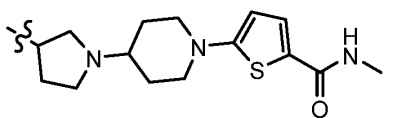
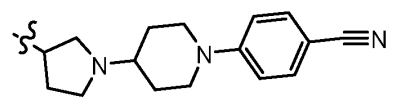
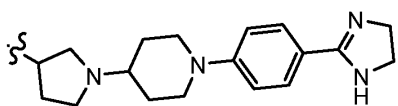
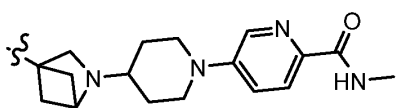
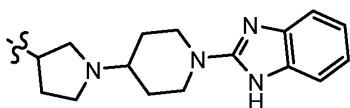
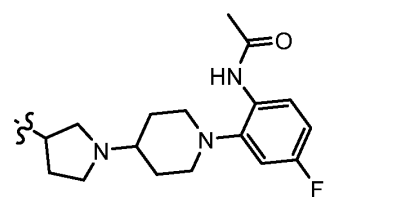


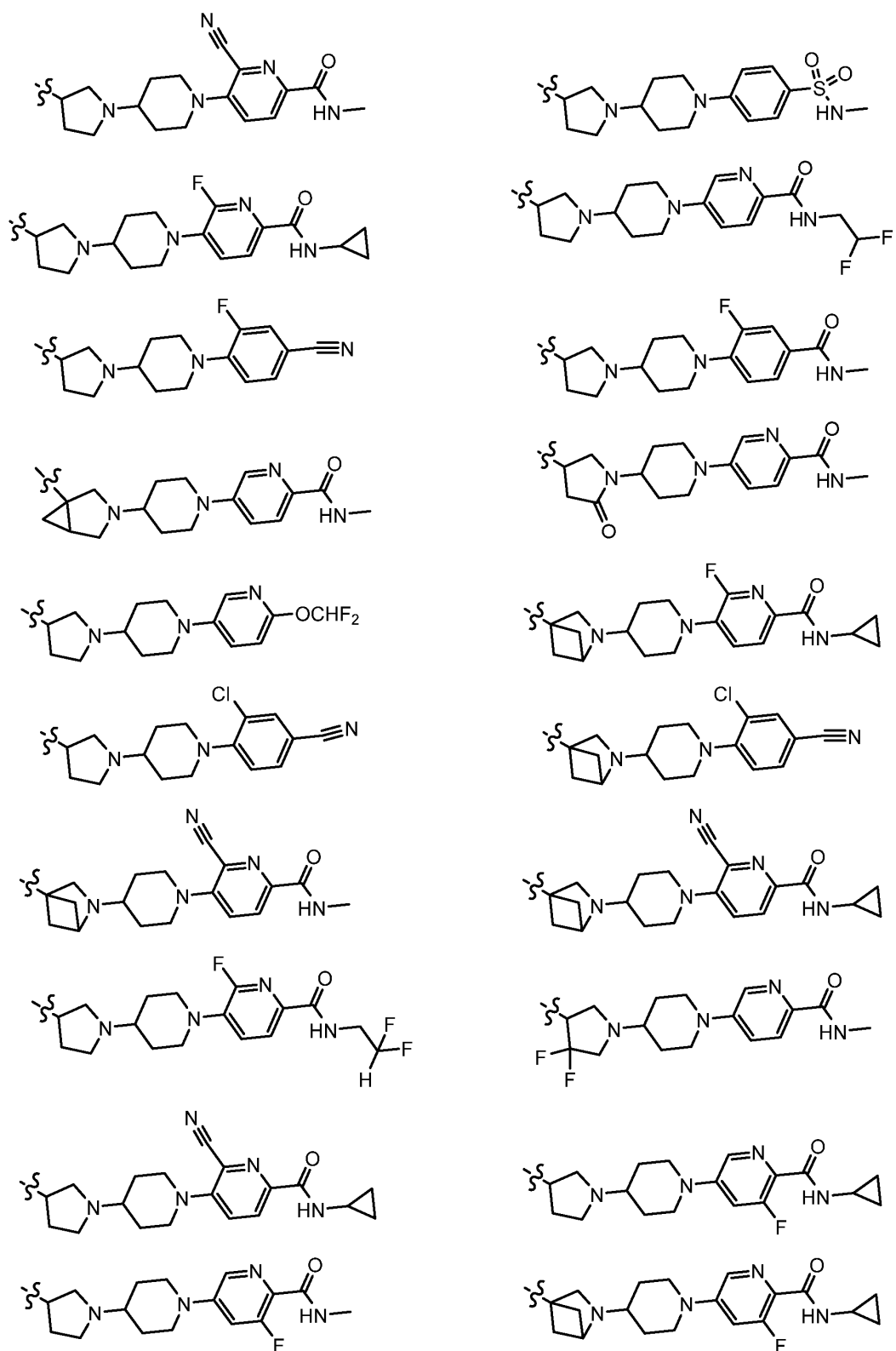


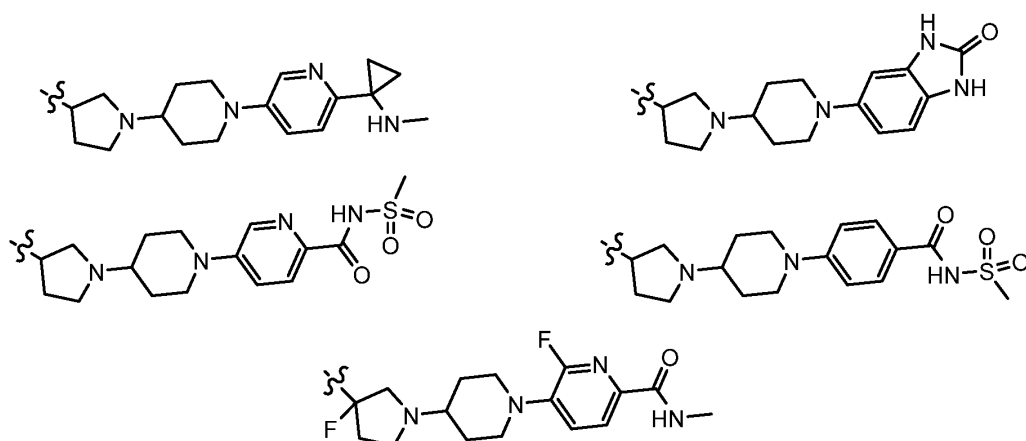




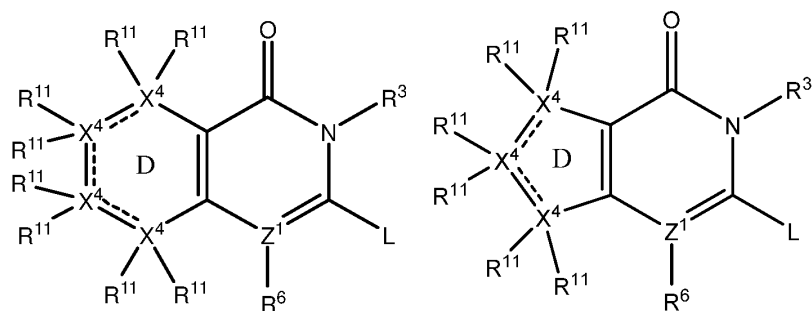






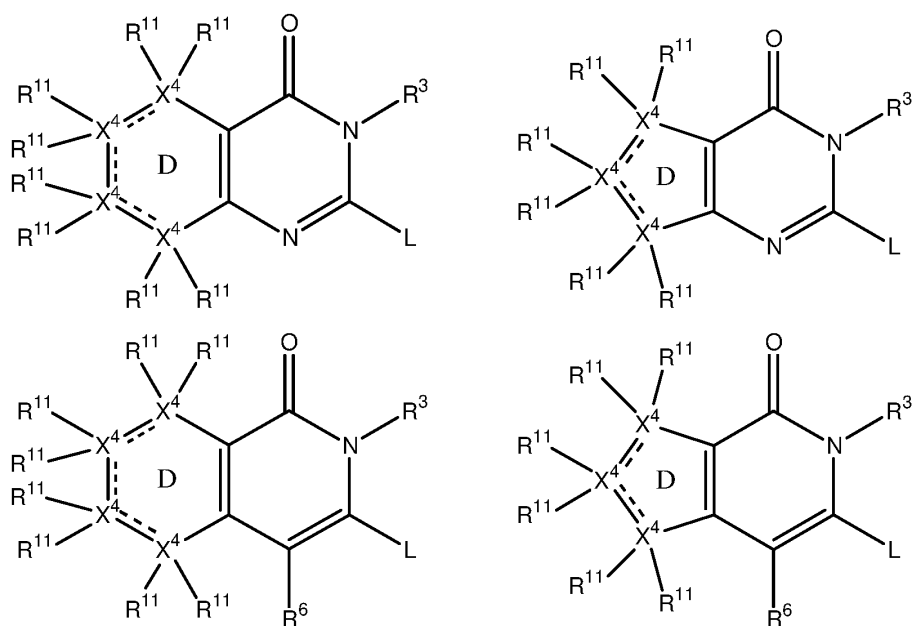


In some embodiments, a compound is provided which comprises any of the following structures:



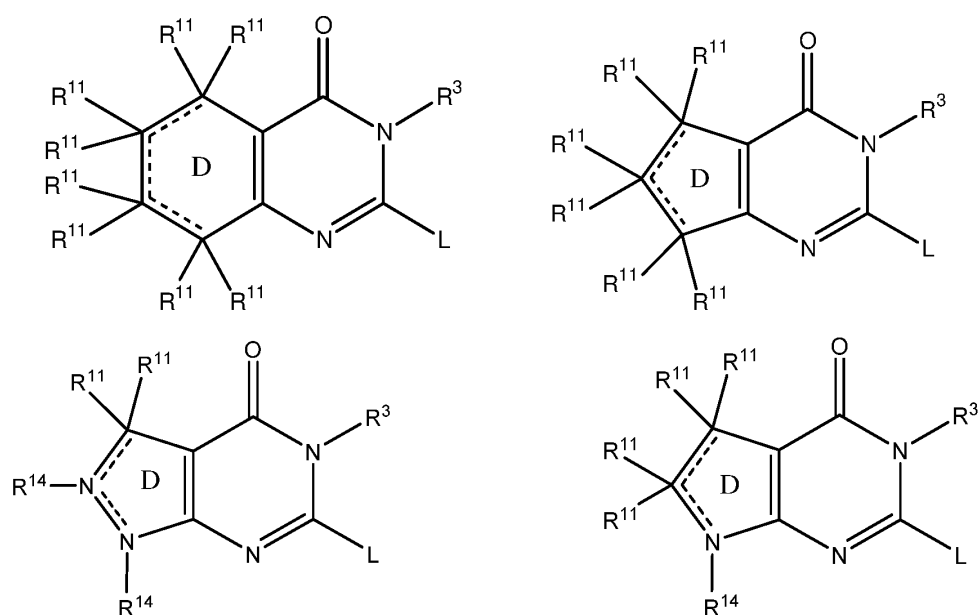
wherein, the dotted lines indicate that the ring D may comprise single bonds, or a combination of both single and double bonds, and may be aliphatic or aromatic; each X^4 may be the same or different and is independently selected from C, N, O and S; each R^{11} may be the same or different and is independently selected from H and a substituted or unsubstituted organic group; and wherein Z^1 , R^3 , R^6 , and L are as defined herein. In some embodiments, one X^4 of the ring D is N. It is preferred that at least one X^4 is C.

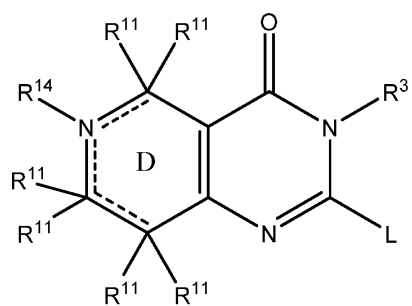
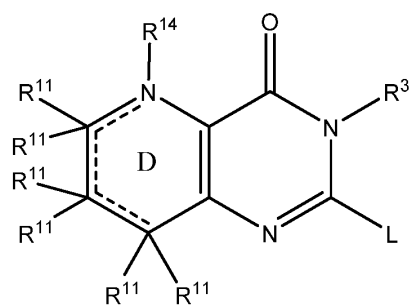
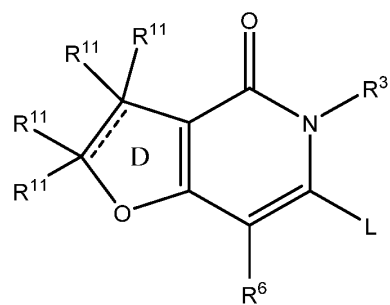
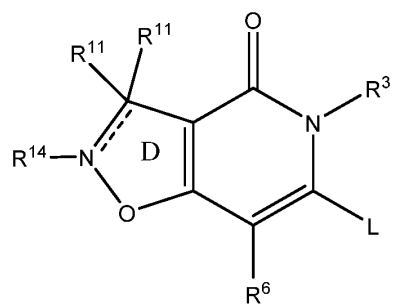
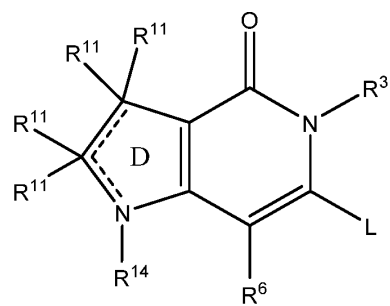
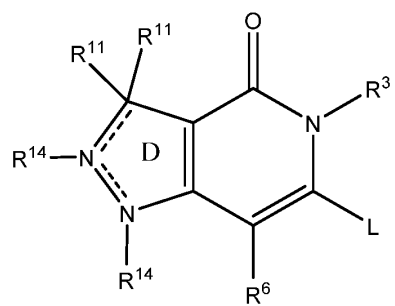
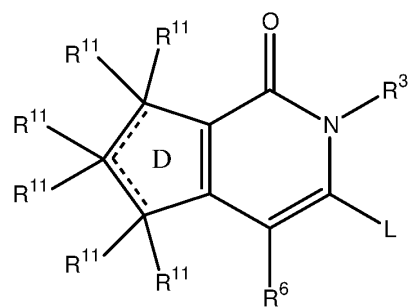
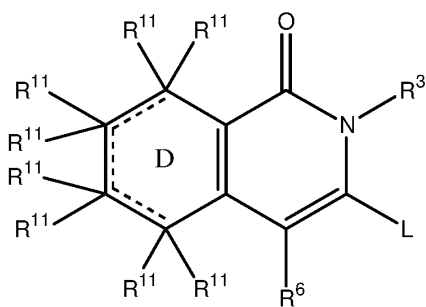
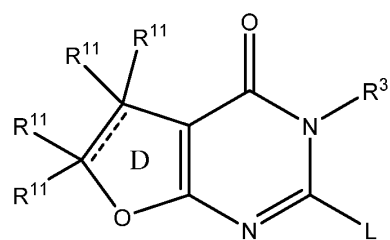
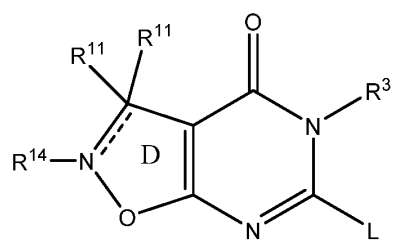
Preferably, the compound comprises any of the following structures:

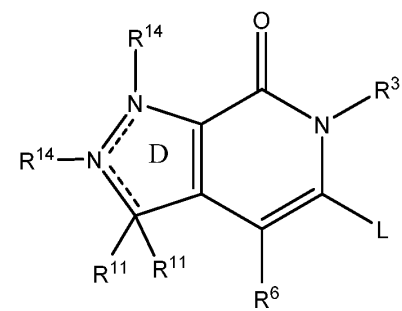
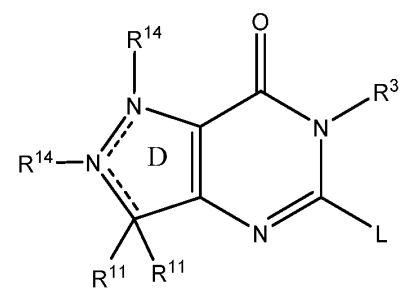
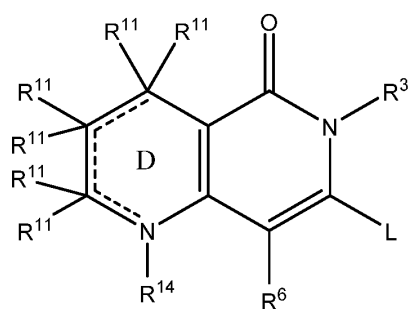
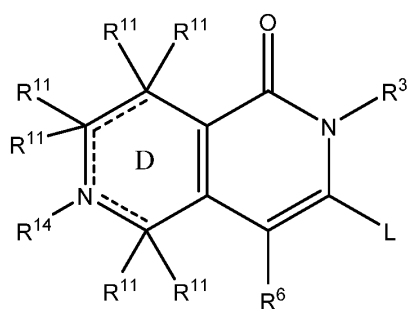
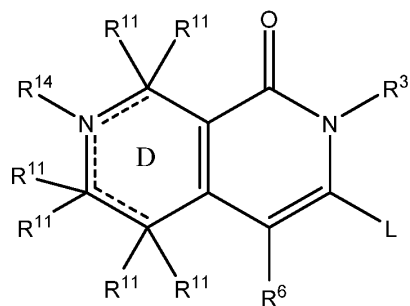
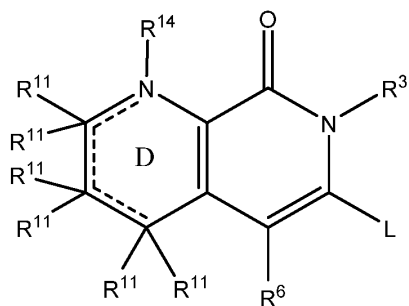
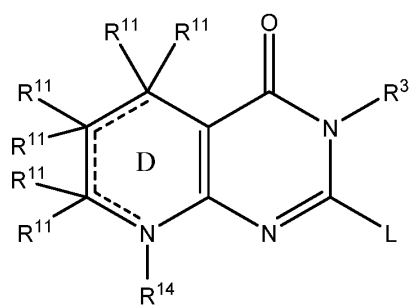
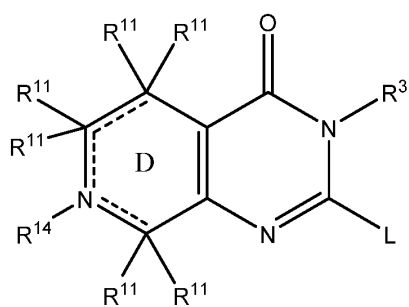


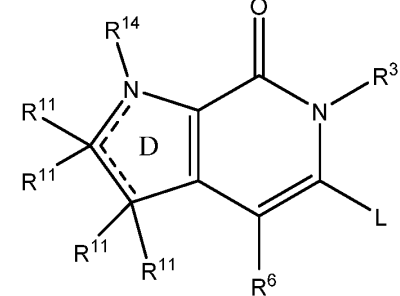
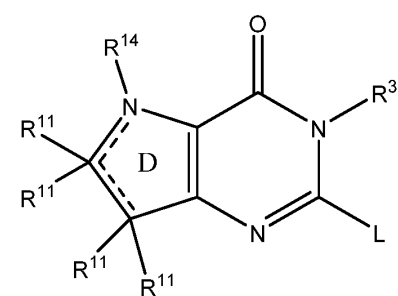
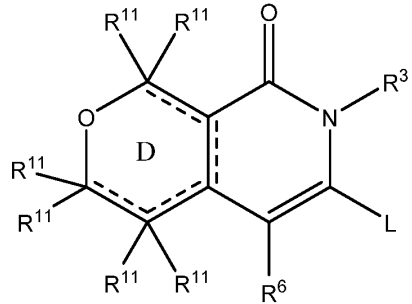
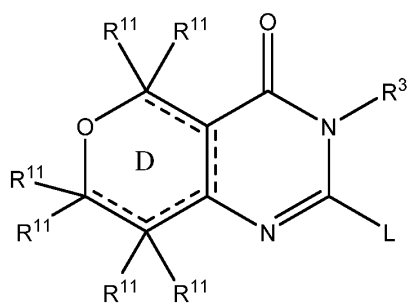
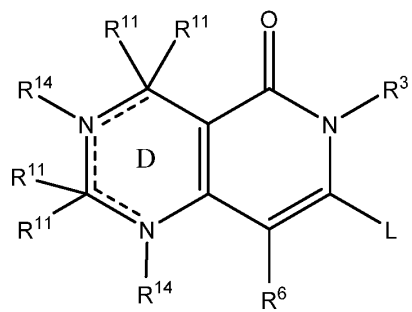
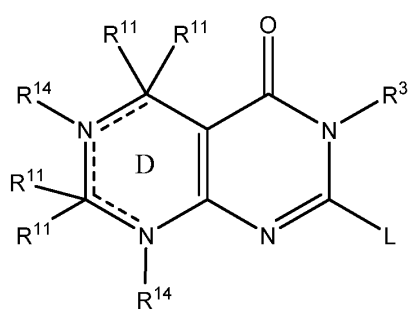
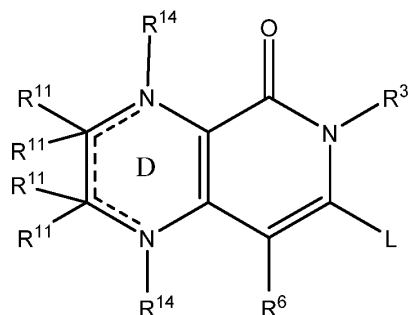
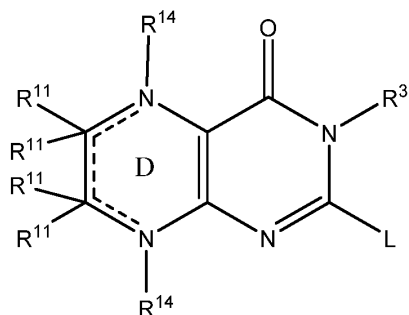
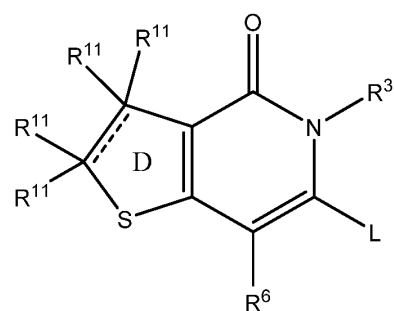
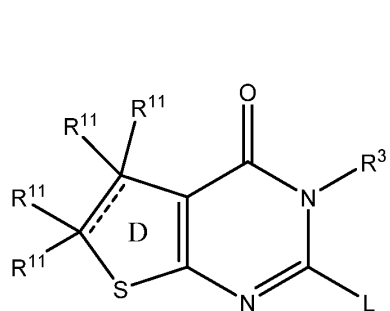
wherein the ring D, X^4 , R^{11} , R^3 , R^6 , and L are as defined herein.

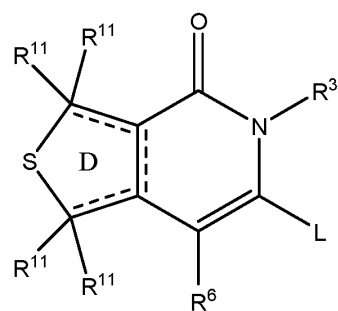
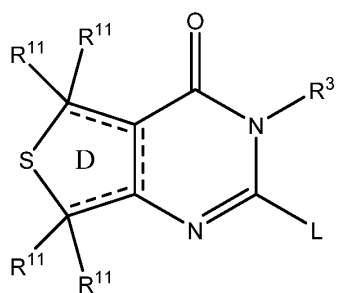
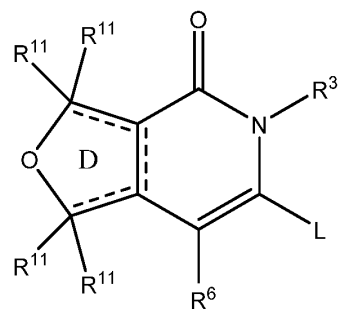
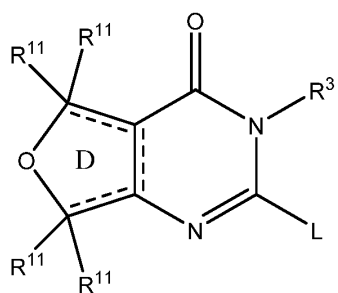
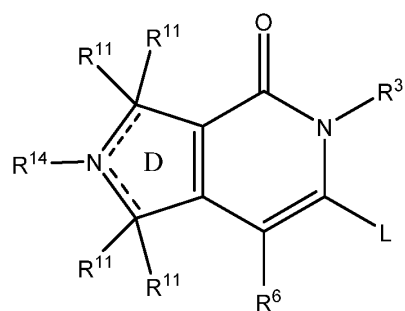
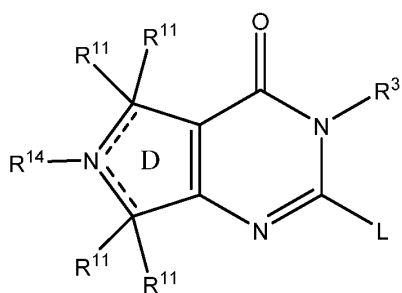
More preferably, the compound comprises any of the following structures:





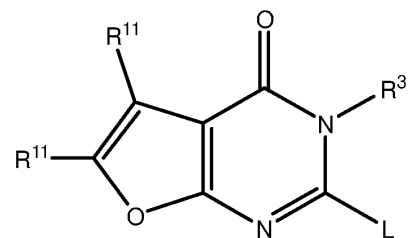
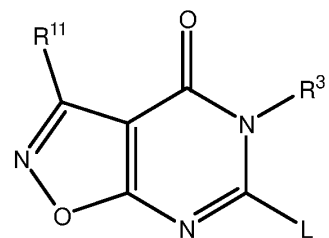
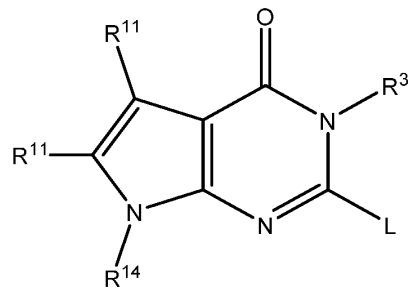
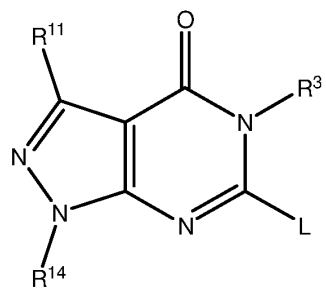
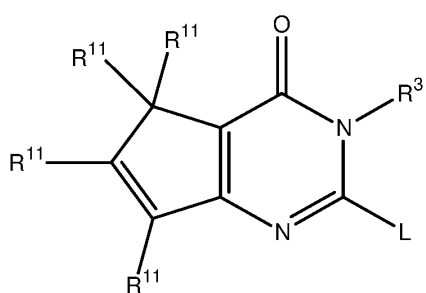
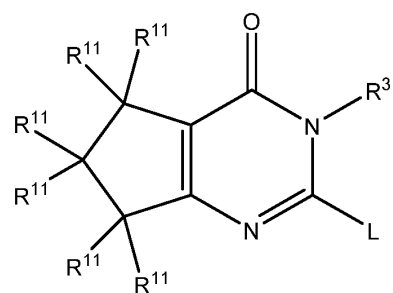
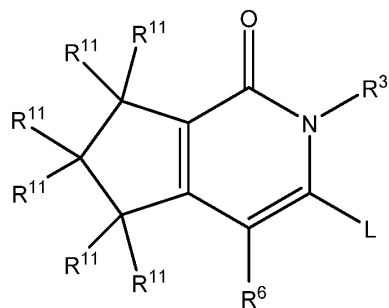
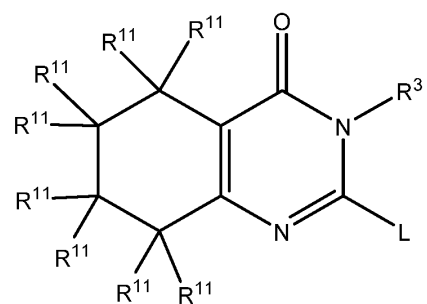
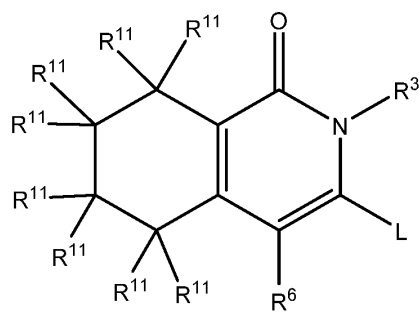
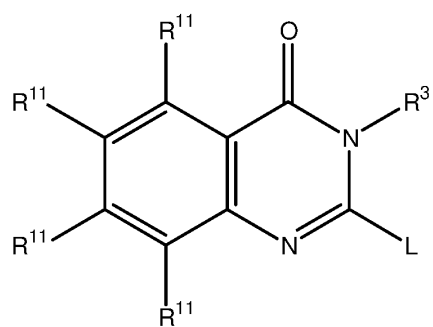


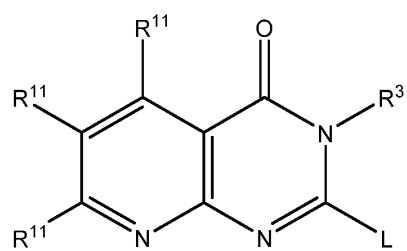
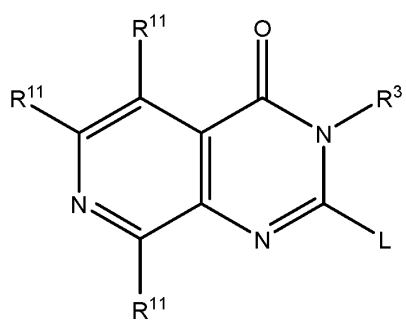
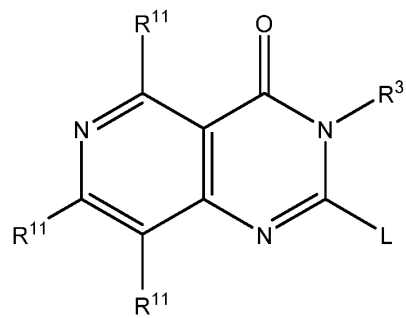
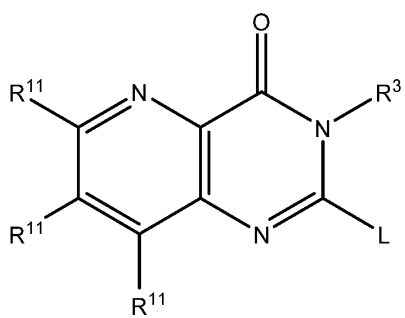
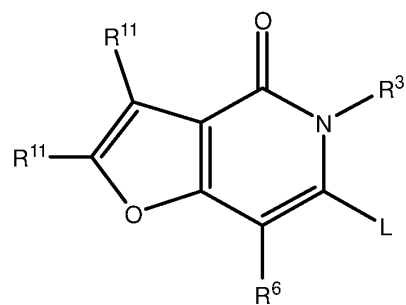
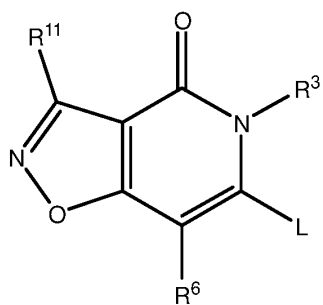
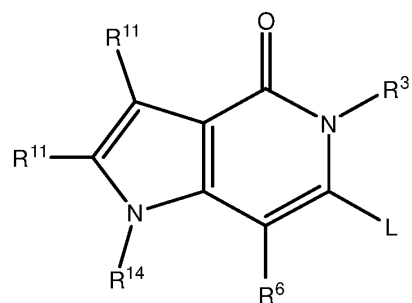
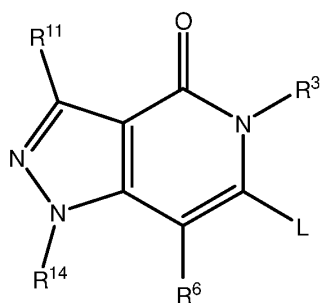
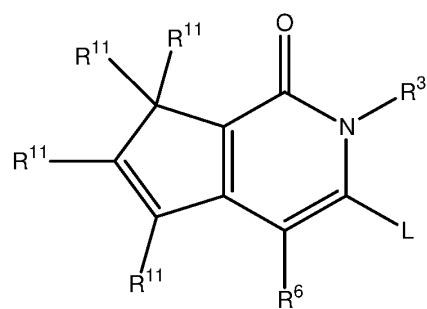
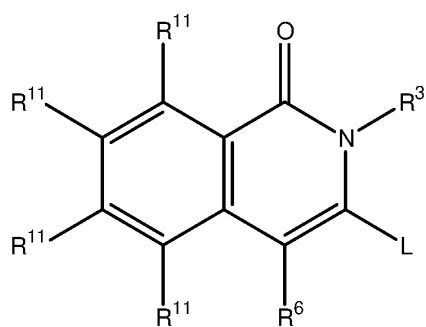


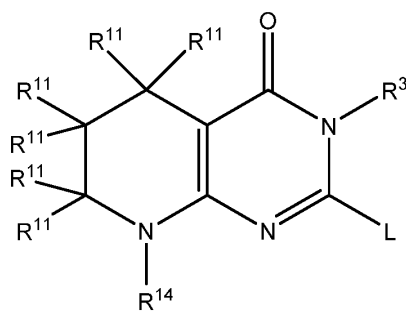
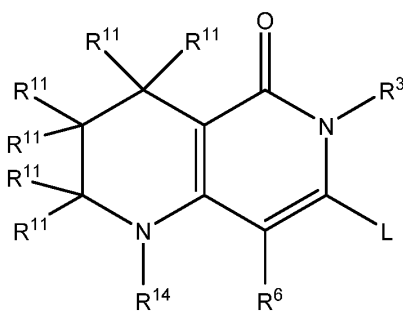
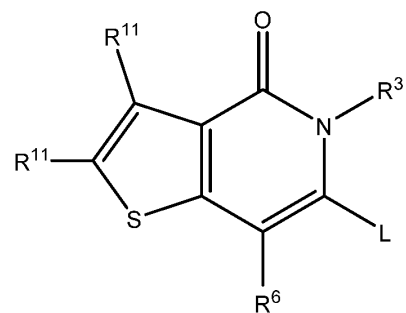
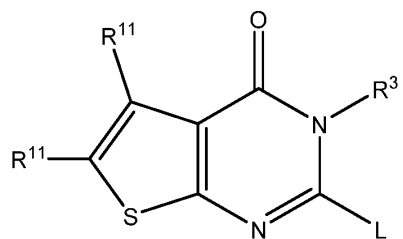
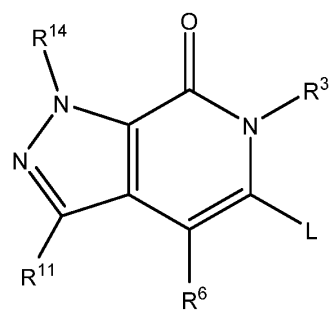
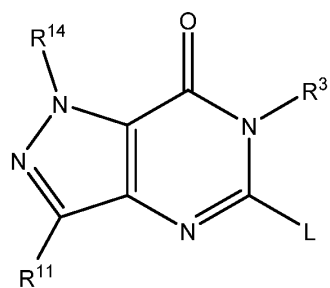
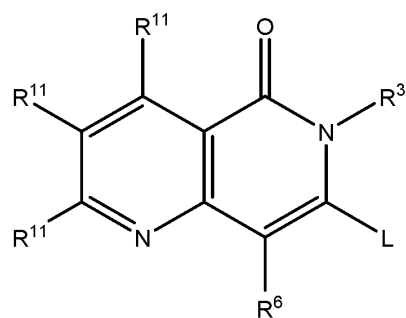
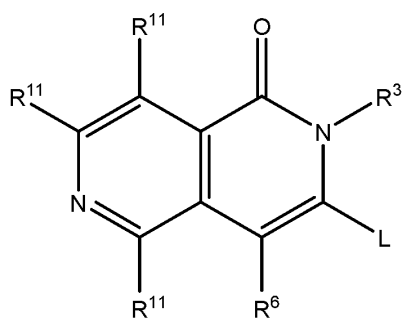
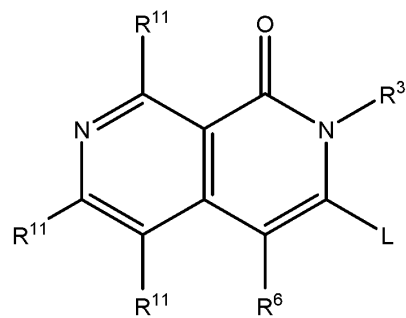
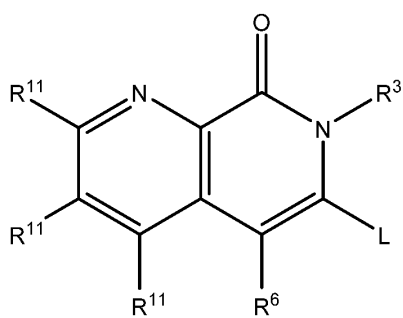


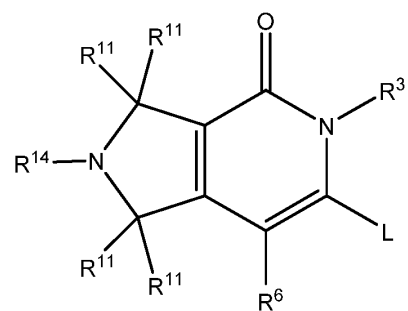
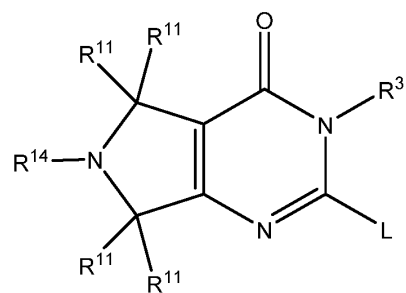
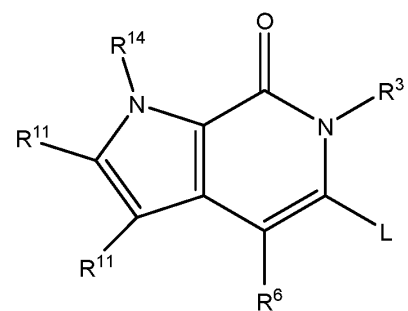
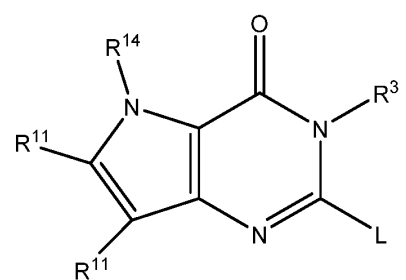
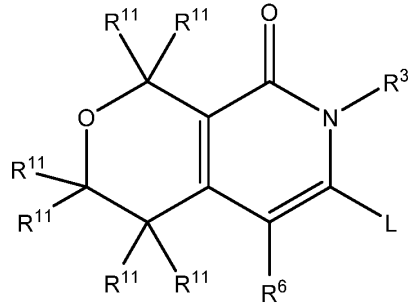
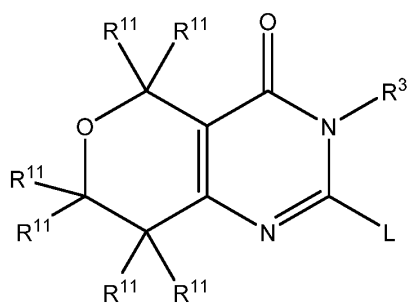
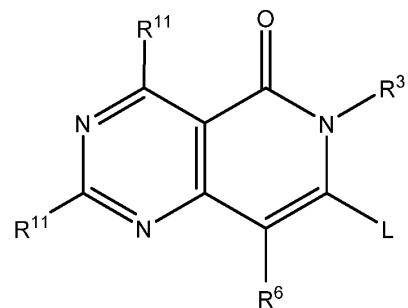
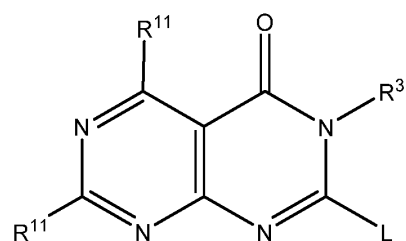
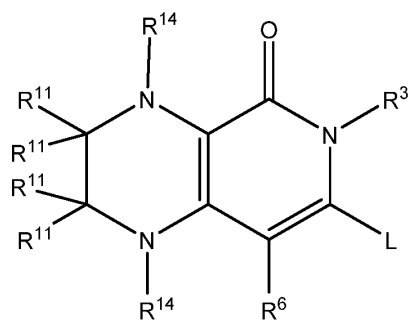
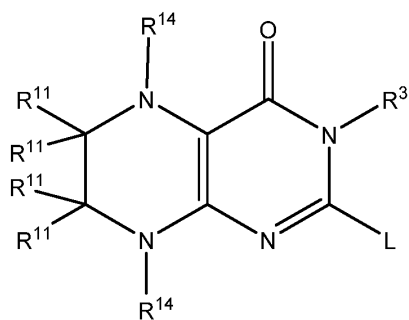
wherein R^{14} is selected from H, C_1 to C_3 alkyl or C_1 to C_3 fluoroalkyl; and wherein R^{11} , ring D, R^3 , R^6 , and L are as defined herein.

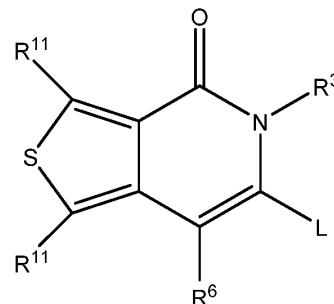
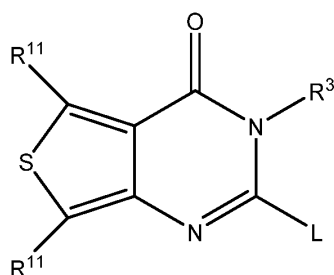
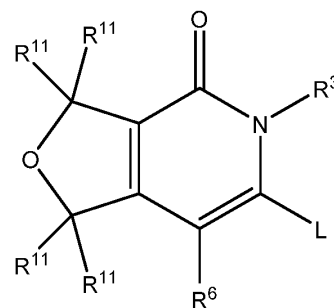
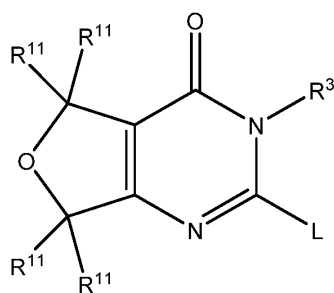
Still more preferably, the compound comprises any of the following structures:









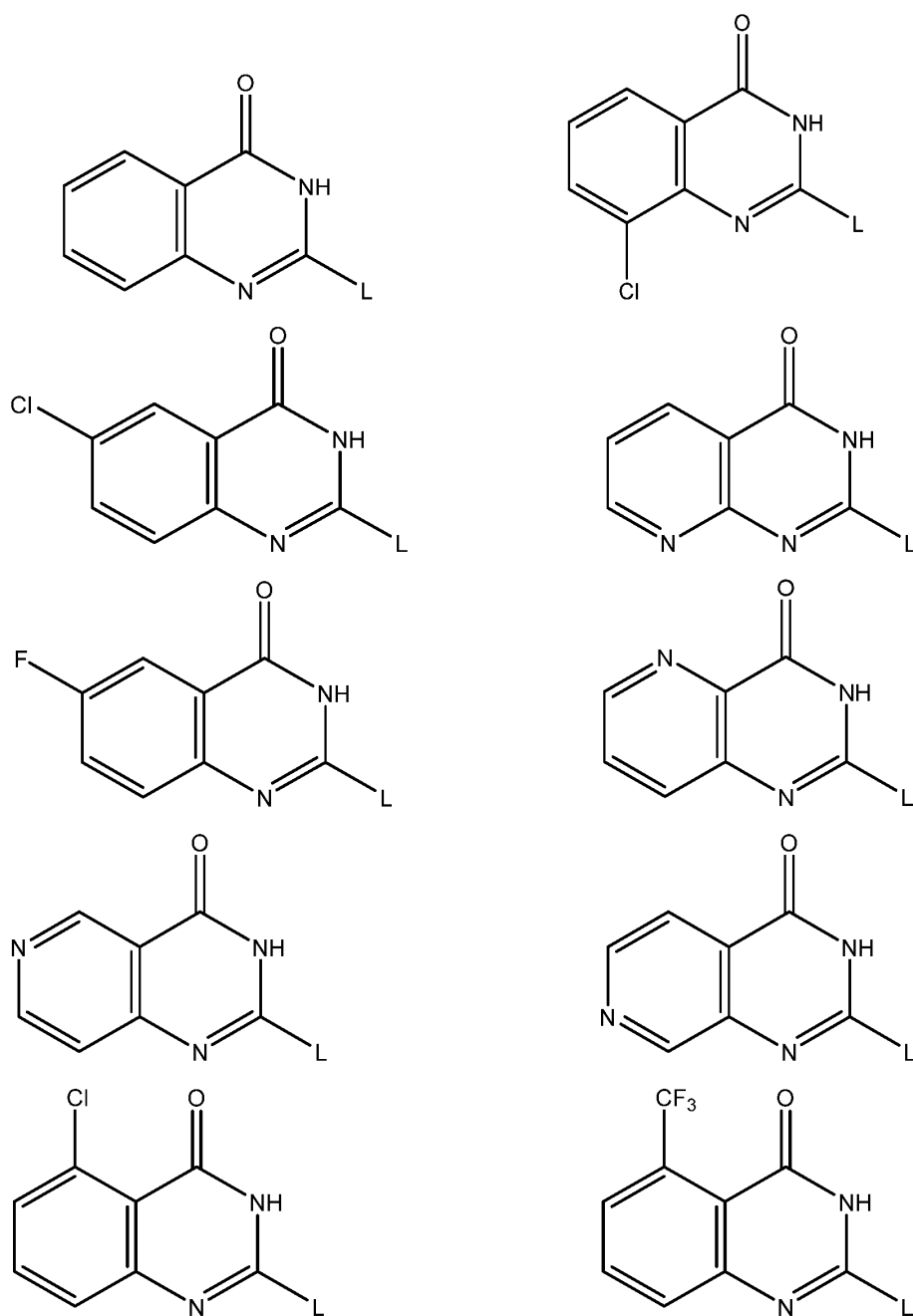


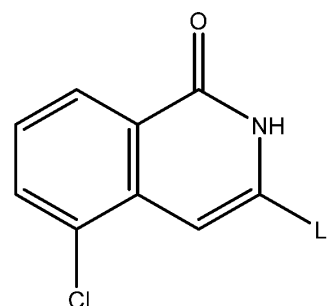
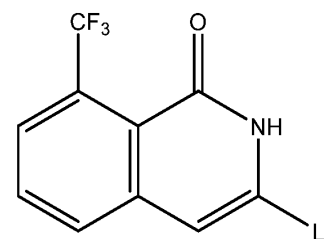
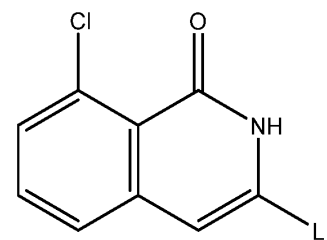
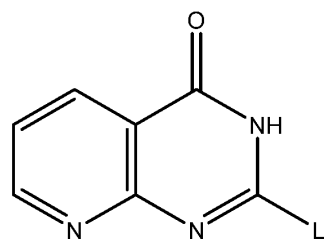
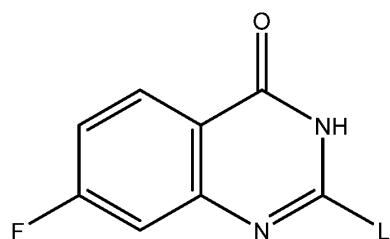
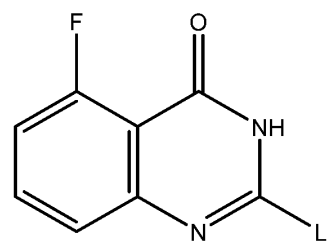
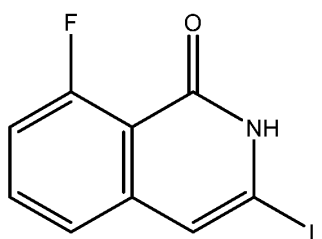
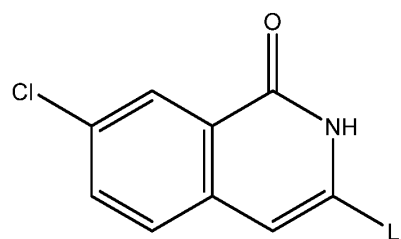
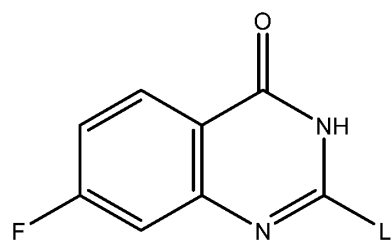
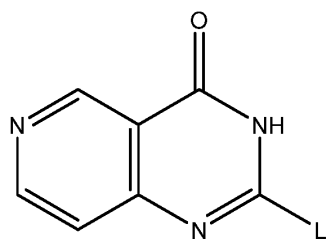
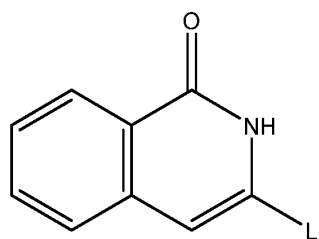
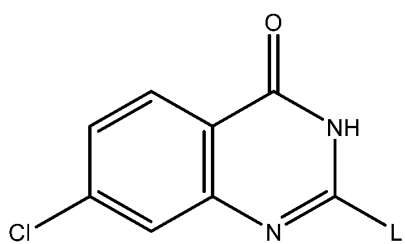
wherein R^3 , R^{11} , R^{14} , R^6 , and L are as defined herein.

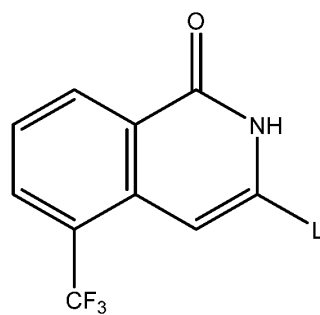
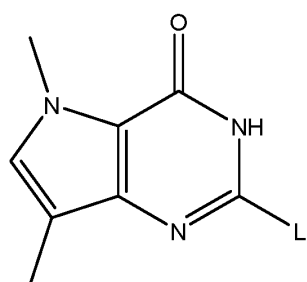
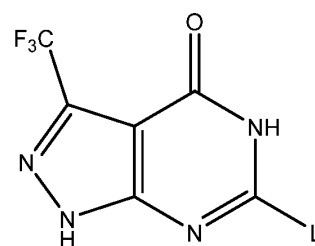
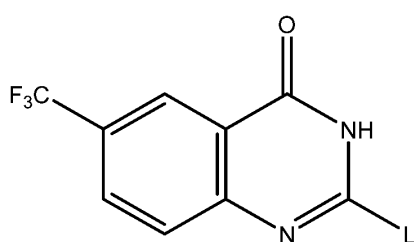
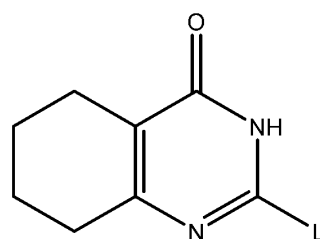
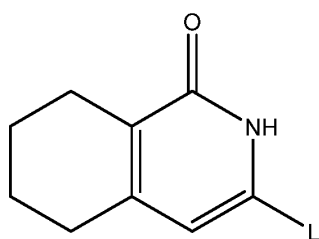
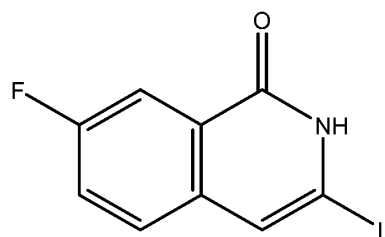
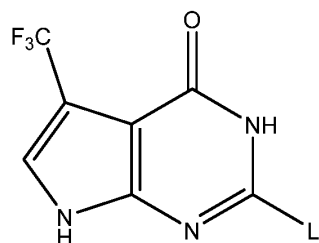
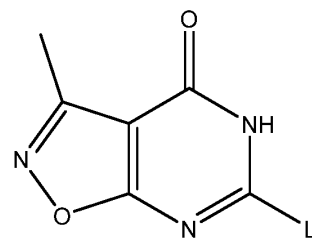
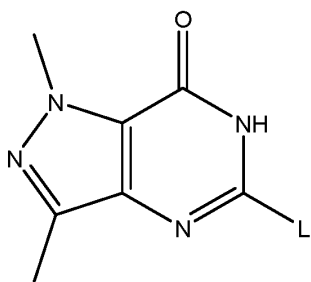
Each R^{11} may independently be selected from H, a halogen, a nitrile group, a linear or branched C_1 - C_3 alkyl group, a linear or branched C_1 - C_3 halogenated alkyl group (preferably fluoroalkyl), an -OH group, a linear or branched C_1 - C_3 alcohol group, a halogenated (preferably fluoro-) linear or branched C_1 - C_3 alcohol group, -NH₂, a linear or branched primary secondary or tertiary C_1 - C_3 amine group, a halogenated (preferably fluoro-) linear or branched primary, secondary or tertiary C_1 - C_3 amine group, a linear or branched C_1 - C_3 alkoxy group, a linear or branched C_1 - C_3 halogenated alkoxy group (preferably fluoroalkoxy), and/or a pair of R^{11} groups attached to the same atom forming =O; and independently, and/or when a pair of R^{11} groups attached to different atoms together forms a ring with ring D atoms, the pair of R^{11} groups comprises -CH₂CH₂CH₂-.

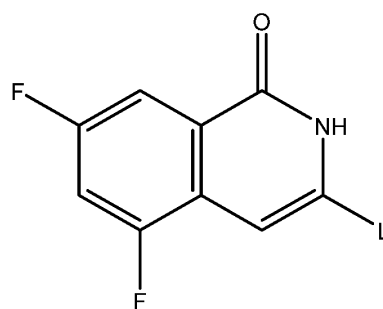
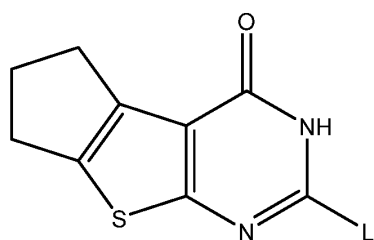
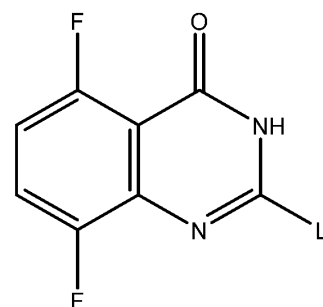
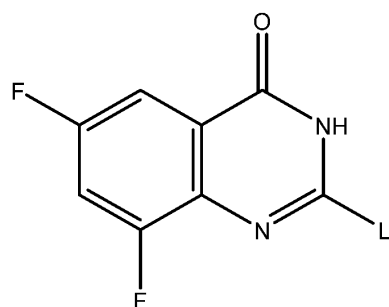
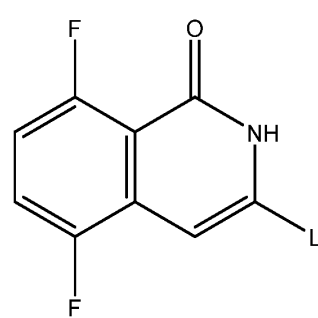
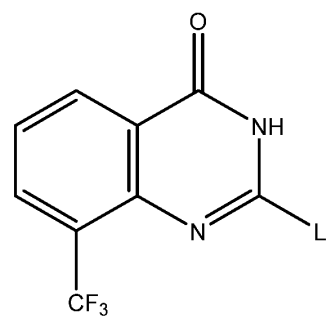
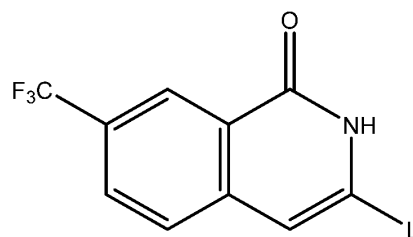
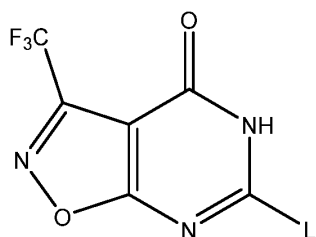
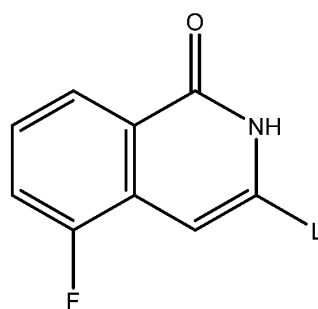
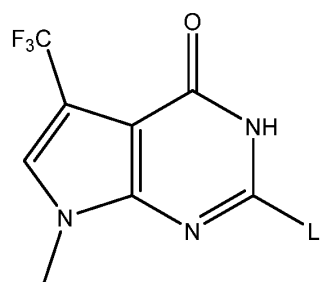
It is preferred that each R^{11} is independently selected from H, Cl, F, CHF₂, CF₃, CH₃, OH, CH₃O, and NH₂, and/or a pair of R^{11} groups attached to the same atom forming =O; and independently, when a pair of R^{11} groups attached to different atoms together forms a ring with ring D atoms, the pair of R^{11} groups comprises -CH₂CH₂CH₂-.

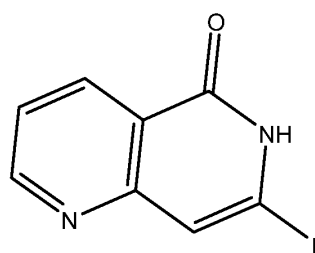
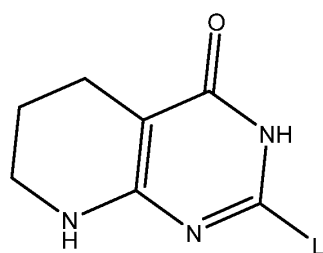
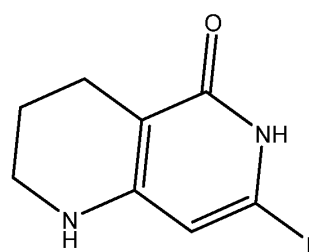
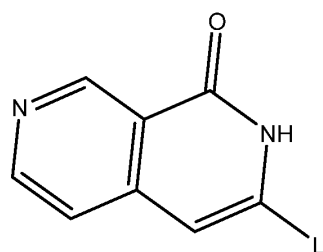
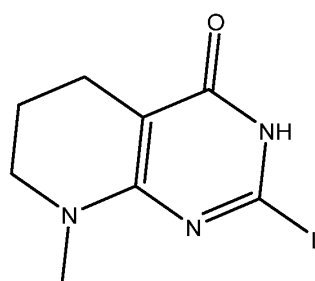
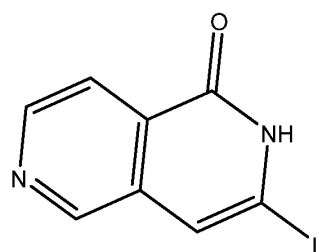
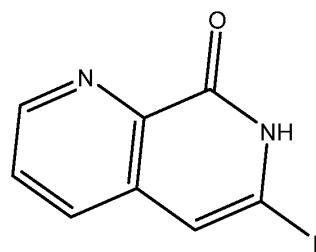
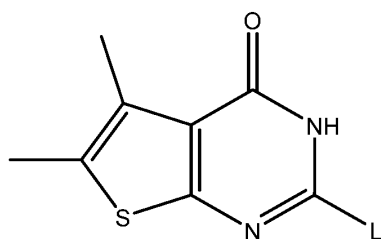
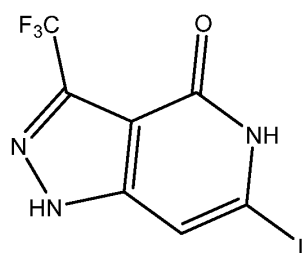
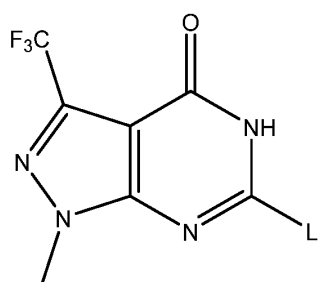
In some embodiments, a compound is provided which comprises any of the following structures:

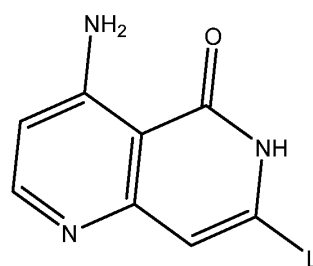
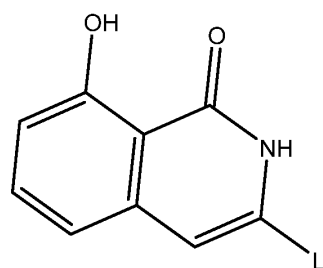
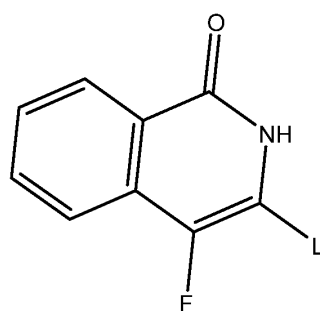
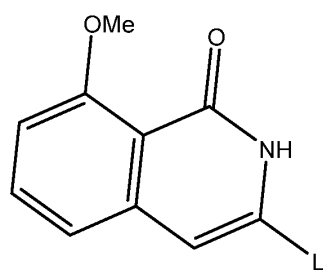
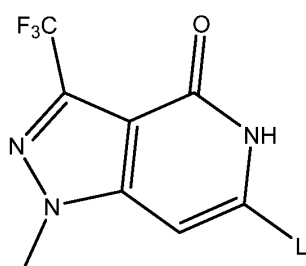
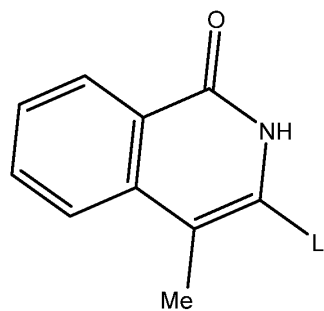
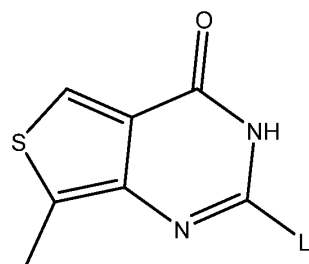
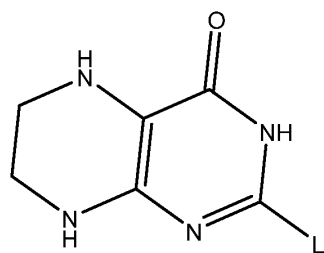
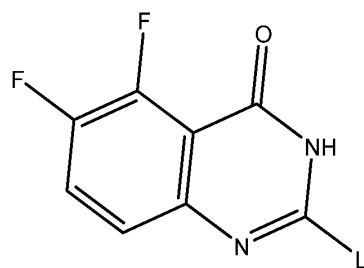
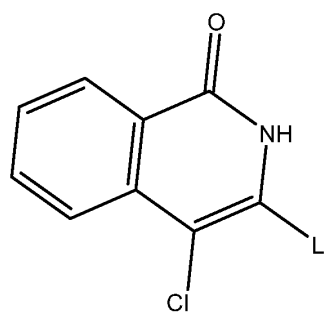


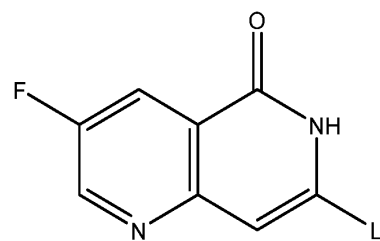
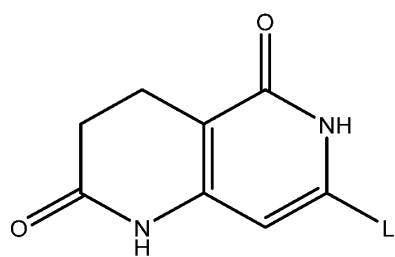
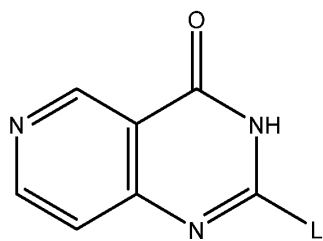
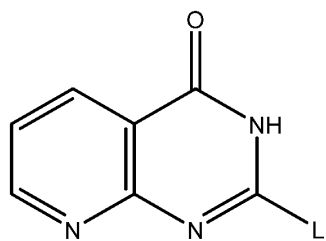
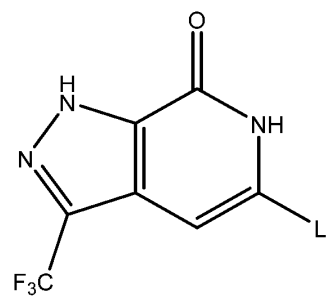
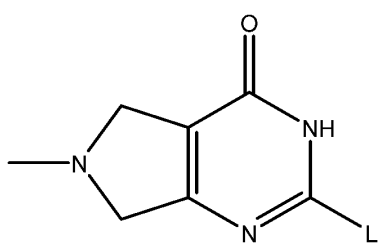
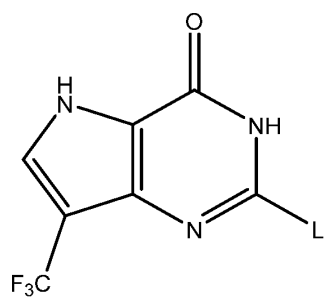
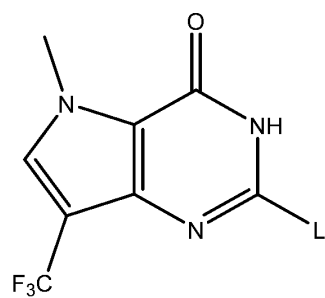
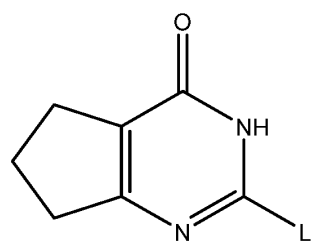
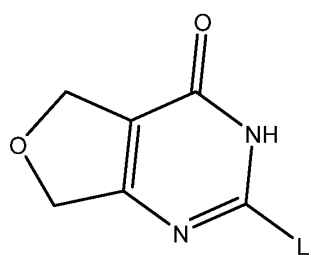


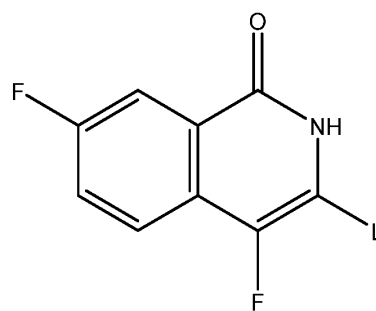
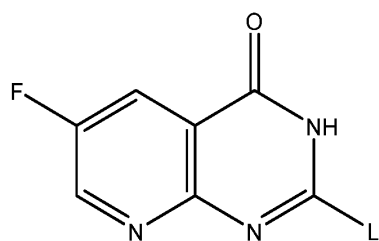
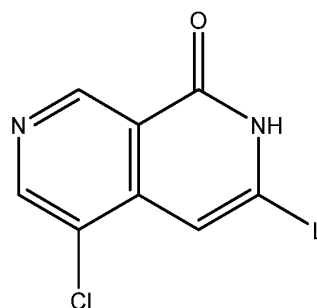
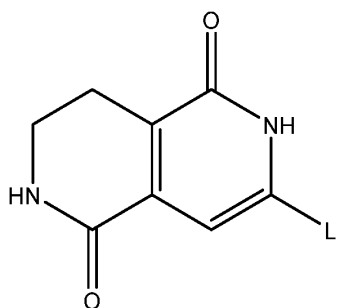
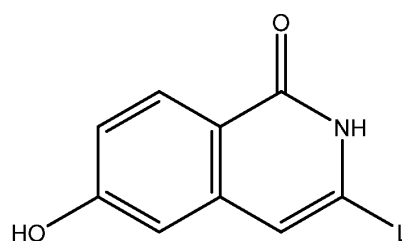
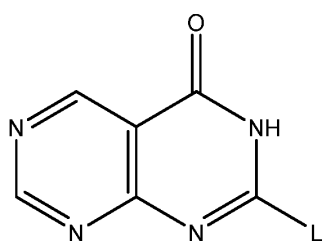
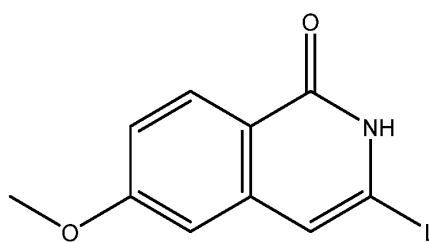
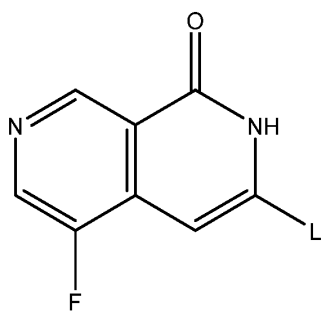
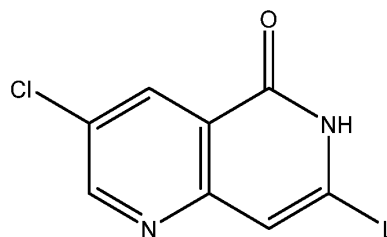
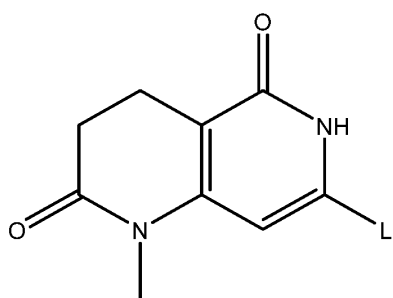


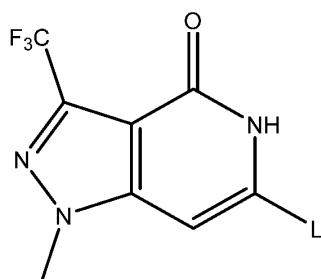
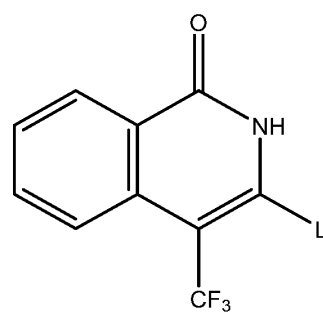
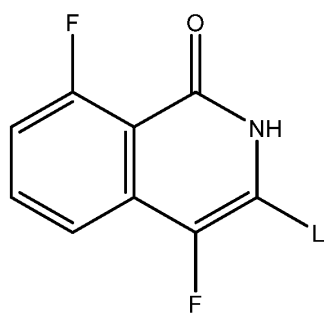
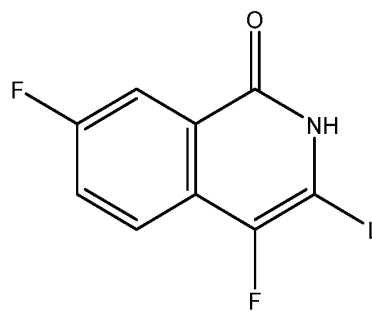
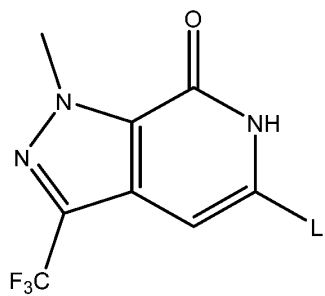
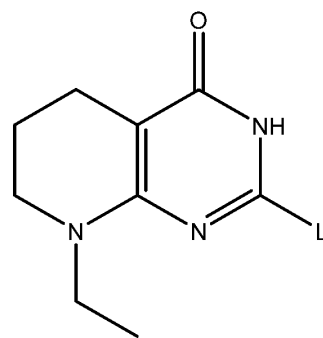
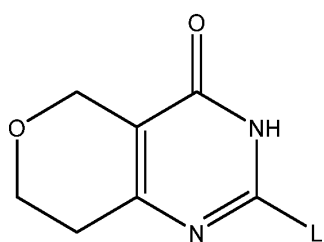
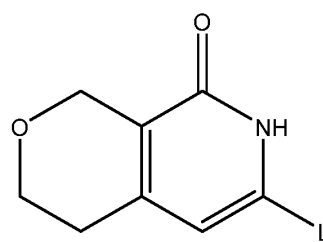
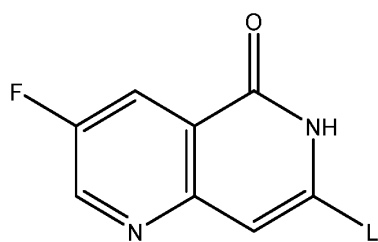






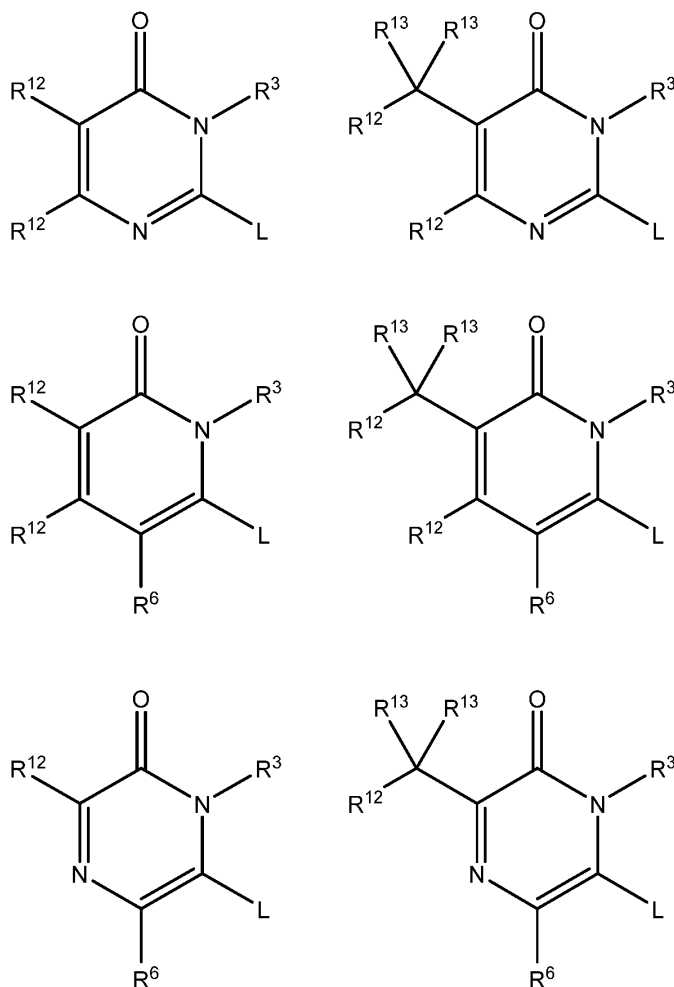






wherein L is as defined herein.

In some embodiments, a compound is provided which comprises any of the following structures:



Wherein each R¹² is independently selected from H and a substituted or unsubstituted organic group, preferably a lower (C₁ to C₆) alkyl, alkoxy or haloalkyl group, a substituted or unsubstituted C₃ to C₆ cycloalkyl or heterocyclic group, and a halogen group, wherein at least one R¹² is not H; and wherein each R¹³ may be the same or different and is independently selected from H and a substituted or unsubstituted organic group; and wherein R³, R⁶, and L are as defined herein.

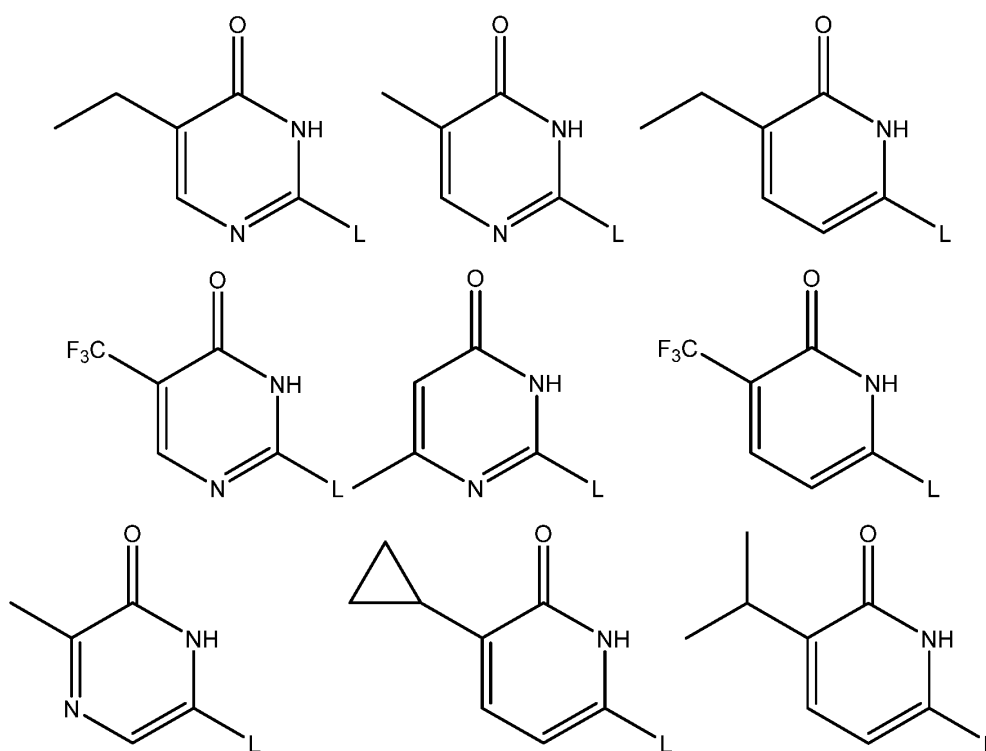
At least one R^{12} is preferably selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2Cl$, $-CHCl_2$, $-CCl_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-Cl$, $-F$, $-Cl$, $-CH_2CF_3$, $-CH_2CH_2F$, $-CH_2CH_2OH$, methoxy, methoxymethyl, methoxyethyl, isopropyl, cyclopropyl or cyclopropylmethyl.

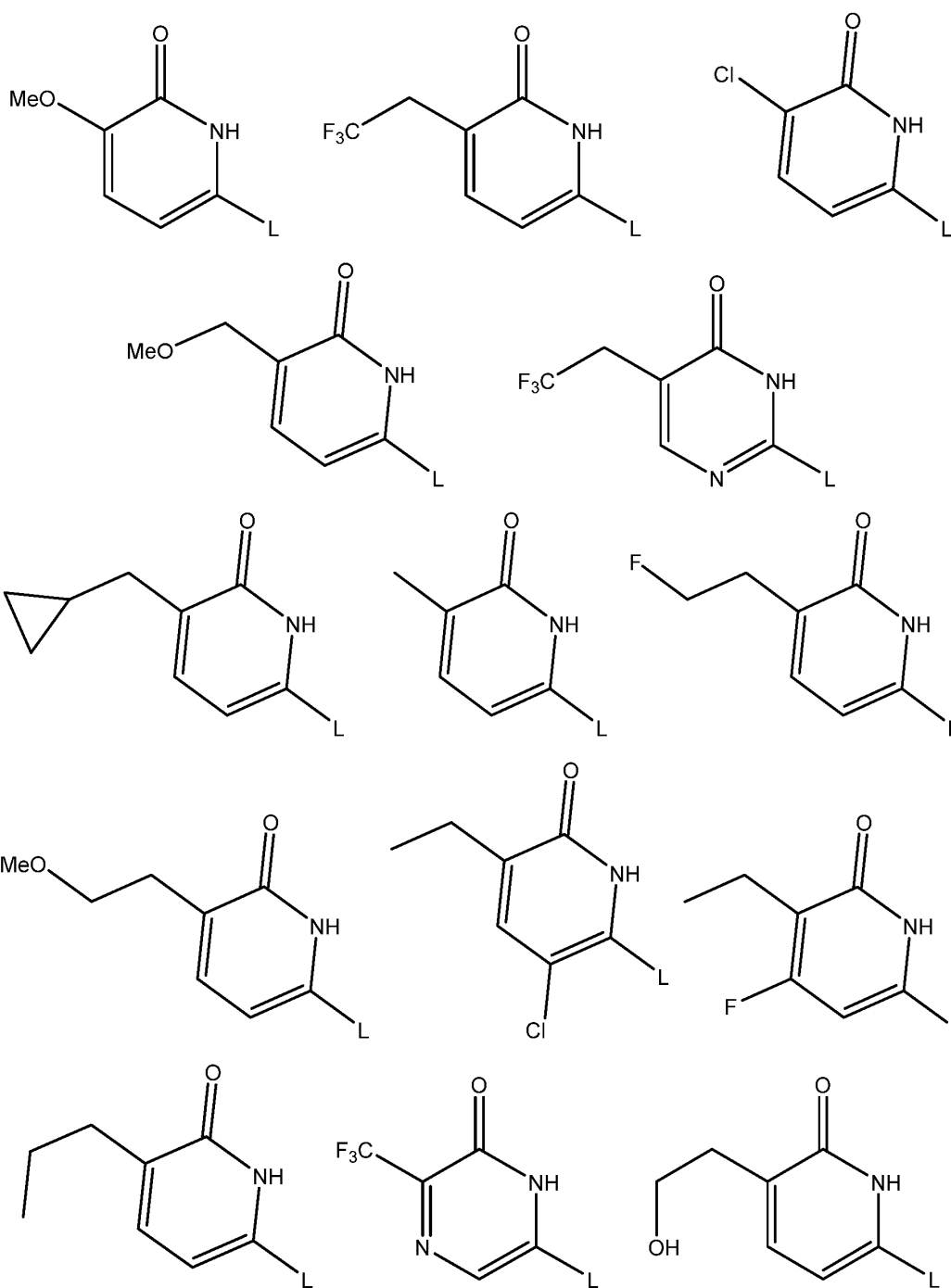
R^{13} is preferably selected from H, F, C_1 to C_3 alkyl or C_1 to C_3 fluoroalkyl.

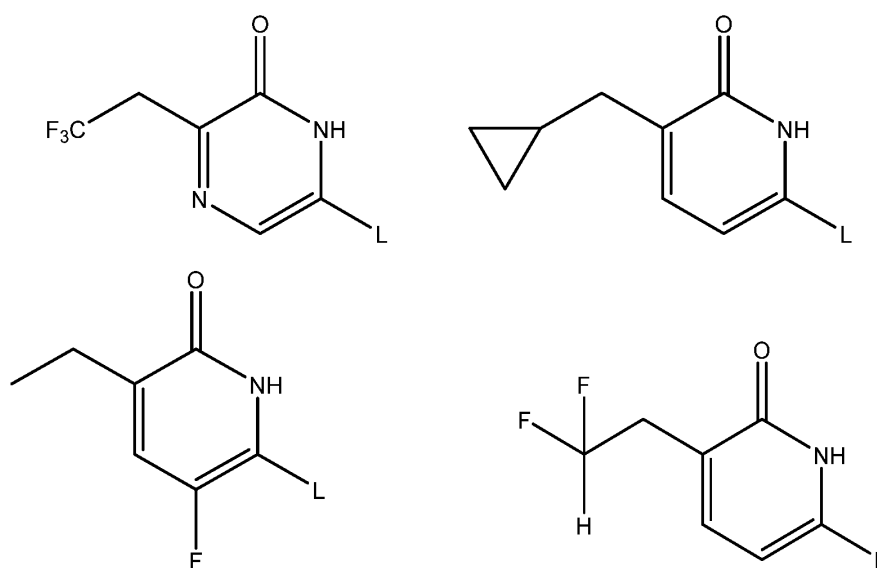
R^3 is preferably H.

R^6 is preferably selected from H, halogen, C_1 to C_3 alkyl, C_1 to C_3 haloalkyl, C_1 to C_3 alcohol or C_1 to C_3 aminoalkyl.

In some embodiments, a compound is provided which comprises any of the following structures:

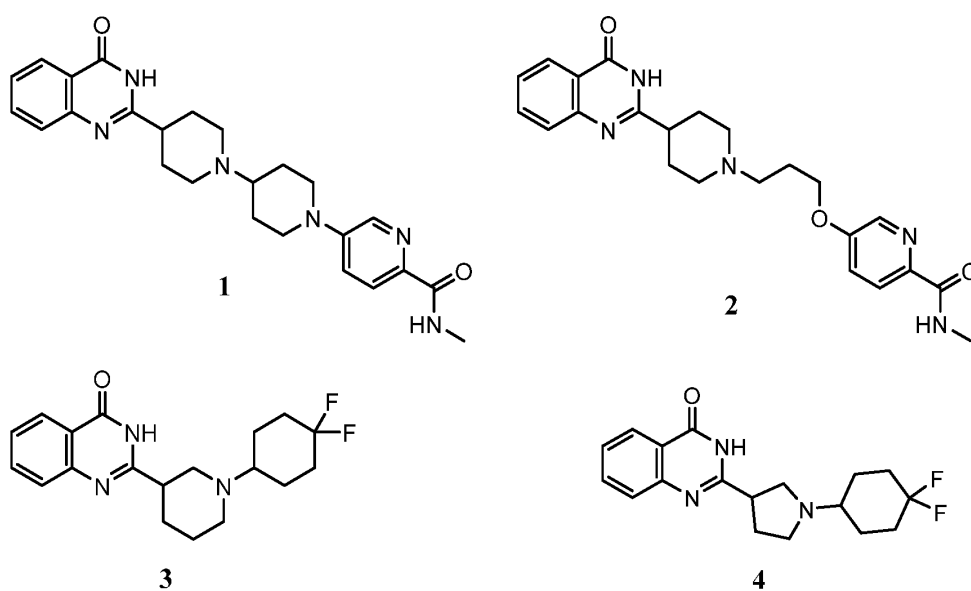


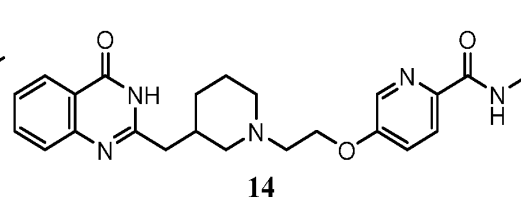
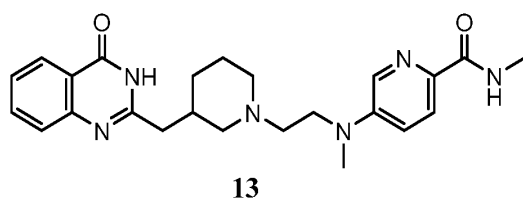
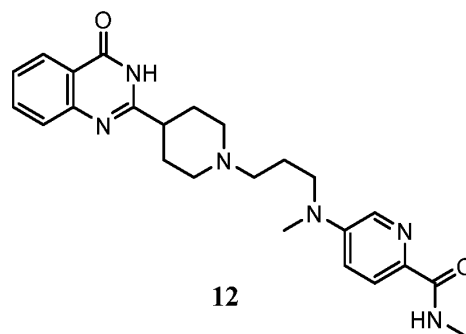
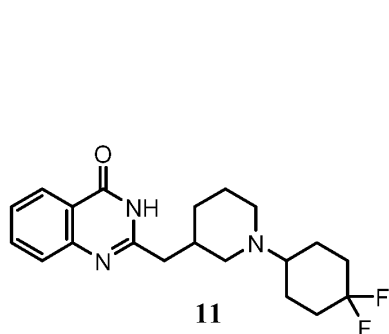
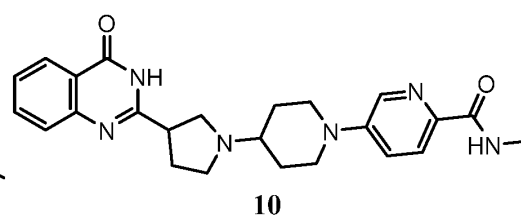
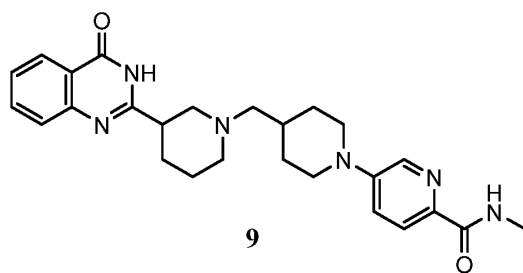
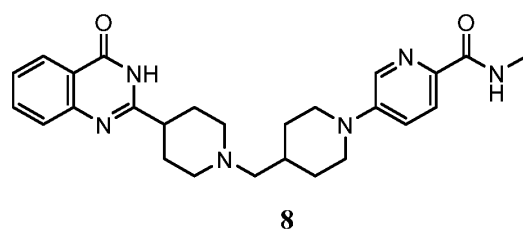
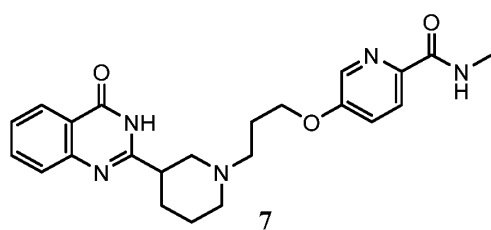
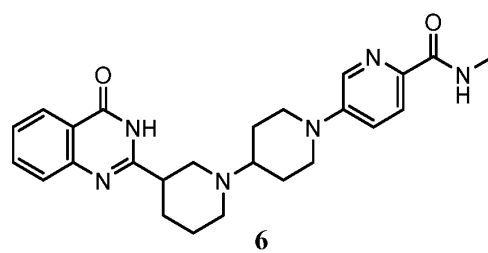
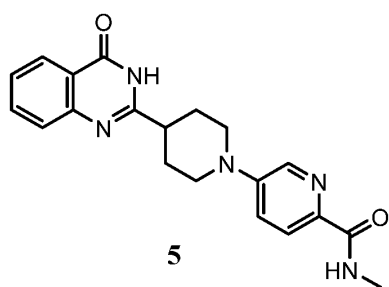


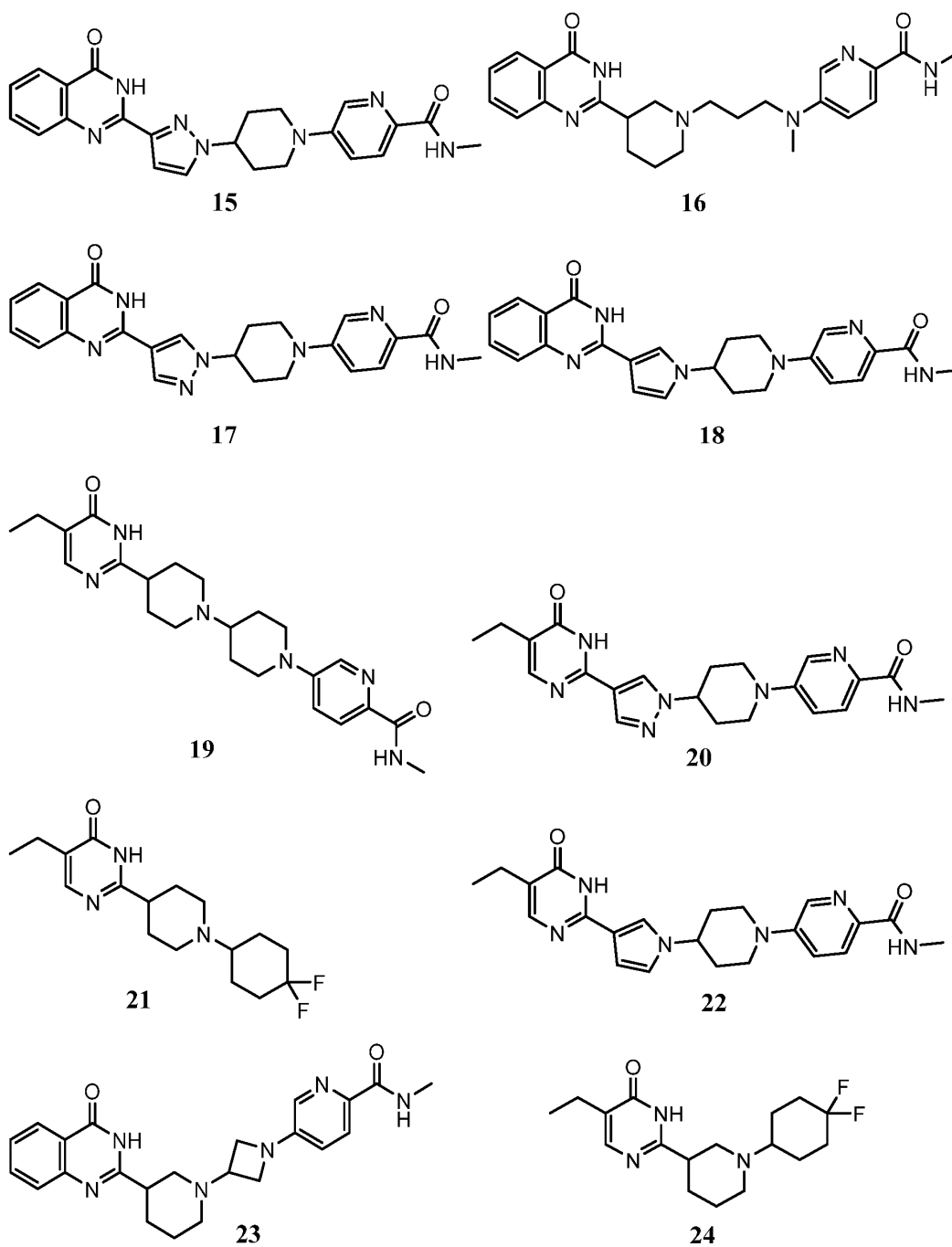


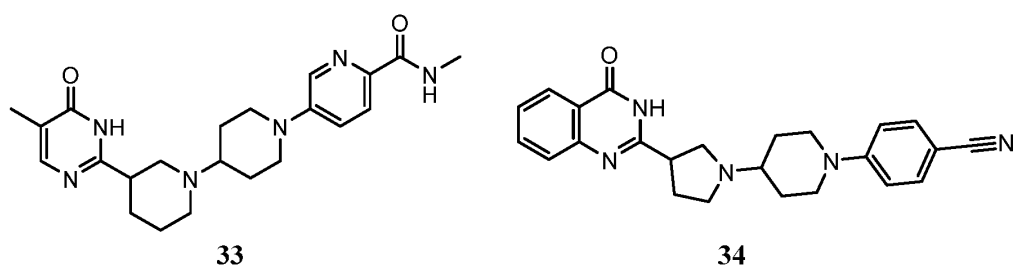
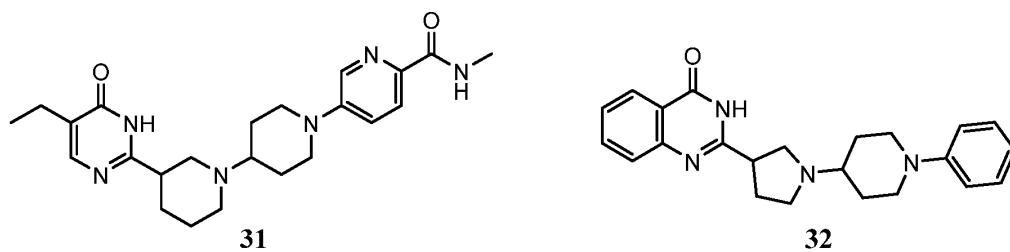
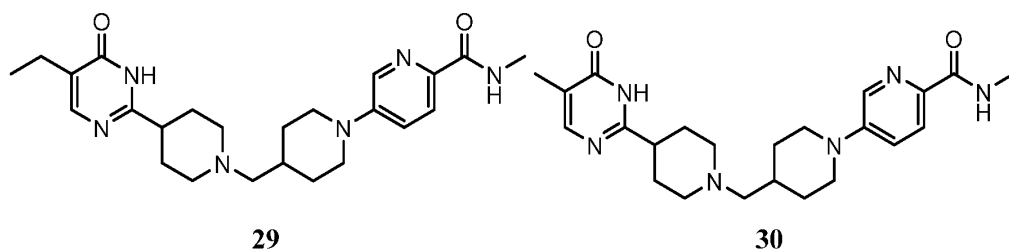
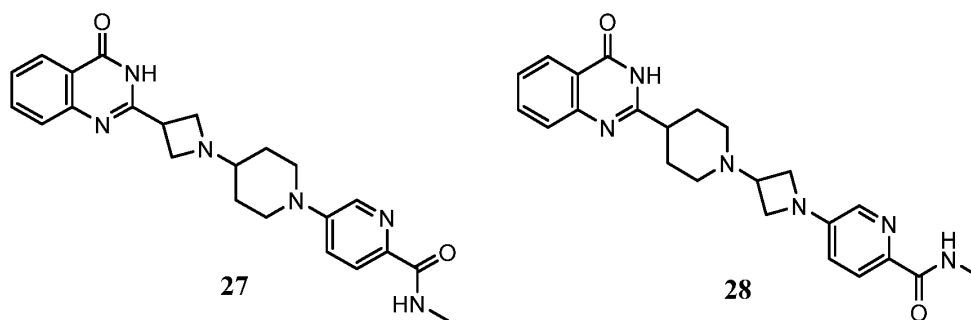
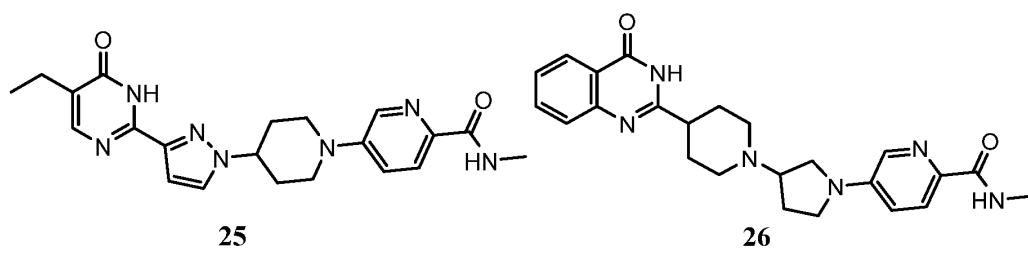
wherein L is as defined herein.

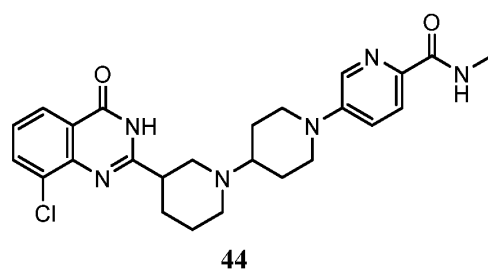
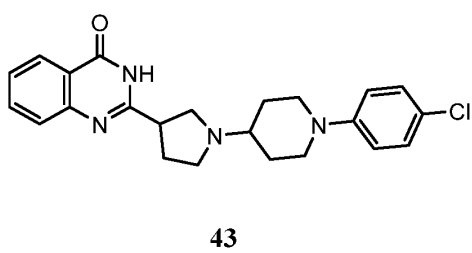
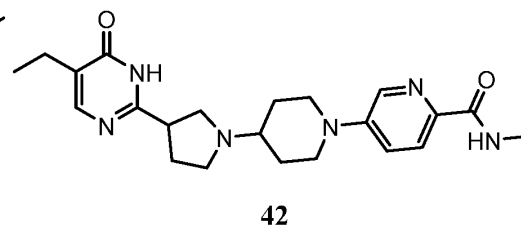
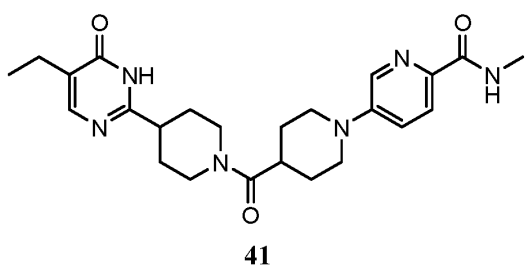
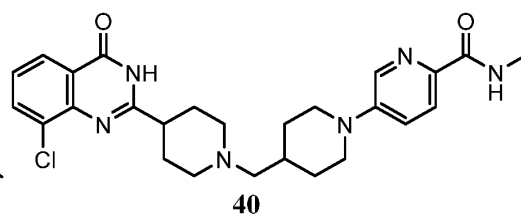
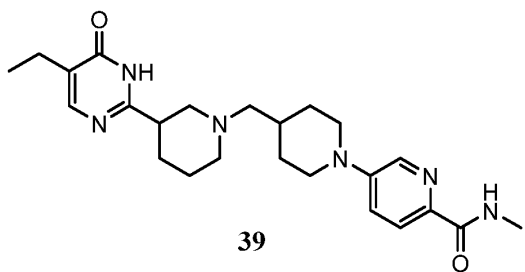
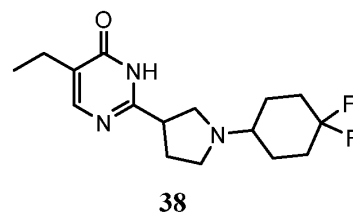
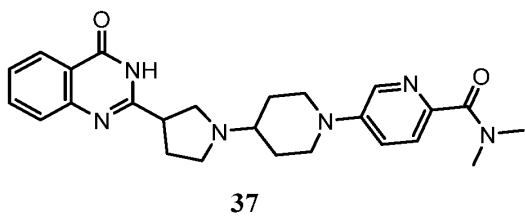
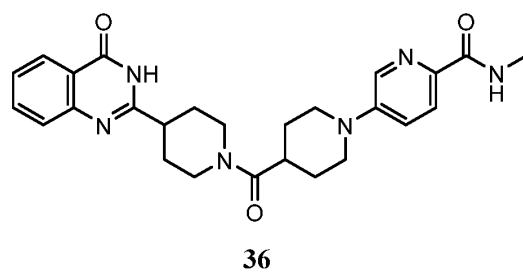
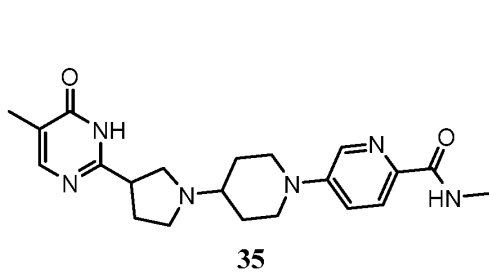
In some embodiments, the present invention provides a PARP1 inhibitor compound which comprises a formula selected from one of the following:

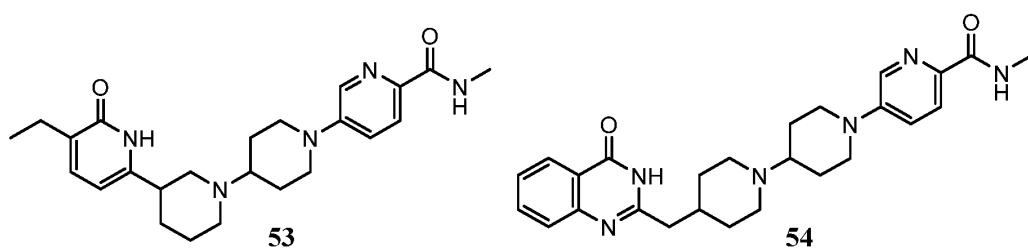
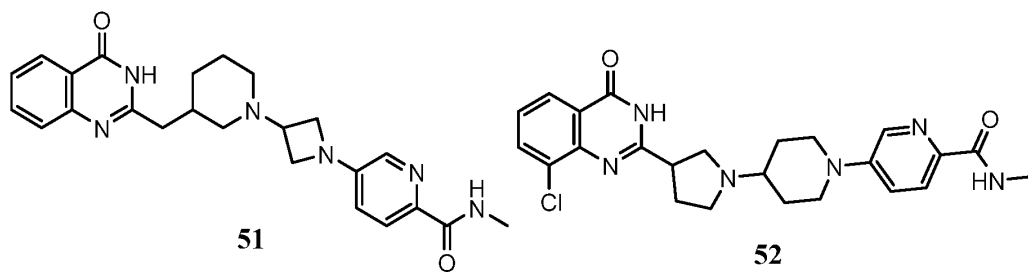
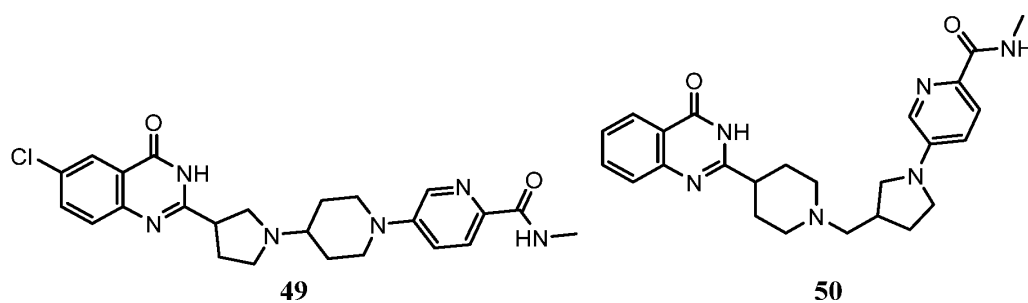
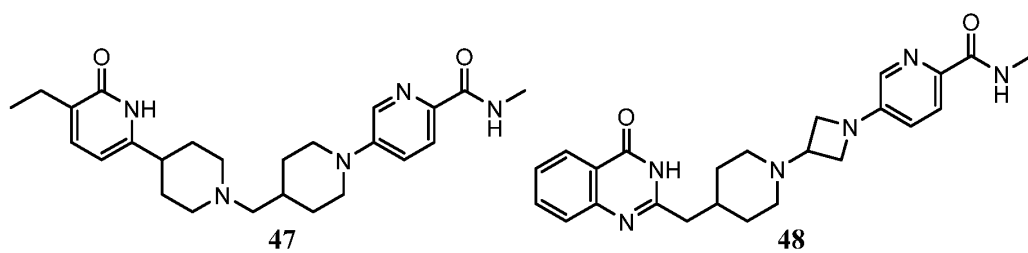
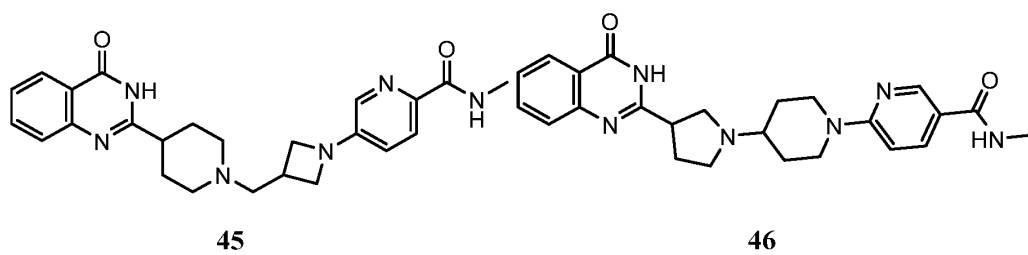


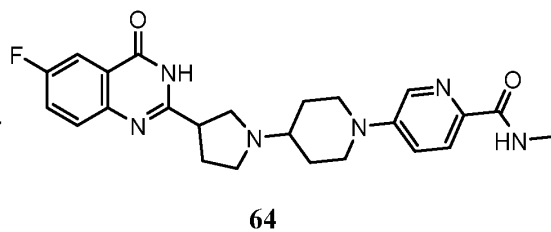
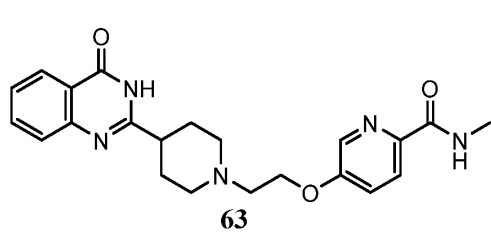
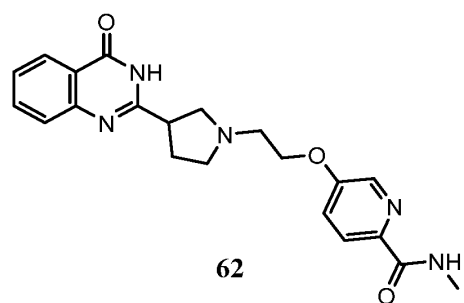
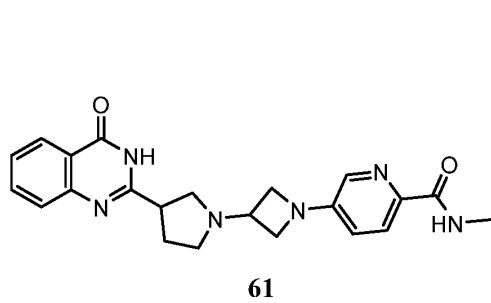
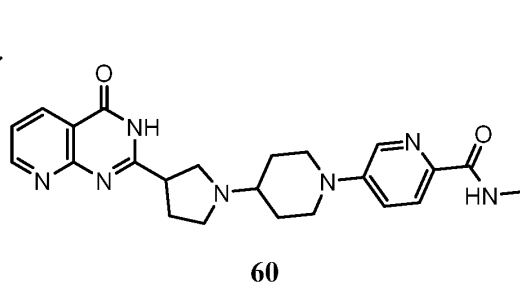
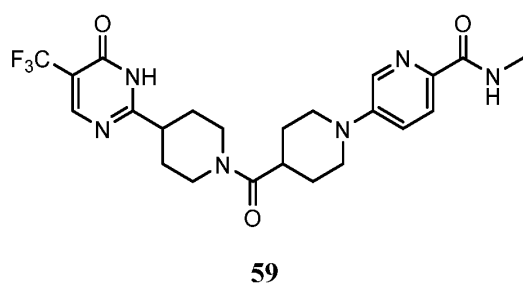
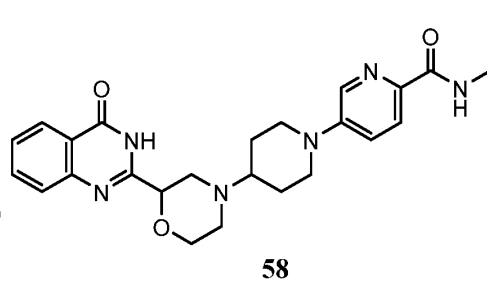
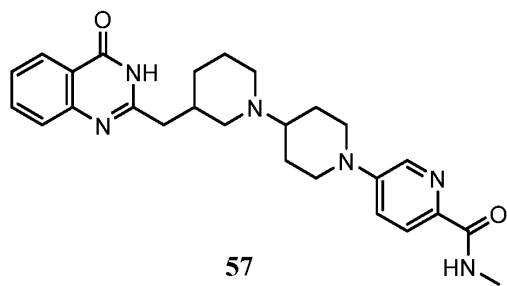
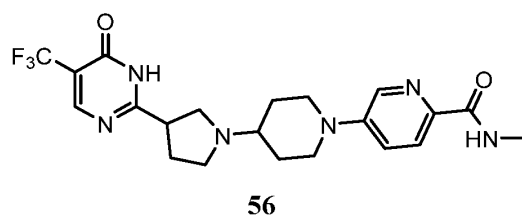
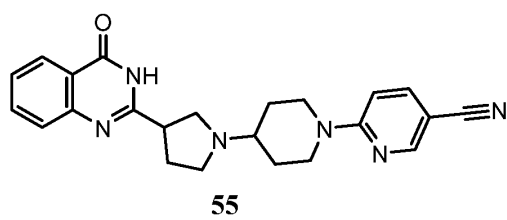


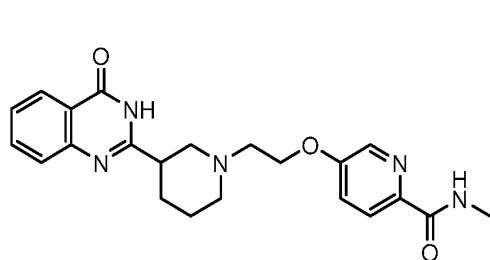




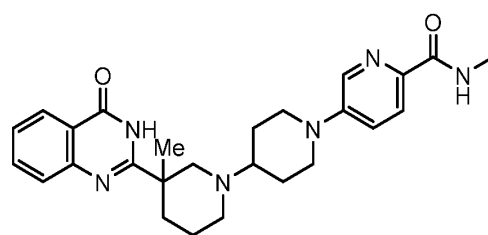




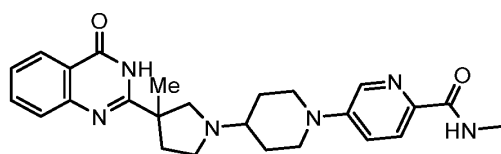




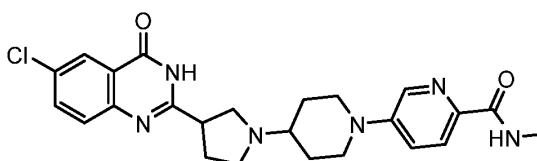
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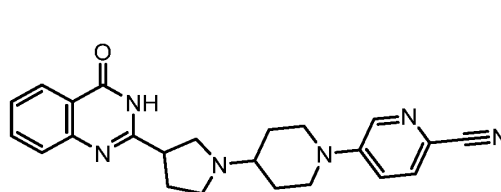
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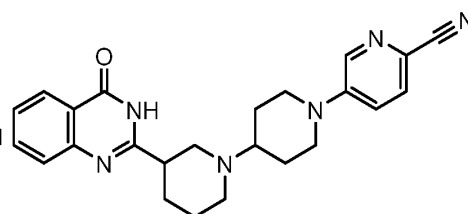
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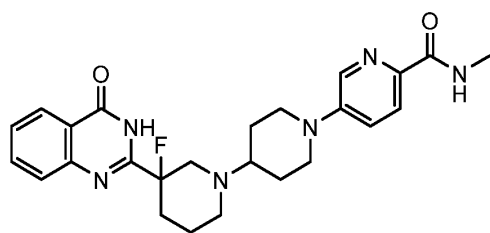
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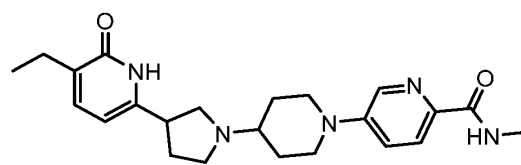
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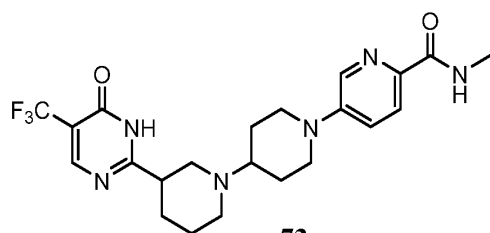
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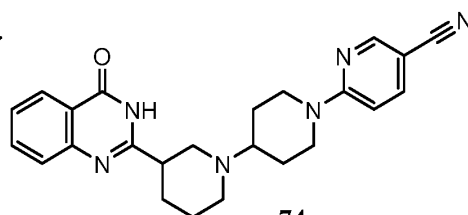
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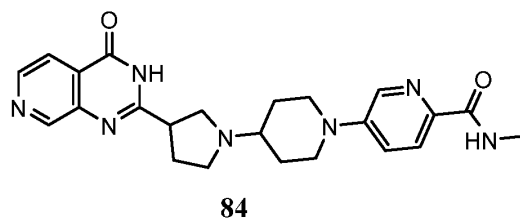
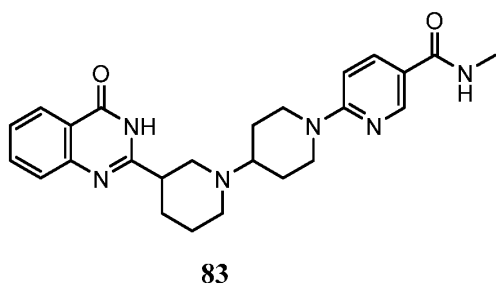
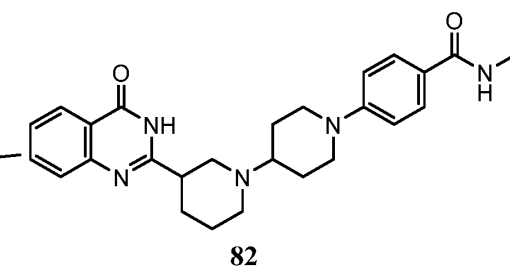
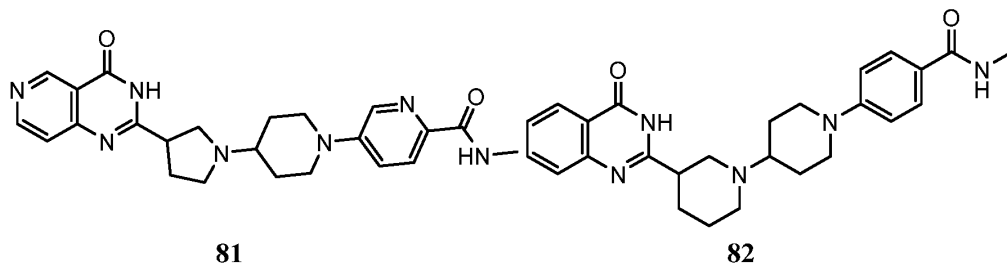
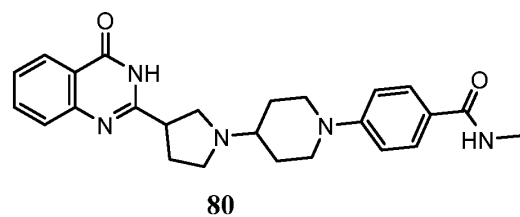
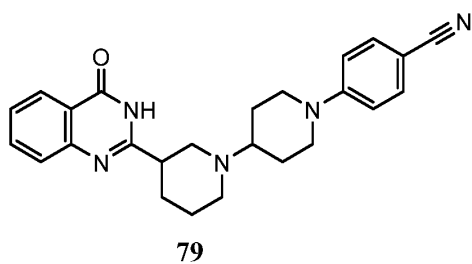
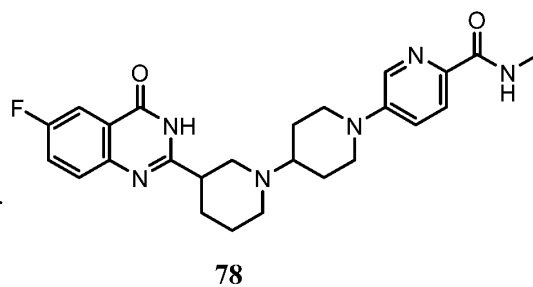
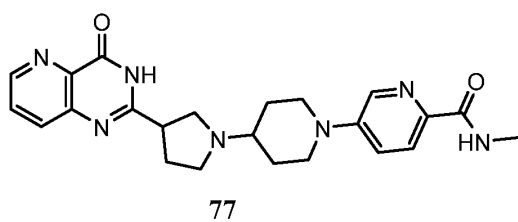
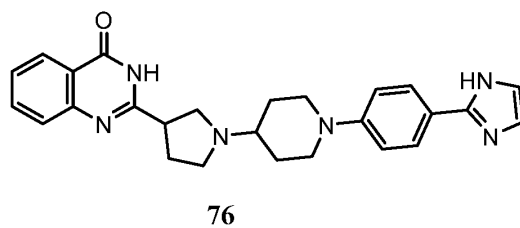
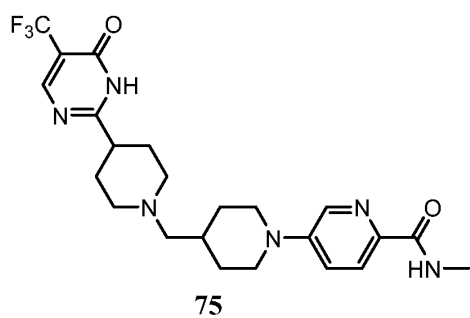
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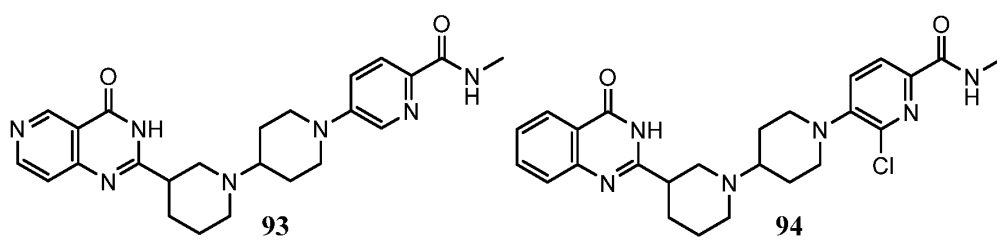
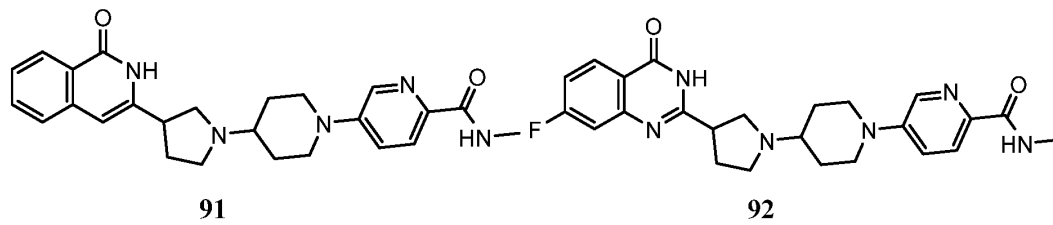
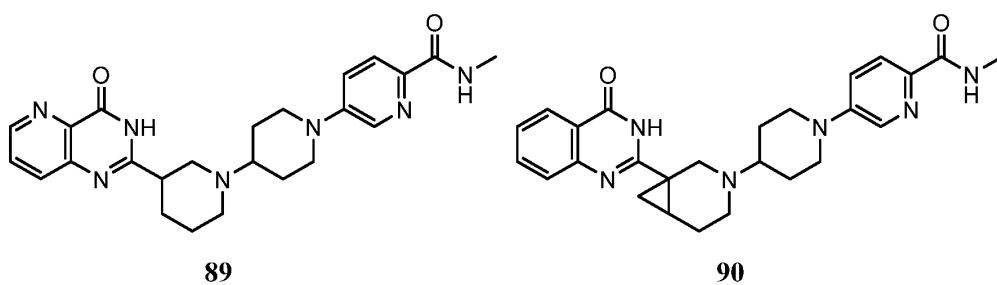
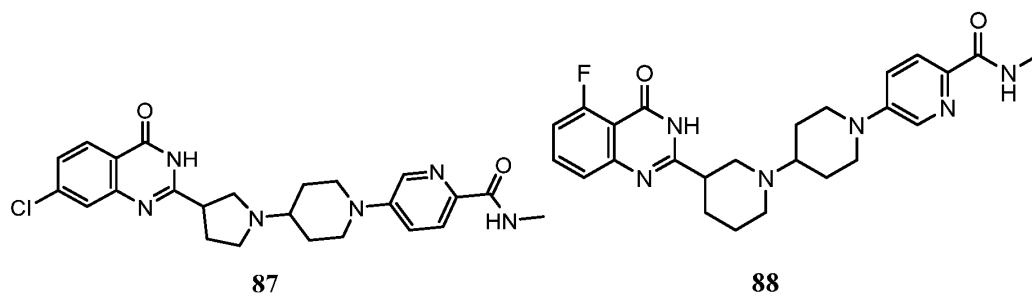
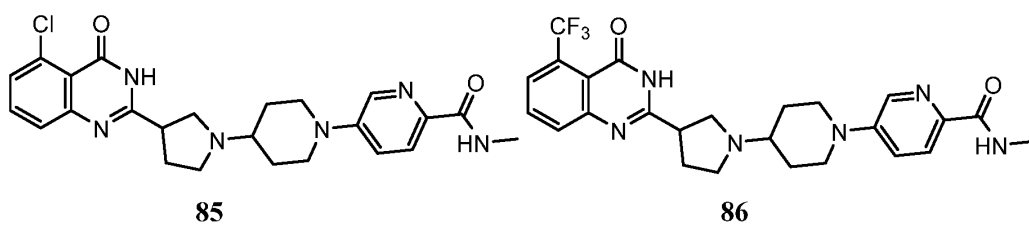


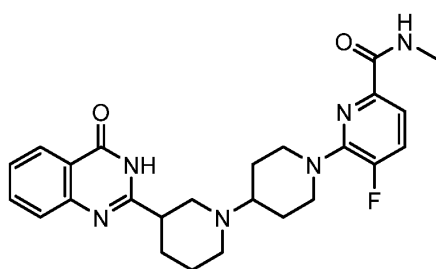
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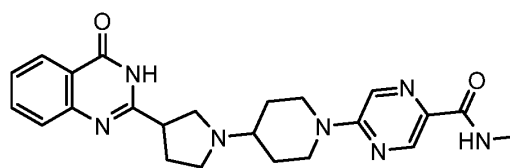
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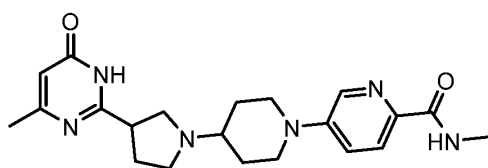




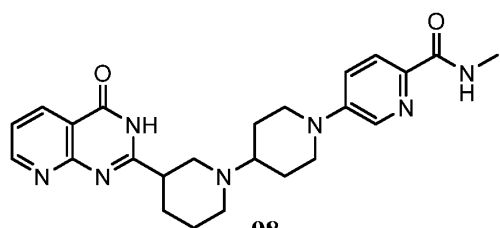
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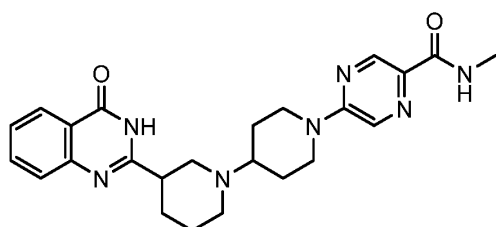
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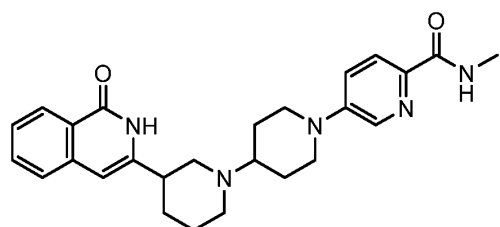
97



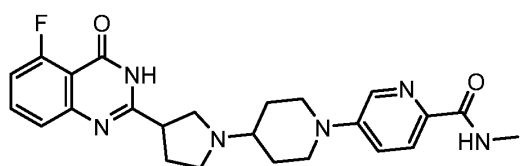
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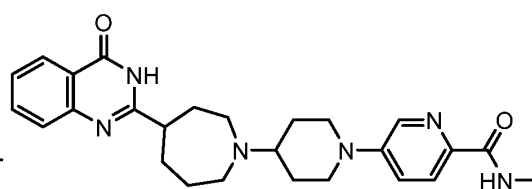
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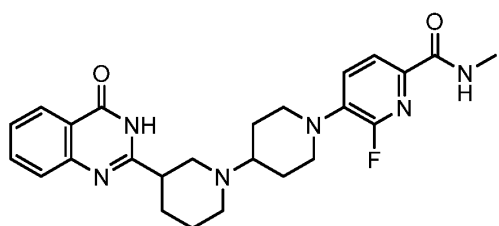
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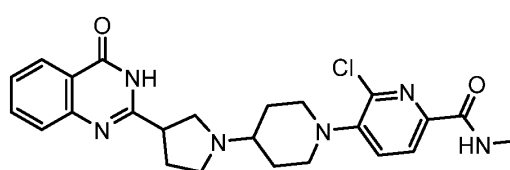
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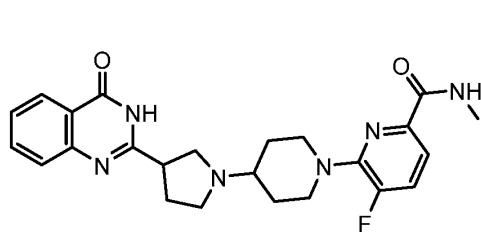
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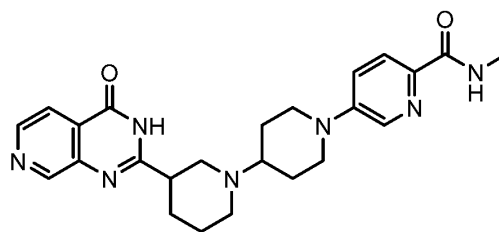
103



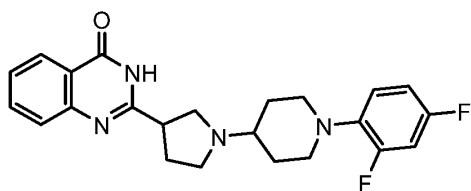
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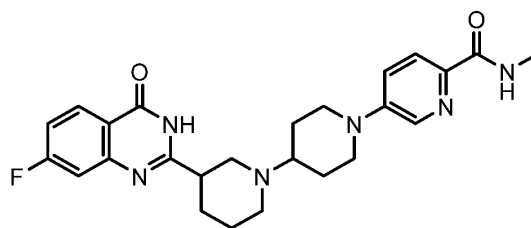
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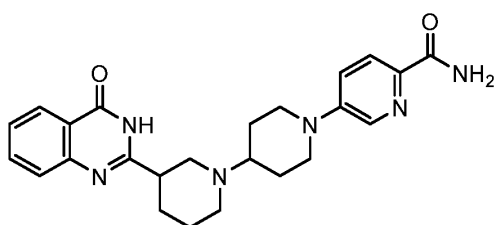
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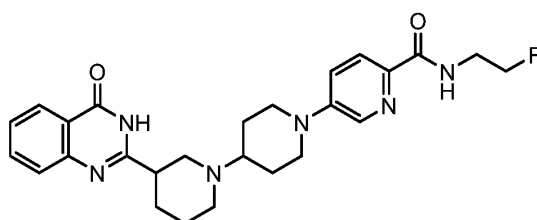
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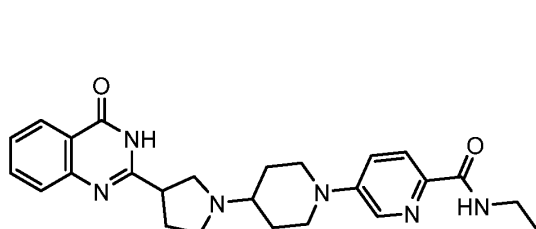
108



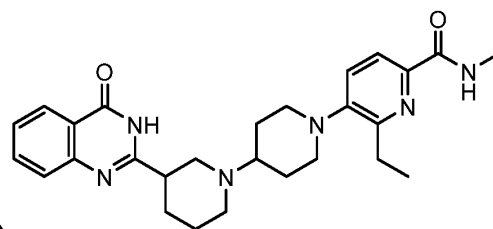
109



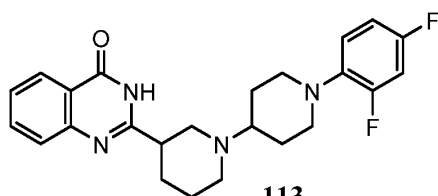
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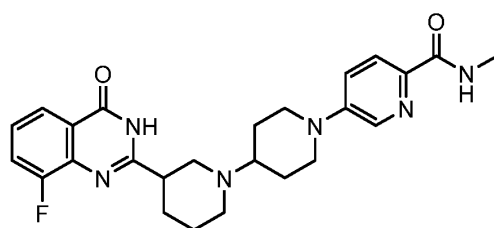
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112

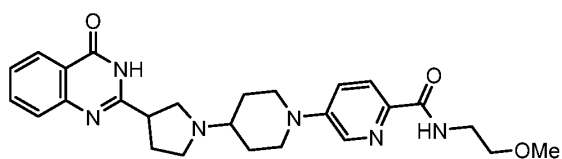


113

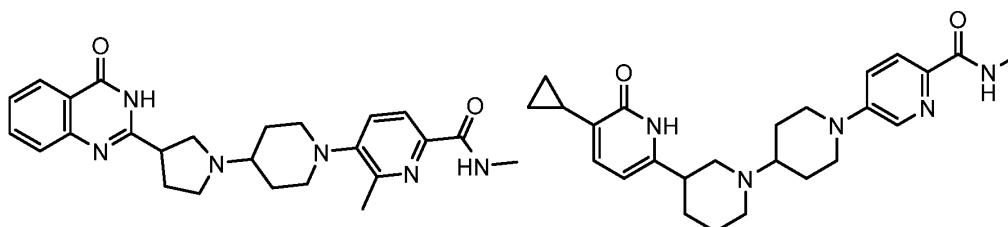


114



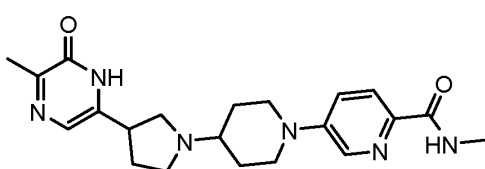


124

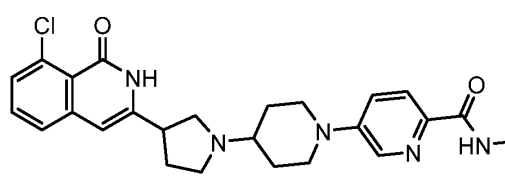


125

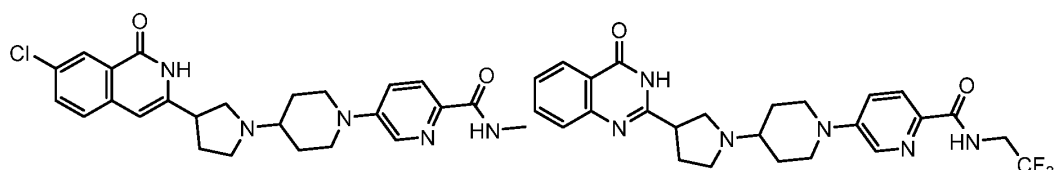
126



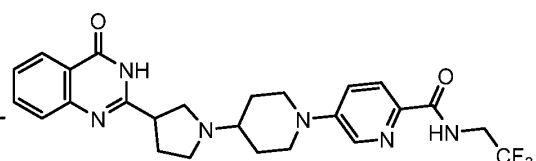
127



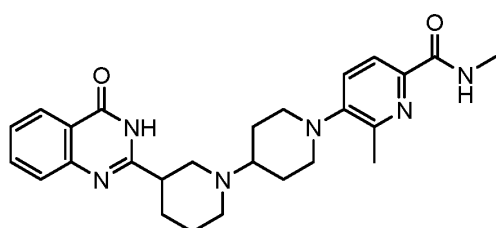
128



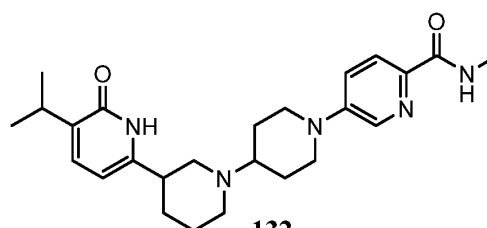
129



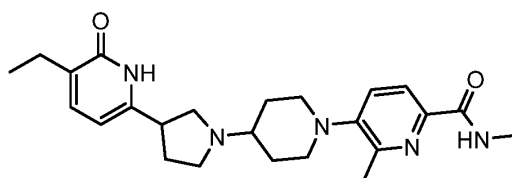
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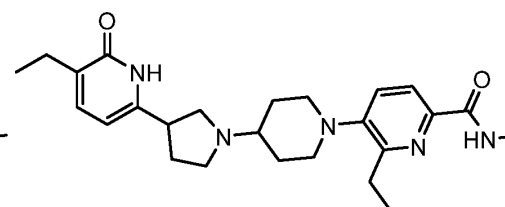
131



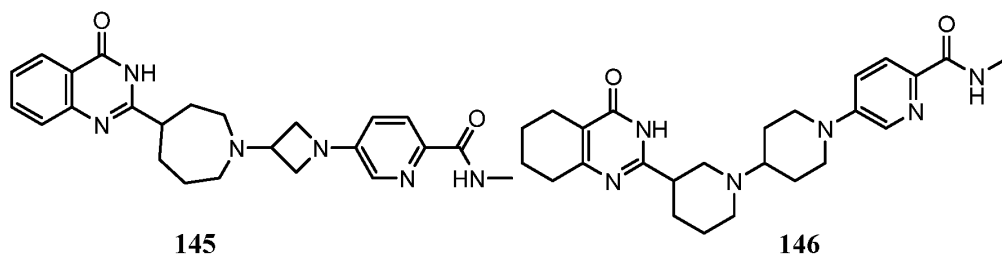
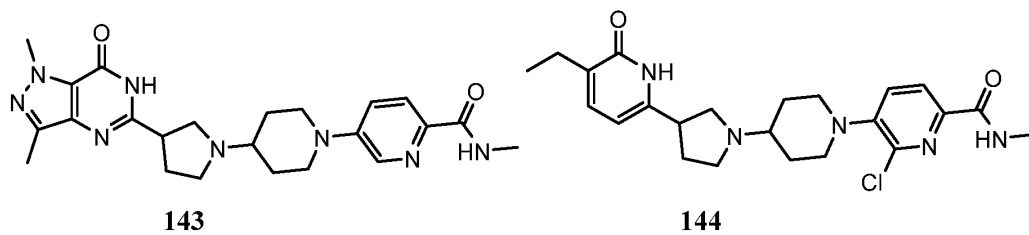
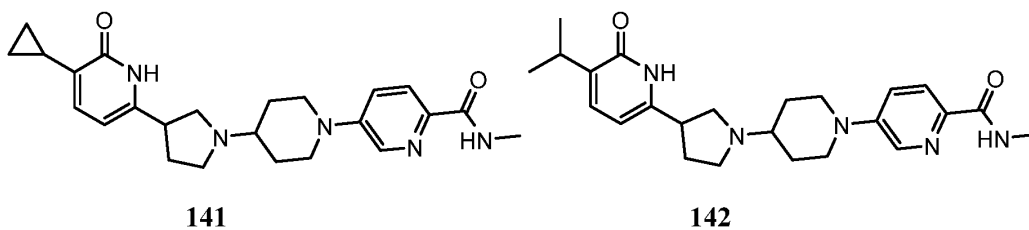
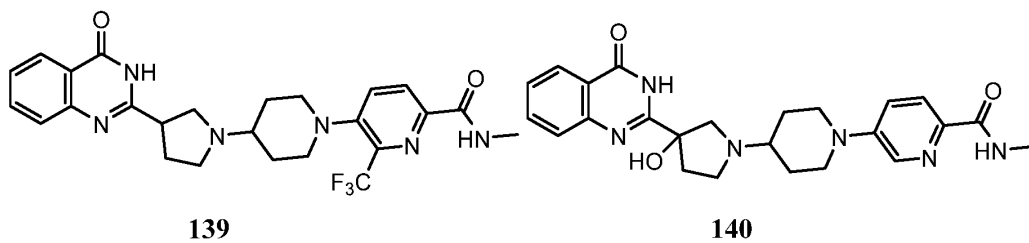
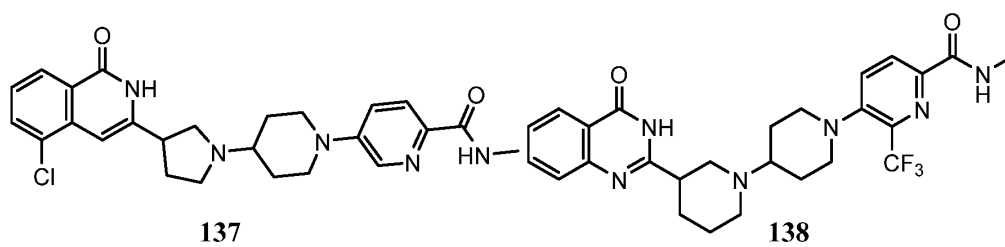
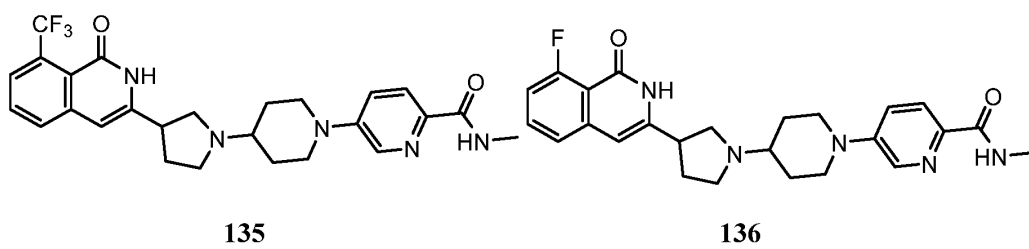
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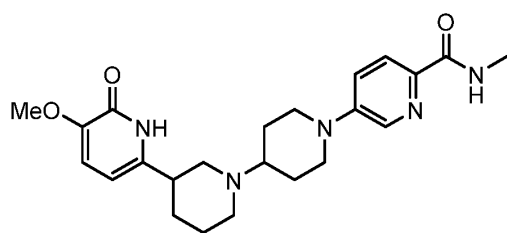


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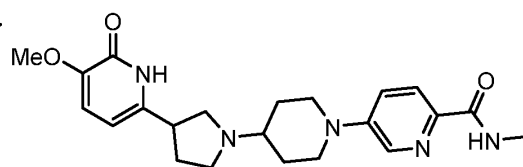


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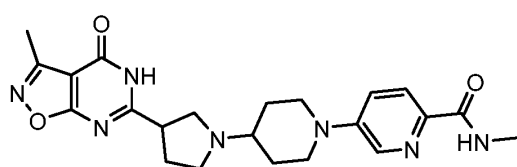




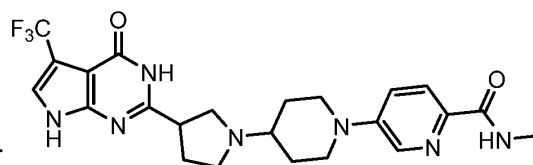
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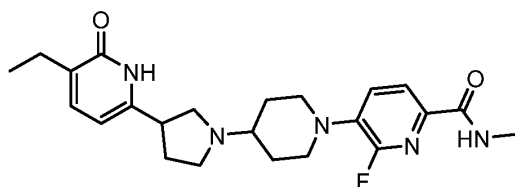
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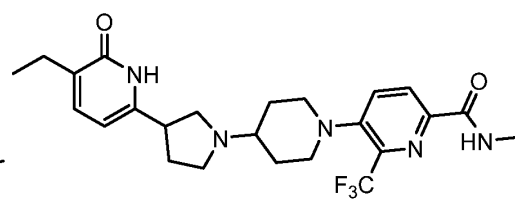
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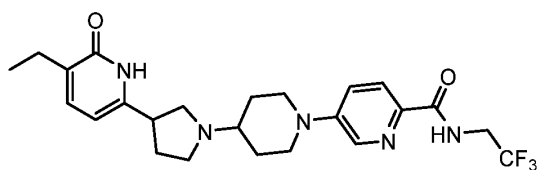
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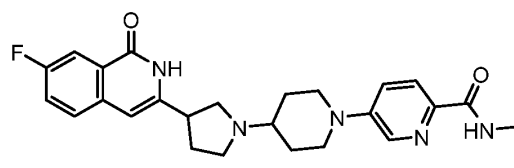
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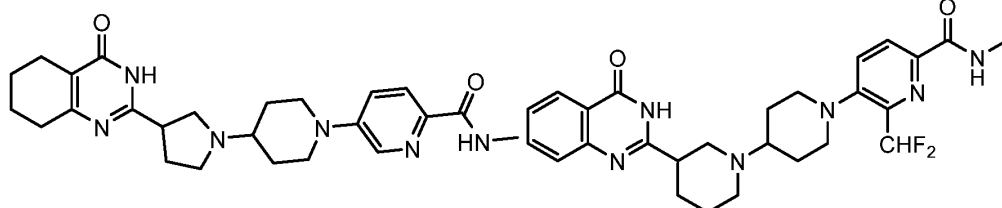
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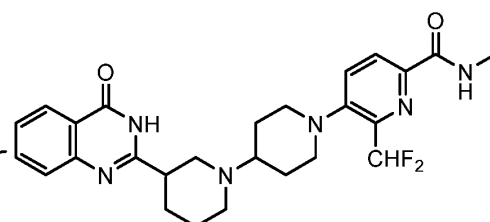
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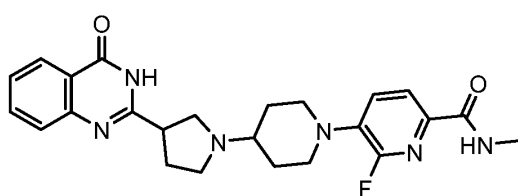
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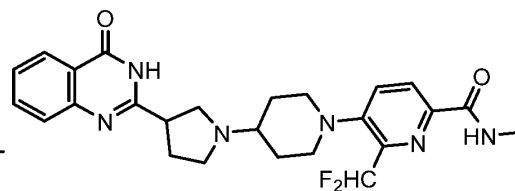
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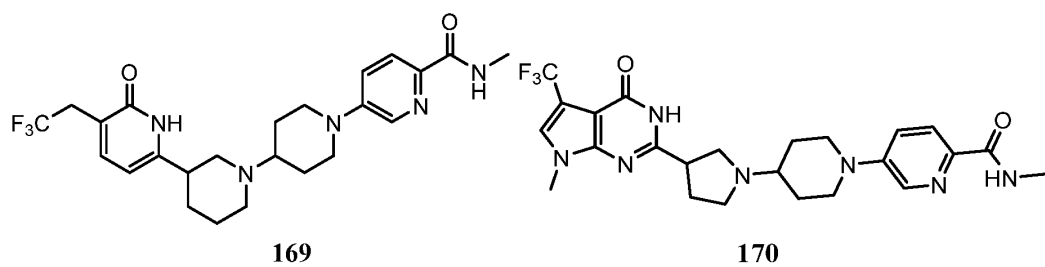
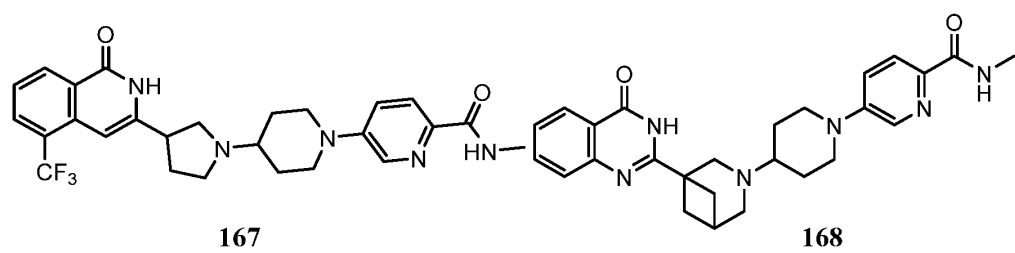
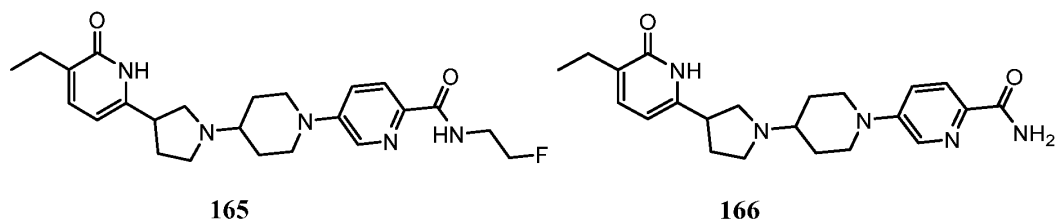
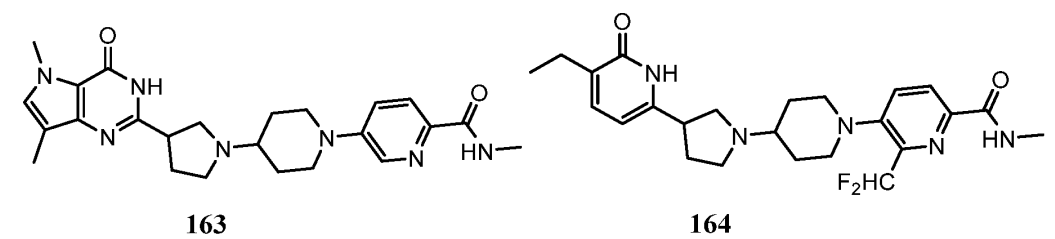
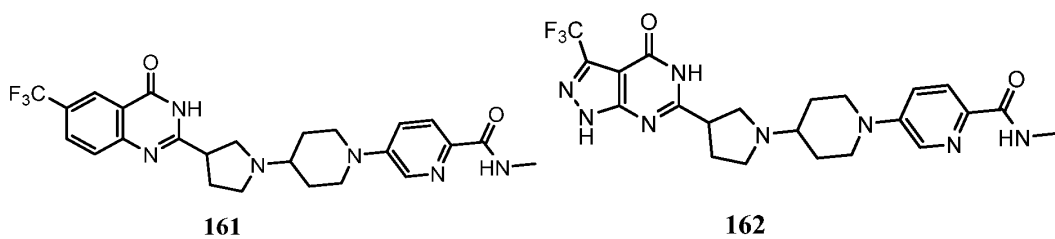
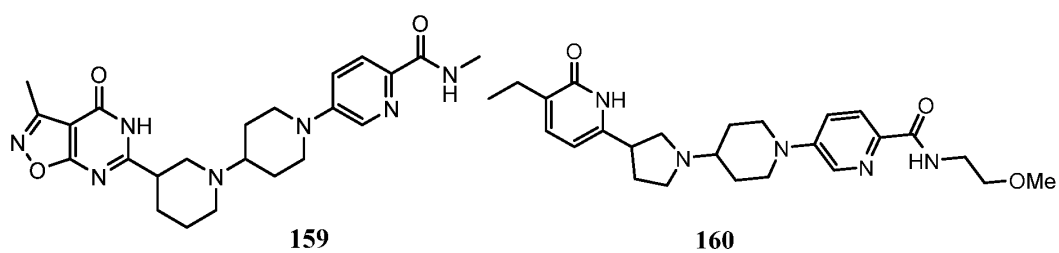
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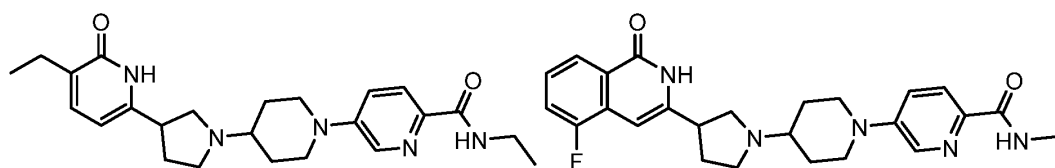


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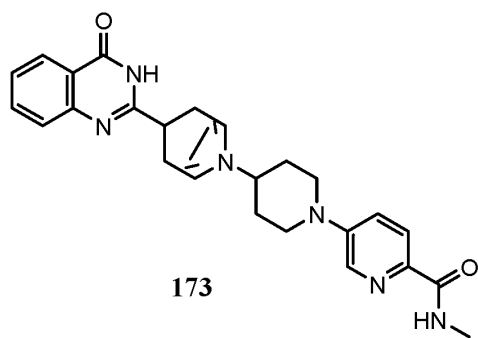
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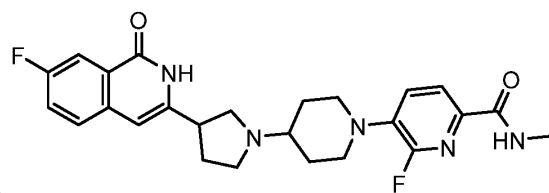


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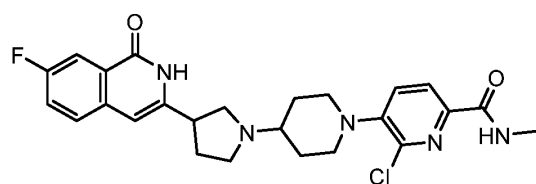
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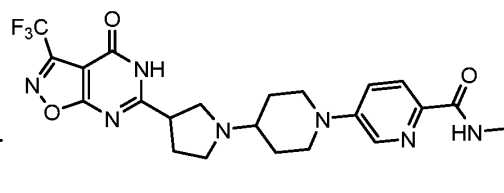
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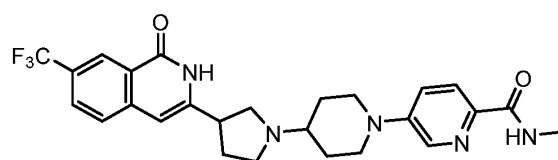
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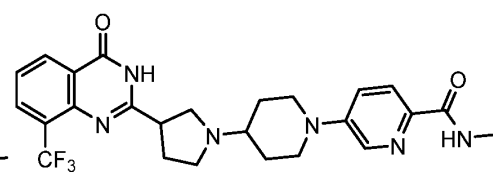
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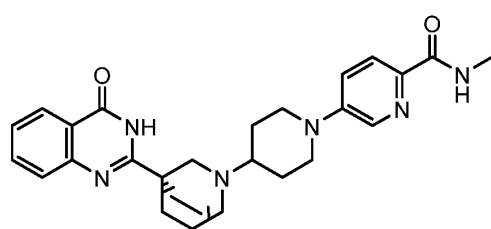
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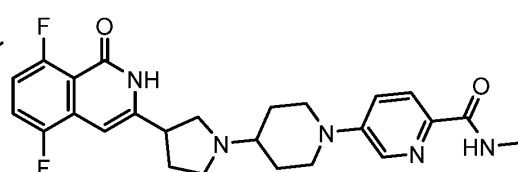
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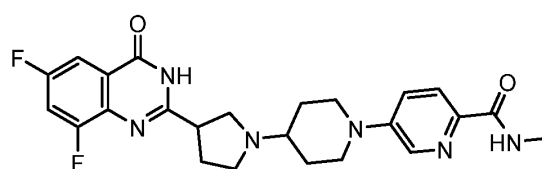
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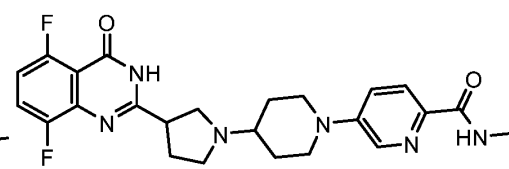
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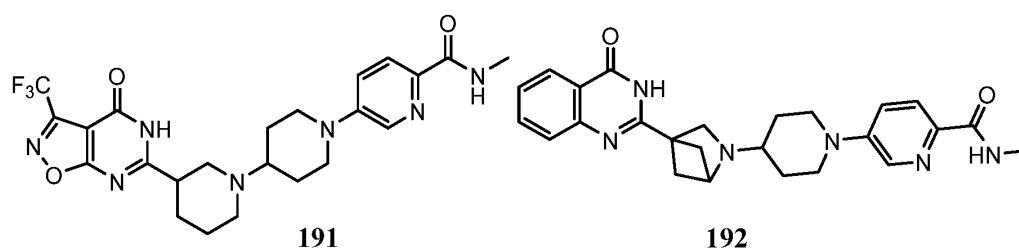
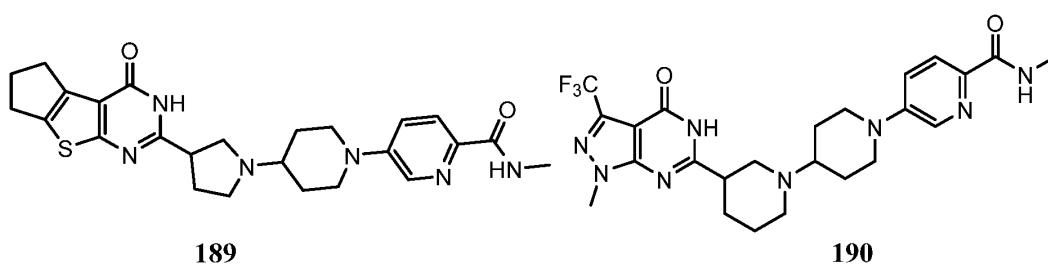
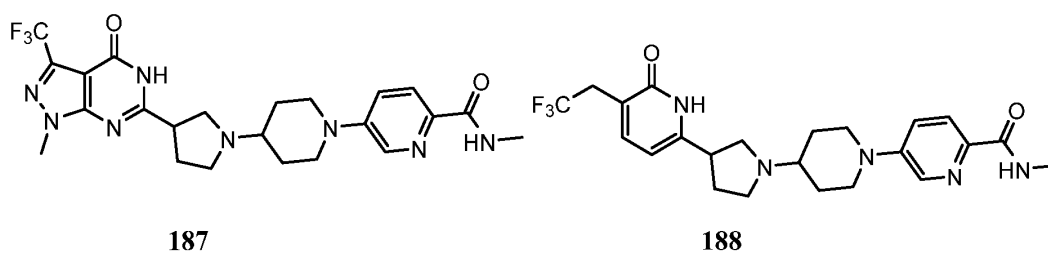
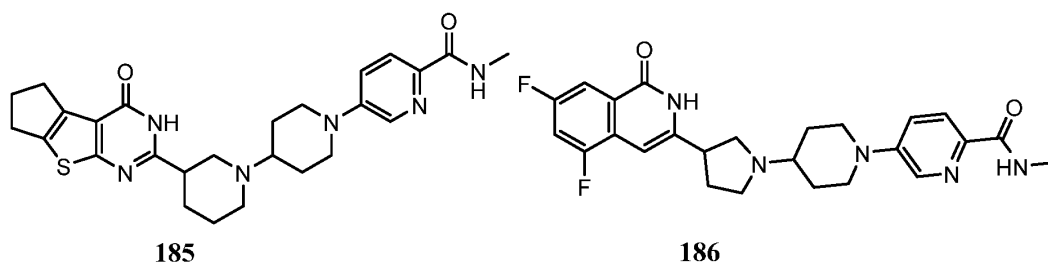
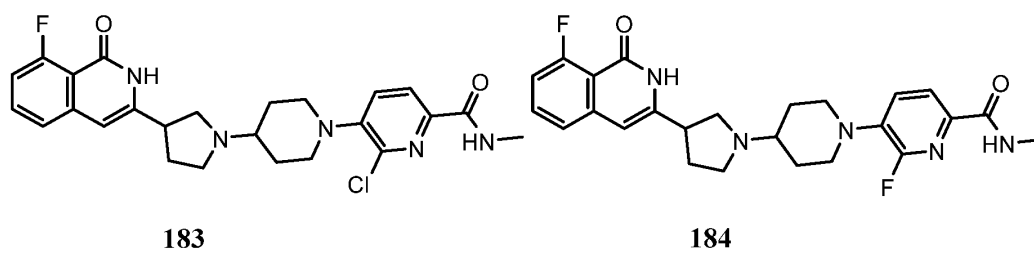
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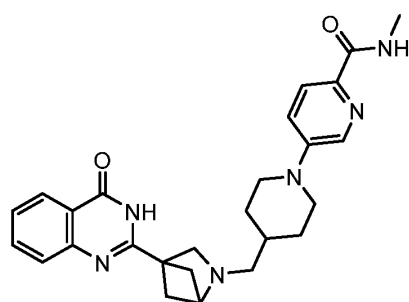


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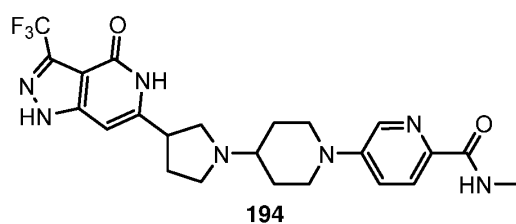


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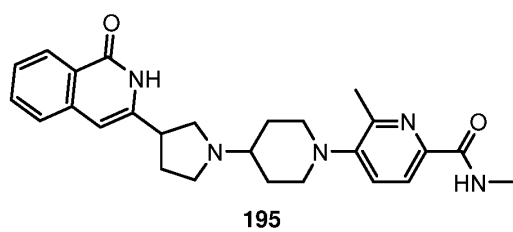




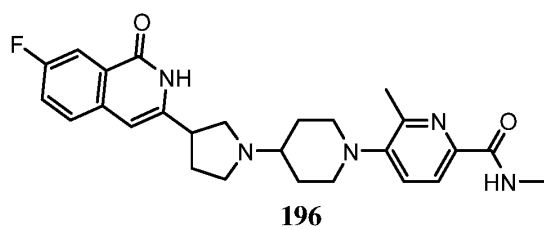
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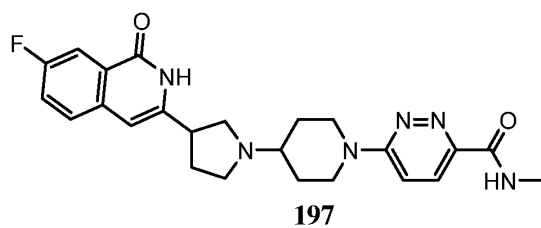
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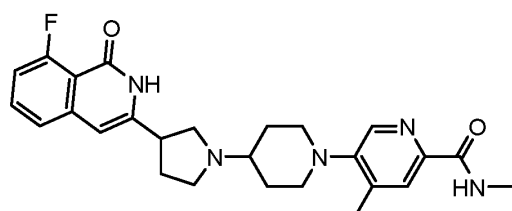
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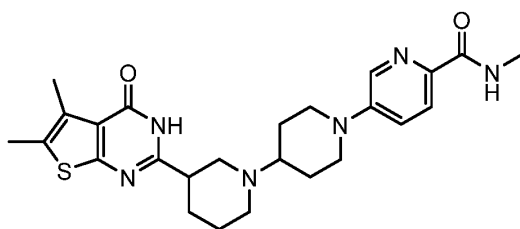
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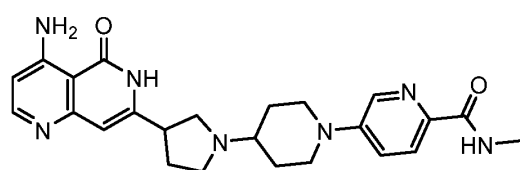
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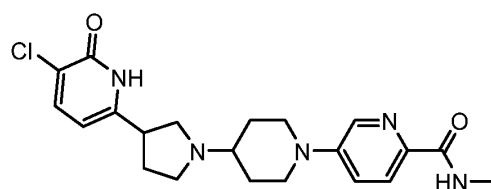
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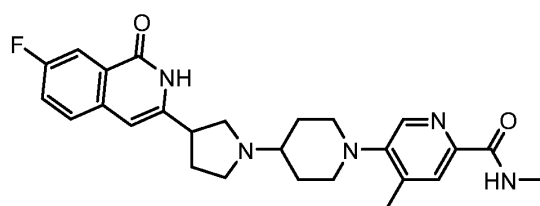
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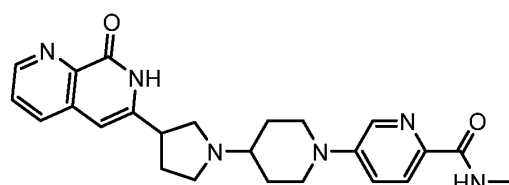
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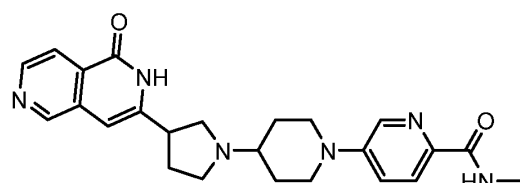
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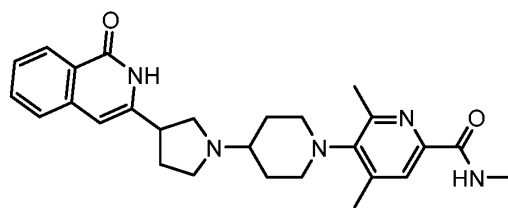
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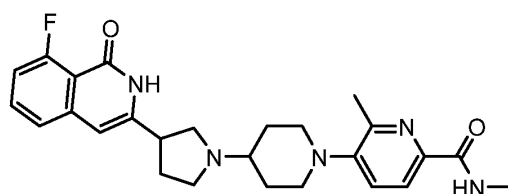
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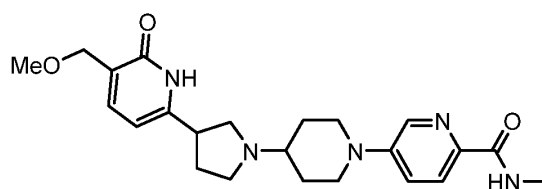
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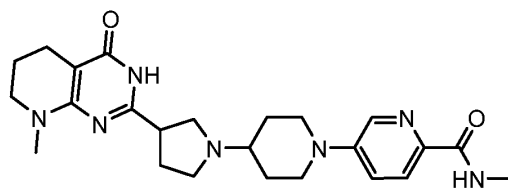
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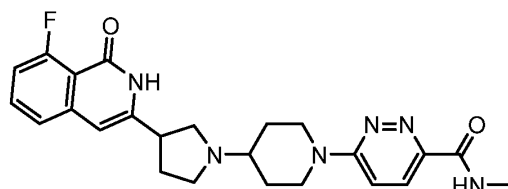
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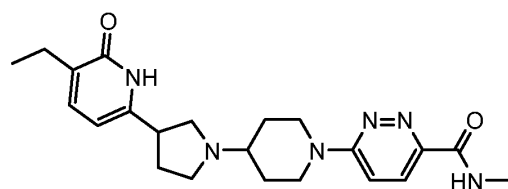
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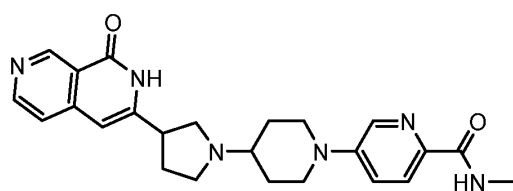
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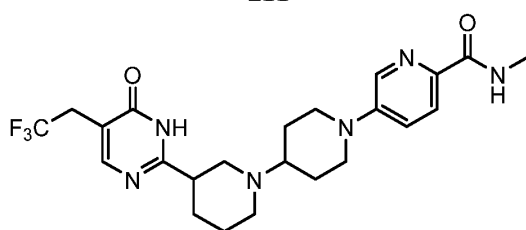
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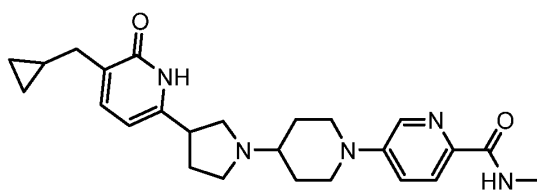
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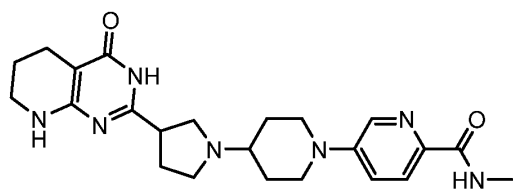
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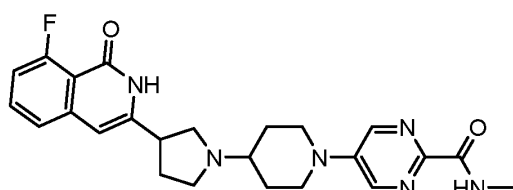
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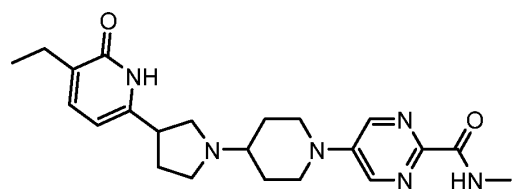
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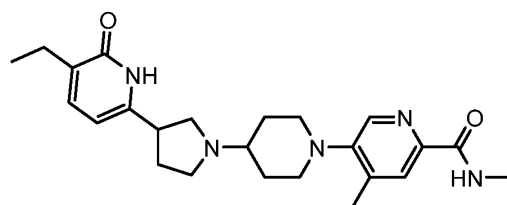
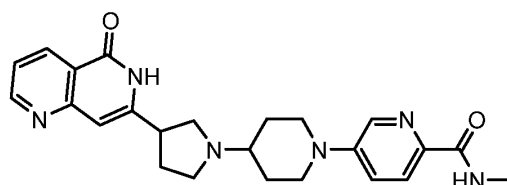
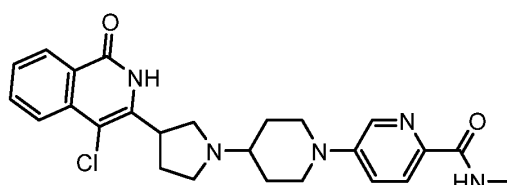
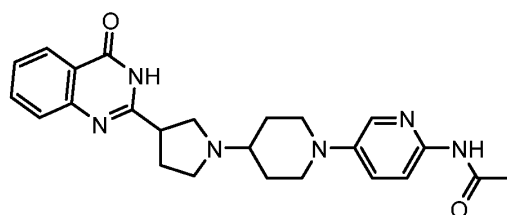
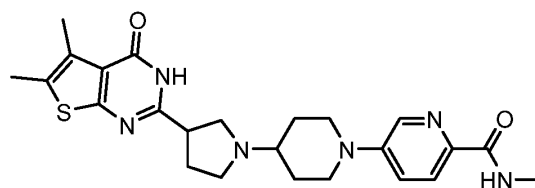
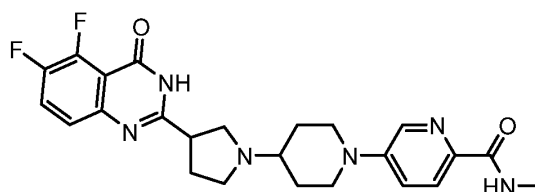
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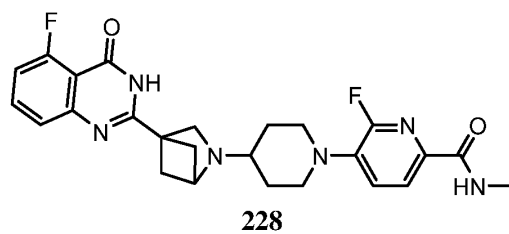
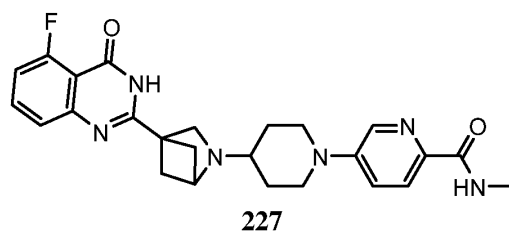
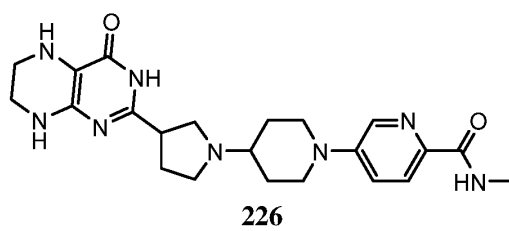
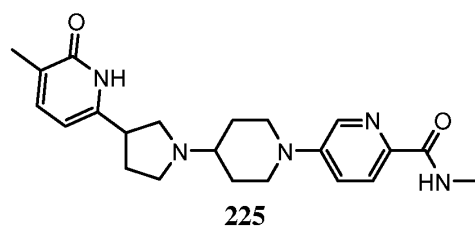
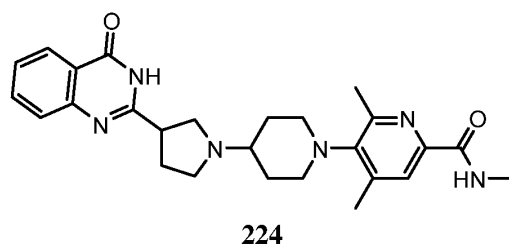
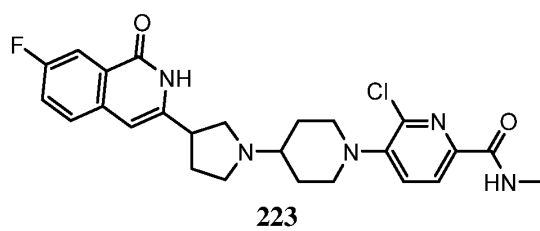


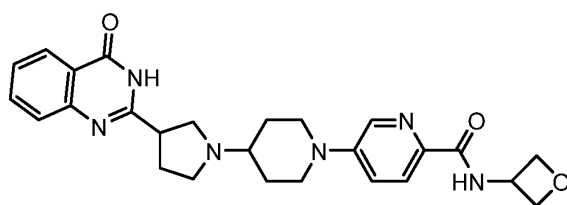
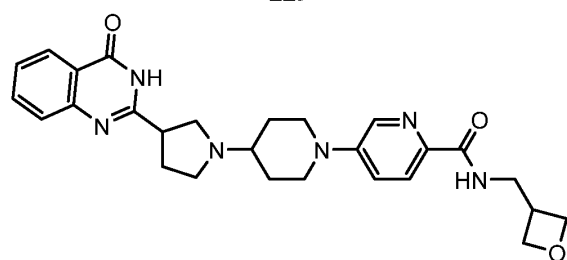
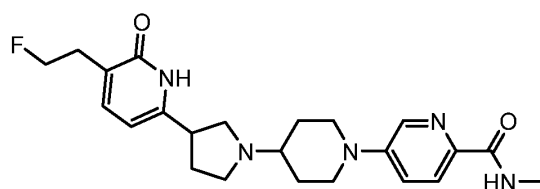
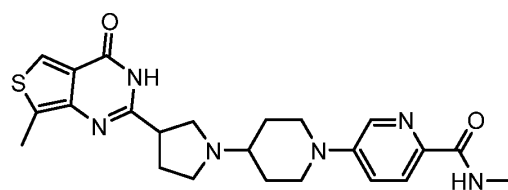
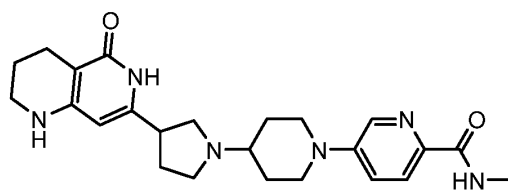
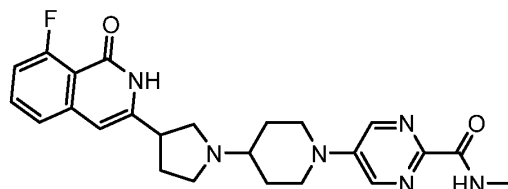
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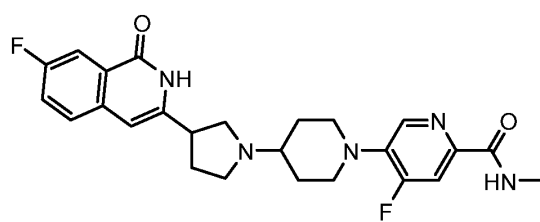


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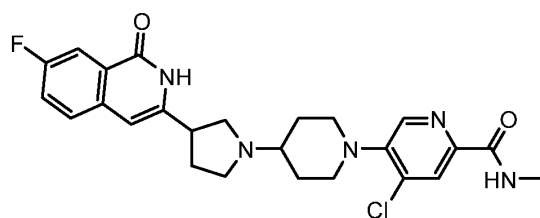
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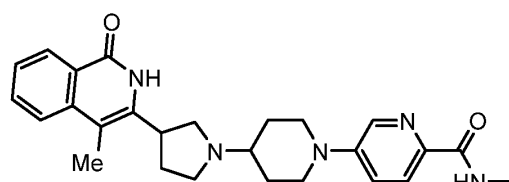
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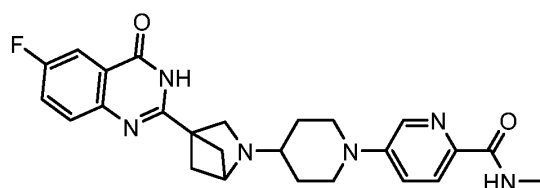
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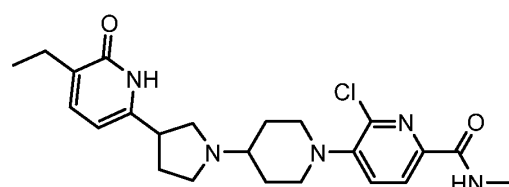
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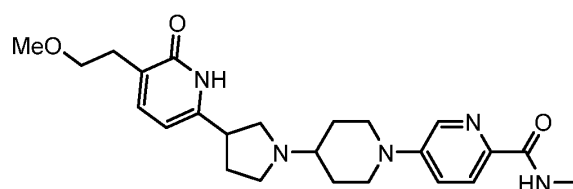
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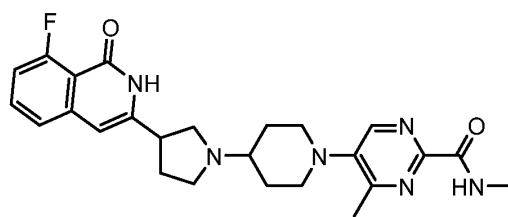
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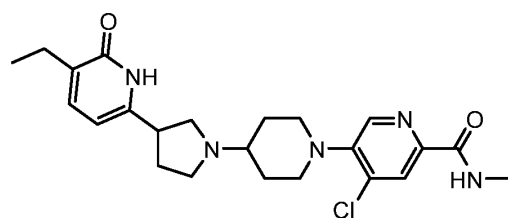
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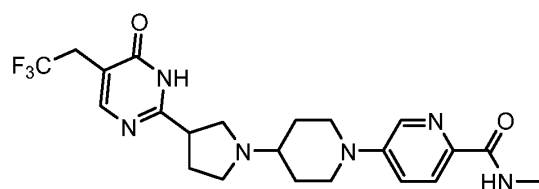
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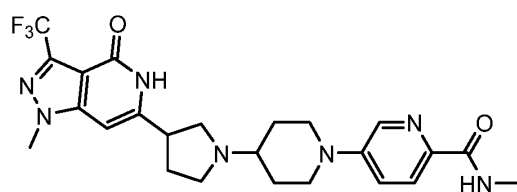
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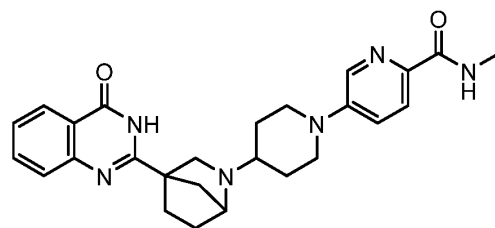
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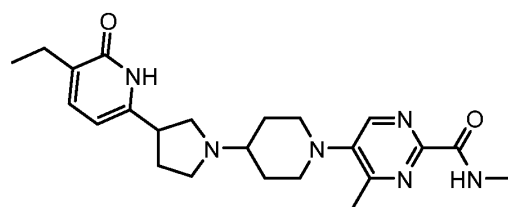
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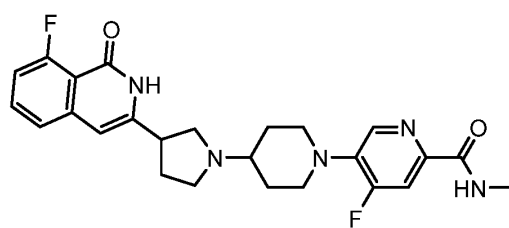
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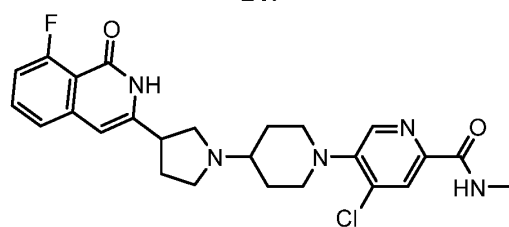
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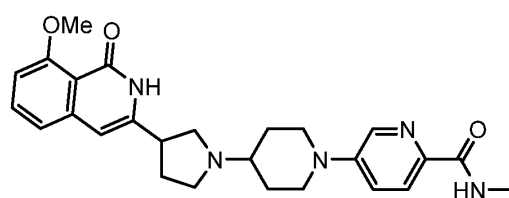
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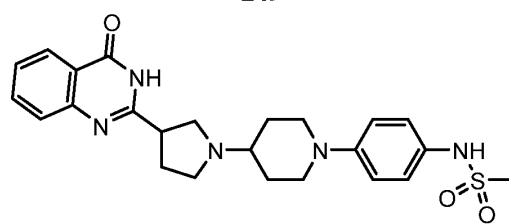
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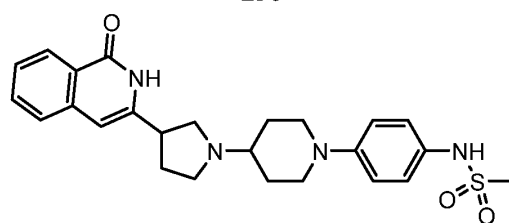
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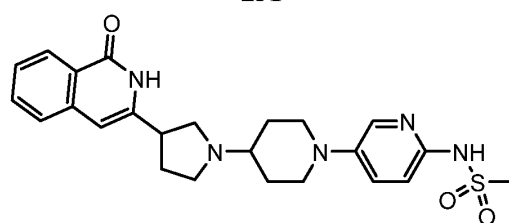
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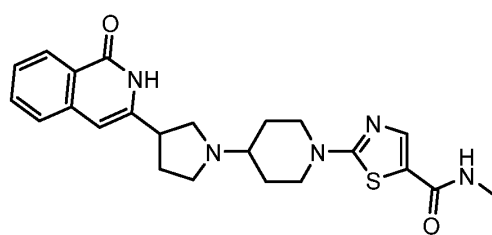
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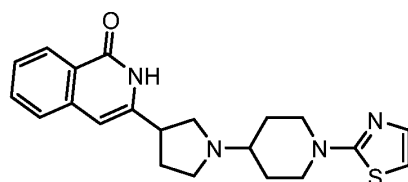
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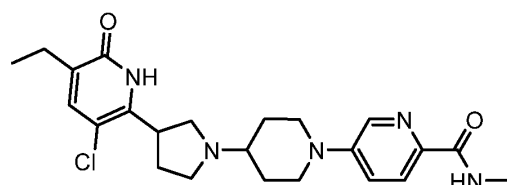
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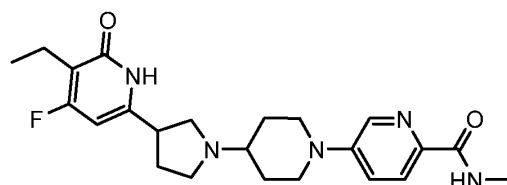
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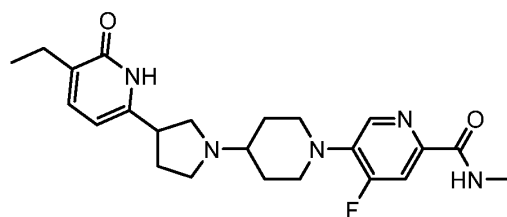
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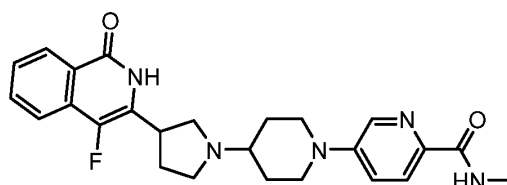
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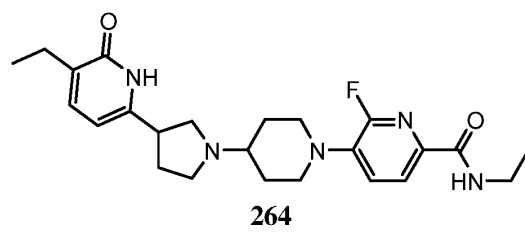
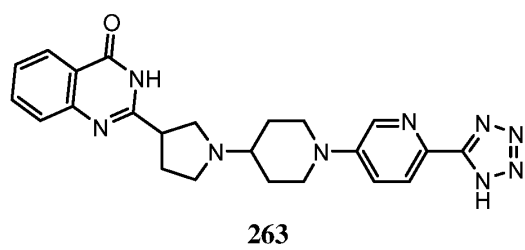
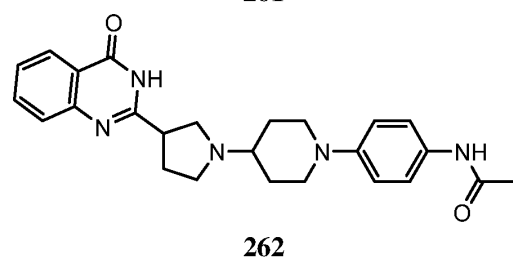
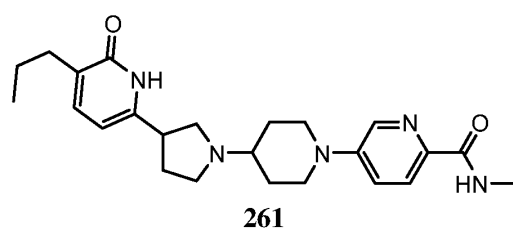
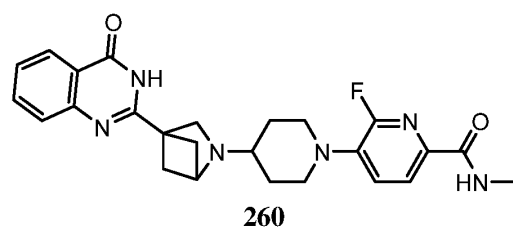
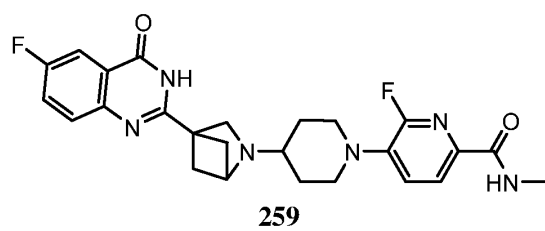
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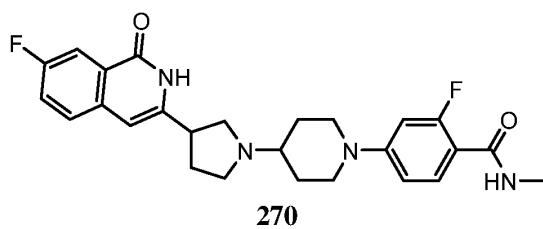
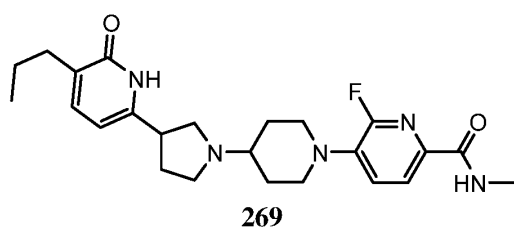
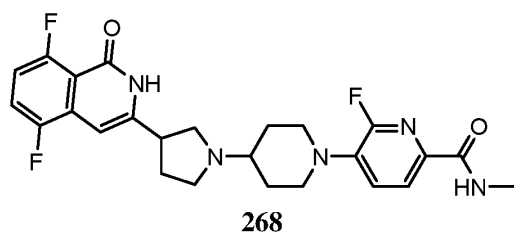
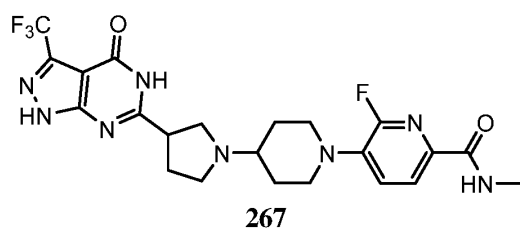
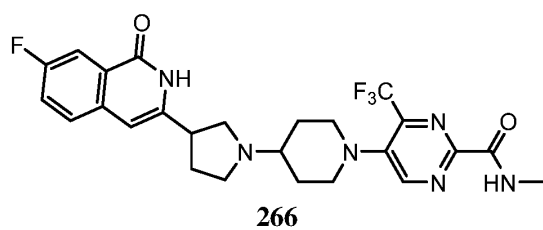
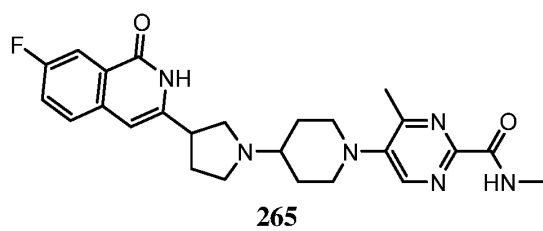


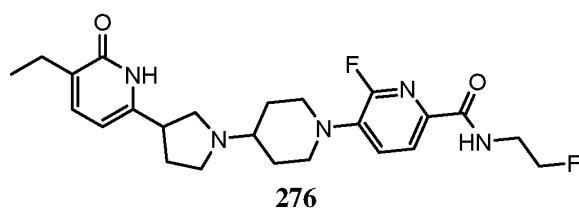
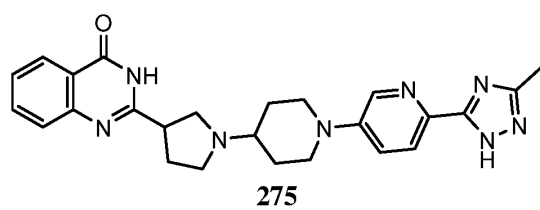
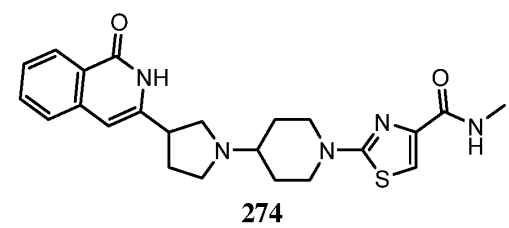
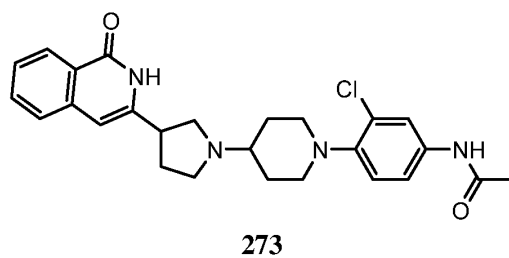
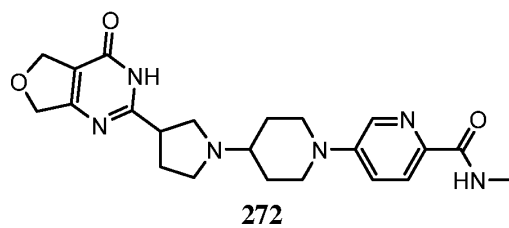
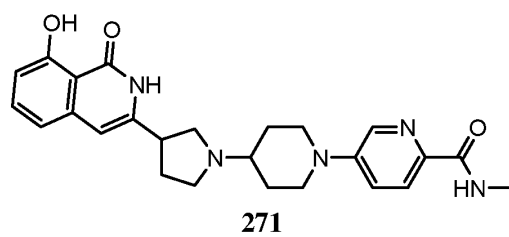
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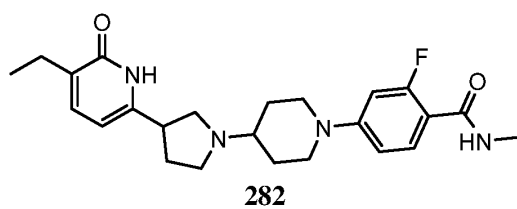
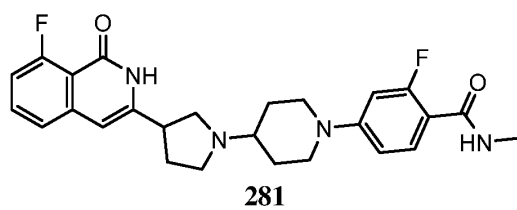
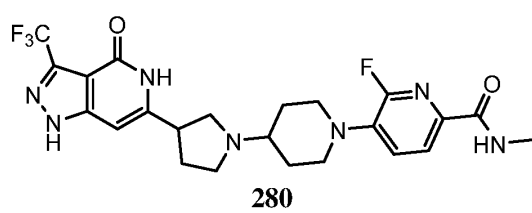
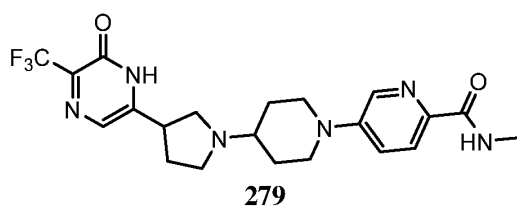
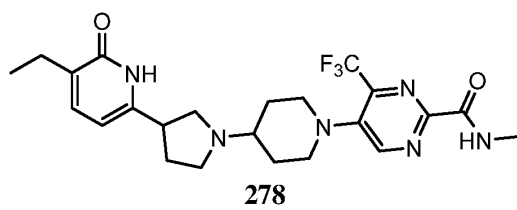
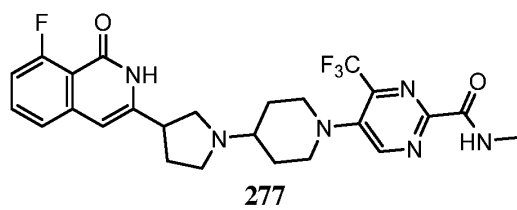


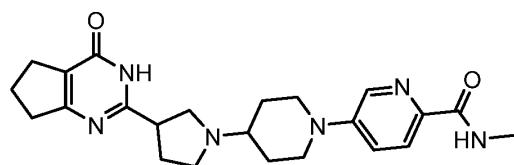
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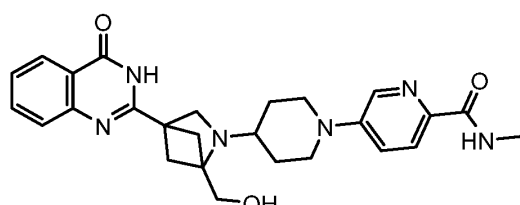




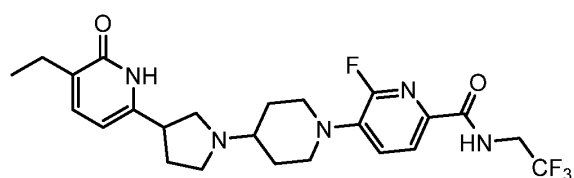




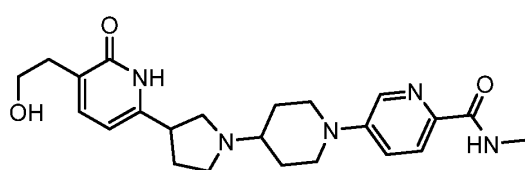
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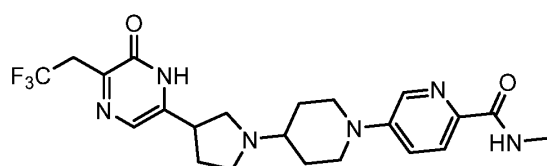
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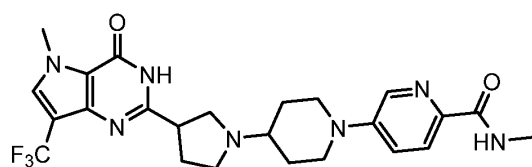
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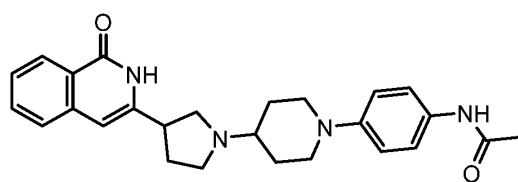
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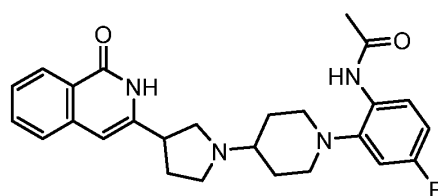
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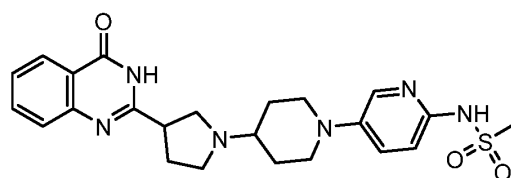
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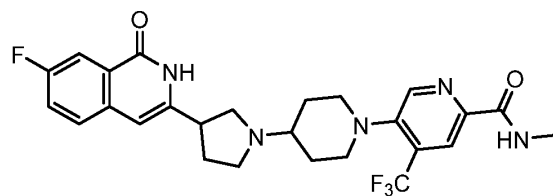
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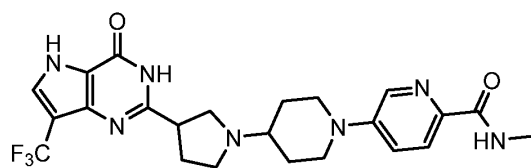
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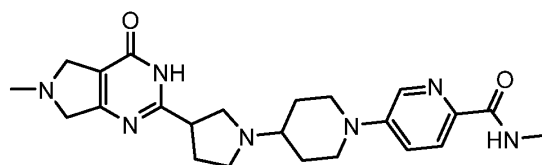
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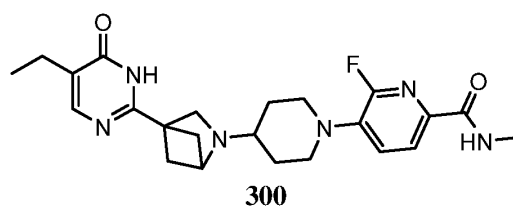
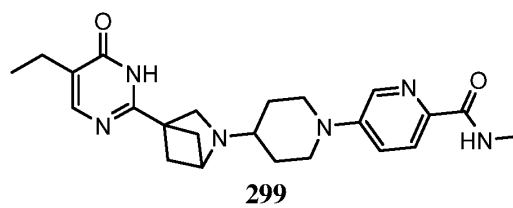
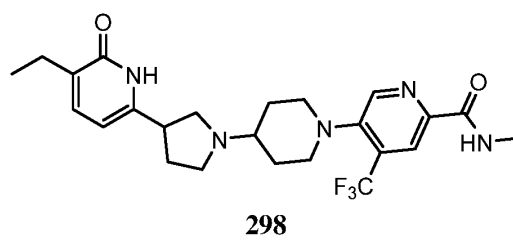
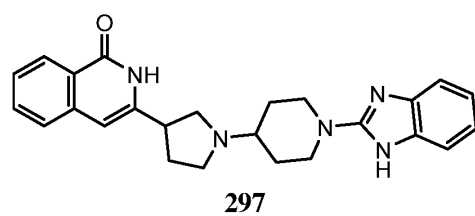
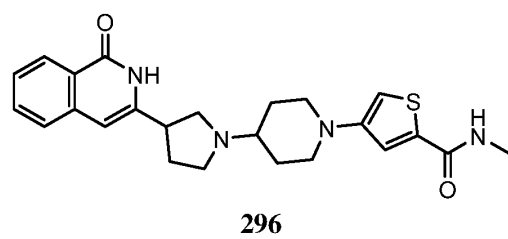
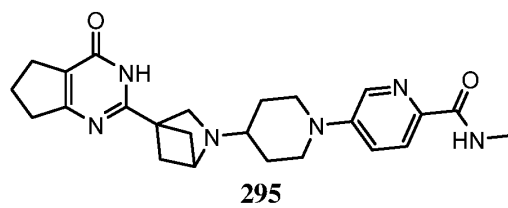
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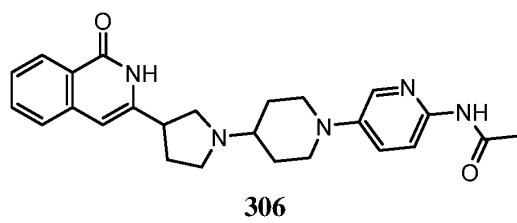
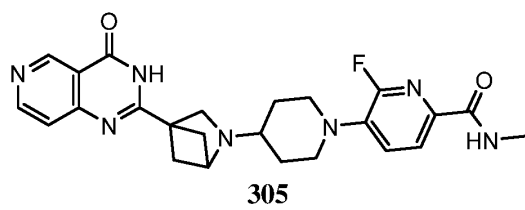
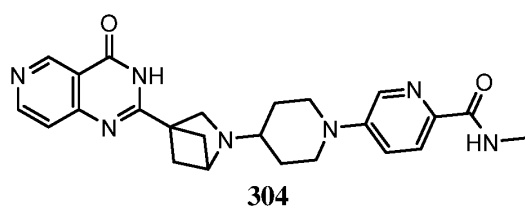
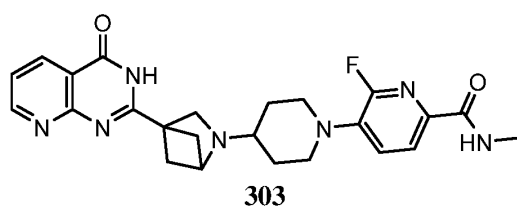
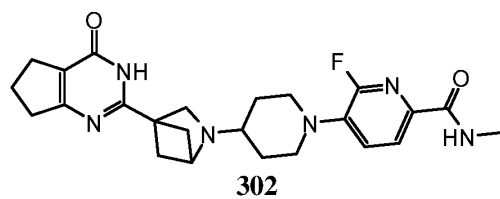
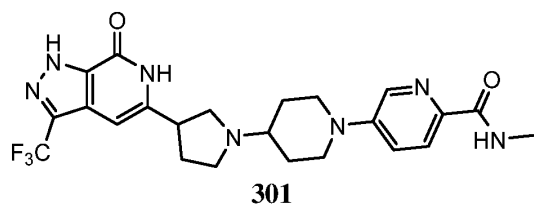


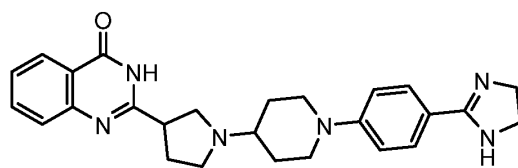
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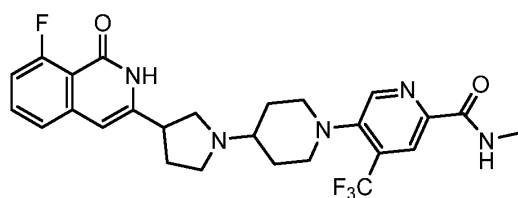
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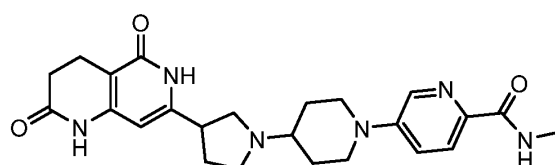




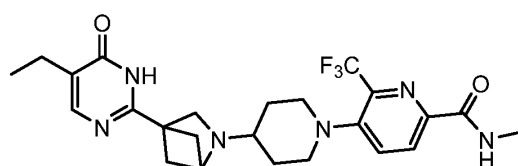
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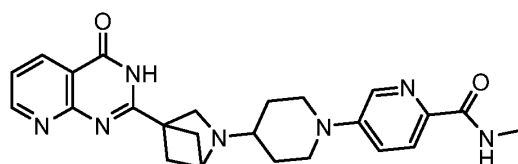
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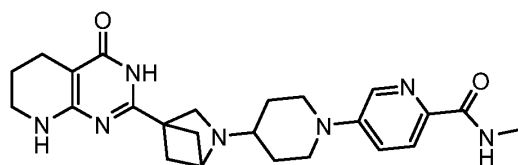
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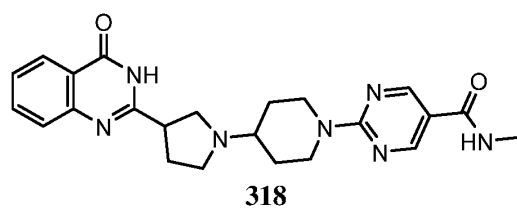
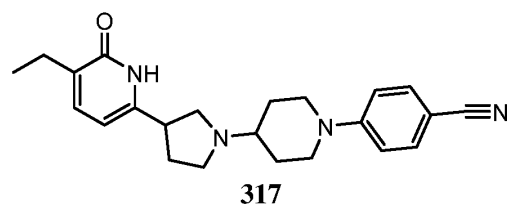
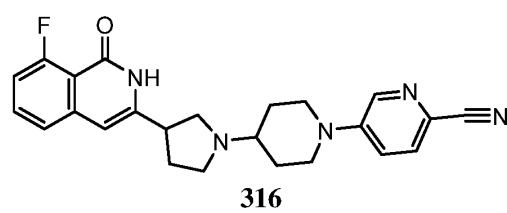
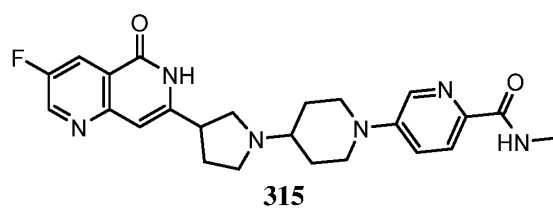
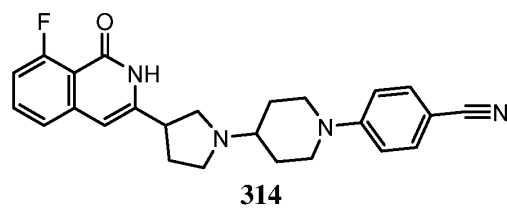
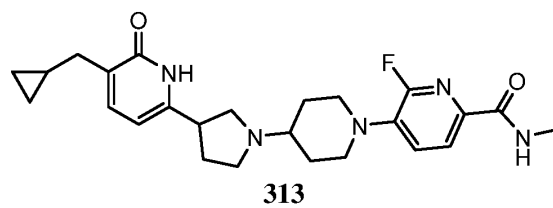
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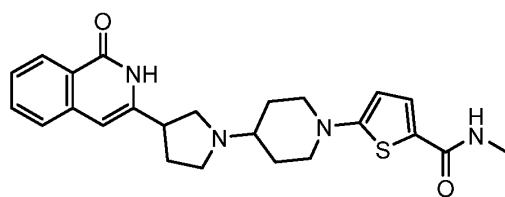
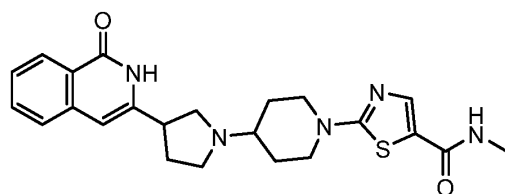
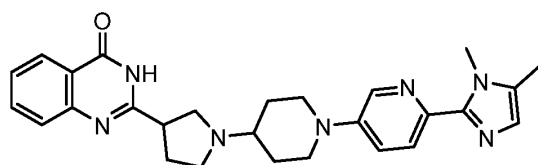
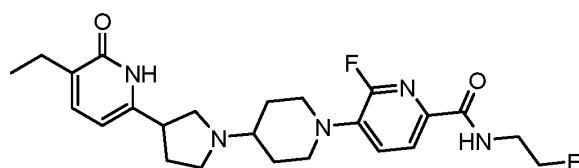
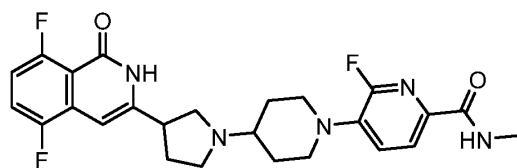
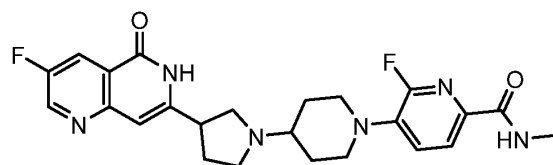


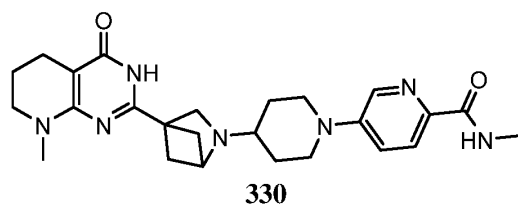
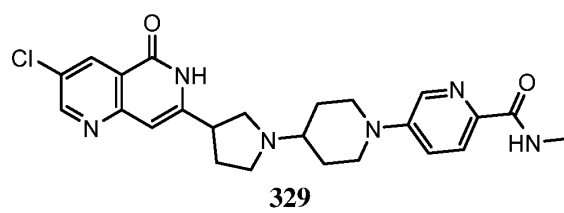
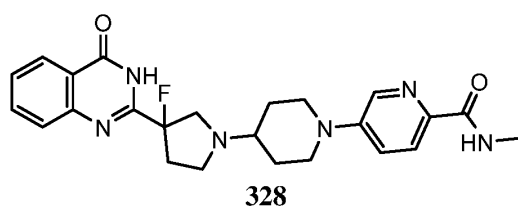
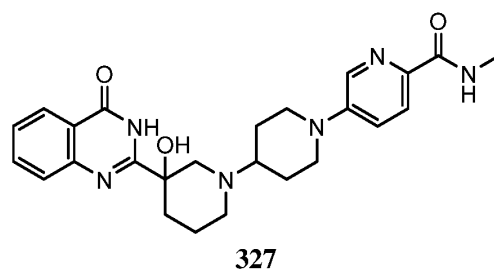
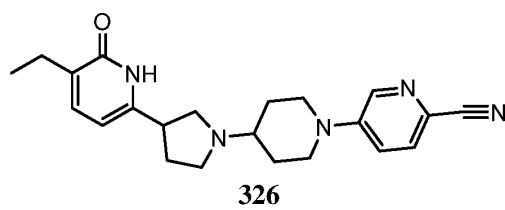
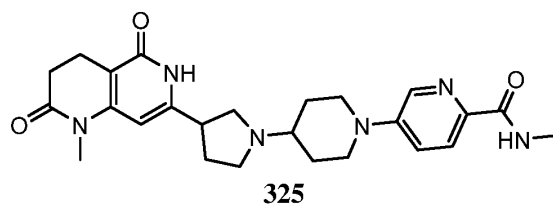
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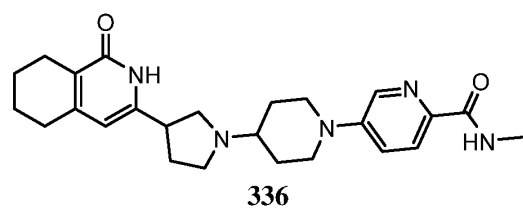
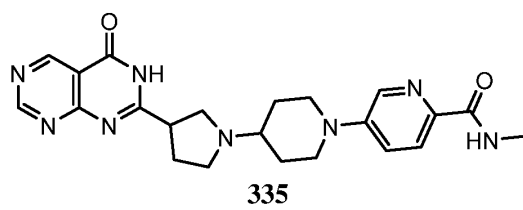
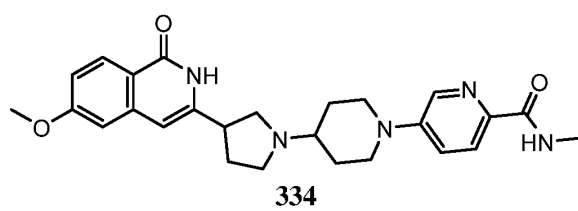
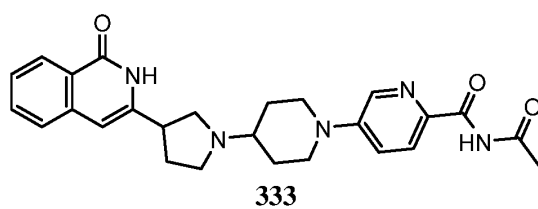
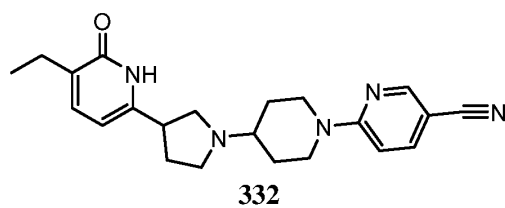
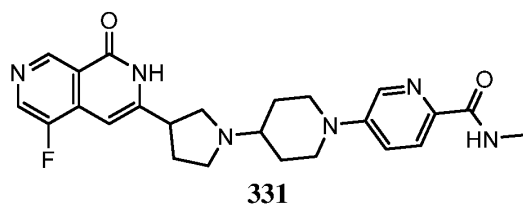


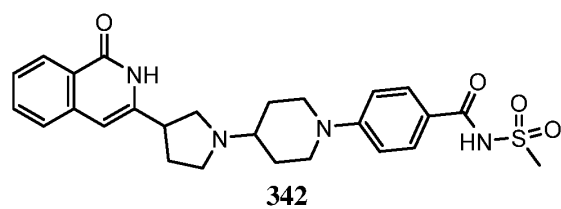
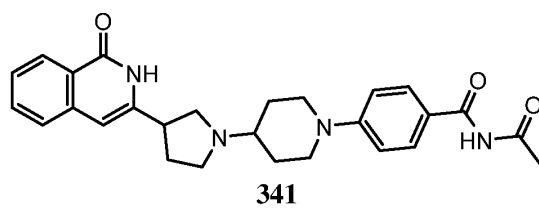
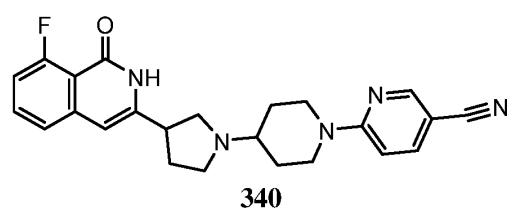
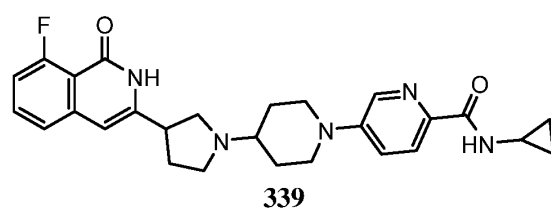
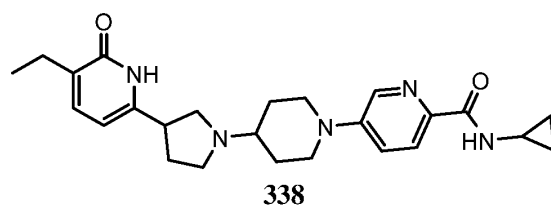
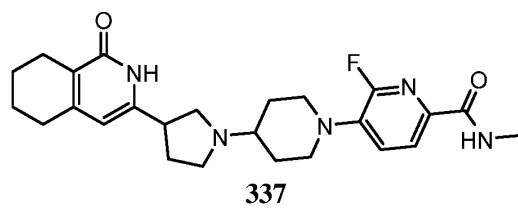
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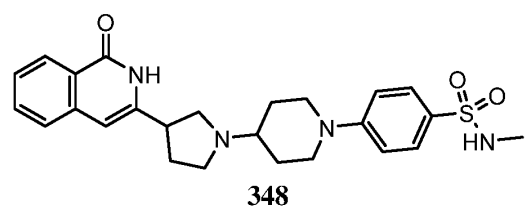
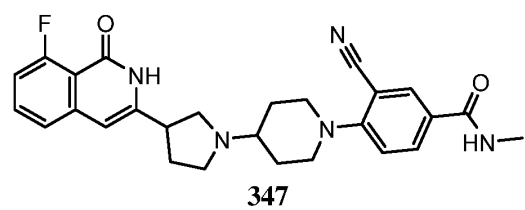
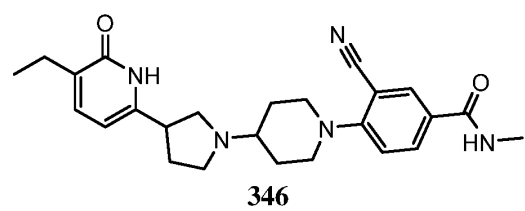
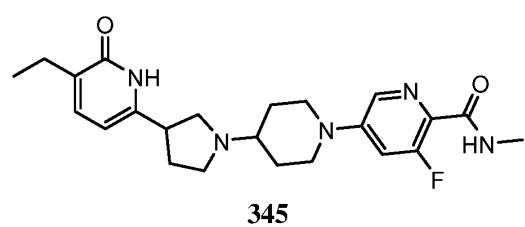
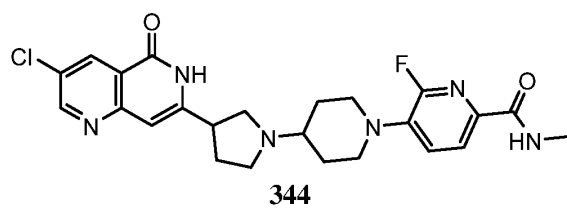
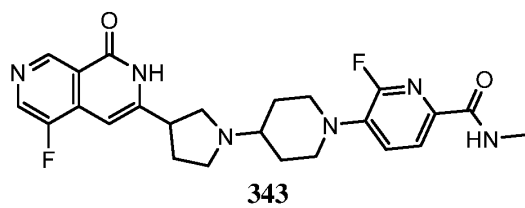


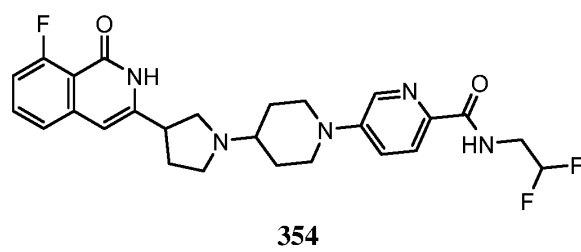
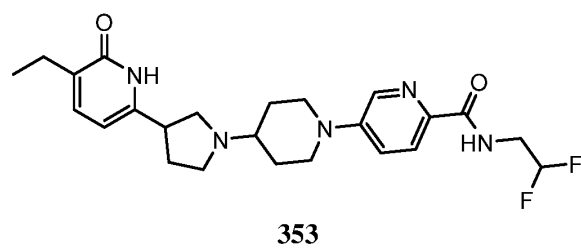
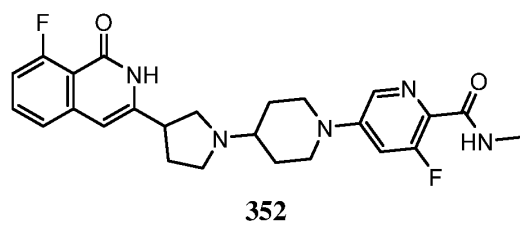
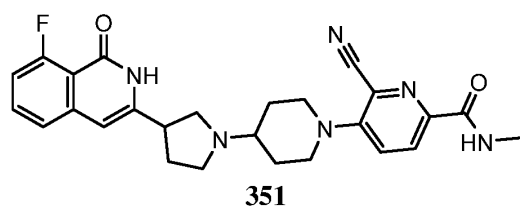
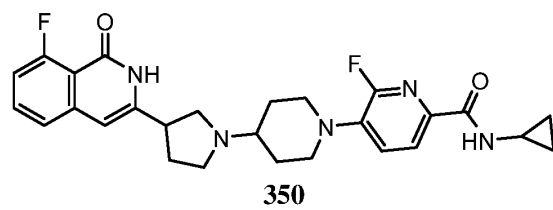
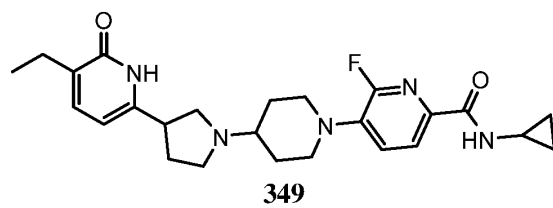
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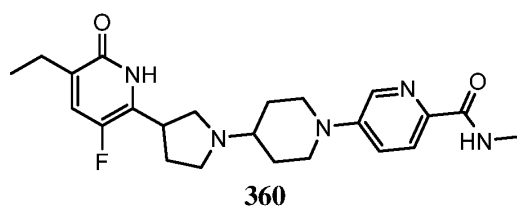
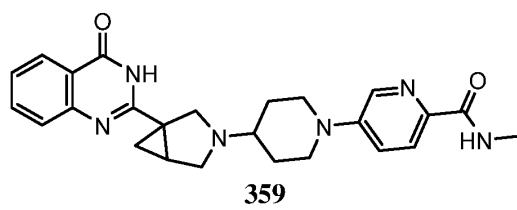
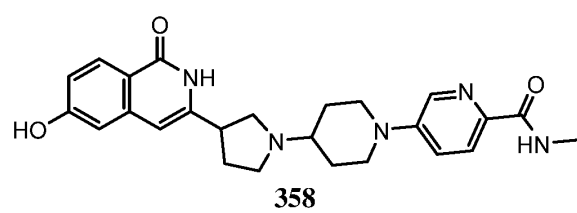
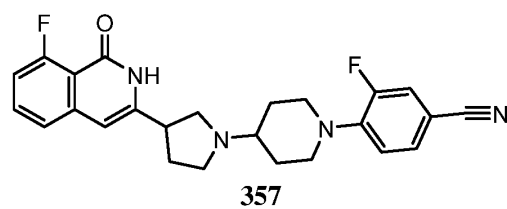
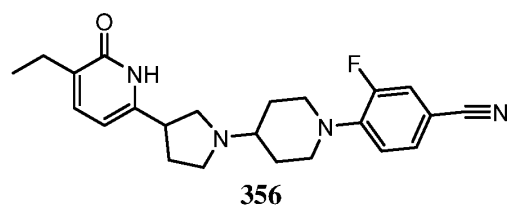
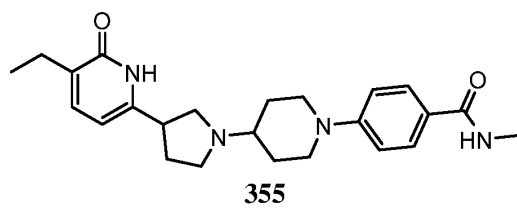


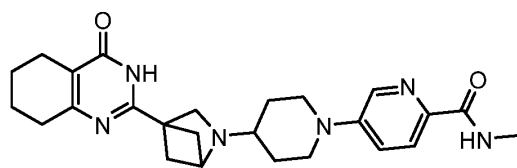




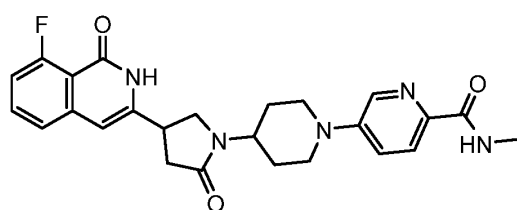




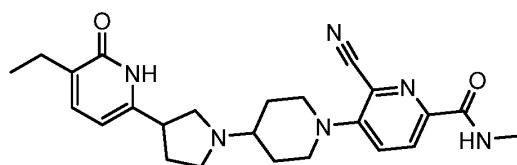




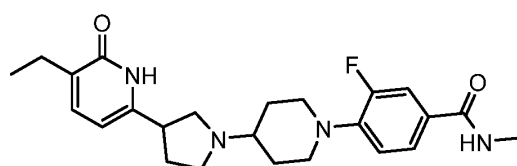
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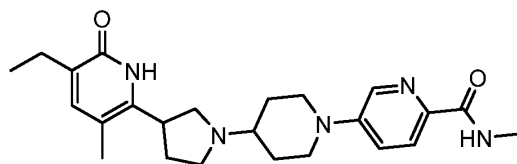
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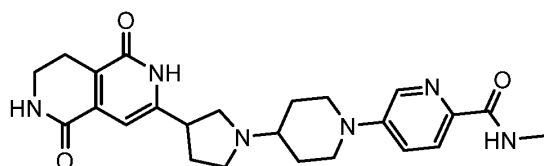
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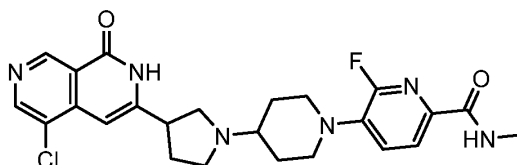
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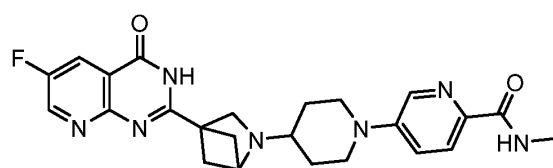
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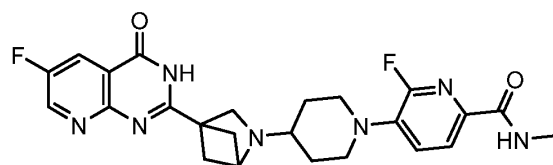
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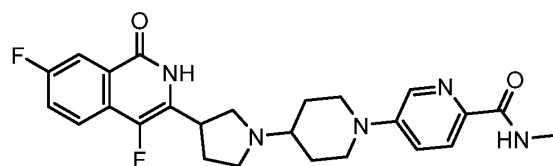
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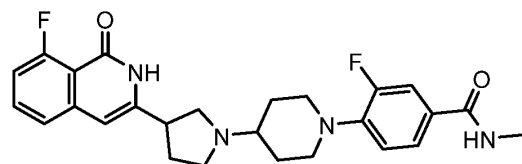
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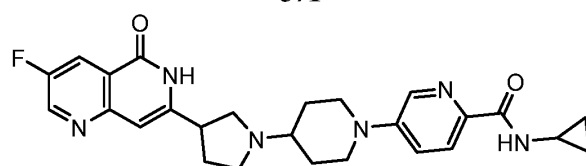
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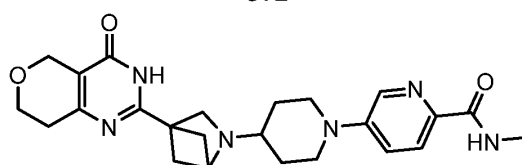
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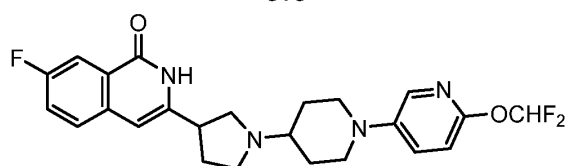
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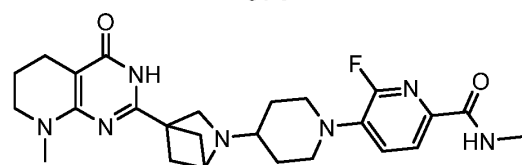
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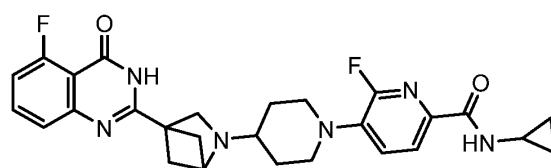
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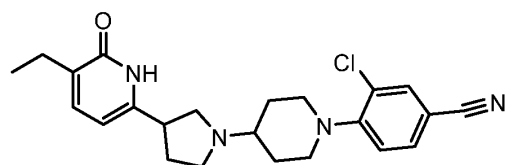
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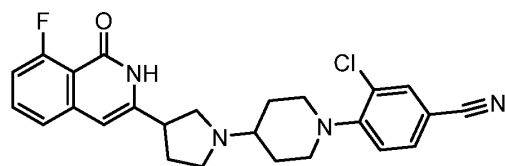
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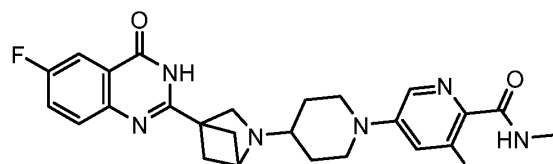
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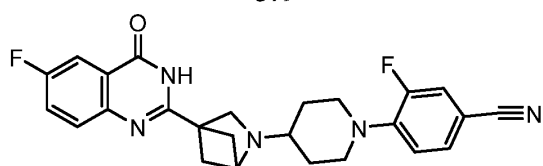
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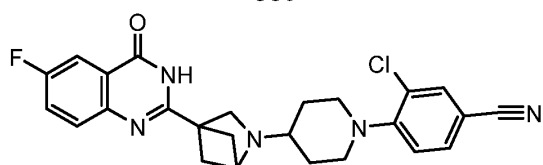
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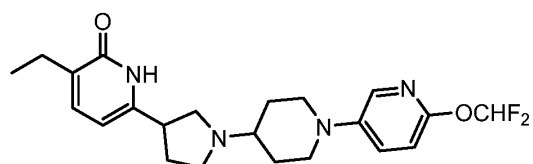
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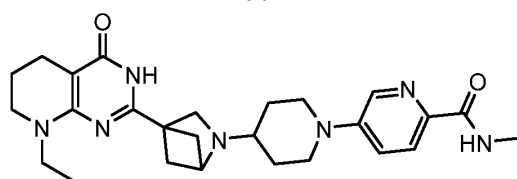
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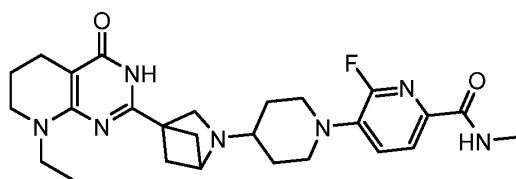
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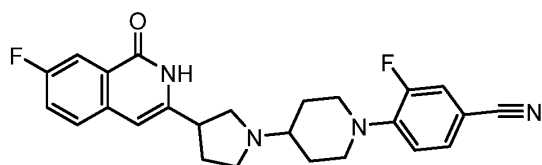
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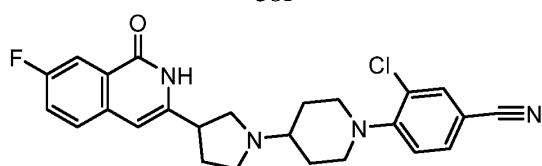
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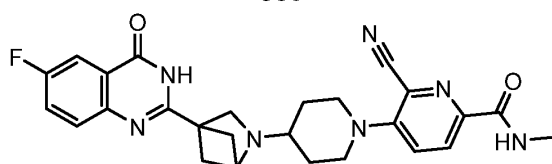
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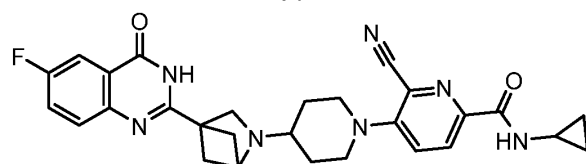
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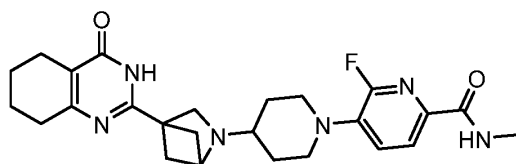
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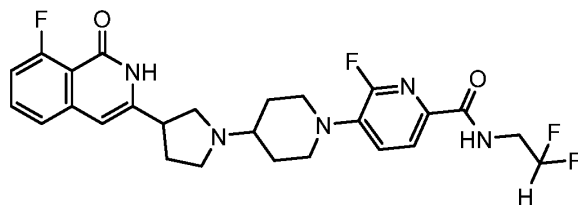
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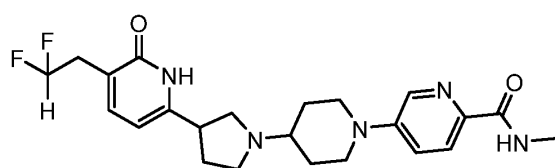
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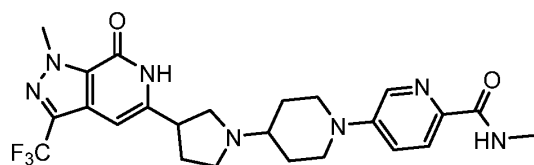
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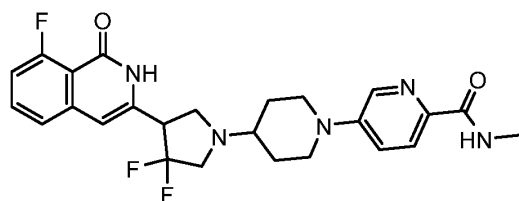
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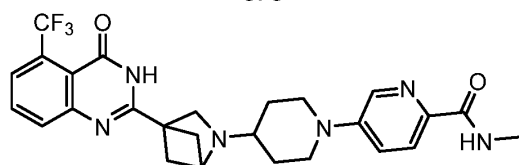
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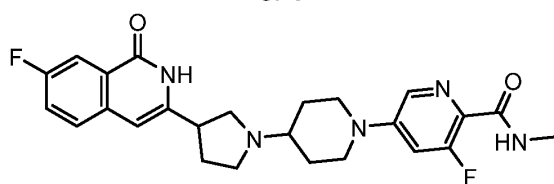
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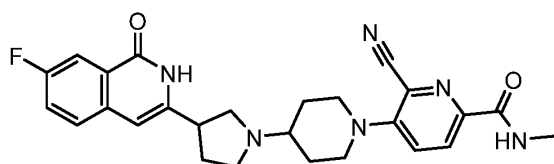
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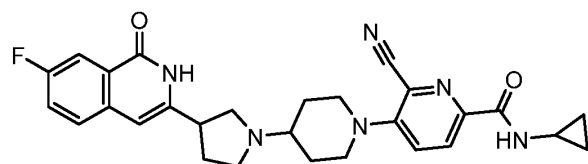
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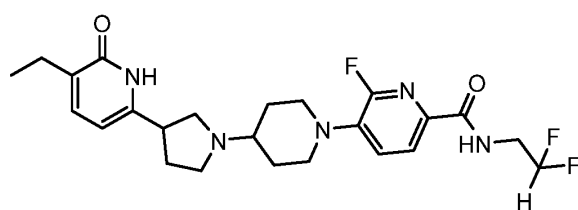
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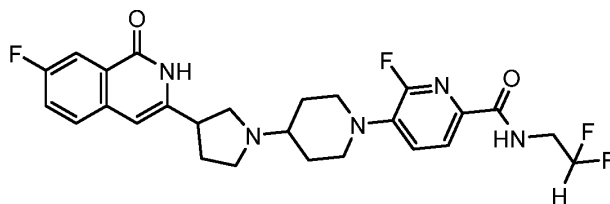
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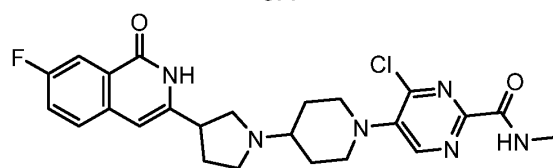
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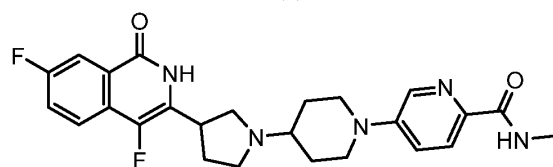
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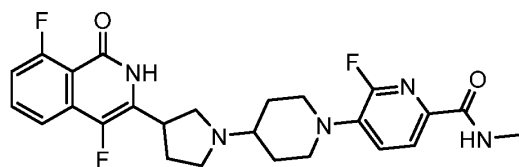
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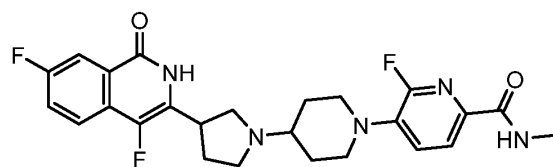
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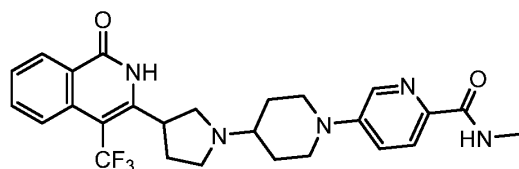
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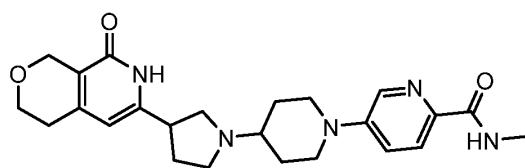
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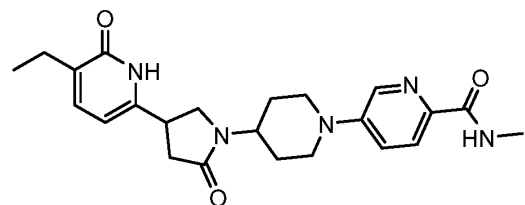
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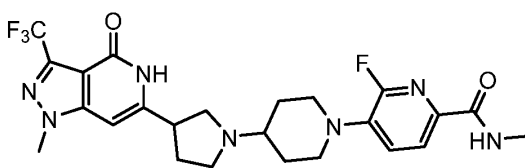
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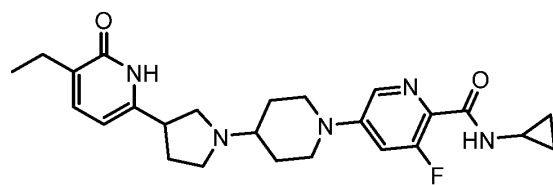
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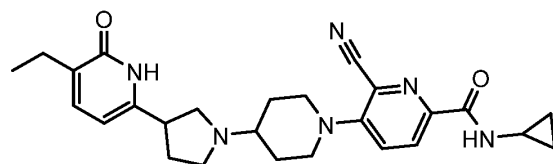
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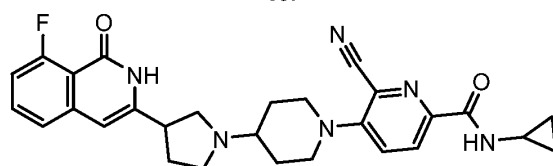
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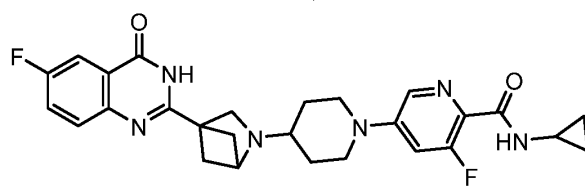
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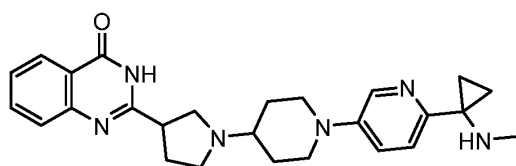
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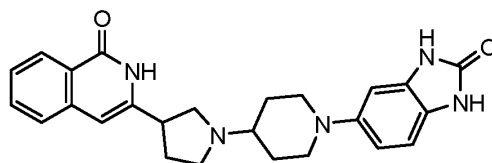
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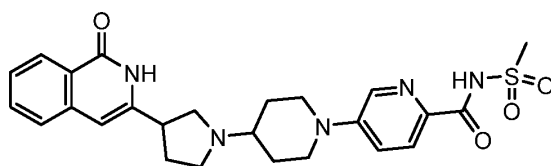
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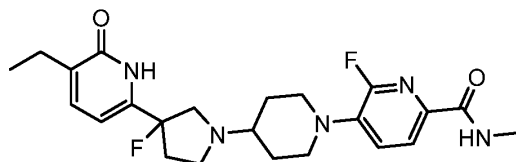
412



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415

The compounds of the present invention have been described in detail above in terms of their structures. For the avoidance of doubt, any compounds for use in the invention may comprise compounds or compositions in accordance with their structure as follows:

- an isolated enantiomer, or
- a mixture of two or more enantiomers, or
- a mixture of two or more diastereomers, and/or epimers, or
- a racemic mixture, or
- one or more tautomers;

of each structure.

For the above numbered compounds, compounds 1, 2, 5, 8, 12, 15, 17 to 22, 25, 27 to 30, 36, 40, 41, 45, 47, 48, 54, 59, 63, 75, 168, 173, 179, 192, 193, 227, 228, 238, 259, 260, 284, 295, 299, 300, 302-305, 310-312, 330, 361, 368, 369, 373, 375, 376, 379-381, 383, 384, 387-389, 394 and 411 are achiral. The remaining compounds represent more than one enantiomeric structure which may have PARP1 inhibitory activity as a racemic mixture and/or as a separated

enantiomer(s). In the examples below, a compound with a suffix “a” (eg 10a) represents an enantiomer eluted as a first fraction when a racemic mixture of the two enantiomers is applied to a Daicel CHIRALPAK chiral chromatography column. In the examples below, a compound with a suffix “b” (eg 10b) represents an enantiomer eluted as a second fraction when a racemic mixture of the two enantiomers is applied to a Daicel CHIRALPAK chiral chromatography column. In the examples below, a compound with no suffix represents either an achiral compound or a racemic mixture of the enantiomers. In the examples below, a compound which bears a suffix “rac” represents a racemic mixture of the enantiomers.

The compounds described herein may be provided for use in medicine. In the context of the present invention, the medicinal use is not especially limited, provided that it is a use which is facilitated by the PARP1 inhibitory effect of the compound. Thus, the compounds of the invention may be for use in any disease, condition or disorder that may be prevented, ameliorated or treated using a PARP1 inhibitor. Typically, this comprises a disease condition and/or a disorder selected from: a cancer, it is not especially limited, provided that the cancer is one which may be treated, prevented or ameliorated by using a PARP1 inhibitor. Thus the cancer may be a cancer selected from: a solid or liquid tumour including cancer of the eye, brain (such as gliomas, glioblastomas, medullablastomas, craniopharyngioma, ependymoma, and astrocytoma), spinal cord, kidney, mouth, lip, throat, oral cavity, nasal cavity, small intestine, colon, parathyroid gland, gall bladder, head and neck, breast, bone, bile duct, cervix, heart, hypopharyngeal gland, lung, bronchus, liver, skin, ureter, urethra, testicles, vagina, anus, laryngeal gland, ovary, thyroid, oesophagus, nasopharyngeal gland, pituitary gland, salivary gland, prostate, pancreas, adrenal glands; an endometrial cancer, oral cancer, melanoma, neuroblastoma, gastric cancer, an angiomas, a hemangioblastoma, a pheochromocytoma, a pancreatic cyst, a renal cell carcinoma, Wilms' tumour, squamous cell carcinoma, sarcoma, osteosarcoma, Kaposi sarcoma, rhabdomyosarcoma, hepatocellular carcinoma, PTEN Hamartoma-Tumor Syndromes (PHTS) (such as Lhermitte-Duclos disease, Cowden syndrome, Proteus syndrome, and Proteus-like syndrome), leukaemias and lymphomas (such as acute lymphoblastic leukaemia, chronic lymphocytic leukaemia, acute myelogenous leukaemia, chronic myelogenous leukaemia, hairy cell leukaemia, T-cell prolymphocytic leukemia (T-PLL), large granular lymphocytic leukemia, adult T-cell leukemia, juvenile myelomonocytic leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, mantle lymphoma, follicular lymphoma, primary effusion lymphoma, AIDS-related lymphoma, Hodgkin lymphoma, diffuse B cell lymphoma, Burkitt lymphoma, and cutaneous T-cell lymphoma). In

addition, the compounds described herein may be of use in cancers where EBV plays a contributing role such as Burkitt's lymphoma, Hodgkin's lymphoma, nasopharyngeal and gastrointestinal cancers.

The compounds described herein may be provided for use in for treating a cancer which is deficient in DNA damage response repair pathways, in particular in Homologous Recombination dependent DNA DSB DNA repair activity. Components of HR dependent DNA DSB repair pathways and other DNA damage response pathways include but are not limited to the following proteins: ATM, ATR, ERCC1, XRCC1, XRCC2, XRCC3, RAD51, RAD51L1, RAD51C, RAD51D, RAD51L3, DMC1, RAD52, RAD54L, RAD54B, RAD50, MRE11A, NBS1, BRCA1, BRCA2, FANCP (SLX4), FEN1, PALB2, PBRM1, SMARCA4, ARID1A, ARID1B, FANCD2, BLM. Other components involved in HR dependent DNA DSB repair include regulatory factors such as ESMY (Hughes-Davies, L. *et al. Cell.* 2003; 115: 523-535). A cancer which is deficient in HR-dependent DNA DSB repair typically becomes dependent on alternative DSB pathway repair mechanisms. Such cancers include but are not limited to cancers of the ovary, prostate, breast, lung, gastrointestinal, blood and pancreas.

In some embodiments, the cancer cells may have a BRCA1 and/or BRCA2 deficient phenotype ie they may be deficient in BRCA1 and/or 2 expression and function by means of mutation, polymorphism or epigenetic silencing in the encoding nucleic acids or by means of amplification, polymorphism, mutation in a gene encoding a regulatory factor eg, the ESMY gene which encodes a BRCA2 regulatory factor (Hughes-Davies, L. *et al. Cell.* 2003; 115: 523-535). Amplification of the ESMY gene is associated with breast and ovarian cancer. Carriers of mutations in the tumour suppressor BRCA1 and/or BRCA2 genes are known to have an elevated risk of developing certain cancers including ovarian, prostate and breast. Wild-type alleles of BRCA1 and/or BRCA2 are frequently lost in tumours of heterozygous carriers (Jasin, M. *et al. Oncogene.* 2002; 21: 8981-93) and their detection, as a means of patient selection, is well known in the art (Radice, PJ. *et al. Exp. Clin. Cancer. Res.* 2002; 21: 9-12; Chappnis, PO and Foulkes WO. *Cancer Treat Res.* 2002; 107: 29-59).

In some embodiments, the compounds described herein are selective PARP1 inhibitors, as defined above. Selective inhibition of PARP1 over PARP2 reduces PARP2 associated side effects including one or more haematological toxicities such as anaemia, neutropenia and thrombocytopenia. This enables treatment of cancer patients with reduced haematological side

effects. This also enables higher doses of PARP1 inhibitors to be administered to patients and for such inhibitors to be administered in combination with chemotherapeutic agents.

The present invention also provides a pharmaceutical composition comprising a compound as defined above. Whilst the pharmaceutical composition is not especially limited, typically the composition further comprises a pharmaceutically acceptable additive and/or excipient. In the pharmaceutical composition, the compound as defined above may be present in the form described above, but may alternatively be in a form suitable for improving bioavailability, solubility, and/or activity, and/or may be in a form suitable for improving formulation. Thus, the compound may be in the form of a pharmaceutically acceptable salt, hydrate, acid, ester, or other alternative suitable form. Typically, the composition is for treating a disease, condition or disorder as defined above. In some instances, the compound may be present in the composition as a pharmaceutically acceptable salt, or other alternative form of the compound, in order to ameliorate pharmaceutical formulation.

In some embodiments the pharmaceutical composition is a composition for treating a cancer, further comprising a further agent for treating cancer. The further agent for treating cancer is not especially limited, provided that it affords some utility for cancer treatment. However, typically the further agent for treating cancer is selected from ionising radiation, chemotherapeutic agents such as anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, senolytic agents, hormones and hormone analogues, signal transduction pathway inhibitors, other DNA damage repair pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, antibody-drug conjugates, immunotherapeutic agents, hormone-deprivation therapies, proapoptotic agents and cell cycle signalling inhibitors. An immunotherapeutic agent may consist of but is not limited to an anti-tumour vaccine, an oncolytic virus, an immune stimulatory antibody such as anti-CTLA4, anti-PD1, anti-PDL-1, anti-OX40, anti-41BB, anti-CD27, anti-CD40, anti-LAG3, anti-TIM3, and anti-GITR, a pattern recognition receptor agonist such as a STING, TLR-9 or RIG-I Helicase agonist, an IDO or TDO inhibitor, a novel adjuvant, a peptide, a cytokine, a chimeric antigen receptor T cell therapy (CAR-T), a small molecule immune modulator, tumour microenvironment modulators, and anti-angiogenic agents.

In still further embodiments the invention provides a pharmaceutical kit for treating a cancer, which pharmaceutical kit comprises:

(a) a compound as defined above; and

(b) a further agent for treating cancer; preferably wherein the further agent for treating cancer is selected from ionising radiation, chemotherapeutic agents such as anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, senolytic agents, hormones and hormone analogues, hormone-deprivation therapies, signal transduction pathway inhibitors, other DNA damage repair pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, antibody-drug conjugates, immunotherapeutic agents, proapoptotic agents and cell cycle signalling inhibitors;

wherein the compound and the further agent are suitable for administration simultaneously, sequentially or separately.

Further provided by the invention is a method of treating a disease and/or a condition and/or a disorder, which method comprises administering to a patient (or subject) a compound, or a composition, or a kit as defined above. The method is typically a method for treating any disease condition or disorder mentioned herein. In typical embodiments, the method is a method for treating a cancer. Preferably such a method comprises administering to a patient (or subject) a compound or a composition as defined above and a further agent for treating cancer as defined above. The compound or composition and the further agent may be administered simultaneously, sequentially or separately, depending upon the agents and patients involved, and the type of cancer indicated.

Typically, in all embodiments of the invention, both above and below, the patient (or subject) is an animal, typically a mammal, including canines, equines and felines, and more typically a human.

Further provided by the invention is a method of synthesis of a compound as defined above, which method comprises conducting a reaction between (i) a first reactant comprising ring E bearing a portion of substituent group L and (ii) a second reactant comprising the remainder of substituent group L, so as to form the PARP1 inhibitor compound.

Typically, in one method of synthesis, the first reactant comprises ring E and ring A, and the second reactant comprises a Q1 or Q2 precursor bearing a reactive group, which method comprises joining the N atom of ring A to the Q1 or Q2 precursor. In this method, the reactive group of the Q1 or Q2 precursor may comprise a carbonyl group, an alkyl halide or an alkyl sulfonate. Typically, the reaction comprises alkylation, reductive amination or amide formation so as to form group L.

Typically, in another method of synthesis, the first reactant comprises ring E, ring A, and at least one of Q1 and Q2, and the second reactant comprises a ring C derivative bearing a leaving group such as a halide or sulfonate. In this method, the reaction comprises a nucleophilic substitution reaction, such as a nucleophilic aromatic substitution reaction, so as to form group L.

The skilled person may select the reaction conditions in these methods with reference to known synthesis techniques depending on the appropriate starting materials. In some embodiments, the method comprises one or more additional steps. Exemplary synthesis methodology is shown in the Examples herein

Typically, the above formulae (and all formulae herein) are shown in non-stereoisomeric form. For the avoidance of doubt, throughout the present disclosure a single formula is intended to represent all possible stereoisomers of a particular structure, including all possible isolated enantiomers corresponding to the formula, all possible mixtures of enantiomers corresponding to the formula, all possible mixtures of diastereomers corresponding to the formula, all possible mixtures of epimers corresponding to the formula and all possible racemic mixtures corresponding to the formula. In addition to this, the above formulae (and all formulae herein) are intended to represent all tautomeric forms equivalent to the corresponding formula.

The term “comprises” as used throughout the description and claims herein means “includes or consists of”. The term denotes the inclusion of at least the features following the term and does not exclude the inclusion of other features which have not been explicitly mentioned. The term may also denote an entity which consists only of the features following the term.

Detailed description of the invention

The invention will now be described in more detail, by way of example only, with reference to the following specific embodiments.

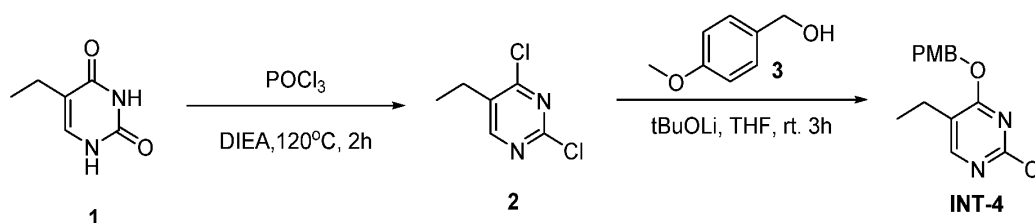
EXAMPLES

Exemplary syntheses of compounds of the invention

The compounds of the invention may be synthesised using readily available starting materials and known reactions. Exemplary syntheses of three compounds are shown below:

Example 1 – Synthesis of Compound 42

INT-4 Synthesis

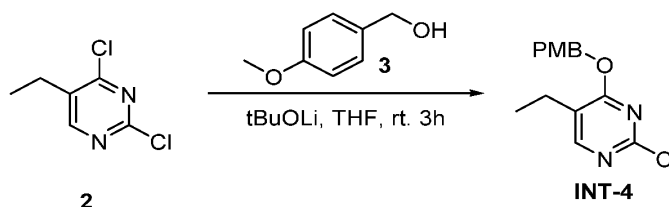


Preparation of 2,4-dichloro-5-ethylpyrimidine (2)

To a solution of 5-ethyl-1,3-dihydropyrimidine-2,4-dione **1** (10.00 g, 0.07 mol) in POCl_3 (55.00 g, 0.36 mol) at 0°C and added DIEA (23.00 g, 0.18 mol). Then the mixture was stirred for 2 h at 120°C . The hot reaction mixture was poured into ice water and the aqueous layer was extracted with ethyl acetate ($50\text{ mL} \times 3$). The combined organic layers were dried over Na_2SO_4 . The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EA = 100 : 0 to 92 : 8) to give 2,4-dichloro-5-ethylpyrimidine **2** (4.80 g, 38% yield) as a white solid.

LCMS (ESI) calcd for $\text{C}_6\text{H}_6\text{Cl}_2\text{N}_2$ $[\text{M} + \text{H}]^+$ m/z 176.99, found 177.00

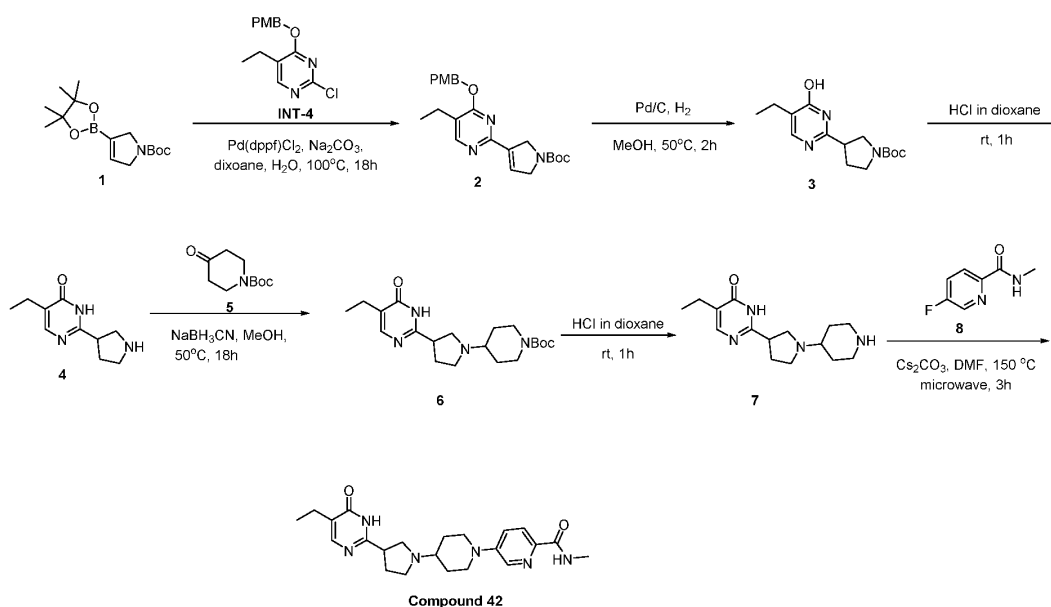
Preparation of 2-chloro-5-ethyl-4-(2-methoxy-5-methylphenoxy)pyrimidine (INT-4)



To a solution of (4-methoxyphenyl) methanol **3** (4.54 g, 32.90 mmol) in THF (20 mL) was added *t*BuOLi (2.30 g, 28.75 mmol) at 70 °C for 15 min. Then 2,4-dichloro-5-ethylpyrimidine **2** (4.80 g, 27.27 mmol) was added to the mixture at 0 °C. The mixture was stirred for 3 h at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 93 : 7) to give 2-chloro-5-ethyl-4-(2-methoxy-5-methylphenoxy)pyrimidine **INT-4** (4.00 g, 53 % yield) as a white solid.

LCMS (ESI) calcd for C₁₄H₁₅ClN₂O₂ [M + H]⁺ *m/z* 279.08, found 279.15.

Compound 42 synthesis



Preparation of tert-butyl 3-(5-ethyl-4-((4-methoxybenzyl)oxy)pyrimidin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (2)

To a solution tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydropyrrole-1-carboxylate **1** (500 mg, 1.69 mmol) in 1,4-dioxane/H₂O=4:1 (15 mL) was added 2-chloro-5-ethyl-4-(2-methoxy-5-methylphenoxy)pyrimidine **INT-4** (377.72 mg, 1.76 mmol) and Na₂CO₃ (189.11 mg, 3.01 mmol), then Pd(dppf)Cl₂ (247.89 mg, 0.34 mmol) was added at room temperature. The reaction mixture was refluxed under nitrogen at 100 °C and stirred for 18 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with petroleum ether/ethyl

acetate = 100 : 0 to 85 : 15) to give tert-butyl 3-(5-ethyl-4-((4-methoxybenzyl)oxy)pyrimidin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **2** (250 mg, 31% yield) as a colorless oil.

LCMS (ESI) calcd for C₂₃H₂₉N₃O₄ [M + H]⁺ m/z 412.22, found 412.28.

Preparation of tert-butyl 3-(5-ethyl-4-hydroxypyrimidin-2-yl)pyrrolidine-1-carboxylate (3)

To a solution 3-(5-ethyl-4-((4-methoxybenzyl)oxy)pyrimidin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **2** (250 mg, 0.61 mmol) in MeOH (15 mL) was added Pd/C (97 mg, 0.91 mmol) at room temperature. The reaction mixture was stirred for 2h at 50 °C under hydrogen. After cooling to room temperature, the mixture was filtered through a Celite pad and the filtrate was concentrated to give tert-butyl 3-(5-ethyl-4-hydroxypyrimidin-2-yl)pyrrolidine-1-carboxylate **3** (150 mg, 80% yield) as a colourless oil.

LCMS (ESI) calcd for C₁₅H₂₃N₃O₃ [M + H]⁺ m/z 294.17, found 294.19.

Preparation of 5-ethyl-2-(pyrrolidin-3-yl)-3H-pyrimidin-4-one (4)

To a solution 3-(5-ethyl-4-hydroxypyrimidin-2-yl)pyrrolidine-1-carboxylate **3** (150 mg, 0.51 mmol) was added HCl in dioxane (4 M, 10 mL) at room temperature. The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure to give 5-ethyl-2-(pyrrolidin-3-yl)-3H-pyrimidin-4-one **4** (100 mg, 94% yield) as a white solid.

LCMS (ESI) calcd for C₁₀H₁₅N₃O [M + H]⁺ m/z 194.12, found 194.19.

Preparation of tert-butyl 4-[3-(5-ethyl-4-oxo-3H-pyrimidin-2-yl)pyrrolidin-1-yl]piperidine-1-carboxylate (6)

To a solution 5-ethyl-2-(pyrrolidin-3-yl)-3H-pyrimidin-4-one **4** (100 mg, 0.52 mmol) in MeOH (15 mL) was added tert-butyl 4-oxopiperidine-1-carboxylate **5** (124.48 mg, 0.61 mmol) and NaBH₃CN (145 mg, 3.11 mmol). The reaction mixture was refluxed under nitrogen at 50 °C and stirred for 18 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 95 : 5) to give tert-butyl 4-[3-(5-ethyl-4-oxo-3H-pyrimidin-2-yl)pyrrolidin-1-yl]piperidine-1-carboxylate **6** (120 mg, 55% yield) as a white solid.

LCMS (ESI) calcd for C₂₀H₃₂N₄O₃ [M + H]⁺ m/z 377.25, found 377.30.

Preparation of 5-ethyl-2-[1-(piperidin-4-yl)pyrrolidin-3-yl]-3H-pyrimidin-4-one (7)

Tert-butyl 4-[3-(5-ethyl-4-oxo-3H-pyrimidin-2-yl)pyrrolidin-1-yl]piperidine-1-carboxylate **6**

(120 mg, 0.32 mmol) was added to HCl in dioxane (4 M, 10 mL) at room temperature. The reaction mixture was stirred for 1 h at room temperature, then concentrated under reduced pressure to give 5-ethyl-2-[1-(piperidin-4-yl)pyrrolidin-3-yl]-3H-pyrimidin-4-one **7** (90 mg, 92% yield) as a white solid.

LCMS (ESI) calcd for C₁₅H₂₄N₄O [M + H]⁺ m/z 277.20, found 277.24.

Preparation of 5-{4-[3-(5-ethyl-4-oxo-3H-pyrimidin-2-yl)pyrrolidin-1-yl]piperidin-1-yl}-N-methylpyridine-2-carboxamide (Compound 42)

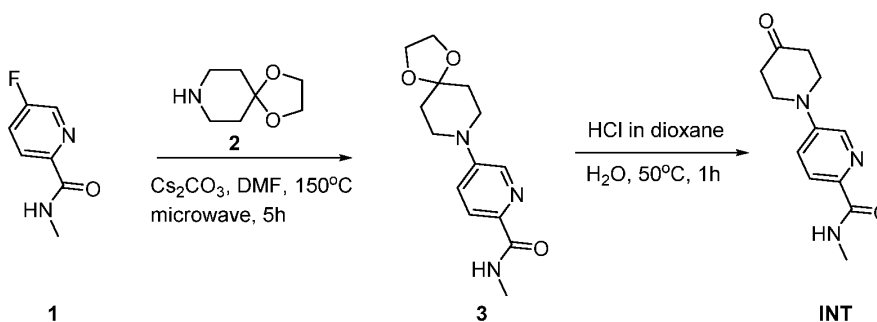
To a solution 5-ethyl-2-[1-(piperidin-4-yl)pyrrolidin-3-yl]-3H-pyrimidin-4-one **7** (90 mg, 0.33 mmol) in DMF (10 mL) was added 5-fluoro-N-methylpyridine-2-carboxamide **8** (104 mg, 0.68 mmol) and Cs₂CO₃ (884 mg, 2.71 mmol). The reaction mixture was irradiated in a microwave reactor at 150 °C for 3 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 95 : 5) to give 5-{4-[3-(5-ethyl-4-oxo-3H-pyrimidin-2-yl)pyrrolidin-1-yl]piperidin-1-yl}-N-methylpyridine-2-carboxamide **Compound 42** (20 mg, 95% purity, 20% yield) as a white solid.

¹H NMR (400 MHz, DMSO) δ 12.16 (s, 1 H), 8.42-8.38 (m, 1 H), 8.28 (d, *J* = 2.4 Hz, 1 H), 7.83 (d, *J* = 8.8 Hz, 1 H), 7.73 (s, 1 H), 7.42-7.39 (dd, *J* = 8.8, 2.8 Hz, 1 H), 3.87 (d, *J* = 12.8 Hz, 2 H), 3.29-3.25 (m, 2 H), 3.17-3.13 (m, 1 H), 2.94-2.74 (m, 8 H), 2.34 (q, *J* = 7.2 Hz, 2 H), 2.18-1.94 (m, 4 H), 1.56-1.47 (m, 2 H), 1.08 (t, *J* = 7.6 Hz, 3 H).

LCMS (ESI) calcd for C₂₂H₃₀N₆O₂ [M + H]⁺ m/z 411.24, found 411.33.

Example 2 – Synthesis of Compound 53

Synthesis of intermediate INT:



Preparation of 5-{1,4-dioxo-8-azaspiro[4.5]decan-8-yl}-N-methylpyridine-2-carboxamide (3)

To a solution of 5-fluoro-N-methylpyridine-2-carboxamide **1** (1.00 g, 6.50 mmol) in DMF (15 mL) was added 1,4-dioxo-8-azaspiro[4.5]decane **2** (1.40 g, 9.75 mmol), then Cs₂CO₃ (2.12 g, 6.50 mmol) was added at room temperature. The reaction mixture was stirred at 150 °C using microwave for 5 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 97 : 3) to give 5-{1,4-dioxo-8-azaspiro[4.5]decan-8-yl}-N-methylpyridine-2-carboxamide **3** (1.50 g, 76% yield) as a white solid.

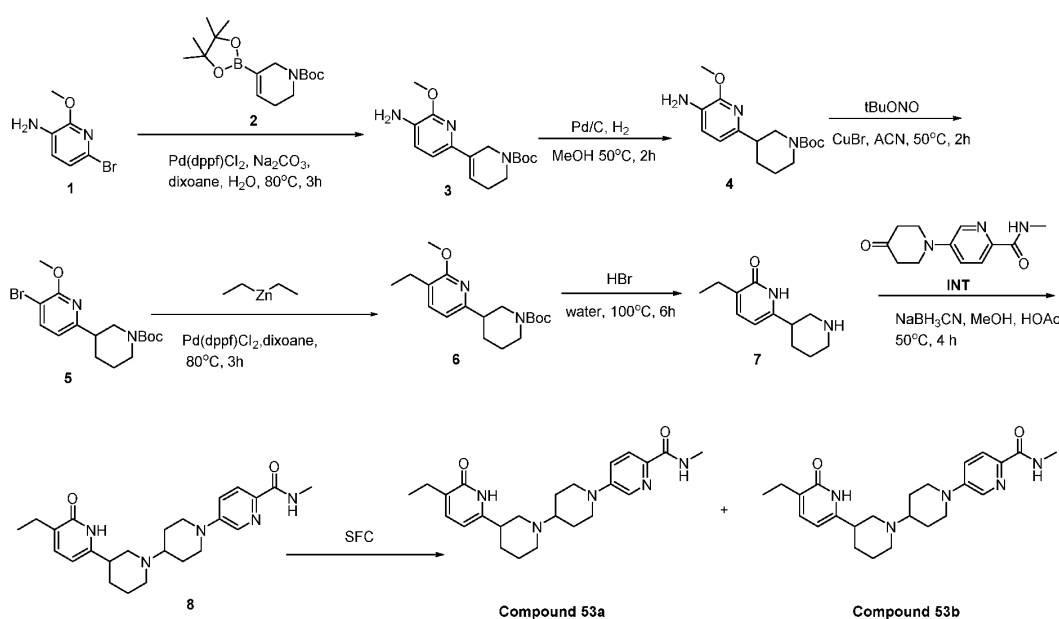
LCMS (ESI) calcd for C₁₄H₁₉N₃O₃ [M + H]⁺ m/z 278.14, found 278.14.

Preparation of N-methyl-5-(4-oxopiperidin-1-yl)picolinamide (INT)

To a solution of 5-{1,4-dioxo-8-azaspiro[4.5]decan-8-yl}-N-methylpyridine-2-carboxamide **3** (1.50 g, 5.40 mmol) in H₂O (10 mL) was added HCl in 1,4-dioxane (4 M, 20 mL) at room temperature. The reaction mixture was stirred at 50 °C for 1 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was adjusted pH > 7 using NaHCO₃ solution, then extracted with EtOAc (50 mL x 3), the organic phase dried by Na₂SO₄ and concentrated to give N-methyl-5-(4-oxopiperidin-1-yl)picolinamide **INT** (1.50 g, 76% yield) as a yellow solid.

LCMS (ESI) calcd for C₁₂H₁₅N₃O₂ [M + H]⁺ m/z 234.12, found 234.18.

Synthesis of Compound 53



Preparation of tert-butyl 3-(5-amino-6-methoxypyridin-2-yl)-5,6-dihydro-2H-pyridine-1-carboxylate (3)

To a solution of 6-bromo-2-methoxypyridin-3-amine **1** (2.00 g, 9.90 mmol) in 1,4-dioxane/H₂O=4:1 (45 mL) was added tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-2H-pyridine-1-carboxylate **2** (3.98 g, 12.87 mmol), then Pd(dppf)Cl₂ (0.72 g, 0.99 mmol) and Na₂CO₃ (3.12 g, 99.00 mmol) were added at room temperature. The reaction mixture was stirred under nitrogen at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EA = 100 : 0 to 85 : 15) to give tert-butyl 3-(5-amino-6-methoxypyridin-2-yl)-5,6-dihydro-2H-pyridine-1-carboxylate **3** (3.00 g, 89% yield) as a white solid.

LCMS (ESI) calcd for C₁₆H₂₃N₃O₃ [M + H]⁺ m/z 306.17, found 306.19.

Preparation of tert-butyl 3-(5-amino-6-methoxypyridin-2-yl)piperidine-1-carboxylate (4)

To a solution of tert-butyl 3-(5-amino-6-methoxypyridin-2-yl)-5,6-dihydro-2H-pyridine-1-carboxylate **3** (2.80 g, 9.20 mmol) in MeOH (50 mL) was added Pd/C (0.78 g, 7.36 mmol) at room temperature. The reaction mixture was stirred under hydrogen at 50 °C for 2 h. After cooling to room temperature, the reaction mixture was filtered, the solution was concentrated under reduced pressure to give product of tert-butyl 3-(5-amino-6-methoxypyridin-2-yl)piperidine-1-carboxylate **4** (2.80 g, 89% yield) as a white solid.

LCMS (ESI) calcd for C₁₆H₂₅N₃O₃ [M + H]⁺ m/z 308.19, found 308.19.

Preparation of tert-butyl 3-(5-bromo-6-methoxypyridin-2-yl)piperidine-1-carboxylate (5)

To a solution of tert-butyl 3-(5-amino-6-methoxypyridin-2-yl)piperidine-1-carboxylate **4** (2.80 g, 9.10 mmol) in ACN (50 mL) was added tert-Butyl nitrite (2.82 g, 27.30 mmol), stirred for 15 minutes, then CuBr (5.22 g, 36.40 mmol) was added at room temperature. The reaction mixture was stirred at 50 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EA = 100 : 0 to 85 : 15) to give tert-butyl tert-butyl 3-(5-bromo-6-methoxypyridin-2-yl)piperidine-1-carboxylate **5** (1.10 g, 30% yield) as a white solid.

LCMS (ESI) calcd for C₁₆H₂₃BrN₂O₃ [M + H]⁺ m/z 371.09, found 371.15.

Preparation of tert-butyl 3-(5-ethyl-6-methoxypyridin-2-yl)piperidine-1-carboxylate (6)

To a solution of tert-butyl 3-(5-bromo-6-methoxypyridin-2-yl)piperidine-1-carboxylate **5** (1.10 g, 2.96 mmol) in 1,4-dioxane (65 mL) was added Pd(dppf)Cl₂ (219 mg, 0.30 mmol). Then Et₂Zn (1M, 11.84 mL, 11.84 mmol) was added at room temperature. The reaction mixture under nitrogen was stirred at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EA = 100 : 0 to 85 : 15) to give tert-butyl 3-(5-ethyl-6-methoxypyridin-2-yl)piperidine-1-carboxylate **6** (700 mg, 67% yield) as a white solid.

LCMS (ESI) calcd for C₁₈H₂₈N₂O₃ [M + H]⁺ m/z 321.21, found 321.30.

Preparation of 3-ethyl-6-(piperidin-3-yl)-1H-pyridin-2-one (7)

To a solution of tert-butyl 3-(5-ethyl-6-methoxypyridin-2-yl)piperidine-1-carboxylate **6** (200 mg, 0.62 mmol) in HBr in water (48%, 6 mL). The reaction mixture was stirred at 100 °C for 6 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to give 3-ethyl-6-(piperidin-3-yl)-1H-pyridin-2-one **7** (80 mg, 56% yield) as a yellow solid.

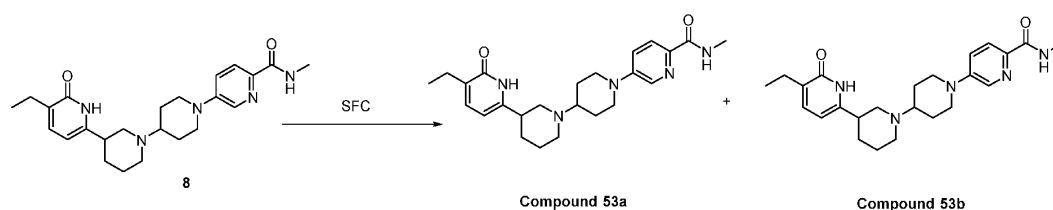
LCMS (ESI) calcd for C₁₂H₁₈N₂O [M + H]⁺ m/z 207.14, found 206.95.

Preparation of 5-{4-[3-(5-ethyl-6-oxo-1H-pyridin-2-yl)piperidin-1-yl]piperidin-1-yl}-N-methylpyridine-2-carboxamide (8)

To a solution of 3-ethyl-6-(piperidin-3-yl)-1H-pyridin-2-one **7** (80 mg, 0.38 mmol) in MeOH (10 mL) was added N-methyl-5-(4-oxopiperidin-1-yl)pyridine-2-carboxamide **INT** (89 mg, 0.38 mmol). Then two drops of acetic acid and NaBH₃CN (24 mg, 0.38 mmol) was added at room temperature. The reaction mixture was stirred at 50 °C for 4 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 95 : 5) to give 5-{4-[3-(5-ethyl-6-oxo-1H-pyridin-2-yl)piperidin-1-yl]piperidin-1-yl}-N-methylpyridine-2-carboxamide **8** (48 mg, 31% yield) as a white solid.

LCMS (ESI) calcd for C₂₄H₃₃N₅O₂ [M + H]⁺ m/z 424.26, found 424.37.

Preparation of 5-{4-[3-(5-ethyl-6-oxo-1H-pyridin-2-yl)piperidin-1-yl]piperidin-1-yl}-N-methylpyridine-2-carboxamide (Compound 53a and Compound 53b)



5-{4-[3-(5-ethyl-6-oxo-1H-pyridin-2-yl)piperidin-1-yl]piperidin-1-yl}-N-methylpyridine-2-carboxamide **8** was separated by SFC (Column: Daicel CHIRALPAK AD-H 250 mm × 20 mm I.D., 5 μm; Mobile phase: CO₂/MeOH[0.1%(NH₃)] = 75/25) and concentrated under reduced pressure to afford the first fraction as **Compound 53a** (7.16 mg, 95% purity, ee%: 100, white solid) and the second fraction as **Compound 53b** (6.57 mg, 99% purity, ee%: 100, white solid)

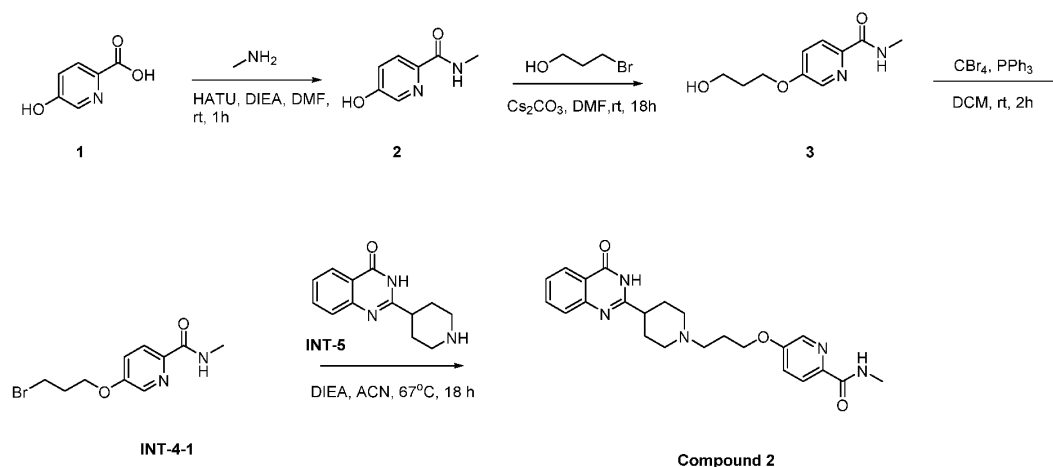
Compound 53a

¹H NMR (400 MHz, DMSO) δ 11.48 (s, 1 H), 8.39 (q, *J* = 4.8 Hz, 1 H), 8.26 (d, *J* = 2.8 Hz, 1 H), 7.81 (d, *J* = 8.8 Hz, 1 H), 7.40 (dd, *J* = 8.8, 2.8 Hz, 1 H), 7.17 (d, *J* = 6.8 Hz, 1 H), 5.98 (d, *J* = 7.2 Hz, 1 H), 3.97 (d, *J* = 12.4 Hz, 2 H), 2.91-2.77 (m, 7 H), 2.67-2.54 (m, 2 H), 2.36-2.28 (m, 4 H), 1.83-1.81 (m, 3 H), 1.68-1.65 (m, 1 H), 1.59-1.40 (m, 4 H), 1.05 (t, *J* = 7.6 Hz, 3 H).

Compound 53b

¹H NMR (400 MHz, DMSO) δ 11.48 (s, 1 H), 8.39 (q, *J* = 4.4 Hz, 1 H), 8.26 (d, *J* = 2.8 Hz, 1 H), 7.81 (d, *J* = 8.8 Hz, 1 H), 7.40 (dd, *J* = 9.2, 3.2 Hz, 1 H), 7.17 (d, *J* = 7.2 Hz, 1 H), 5.98 (d, *J* = 6.8 Hz, 1 H), 3.97 (d, *J* = 12.4 Hz, 2 H), 2.91-2.77 (m, 7 H), 2.66-2.54 (m, 2 H), 2.36-2.25 (m, 4 H), 1.83-1.80 (m, 3 H), 1.67-1.64 (m, 1 H), 1.59-1.36 (m, 4 H), 1.05 (t, *J* = 7.6 Hz, 3 H).

Example 3 – Synthesis of Compound 2



Preparation of 5-hydroxy-N-methylpicolinamide (2)

To a solution of 5-hydroxypicolinic acid **1** (4.00 g, 28.72 mmol) in DMF (15 mL) was added HATU (12.55 g, 33.01 mmol) and DIEA (9.28 g, 71.80 mmol). Then methanamine (2M, 15 mL, 30.00 mmol) was added at room temperature. Then the mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 93 : 7) to give **5-hydroxy-N-methylpicolinamide 2** (2.00 g, 46 % yield) as a white solid.

LCMS (ESI) calcd for C₇H₈N₂O₂ [M + H]⁺ m/z 153.06, found 153.10

Preparation of 5-(3-hydroxypropoxy)-N-methylpicolinamide (3)

To a solution of 5-hydroxy-N-methylpicolinamide **2** (1.00 g, 6.61 mmol) in DMF (10 mL) was added 3-bromopropan-1-ol (2.75 g, 19.58 mmol) and Cs₂CO₃ (3.23 g, 9.93 mmol) at room temperature. Then the mixture was stirred for 18 h at room temperature. The reaction mixture was filtered to give 5-(3-hydroxypropoxy)-N-methylpicolinamide **3** (1.00 g, 65 % yield) as an oil.

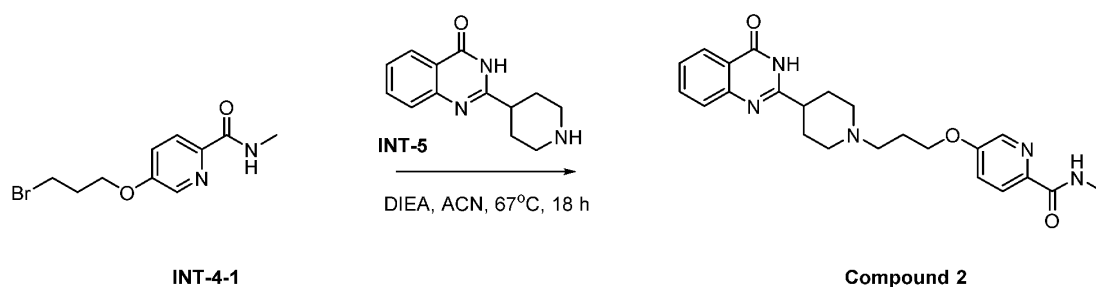
LCMS (ESI) calcd for C₁₀H₁₄N₂O₃ [M + H]⁺ m/z 211.10, found 211.05.

Preparation of 5-(3-bromopropoxy)-N-methylpicolinamide (INT-4-1)

To a solution of 5-(3-hydroxypropoxy)-N-methylpicolinamide **3** (250.00 mg, 1.19 mmol) in DCM (15 mL) was added CBr₄ (788.74 mg, 2.38 mmol). Then PPh₃ (623.83 mg, 2.38 mmol) was added at room temperature. Then the mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 95 : 5) to give 5-(3-bromopropoxy)-N-methylpicolinamide **INT-4-1** (300 mg, 69% yield) as a white solid.

LCMS (ESI) calcd for C₁₀H₁₃BrN₂O₂ [M + H]⁺ m/z 273.02, found 274.85.

Preparation of N-methyl-5-(3-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)piperidin-1-yl)propoxy)picolinamide (Compound 2)

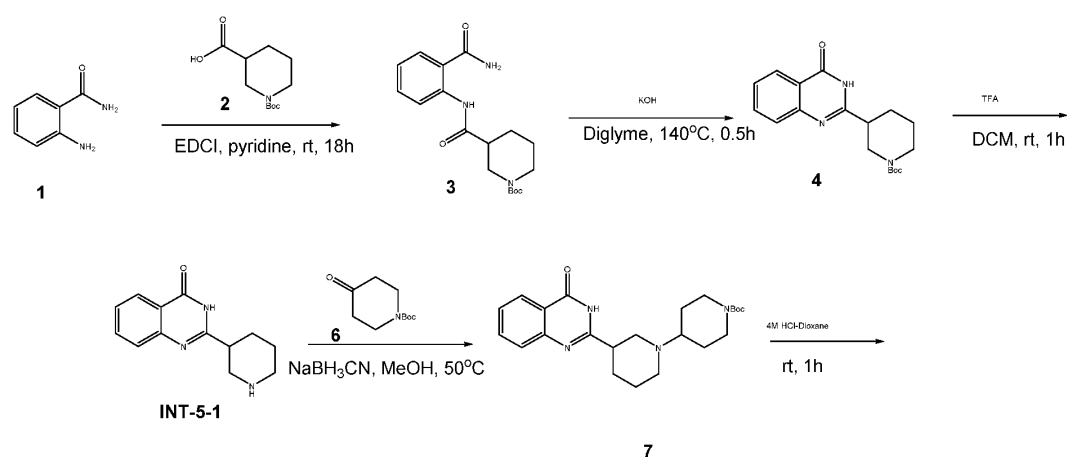


To a solution of 5-(3-bromopropoxy)-N-methylpicolinamide **INT-4-1** (150.00 mg, 0.55 mmol) in ACN (10mL) was added 2-(piperidin-4-yl)-3H-quinazolin-4-one **INT-5** (151.10 mg, 0.66 mmol). Then DIEA (212.94 mg, 1.65 mmol) was added at room temperature. Then the mixture was stirred for 18 h at 67 °C. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 92 : 8) to give N-methyl-5-(3-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)piperidin-1-yl)propoxy)picolinamide **Compound 2** (100 mg, 78% yield) as a white solid.

¹H NMR (400 MHz, DMSO) δ 12.15 (s, 1 H), 8.57-8.54 (m, 1 H), 8.29 (d, J = 2.8 Hz, 1 H), 8.08 (d, J = 8.0 Hz, 1 H), 7.98 (d, J = 8.8 Hz, 1 H), 7.78 (t, J = 7.6 Hz, 1 H), 7.60 (d, J = 8.0 Hz, 1 H), 7.54 (dd, J = 8.8, 2.8 Hz, 1 H), 7.47 (t, J = 7.6 Hz, 1 H), 4.18 (t, J = 5.6 Hz, 2 H), 3.10-2.86 (m, 2 H), 2.79 (d, J = 4.8 Hz, 3 H), 2.65-2.53 (m, 1 H), 2.49-2.41 (m, 2 H), 1.94 (s, 8 H).

LCMS (ESI) calcd for C₂₃H₂₇N₅O₃ [M + H]⁺ m/z 422.21, found 422.30.

Example 4 – Synthesis of Compound 6





LCMS (ESI) calcd for C₁₈H₂₅N₃O₄ [M - H]⁻ m/z 346.18, found 346.20.

To the solution of tert-butyl 3-((2-carbamoylphenyl)carbamoyl)piperidine-1-carboxylate **3** (12.00 g, 34.50 mmol) in Diglyme (80 mL) was added KOH (2.13 g, 37.95 mmol), heated to 140 °C stirred for 2 h, cooled to 0 °C, ice-water (100 mL) added then adjusted pH < 7 using 1M HCl solution, precipitate formed, filtered, the filter cake washed with ice-water (50 mL*3), then dried to give product of tert-butyl 3-(4-oxo-3,4-dihydroquinazolin-2-yl)piperidine-1-carboxylate **4** (11.00 g, 97% yield) as a white solid .

LCMS (ESI) calcd for C₁₈H₂₃N₃O₃ [M + H]⁺ m/z 330.17, found 330.20.

To the solution of tert-butyl 3-(4-oxo-3,4-dihydroquinazolin-2-yl)piperidine-1-carboxylate **4** (3.30 g, 10.00 mmol) in DCM (10 mL) were added TFA (10 mL), stirred for 1 h at room

temperature, the mixture was concentrated under reduced pressure to give crude product, ice-water (20 mL) added then adjusted pH > 7 using ammonium hydroxide solution, precipitate formed, filtered, the filter cake washed with ice-water (50 mL*3), then dried to give product of 2-(piperidin-3-yl)quinazolin-4(3H)-one **INT-5-1** (1.50 g, 66% yield) as a white solid. LCMS (ESI) calcd for C₁₃H₁₅N₃O [M + H]⁺ m/z 230.12, found 230.00.

Preparation of tert-butyl 3-(4-oxo-3,4-dihydroquinazolin-2-yl)-[1,4'-bipiperidine]-1'-carboxylate (7)

To a solution of 2-(piperidin-3-yl)quinazolin-4(3H)-one **INT-5-1** (460 mg, 2.01 mmol) in MeOH (15 mL) was added tert-butyl 4-oxopiperidine-1-carboxylate **6** (8.45 g, 44.10 mmol), then two drops of acetic acid and NaBH₃CN (189.11 mg, 3.01 mmol) were added at room temperature. The reaction mixture stirred at 50 °C for 18 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 93 : 7) to give tert-butyl 3-(4-oxo-3,4-dihydroquinazolin-2-yl)-[1,4'-bipiperidine]-1'-carboxylate **7** (300 mg, 36% yield) as a white solid.

¹H NMR (400 MHz, DMSO) δ 12.40 (s, 1 H), 8.11 (d, *J* = 7.2 Hz, 1 H), 7.81 (s, 1 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.51 (s, 1 H), 4.10-3.99 (m, 2 H), 3.53-3.44 (m, 1H), 3.16 -3.04 (m, 1 H), 2.94-2.62 (m, 4 H), 1.99 (d, *J* = 2.4 Hz, 4 H), 1.91 (d, *J* = 2.4 Hz, 2 H), 1.82-1.53 (m, 4 H), 1.41 (s, 9 H).

Preparation of 2-([1,4'-bipiperidin]-3-yl)quinazolin-4(3H)-one (8)

Tert-butyl 3-(4-oxo-3,4-dihydroquinazolin-2-yl)-[1,4'-bipiperidine]-1'-carboxylate **7** (300 mg, 0.65 mmol) was added to HCl in dioxane (4 M, 10 mL), stirred for 1 h at room temperature, the reaction mixture was concentrated under reduced pressure to give 2-([1,4'-bipiperidin]-3-yl)quinazolin-4(3H)-one **8** (200 mg, 88% yield) as a white solid.

LCMS (ESI) calcd for C₁₈H₂₄N₄O [M + H]⁺ m/z 313.20, found 313.15.

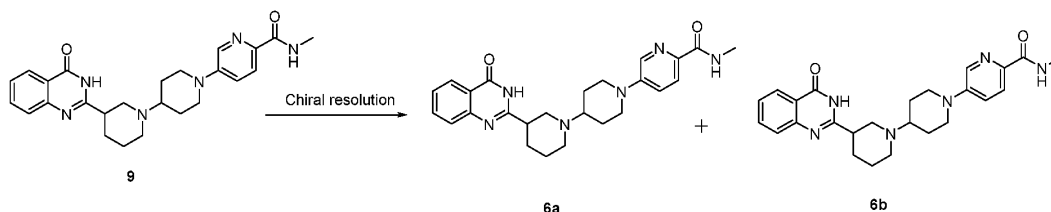
Preparation of N-methyl-5-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)-[1,4'-bipiperidin]-1'-yl)picolinamide (9)

To a solution 2-([1,4'-bipiperidin]-3-yl)quinazolin-4(3H)-one **8** (200.00 mg, 0.64 mmol) in DMF (10 mL) was added Cs₂CO₃ (1042.94 mg, 3.20 mmol) and 5-fluoro-N-methylpicolinamide (148.02 mg, 0.96 mmol). The mixture was stirred for 6 h under 150 °C using microwave. The reaction mixture was concentrated under reduced pressure. The residue

was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 92 : 8) to N-methyl-5-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)-[1,4'-bipiperidin]-1'-yl)picolinamide **9** (100 mg, 95% purity, 33% yield) as a yellow solid.

LCMS (ESI) calcd for C₂₅H₃₀N₆O₂ [M + H]⁺ m/z 447.24, found 447.20

Chiral resolution of N-methyl-5-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)-[1,4'-bipiperidin]-1'-yl)picolinamide (Compound 6a & Compound 6b)



Compound **9** was separated by SFC (Column: Daicel CHIRALPAK OJ -H 250 mm × 20 mm I.D., 5 μm; Mobile phase: CO₂/MeOH[0.1%(NH₃)] = 70/30) and concentrated under reduced pressure to afford the first fraction as **Compound 6a** (40.6 mg, 100% purity, ee%: 100, white solid) and the second fraction as **Compound 6b** (39.5 mg, 99% purity, ee%: 100, white solid)

Compound 6a

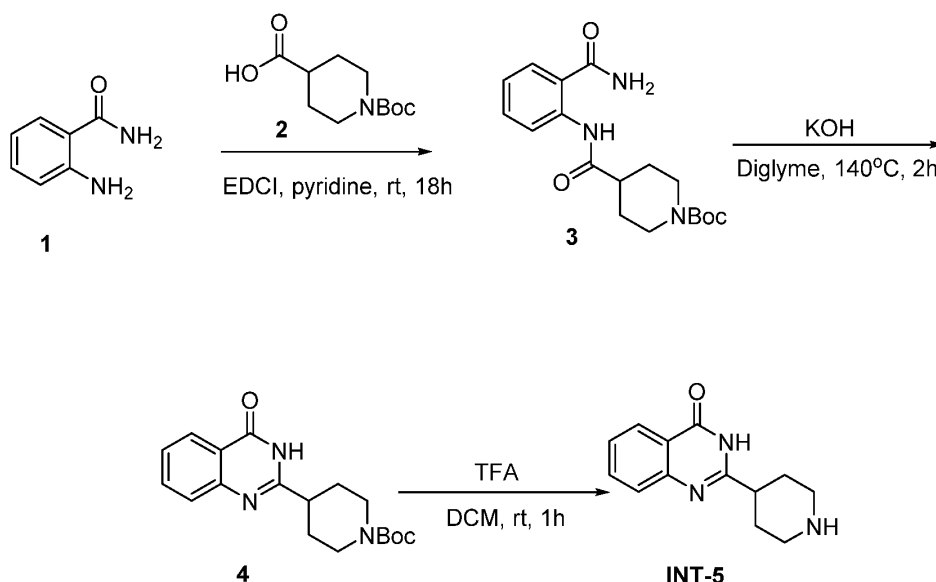
¹H NMR (400 MHz, DMSO) δ 12.25 (s, 1 H), 8.40 (q, *J* = 4.8 Hz, 1 H), 8.29 (d, *J* = 2.8 Hz, 1 H), 8.10 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.85-7.78 (m, 2 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 7.49 (t, *J* = 7.4 Hz, 1 H), 7.42 (dd, *J* = 8.8, 2.8 Hz, 1 H), 3.99 (d, *J* = 12.8 Hz, 2 H), 3.08 (d, *J* = 8.8 Hz, 1 H), 2.87-2.81 (m, 4 H), 2.80 (d, *J* = 4.8 Hz, 3 H), 2.61-2.55 (m, 2 H), 2.32 (t, *J* = 9.8 Hz, 1 H), 1.98-1.96 (m, 1 H), 1.87 (d, *J* = 12.4 Hz, 2 H), 1.78-1.75 (m, 1 H), 1.69-1.55 (m, 4 H).

LCMS (ESI) calcd for C₂₅H₃₀N₆O₂ [M + H]⁺ m/z 447.24, found 447.

Compound 6b

¹H NMR (400 MHz, DMSO) δ 12.25 (s, 1 H), 8.39 (q, *J* = 4.8 Hz, 1 H), 8.29 (d, *J* = 2.8 Hz, 1 H), 8.10 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.84-7.78 (m, 2 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 7.50- 7.47 (m, 1 H), 7.42 (dd, *J* = 8.8, 2.8 Hz, 1 H), 3.99 (d, *J* = 12.8 Hz, 2 H), 3.08 (d, *J* = 8.8 Hz, 1 H), 2.87-2.81 (m, 4 H), 2.80 (d, *J* = 4.8 Hz, 3 H), 2.61-2.55 (m, 2 H), 2.31 (t, *J* = 9.6 Hz, 1 H), 1.98-1.96 (m, 1 H), 1.87 (d, *J* = 12.4 Hz, 2 H), 1.78-1.75 (m, 1 H), 1.63-1.55 (m, 4 H).

LCMS (ESI) calcd for C₂₅H₃₀N₆O₂ [M + H]⁺ m/z 447.24, found 447.

Example 5 – Synthesis of Compound 8**Synthesis of INT-5*****Preparation of tert-butyl 4-((2-carbamoylphenyl)carbamoyl)piperidine-1-carboxylate (3)***

To a solution of 2-aminobenzamide **1** (6.00 g, 44.10 mmol) and 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid **2** (10.11 g, 44.10 mmol) in pyridine (50 mL) was added EDCI (8.45 g, 44.10 mmol). then the mixture was stirred for 18 h at room temperature. The reaction mixture was quenched with water, the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers was washed by 1M HCl solution and brine, dried over Na₂SO₄, concentrated under reduced pressure to give product of tert-butyl 4-((2-carbamoylphenyl)carbamoyl)piperidine-1-carboxylate **3** (12.00 g, 79% yield) as a white solid.

LCMS (ESI) calcd for C₁₈H₂₅N₃O₄ [M + Na]⁺ m/z 370.42, found 370.15.

Preparation of tert-butyl 4-(4-oxo-3,4-dihydroquinazolin-2-yl)piperidine-1-carboxylate (4)

To the solution of tert-butyl 4-((2-carbamoylphenyl)carbamoyl)piperidine-1-carboxylate **3** (12.00 g, 34.50 mmol) in Diglyme (80 mL) was added KOH (2.13 g, 37.95 mmol), heated to 140 °C stirred for 2 h, cooled to 0 °C, ice-water (100 mL) added then adjusted pH < 7 using

1M HCl solution, precipitate formed, filtered, the filter cake washed with ice-water (50 mL*3), then dried to give product of tert-butyl 4-(4-oxo-3,4-dihydroquinazolin-2-yl)piperidine-1-carboxylate **4** (11.00 g, 97% yield) as a white solid.

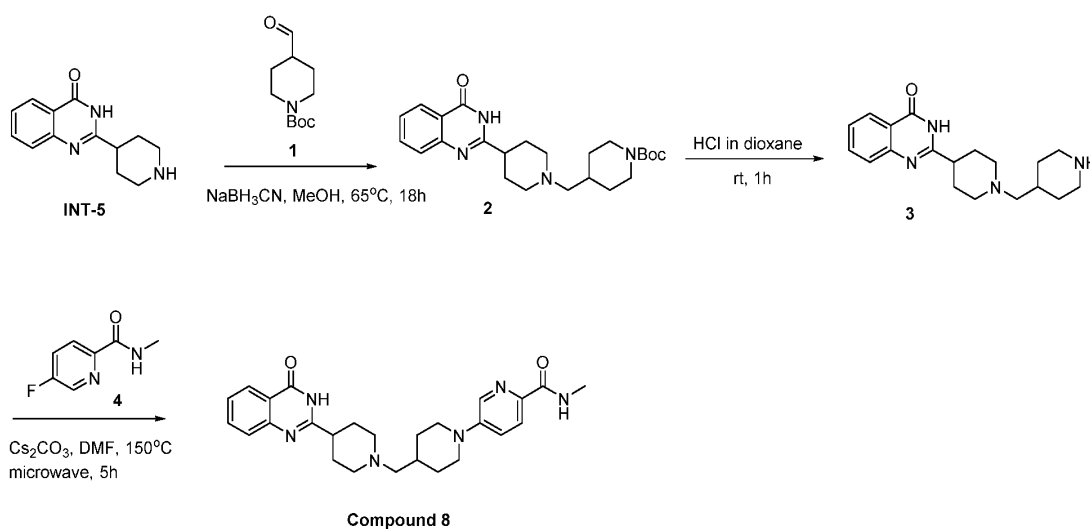
LCMS (ESI) calcd for C₁₈H₂₃N₃O₃ [M + H]⁺ m/z 330.17, found 330.20.

Preparation of 2-(piperidin-4-yl)quinazolin-4(3H)-one (INT-5)

To the solution of tert-butyl 4-(4-oxo-3,4-dihydroquinazolin-2-yl)piperidine-1-carboxylate **4** (3.30 g, 10.00 mmol) in DCM (10 mL) were added TFA (10 mL), stirred for 1 h at room temperature, the mixture was concentrated under reduced pressure to give crude product, ice-water (20 mL) added then adjusted pH > 7 using ammonium hydroxide solution, precipitate formed, filtered, the filter cake washed with ice-water (50 mL*3), then dried to give product of 2-(piperidin-4-yl)quinazolin-4(3H)-one **INT-5** (1.50 g, 66% yield) as a white solid.

LCMS (ESI) calcd for C₁₃H₁₅N₃O [M + H]⁺ m/z 230.12, found 230.20.

Compound 8 Synthesis



Preparation of tert-butyl 4-formylpiperidine-1-carboxylate (2)

To a solution of tert-butyl 4-formylpiperidine-1-carboxylate **1** (837.00 mg, 3.85 mmol) in MeOH (50 mL) was added 2-(piperidin-4-yl) quinazolin-4(3H)-one **INT-5** (300.00 mg, 1.31 mmol). Then two drops of acetic acid and NaBH₃CN (400.00 mg, 6.37 mmol) were added at room temperature. Then the mixture was stirred for 18 h at 65 °C. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 92 : 8) to give tert-

butyl 4-((4-(4-oxo-3,4-dihydroquinazolin-2-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate **2** (500.00 mg, 90% yield) as a white solid.

LCMS (ESI) calcd for C₂₄H₃₄N₄O₃ [M + H]⁺ m/z 427.26, found 427.30.

Preparation of tert-butyl 4-((4-(4-oxo-3,4-dihydroquinazolin-2-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate (3)

To a solution of tert-butyl 4-((4-(4-oxo-3,4-dihydroquinazolin-2-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate **2** (500.00 mg, 1.17 mmol) in MeOH (5 mL) was added 4M HCl-Dioxane (10 mL) at room temperature. The reaction mixture stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give 2-(1-(piperidin-4-ylmethyl) piperidin-4-yl) quinazolin-4(3H)-one **3** (350.00 mg, 87% yield) as a white solid.

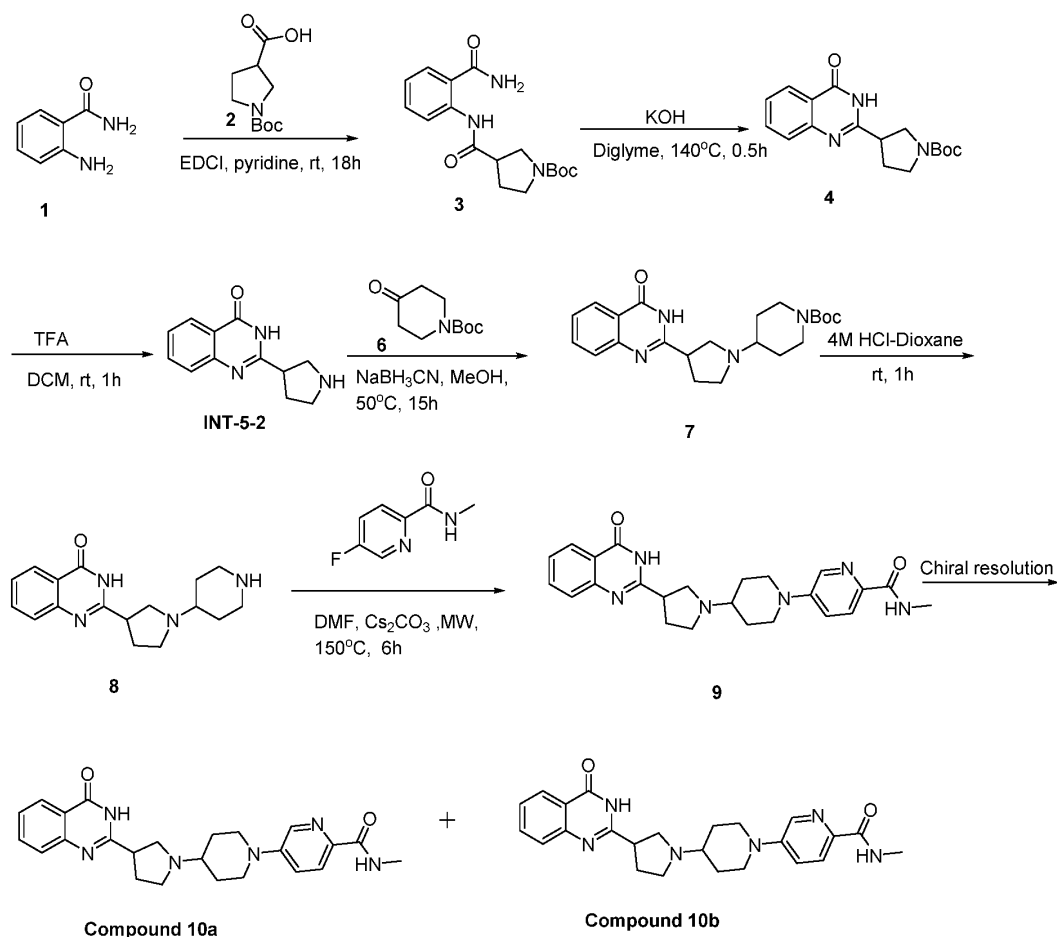
LCMS (ESI) calcd for C₁₉H₂₆N₄O [M + H]⁺ m/z 327.21, found 327.15.

Preparation of N-methyl-5-(4-((4-(4-oxo-3,4-dihydroquinazolin-2-yl)piperidin-1-yl)methyl)piperidin-1-yl)picolinamide (Compound 8)

To a solution of 2-(1-(piperidin-4-ylmethyl)piperidin-4-yl)quinazolin-4(3H)-one **3** (300.00 mg, 0.92 mmol) in DMF (5 mL) was added 5-fluoro-N-methylpicolinamide **4** (354.14 mg, 2.30 mmol). Then Cs₂CO₃ (2994.20 mg, 9.19 mmol) was added at room temperature. The reaction mixture was irradiated in a microwave reactor at 150 °C for 5 h. the reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (columns: Gemini 5 um C18 150 × 21.2 mm, mobile phase: ACN - H₂O (0.1% FA), gradient: 15-25) to give N-methyl-5-(4-((4-(4-oxo-3,4-dihydroquinazolin-2-yl)piperidin-1-yl)methyl)piperidin-1-yl)picolinamide **Compound 8** (100 mg, 98% purity, 24% yield) as a white sold.

LCMS (ESI) calcd for C₂₆H₃₂N₆O₂ [M + H]⁺ m/z 461.26, found 461.20.

¹H NMR (400 MHz, DMSO) δ 12.13 (s, 1 H), 8.37 (d, *J* = 4.8 Hz, 1 H), 8.26 (d, *J* = 2.8 Hz, 1 H), 8.08 (d, *J* = 7.6 Hz, 1 H), 7.82-7.76 (m, 2 H), 7.60 (d, *J* = 8.0 Hz, 1 H), 7.50-7.35 (m, 2 H), 3.91 (d, *J* = 12.4 Hz, 2 H), 2.95 (d, *J* = 10.8 Hz, 2 H), 2.89-2.75 (m, 5 H), 2.62-2.53 (m, 1 H), 2.18 (d, *J* = 6.4 Hz, 2 H), 1.98-1.73 (m, 9 H), 1.23-1.17 (m, 2 H).

Example 6 – Synthesis of Compound 10**Compound 10 Synthesis****Preparation of tert-butyl 3-((2-carbamoylphenyl)carbamoyl)pyrrolidine-1-carboxylate (**3**)**

To a solution of 2-aminobenzamide **1** (6.00 g, 44.10 mmol) and 1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid **2** (9.49 g, 44.10 mmol) in pyridine (50 mL) was added EDCI (8.45 g, 44.10 mmol). then the mixture was stirred for 18 h at room temperature. The reaction mixture was quenched with water and the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers was washed by 1M HCl solution and brine, dried over Na₂SO₄, concentrated under reduced pressure to give tert-butyl 3-((2-carbamoylphenyl)carbamoyl)pyrrolidine-1-carboxylate **3** (12.00 g, 77% yield) as a white solid.

LCMS (ESI) calcd for C₁₇H₂₃N₃O₄ [M + Na]⁺ m/z 356.17, found 356.00.

Preparation of tert-butyl 3-(4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidine-1-carboxylate (4)

To the solution of tert-butyl 3-((2-carbamoylphenyl)carbamoyl)pyrrolidine-1-carboxylate **3** (12.00 g, 36.04 mmol) in Diglyme (80 mL) was added KOH (2.42 g, 43.25 mmol), heated to 140 °C stirred for 0.5 h, cooled to 0 °C, ice-water (100 mL) added then adjusted pH < 7 using 1M HCl solution, precipitate formed, filtered, the filter cake washed with ice-water (50 mL*3), then dried to give product of tert-butyl 3-(4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidine-1-carboxylate **4** (10.00 g, 83% yield) as a white solid.

LCMS (ESI) calcd for C₁₇H₂₁N₃O₃ [M + H]⁺ m/z 316.16, found 316.05.

Preparation of 2-(pyrrolidin-3-yl)quinazolin-4(3H)-one (INT-5-2)

To the solution of tert-butyl 3-(4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidine-1-carboxylate **4** (10.00 g, 31.75 mmol) in DCM (20 mL) was added TFA (20 mL), stirred for 1 h at room temperature, the mixture was concentrated under reduced pressure to give crude product, ice-water (20 mL) added then adjusted pH > 7 using ammonium hydroxide solution, precipitate formed, filtered, the filter cake washed with ice-water (50 mL*3), then dried to give product of 2-(pyrrolidin-3-yl)quinazolin-4(3H)-one **INT-5-2** (8.00 g, 80% yield) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ 8.14-8.07 (m, 1 H), 7.87-7.76 (m, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.57-7.44 (m, 1 H), 3.76-3.61 (m, 1 H), 3.61-3.49 (m, 2 H), 3.43-3.33 (m, 1 H), 3.29 (dt, *J* = 11.4, 5.6 Hz, 1 H), 2.37 (td, *J* = 14.0, 7.1 Hz, 1 H), 2.21 (td, *J* = 13.5, 7.2 Hz, 1 H).

LCMS (ESI) calcd for C₁₂H₁₃N₃O [M - H]⁻ m/z 216.11, found 215.95.

Preparation of tert-butyl 4-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidin-1-yl)piperidine-1-carboxylate (7)

To a solution of 2-(pyrrolidin-3-yl)quinazolin-4(3H)-one **INT-5-2** (600.00 mg, 2.79 mmol) in MeOH (30 mL) was added tert-butyl 4-oxopiperidine-1-carboxylate **6** (1.67 g, 8.36 mmol), then two drops of acetic acid and NaBH₃CN (1.05 g, 16.72 mmol) were added at room temperature. The reaction mixture stirred at 50 °C for 18 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 93 : 7) to give tert-butyl 4-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidin-1-yl)piperidine-1-carboxylate **7** (400 mg, 34%

yield) as a white solid.

LCMS (ESI) calcd for C₂₂H₃₀N₄O₃ [M + H]⁺ m/z 399.23, found 399.30.

Preparation of 2-(1-(piperidin-4-yl)pyrrolidin-3-yl)quinazolin-4(3H)-one (8)

Tert-butyl 4-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidin-1-yl)piperidine-1-carboxylate **7** (400 mg, 0.81 mmol) was added to HCl in dioxane (4 M, 10 mL), stirred for 1 h at room temperature, the reaction mixture was concentrated under reduced pressure to give 2-(1-(piperidin-4-yl)pyrrolidin-3-yl)quinazolin-4(3H)-one **8** (200.00 mg, 79% yield) as a white solid.

LCMS (ESI) calcd for C₁₇H₂₂N₄O [M + H]⁺ m/z 299.18, found 299.25.

Preparation of N-methyl-5-(4-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide (9)

To a solution 2-(1-(piperidin-4-yl)pyrrolidin-3-yl)quinazolin-4(3H)-one **8** (200.00 mg, 0.67 mmol) in DMF (10 mL) was added Cs₂CO₃ (2.18 g, 6.70 mmol) and 5-fluoro-N-methylpicolinamide **9** (432.44 mg, 2.01 mmol). The mixture was stirred for 6 h under 150 °C using microwave. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 92 : 8) to N-methyl-5-(4-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide **9** (100 mg, 95% purity, 33 % yield) as a yellow solid.

LCMS (ESI) calcd for C₂₄H₂₈N₆O₂ [M + H]⁺ m/z 433.23, found 433.25.

Chiral resolution of N-methyl-5-(4-(3-(4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide (9)

Compound **9** was separated by SFC (Column: Daicel CHIRALPAK OJ -H 250 mm × 20 mm I.D., 5 μmm; Mobile phase: CO₂/MeOH[0.1%(NH₃)] = 70/30) and concentrated under reduced pressure to afford the first fraction as **Compound 10a** (16.4. mg, 100% purity, ee%: 100, off-white solid) and the second fraction as **Compound 10b** (12.3 mg, 100% purity, ee%: 100, off-white solid)

Compound 10a

¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ 12.16 (s, 1 H), 8.40-8.37 (m, 1 H), 8.27 (d, *J* = 2.8 Hz, 1 H), 8.07 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.82-7.75 (m, 2 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.48-7.44 (m, 1 H), 7.40 (dd, *J* = 8.8, 2.8 Hz, 1 H), 3.82 (d, *J* = 12.8 Hz, 2 H), 3.07 (t, *J* = 8.6 Hz, 2 H),

2.95 (t, $J = 10.8$ Hz, 2 H), 2.86-2.79 (m, 2 H), 2.78-2.77 (m, 3 H), 2.69-2.63 (m, 1 H), 2.33-2.32 (m, 1H), 2.20-2.13 (m, 2 H), 1.96-1.93 (m, 2 H), 1.58-1.47 (m, 2 H).

LCMS (ESI) calcd for $C_{24}H_{28}N_6O_2$ $[M + H]^+$ m/z 433.23, found 433.20.

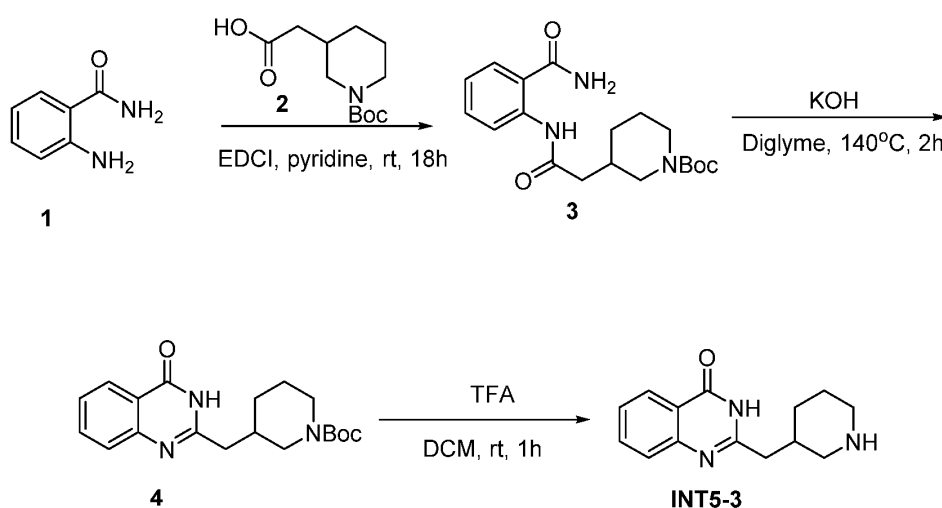
Compound 10b

^1H NMR (400 MHz, DMSO- d_6 , ppm) δ 8.39-8.38 (m, 1 H), 8.28 (d, $J = 3.2$ Hz, 1 H), 8.08 (dd, $J = 7.6, 1.6$ Hz, 1 H), 7.83-7.76 (m, 2 H), 7.61 (d, $J = 8.0$ Hz, 1 H), 7.47 (t, $J = 7.6$ Hz, 1 H), 7.40 (dd, $J = 8.8, 2.8$ Hz, 1 H), 3.83 (d, $J = 12.8$ Hz, 2 H), 3.09 (d, $J = 8.4$ Hz, 2 H), 2.95 (t, $J = 12.4$ Hz, 2 H), 2.88-2.79 (m, 2 H), 2.79 (d, $J = 4.8$ Hz, 3 H), 2.68-2.66 (m, 1 H), 2.39-2.31 (m, 1H), 2.21-2.14 (m, 2 H), 1.97-1.94 (m, 2 H), 1.59-1.47 (m, 2 H).

LCMS (ESI) calcd for $C_{24}H_{28}N_6O_2$ $[M + H]^+$ m/z 433.23, found 433.20.

Example 7 – Synthesis of Compound 14

Preparation of INT5-3



Preparation of tert-butyl 3-(2-((2-carbamoylphenyl)amino)-2-oxoethyl)piperidine-1-carboxylate (3)

To a solution of 2-aminobenzamide **1** (2.80 g, 20.60 mmol) and 2-(1-(tert-butoxycarbonyl)

piperidin-3-yl)acetic acid **2** (5.00 g, 20.60 mmol) in pyridine (50 mL) was added EDCI (3.95 g, 20.60 mmol). then the mixture was stirred for 18 h at room temperature. The reaction mixture was quenched with water, the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers was washed with 1M HCl solution and brine, dried over Na₂SO₄, concentrated under reduced pressure to give product of tert-butyl 3-(2-((2-carbamoylphenyl)amino)-2-oxoethyl)piperidine-1-carboxylate **3** (7.00 g, 94% yield) as a white solid .

LCMS (ESI) calcd for C₁₉H₂₇N₃O₄ [M + H]⁺ m/z 362.20, found 362.25.

Preparation of tert-butyl 3-((4-oxo-3,4-dihydroquinazolin-2-yl)methyl)piperidine-1-carboxylate (4)

To the solution of tert-butyl 3-(2-((2-carbamoylphenyl)amino)-2-oxoethyl)piperidine-1-carboxylate **3** (7.60 g, 21.00 mmol) in Diglyme (80 mL) was added KOH (1.18 g, 21.00 mmol), heated to 140 °C stirred for 2 h, cooled to 0 °C, ice-water (100 mL) added then adjusted pH < 7 using 1M HCl solution, precipitate formed, filtered, the filter cake washed with ice-water (50 mL*3), then dried to give product of tert-butyl 3-((4-oxo-3,4-dihydroquinazolin-2-yl)methyl)piperidine-1-carboxylate **4** (6.80 g, 94% yield) as a white solid .

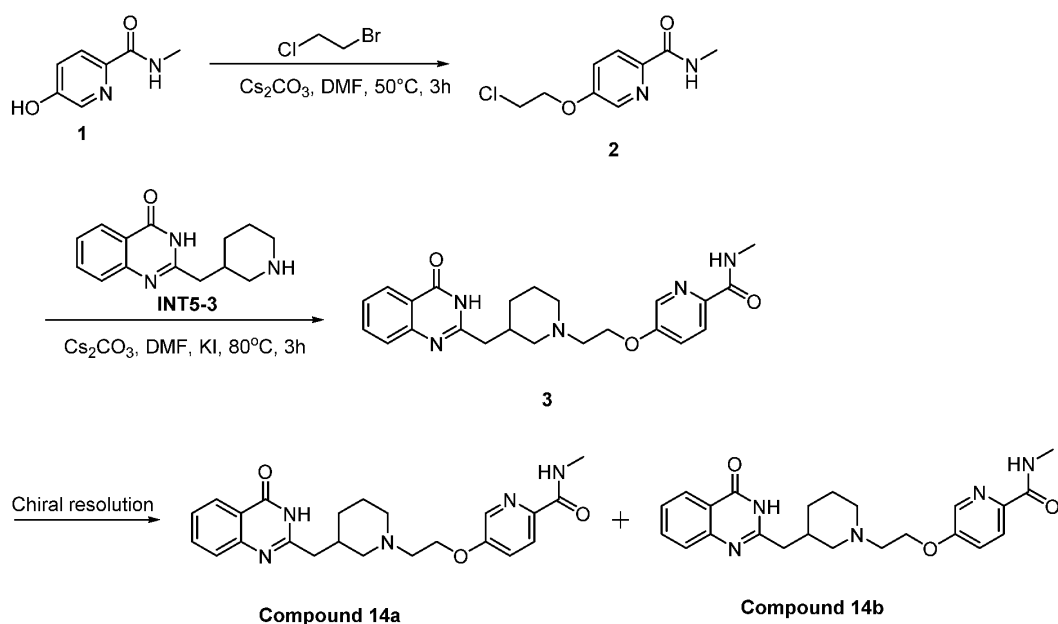
LCMS (ESI) calcd for C₁₉H₂₅N₃O₃ [M + H]⁺ m/z 344.19, found 344.15.

Preparation of 2-(piperidin-3-ylmethyl)quinazolin-4(3H)-one (INT-5-3)

To a solution of tert-butyl 3-((4-oxo-3,4-dihydroquinazolin-2-yl)methyl)piperidine-1-carboxylate **4** (2.00 g, 5.80 mmol) in DCM (10 mL) were added TFA (10 mL) , stirred for 1 h at room temperature, the mixture was concentrated under reduced pressure to give crude product, ice-water (20 mL) added then adjusted pH > 7 using ammonium hydroxide solution, precipitate formed, filtered, the filter cake washed with ice-water (50 mL*3), then dried to give product of 2-(piperidin-3-ylmethyl)quinazolin-4(3H)-one **INT-5-3** (1.20 g, 85% yield) as a white solid .

LCMS (ESI) calcd for C₁₄H₁₇N₃O [M + H]⁺ m/z 244.14, found 244.20.

Compound 14 Synthesis

**Preparation of tert-butyl 4-((2-carbamoylphenyl)carbamoyl)piperidine-1-carboxylate (2)**

To a solution of 5-hydroxy-N-methylpicolinamide **1** (500.00 mg, 3.29 mmol) and Cs_2CO_3 (3.22 g, 9.87 mmol) in DMF (15 mL) was added 1-bromo-2-chloroethane **2** (943.64 mg, 6.58 mmol). then the mixture was stirred for 3 h at 50 °C. The reaction mixture was quenched with water, aqueous layer was extracted with EtOAc (50 mL x 3), the combined organic layers was concentrated under reduced pressure. the residue was purified by flash chromatography (eluting with PE/ EtOAc = 100 : 0 to 80 : 20) to give tert-butyl 4-((2-carbamoylphenyl)carbamoyl)piperidine-1-carboxylate **2** (500.00 mg, 71% yield) as a colorless oil.

LCMS (ESI) calcd for $\text{C}_9\text{H}_{11}\text{ClN}_2\text{O}_2$ $[\text{M} + \text{H}]^+ m/z$ 215.05, found 215.00.

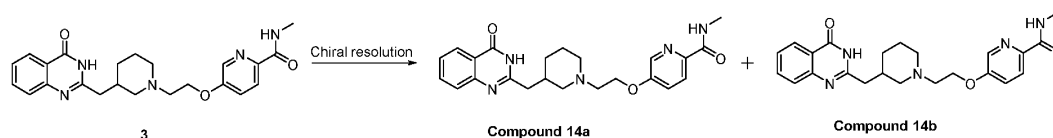
Preparation of N-methyl-5-(2-(3-((4-oxo-3,4-dihydroquinazolin-2-yl)methyl)piperidin-1-yl)ethoxy)picolinamide (3)

To a solution of tert-butyl 4-((2-carbamoylphenyl)carbamoyl)piperidine-1-carboxylate **2** (500.00 mg, 2.33 mmol) and Cs_2CO_3 (2.28 g, 6.99 mmol) in DMF (15 mL) were added 2-(piperidin-3-ylmethyl)quinazolin-4(3H)-one **INT5-3** (566.91 mg, 2.33 mmol) and KI (1.16 g, 6.99 mmol). then the mixture was stirred for 3 h at 80 °C. The reaction mixture was quenched

with water, aqueous layer was extracted with EtOAc (50 mL x 3), the combined organic layers was concentrated under reduced pressure. the residue was purified by flash chromatography (eluting with DCM/ MeOH = 100 : 0 to 92 : 8) to give N-methyl-5-(2-(3-((4-oxo-3,4-dihydroquinazolin-2-yl)methyl)piperidin-1-yl)ethoxy)picolinamide **3** (200.00 mg, 20% yield) as a yellow solid.

LCMS (ESI) calcd for C₂₃H₂₇N₅O₃ [M + H]⁺ m/z 422.21, found 422.10.

Chiral resolution of N-methyl-5-(2-(3-((4-oxo-3,4-dihydroquinazolin-2-yl)methyl)piperidin-1-yl)ethoxy)picolinamide (Compound 14)



Compound **3** was separated by SFC (Column: Daicel CHIRALPAK OJ -H 250 mm × 20 mm I.D., 5 μm; Mobile phase: CO₂/MeOH[0.1%(FA)] = 70/30) and concentrated under reduced pressure to afford the first fraction as **Compound 14a** (31.6 mg, 100% purity, ee%: 100, white solid) and the second fraction as **Compound 14b** (28.1 mg, 99% purity, ee%: 99, white solid)

Compound 14a

¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ 12.15 (s, 1 H), 8.53 (q, *J* = 9.6, 4.8 Hz, 1 H), 8.23 (d, *J* = 2.8 Hz, 1 H), 8.07 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.92 (d, *J* = 8.8 Hz, 1 H), 7.79-7.73 (m, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 7.49-7.42 (m, 2 H), 4.18 (t, *J* = 5.6 Hz, 2 H), 2.90-2.81 (m, 2 H), 2.79 (d, *J* = 4.8 Hz, 3 H), 2.73-2.65 (m, 2 H), 2.55-2.51 (m, 2 H), 2.17-2.00 (m, 2 H), 1.93-1.85 (m, 1 H), 1.70-1.59 (m, 2 H), 1.51-1.38 (m, 1 H), 1.02-0.99 (m, 1 H).

LCMS (ESI) calcd for C₂₃H₂₇N₅O₃ [M + H]⁺ m/z 422.21, found 422.25.

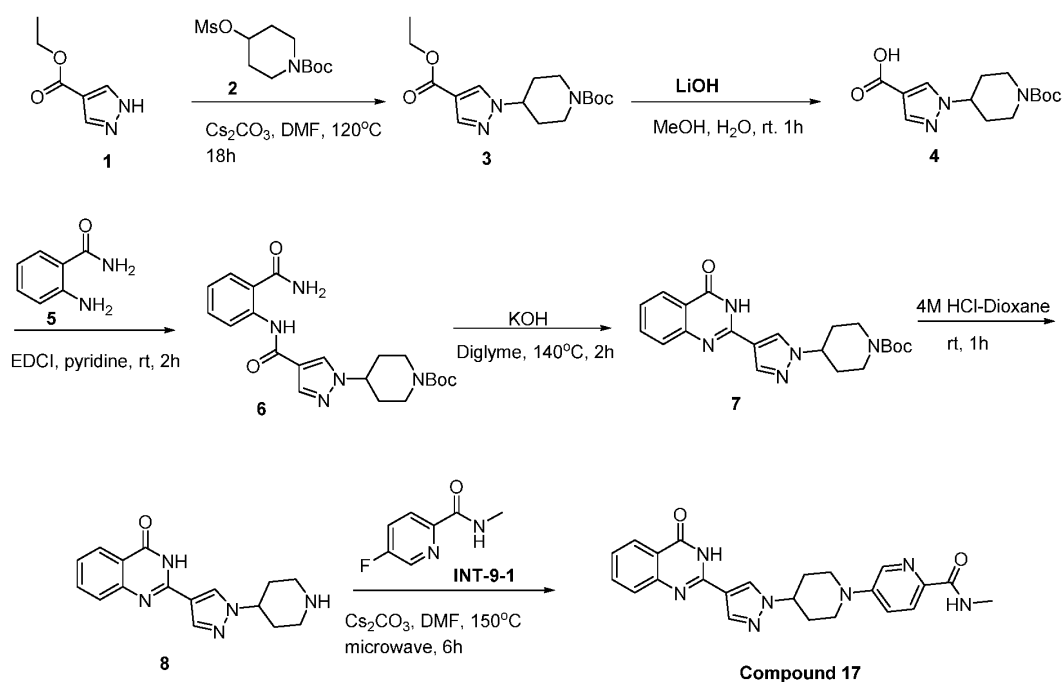
Compound 14b

¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ 12.15 (s, 1 H), 8.53 (q, *J* = 9.6, 4.8 Hz, 1 H), 8.23 (d, *J* = 2.8 Hz, 1 H), 8.07 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.92 (d, *J* = 8.8 Hz, 1 H), 7.79-7.73 (m, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 7.49-7.42 (m, 2 H), 4.18 (t, *J* = 5.6 Hz, 2 H), 2.90-2.81 (m, 2 H), 2.79 (d, *J* = 4.8 Hz, 3 H), 2.73-2.65 (m, 2 H), 2.55-2.51 (m, 2 H), 2.17-2.00 (m, 2 H), 1.93-1.85 (m, 1 H), 1.70-1.59 (m, 2 H), 1.51-1.38 (m, 1 H), 1.02-0.99 (m, 1 H).

LCMS (ESI) calcd for C₂₃H₂₇N₅O₃ [M + H]⁺ m/z 422.21, found 422.25.

Example 8 – Synthesis of Compound 17

Compound 17 Synthesis



Preparation of tert-butyl 4-(4-(ethoxycarbonyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (3)

To a solution of ethyl 1H-pyrazole-4-carboxylate **1** (2.00 g, 14.30 mmol) and tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate **2** (4.99 g, 17.87 mmol) in DMF (60 mL) was added Cs₂CO₃ (10.02 g, 30.74 mmol). Then the mixture was stirred for 18 h at 120 °C. The reaction mixture was quenched with water, the aqueous layer was extracted with EtOAc (200 mL x 3). The combined organic layer was washed with brine, dried over Na₂SO₄, concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 95 : 5) to give product of tert-butyl 4-(4-(ethoxycarbonyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate **3** (2.00 g, 41% yield) as a white solid.

LCMS (ESI) calcd for C₁₆H₂₅N₃O₄ [M + H]⁺ m/z 324.18, found 324.20.

Preparation of 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-pyrazole-4-carboxylic acid (4)

To a solution of tert-butyl 4-(4-(ethoxycarbonyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate **3** (1.50 g, 4.80 mmol) in MeOH/H₂O = 1 : 1 (40 mL) was added LiOH (460.00 mg, 19.20 mmol). The mixture was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure at 40 °C to obtain residue. To this was added water and acidified with 1 M aqueous HCl to adjust pH= 4 ~ 5 at 0 °C, the aqueous layer was extracted with EtOAc (200 mL x 3). The combined organic layer was washed with brine, dried over Na₂SO₄, concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 95 : 5) to give 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-pyrazole-4-carboxylic acid **4** (1.00 g, 67% yield) as a white solid .

LCMS (ESI) calcd for C₁₄H₂₁N₃O₄ [M - 56 + H]⁺ m/z 240.15, found 240.20.

¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ 12.29 (s, 1 H), 8.30 (s, 1H), 7.81 (s, 1 H), 4.52-4.30 (m, 1 H), 4.03 (d, *J* = 11.2 Hz, 2 H), 2.88 (s, 2 H), 1.99 (d, *J* = 12.4 Hz, 2 H), 1.78 (dt, *J* = 12.4, 8.0 Hz, 2 H), 1.41 (s, 9 H).

Preparation of tert-butyl 4-(4-((2-carbamoylphenyl)carbamoyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (6)

To a solution of 2-aminobenzamide **5** (299.66 mg, 2.20 mmol) and 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-pyrazole-4-carboxylic acid **4** (650.00 mg, 2.20 mmol) in pyridine (25 mL) was added EDCI (421.91 mg, 2.20 mmol). then the mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with water, the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers was washed by 1M HCl solution and brine, dried over Na₂SO₄, concentrated under reduced pressure to give product of tert-butyl 4-(4-((2-carbamoylphenyl)carbamoyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate **6** (720.00 mg, 71% yield) as a white solid .

LCMS (ESI) calcd for C₂₁H₂₇N₅O₄ [M + H]⁺ m/z 414.21, found 414.25.

Preparation of tert-butyl 4-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (7)

To the solution of tert-butyl 4-(4-((2-carbamoylphenyl)carbamoyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate **6** (700.00 mg, 1.69 mmol) in Diglyme (15 mL) was added KOH (113.99 mg, 2.03 mmol), heated to 140 °C stirred for 2 h, cooled to 0 °C, ice-water (10 mL) added then adjusted pH < 7 using 1M HCl solution, precipitate formed, filtered, the filter cake

washed with ice-water (50 mL*3), then dried to give product of tert-butyl 4-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate **7** (600 mg, 67% yield) as a white solid.

LCMS (ESI) calcd for $C_{21}H_{25}N_5O_3$ $[M + H]^+$ m/z 396.20, found 396.25.

Preparation of 2-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)quinazolin-4(3H)-one (8)

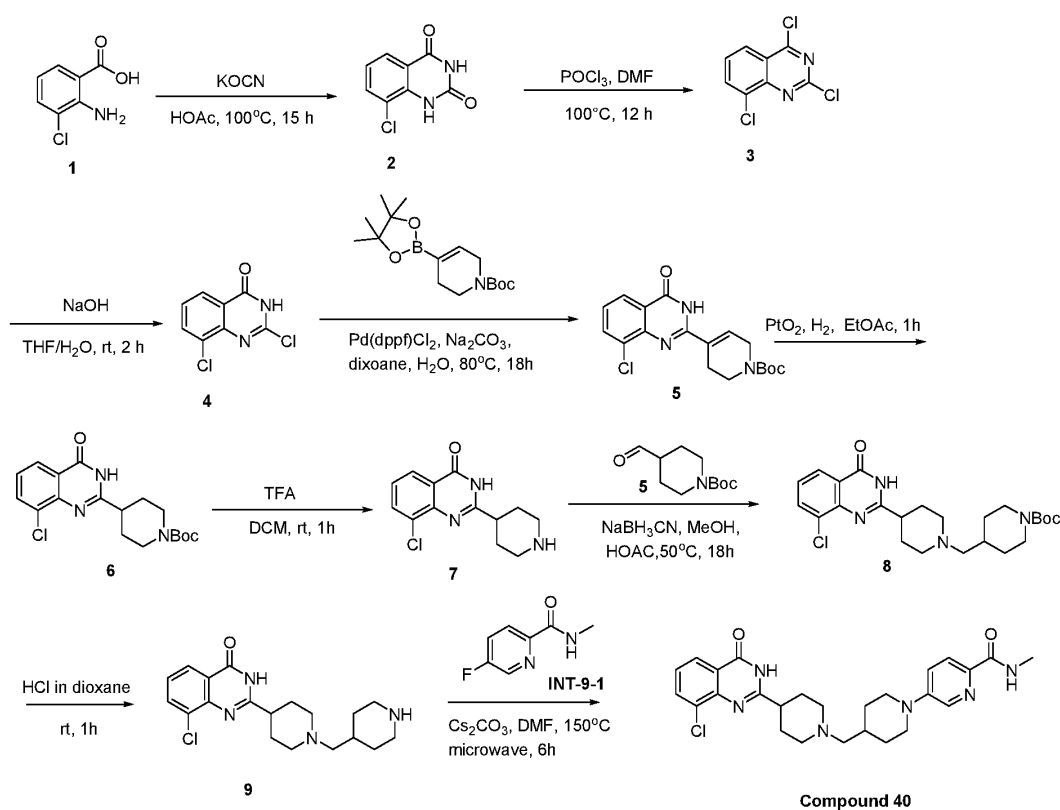
To a solution of tert-butyl 4-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate **7** (350.00 mg, 0.88 mmol) at room temperature was added HCl-Dioxane (4 M, 40 mL). The reaction mixture was stirred at room temperature for 1h. After reaction completed, the mixture was concentrated under reduced pressure to obtain crude 2-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)quinazolin-4(3H)-one **8** (200 mg, 73% yield) as a white solid. LCMS (ESI) calcd for $C_{16}H_{17}N_5O$ $[M + H]^+$ m/z 296.14, found 296.25.

Preparation of N-methyl-5-(4-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)-1H-pyrazol-1-yl)piperidin-1-yl)picolinamide (Compound 17)

To a solution 2-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)quinazolin-4(3H)-one **8** (200.00 mg, 0.68 mmol) in DMF (10 mL) was added Cs_2CO_3 (2.21 g, 6.77 mmol) and 5-fluoro-N-methylpicolinamide **INT-9-1** (260.96 mg, 1.69 mmol). The mixture was stirred for 6 h under 150 °C using microwave. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 92 : 8) to give crude product which was purified by prep-HPLC (Gemini 5um C18 150 × 21.2 mm, mobile phase: ACN - H₂O (0.1% FA), gradient: 25 - 75) to give N-methyl-5-(4-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)-1H-pyrazol-1-yl)piperidin-1-yl)picolinamide **Compound 17** (30 mg, 98% purity, 9% yield) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ 12.30 (s, 1 H), 8.67 (s, 1 H), 8.43-8.40 (m, 1 H), 8.35 (d, *J* = 2.8 Hz, 1 H), 8.26 (s, 1 H), 8.09 (d, *J* = 8.0 Hz, 1 H), 7.85 (d, *J* = 8.8 Hz, 1 H), 7.80-7.76 (m, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.50-7.42 (m, 2 H), 4.56-4.53 (m, 1 H), 4.08 (d, *J* = 12.8 Hz, 2 H), 3.10 (t, *J* = 11.6, 10.8 Hz, 2 H), 2.79 (d, *J* = 4.8 Hz, 3 H), 2.19-2.17 (m, 2 H), 2.06-1.98 (m, 2 H).

LCMS (ESI) calcd for $C_{23}H_{23}N_7O_2$ $[M + H]^+$ m/z 430.19, found 430.25.

Example 9 – Synthesis of Compound 40**Compound 40 Synthesis****Preparation of 8-chloroquinazoline-2,4(1H,3H)-dione (2)**

To a solution of 2-amino-3-chlorobenzoic acid **1** (10.00 g, 58.30 mmol) in HOAc (100 mL) was added KOCN (14.19 g, 174.90 mmol) slowly at room temperature. The mixture was heated to 100 °C stirred for 15 hours, cooled to 0 °C, ice-water (30 mL) added. The precipitate was collected by filtration, washed with petroleum ether:EtOAc = 5:1 (100 mL), filtered to provide 8-chloroquinazoline-2,4(1H,3H)-dione **2** (5.00 g, 40% yield) as a white solid which was used directly in next step without further purification.

LCMS (ESI) calcd for C₈H₅ClN₂O₂ [M + H]⁺ m/z 197.00, found 196.95.

Preparation of 2,4,8-trichloroquinazoline (3)

To a solution of 8-chloroquinazoline-2,4(1H,3H)-dione **2** (5.00 g, 25.40 mmol) in POCl₃ (45 mL) was added DMF (3 mL) slowly at room temperature. The mixture was heated to 100 °C for 12 hours. The resulting mixture was diluted with ice water (200 mL) and extracted with EtOAc (400 mL x 3). The combine organic phases were washed with brine, dried over sodium sulfate, concentrated and purified by silica gel column chromatography (eluting with EtOAc/petroleum ether, 100: 0 to 50 :50) to give 2,4,8-trichloroquinazoline **3** (2.00 g, 32% yield) as a white solid.

LCMS (ESI) calcd for C₈H₃Cl₃N₂ [M + H]⁺ m/z 232.94, found 232.90.

Preparation of 2,8-dichloroquinazolin-4(3H)-one (4)

To a solution of 2,4,8-trichloroquinazoline **3** (2.00 g, 8.60 mmol) in THF/H₂O = 1:1 (200 mL) was added NaOH (690 mg, 17.20 mmol). The mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure at 40 °C to obtain residue. To this was added water and acidified with 1 M aqueous HCl to adjust pH 4 ~ 5 at 0 °C. The mixture was extracted with EtOAc (200 mL x 3). The combined organic phases were washed with brine (100 mL x 3), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by Flash chromatography (eluent: DCM/MeOH =100: 0 to 95 :5) to afford 2,8-dichloroquinazolin-4(3H)-one **4** (1.60 g, 82% yield) as a white solid.

LCMS (ESI) calcd for C₈H₄Cl₂N₂O [M + H]⁺ m/z 214.97, found 214.95.

Preparation of tert-butyl 4-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (5)

To a solution of 2,8-dichloroquinazolin-4(3H)-one **4** (400 mg, 1.86 mmol) in Dioxane/H₂O=10:1 (40 mL) were added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (690 mg, 2.23 mmol), Pd(dppf)Cl₂ (50 mg, 0.07 mmol) and Na₂CO₃ (591 mg, 5.58 mmol) successively at room temperature. The reaction mixture was stirred at 80 °C for 18 h under N₂. The mixture was diluted with water (50 mL) and extracted with EtOAc (100 mL x 3). The combined organic layer was washed with brine (100 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuo to get crude product, which was purified by flash column chromatography (PE/EtOAc = 100: 0 to 20: 80) to afford tert-butyl 4-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate **5** (550 mg, 77% yield) as a yellow solid.

LCMS (ESI) calcd for C₁₈H₂₀ClN₃O₃ [M + H]⁺ m/z 362.12, found 362.10.

Preparation of tert-butyl 4-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)piperidine-1-carboxylate (6)

To a solution of tert-butyl 4-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate **5** (550 mg, 1.52 mmol) in EtOAc (200 mL) was added PtO_2 (110 mg). The mixture was evacuated and backfilled with hydrogen three times and then charged with hydrogen. The resulting mixture was stirred at room temperature for 1 hour. Then the mixture was filtered through celite and concentrated under vacuum to give crude product, which was purified by flash column chromatography (PE/EtOAc = 100: 0 to 50: 50) to afford tert-butyl 4-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)piperidine-1-carboxylate **6** (400 mg, 65% yield) as a yellow solid.

LCMS (ESI) calcd for $\text{C}_{18}\text{H}_{22}\text{ClN}_3\text{O}_3$ $[\text{M} + \text{H}]^+$ m/z 364.13, found 364.10.

Preparation of 8-chloro-2-(piperidin-4-yl)quinazolin-4(3H)-one (7)

To a solution of tert-butyl 4-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)piperidine-1-carboxylate **6** (400 mg, 1.21 mmol) in DCM (5 mL) was added TFA (2 mL), stirred for 1 h at room temperature, the mixture was concentrated under reduced pressure to give crude product, ice-water (2 mL) added then adjusted pH > 7 using ammonium hydroxide solution, precipitate formed, filtered, the filter cake washed with ice-water (5 mL*3), then dried to give product of 8-chloro-2-(piperidin-4-yl)quinazolin-4(3H)-one **7** (300 mg, 89% yield) as a white solid.

LCMS (ESI) calcd for $\text{C}_{13}\text{H}_{14}\text{ClN}_3\text{O}$ $[\text{M} + \text{H}]^+$ m/z 264.08, found 264.10.

Preparation of tert-butyl 4-((4-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate (8)

To a solution of 8-chloro-2-(piperidin-4-yl)quinazolin-4(3H)-one **7** (300 mg, 1.14 mmol) in MeOH (60 mL) was added tert-butyl 4-oxopiperidine-1-carboxylate (727 mg, 3.41 mmol), then two drops of acetic acid and NaBH_3CN (428 mg, 6.82 mmol) were added at room temperature. The reaction mixture stirred at 50 °C for 18 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 90 : 10) to give tert-butyl 4-((4-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate **8** (300 mg, 51% yield) as a white solid.

LCMS (ESI) calcd for $\text{C}_{24}\text{H}_{33}\text{ClN}_4\text{O}_3$ $[\text{M} + \text{H}]^+$ m/z 361.17, found 361.05.

Preparation of 8-chloro-2-(1-(piperidin-4-ylmethyl)piperidin-4-yl)quinazolin-4(3H)-one (9)

Tert-butyl 4-((4-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)piperidin-1-yl)methyl)piperidine-1-carboxylate **8** (300 mg, 0.65 mmol) was added to HCl in dioxane (4 M, 30 mL), stirred for 1 h at room temperature, the reaction mixture was concentrated under reduced pressure to give 8-chloro-2-(1-(piperidin-4-ylmethyl)piperidin-4-yl)quinazolin-4(3H)-one **9** (200 mg, 81% yield) as a white solid.

LCMS (ESI) calcd for C₁₉H₂₅ClN₄O [M + H]⁺ m/z 361.17, found 361.05.

Preparation of 5-(4-((4-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)piperidin-1-yl)methyl)piperidin-1-yl)-N-methylpicolinamide (Compound 40)

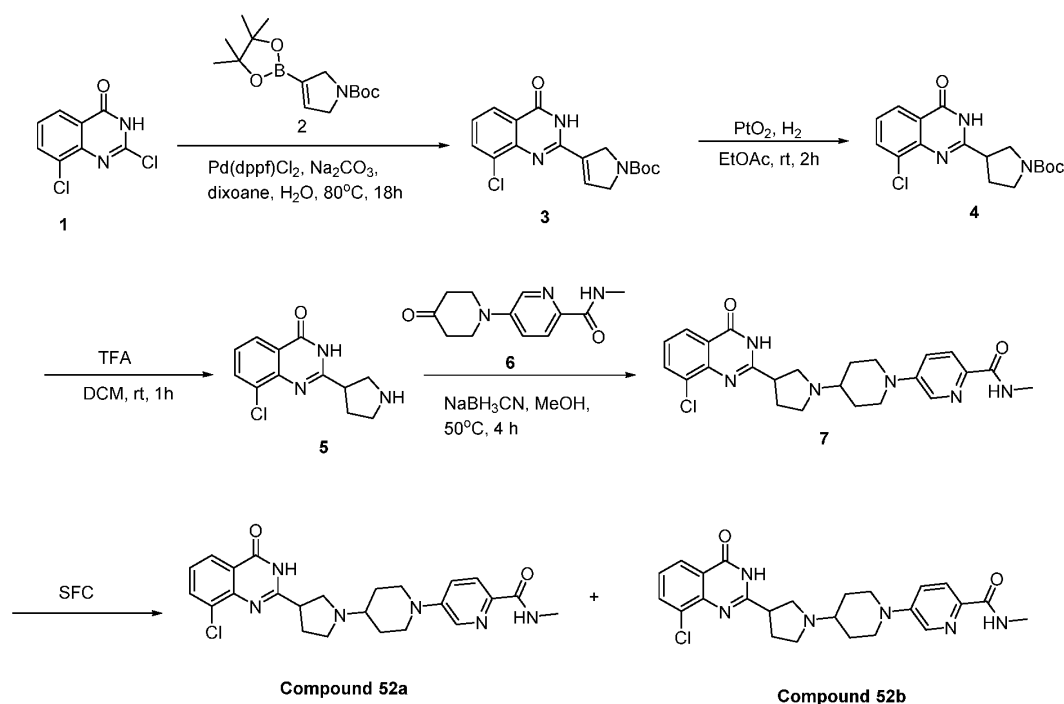
To a solution 8-chloro-2-(1-(piperidin-4-ylmethyl)piperidin-4-yl)quinazolin-4(3H)-one **9** (150 mg, 0.42 mmol) in DMF (10 mL) were added Cs₂CO₃ (1.35 g, 4.16 mmol) and 5-fluoro-N-methylpicolinamide **INT-9-1** (160 mg, 1.03 mmol). The mixture was stirred for 6 h under 150 °C using microwave. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 90 : 10) to give crude 5-(4-((4-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)piperidin-1-yl)methyl)piperidin-1-yl)-N-methylpicolinamide **Compound 40** as a yellow solid. The crude product was purified by prep-HPLC (Gemini 5um C18 150 × 21.2 mm, mobile phase: ACN - H₂O (0.1% FA), gradient: 20 - 80) to give 5-(4-((4-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)piperidin-1-yl)methyl)piperidin-1-yl)-N-methylpicolinamide **Compound 40** (24.2 mg, 96% purity, 11% yield) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ 12.39 (s, 1 H), 8.40-8.37 (m, 1 H), 8.26 (d, *J* = 2.8 Hz, 1 H), 8.04 (dd, *J* = 7.6, 1.2 Hz, 1 H), 7.94 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.81 (d, *J* = 8.8 Hz, 1 H), 7.46-7.36 (m, 2 H), 3.91 (d, *J* = 12.8 Hz, 2 H), 2.97-2.94 (m, 2 H), 2.86-2.81 (m, 2 H), 2.77 (d, *J* = 4.8 Hz, 3 H), 2.65-2.53 (m, 1 H), 2.18 (d, *J* = 6.8 Hz, 2 H), 1.97-1.80 (m, 9 H), 1.23-1.17 (m, 2 H).

LCMS (ESI) calcd for C₂₆H₃₁ClN₆O₂ [M + H]⁺ m/z 495.22, found 495.15.

Example 10 – Synthesis of Compound 52

Compound 52 synthesis



Preparation of tert-butyl 3-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (3)

To a solution of 2,8-dichloroquinazolin-4(3H)-one **1** (500 mg, 2.35 mmol) in 1,4-dioxane/H₂O=5:1 (60 mL) was added tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **2** (900 mg, 3.00 mmol), Pd(dppf)Cl₂ (170 mg, 0.23 mmol) and Na₂CO₃ (740 mg, 6.98 mmol) under N₂. The reaction mixture was stirred at 80 °C for 18 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 91 : 9) to give tert-butyl 3-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **3** (400 mg, 40% yield) as a white solid.

LCMS (ESI) calcd for C₁₇H₁₈ClN₃O₃ [M + H]⁺ m/z 348.10, found 348.17.

Preparation of tert-butyl 3-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidine-1-carboxylate (4)

To a solution of tert-butyl 3-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **3** (400 mg, 1.15 mmol) in EtOAc (50 mL) was added PtO₂ (80 mg, 0.35 mmol) under H₂. The reaction mixture stirred for 2h at room temperature. The mixture was filtered through a Celite pad, and the filtrate was concentrated to give crude product of tert-

butyl 3-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidine-1-carboxylate **4** (200 mg, 50 % yield) as a white solid.

LCMS (ESI) calcd for C₁₇H₂₀ClN₃O₃ [M + H]⁺ m/z 350.12, found 350.18.

Preparation of 8-chloro-2-(pyrrolidin-3-yl)quinazolin-4(3H)-one (5)

Tert-butyl 3-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidine-1-carboxylate **4** (200 mg, 0.57 mmol) was added to HCl in dioxane (4 M, 5 mL), stirred for 1 h at room temperature, the reaction mixture was concentrated under reduced pressure to give product of 8-chloro-2-(pyrrolidin-3-yl)quinazolin-4(3H)-one **5** (130 mg, 82% yield) as a white solid .

LCMS (ESI) calcd for C₁₂H₁₂ClN₃O [M + H]⁺ m/z 250.07, found 250.12.

Preparation of 5-(4-(3-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide (7)

To a solution of 8-chloro-2-(pyrrolidin-3-yl)quinazolin-4(3H)-one **5** (80 mg, 0.32 mmol) in MeOH (10 mL) was added N-methyl-5-(4-oxopiperidin-1-yl)picolinamide **6** (50 mg, 0.21 mmol), then three drops of acetic acid and NaBH₃CN (15 mg, 0.24 mmol) were added at room temperature. The reaction mixture stirred at 50 °C for 4 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 92 : 8) to give 5-(4-(3-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide **7** (40 mg, 40% yield) as a white solid.

LCMS (ESI) calcd for C₂₄H₂₇ClN₆O₂ [M + H]⁺ m/z 467.19, found 467.28.

Preparation of 5-(4-(3-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide (Compound 52a and Compound 52b)

5-(4-(3-(8-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide **7** was separated by SFC (Column: DAICEL AS-H 4.6mm I.D.*250mm L 5µm; Mobile phase: CO₂/IPA[0.1%NH₃(7M Solution in MeOH)]=60/40) and concentrated under reduced pressure to afford the first fraction as **Compound 52a** (14.4 mg, 97% purity, ee%: 100, white solid) and the second fraction as **Compound 52b** (15.4 mg, 99% purity, ee%: 100, white solid)

Compound 52a

^1H NMR (400 MHz, DMSO) δ 8.42 (d, J = 4.8 Hz, 1 H), 8.27 (d, J = 2.8 Hz, 1 H), 8.05 (d, J = 8.0 Hz, 1 H), 7.94 (d, J = 8.0 Hz, 1 H), 7.82 (d, J = 8.8 Hz, 1 H), 7.48-7.38 (m, 2 H), 3.83 (d, J = 12.8 Hz, 2 H), 3.40-3.32 (m, 1 H), 3.06 (t, J = 9.2 Hz, 1 H), 2.95 (dd, J = 22.0, 12.0 Hz, 3 H), 2.80-2.68 (m, 5 H), 2.38 (t, J = 10.4 Hz, 1 H), 2.24-2.15 (m, 2 H), 1.96 (d, J = 11.2 Hz, 2 H), 1.53 (dd, J = 22.8, 10.8 Hz, 2 H).

LCMS (ESI) calcd for $\text{C}_{24}\text{H}_{27}\text{ClN}_6\text{O}_2$ $[\text{M} + \text{H}]^+ m/z$ 467.19, found 467.28.

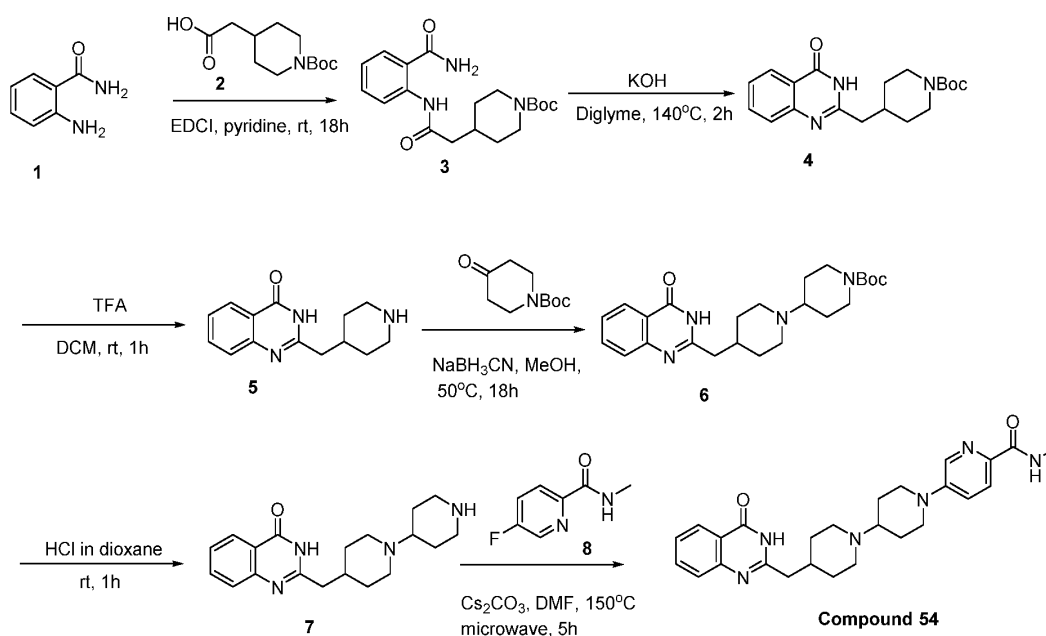
Compound 52b

^1H NMR (400 MHz, DMSO) δ 8.49 (d, J = 4.8 Hz, 1 H), 8.34 (d, J = 2.4 Hz, 1 H), 8.11 (d, J = 7.6 Hz, 1 H), 8.01 (d, J = 7.6 Hz, 1 H), 7.89 (d, J = 8.8 Hz, 1 H), 7.55-7.45 (m, 2 H), 3.90 (d, J = 12.4 Hz, 2 H), 3.45-3.39 (m, 1 H), 3.13 (t, J = 8.8 Hz, 1 H), 3.01 (dd, J = 22.8, 11.6 Hz, 3 H), 2.87-2.77 (m, 5 H), 2.43 (d, J = 10.0 Hz, 1 H), 2.26 (d, J = 6.4 Hz, 2 H), 2.02 (d, J = 11.2 Hz, 2 H), 1.59 (d, J = 12.0 Hz, 2 H).

LCMS (ESI) calcd for $\text{C}_{24}\text{H}_{27}\text{ClN}_6\text{O}_2$ $[\text{M} + \text{H}]^+ m/z$ 467.19, found 467.28.

Example 11 – Synthesis of Compound 54

Compound 54 synthesis



Preparation of tert-butyl 4-[(2-carbamoylphenyl)carbamoyl]methyl]piperidine-1-carboxylate (3)

To a solution of 2-aminobenzamide **1** (2.00 g, 14.70 mmol) and {1-[(tert-butoxy)carbonyl]piperidin-4-yl}acetic acid **2** (3.58 g, 14.70 mmol) in pyridine (50 mL) was added EDCI (2.82 g, 14.70 mmol). then the mixture was stirred for 18 h at room temperature. The reaction mixture was quenched with water, the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers was washed by 1M HCl solution and brine, dried over Na₂SO₄, concentrated under reduced pressure to give tert-butyl 4-[(2-carbamoylphenyl)carbamoyl]methyl]piperidine-1-carboxylate **3** (5.76 g, 92% yield) as a yellow oil.

LCMS (ESI) calcd for C₁₉H₂₇N₃O₄ [M + H]⁺ m/z 362.20, found 262.30.

Preparation of tert-butyl 4-[(4-oxo-3H-quinazolin-2-yl)methyl]piperidine-1-carboxylate (4)

To the solution of tert-butyl 4-[(2-carbamoylphenyl)carbamoyl]methyl]piperidine-1-carboxylate **3** (5.76 g, 15.90 mmol) in Diglyme (40 mL) was added KOH (1.16 g, 20.67 mmol), heated to 140 °C stirred for 2 h, cooled to 0 °C, ice-water (50 mL) added then adjusted pH < 7 using 1M HCl solution, precipitate formed, filtered, the filter cake washed with ice-water (50 mL*3), then dried to give product of tert-butyl 4-[(4-oxo-3H-quinazolin-2-yl)methyl]piperidine-1-carboxylate **4** (4.20 g, 73% yield) as a white solid.

LCMS (ESI) calcd for C₁₉H₂₅N₃O₃ [M + H]⁺ m/z 344.19, found 344.25.

Preparation of 2-(piperidin-4-ylmethyl)-3H-quinazolin-4-one (5)

To a solution of tert-butyl 4-[(4-oxo-3H-quinazolin-2-yl)methyl]piperidine-1-carboxylate **4** (4.20 g, 10.00 mmol) in DCM (13 mL) was added TFA (13 mL), stirred for 1 h at room temperature, the mixture was concentrated under reduced pressure to give crude product, ice-water (20 mL) added then adjusted pH > 7 using ammonium hydroxide solution, precipitate formed, filtered, the filter cake washed with ice-water (50 mL*3), then dried to give product of 2-(piperidin-4-ylmethyl)-3H-quinazolin-4-one **5** (2.32 g, 90% yield) as a white solid.

LCMS (ESI) calcd for C₁₄H₁₇N₃O [M + H]⁺ m/z 244.14, found 244.25.

Preparation of tert-butyl 4-{4-[(4-oxo-3H-quinazolin-2-yl)methyl]piperidin-1-yl}piperidine-1-carboxylate (6)

To a solution of 2-(piperidin-4-ylmethyl)-3H-quinazolin-4-one **5** (500 mg, 2.06 mmol) in MeOH (50 mL) was added tert-butyl 4-oxopiperidine-1-carboxylate (532 mg, 2.67 mmol), then

two drops of acetic acid and NaBH₃CN (504 mg, 8.01 mmol) were added at room temperature. The reaction mixture stirred at 50 °C for 18 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 91 : 9) to give tert-butyl 4-{4-[(4-oxo-3H-quinazolin-2-yl)methyl]piperidin-1-yl}piperidine-1-carboxylate **6** (244 mg, 25% yield) as a white solid.

LCMS (ESI) calcd for C₂₄H₃₄N₄O₃ [M + H]⁺ m/z 427.26, found 427.40.

Preparation of tert-butyl 4-[(4-oxo-3H-quinazolin-2-yl)methyl]piperidine-1-carboxylate (7)

Tert-butyl 4-{4-[(4-oxo-3H-quinazolin-2-yl)methyl]piperidin-1-yl}piperidine-1-carboxylate **6** (244 mg, 0.57 mmol) was added to HCl in dioxane (4 M, 8 mL), stirred for 1 h at room temperature, the reaction mixture was concentrated under reduced pressure to give 2-[[1-(piperidin-4-yl)piperidin-4-yl]methyl]-3H-quinazolin-4-one **7** (187 mg, 90% yield) as a white solid.

LCMS (ESI) calcd for C₁₉H₂₆N₄O [M + H]⁺ m/z 327.21, found 327.44.

Preparation of N-methyl-5-(4-{4-[(4-oxo-3H-quinazolin-2-yl)methyl]piperidin-1-yl}piperidin-1-yl)pyridine-2-carboxamide (Compound 54)

To a solution of 2-[[1-(piperidin-4-yl)piperidin-4-yl]methyl]-3H-quinazolin-4-one **7** (200 mg, 0.61 mmol) in DMF (16 mL) were added Cs₂CO₃ (1.20 g, 3.68 mmol) and 5-fluoro-N-methylpyridine-2-carboxamide **5** (208 mg, 1.35 mmol). The mixture was stirred for 5 h under 150 °C using microwave. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 91 : 9) to give N-methyl-5-(4-{4-[(4-oxo-3H-quinazolin-2-yl)methyl]piperidin-1-yl}piperidin-1-yl)pyridine-2-carboxamide **Compound 54** (20.11 mg, 99% purity, 7% yield) as a white solid.

¹H NMR (400 MHz, DMSO) δ 12.16 (s, 1 H), 8.37 (d, *J* = 4.8 Hz, 1 H), 8.25 (d, *J* = 2.8 Hz, 1 H), 8.07 (d, *J* = 8.0 Hz, 1 H), 7.83-7.74 (m, 2 H), 7.59 (d, *J* = 8.0 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.37 (dd, *J* = 8.8, 2.8 Hz, 1 H), 3.93 (d, *J* = 12.4 Hz, 2 H), 2.90-2.74 (m, 8 H), 2.14 (t, *J* = 10.8 Hz, 2 H), 1.81 (d, *J* = 11.6 Hz, 3 H), 1.64 (d, *J* = 10.8 Hz, 2 H), 1.49 (d, *J* = 8.8 Hz, 2 H), 1.23 (d, *J* = 9.2 Hz, 3 H).

LCMS (ESI) calcd for C₂₄H₂₈N₆O₂ [M + H]⁺ m/z 461.26, found 461.40.

ml) was added dropwise. The internal temperature was maintained below -70°C during the entire addition process. After 0.5 h at -78°C a solution of N,N-diethyl-2-fluoro-6-methylbenzamide **3** (300 mg, 1.43 mmol) in anhydrous THF (10 ml) was added dropwise and the mixture was stirred for 1 h, then tert-butyl 3-cyanopyrrolidine-1-carboxylate **4** (366 mg, 1.86 mmol) was added at -78°C . The mixture was stirred for 18 h at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 80 : 20) to give 3-hydroxy-1-(1-methylphenyl)pyrrolidine-3-carboxylic acid **5** (160 mg, 32% yield) as a white solid.

LCMS (ESI) calcd for $\text{C}_{18}\text{H}_{21}\text{FN}_2\text{O}_3$ $[\text{M} + \text{H}]^+$ m/z 333.15, found 333.25.

Preparation of 8-fluoro-3-(pyrrolidin-3-yl)-2H-isoquinolin-1-one (6)

3-Hydroxy-1-(1-methylphenyl)pyrrolidine-3-carboxylic acid **5** (160 mg, 0.48 mmol) was added to HCl-dioxane (4M, 10 mL). The mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure to give 8-fluoro-3-(pyrrolidin-3-yl)-2H-isoquinolin-1-one **6** (120 mg, 97% yield) as a white solid.

LCMS (ESI) calcd for $\text{C}_{13}\text{H}_{13}\text{FN}_2\text{O}$ $[\text{M} + \text{H}]^+$ m/z 233.10, found 233.12.

Preparation of 5-{4-[3-(8-fluoro-1-oxo-2H-isoquinolin-3-yl)pyrrolidin-1-yl]piperidin-1-yl}-N-methylpyridine-2-carboxamide (Compound 136rac)

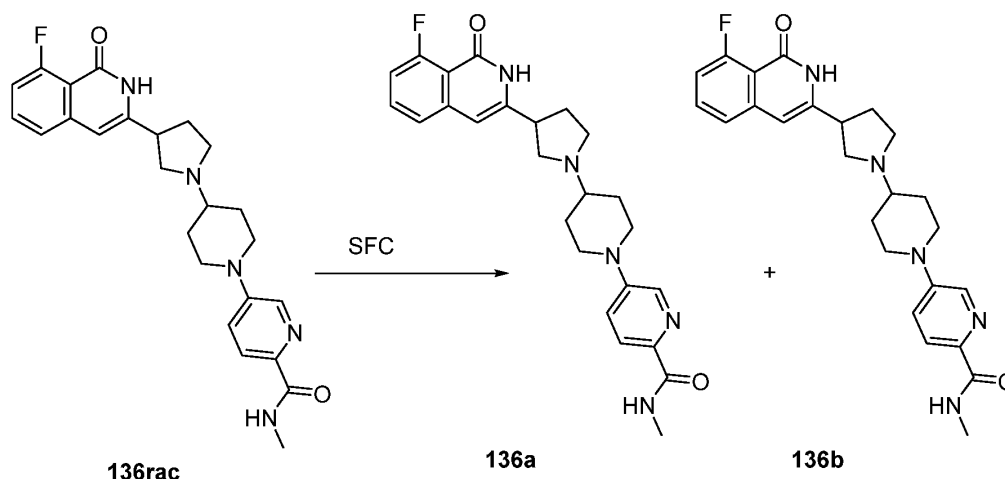
To a solution of 8-fluoro-3-(pyrrolidin-3-yl)-2H-isoquinolin-1-one **6** (120 mg, 0.52 mmol) in MeOH (15 mL) was added N-methyl-5-(4-oxopiperidin-1-yl)pyridine-2-carboxamide **INT** (100 mg, 0.55 mmol), then two drops of acetic acid and NaBH_3CN (30 mg, 0.46 mmol) were added at room temperature. The reaction mixture stirred at 50°C for 4 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 92 : 8) to give 5-{4-[3-(8-fluoro-1-oxo-2H-isoquinolin-3-yl)pyrrolidin-1-yl]piperidin-1-yl}-N-methylpyridine-2-carboxamide **Compound 136rac** (65 mg, 25% yield, 99% purity) as a yellow solid.

Compound 136rac

^1H NMR (400 MHz, DMSO) δ 11.10 (s, 1 H), 8.41-8.38 (m, 1 H), 8.28 (d, $J = 2.8$ Hz, 1 H), 7.83 (d, $J = 8.8$ Hz, 1 H), 7.62-7.58 (m, 1 H), 7.45-7.36 (m, 2 H), 7.10 (dd, $J = 11.6, 8.0$ Hz, 1 H), 6.46 (d, $J = 1.6$ Hz, 1 H), 3.84-3.80 (m, 2 H), 3.23-3.16 (m, 1 H), 3.00-2.92 (m, 3 H), 2.84-2.65 (m, 6 H), 2.38-2.33 (m, 1 H), 2.24-2.18 (m, 1 H), 1.97-1.97 (m, 2 H), 1.84-1.76 (m, 1 H), 1.60-1.49 (m, 2 H).

LCMS (ESI) calcd for C₂₅H₂₈FN₅O₂ [M + H]⁺ m/z 450.22, found 450.30.

Preparation of 5-{4-[3-(8-fluoro-1-oxo-2H-isoquinolin-3-yl)pyrrolidin-1-yl]piperidin-1-yl}-N-methylpyridine-2-carboxamide (Compound 136a and Compound 136b)



5-{4-[3-(8-fluoro-1-oxo-2H-isoquinolin-3-yl)pyrrolidin-1-yl]piperidin-1-yl}-N-methylpyridine-2-carboxamide **136rac** was separated by SFC (Column: Daicel CHIRALPAK OJ-H 250 mm × 20 mm I.D., 5 μm; Mobile phase: CO₂/MeOH[0.1%(NH₃)] = 70/30) and concentrated under reduced pressure to afford the first fraction as **Compound 136a** (12.8 mg, 99% purity, ee%: 100, white solid) and the second fraction as **Compound 136b** (13.8 mg, 99% purity, ee%: 97, white solid)

Compound 136a

¹H NMR (400 MHz, DMSO) δ 11.10 (s, 1 H), 8.41 (q, *J* = 4.4 Hz, 1 H), 8.28 (d, *J* = 2.8 Hz, 1 H), 7.83 (d, *J* = 8.8 Hz, 1 H), 7.62-7.58 (m, 1 H), 7.42-7.36 (m, 2 H), 7.10 (dd, *J* = 12.0, 8.0 Hz, 1 H), 6.46 (s, 1 H), 3.84-3.80 (m, 2 H), 3.22-3.15 (m, 1 H), 3.00-2.90 (m, 3 H), 2.81-2.63 (m, 6 H), 2.36-2.31 (m, 1 H), 2.23-2.18 (m, 1 H), 1.97-1.93 (m, 2 H), 1.87-1.79 (m, 1 H), 1.56-1.52 (m, 2 H).

LCMS (ESI) calcd for C₂₅H₂₈FN₅O₂ [M + H]⁺ m/z 450.22, found 450.20.

Compound 136b

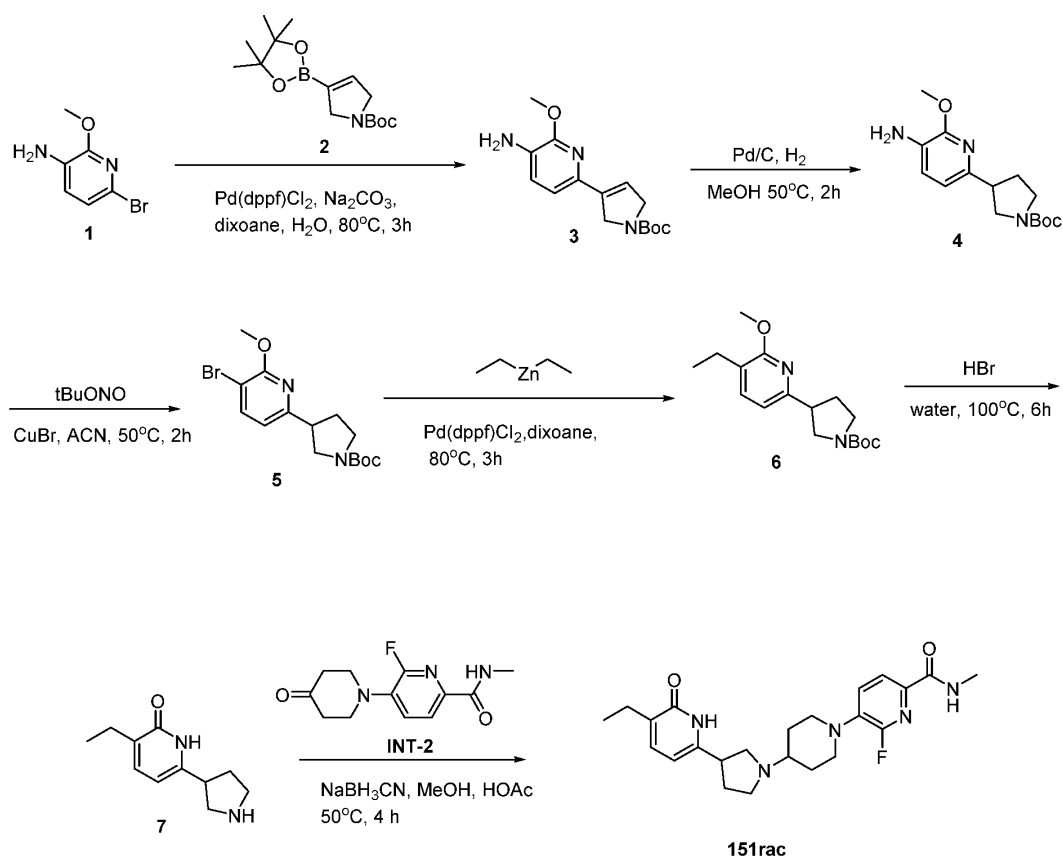
¹H NMR (400 MHz, DMSO) δ 11.10 (s, 1 H), 8.40 (q, *J* = 4.8 Hz, 1 H), 8.28 (d, *J* = 2.8 Hz, 1 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.61-7.58 (m, 1 H), 7.42-7.36 (m, 2 H), 7.10 (dd, *J* = 11.6, 8.0

Hz, 1 H), 6.46 (s, 1 H), 3.84-3.80 (m, 2 H), 3.22-3.15 (m, 1 H), 3.00-2.90 (m, 3 H), 2.81-2.63 (m, 6 H), 2.36-2.31 (m, 1 H), 2.25-2.18 (m, 1 H), 1.97-1.94 (m, 2 H), 1.87-1.79 (m, 1H), 1.56-1.52 (m, 2 H).

LCMS (ESI) calcd for C₂₅H₂₈FN₅O₂ [M + H]⁺ m/z 450.22, found 450.25.

Example 13 - Synthesis of Compounds 151rac, 151a and 151b

Synthesis of Compounds 151rac, 151a and 151b



Preparation of tert-butyl 3-(5-amino-6-methoxypyridin-2-yl)-2,5-dihydropyrrole-1-carboxylate (3**)**

To a solution of 6-bromo-2-methoxypyridin-3-amine **1** (1.38 g, 6.80 mmol) in 1,4-dioxane/H₂O=4:1 (20 mL) was added tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)-2,5-dihydropyrrole-1-carboxylate **2** (2.01 g, 6.80 mmol), then Pd(dppf)Cl₂ (0.50 g, 0.68 mmol) and Na₂CO₃ (2.23 g, 21.08 mmol) were added at room temperature. The reaction mixture was stirred under nitrogen at 80 °C for 3 h under N₂. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EA = 100 : 0 to 85 : 15) to give tert-butyl 3-(5-amino-6-methoxypyridin-2-yl)-2,5-dihydropyrrole-1-carboxylate **3** (1.50 g, 72% yield) as a white solid.

LCMS (ESI) calcd for C₁₅H₂₁N₃O₃ [M + H]⁺ m/z 292.16, found 292.19.

Preparation of tert-butyl 3-(5-amino-6-methoxypyridin-2-yl) pyrrolidine-1-carboxylate (4)

To a solution of tert-butyl 3-(5-amino-6-methoxypyridin-2-yl)-2,5-dihydropyrrole-1-carboxylate **3** (1.50 g, 5.10 mmol) in MeOH (20 mL) was added Pd/C (0.54 g, 5.10 mmol) at room temperature. The reaction mixture was stirred under hydrogen at 50 °C for 2 h. After cooling to room temperature, the reaction mixture was filtered, the solution was concentrated under reduced pressure to give product of tert-butyl 3-(5-amino-6-methoxypyridin-2-yl)pyrrolidine-1-carboxylate **4** (1.20 g, 76% yield) as a white solid.

LCMS (ESI) calcd for C₁₅H₂₃N₃O₃ [M + H]⁺ m/z 294.17, found 294.18.

Preparation of tert-butyl 3-(5-bromo-6-methoxypyridin-2-yl)pyrrolidine-1-carboxylate (5)

To a solution of tert-butyl 3-(5-amino-6-methoxypyridin-2-yl)pyrrolidine-1-carboxylate **4** (1.40 g, 4.80 mmol) in ACN (20 mL) was added tert-Butyl nitrite (1.14 g, 11.04 mmol). Then CuBr (1.38 g, 9.60 mmol) was added at room temperature. The reaction mixture was stirred at 50 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EA = 100 : 0 to 85 : 15) to give tert-butyl 3-(5-bromo-6-methoxypyridin-2-yl)pyrrolidine-1-carboxylate **5** (0.65 g, 35% yield) as a white solid.

LCMS (ESI) calcd for C₁₅H₂₁BrN₂O₃ [M + H]⁺ m/z 357.07, found 357.11.

Preparation of tert-butyl 3-(5-ethyl-6-methoxypyridin-2-yl)pyrrolidine-1-carboxylate (6)

To a solution of tert-butyl 3-(5-bromo-6-methoxypyridin-2-yl)pyrrolidine-1-carboxylate **5** (300 mg, 0.84 mmol) in 1,4-dioxane (15 mL) was added Pd(dppf)Cl₂ (61 mg, 0.08 mmol). Then Et₂Zn (5 mL, 0.14mmol) was added at room temperature. The reaction mixture under

nitrogen was stirred at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EA = 100 : 0 to 85 : 15) to give tert-butyl 3-(5-ethyl-6-methoxypyridin-2-yl)pyrrolidine-1-carboxylate **6** (120 mg, 44% yield) as a white solid.

LCMS (ESI) calcd for C₁₇H₂₆N₂O₃ [M + H]⁺ m/z 307.19, found 307.25.

Preparation of 3-ethyl-6-(pyrrolidin-3-yl)-1H-pyridin-2-one (**7**)

Tert-butyl 3-(5-ethyl-6-methoxypyridin-2-yl)pyrrolidine-1-carboxylate **6** (120 mg, 0.39 mmol) was added to HBr in water (48%, 15 mL). The reaction mixture was stirred at 100 °C for 6 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to give 3-ethyl-6-(pyrrolidin-3-yl)-1H-pyridin-2-one **7** (70 mg, 88% yield) as a white solid.

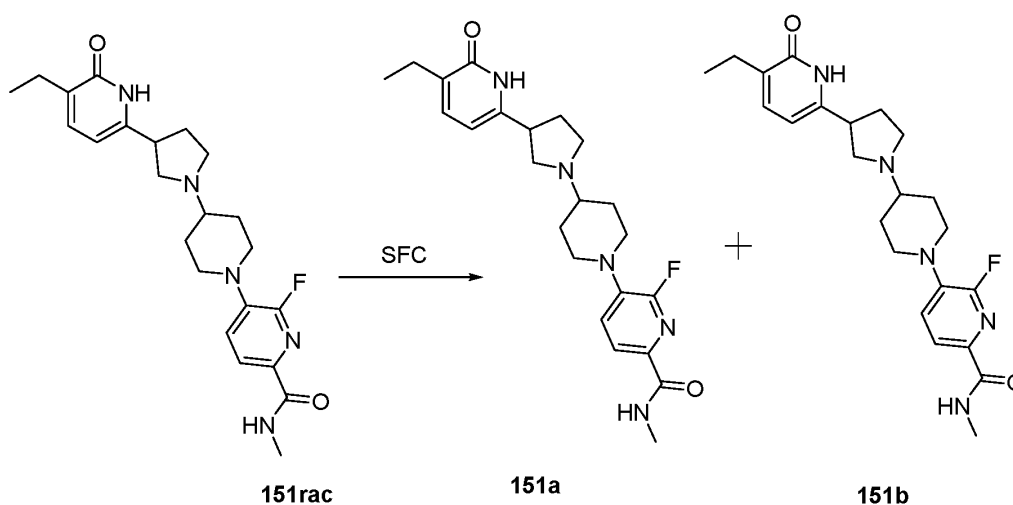
LCMS (ESI) calcd for C₁₁H₁₆N₂O [M + H]⁺ m/z 193.13, found 193.14.

Preparation of 5-(4-(3-(5-ethyl-6-oxo-1,6-dihydropyridin-2-yl)pyrrolidin-1-yl)piperidin-1-yl)-6-fluoro-N-methylpicolinamide (**151rac**)

To a solution of 6-fluoro-N-methyl-5-(4-oxopiperidin-1-yl)picolinamide **INT-2** (100 mg, 0.40 mmol) in MeOH (40 mL) was added 3-ethyl-6-(pyrrolidin-3-yl)-1H-pyridin-2-one **7** (115 mg, 0.60 mmol), then two drops of acetic acid and NaBH₃CN (38 mg, 0.61 mmol) were added at room temperature. The reaction mixture stirred at 50 °C for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 90 : 10) to afford 5-(4-(3-(5-ethyl-6-oxo-1,6-dihydropyridin-2-yl)pyrrolidin-1-yl)piperidin-1-yl)-6-fluoro-N-methylpicolinamide **151rac** (40 mg, 95% purity, 22.34% yield) as a white solid.

LCMS (ESI) calcd for C₂₃H₃₀FN₅O₂ [M + H]⁺ m/z 428.24, found 428.10.

Chiral resolution of 5-(4-(3-(5-ethyl-6-oxo-1,6-dihydropyridin-2-yl)pyrrolidin-1-yl)piperidin-1-yl)-6-fluoro-N-methylpicolinamide (Compound **151a** and Compound **151b**)



Compound **151** was separated by SFC (Column: Daicel Chiralpak AD-H SFC 250 mm × 20 mm I.D., 5 μm; Mobile phase: CO₂/MeOH[0.1%(NH₃)] = 80/20) and concentrated under reduced pressure to afford the first fraction as **Compound 151a** (15.8 mg, 92% purity, ee%: 100, white solid) and the second fraction as **Compound 151b** (15.9 mg, 95% purity, ee%: 100, white solid)

Compound **151a**

¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ: 11.28 (s, 1 H), 8.44-8.37 (m, 1 H), 7.83 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.61-7.52 (m, 1 H), 7.17 (d, *J* = 7.2 Hz, 1 H), 6.03 (d, *J* = 6.4 Hz, 1 H), 3.56-3.43 (m, 2 H), 3.17-3.09 (m, 1 H), 2.90-2.74 (m, 7 H), 2.68-2.60 (m, 2 H), 2.35-2.17 (m, 4 H), 1.96 (d, *J* = 12.0 Hz, 2 H), 1.79-1.70 (m, 1 H), 1.63-1.52 (m, 2 H), 1.06 (t, *J* = 7.2 Hz, 3 H).

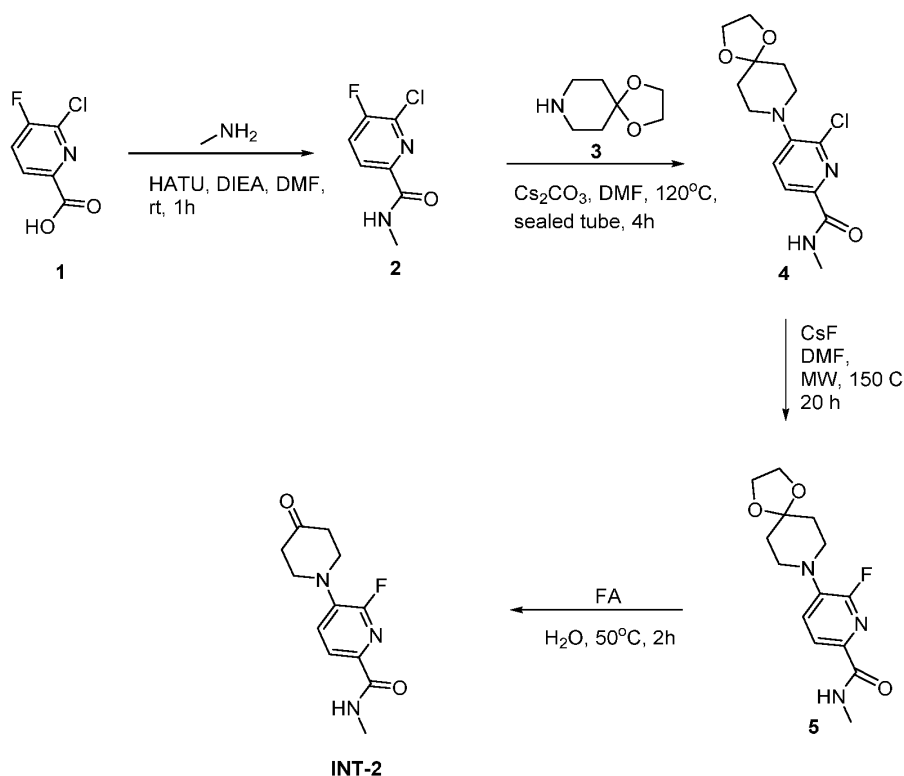
LCMS (ESI) calcd for C₂₃H₃₀FN₅O₂ [M + H]⁺ *m/z* 428.24, found 428.10.

Compound **151b**

¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ: 11.28 (s, 1 H), 8.45-8.35 (m, 1 H), 7.83 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.64-7.51 (m, 1 H), 7.17 (d, *J* = 6.8 Hz, 1 H), 6.03 (d, *J* = 6.8 Hz, 1 H), 3.58-3.41 (m, 2 H), 3.17-3.09 (m, 1 H), 2.93-2.74 (m, 7 H), 2.68-2.60 (m, 2 H), 2.35-2.16 (m, 4 H), 2.01-1.92 (m, 2 H), 1.79-1.70 (m, 1 H), 1.64-1.52 (m, 2 H), 1.06 (t, *J* = 7.2 Hz, 3 H).

LCMS (ESI) calcd for C₂₃H₃₀FN₅O₂ [M + H]⁺ *m/z* 428.24, found 428.20.

Synthesis of INT-2



Preparation of 6-chloro-5-fluoro-N-methylpicolinamide (2)

To a solution of 6-chloro-5-fluoropicolinic acid **1** (2.00 g, 11.40 mmol) in DMF (50 mL) was added methanamine (420 mg, 13.68 mmol), DIEA (4.42 g, 34.20 mmol), HATU (6.50 g, 17.10 mmol) at room temperature successively. The mixture was kept stirring at room temperature for 1 h. The resulting mixture was diluted with water and extracted with EtOAc (200 mL x 3). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 70 : 30) to afford 6-chloro-5-fluoro-N-methylpicolinamide **2** (2.00 g, 88 % yield) as a white solid. LCMS (ESI) calcd for $\text{C}_7\text{H}_6\text{ClFN}_2\text{O}$ $[\text{M} + \text{H}]^+$ m/z 189.02, found 188.90.

Preparation of 6-chloro-N-methyl-5-(1,4-dioxaspiro[4.5]decan-8-yl)picolinamide (4)

To a solution 6-chloro-5-fluoro-N-methylpicolinamide **2** (2.00 g, 10.60 mmol) in DMF (20 mL) was added Cs_2CO_3 (6.91 g, 21.20 mmol) and 1,4-dioxaspiro[4.5]decan-8-yl)picolinamide **3** (3.04 g, 21.20 mmol). The mixture was stirred for 4 h under 120°C using a sealed tube. The reaction

mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 50 : 50) to afford 6-chloro-N-methyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)picolinamide **4** (1.60 g, 42 % yield) as a white solid. LCMS (ESI) calcd for C₁₄H₁₈ClN₃O₃ [M + H]⁺ m/z 312.10, found 311.95.

Preparation of 6-fluoro-N-methyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)picolinamide (5)

To a solution 6-chloro-N-methyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)picolinamide **4** (300 mg, 0.96 mmol) in DMF (20 mL) was added CsF (293 mg, 1.93 mmol). The mixture was stirred for 20 h under 150 °C using microwave. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 30 : 70) to 6-fluoro-N-methyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)picolinamide **5** (200 mg, 69% yield) as a yellow solid.

LCMS (ESI) calcd for C₁₄H₁₈FN₃O₃ [M + H]⁺ m/z 296.13, found 295.95.

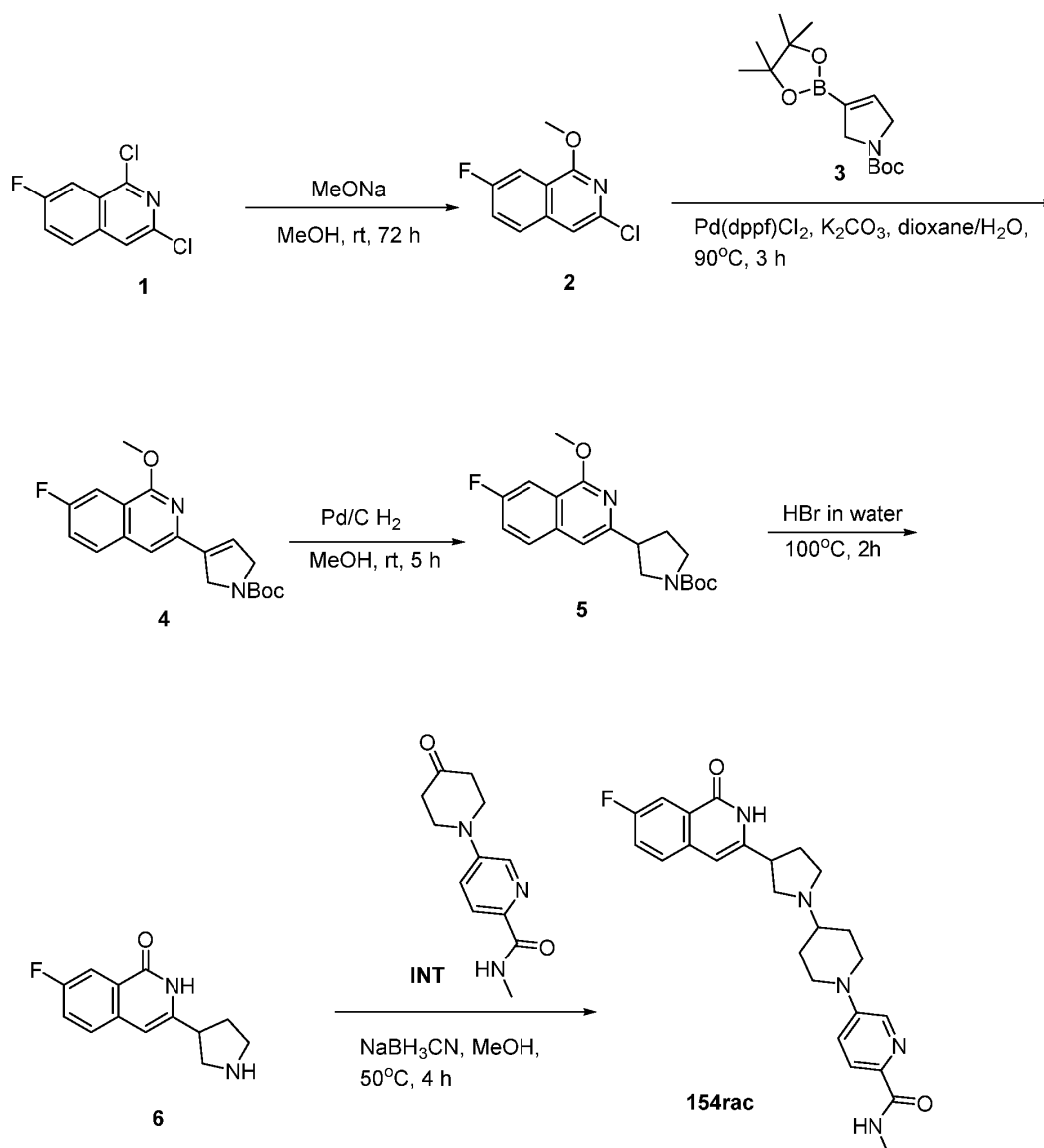
Preparation of 6-fluoro-N-methyl-5-(4-oxopiperidin-1-yl)picolinamide (INT-2)

To the solution of 6-fluoro-N-methyl-5-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)picolinamide **5** (200 mg, 0.68 mmol) in H₂O (3 mL) was added formic acid (2 mL), stirred at 50 °C for 1 h, The aqueous solution was adjusted to pH 7-8 with aqueous NaHCO₃ solution. The mixture was diluted with water (50 mL) and extracted with EtOAc (100 mL × 3). The combined organic layer was washed with brine (100 mL × 2), dried over Na₂SO₄, concentrated to give crude product of 6-fluoro-N-methyl-5-(4-oxopiperidin-1-yl)picolinamide **INT-2** (100 mg, 47% yield) as a yellow solid .

LCMS (ESI) calcd for C₁₂H₁₄FN₃O₂ [M + H]⁺ m/z 252.11, found 251.90.

Example 14 - Synthesis of Compounds 154rac, 154a and 154b

Synthesis of Compounds 154rac, 154a and 154b



Preparation of 3-chloro-7-fluoro-1-methoxyisoquinoline (2)

To a solution of 1,3-dichloro-7-fluoroisoquinoline **1** (500 mg, 2.32 mmol) in MeOH (50 mL), was added MeONa (150 mg, 2.78 mmol) at room temperature. The mixture was stirred for 72 h at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 98 : 2) to give 3-chloro-7-fluoro-1-methoxyisoquinoline **2** (160 mg, 33% yield) as a white solid.

LCMS (ESI) calcd for C₁₀H₇ClFNO [M + H]⁺ m/z 212.02, found 211.90.

Preparation of tert-butyl 3-(7-fluoro-1-methoxyisoquinolin-3-yl)-2,5-dihydro-1H-pyrrole-1-

carboxylate (4)

To a solution of 3-chloro-7-fluoro-1-methoxyisoquinoline **2** (160 mg, 0.76 mmol) in dioxane:H₂O=5:1 (20 mL) was added tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **3** (270 mg, 0.92 mmol), Pd(dppf)Cl₂ (50 mg, 0.07 mmol) and K₂CO₃ (250 mg, 1.81 mmol) at room temperature. The reaction mixture was stirred under N₂ at 90 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 95 : 5) to afford tert-butyl 3-(7-fluoro-1-methoxyisoquinolin-3-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **4** (160 mg, 61% yield) as a white solid.

LCMS (ESI) calcd for C₁₉H₂₁FN₂O₃ [M + H]⁺ m/z 345.15, found 345.11.

Preparation of tert-butyl 3-(7-fluoro-1-methoxyisoquinolin-3-yl)pyrrolidine-1-carboxylate (5)

To a solution of tert-butyl 3-(7-fluoro-1-methoxyisoquinolin-3-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **4** (160 g, 0.46 mmol) in MeOH (20 mL) was added Pd/C (35 mg, 0.29 mmol) under H₂. The reaction mixture was stirred at room temperature for 5 h. The mixture was filtered through a Celite pad and the filtrate was concentrated to give tert-butyl 3-(7-fluoro-1-methoxyisoquinolin-3-yl)pyrrolidine-1-carboxylate **5** (140 mg, 88 % yield) as a white solid.

LCMS (ESI) calcd for C₁₉H₂₃FN₂O₃ [M + H]⁺ m/z 347.17, found 347.18.

Preparation of 7-fluoro-3-(pyrrolidin-3-yl)isoquinolin-1(2H)-one (6)

Tert-butyl 3-(7-fluoro-1-methoxyisoquinolin-3-yl)pyrrolidine-1-carboxylate **5** (140 mg, 0.40 mmol) was added to HBr in water (48 %, 3 mL). The mixture was stirred at 100 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give 7-fluoro-3-(pyrrolidin-3-yl)isoquinolin-1(2H)-one **6** (90 mg, 97% yield) as a white solid.

LCMS (ESI) calcd for C₁₃H₁₃FN₂O [M + H]⁺ m/z 233.10, found 232.95.

Preparation of 5-(4-(3-(7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide (Compound 154rac)

To a solution of 7-fluoro-3-(pyrrolidin-3-yl)isoquinolin-1(2H)-one **6** (90 mg, 0.39 mmol) in MeOH (15 mL) was added N-methyl-5-(4-oxopiperidin-1-yl)picolinamide (**INT**, 100 mg, 0.43 mmol), then two drops of acetic acid and NaBH₃CN (25 mg, 0.40 mmol) were added at room temperature. The reaction mixture stirred at 50 °C for 4 h. After cooling to room temperature,

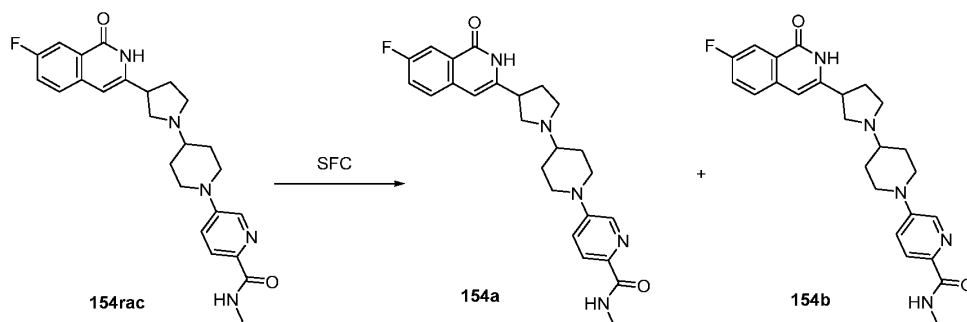
the residue was purified by prep-HPLC (columns: Gemini 5 μ m C18 150 $\times$ 21.2 mm, mobile phase: ACN - H₂O (0.1% FA), gradient: 10 - 25) to give 5-(4-(3-(7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide **154rac** (35 mg, 99% purity, 20% yield) as a white solid.

Compound **154rac**

¹H NMR (400 MHz, DMSO) δ 11.35 (s, 1 H), 8.39 (q, J = 4.8 Hz, 1 H), 8.30 (d, J = 2.8 Hz, 1 H), 7.87-7.76 (m, 2 H), 7.70 (dd, J = 8.8, 5.2 Hz, 1 H), 7.59 (td, J = 8.8, 2.8 Hz, 1 H), 7.43 (dd, J = 8.8, 2.8 Hz, 1 H), 6.57 (s, 1 H), 4.02-3.85 (m, 2 H), 3.31-2.71 (m, 11 H), 2.40-2.25 (m, 1 H), 2.13-1.88 (m, 3 H), 1.68-1.52 (m, 2 H).

LCMS (ESI) calcd for C₂₅H₂₈FN₅O₂ [M + H]⁺ m/z 450.22, found 450.23.

Preparation of 5-(4-(3-(7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide (**154a** and **154b**)



5-(4-(3-(7-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide **154rac** was separated by SFC (Column: DAICEL OJ-H 4.6mm I.D.*250mmL 5 μ m; Mobile phase: CO₂/MeOH[0.1%NH₃(7M Solution in MeOH)]=75/25) and concentrated under reduced pressure to afford the first fraction as **154a** (10 mg, 99% purity, ee%: 100, white solid) and the second fraction as **154b** (10 mg, 97% purity, ee%: 100, white solid)

Compound **154a**

¹H NMR (400 MHz, DMSO) δ 11.25 (s, 1 H), 8.39 (d, J = 4.8 Hz, 1 H), 8.28 (d, J = 2.8 Hz, 1 H), 7.82 (d, J = 8.4 Hz, 1 H), 7.77 (dd, J = 9.2, 2.8 Hz, 1 H), 7.68 (dd, J = 8.8, 5.6 Hz, 1 H), 7.56 (td, J = 8.8, 2.8 Hz, 1 H), 7.40 (dd, J = 8.8, 2.8 Hz, 1 H), 6.51 (s, 1 H), 3.87-3.77 (m, 2 H), 3.25-3.17 (m, 1 H), 3.03-2.91 (m, 3 H), 2.85-2.75 (m, 4 H), 2.74-2.66 (m, 2 H), 2.35-2.32

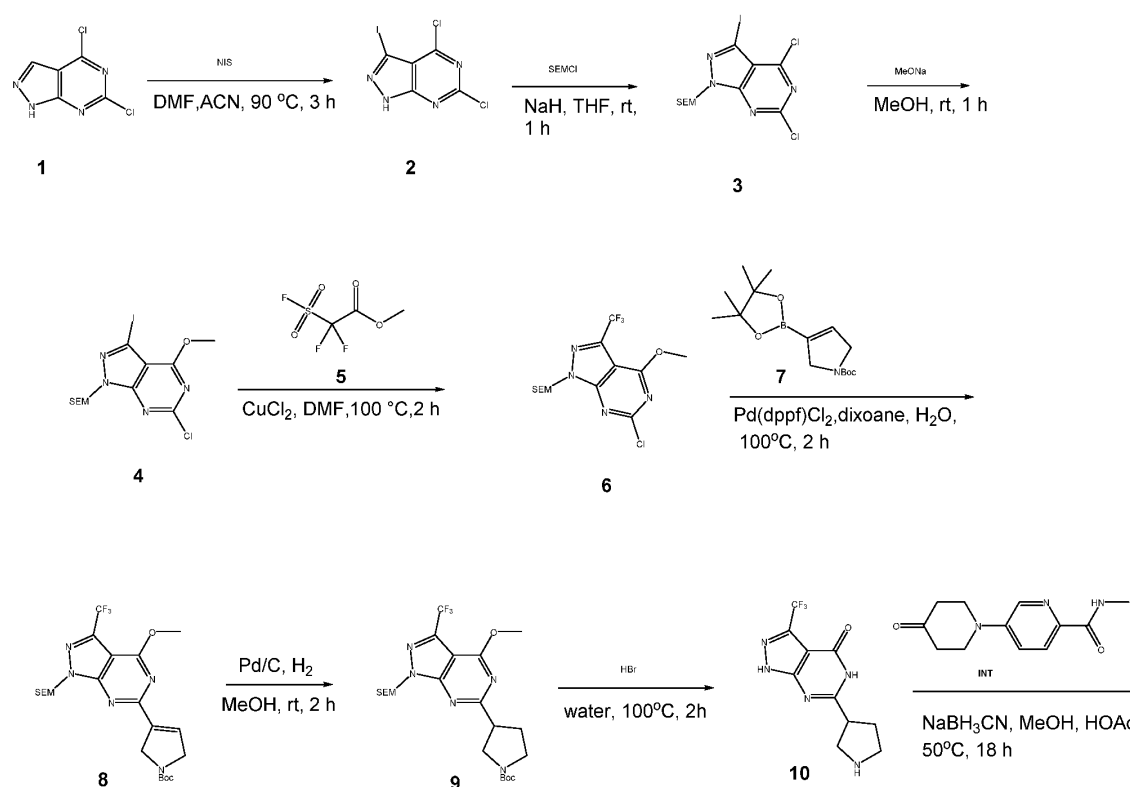
(m, 1 H), 2.28-2.17 (m, 1 H), 2.01-1.90 (m, 2 H), 1.88-1.78 (m, 1 H), 1.60-1.47 (m, 2 H).
LCMS (ESI) calcd for C₂₅H₂₈FN₅O₂ [M + H]⁺ m/z 450.22, found 450.20.

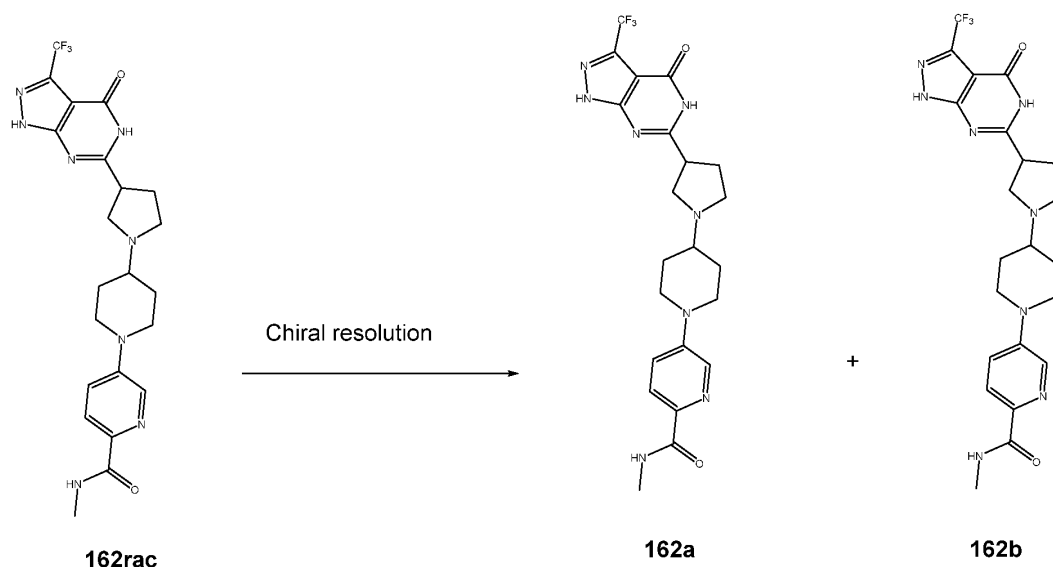
Compound 154b

¹H NMR (400 MHz, DMSO) δ 11.25 (s, 1 H), 8.39 (d, *J* = 4.8 Hz, 1 H), 8.28 (d, *J* = 2.8 Hz, 1 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.77 (dd, *J* = 9.2, 2.8 Hz, 1 H), 7.68 (dd, *J* = 8.8, 5.2 Hz, 1 H), 7.56 (td, *J* = 8.8, 2.8 Hz, 1 H), 7.40 (dd, *J* = 8.8, 2.8 Hz, 1 H), 6.51 (s, 1 H), 3.88-3.78 (m, 2 H), 3.26-3.16 (m, 1 H), 3.03-2.91 (m, 3 H), 2.83-2.78 (m, 4 H), 2.74-2.66 (m, 2 H), 2.35-2.31 (m, 1 H), 2.28-2.17 (m, 1 H), 2.00-1.92 (m, 2 H), 1.89-1.79 (m, 1 H), 1.61-1.47 (m, 2 H).
LCMS (ESI) calcd for C₂₅H₂₈FN₅O₂ [M + H]⁺ m/z 450.22, found 450.20.

Example 15 - Synthesis of Compounds 162rac, 162a and 162b

Synthesis of Compounds 162rac, 162a and 162b





Preparation of 4,6-dichloro-3-iodo-1H-pyrazolo[3,4-d]pyrimidine (2)

To a solution of 4,6-dichloro-1H-pyrazolo[3,4-d]pyrimidine **1** (5 g, 26.50 mmol) in ACN/DMF = 1:1 (100 mL) was added NIS (8.9 g, 39.75 mmol). The resulting mixture was stirred at 90 °C for 3 h. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100: 0 to 72: 28) to give 4,6-dichloro-3-iodo-1H-pyrazolo[3,4-d]pyrimidine **2** (2.9 g, 35% yield) as white solid.

LCMS (ESI) calcd for C₅HCl₂IN₄ [M + H]⁺ m/z 314.86, found 314.85.

Preparation of 4,6-dichloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidine (3)

To a solution of 4,6-dichloro-3-iodo-1H-pyrazolo[3,4-d]pyrimidine **2** (2.9 g, 9.24 mmol) in THF (40 mL) was added NaH (290 mg, 11.96 mmol) at 0 °C, stirred 10 min, then added SEMCl (2.3 g, 13.80 mmol). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give 4,6-dichloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidine **3** (3.6 g, 88% yield) as white solid.

LCMS (ESI) calcd for C₁₁H₁₅Cl₂IN₄OSi [M + H]⁺ m/z 444.94, found 444.85.

Preparation of 6-chloro-3-iodo-4-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidine (4)

To a solution of 4,6-dichloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidine **3** (1.5 g, 3.39 mmol) in MeOH (45 mL) was added MeONa (183 mg, 3.39 mmol). The mixture was stirred at room temperature for 1 h. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100: 0 to 95: 5) to give 6-chloro-3-iodo-4-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidine **4** (282 mg, 19% yield) as a white solid.

LCMS (ESI) calcd for C₁₂H₁₈ClIIN₄O₂Si [M + H]⁺ m/z 440.99 found 441.01.

Preparation of 6-chloro-4-methoxy-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidine (6)

To a solution of 6-chloro-3-iodo-4-methoxy-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidine **4** (282 mg, 0.64 mmol) and methyl 2,2-difluoro-2-(fluorosulfonyl)acetate **5** (491 mg, 2.56 mmol) in DMF (15 mL) was added CuCl₂ (131 mg, 0.98 mmol) under N₂. The reaction mixture was stirred at 100 °C for 2 h. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100: 0 to 96: 4) to 6-chloro-4-methoxy-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidine **6** (220 mg, 90% yield) as a white solid.

LCMS (ESI) calcd for C₁₃H₁₈ClF₃N₄O₂Si [M + H]⁺ m/z 383.08, found 383.08.

Preparation of tert-butyl 3-(4-methoxy-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (8)

To a solution of tert-butyl 3-(4-methoxy-5-(trifluoromethyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **6** (200 mg, 0.52 mmol), tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **7** (154 mg, 0.52 mmol) and Pd(dppf)Cl₂ (23 mg, 0.031 mmol) in 1,4-dioxane/H₂O=10:1 (11 mL) was added Na₂CO₃ (165 mg, 1.56 mmol) under N₂. The reaction mixture was stirred at 100 °C for 2 h. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100: 0 to 93: 7) to give tert-butyl 3-(4-methoxy-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **8** (280 mg, 94% yield) as an orange oil.

LCMS (ESI) calcd for C₂₇H₃₂F₃N₅O₄Si [M + H]⁺ m/z 516.22, found 516.23.

Preparation of tert-butyl 3-(4-methoxy-3-(trifluoromethyl)-1-((2-

(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)pyrrolidine-1-carboxylate (9)

To a solution of tert-butyl 3-(4-methoxy-5-(trifluoromethyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)pyrrolidine-1-carboxylate **8** (280 mg, 0.54 mmol) in MeOH (15 mL) was added Pd/C (114 mg, 1.08 mmol) under H₂. The reaction mixture was stirred at room temperature for 2 h. Then the mixture was filtered through celite and concentrated under vacuum to give tert-butyl 3-(4-methoxy-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)pyrrolidine-1-carboxylate **9** (158 mg, 56% yield) as a white solid.

LCMS (ESI) calcd for C₂₂H₃₄F₃N₅O₄Si [M + H] + m/z 518.23, found 518.25.

Preparation of 6-(pyrrolidin-3-yl)-3-(trifluoromethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (10)

Tert-butyl 3-(4-methoxy-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[3,4-d]pyrimidin-6-yl)pyrrolidine-1-carboxylate **9** (158 mg, 0.31 mmol) was added to HBr water (5 mL). The reaction mixture was stirred at 100 °C for 2 h. Then the mixture was concentrated under vacuum to give 6-(pyrrolidin-3-yl)-3-(trifluoromethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one **10** (80 mg, 96% yield) as a white solid.

LCMS (ESI) calcd for C₁₀H₁₀F₃N₅O [M + H] + m/z 274.08, found 274.00.

Preparation of N-methyl-5-(4-(3-(4-oxo-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide (162rac)

To a solution of 6-(pyrrolidin-3-yl)-3-(trifluoromethyl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one **10** (80 mg, 0.29 mmol), N-methyl-5-(4-oxopiperidin-1-yl)picolinamide **INT** (90 mg, 0.29 mmol) and sodium triacetoxyborohydride (92 mg, 0.44 mmol) in MeOH (10 mL) was added two drops of HOAc and the solution was stirred for 0.5 h at 50 °C. Then was added NaBH₃CN (22 mg, 0.35 mmol). The mixture was stirred for 18 h at 50 °C. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 90 : 10) to give product of N-methyl-5-(4-(3-(4-oxo-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide **162rac** (69 mg, 48% yield) as white solid.

LCMS (ESI) calcd for C₂₂H₂₅F₃N₈O₂ [M + H] + m/z 491.21, found 491.25.

Chiral resolution of N-methyl-5-(4-(3-(4-oxo-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide (162a and 162b)

Compound **162rac** was separated by SFC (Column: DAICEL OJ-H 4.6 mmI.D.*250 mmL, 5 μ m; Mobile phase: CO₂/MeOH[0.1% NH₃ (7M Solution in MeOH)] = 70/30) and concentrated under reduced pressure to afford the first fraction as **162a** (39 mg, 93% purity, ee%: 100, white solid) and the second fraction as **162b** (31 mg, 99% purity, ee%: 100, white solid)

Compound 162a

¹H NMR (400 MHz, DMSO) δ 14.37 (s, 1 H), 12.27 (s, 1 H), 8.39 (q, J = 4.4 Hz, 1 H), 8.27 (d, J = 2.8 Hz, 1 H), 7.82 (d, J = 8.8 Hz, 1 H), 7.40 (dd, J = 8.4, 2.8 Hz, 1 H), 3.83 (d, J = 12.8 Hz, 2 H), 3.38-3.35 (m, 1 H), 3.06 (t, J = 8.4 Hz, 1 H), 2.98-2.88 (m, 2 H), 2.83-2.73 (m, 5 H), 2.68-2.61 (m, 1 H), 2.39-2.29 (m, 1 H), 2.21-2.09 (m, 2 H), 1.93 (d, J = 11.6 Hz, 2 H), 1.55-1.43 (m, 2 H).

LCMS (ESI) calcd for C₂₂H₂₅F₃N₈O₂ [M + H] + m/z 491.21, found 491.26.

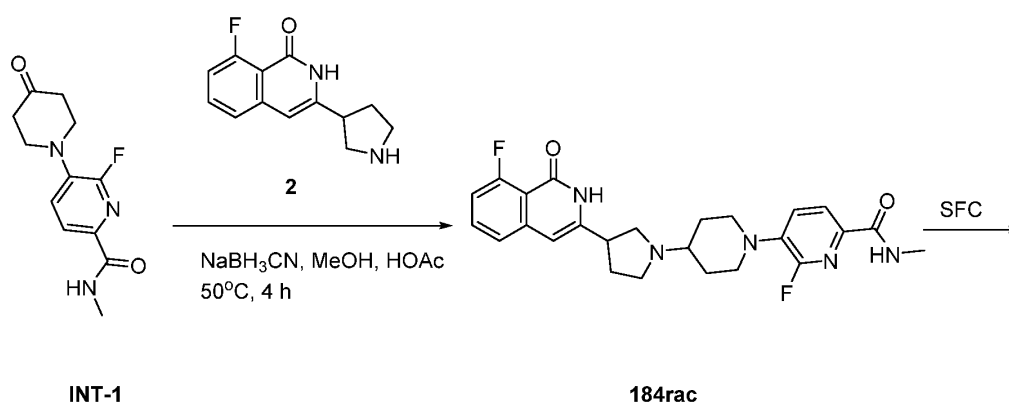
Compound 162b

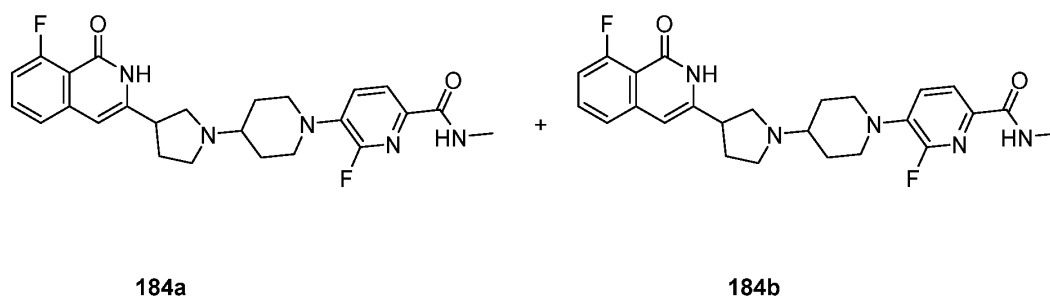
¹H NMR (400 MHz,) δ 14.41 (s, 1 H), 12.41 (s, 1 H), 8.39 (q, J = 4.8 Hz, 1 H), 8.28 (d, J = 2.0 Hz, 1 H), 7.82 (d, J = 8.8 Hz, 1 H), 7.41 (dd, J = 8.8, 2.0 Hz, 1 H), 3.86 (s, 1 H), 3.30-3.27 (m, 1 H), 3.16-3.03 (m, 1 H), 2.96-2.58 (m, 8 H), 2.34-2.10 (m, 3 H), 2.03-1.88 (m, 2 H), 1.63-1.44 (m, 2 H).

LCMS (ESI) calcd for C₂₂H₂₅F₃N₈O₂ [M + H] + m/z 491.21, found 491.25.

Example 16 - Synthesis of Compounds 184rac, 184a and 184b

Synthesis of Compounds 184rac, 184a and 184b





Preparation of 6-fluoro-5-{4-[3-(8-fluoro-1-oxo-2H-isoquinolin-3-yl)pyrrolidin-1-yl]piperidin-1-yl}-N-methylpyridine-2-carboxamide (184rac)

To a solution of 6-fluoro-N-methyl-5-(4-oxopiperidin-1-yl)pyridine-2-carboxamide **INT-1** (92 mg, 0.40 mmol) in MeOH (10 mL) was added N-methyl-5-(4-oxopiperidin-1-yl)pyridine-2-carboxamide **2** (intermediate **6** in synthesis of compound **136**) (100 mg, 0.40 mmol). Then two drops of acetic acid and NaBH₃CN (25 mg, 0.26 mmol) was added at room temperature. The reaction mixture was stirred at 50 °C for 4 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 92 : 8) to give product of 6-fluoro-5-{4-[3-(8-fluoro-1-oxo-2H-isoquinolin-3-yl)pyrrolidin-1-yl]piperidin-1-yl}-N-methylpyridine-2-carboxamide **184rac** (60 mg, 27% yield) as a colorless oil.

LCMS (ESI) calcd for C₂₅H₂₇F₂N₅O₂ [M + H]⁺ m/z 468.21, found 468.26.

Preparation of 6-fluoro-5-{4-[3-(8-fluoro-1-oxo-2H-isoquinolin-3-yl)pyrrolidin-1-yl]piperidin-1-yl}-N-methylpyridine-2-carboxamide (184a and 184b)

6-chloro-5-{4-[3-(8-fluoro-1-oxo-2H-isoquinolin-3-yl)pyrrolidin-1-yl]piperidin-1-yl}-N-methylpyridine-2-carboxamide **184rac** was separated by SFC (Column: Daicel CHIRALPAK OJ-H 250 mm × 20 mm I.D., 5 μm; Mobile phase: CO₂/MeOH[0.1%(NH₃)] = 80/20) and concentrated under reduced pressure to afford the first fraction as **184a** (24.5 mg, 98% purity, ee%: 100, white solid) and the second fraction as **184b** (24.4 mg, 99% purity, ee%: 97, white solid).

Compound 184a

¹H NMR (400 MHz, DMSO) δ 11.10 (s, 1 H), 8.41 (q, *J* = 5.2 Hz, 1 H), 7.85 (d, *J* = 7.2 Hz, 1 H), 7.64-7.56 (m, 2 H), 7.39 (d, *J* = 7.6 Hz, 1 H), 7.10 (dd, *J* = 12.0, 8.0 Hz, 1 H), 6.47 (s, 1 H), 3.52-3.51 (m, 2 H), 3.22-3.16 (m, 1 H), 2.91-2.73 (m, 8 H), 2.67-2.63 (m, 1 H), 2.30-2.22

(m, 2 H), 2.00-1.97 (m, 2 H), 1.86-1.79 (m, 1 H), 1.68-1.53 (m, 2 H).

LCMS (ESI) calcd for C₂₅H₂₇F₂N₅O₂ [M + H]⁺ m/z 468.21, found 468.22.

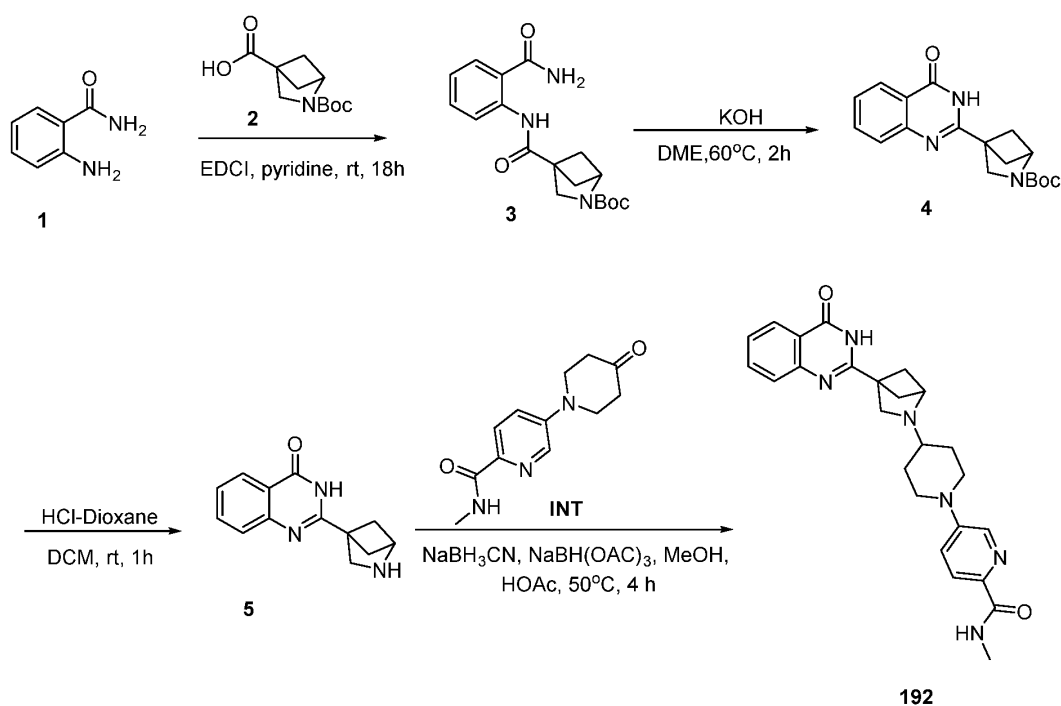
Compound 184b

¹H NMR (400 MHz, DMSO) δ 11.10 (s, 1 H), 8.41 (q, *J* = 4.8 Hz, 1 H), 7.85 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.64-7.56 (m, 2 H), 7.39 (d, *J* = 7.6 Hz, 1 H), 7.11 (dd, *J* = 11.6, 8.0 Hz, 1 H), 6.46 (s, 1 H), 3.53-3.49 (m, 2 H), 3.21-2.87 (m, 1 H), 2.93-2.71 (m, 8 H), 2.68-2.63 (m, 1 H), 2.28-2.19 (m, 2 H), 2.00-1.97 (m, 2 H), 1.88-1.79 (m, 1 H), 1.64-1.54 (m, 2 H).

LCMS (ESI) calcd for C₂₅H₂₇F₂N₅O₂ [M + H]⁺ m/z 468.21, found 468.18.

Example 17 - Synthesis of compound 192

Synthesis of compound 192



Preparation of tert-butyl 4-((2-carbamoylphenyl)carbamoyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (3)

To a solution of 2-aminobenzamide **1** (360 mg, 2.64 mmol) and 2-(tert-butoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxylic acid **2** (500 mg, 2.20 mmol) in pyridine (30 mL) was added EDCI (422 mg, 2.20 mmol). Then the mixture was stirred for 18 h at room temperature. The reaction mixture was quenched with water, the aqueous layer was extracted with EtOAc (200 mL x 3). The combined organic layers was washed by 1M HCl solution and brine, dried over Na₂SO₄, concentrated under reduced pressure to give product of tert-butyl 4-((2-carbamoylphenyl)carbamoyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **3** (600 mg, 90% yield) as a white solid.

LCMS (ESI) calcd for C₁₈H₂₃N₃O₄ [M + Na]⁺ m/z 368.17, found 368.05.

Preparation of tert-butyl 4-(4-oxo-3,4-dihydroquinazolin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (4)

To the solution of tert-butyl 4-((2-carbamoylphenyl)carbamoyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **3** (600 mg, 1.74 mmol) in DME (60 mL) was added KOH (195 mg, 3.47 mmol), heated to 60 °C stirred for 2 h, cooled to 25 °C, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 90 : 10) to give tert-butyl 4-(4-oxo-3,4-dihydroquinazolin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **4** (400 mg, 63% yield) as a white solid.

LCMS (ESI) calcd for C₁₈H₂₁N₃O₃ [M + H]⁺ m/z 328.16, found 328.05.

Preparation of 2-(2-azabicyclo[2.1.1]hexan-4-yl)quinazolin-4(3H)-one (5)

Tert-butyl 4-(4-oxo-3,4-dihydroquinazolin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **4** (400 mg, 0.56 mmol) was added to HCl in dioxane (4M, 10 mL). The mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure to give product of 2-(2-azabicyclo[2.1.1]hexan-4-yl)quinazolin-4(3H)-one **5** (320 mg, 93% yield) as a white solid.

LCMS (ESI) calcd for C₁₃H₁₃N₃O [M + H]⁺ m/z 228.11, found 228.02.

Preparation of N-methyl-5-(4-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)-2-azabicyclo[2.1.1]hexan-2-yl)piperidin-1-yl)picolinamide (compound 192)

To a solution of 2-(2-azabicyclo[2.1.1]hexan-4-yl)quinazolin-4(3H)-one **5** (80 mg, 0.35 mmol) in MeOH (40 mL) was added N-methyl-5-(4-oxopiperidin-1-yl)picolinamide (**INT**, 98 mg, 0.42 mmol), then two drops of acetic acid and NaBH(OAc)₃ (149 mg, 0.70 mmol) were added at room temperature. The reaction mixture stirred at 50 °C for 1 h. Then was added NaBH₃CN

(11.06 mg, 0.176 mmol). The reaction mixture stirred at 50 °C for 4 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by C18 column (mobile phase: ACN - H₂O (0.1% FA), gradient: 10 - 95) to give N-methyl-5-(4-(4-(4-oxo-3,4-dihydroquinazolin-2-yl)-2-azabicyclo[2.1.1]hexan-2-yl)piperidin-1-yl)picolinamide **192** (25.6 mg, 99 % purity, 16% yield) as a white solid.

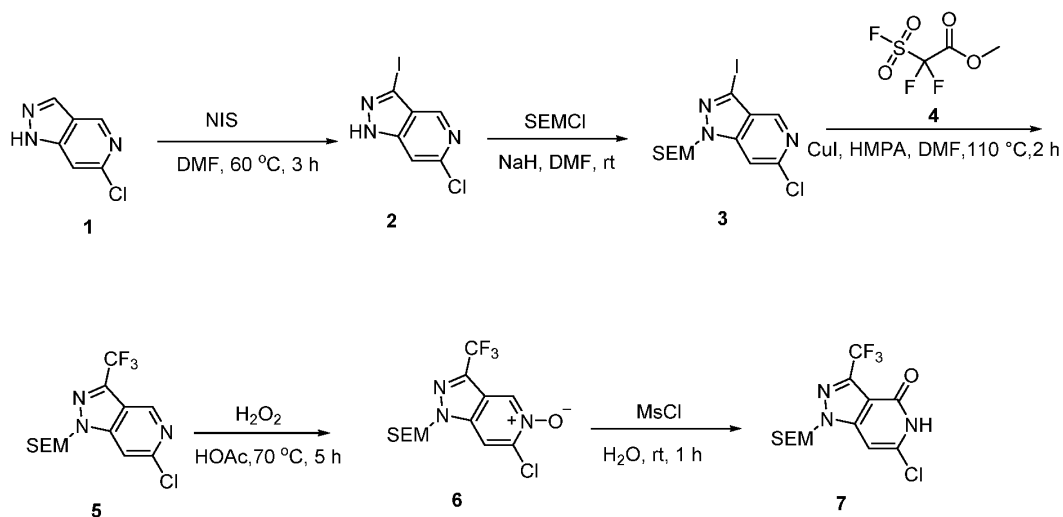
Compound 192

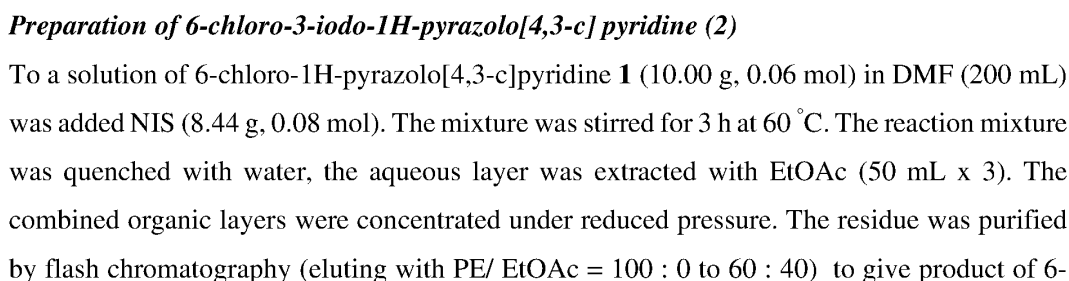
¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ: 12.17 (s, 1 H), 8.43-8.36 (m, 1 H), 8.29 (d, *J* = 2.8 Hz, 1 H), 8.17 (s, 1 H), 8.10 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.86-7.76 (m, 2 H), 7.62 (d, *J* = 7.8 Hz, 1 H), 7.52-7.47 (m, 1 H), 7.42 (dd, *J* = 8.8, 2.9 Hz, 1 H), 3.93-3.86 (m, 2 H), 3.76 (s, 1 H), 3.12 (s, 2 H), 2.97-2.90 (m, 2 H), 2.78 (d, *J* = 4.8 Hz, 3 H), 2.69-2.62 (m, 1 H), 2.19-2.14 (m, 2 H), 2.02-1.90 (m, 4 H), 1.54-1.44 (m, 2 H).

LCMS (ESI) calcd for C₂₅H₂₈N₆O₂ [M + H]⁺ *m/z* 445.23, found 445.15.

Example 18 – Synthesis of compound 194a and 194b

Synthesis of compounds 194a and 194b





To a solution of 6-chloro-1H-pyrazolo[4,3-c]pyridine **1** (10.00 g, 0.06 mol) in DMF (200 mL) was added NIS (8.44 g, 0.08 mol). The mixture was stirred for 3 h at 60 °C. The reaction mixture was quenched with water, the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/ EtOAc = 100 : 0 to 60 : 40) to give product of 6-

To a solution of 6-chloro-1H-pyrazolo[4,3-c]pyridine **1** (10.00 g, 0.06 mol) in DMF (200 mL) was added NIS (8.44 g, 0.08 mol). The mixture was stirred for 3 h at 60 °C. The reaction mixture was quenched with water, the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/ EtOAc = 100 : 0 to 60 : 40) to give product of 6-

chloro-3-iodo-1H-pyrazolo[4,3-c]pyridine **2** (10.5 g, 64% yield) as a yellow solid.

LCMS (ESI) calcd for C₆H₃ClIN₃ [M + H]⁺ m/z 279.91, found 280.00.

Preparation of 6-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-c]pyridine (3)

A suspension of 6-chloro-3-iodo-1H-pyrazolo[4,3-c]pyridine **2** (10.50 g, 0.04 mol) and NaH (2.70 g, 0.11 mol) in DMF (200 mL) was stirred for 30 min at 0 °C, then SEMCl (12.30 g, 0.08 mol) was added. The mixture was stirred for 3 h at room temperature. The reaction mixture was quenched with water, the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layer was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/ EtOAc = 100 : 0 to 70 : 30) to give product of 6-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-c]pyridine **3** (9.90 g, 61% yield) as a yellow solid.

LCMS (ESI) calcd for C₁₂H₁₇ClIN₃OSi [M + H]⁺ m/z 409.99, found 410.05.

Preparation of 6-chloro-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-c]pyridine (5)

To a solution of 6-chloro-3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-c]pyridine **3** (9.90 g, 0.02 mol) and methyl 2,2-difluoro-2-(fluorosulfonyl)acetate **4** (23.04 g, 0.12 mol) in DMF (80 mL) were added CuI (9.15 g, 0.04 mmol) and HMPA (21.35g, 0.12 mmol) at room temperature. The mixture was stirred for 2 h at 110 °C. The reaction mixture was quenched with water, the aqueous layer was extracted with EtOAc (50 mL x 3). The combined organic layer was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/ EtOAc = 100 : 0 to 80 : 20) to give product of 6-chloro-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-c]pyridine **5** (3.30 g, 38% yield) as a yellow solid.

LCMS (ESI) calcd for C₁₃H₁₇ClF₃N₃OSi [M + H]⁺ m/z 352.08, found 352.20.

Preparation of 6-chloro-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-c]pyridine 5-oxide (6)

To a solution of 6-chloro-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-c]pyridine **5** (3.30 g, 0.01 mmol) in HOAc (20 mL) was added H₂O₂ (20 mL). The reaction mixture stirred at 70 °C for 5 h. After cooling to room temperature, the reaction mixture was quenched with water, the aqueous layer was extracted with EtOAc (30 mL x 3).

The combined organic layer was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/ EtOAc = 100 : 0 to 55 : 45) to give product of 6-chloro-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-c]pyridine 5-oxide **6** (1.60 g, 48% yield) as a yellow oil.

LCMS (ESI) calcd for C₁₃H₁₇ClF₃N₃O₂Si [M + H]⁺ m/z 368.07, found 367.97.

Preparation of 6-chloro-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (7)

To a solution of 6-chloro-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazolo[4,3-c]pyridine 5-oxide **6** (800 mg, 2.16 mmol) in H₂O (15 mL) and MsCl (1.00 g, 8.62 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with water, the aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layer was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/ EtOAc = 100 : 0 to 85 : 15) to give product of 6-chloro-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one **7** (400 mg, 48% yield) as a yellow oil.

LCMS (ESI) calcd for C₁₃H₁₇ClF₃N₃O₂Si [M + H]⁺ m/z 368.07, found 368.01.

Preparation of 6-chloro-5-(4-methoxybenzyl)-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (8)

To a solution of 6-chloro-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one **7** (400 mg, 1.07 mmol) and Cs₂CO₃ (1.25 g, 3.85 mmol) in DMF (15 mL) was added PMBCl (0.84 g, 5.35 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 2 h. After cooling to room temperature, the combined organic layer was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/ EtOAc = 100 : 0 to 85 : 15) to give product of 6-chloro-5-(4-methoxybenzyl)-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one **8** (200 mg, 32% yield) as a yellow oil.

LCMS (ESI) calcd for C₂₁H₂₅ClF₃N₃O₃Si [M + H]⁺ m/z 488.13, found 488.15.

Preparation of tert-butyl 3-(5-(4-methoxybenzyl)-4-oxo-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-6-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (10)

To a solution of 6-chloro-5-(4-methoxybenzyl)-3-(trifluoromethyl)-1-((2-

(trimethylsilyl)ethoxy)methyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one **8** (200 mg, 0.48 mmol) and tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydropyrrole-1-carboxylate **9** (150 mg, 0.50 mmol) in Dioxan:H₂O=5:1 (15 mL) was added Pd(dppf)Cl₂ (50 mg, 0.07 mmol) and Na₂CO₃ (70 mg, 0.06 mmol) at room temperature. The reaction mixture stirred under nitrogen at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography (eluting with PE/ EtOAc = 100 : 0 to 80 : 20) to give product of tert-butyl 3-(5-(4-methoxybenzyl)-4-oxo-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-6-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **10** (140 mg, 60% yield) as a yellow oil. LCMS (ESI) calcd for C₃₀H₃₉F₃N₄O₅Si [M + H]⁺ m/z 621.26, found 621.30.

Preparation of tert-butyl 3-(5-(4-methoxybenzyl)-4-oxo-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-6-yl)pyrrolidine-1-carboxylate (11)

To a solution of tert-butyl 3-(5-(4-methoxybenzyl)-4-oxo-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-6-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **10** (140 mg, 0.30 mmol) in MeOH (15 mL) was added Pd/C (60 mg, 0.57 mmol). The reaction mixture stirred under hydrogen at room temperature for 2 h. The reaction mixture was filtered, the solution was concentrated under reduced pressure to give product of tert-butyl 3-(5-(4-methoxybenzyl)-4-oxo-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-6-yl)pyrrolidine-1-carboxylate **11** (120 mg, 80% yield) as a colourless oil.

LCMS (ESI) calcd for C₃₀H₄₁F₃N₄O₅Si [M + H]⁺ m/z 623.28, found 623.30.

Preparation of 6-(pyrrolidin-3-yl)-3-(trifluoromethyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one (12)

To a solution of tert-butyl 3-(5-(4-methoxybenzyl)-4-oxo-3-(trifluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-6-yl)pyrrolidine-1-carboxylate **11** (120 mg, 0.19 mmol) in TFA (5 mL) was added two drops of TfOH. The reaction mixture was stirred at 50 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give product of 6-(pyrrolidin-3-yl)-3-(trifluoromethyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one **12** (50 mg, 90% yield) as a yellow oil.

LCMS (ESI) calcd for C₁₁H₁₁F₃N₄O [M + H]⁺ m/z 273.09, found 273.15.

Preparation of N-methyl-5-(4-(3-(4-oxo-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-6-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide (racemic mixture of 194a and 194b)

To a solution of 6-(pyrrolidin-3-yl)-3-(trifluoromethyl)-1,5-dihydro-4H-pyrazolo[4,3-c]pyridin-4-one **12** (50 mg, 0.18 mmol) in MeOH (10 mL) was added N-methyl-5-(4-oxopiperidin-1-yl)pyridine-2-carboxamide **INT** (43 mg, 0.18 mmol). Then two drops of acetic acid and NaBH₃CN (12 mg, 0.18 mmol) were added at room temperature. The reaction mixture was stirred at 50 °C for 4 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 92 : 8) to give N-methyl-5-(4-(3-(4-oxo-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-6-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide a racemic mixture of compounds **194a** and **194b** (30 mg, 32% yield) as a white solid.

LCMS (ESI) calcd for C₂₃H₂₆F₃N₇O₂ [M + H]⁺ m/z 490.21, found 490.17.

Chiral separation of N-methyl-5-(4-(3-(4-oxo-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-6-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide (compounds 194a and 194b)

A racemic mixture of N-methyl-5-(4-(3-(4-oxo-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazolo[4,3-c]pyridin-6-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide (**194rac**) was separated by SFC (Column: Daicel CHIRALPAK OJ-H 250 mm × 20 mm I.D., 5 μm; Mobile phase: CO₂/MeOH[0.1%(NH₃)] = 70/30) and concentrated under reduced pressure to afford the first fraction as **194a** (9.9 mg, 98% purity, ee%: 100, white solid) and the second fraction as **194b** (9.4 mg, 100% purity, ee%: 98, white solid)

Compound 194a

¹H NMR (400 MHz, DMSO) δ 13.82 (s, 1 H), 11.10 (s, 1 H), 8.39 (q, *J* = 4.4 Hz, 1 H), 8.28 (d, *J* = 2.8 Hz, 1 H), 7.83 (d, *J* = 8.8 Hz, 1 H), 7.41 (dd, *J* = 8.8, 2.8 Hz, 1 H), 6.39 (s, 1 H), 3.84-3.81 (m, 2 H), 3.29-3.25 (m, 1 H), 2.98 (t, *J* = 11.2 Hz, 2 H), 2.89-2.85 (m, 1 H), 2.81-2.78 (m, 5 H), 2.60-2.56 (m, 1 H), 2.39-2.30 (m, 1 H), 2.30-2.17 (m, 1 H), 1.97 (d, *J* = 12.0 Hz, 2 H), 1.83-1.77 (m, 1 H), 1.56-1.51 (m, 2 H).

LCMS (ESI) calcd for C₂₃H₂₆F₃N₇O₂ [M + H]⁺ m/z 490.21, found 490.20.

Compound 194b

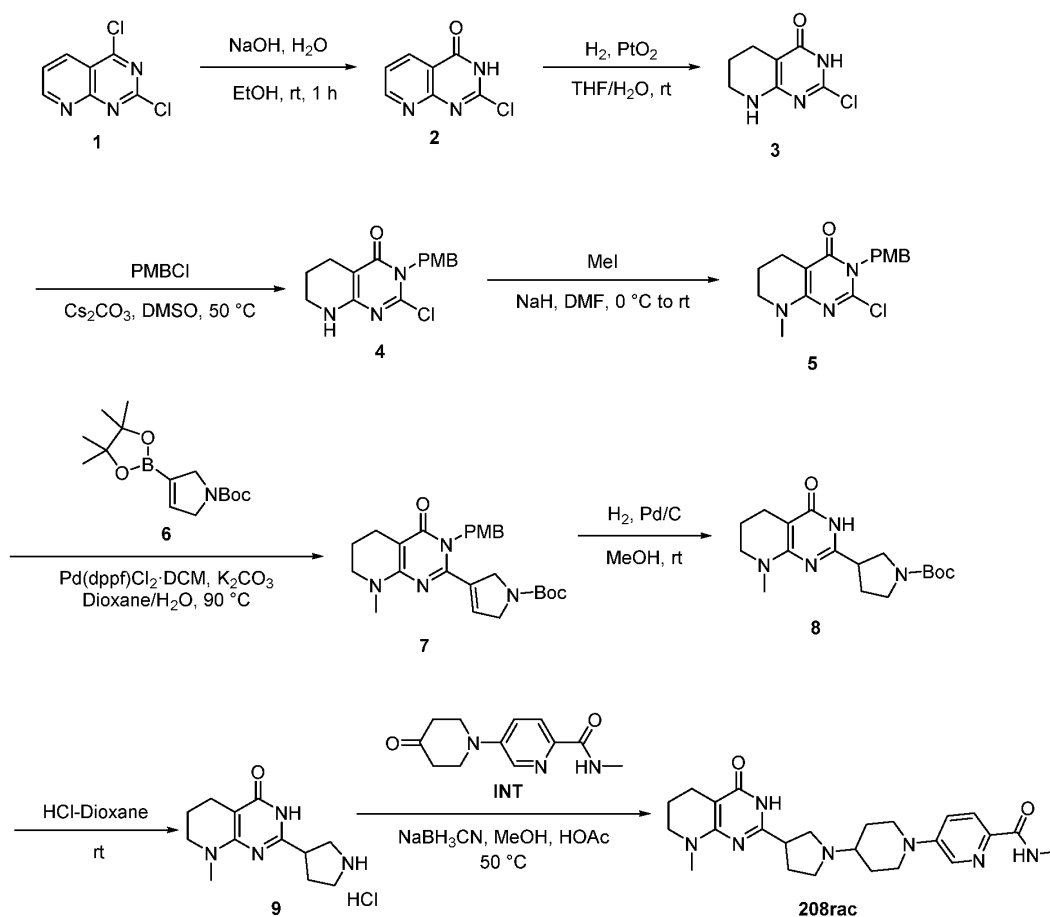
¹H NMR (400 MHz, DMSO) δ 13.81 (s, 1 H), 11.11 (s, 1 H), 8.39 (q, *J* = 4.8 Hz, 1 H), 8.28

(d, $J = 2.8$ Hz, 1 H), 7.83 (d, $J = 8.8$ Hz, 1 H), 7.40 (dd, $J = 8.8, 2.8$ Hz, 1 H), 6.40 (s, 1 H), 3.91-3.81 (m, 2 H), 3.27-3.23 (m, 1 H), 2.98 (t, $J = 11.6$ Hz, 2 H), 2.90-2.86 (m, 1 H), 2.80-2.77 (m, 5 H), 2.60-2.54 (m, 1 H), 2.36-2.33 (m, 1 H), 2.25-2.19 (m, 1 H), 1.97 (d, $J = 11.2$ Hz, 2 H), 1.86-1.75 (m, 1 H), 1.58-1.48 (m, 2 H).

LCMS (ESI) calcd for $C_{23}H_{26}F_3N_7O_2$ $[M + H]^+$ m/z 490.21, found 490.16.

Example 19 – Synthesis of compounds 208a and 208b

Synthesis of compounds 208a and 208b



Preparation of 2-chloropyrido[2,3-d]pyrimidin-4(3H)-one (2)

To a solution of 2,4-dichloropyrido[2,3-d] pyrimidine **1** (1.5 g, 0.0075 mol) in EtOH (30 mL) at room temperature was added NaOH (0.66 g, 0.017 mol) in H₂O (16.5 mL) at rt. The reaction

mixture was stirred at rt for 1 h. The reaction solution was quenched with water, then adjusted pH to 4~5 with 1 M HCl. The solution was filtered, and the filter cake was collected and dried *in vacuo* pressure to give 2-chloropyrido[2,3-d]pyrimidin-4(3H)-one **2** (1.1 g, 90% purity, 73% yield) as yellow solid.

LCMS (ESI) calcd for C₇H₄ClN₃O [M + H]⁺ m/z 182.00, found 181.90.

Preparation of 2-chloro-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one (3)

To a solution of 2-chloropyrido[2,3-d] pyrimidin-4(3H)-one **2** (1.1 g, 0.0061 mol) in THF/H₂O = 4:1 (50 mL) was added PtO₂ (0.14 g). Then the mixture was stirred under hydrogen for 18 h at rt. The mixture was filtered through a celite pad, and the filtrate was concentrated under reduced pressure to give 2-chloro-5,6,7,8-tetrahydropyrido[2,3-d] pyrimidin-4(3H)-one **3** (1.1 g, 95% purity, 91% yield) as a yellow solid.

LCMS (ESI) calcd for C₇H₈ClN₃O [M + H]⁺ m/z 186.04, found 185.95.

Preparation of 2-chloro-3-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one (4)

To a solution of 2-chloro-5,6,7,8-tetrahydropyrido[2,3-d] pyrimidin-4(3H)-one **3** (0.9 g, 4.85 mmol) in DMSO (150 mL) at room temperature were added Cs₂CO₃ (4.7 g, 14.5 mmol) and PMBCl (1.52 g, 9.7 mmol). The reaction mixture was stirred at 50 °C for 1 h. The reaction solution was quenched with water and extracted with EtOAc (100 mL × 3). The combined organic phase was washed three times with brine and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 50: 50) to give 2-chloro-3-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one **4** (1.23 g, 90% purity, 74% yield) as white solid.

LCMS (ESI) calcd for C₁₅H₁₆ClN₃O₂ [M + H]⁺ m/z 306.09, found 305.80.

Preparation of 2-chloro-3-(4-methoxybenzyl)-8-methyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one (5)

To a solution of 2-chloro-3-(4-methoxybenzyl)-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one **4** (1.2 g, 0.004 mol) in DMF (50 mL) at 0 °C were added MeI (3.05 g, 0.02 mol) and NaH (60% in mineral oil, 0.32 g, 0.008 mol). The reaction mixture was stirred at rt for 2 h. The reaction solution was quenched with water and extracted with EtOAc (100 mL × 3). The combined organic phase was washed three times with brine and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0

to 50: 50) to give 2-chloro-3-(4-methoxybenzyl)-8-methyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one **5** (450 mg, 90% purity, 33% yield) as yellow oil.

LCMS (ESI) calcd for $C_{16}H_{18}ClN_3O_2$ $[M + H]^+$ m/z 320.11, found 320.00.

Preparation of tert-butyl 3-(3-(4-methoxybenzyl)-8-methyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (7)

To a solution of 2-chloro-3-(4-methoxybenzyl)-8-methyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one **5** (450 mg, 1.41 mmol) in dioxane/ H_2O = 5:1 (30 mL) at room temperature were added tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **6** (500 mg, 1.69 mmol), $Pd(dppf)Cl_2 \cdot DCM$ (115 mg, 0.14 mmol) and K_2CO_3 (587 mg, 4.22 mmol). The reaction mixture was stirred at 90 °C for 3 h. The reaction solution was quenched with water and extracted with EtOAc (50 mL $\times$ 3). The combined organic phase was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 50: 50) to give tert-butyl 3-(3-(4-methoxybenzyl)-8-methyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **7** (550 mg, 90% purity, 77% yield) as white solid.

LCMS (ESI) calcd for $C_{25}H_{32}N_4O_4$ $[M + H]^+$ m/z 453.24, found 453.20.

Preparation of tert-butyl 3-(8-methyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)pyrrolidine-1-carboxylate (8)

To a solution of tert-butyl 3-(3-(4-methoxybenzyl)-8-methyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **7** (550 mg, 1.2 mmol) in MeOH (15 mL) at room temperature were added Pd/C (55 mg). The reaction mixture was stirred at rt for 18 h under a hydrogen atmosphere. The reaction solution was filtered, and the filter cake was washed with MeOH (5 mL $\times$ 2). The filtrate was concentrated under reduced pressure to give tert-butyl 3-(8-methyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)pyrrolidine-1-carboxylate **8** (400 mg, 90% purity, 88% yield) as yellow oil.

LCMS (ESI) calcd for $C_{17}H_{26}N_4O_3$ $[M + H]^+$ m/z 335.20, found 335.30.

Preparation of 8-methyl-2-(pyrrolidin-3-yl)-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one hydrochloride (9)

A solution of tert-butyl 3-(8-methyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)pyrrolidine-1-carboxylate **8** (200 mg, 0.60 mmol) in HCl-dioxane (4 M, 10 mL) was stirred

at room temperature for 2 h under N₂ atmosphere. The precipitate formed was washed with DCM (5 mL × 3), collected and dried under reduced pressure to obtain 8-methyl-2-(pyrrolidin-3-yl)-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one hydrochloride **9** (110 mg, 90% purity, 70% yield) as white solid.

LCMS (ESI) calcd for C₁₂H₁₈N₄O [M + H]⁺ m/z 235.15, found 235.00.

Preparation of N-methyl-5-(4-(3-(8-methyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide (208a and 208b)

To a solution of 8-methyl-2-(pyrrolidin-3-yl)-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one hydrochloride **9** (110 mg, 0.46 mmol) in MeOH (1 mL) was added TEA (1 mL) at rt and stirred for 5 mins, then the reaction was concentrated to dryness under reduced pressure. The residue was dissolved in MeOH (15 mL) and AcOH (0.01 mL) at room temperature. N-methyl-5-(4-oxopiperidin-1-yl)picolinamide **INT** (131 mg, 0.56 mmol) and NaBH₃CN (88 mg, 1.40 mmol) were added. The reaction mixture was stirred at 50 °C for 1 h. The reaction solution was concentrated under reduced pressure and the residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 90: 10) to give a racemic mixture of N-methyl-5-(4-(3-(8-methyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide **208rac** (120 mg, 99% purity, 55 % yield) as a white solid.

LCMS (ESI) calcd for C₂₄H₃₃N₇O₂ [M + H]⁺ m/z 452.27, found 452.20.

Chiral resolution of N-methyl-5-(4-(3-(8-methyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide (208rac)

A racemic mixture of compounds **208a** and **208b** was separated by SFC (Column: Daicel Chiralpak IH SFC, 250 mm × 20 mm I.D., 5 μm; Mobile phase: CO₂/MeOH [0.1% NH₃] = 70/30) and concentrated under reduced pressure to afford the first fraction as **208a** (52.3 mg, 99% purity, 100% ee, white solid) and the second fraction as **208b** (54.2 mg, 100% purity, 98% ee, white solid).

Compound 208a

¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ: 11.37 (s, 1 H), 8.43-8.34 (m, 1 H), 8.26 (d, *J* = 2.8 Hz, 1 H), 7.81 (d, *J* = 8.8 Hz, 1 H), 7.39 (dd, *J* = 8.8, 3.2 Hz, 1 H), 3.82-3.77 (m, 2 H), 3.23-3.20 (m, 2 H), 3.13-3.09 (m, 1 H), 3.03 (s, 3 H), 2.99-2.92 (m, 3 H), 2.78 (d, *J* = 4.8 Hz, 3 H), 2.68-2.66 (m, 1 H), 2.59-2.57 (m, 1 H), 2.35-2.26 (m, 4 H), 2.07-2.00 (m, 2 H), 1.94-1.88 (m, 2 H), 1.78-1.72 (m, 2 H), 1.53-1.44 (m, 2 H).

LCMS (ESI) calcd for $C_{24}H_{33}N_7O_2$ $[M + H]^+$ m/z 452.27, found 452.30.

Compound 208b

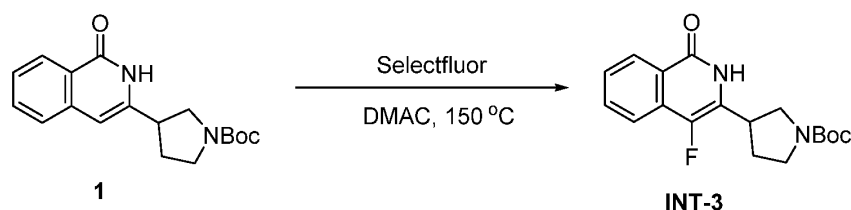
^1H NMR (400 MHz, DMSO- d_6 , ppm) δ : 11.35 (s, 1 H), 8.41-8.33 (m, 1 H), 8.26 (d, $J = 2.8$ Hz, 1 H), 7.81 (d, $J = 8.8$ Hz, 1 H), 7.39 (dd, $J = 8.8, 2.8$ Hz, 1 H), 3.85-3.75 (m, 2 H), 3.24-3.19 (m, 2 H), 3.14-3.07 (m, 1 H), 3.03 (s, 3 H), 3.00-2.88 (m, 3 H), 2.77 (d, $J = 4.8$ Hz, 3 H), 2.67-2.62 (m, 1 H), 2.61-2.56 (m, 1 H), 2.35-2.21 (m, 4 H), 2.09-1.99 (m, 2 H), 1.96-1.87 (m, 2 H), 1.79-1.70 (m, 2 H), 1.55-1.43 (m, 2 H).

LCMS (ESI) calcd for $C_{24}H_{33}N_7O_2$ $[M + H]^+$ m/z 452.27, found 452.30.

Example 20 – Synthesis of INT-3

Synthesis of INT-3

Preparation of tert-butyl 3-(4-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)pyrrolidine-1-carboxylate (INT-3)

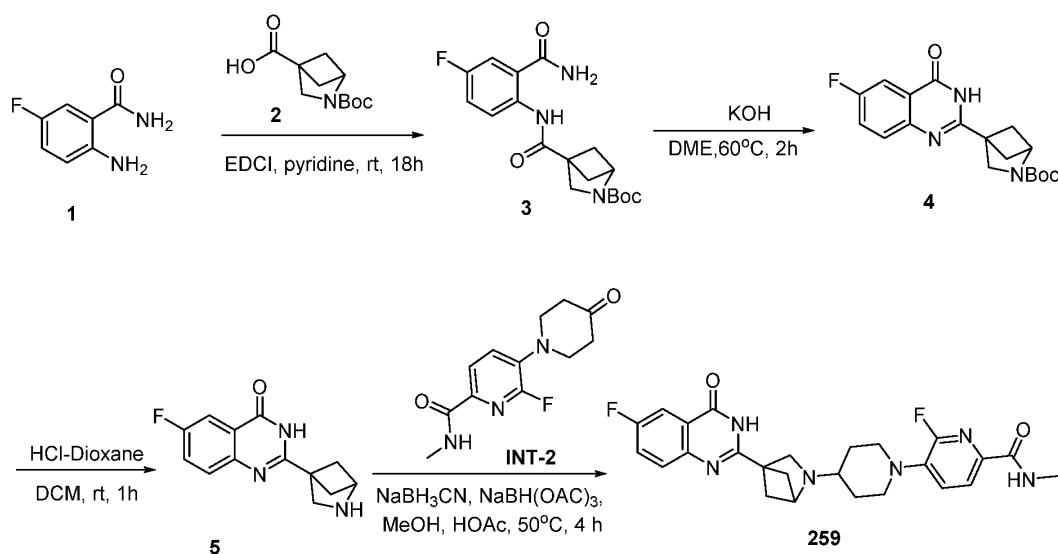


To a solution of tert-butyl 3-(1-oxo-1,2-dihydroisoquinolin-3-yl)pyrrolidine-1-carboxylate **1** (500 mg, 1.59 mmol) in DMAC (20 mL) was added Selectfluor (563 mg, 1.59 mmol) at rt. The mixture was stirred at 150 °C for 10 min. After cooling to rt, the reaction mixture was added into cold water and then extracted with EtOAc (100 mL $\times$ 3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash silica chromatography (eluting with PE/EtOAc = 100 : 0 to 50 : 50) to give tert-butyl 3-(4-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)pyrrolidine-1-carboxylate **INT-3** (100 mg, 60% purity, 11% yield) as yellow oil.

LCMS (ESI) calcd for $C_{18}H_{21}FN_2O_3$ $[M + H]^+$ m/z 333.15, found 332.90.

Example 21 – synthesis of compound 259

Synthesis of compound 259



Preparation of *tert*-butyl 4-((2-carbamoyl-4-fluorophenyl)carbamoyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (3)

To a solution of 2-amino-5-fluorobenzamide **1** (30 mg, 2.21 mmol) and 2-(*tert*-butoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxylic acid **2** (520 mg, 2.20 mmol) in pyridine (20 mL) was added EDCI (423 mg, 2.21 mmol), then the mixture was stirred for 18 h at room temperature. The reaction mixture was quenched with water, the aqueous layer was extracted with EtOAc (150 mL x 3). The combined organic layers were washed with 1M HCl solution and brine, dried over Na₂SO₄, concentrated under reduced pressure to give product of *tert*-butyl 4-((2-carbamoyl-4-fluorophenyl)carbamoyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **3** (500 mg, 56% yield) as a white solid.

LCMS (ESI) calcd for C₁₈H₂₂FN₃O₄ [M + Na]⁺ m/z 386.16, found 385.95.

Preparation of *tert*-butyl 4-(6-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (4)

To the solution of *tert*-butyl 4-((2-carbamoyl-4-fluorophenyl)carbamoyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **3** (500 mg, 1.38 mmol) in DME (50 mL) was added KOH (154 mg, 2.75 mmol). The solution was stirred at 60 °C for 2 h, cooled to room temperature, then the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 90 : 10) to give *tert*-butyl 4-(6-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-azabicyclo[2.1.1]hexane-2-

carboxylate **4** (400 mg, 76% yield) as a white solid.

LCMS (ESI) calcd for C₁₈H₂₀FN₃O₃ [M + H]⁺ m/z 346.15, found 345.85.

Preparation of 2-(2-azabicyclo[2.1.1]hexan-4-yl)-6-fluoroquinazolin-4(3H)-one (5)

To a solution of tert-butyl 4-(6-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **4** (400 mg, 1.16 mmol) in DCM (10 mL) was added HCl in dioxane (4M, 20 mL). The mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure to give product of 2-(2-azabicyclo[2.1.1]hexan-4-yl)-6-fluoroquinazolin-4(3H)-one **5** (200 mg, 63% yield) as a white solid.

LCMS (ESI) calcd for C₁₅H₁₇N₃O [M + H]⁺ m/z 246.10, found 245.95.

Preparation of 6-fluoro-5-(4-(4-(6-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-azabicyclo[2.1.1]hexan-2-yl)piperidin-1-yl)-N-methylpicolinamide (Compound 259)

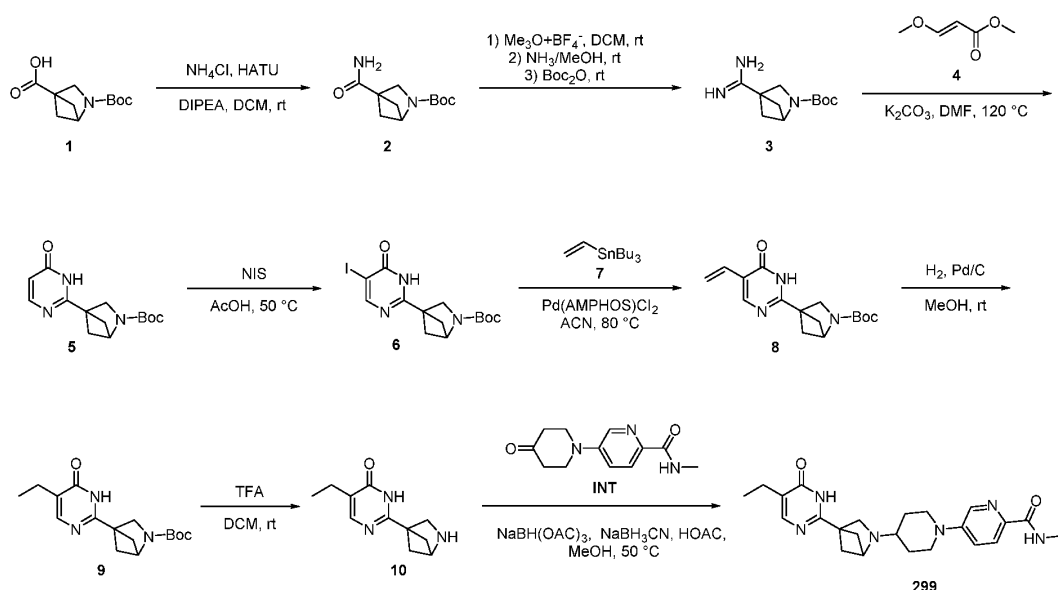
To a solution of 2-(2-azabicyclo[2.1.1]hexan-4-yl)-6-fluoroquinazolin-4(3H)-one **5** (60 mg, 0.24 mmol) in MeOH (20 mL) was added 6-fluoro-N-methyl-5-(4-oxopiperidin-1-yl)picolinamide **INT-2** (61 mg, 0.24 mmol), then two drops of acetic acid and NaBH(OAc)₃ (104 mg, 0.49 mmol) were added at room temperature. After 1 h, NaBH₃CN (8 mg, 0.13 mmol) was added. The reaction mixture stirred at 50 °C for 4 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by C₁₈ column (mobile phase: ACN - H₂O (0.1% FA), gradient: 10 - 95) to give 6-fluoro-5-(4-(4-(6-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl)-2-azabicyclo[2.1.1]hexan-2-yl)piperidin-1-yl)-N-methylpicolinamide **259** (45.5 mg, 99 % purity, 15% yield) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ: 12.29 (s, 1 H), 8.40 (q, 1 H), 7.84 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.77 (dd, *J* = 8.4, 2.8 Hz, 1 H), 7.72-7.65 (m, 2 H), 7.62-7.56 (m, 1 H), 3.70 (s, 1 H), 3.59-3.53 (m, 2 H), 3.05 (s, 2 H), 2.86 (t, *J* = 11.2 Hz, 2 H), 2.77 (d, *J* = 4.8 Hz, 3 H), 2.57-2.52 (m, 1 H), 2.15-2.09 (m, 2 H), 1.99 (d, *J* = 10.8 Hz, 2 H), 1.92-1.86 (m, 2 H), 1.58-1.47 (m, 2 H).

LCMS (ESI) calcd for C₂₅H₂₆F₂N₆O₂ [M + H]⁺ m/z 481.21, found 481.05.

Example 22 – synthesis of compound 299

Synthesis of compound 299



Preparation of tert-butyl ((1-(6-(methylcarbamoyl)pyridin-3-yl)piperidin-4-yl)methyl)carbamate (**2**)

To a solution of 2-(tert-butoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxylic acid **1** (500 mg, 2.19 mmol) in DCM (20 mL) were added NH_4Cl (234 mg, 4.38 mmol), DIPEA (1415 mg, 10.95 mmol) and HATU (1249 mg, 3.28 mmol) at room temperature successively. The mixture was kept stirring at room temperature for 1 h. The resulting mixture was diluted with water and extracted with DCM (50 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with MeOH/DCM, 3% to 5%) to give tert-butyl 4-carbamoyl-2-azabicyclo[2.1.1]hexane-2-carboxylate **2** (400 mg, 90% purity, 72% yield) as a white solid. LCMS (ESI) calcd for $\text{C}_{11}\text{H}_{18}\text{N}_2\text{O}_3$ [$\text{M} - 56 + \text{H}$] $^+$ m/z 171.13, found 171.10.

Preparation of tert-butyl 4-carbamimidoyl-2-azabicyclo[2.1.1]hexane-2-carboxylate (**3**)

Tert-butyl 4-carbamoyl-2-azabicyclo[2.1.1]hexane-2-carboxylate **2** (400 mg, 1.76 mmol) was added to a suspension of $\text{Me}_3\text{O}^+\text{BF}_4^-$ (312 mg, 2.1 mmol) in anhydrous DCM (10 mL). The mixture was stirred under argon atmosphere at rt for 2 h. Solvent was then removed to provide crude imidate salt. This crude was dissolved in NH_3/MeOH (7 M, 10 mL) and stirred at rt for 16 h. Then Boc_2O (1152 mg, 5.28 mmol) was added. The mixture was stirred at rt for 10 min

and then concentrated to give crude tert-butyl 4-carbamimidoyl-2-azabicyclo[2.1.1]hexane-2-carboxylate **3** (500 mg, 50% purity, 62% yield) as a white solid.

LCMS (ESI) calcd for $C_{11}H_{19}N_3O_2$ $[M + H]^+$ m/z 226.15, found 226.05.

Preparation of tert-butyl 4-(6-oxo-1,6-dihydropyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (5)

To a solution of tert-butyl 4-carbamimidoyl-2-azabicyclo[2.1.1]hexane-2-carboxylate **3** (500 mg, 2.21 mmol) in DMF (20 mL) were added K_2CO_3 (916 mg, 6.63 mmol) and methyl (E)-3-methoxyacrylate **4** (770 mg, 6.63 mmol) in one portion. The reaction mixture was heated with stirring at 120 °C for 2 h. The reaction mixture was concentrated and purified by silica gel column chromatography (eluting with EtOAc/PE, 50% to 100%) to obtain tert-butyl 4-(6-oxo-1,6-dihydropyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **5** (200 mg, 90% purity, 29% yield) as a white solid.

LCMS (ESI) calcd for $C_{14}H_{19}N_3O_3$ $[M + H]^+$ m/z 278.15, found 277.95.

Preparation of tert-butyl 4-(5-iodo-6-oxo-1,6-dihydropyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (6)

To a solution of tert-butyl 4-(6-oxo-1,6-dihydropyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **5** (215 mg, 0.77 mmol) in AcOH (5 mL) was added NIS (260 mg, 1.16 mmol) in one portion. The reaction mixture was heated with stirring at 50 °C for 2 h. The reaction mixture was concentrated and purified by silica gel column chromatography (eluting with EtOAc/PE, 50% to 70%) to obtain tert-butyl 4-(5-iodo-6-oxo-1,6-dihydropyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **6** (180 mg, 90% purity, 51% yield) as a white solid.

LCMS (ESI) calcd for $C_{14}H_{18}IN_3O_3$ $[M + H]^+$ m/z 404.04, found 403.85.

Preparation of tert-butyl 4-(6-oxo-5-vinyl-1,6-dihydropyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (8)

A solution of tert-butyl 4-(5-iodo-6-oxo-1,6-dihydropyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **6** (180 mg, 0.44 mmol), tributyl(vinyl)stannane **7** (282 mg, 0.89 mmol) and $Pd(AMPHOS)Cl_2$ (32 mg, 0.04 mmol) in ACN (10 mL) was purged with N_2 for 2 min and then stirred at 80 °C for 1 h. After cooling to rt, the reaction mixture was concentrated and purified by flash chromatography (eluting with EtOAc/PE, 50% to 70%) to give tert-butyl 4-(6-oxo-5-vinyl-1,6-dihydropyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **8** (120 mg, 90% purity, 79% yield) as a white solid.

LCMS (ESI) calcd for C₁₆H₂₁N₃O₃ [M + H]⁺ m/z 304.16, found 304.20.

Preparation of tert-butyl 4-(5-ethyl-6-oxo-1,6-dihydropyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (9)

To a solution of give tert-butyl 4-(6-oxo-5-vinyl-1,6-dihydropyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **8** (120 mg, 0.40 mmol) in MeOH (5 mL) was added 10% Pd/C (12 mg). The mixture was evacuated and backfilled with nitrogen three times and then charged with hydrogen. The resulting mixture was stirred at room temperature for 16 hours. Then the mixture was filtered through celite and concentrated under vacuum to give crude tert-butyl 4-(5-ethyl-6-oxo-1,6-dihydropyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **9** (120 mg, 90% purity, 89% yield) as a white solid which was used directly in the next step without further purification.

LCMS (ESI) calcd for C₁₆H₂₃N₃O₃ [M + H]⁺ m/z 306.18, found 306.00.

Preparation of 2-(2-azabicyclo[2.1.1]hexan-4-yl)-5-ethylpyrimidin-4(3H)-one (10)

To a solution of tert-butyl 4-(5-ethyl-6-oxo-1,6-dihydropyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **9** (120 mg, 0.39 mmol) in DCM (4 mL) was added TFA (1 mL) dropwise at 0 °C. The reaction solution was stirred at room temperature for 1 hour then concentrated under vacuum. The resulted mixture quenched with Et₃N and concentrated under vacuum to afford 2-(2-azabicyclo[2.1.1]hexan-4-yl)-5-ethylpyrimidin-4(3H)-one **10** (120 mg, 50% purity, 74% yield).

LCMS (ESI) calcd for C₁₁H₁₅N₃O [M + H]⁺ m/z 206.12, found 206.00.

Preparation of 5-(4-(4-(5-ethyl-6-oxo-1,6-dihydropyrimidin-2-yl)-2-azabicyclo[2.1.1]hexan-2-yl)piperidin-1-yl)-N-methylpicolinamide (299)

To a solution of 2-(2-azabicyclo[2.1.1]hexan-4-yl)-5-ethylpyrimidin-4(3H)-one **10** (40 mg, 0.19 mmol) in MeOH (5 mL) was added N-methyl-5-(4-oxopiperidin-1-yl)picolinamide **INT** (68 mg, 0.29 mmol), then two drops of acetic acid and NaBH(OAc)₃ (82 mg, 0.39 mmol) were added at room temperature. After 1 h, NaBH₃CN (12 mg, 0.19 mmol) was added. The reaction mixture stirred at 50 °C for 1 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (Gemini 5 um C18 150 × 21.2 mm, eluting with 10% to 40% ACN/H₂O containing 0.1% NH₃·H₂O) and prep-TLC (MeOH/DCM, 1/20) to give 5-(4-(4-(5-ethyl-6-oxo-1,6-dihydropyrimidin-2-yl)-2-

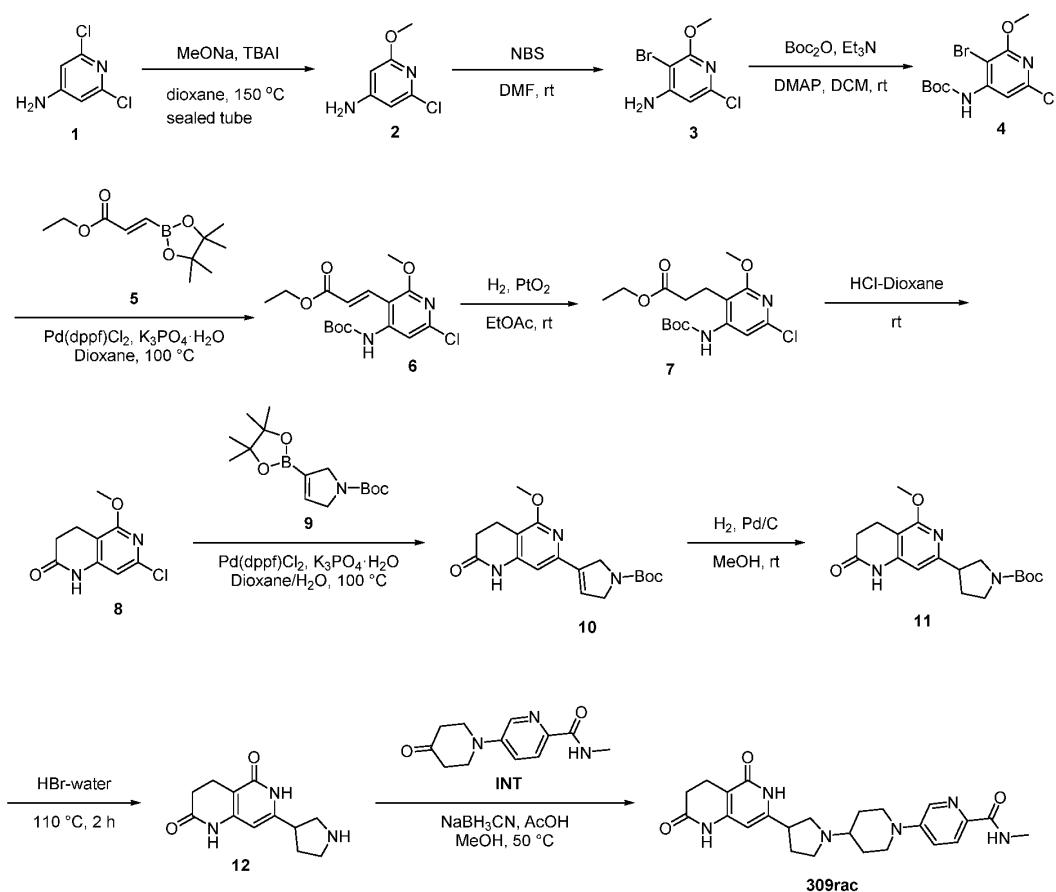
azabicyclo[2.1.1]hexan-2-yl)piperidin-1-yl)-N-methylpicolinamide **299** (3.2 mg, 99% purity, 3% yield) as a white solid.

^1H NMR (400 MHz, DMSO- d_6 , ppm) δ : 12.30 (s, 1 H), 8.39 (q, J = 4.8 Hz, 1 H), 8.27 (d, J = 2.8 Hz, 1 H), 7.81 (d, J = 8.8 Hz, 1 H), 7.72 (s, 1 H), 7.40 (dd, J = 8.8, 2.8 Hz, 1 H), 3.94-3.81 (m, 2 H), 3.64 (s, 1 H), 3.00-2.85 (m, 4 H), 2.78 (d, J = 4.8 Hz, 3 H), 2.57-2.52 (m, 1 H), 2.40-2.27 (m, 2 H), 2.07-2.01 (m, 2 H), 1.96-1.91 (m, 2 H), 1.87-1.72 (m, 2 H), 1.50-1.36 (m, 2 H), 1.07 (t, J = 7.6 Hz, 3 H).

LCMS (ESI) calcd for $\text{C}_{23}\text{H}_{30}\text{N}_6\text{O}_2$ $[\text{M} + \text{H}]^+ m/z$ 423.25, found 423.15

Example 23 - synthesis of compounds 309a and 309b

Synthesis of compounds 309a and 309b



Preparation of 2-chloro-6-methoxypyridin-4-amine (2)

To a solution of 2,6-dichloropyridin-4-amine **1** (1.0 g, 6.1 mmol) in dioxane (15 mL) was added MeONa (3.3 g, 61.0 mmol) and TBAI (230 mg, 0.6 mmol) at rt. The reaction mixture was stirred at 150 °C for 15 h in a sealed tube. The reaction solution was cooled to rt and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with PE/EtOAc = 100 : 0 to 95 : 5) to afford 2-chloro-6-methoxypyridin-4-amine **2** (880 mg, 90% purity, 81% yield) as a white solid.

LCMS (ESI) calcd for C₆H₇ClN₂O [M + H]⁺ m/z 159.02, found 158.93.

Preparation of 3-bromo-6-chloro-2-methoxypyridin-4-amine (3)

To a solution of 2-chloro-6-methoxypyridin-4-amine **2** (880 mg, 5.5 mmol) in DMF (40 mL) was added NBS (1.2 g, 6.7 mmol) at rt. The reaction mixture was stirred at rt for 1 h. The reaction mixture was poured into water. The aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (100 mL × 3), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with PE/EtOAc = 100 : 0 to 70 : 30) to afford 3-bromo-6-chloro-2-methoxypyridin-4-amine **3** (950 mg, 90% purity, 64% yield) as a white solid.

LCMS (ESI) calcd for C₆H₆BrClN₂O [M + H]⁺ m/z 236.94, found 236.87.

Preparation of tert-butyl (3-bromo-6-chloro-2-methoxypyridin-4-yl)carbamate (4)

To a solution of 3-bromo-6-chloro-2-methoxypyridin-4-amine **3** (950 mg, 4.0 mmol) in DCM (30 mL) was added Boc₂O (1.31 g, 6.0 mmol), Et₃N (810 mg, 8.0 mmol) and DMAP (244 mg, 2.0 mmol) successively at rt. The reaction mixture was stirred at rt for 1 h. The reaction solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with PE/EtOAc = 100 : 0 to 80 : 20) to afford a mixture of tert-butyl (3-bromo-6-chloro-2-methoxypyridin-4-yl)carbamate **4** and tert-butyl (3-bromo-6-chloro-2-methoxypyridin-4-yl)(tert-butoxycarbonyl)carbamate **4a** (750 mg, 90% purity, 49% yield) as a white solid.

LCMS (ESI) calcd for C₁₁H₁₄BrClN₂O₃ [M + H]⁺ m/z 336.99, found 336.92.

Preparation of ethyl (E)-3-(4-((tert-butoxycarbonyl)amino)-6-chloro-2-methoxypyridin-3-yl)acrylate (6)

To a solution of the mixture of tert-butyl (3-bromo-6-chloro-2-methoxypyridin-4-yl)carbamate **4** and tert-butyl (3-bromo-6-chloro-2-methoxypyridin-4-yl)(tert-butoxycarbonyl)carbamate **4a**

(750 mg, 2.2 mmol) in dioxane/H₂O (25 mL, 10:1) was added ethyl (E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate **5** (751 mg, 3.3 mmol), Pd(dppf)Cl₂·DCM (181 mg, 0.22 mmol) and K₃PO₄·H₂O (1.5 g, 6.6 mmol) successively at rt. The reaction mixture was stirred at 100 °C for 6 h under N₂. The reaction solution was cooled to rt and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with PE/EtOAc = 100 : 0 to 70 : 30) to afford a mixture of ethyl (E)-3-(4-((tert-butoxycarbonyl)amino)-6-chloro-2-methoxypyridin-3-yl)acrylate **6** and ethyl (E)-3-(4-(bis(tert-butoxycarbonyl)amino)-6-chloro-2-methoxypyridin-3-yl)acrylate **6a** (410 mg, 90% purity, 46% yield) as a white solid.

LCMS (ESI) calcd for C₁₆H₂₁ClN₂O₅ [M + H]⁺ m/z 357.11, found 357.00.

Preparation of ethyl 3-(4-((tert-butoxycarbonyl)amino)-6-chloro-2-methoxypyridin-3-yl)propanoate (7)

A solution of the mixture of ethyl (E)-3-(4-((tert-butoxycarbonyl)amino)-6-chloro-2-methoxypyridin-3-yl)acrylate **6** and ethyl (E)-3-(4-(bis(tert-butoxycarbonyl)amino)-6-chloro-2-methoxypyridin-3-yl)acrylate **6a** (410 mg, 0.9 mmol), and PtO₂ (50 mg) in EtOAc (10 mL) was stirred at rt for 1 h under H₂ atmosphere. The resulting solution was filtered through diatomaceous earth and the filter cake was washed with DCM (20 mL). The filtrate was concentrated under reduced pressure to give a mixture of ethyl 3-(4-((tert-butoxycarbonyl)amino)-6-chloro-2-methoxypyridin-3-yl)propanoate **7** and ethyl 3-(4-(bis(tert-butoxycarbonyl)amino)-6-chloro-2-methoxypyridin-3-yl)propanoate **7a** (210 mg, 90% purity, 45% yield) as a colorless oil.

LCMS (ESI) calcd for C₁₆H₂₃ClN₂O₅ [M + H]⁺ m/z 359.13, found 359.08.

Preparation of 7-chloro-5-methoxy-3,4-dihydro-1,6-naphthyridin-2(1H)-one (8)

A solution of the mixture of ethyl 3-(4-((tert-butoxycarbonyl)amino)-6-chloro-2-methoxypyridin-3-yl)propanoate **7** and ethyl 3-(4-(bis(tert-butoxycarbonyl)amino)-6-chloro-2-methoxypyridin-3-yl)propanoate **7a** (210 mg, 0.6 mmol) in HCl-dioxane (10 mL, 4 M) was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure to give 7-chloro-5-methoxy-3,4-dihydro-1,6-naphthyridin-2(1H)-one **8** (110 mg, 90% purity, 79% yield) as a white solid.

LCMS (ESI) calcd for C₉H₉ClN₂O₂ [M + H]⁺ m/z 213.04, found 212.92.

Preparation of tert-butyl 3-(5-methoxy-2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (10)

To a solution of 7-chloro-5-methoxy-3,4-dihydro-1,6-naphthyridin-2(1H)-one **8** (110 mg, 0.5 mmol) in dioxane/H₂O (10 mL, 10:1) was added tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **9** (184 mg, 0.6 mmol), Pd(dppf)Cl₂ (42 mg, 0.06 mmol) and K₃PO₄·H₂O (357 mg, 1.6 mmol) successively at rt. The reaction mixture was stirred at 100 °C for 6 h under N₂ atmosphere. The reaction solution was cooled to rt and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with PE/EtOAc = 100 : 0 to 20 : 80) to afford tert-butyl 3-(5-methoxy-2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **10** (150 mg, 90% purity, 75% yield) as a white solid.

LCMS (ESI) calcd for C₁₈H₂₃N₃O₄ [M + H]⁺ m/z 346.17, found 346.05.

Preparation of tert-butyl 3-(5-methoxy-2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)pyrrolidine-1-carboxylate (11)

A solution of tert-butyl 3-(5-methoxy-2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **10** (150 mg, 0.4 mmol) and Pd/C (20 mg) in MeOH (10 mL) was stirred at rt for 2 h under H₂ atmosphere. The resulting solution was filtered through diatomaceous earth and the filter cake was washed with DCM (20 mL × 3). The filtrate was concentrated under reduced pressure to give tert-butyl 3-(5-methoxy-2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)pyrrolidine-1-carboxylate **11** (140 mg, 90% purity, 83% yield) as a colorless oil.

LCMS (ESI) calcd for C₁₈H₂₅N₃O₄ [M + H]⁺ m/z 348.18, found 347.95.

Preparation of 7-(pyrrolidin-3-yl)-4,6-dihydro-1,6-naphthyridine-2,5(1H,3H)-dione (12)

A solution of tert-butyl 3-(5-methoxy-2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)pyrrolidine-1-carboxylate **11** (120 mg, 0.34 mmol) in HBr (48% in H₂O, 5 mL) was stirred at 110 °C for 2 h. The reaction solution was cooled to rt and concentrated under reduced pressure. The residue was dissolved in MeOH (5 mL) and Et₃N (1 mL) was added dropwise. The reaction mixture was stirred at rt for 5 min. The reaction solution was concentrated under reduced pressure to give 7-(pyrrolidin-3-yl)-4,6-dihydro-1,6-naphthyridine-2,5(1H,3H)-dione **12** (65 mg, 90% purity, 72% yield) as a brown solid.

LCMS (ESI) calcd for C₁₂H₁₅N₃O₂ [M + H]⁺ m/z 234.12, found 234.06.

Preparation of 5-(4-(3-(2,5-dioxo-1,2,3,4,5,6-hexahydro-1,6-naphthyridin-7-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide (racemic mixture of compounds 309a and 309b)

To a solution of 7-(pyrrolidin-3-yl)-4,6-dihydro-1,6-naphthyridine-2,5(1H,3H)-dione **12** (65 mg, 0.3 mmol) in MeOH (10 mL) was added *N*-methyl-5-(4-oxopiperidin-1-yl)picolinamide **INT** (78 mg, 0.3 mmol), AcOH (2 drops) and NaBH₃CN (35 mg, 0.6 mmol) and at rt. The reaction mixture was stirred at 50 ° C for 1 h. The reaction mixture was quenched with water (2 mL) and the reaction solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with DCM/MeOH = 100 : 0 to 90 : 10) to afford 5-(4-(3-(2,5-dioxo-1,2,3,4,5,6-hexahydro-1,6-naphthyridin-7-yl)pyrrolidin-1-yl)piperidin-1-yl)-*N*-methylpicolinamide a racemic mixture of compounds **309a** and **309b** (35 mg, 98% purity, 27% yield) as a white solid.

Chiral resolution of 5-(4-(3-(2,5-dioxo-1,2,3,4,5,6-hexahydro-1,6-naphthyridin-7-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide (racemic mixture of compounds 309a and 309b)

A racemic mixture of compounds **309a** and **309b** was separated by SFC (Column: Daicel Chiralpak IH SFC; 20 mm I.D. × 250 mm, 5 μm; Mobile phase: CO₂/MeOH [0.1% NH₃ (7 M Solution in MeOH)]=60/40) and concentrated under reduced pressure to afford the first fraction as **309a** (4.8 mg, 95% purity, 100% ee, white solid) and the second fraction as **309b** (8.7 mg, 95% purity, 100% ee, white solid).

Compound 309a

¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ: 11.08 (s, 1 H), 10.04 (s, 1 H), 8.43-8.34 (m, 1 H), 8.27 (d, *J* = 2.8 Hz, 1 H), 7.81 (d, *J* = 8.8 Hz, 1 H), 7.48-7.36 (m, 1 H), 5.83 (s, 1 H), 3.89-3.76 (m, 2 H), 3.14-3.07 (m, 1 H), 3.01-2.91 (m, 2 H), 2.84-2.72 (m, 5 H), 2.60-2.56 (m, 3 H), 2.43-2.41 (m, 3 H), 2.24-2.10 (m, 2 H), 1.96-1.88 (m, 2 H), 1.72-1.62 (m, 1 H), 1.55-1.46 (m, 2 H).

LCMS (ESI) calcd for C₂₄H₃₀N₆O₃ [M + H]⁺ *m/z* 451.24, found 451.40.

Compound 309b

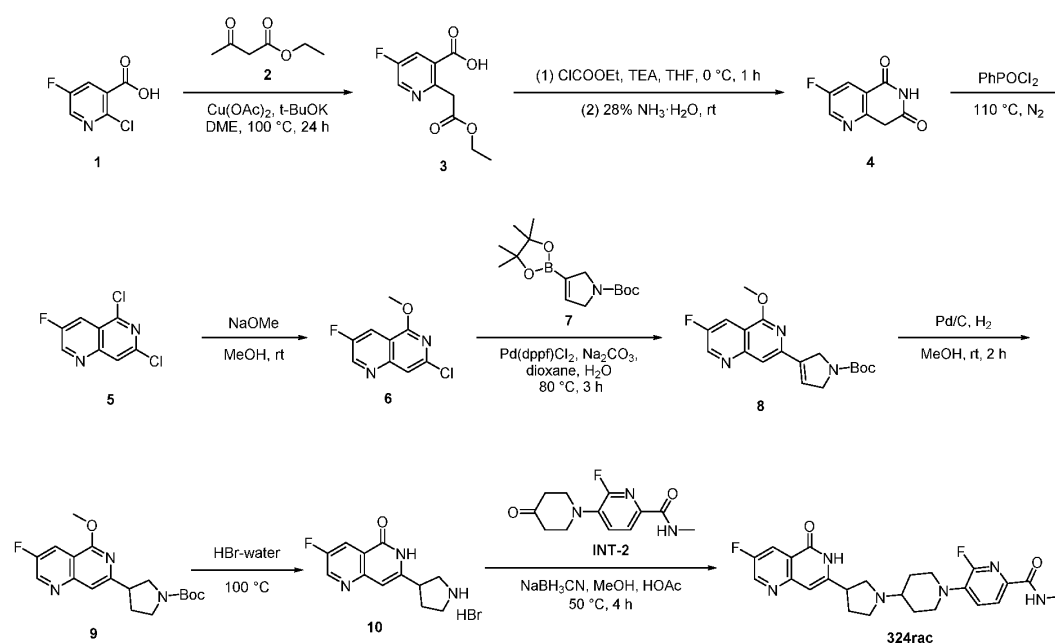
¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ: 11.07 (s, 1 H), 10.04 (s, 1 H), 8.46-8.32 (m, 1 H), 8.27 (d, *J* = 2.8 Hz, 1 H), 7.81 (d, *J* = 8.8 Hz, 1 H), 7.40 (dd, *J* = 8.8, 2.8 Hz, 1 H), 5.83 (s, 1 H), 3.87-3.76 (m, 2 H), 3.14-3.04 (m, 1 H), 3.02-2.91 (m, 2 H), 2.84-2.75 (m, 5 H), 2.58-2.54 (m, 3 H), 2.44-2.37 (m, 3 H), 2.30-2.24 (m, 1 H), 2.23-2.12 (m, 1 H), 1.97-1.90 (m, 2 H), 1.75-1.63

(m, 1 H), 1.59-1.44 (m, 2 H).

LCMS (ESI) calcd for $C_{24}H_{30}N_6O_3$ $[M + H]^+$ m/z 451.24, found 451.20.

Example 24 – synthesis of compound 324rac

Synthesis of compound 324rac



Preparation of 2-(2-ethoxy-2-oxoethyl)-5-fluoropyridine-3-carboxylic acid (3)

To a solution of ethyl 3-oxobutanoate **2** (4.57 g, 0.0351 mol) in DME (250 mL) was added *t*-BuOK (5.25 g, 0.0468 mol). The mixture was stirred at room temperature for 1 hour. $Cu(OAc)_2$ (1.70 g, 0.00936 mol) and 2-chloro-5-fluoropyridine-3-carboxylic acid **1** (4.1 g, 0.0234 mol) were added and the resulting mixture was stirred at 100 °C for 24 hours under nitrogen atmosphere. The mixture was diluted with water, acidified with 1 M HCl to pH = 2 and extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (DCM/MeOH = 100: 0 to 90: 10) to afford 2-(2-ethoxy-2-oxoethyl)-5-fluoropyridine-3-carboxylic acid **3** (2.4 g, 90% purity, 40% yield) as a white solid.

LCMS (ESI) calcd for $C_{10}H_{10}FNO_4$ $[M + H]^+$ m/z 228.06, found 228.00.

Preparation of 3-fluoro-6,8-dihydro-1,6-naphthyridine-5,7-dione (4)

To a solution of 2-(2-ethoxy-2-oxoethyl)-5-fluoropyridine-3-carboxylic acid **3** (2400 mg, 10.56 mmol) and TEA (2137 mg, 21.12 mmol) in THF (40 mL) was added ethyl carbonochloridate (2281 mg, 21.12 mmol) dropwise at 0 °C under N₂ atmosphere. The mixture was stirred at this temperature for 1 hour before NH₃·H₂O (28%, 1285 mg) was added dropwise and the resulting mixture was stirred at room temperature for 1 hour. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by Biotage Isolera One (C₁₈ column, eluting with 5% to 90% MeCN/H₂O containing 0.1% FA) to afford 3-fluoro-6,8-dihydro-1,6-naphthyridine-5,7-dione **4** (505 mg, 90% purity, 23% yield) as a white solid.

LCMS (ESI) calcd for C₈H₅FN₂O₂ [M + H]⁺ m/z 181.03, found 180.90.

Preparation of 5,7-dichloro-3-fluoro-1,6-naphthyridine (5)

A solution of 3-fluoro-6,8-dihydro-1,6-naphthyridine-5,7-dione **4** (300 mg, 1.66 mmol) in PhPOCl₂ (3 mL) was stirred at 110 °C for 12 hours under nitrogen atmosphere. The mixture was cooled and adjusted pH to 9 ~ 10 with aqueous KOH (5% wt) and diluted with ethyl acetate. The mixture was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc = 100 : 0 to 50 : 50) to afford 5,7-dichloro-3-fluoro-1,6-naphthyridine **5** (125 mg, 90% purity, 31% yield) as a white solid.

LCMS (ESI) calcd for C₈H₃Cl₂FN₂ [M + H]⁺ m/z 216.97, found 216.90.

Preparation of 7-chloro-3-fluoro-5-methoxy-1,6-naphthyridine (6)

To a solution of 5,7-dichloro-3-fluoro-1,6-naphthyridine **5** (195 mg, 0.8985 mmol) in MeOH (20 mL) was added MeONa (48 mg, 0.8985 mmol), then stirred for 2 h at room temperature. The reaction mixture was separated with EtOAc (20 mL × 3) and brine. The combined organic phase was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 95 : 5) to give 7-chloro-3-fluoro-5-methoxy-1,6-naphthyridine **6** (135 mg, 90% purity, 63% yield) as white solid.

LCMS (ESI) calcd for C₉H₆ClFN₂O [M + H]⁺ m/z 213.02, found 212.90.

Preparation of tert-butyl 3-(3-fluoro-5-methoxy-1,6-naphthyridin-7-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (8)

A mixture of 7-chloro-3-fluoro-5-methoxy-1,6-naphthyridine **6** (100 mg, 0.470 mmol), tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **7** (167 mg, 0.564 mmol), Pd(dppf)Cl₂ (38 mg, 0.047 mmol) and Na₂CO₃ (306 mg, 0.941 mmol) in dioxane and H₂O (3:1, 2 mL) was degassed with N₂ and heated at 80 °C for 3 h under N₂ atmosphere. The reaction mixture was concentrated and purified by flash silica chromatography to obtain tert-butyl 3-(3-fluoro-5-methoxy-1,6-naphthyridin-7-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **8** (100 mg, 90% purity, 24% yield) as a colorless oil. LCMS (ESI) calcd for C₁₈H₂₀FN₃O₃ [M + H]⁺ m/z 346.15, found 346.15.

Preparation of tert-butyl 3-(3-fluoro-5-methoxy-1,6-naphthyridin-7-yl)pyrrolidine-1-carboxylate (9)

A mixture of 3-(3-fluoro-5-methoxy-1,6-naphthyridin-7-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **8** (100 mg, 0.289 mmol) and Pd/C (31 mg) in MeOH (2 mL) was degassed with H₂ and stirred at rt for 2 h under H₂ atmosphere. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure to obtain tert-butyl 3-(3-fluoro-5-methoxy-1,6-naphthyridin-7-yl)pyrrolidine-1-carboxylate **9** (100 mg, 60% purity, 59% yield) as a yellow oil.

LCMS (ESI) calcd for C₁₈H₂₂FN₃O₃ [M + H]⁺ m/z 348.16, found 348.05.

Preparation of 3-fluoro-7-(pyrrolidin-3-yl)-1,6-naphthyridin-5(6H)-one hydrobromide (10)

A solution of tert-butyl 3-(3-fluoro-5-methoxy-1,6-naphthyridin-7-yl)pyrrolidine-1-carboxylate **9** (100 mg, 0.287 mmol) in HBr-water (48%, 10 mL) was heated at 100 °C for 2 h. The mixture was concentrated under reduced pressure to obtain 3-fluoro-7-(pyrrolidin-3-yl)-1,6-naphthyridin-5(6H)-one hydrobromide **10** (80 mg, 90% purity, 79% yield) as a white solid. LCMS (ESI) calcd for C₁₂H₁₂FN₃O [M + H]⁺ m/z 234.10, found 233.95.

Preparation of 6-fluoro-5-(4-(3-(3-fluoro-5-oxo-5,6-dihydro-1,6-naphthyridin-7-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide (compound 324rac)

To a solution of 3-fluoro-7-(pyrrolidin-3-yl)-6H-1,6-naphthyridin-5-one hydrobromide **10** (40 mg, 0.127 mmol) in MeOH (10 mL) was added 6-fluoro-N-methyl-5-(4-oxopiperidin-1-yl)pyridine-2-carboxamide **INT-2** (32 mg, 0.127 mmol), then two drops of acetic acid and NaBH₃CN (40 mg, 0.636 mmol) were added at room temperature. The reaction mixture stirred at 50 °C for 4 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to give 6-fluoro-5-

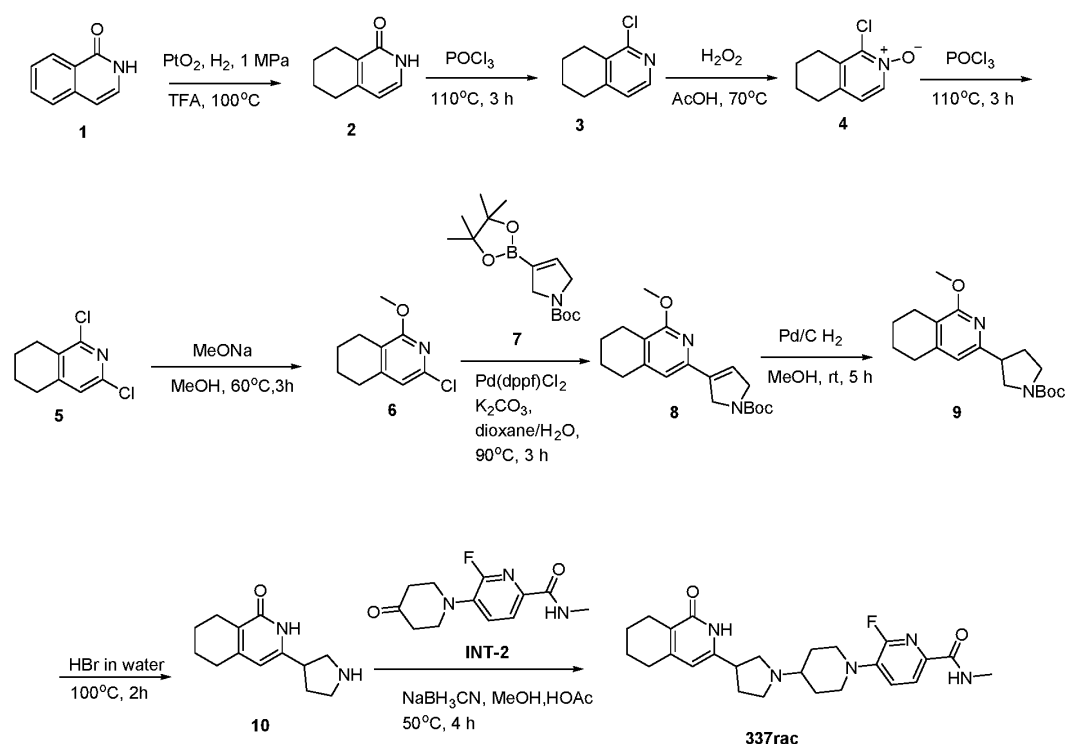
(4-(3-(3-fluoro-5-oxo-5,6-dihydro-1,6-naphthyridin-7-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide racemic **324rac** (13.2 mg, 95% purity, 21% yield) as a white solid.

^1H NMR (400 MHz, DMSO- d_6 ppm) δ 11.56 (s, 1 H), 8.92 (d, J = 2.8 Hz, 1 H), 8.42-8.35 (m, 1 H), 8.23-8.17 (m, 1 H), 8.16 (s, 1 H), 7.84 (d, J = 8.0 Hz, 1 H), 7.62-7.54 (m, 1 H), 6.61 (s, 1 H), 3.54-3.49 (m, 2 H), 3.31-3.27 (m, 1 H), 2.97-2.84 (m, 4 H), 2.83-2.79 (m, 1 H), 2.77 (d, J = 4.8 Hz, 3 H), 2.70-2.64 (m, 1 H), 2.38-2.31 (m, 1 H), 2.30-2.23 (m, 1 H), 1.99 (d, J = 12.4 Hz, 2 H), 1.92-1.81 (m, 1 H), 1.67-1.55 (m, 2 H).

LCMS (ESI) calcd for $\text{C}_{24}\text{H}_{26}\text{F}_2\text{N}_6\text{O}_2$ $[\text{M} + \text{H}]^+ m/z$ 469.21, found 469.10.

Example 25 - Synthesis of compounds 337a and 337b

Synthesis of compounds 337a and 337b



Preparation of 5,6,7,8-tetrahydroisoquinolin-1(2H)-one (2)

2H-isoquinolin-1-one (8 g, 0.05 mol) and PtO_2 (0.9 g, 0.003 mol) were added to TFA (80 mL), stirred under H_2 (1 MPa) at 100°C for 12 h. The precipitate was collected by filtration, extracted

with EtOAc (400 mL x 3). The combine organic phases were washed with brine, dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (eluent: PE/EtOAc =100: 0 to 80 :20) to give 5,6,7,8-tetrahydroisoquinolin-1(2H)-one **2** (7.00 g, 77% yield) as a black oil.

LCMS (ESI) calcd for C₉H₁₁NO [M + H]⁺ m/z 150.08, found 150.00

Preparation of 1-chloro-5,6,7,8-tetrahydroisoquinoline (3)

A solution of sodium 5,6,7,8-tetrahydro-2H-isoquinolin-1-one **2** (7 g, 0.047 mmol) in POCl₃ (100 mL) was stirred at 110 °C for 3 h. After completion of the reaction, the mixture was cooled to room temperature, taken into ice-water, neutralized with NH₃.H₂O under cooling, extracted with EtOAc (300 mLx3). The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (eluting with PE/EtOAc = 100 : 0 to 80 : 20) to afford 1-chloro-5,6,7,8-tetrahydroisoquinoline **3** (5 g, 90% purity, 57% yield) as a colorless oil.

LCMS (ESI) calcd for C₉H₁₀ClN [M + H]⁺ m/z 168.05, found 168.00.

Preparation of 1-chloro-5,6,7,8-tetrahydroisoquinoline 2-oxide (4)

1-chloro-5,6,7,8-tetrahydroisoquinoline **3** (5 g, 0.029 mol) was added to AcOH/H₂O₂ (100 mL). The reaction mixture was stirred at 70 °C for 2 h. The precipitate was collected by filtration, extracted with EtOAc (200 mL x 3). The combine organic phases were washed with brine, dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (eluent: DCM/MeOH =100: 0 to 90 :10) to give 1-chloro-5,6,7,8-tetrahydroisoquinoline 2-oxide **4** (2.00 g, 73% yield) as a yellow oil.

LCMS (ESI) calcd for C₉H₁₀ClNO [M + H]⁺ m/z 184.05, found 184.00.

Preparation of 1,3-dichloro-5,6,7,8-tetrahydroisoquinoline (5)

1-chloro-5,6,7,8-tetrahydroisoquinoline 2-oxide **4** (2.00 g, 0.019 mmol) was added to POCl₃ (50 mL) slowly at room temperature. The mixture was heated to 110 °C stirred for 3 h. The resulting mixture was diluted with ice water (200 mL) and extracted with EtOAc (400 mL x 3). The combined organic phases were washed with brine, dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (eluent: PE/EtOAc =100: 0 to 70 :30) to give 1,3-dichloro-5,6,7,8-tetrahydroisoquinoline **5** (370 mg, 15% yield) as a yellow oil.

LCMS (ESI) calcd for C₉H₉Cl₂N [M + H]⁺ m/z 202.01, found 201.95.

Preparation of 3-chloro-1-methoxy-5,6,7,8-tetrahydroisoquinoline (6)

To a solution of 1,3-dichloro-5,6,7,8-tetrahydroisoquinoline **5** (350 mg, 1.73 mmol) in MeOH (15 mL) was added MeONa (280 mg, 5.20 mmol), the mixture was heated to 60 °C with stirring for 3h. The precipitate was collected by filtration, extracted with EtOAc (100 mL x 3). The combined organic phases were washed with brine, dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (eluent: PE/EtOAc = 100: 0 to 90 :10) to afford 3-chloro-1-methoxy-5,6,7,8-tetrahydroisoquinoline **6** (250 mg, 66% yield) as a white solid.

LCMS (ESI) calcd for C₁₀H₁₂ClNO [M + H]⁺ m/z 198.06, found 197.95.

Preparation of tert-butyl 3-(1-methoxy-5,6,7,8-tetrahydroisoquinolin-3-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (8)

To a solution of 3-chloro-1-methoxy-5,6,7,8-tetrahydroisoquinoline **6** (240 mg, 1.21 mmol) in dioxane/H₂O=10:1 (60 mL) were added tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **7** (394 mg, 1.33 mmol), Pd(dppf)Cl₂ (88 mg, 0.12 mmol) and Na₂CO₃ (503 mg, 3.64 mmol) successively at room temperature. The reaction mixture was stirred at 90 °C for 3 h under N₂. The mixture was diluted with water (50 mL) and extracted with EtOAc (100 mL x 3). The combined organic layer was washed with brine (100 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuo to obtain the crude product, which was purified by flash column chromatography (PE/EtOAc = 100: 0 to 85: 15) to afford tert-butyl 3-(1-methoxy-5,6,7,8-tetrahydroisoquinolin-3-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **8** (140 mg, 31% yield) as a yellow solid.

LCMS (ESI) calcd for C₁₉H₂₆N₂O₃ [M + H]⁺ m/z 331.19, found 331.15.

Preparation of tert-butyl 3-(1-methoxy-5,6,7,8-tetrahydroisoquinolin-3-yl)pyrrolidine-1-carboxylate (9)

To a solution of tert-butyl 3-(1-methoxy-5,6,7,8-tetrahydroisoquinolin-3-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **8** (130 mg, 0.39 mmol) in MeOH (50 mL) was added Pd/C (30 mg). The mixture was evacuated and backfilled with hydrogen three times and then charged with hydrogen. The resulting mixture was stirred at room temperature for 5 h. Then the mixture was filtered through celite and concentrated under vacuum to give crude product, which was purified by flash column chromatography (PE/EtOAc = 100: 0 to 50: 50) to afford tert-butyl 3-(1-methoxy-5,6,7,8-tetrahydroisoquinolin-3-yl)pyrrolidine-1-carboxylate **9** (130 mg, 89%

yield) as a yellow solid.

LCMS (ESI) calcd for $C_{19}H_{28}N_2O_3$ $[M + H]^+$ m/z 333.21, found 333.10.

Preparation of 3-(pyrrolidin-3-yl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one (10)

Tert-butyl 3-(1-methoxy-5,6,7,8-tetrahydroisoquinolin-3-yl)pyrrolidine-1-carboxylate **9** (115 mg, 0.71 mmol) was added to HBr in water (10 mL). The mixture was stirred for 2 h at 100°C. The reaction mixture was concentrated under reduced pressure to give product of 3-(pyrrolidin-3-yl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one **10** (80 mg, 95% yield) as a white solid.

LCMS (ESI) calcd for $C_{13}H_{18}N_2O$ $[M + H]^+$ m/z 219.14, found 219.05.

Preparation of 6-fluoro-N-methyl-5-(4-(3-(1-oxo-1,2,5,6,7,8-hexahydroisoquinolin-3-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide (racemic mixture of compounds 337a and 337b)

To a solution of 3-(pyrrolidin-3-yl)-5,6,7,8-tetrahydroisoquinolin-1(2H)-one **10** (60 mg, 0.27 mmol), 6-fluoro-N-methyl-5-(4-oxopiperidin-1-yl)pyridine-2-carboxamide **INT-2** (69 mg, 0.27 mmol) and AcOH (two drops) in MeOH (5 mL) was added sodium triacetoxyborohydride (146 mg, 0.69 mmol) and then stirred at 50 °C for 1 h, then $NaBH_3CN$ (21 mg, 0.33 mmol) was added and stirred for 4 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100: 0 to 90: 10) to give 6-fluoro-N-methyl-5-(4-(3-(1-oxo-1,2,5,6,7,8-hexahydroisoquinolin-3-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide, a racemic mixture of compounds **337a** and **337b** (22 mg, 18 % yield) as a white solid.

LCMS (ESI) calcd for $C_{25}H_{32}FN_5O_2$ $[M + H]^+$ m/z 454.25, found 454.15.

Chiral resolution of 6-fluoro-N-methyl-5-(4-(3-(1-oxo-1,2,5,6,7,8-hexahydroisoquinolin-3-yl)pyrrolidin-1-yl)piperidin-1-yl)picolinamide (racemic mixture of compounds 337a and 337b)

A racemic mixture of compounds **337a** and **337b** was separated by SFC (Column: DAICEL OD-H 4.6mmI.D.*250mmL 5 μ m; Mobile phase: $CO_2/MeOH$ [0.1% NH_3 (7M Solution in $MeOH$)] = 70/30) and concentrated under reduced pressure to afford the first fraction as **337a** (7 mg, 95% purity, ee%: 100, white solid) and the second fraction as **337b** (5 mg, 92% purity, ee%: 100, white solid).

Compound 337a

¹H NMR (400 MHz, DMSO) δ 11.03 (s, 1H), 8.40 (d, J = 4.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.57 (dd, J = 10.6, 8.4 Hz, 1H), 5.83 (s, 1H), 3.55-3.44 (m, 2H), 3.14-3.04 (m, 1H), 2.86 (t, J = 11.6 Hz, 3H), 2.75 (t, J = 6.4 Hz, 4H), 2.63 (dd, J = 14.8, 8.0 Hz, 2H), 2.44 (s, 2H), 2.27 (s, 3H), 2.21-2.10 (m, 1H), 1.95 (d, J = 13.2 Hz, 2H), 1.73 (dd, J = 12.8, 8.4 Hz, 1H), 1.58 (dd, J = 22.4, 12.0 Hz, 6H).

LCMS (ESI) calcd for C₂₅H₃₂FN₅O₂ [M + H]⁺ m/z 454.25, found 454.20.

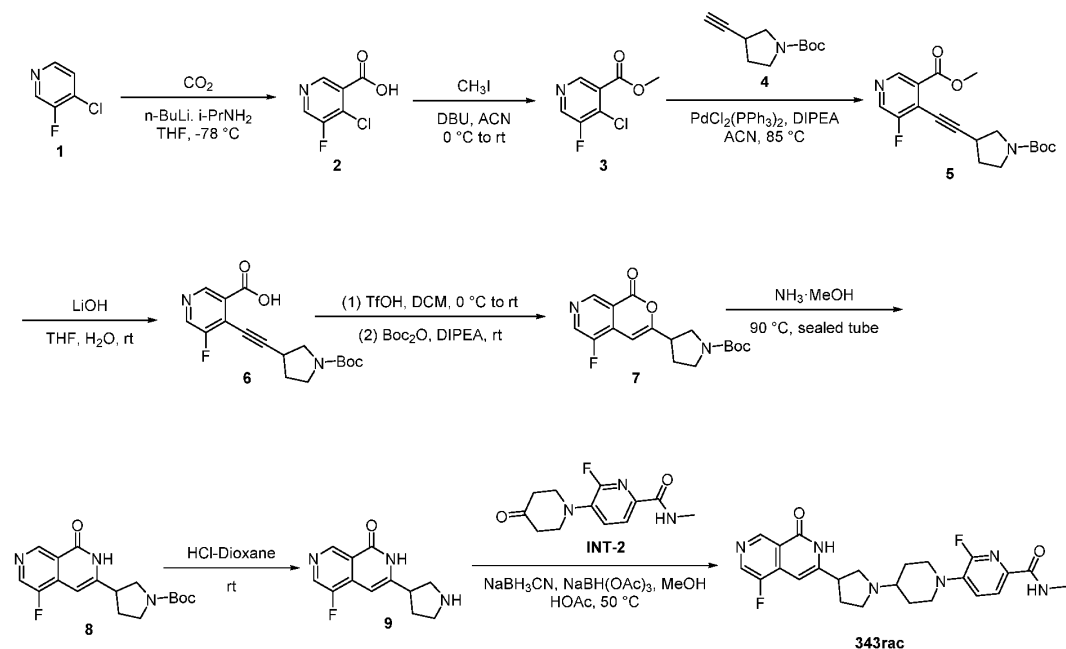
Compound 337b

¹H NMR (400 MHz, DMSO) δ 11.03 (s, 1H), 8.40 (d, J = 4.4 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.70-7.45 (m, 1H), 5.83 (s, 1H), 3.49 (d, J = 11.2 Hz, 2H), 3.08 (d, J = 6.4 Hz, 1H), 2.85 (t, J = 11.2 Hz, 3H), 2.76 (d, J = 4.4 Hz, 4H), 2.69-2.57 (m, 2H), 2.44 (s, 2H), 2.27 (s, 3H), 2.20-2.10 (m, 1H), 1.95 (d, J = 12.4 Hz, 2H), 1.80-1.68 (m, 1H), 1.68-1.51 (m, 6H).

LCMS (ESI) calcd for C₂₅H₃₂FN₅O₂ [M + H]⁺ m/z 454.25, found 454.15.

Example 26 - Synthesis of compounds 343a and 343b

Synthesis of compounds 343a and 343b



Preparation of 4-chloro-5-fluoronicotinic acid (2)

N-BuLi (2.4 M in hexanes, 10 mL, 23.9 mmol) was added to THF (100 mL) and cooled to -78 °C. To this solution was added i-PrNH₂ (2.54 g, 25.0 mmol) slowly followed by 4-chloro-3-fluoropyridine **1** (3 g, 22.8 mmol). After stirring for 2 h at -78 °C, crushed dry ice was added in one portion. The reaction mixture was kept stirring until the reaction mixture warmed to room temperature. The reaction was quenched by addition of aqueous ammonium chloride solution and acidified to pH = 2 using conc. HCl and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure to afford 4-chloro-5-fluoronicotinic acid **2** (2.2 g, 70% purity, 36% yield) as a yellow solid.

LCMS (ESI) calcd for C₆H₃ClFNO₂ [M + H]⁺ m/z 175.99, found 175.80.

Preparation of methyl 4-chloro-5-fluoronicotinate (3)

To a solution of 4-chloro-5-fluoronicotinic acid **2** (2.2 g, 11.6 mmol) in ACN (100 mL) were added DBU (5.29 g, 34.8 mmol) and CH₃I (8.2 g, 58.0 mmol) dropwise at 0 °C. The mixture was stirred at rt for 5 hours. The resulting mixture was diluted with water (300 mL) and extracted with EtOAc (100 mL x 3). The combined organic phases were washed with brine, dried over sodium sulfate, concentrated, and purified by silica gel column chromatography (eluting with EtOAc/PE, 20% to 50%) to give methyl 4-chloro-5-fluoronicotinate **3** (1.5 g, 90% purity, 63% yield) as a white solid.

LCMS (ESI) calcd for C₇H₅ClFNO₂ [M + H]⁺ m/z 190.00, found 189.95.

Preparation of methyl 4-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)ethynyl)-5-fluoronicotinate (5)

A mixture of methyl 4-chloro-5-fluoronicotinate **3** (150 mg, 0.79 mmol), tert-butyl 3-ethynylpyrrolidine-1-carboxylate **4** (233 mg, 1.19 mmol), PdCl₂(PPh₃)₂ (55 mg, 0.079 mmol) and DIPEA (511 mg, 3.96 mmol) in ACN (15 mL) was heated at 85 °C for 5 hours under an atmosphere of N₂. After cooling to ambient temperature, the mixture was filtered through celite, and the filtrate was concentrated under vacuum. The residue was diluted with water and extracted with EtOAc. The combined organic phases were washed with water and brine, dried over sodium sulfate, concentrated under reduced pressure, and purified by flash chromatography (eluting with EtOAc/PE, 20% to 40%) to obtain methyl 4-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)ethynyl)-5-fluoronicotinate **5** (150 mg, 90% purity, 48% yield) as a yellow solid.

LCMS (ESI) calcd for $C_{18}H_{21}FN_2O_4$ $[M + H]^+$ m/z 349.15, found 348.95.

Preparation of 4-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)ethynyl)-5-fluoronicotinic acid (6)

To a solution of methyl 4-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)ethynyl)-5-fluoronicotinate **5** (150 mg, 0.43 mmol) in THF/H₂O (3/1, 10 mL) was added LiOH (31 mg, 1.29 mmol). The mixture was stirred at room temperature for 2 h. Then the organic solvent was removed under reduced pressure. The aqueous solution was adjusted to pH 3-4 with 1 M HCl and extracted with DCM (50 mL $\times$ 3). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give 4-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)ethynyl)-5-fluoronicotinic acid **6** (120 mg, 90% purity, 75% yield) as a yellow oil.

LCMS (ESI) calcd for $C_{17}H_{19}FN_2O_4$ $[M + H]^+$ m/z 335.14, found 335.00.

Preparation of tert-butyl 3-(5-fluoro-1-oxo-1H-pyrano[3,4-c]pyridin-3-yl)pyrrolidine-1-carboxylate (7)

To a solution of 4-((1-(tert-butoxycarbonyl)pyrrolidin-3-yl)ethynyl)-5-fluoronicotinic acid **6** (120 mg, 0.36 mmol) in DCM (10 mL) was added TfOH (161 mg, 1.07 mmol) dropwise at 0 °C. The mixture was stirred at rt for 16 hours. The reaction was quenched with DIPEA (231 mg, 1.79 mmol), then Boc₂O (156 mg, 0.716 mmol) was added. After stirring at rt for 1 h, the resulting mixture were concentrated under reduced pressure and the residue was purified by silica gel column chromatography (eluting with EtOAc/PE, 20% to 40%) to give tert-butyl 3-(5-fluoro-1-oxo-1H-pyrano[3,4-c]pyridin-3-yl)pyrrolidine-1-carboxylate **7** (70 mg, 90% purity, 52% yield) as a white solid.

LCMS (ESI) calcd for $C_{17}H_{19}FN_2O_4$ $[M - t-Bu + H]^+$ m/z 279.14, found 278.85.

Preparation of tert-butyl 3-(5-fluoro-1-oxo-1,2-dihydro-2,7-naphthyridin-3-yl)pyrrolidine-1-carboxylate (8)

A solution of tert-butyl 3-(5-fluoro-1-oxo-1H-pyrano[3,4-c]pyridin-3-yl)pyrrolidine-1-carboxylate **7** (70 mg, 0.21 mmol) in NH₃-MeOH (7 M, 5 mL) was stirred at 90 °C for 1 h in a sealed tube. Then the reaction was concentrated under reduced pressure to provide tert-butyl 3-(5-fluoro-1-oxo-1,2-dihydro-2,7-naphthyridin-3-yl)pyrrolidine-1-carboxylate **8** (70 mg, 90% purity, 90% yield) as a yellow solid.

LCMS (ESI) calcd for $C_{17}H_{20}FN_3O_3$ $[M + H]^+$ m/z 334.15, found 333.95.

Preparation of 5-fluoro-3-(pyrrolidin-3-yl)-2,7-naphthyridin-1(2H)-one (9)

A mixture of tert-butyl 3-(5-fluoro-1-oxo-1,2-dihydro-2,7-naphthyridin-3-yl)pyrrolidine-1-carboxylate **8** (70 mg, 0.44 mmol) in HCl dioxane solution (4 M, 5 mL) was stirred at room temperature for 1 hours. The mixture was concentrated under reduced pressure then quenched with Et₃N. The resulting solution was concentrated under vacuum to give 5-fluoro-3-(pyrrolidin-3-yl)-2,7-naphthyridin-1(2H)-one **9** (50 mg, 90% purity, 92% yield) as a yellow oil.

LCMS (ESI) calcd for C₁₂H₁₂FN₃O [M + H]⁺ m/z 234.10, found 234.05.

Preparation of 6-fluoro-5-(4-(3-(5-fluoro-1-oxo-1,2-dihydro-2,7-naphthyridin-3-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide (racemic mixture of compounds 343a and 343b)

To a solution of 5-fluoro-3-(pyrrolidin-3-yl)-2,7-naphthyridin-1(2H)-one **9** (70 mg, 0.30 mmol) in MeOH (10 mL) was added 6-fluoro-N-methyl-5-(4-oxopiperidin-1-yl)picolinamide **INT-2** (113 mg, 0.45 mmol), then two drops of acetic acid, NaBH₃CN (19 mg, 0.30 mmol) and NaBH(OAc)₃ (191 mg, 0.90 mmol) were added at room temperature. The reaction mixture stirred at 50 °C for 1 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 90 : 10) to give 6-fluoro-5-(4-(3-(5-fluoro-1-oxo-1,2-dihydro-2,7-naphthyridin-3-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide, a racemic mixture of compounds **343a** and **343b** (50 mg, 95% purity, 33% yield) as a white solid.

Chiral resolution of 6-fluoro-5-(4-(3-(5-fluoro-1-oxo-1,2-dihydro-2,7-naphthyridin-3-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide (racemic mixture of compounds 343a and 343b)

A racemic mixture of compounds **343a** and **343b** was separated by SFC (Column: Daicel Chiralpak IH 20 mm I.D. × 250 mm, 5 μm; Mobile phase: CO₂/MeOH [0.1% (NH₃)] = 70/30) and concentrated under reduced pressure to afford the first fraction as **343a** (19.7 mg, 99% purity, 100% ee, white solid) and the second fraction as **343b** (24.7 mg, 98% purity, 90% ee, white solid)

Compound 343a

¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ: 11.74 (s, 1 H), 9.09 (s, 1 H), 8.68 (d, *J* = 2.0 Hz, 1 H), 8.40 (d, *J* = 4.8 Hz, 1 H), 7.87-7.80 (m, 1 H), 7.58 (dd, *J* = 10.6, 8.2 Hz, 1 H), 6.54 (s, 1 H),

3.58-3.47 (m, 2 H), 3.29-3.16 (m, 1 H), 2.91-2.83 (m, 5 H), 2.77 (d, $J = 4.8$ Hz, 3 H), 2.72-2.58 (m, 1 H), 2.47-2.23 (m, 2 H), 2.10-1.96 (m, 2 H), 1.95-1.81 (m, 1 H), 1.77-1.50 (m, 2 H).

LCMS (ESI) calcd for $C_{24}H_{26}F_2N_6O_2$ $[M + H]^+$ m/z 469.21, found 469.07.

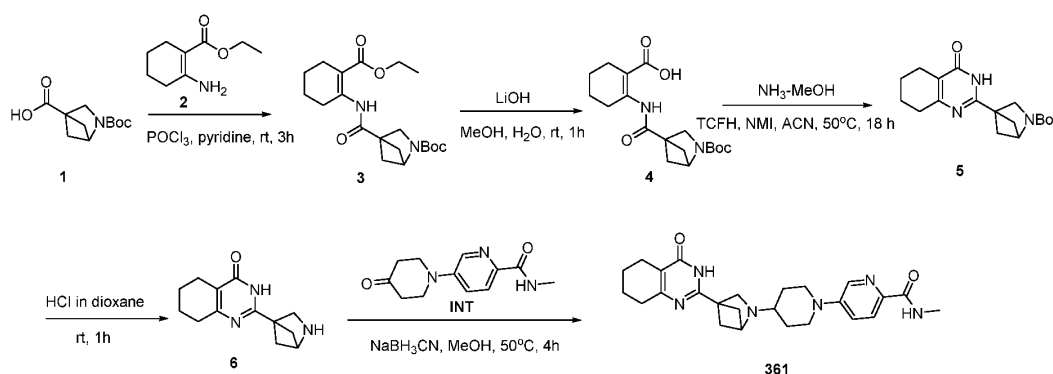
Compound 343a

^1H NMR (400 MHz, DMSO- d_6 , ppm) δ : 11.77 (s, 1 H), 9.09 (s, 1 H), 8.68 (d, $J = 2.0$ Hz, 1 H), 8.45-8.31 (m, 1 H), 7.89-7.76 (m, 1 H), 7.58 (dd, $J = 10.6, 8.2$ Hz, 1 H), 6.55 (s, 1 H), 3.54-3.46 (m, 2 H), 3.29-3.23 (m, 1 H), 2.94-2.82 (m, 5 H), 2.77 (d, $J = 4.8$ Hz, 3 H), 2.69-2.58 (m, 1 H), 2.36-2.25 (m, 2 H), 2.02-1.94 (m, 2 H), 1.91-1.78 (m, 1 H), 1.67-1.56 (m, 2 H).

LCMS (ESI) calcd for $C_{24}H_{26}F_2N_6O_2$ $[M + H]^+$ m/z 469.21, found 469.10.

Example 27 - Synthesis of compound 361

Synthesis of compound 361



Preparation of tert-butyl 4-((2-(ethoxycarbonyl)cyclohex-1-en-1-yl)carbamoyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (3)

To a solution of 2-(tert-butoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxylic acid **1** (110 mg, 0.48 mmol) in pyridine (10 mL) was added ethyl 2-aminocyclohex-1-ene-1-carboxylate **2** (160 mg, 0.95 mmol) at room temperature, then added 10 drops of $POCl_3$. The reaction mixture stirred at room temperature for 3 h. After cooling to room temperature, the reaction mixture was poured into water. The aqueous was extracted with organic solvent (50 mL) 3 times. The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4 , then concentrated under reduced pressure. The residue was purified by flash chromatography

(eluting with PE/EtOAc = 100: 0 to 85: 15) to give tert-butyl 4-((2-(ethoxycarbonyl)cyclohex-1-en-1-yl)carbamoyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **3** (100 mg, 55% yield) as a white solid.

LCMS (ESI) calcd for C₂₀H₃₀N₂O₅ [M – 56 + H]⁺ m/z 323.22, found 323.05.

Preparation of 2-(2-(tert-butoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxamido)cyclohex-1-ene-1-carboxylic acid (4)

To a solution of tert-butyl 4-((2-(ethoxycarbonyl)cyclohex-1-en-1-yl)carbamoyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **3** (100 mg, 0.26 mmol) in MeOH : H₂O=1 : 1 (10 mL) was added LiOH (30 mg, 1.25 mmol). The reaction mixture stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to give 2-(2-(tert-butoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxamido)cyclohex-1-ene-1-carboxylic acid **4** (80 mg, 88 % yield) as a white solid.

LCMS (ESI) calcd for C₁₈H₂₆N₂O₅ [M – 56 + H]⁺ m/z 295.18, found 295.05.

Preparation of tert-butyl 4-(4-oxo-3,4,5,6,7,8-hexahydroquinazolin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (5)

To a solution of 2-(2-(tert-butoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxamido)cyclohex-1-ene-1-carboxylic acid **4** (80 mg, 0.23 mmol) in ACN (10 mL) was added N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate / TCFH (150 mg, 0.54 mmol) and N-methyl imidazole / NMI (50 mg, 0.61 mmol) at room temperature. After 10 mins, excess of NH₃-MeOH (7 M, 5 mL) was added at 50 °C. The mixture was stirred at 50 °C for 18 h. The residue was concentrated under reduced pressure, then purified by flash chromatography (eluting with DCM/MeOH = 100: 0 to 96: 4) to give tert-butyl 4-(4-oxo-3,4,5,6,7,8-hexahydroquinazolin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **5** (60 mg, 79% yield) as a white solid.

LCMS (ESI) calcd for C₁₈H₂₅N₃O₃ [M + H]⁺ m/z 332.19, found 332.10.

Preparation of 2-(2-azabicyclo[2.1.1]hexan-4-yl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (6)

Tert-butyl 4-(4-oxo-3,4,5,6,7,8-hexahydroquinazolin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **5** (60 mg, 0.18 mmol) was added to HCl in dioxane (4 M, 3 mL), stirred for 1 h at room temperature, the reaction mixture was concentrated under reduced pressure to give 2-(2-azabicyclo[2.1.1]hexan-4-yl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one **6** (40 mg, 96 % yield

) as a white solid.

LCMS (ESI) calcd for C₁₃H₁₇N₃O [M + H]⁺ m/z 232.14, found 232.05.

Preparation of N-methyl-5-(4-(4-(4-oxo-3,4,5,6,7,8-hexahydroquinazolin-2-yl)-2-azabicyclo[2.1.1]hexan-2-yl)piperidin-1-yl)picolinamide (compound 361)

To a solution of 2-(2-azabicyclo[2.1.1]hexan-4-yl)-5,6,7,8-tetrahydroquinazolin-4(3H)-one **6** (40 mg, 0.17 mmol) in MeOH (10 mL) was added N-methyl-5-(4-oxopiperidin-1-yl)picolinamide **INT** (40 mg, 0.17 mmol) and 3 drops of HOAc, then added NaBH₃CN (10 mg, 0.16 mmol). The reaction mixture stirred at 50 °C for 4 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (columns: Gemini 5 um C18 150 × 21.2 mm, mobile phase: ACN - H₂O (0.1% FA), gradient: 10 - 25) to give N-methyl-5-(4-(4-(4-oxo-3,4,5,6,7,8-hexahydroquinazolin-2-yl)-2-azabicyclo[2.1.1]hexan-2-yl)piperidin-1-yl)picolinamide **361** (30 mg, 97% purity, 38% yield) as a white solid.

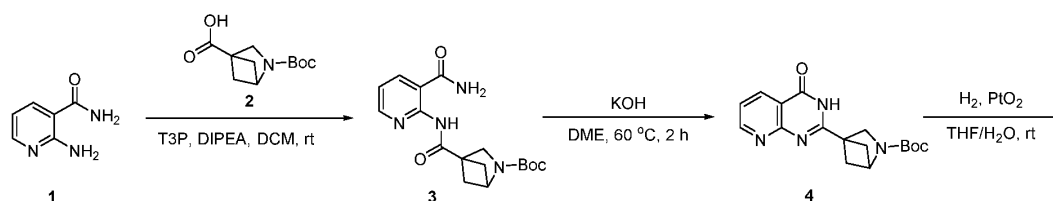
Compound 361

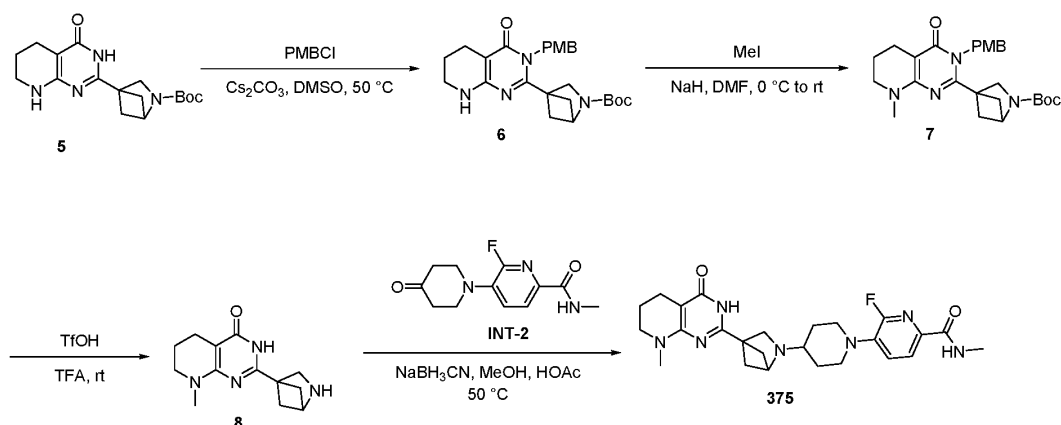
¹H NMR (400 MHz, DMSO) δ 12.11 (s, 1 H), 8.38 (q, *J* = 4.8 Hz, 1 H), 8.28 (d, *J* = 2.8 Hz, 1 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.40 (dd, *J* = 8.8, 2.8 Hz, 1 H), 3.87 (d, *J* = 12.8 Hz, 2 H), 3.69 (s, 1 H), 2.98 (s, 2 H), 2.91 (t, *J* = 11.2 Hz, 2 H), 2.78 (d, *J* = 4.8 Hz, 3 H), 2.61-2.54 (m, 1 H), 2.48-2.44 (m, 2 H), 2.31 (t, *J* = 6.0 Hz, 2 H), 2.09-2.02 (m, 2 H), 1.99-1.92 (m, 2 H), 1.84-1.78 (m, 2 H), 1.72-1.59 (m, 4 H), 1.51-1.41 (m, 2 H).

LCMS (ESI) calcd for C₂₅H₃₂N₆O₂ [M + H]⁺ m/z 449.26, found 449.20.

Example 28 – Synthesis of compound 375

Synthesis of compound 375





Preparation of tert-butyl 4-((3-carbamoylpyridin-2-yl)carbamoyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (3)

To a solution of 2-(tert-butoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxylic acid **2** (500 mg, 2.19 mmol) in DCM (15 mL) were added 2-aminonicotinamide **1** (330 mg, 2.41 mmol), T3P (50% wt in EtOAc, 4.18 g, 6.57 mmol) and DIPEA (850 mg, 6.57 mmol) at room temperature successively. The mixture was kept stirring at room temperature for 1 h. The reaction solution was concentrated under reduced pressure and the residue was purified by flash chromatography (eluting with DCM/ MeOH = 100 : 0 to 90 : 10) to give tert-butyl 4-((3-carbamoylpyridin-2-yl)carbamoyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **3** (330 mg, 90% purity, 39% yield) as white solid.

LCMS (ESI) calcd for $C_{17}H_{22}N_4O_4$ $[M + H]^+$ m/z 347.16, found 346.85.

Preparation of tert-butyl 4-(4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (4)

To a solution of tert-butyl 4-((3-carbamoylpyridin-2-yl)carbamoyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **3** (330 mg, 0.95 mmol) in DME (20 mL) at rt was added KOH (160 mg, 2.85 mmol). The reaction mixture was stirred at 60 °C for 6 h. The reaction solution was filtered to remove KOH. The filtrate was diluted with water and extracted with EtOAc (10 mL $\times$ 3). The water phase was purified by silica gel C18 column (eluting with 10% to 50% MeCN/H₂O, containing 0.1% formic acid) to give tert-butyl 4-(4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **4** (220 mg, 80% purity, 56% yield) as white solid.

LCMS (ESI) calcd for $C_{17}H_{20}N_4O_3$ $[M + H]^+$ m/z 329.15, found 329.00.

Preparation of tert-butyl 4-(4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (5)

To a solution of tert-butyl 4-(4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **4** (200 mg, 0.607 mmol) in THF/H₂O = 4:1 (20 mL) was added PtO₂ (41 mg). Then the mixture was stirred under hydrogen for 18 h at rt. The mixture was filtered through a celite pad, and the filtrate was concentrated under reduced pressure to give tert-butyl 4-(4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **5** (200 mg, 90% purity, 88% yield) as a yellow solid. LCMS (ESI) calcd for C₁₇H₂₄N₄O₃ [M + H]⁺ m/z 333.18, found 333.25.

Preparation of tert-butyl 4-(3-(4-methoxybenzyl)-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (6)

To a solution of tert-butyl 4-(4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **5** (200 mg, 0.6 mmol) in DMSO (10 mL) at room temperature were added Cs₂CO₃ (586 mg, 1.8 mmol) and PMBCl (188 mg, 1.2 mmol). The reaction mixture was stirred at 50 °C for 1 h. The reaction solution was quenched with water and extracted with EtOAc (30 mL × 3). The combined organic phase was washed three times with brine and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 50: 50) to give tert-butyl 4-(3-(4-methoxybenzyl)-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **6** (150 mg, 90% purity, 49% yield) as white solid. LCMS (ESI) calcd for C₂₅H₃₂N₄O₄ [M + H]⁺ m/z 453.24, found 453.05.

Preparation of tert-butyl 4-(3-(4-methoxybenzyl)-8-methyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (7)

To a solution of methyl tert-butyl 4-(3-(4-methoxybenzyl)-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **6** (50 mg, 0.11 mmol) in DMF (10 mL) at 0 °C were added NaH (7 mg, 0.17 mmol, 60% wt) and MeI (24 mg, 0.17 mmol). The reaction mixture was stirred at rt for 1 h. The reaction solution was quenched with water and extracted with EtOAc (50 mL × 3). The organic phase was concentrated under reduced pressure and the residue was purified by flash chromatography (eluting with PE/EtOAc = 100 : 0 to 70: 30) to give tert-butyl 4-(3-(4-methoxybenzyl)-8-

methyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **7** (30 mg, 90% purity, 52% yield) as white solid.

LCMS (ESI) calcd for C₂₆H₃₄N₄O₄ [M + H]⁺ m/z 467.26, found 467.30.

Preparation of 2-(2-azabicyclo[2.1.1]hexan-4-yl)-8-methyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one (8)

To a solution of tert-butyl 4-(3-(4-methoxybenzyl)-8-methyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate **7** (30 mg, 0.064 mmol) in TFA (5 mL) was added TfOH (0.2 mL). The reaction was stirred at rt for 0.5 h. The reaction solution was adjusted to pH 8 with saturated aqueous NaHCO₃ at 0 °C. The basified solution was extracted with DCM (10 mL × 3). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give 2-(2-azabicyclo[2.1.1]hexan-4-yl)-8-methyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one **8** (25 mg, 60% purity, 94% yield) as a yellow oil.

LCMS (ESI) calcd for C₁₃H₁₈N₄O [M + H]⁺ m/z 247.15, found 247.25.

Preparation of 6-fluoro-N-methyl-5-(4-(4-(8-methyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.1.1]hexan-2-yl)piperidin-1-yl)picolinamide (compound 375)

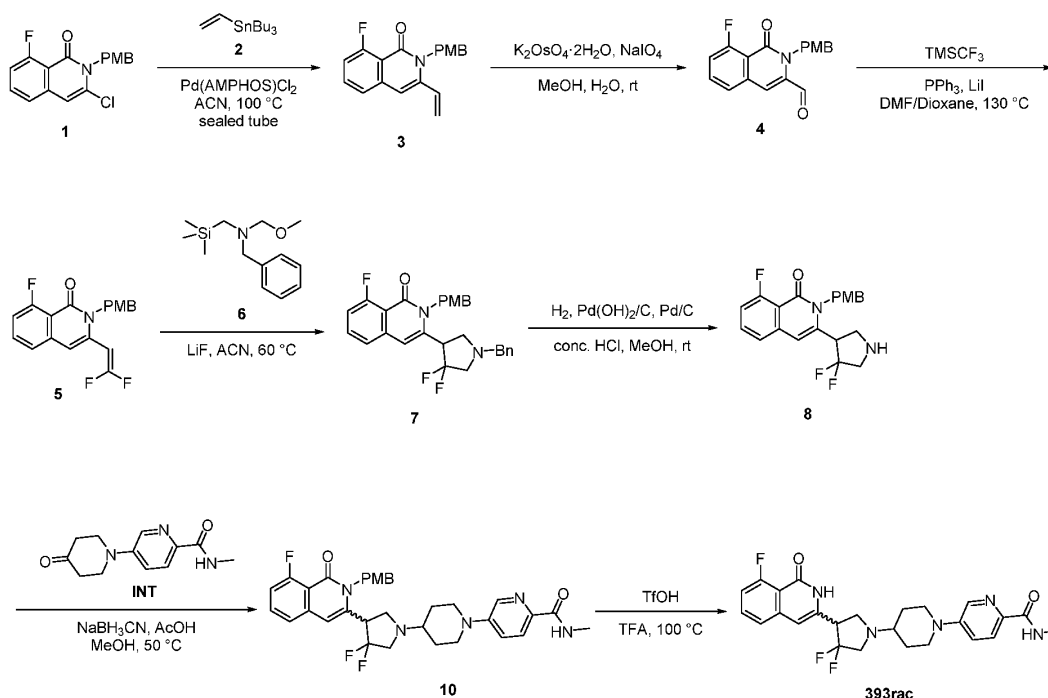
To a solution of 2-(2-azabicyclo[2.1.1]hexan-4-yl)-8-methyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-4(3H)-one **8** (25 mg, 0.10 mmol) in MeOH (15 mL) and AcOH (0.01 mL) at room temperature was added 6-fluoro-N-methyl-5-(4-oxopiperidin-1-yl)picolinamide **INT-2** (31 mg, 0.12 mmol) and NaBH₃CN (10 mg, 0.15 mmol). The reaction mixture was stirred at 50 °C for 1 h. The reaction solution was concentrated under reduced pressure and the residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 90: 10) and prep-HPLC (Gemini 5um C18 150 × 21.2mm, mobile phase: ACN - H₂O (0.05% NH₃), gradient: 25 - 95) to give 6-fluoro-N-methyl-5-(4-(4-(8-methyl-4-oxo-3,4,5,6,7,8-hexahydropyrido[2,3-d]pyrimidin-2-yl)-2-azabicyclo[2.1.1]hexan-2-yl)piperidin-1-yl)picolinamide **375** (5.0 mg, 97% purity, 10 % yield) as white solid.

¹H NMR (400 MHz, DMSO-*d*₆, ppm) δ: 11.32 (s, 1 H), 8.43-8.35 (m, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.63-7.53 (m, 1 H), 3.61 (s, 1 H), 3.57-3.50 (m, 2 H), 3.25-3.18 (m, 2 H), 3.03 (s, 3 H), 2.91 (s, 2 H), 2.84 (t, *J* = 11.2 Hz, 2 H), 2.76 (d, *J* = 4.8 Hz, 3 H), 2.47-2.42 (m, 1 H), 2.37-2.31 (m, 2 H), 2.03-1.90 (m, 4 H), 1.80-1.71 (m, 4 H), 1.55-1.42 (m, 2 H).

LCMS (ESI) calcd for $C_{25}H_{32}FN_7O_2$ $[M + H]^+$ m/z 482.26, found 482.15.

Example 29 – Synthesis of compound 393rac

Synthesis of compound 393rac



Preparation of 8-fluoro-2-(4-methoxybenzyl)-3-vinylisoquinolin-1(2H)-one (3)

To a solution of 3-chloro-8-fluoro-2-(4-methoxybenzyl)isoquinolin-1(2H)-one **1** (2000 mg, 6.294 mmol) and $Pd(AMPHOS)Cl_2$ (445 mg, 0.6294 mmol) in ACN (30 mL) was added tributyl(vinyl)stannane **2** (1995 mg, 6.294 mmol). The mixture was heated at 100 °C in sealed tube for 5 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with EtOAc/PE, 0 to 15%) to give 8-fluoro-2-(4-methoxybenzyl)-3-vinylisoquinolin-1(2H)-one **3** (1500 mg, 90% purity, 69% yield) as a white solid.

LCMS (ESI) calcd for $C_{19}H_{16}FNO_2$ $[M + H]^+$ m/z 310.12, found 309.90.

Preparation of 8-fluoro-2-(4-methoxybenzyl)-1-oxo-1,2-dihydroisoquinoline-3-carbaldehyde (4)

To a solution of 8-fluoro-2-(4-methoxybenzyl)-3-vinylisoquinolin-1(2H)-one **3** (1500 mg, 4.85 mmol) in MeOH/H₂O (3:1, 80 mL) was added NaIO₄ (4150 mg, 19.40 mmol) and K₂OsO₄·2H₂O (178 mg, 0.48 mmol). The reaction stirred for 1 h at room temperature. The reaction mixture was diluted with water and extracted with EtOAc (200 mL x 3). The combined organic layers were washed by brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluting with EtOAc/PE, 0 to 25%) to give 8-fluoro-2-(4-methoxybenzyl)-1-oxo-1,2-dihydroisoquinoline-3-carbaldehyde **4** (430 mg, 90% purity, 25% yield) as a yellow solid.

LCMS (ESI) calcd for C₁₈H₁₄FNO₃ [M + H]⁺ m/z 312.10, found 311.90.

Preparation of 3-(2,2-difluorovinyl)-8-fluoro-2-(4-methoxybenzyl)isoquinolin-1(2H)-one (5)

To a solution of 8-fluoro-2-(4-methoxybenzyl)-1-oxo-1,2-dihydroisoquinoline-3-carbaldehyde **4** (430 mg, 1.38 mmol), PPh₃ (724 mg, 2.76 mmol) and LiI (369 mg, 2.76 mmol) in DMF/Dioxane (8%, 10 mL) was added TMSCF₃ (491 mg, 3.45 mmol). The mixture was heated at 130 °C in a sealed tube for 3 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with EtOAc/PE, 0 to 15%) to give 3-(2,2-difluorovinyl)-8-fluoro-2-(4-methoxybenzyl)isoquinolin-1(2H)-one **5** (200 mg, 60% purity, 25% yield) as a white solid.

LCMS (ESI) calcd for C₁₉H₁₄F₃NO₂ [M + H]⁺ m/z 346.10, found 346.00.

Preparation of 3-(1-benzyl-4,4-difluoropyrrolidin-3-yl)-8-fluoro-2-(4-methoxybenzyl)isoquinolin-1(2H)-one (7)

To a solution of 3-(2,2-difluorovinyl)-8-fluoro-2-(4-methoxybenzyl)isoquinolin-1(2H)-one **5** (260 mg, 0.75 mmol) and LiF (39 mg, 1.51 mmol) in ACN (50 mL) was added N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine **6** (357 mg, 1.51 mmol). The mixture was kept stirring at 60 °C for 16 h. The resulting mixture was diluted with water and extracted with DCM (30 mL x 3). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with EtOAc/PE, 0 to 15%) to give 3-(1-benzyl-4,4-difluoropyrrolidin-3-yl)-8-fluoro-2-(4-methoxybenzyl)isoquinolin-1(2H)-one **7** (25 mg, 90% purity, 6% yield) as a white solid.

LCMS (ESI) calcd for C₂₈H₂₅F₃N₂O₂ [M + H]⁺ m/z 479.19, found 479.20.

Preparation of 3-(4,4-difluoropyrrolidin-3-yl)-8-fluoro-2-(4-methoxybenzyl)isoquinolin-

1(2H)-one (7)

To a solution of 3-(1-benzyl-4,4-difluoropyrrolidin-3-yl)-8-fluoro-2-(4-methoxybenzyl)isoquinolin-1(2H)-one **7** (130 mg, 0.271 mmol) in MeOH (5 mL) was added one drop of conc. HCl, 10% Pd/C (20 mg) and 10% Pd(OH)₂/C (20 mg). The mixture was evacuated and backfilled with hydrogen three times and then charged with hydrogen. The resulting mixture was stirred at room temperature for 16 hours. Then the mixture was filtered through celite and concentrated under vacuum to give crude 3-(4,4-difluoropyrrolidin-3-yl)-8-fluoro-2-(4-methoxybenzyl)isoquinolin-1(2H)-one **8** (100 mg, 50% purity, 47% yield) as a white solid which was used directly in next step without further purification.

LCMS (ESI) calcd for C₂₁H₁₉F₃N₂O₂ [M + H]⁺ m/z 389.14, found 389.00.

Preparation of 5-(4-(3,3-difluoro-4-(8-fluoro-2-(4-methoxybenzyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide (10)

To a solution of 3-(4,4-difluoropyrrolidin-3-yl)-8-fluoro-2-(4-methoxybenzyl)isoquinolin-1(2H)-one **8** (100 mg, 0.257 mmol) in MeOH (10 mL) was added N-methyl-5-(4-oxopiperidin-1-yl)picolinamide **INT** (90 mg, 0.386 mmol), then two drops of acetic acid and NaBH₃CN (24 mg, 0.386 mmol) were added at room temperature. The reaction mixture stirred at 50 °C for 1 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with DCM/MeOH = 100 : 0 to 90 : 10) to give 5-(4-(3,3-difluoro-4-(8-fluoro-2-(4-methoxybenzyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide **10** (80 mg, 50% purity, 25% yield) as a white solid.

LCMS (ESI) calcd for C₃₃H₃₄F₃N₅O₃ [M + H]⁺ m/z 606.26, found 606.20.

Preparation of 5-(4-(3,3-difluoro-4-(8-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide (compound 393rac)

To a solution of 5-(4-(3,3-difluoro-4-(8-fluoro-2-(4-methoxybenzyl)-1-oxo-1,2-dihydroisoquinolin-3-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide **10** (80 mg, 0.13 mmol) in TFA (5 mL) was added TfOH (1 mL) dropwise at rt. The reaction mixture was stirred at 100 °C for 5 min. The pH of the resulting mixture was adjusted to around 8.0 by progressively adding saturated NaHCO₃ solution, and then extracted with DCM (50 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by

prep-HPLC (Gemini 5 μ m C18 150 $\times$ 21.2 mm, eluting with 35% to 40% ACN/H₂O containing 0.1% FA) to give 5-(4-(3,3-difluoro-4-(8-fluoro-1-oxo-1,2-dihydroisoquinolin-3-yl)pyrrolidin-1-yl)piperidin-1-yl)-N-methylpicolinamide **393rac** (6.2 mg, 93% purity, 9% yield) as a brown solid. ¹H NMR (400 MHz, CD₃OD_SPE, ppm) δ : 8.31 (d, J = 2.8 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 1 H), 7.72-7.65 (m, 1 H), 7.57-7.47 (m, 1 H), 7.43 (d, J = 8.0 Hz, 1 H), 7.17 (dd, J = 11.8, 8.2 Hz, 1 H), 6.76-6.68 (m, 1 H), 4.10-3.94 (m, 2 H), 3.85-3.50 (m, 5 H), 3.28-3.25 (m, 1 H), 3.07 (t, J = 12.4 Hz, 2 H), 2.96-2.90 (m, 3 H), 2.24-2.09 (m, 2 H), 1.84-1.66 (m, 2 H). LCMS (ESI) calcd for C₂₅H₂₆F₃N₅O₂ [M + H]⁺ m/z 486.21, found 486.40.

Assays

Exemplary compounds of the invention were prepared and tested to determine their effect as PARP1 and PARP2 inhibitors. Typical assays are described below.

PARP1 biochemical dissociation-enhanced lanthanide fluorescence immunoassay (DELFI assay)

Optiplate HB 384-well plates were coated with anti-FLAG antibody, supplied as a 4 mg/ml solution, using a Na₂CO₃/HCO₃ coating buffer at pH 9.6, overnight at 4°C, in order to achieve a final immobilisation per well of 0.3 μ g. Wells were then washed 3 x 5 min in coating wash buffer (PBS/0.05 % Tween (v/v)), and blocked with 2 % BSA (w/v) in coating wash buffer overnight at 4°C. Prior to assay, wells were washed 3 x 5 min in coating wash buffer. For the assay 20 μ l of 2.5 nM recombinant full length human N-terminally FLAG-tagged PARP1 was added to each well of the 384-well plate for 30 min at room temperature followed by addition of 50 nL of compound solution in DMSO using pintool technology. Following incubation for 30 min at room temperature, 5 μ l of 10 μ M biotin-NAD⁺ and 10 nM activation DNA (sequence shown below) in solution in 20 mM HEPES (pH 7.5), 100 mM NaCl, 2 mM DTT, 0.1 % BSA (w/v), 0.02 % Tween (v/v) assay buffer. Auto-PARylation proceeded for 2 h at room temperature prior to the addition of 5 μ l of 12 mM NAD⁺ quenching solution. After 30 min at room temperature, assay solution was removed and following washing 5 times for 3 min, 100 μ l of a 1:1000 dilution of DELFIA Eu-N1 Streptavidin reagent was added. Plates were then incubated for 30 min at room temperature. Reaction mixture was removed and plates washed 5 times for 3 min prior to the addition of 25 μ l DELFIA enhancement solution. Following

incubation for 30 min at room temperature, fluorescence was measured on a Pherastar FS (Ex337 nm, Em620 nm; integration start 60 μ s; integration time 400 μ s).

Typically compounds were tested from 20 μ M at 3-fold dilution intervals in 12-point concentration-response curves to determine IC₅₀ values. Data was analysed using ActivityBase software and replicate values for the low (without enzyme, 0.2% DMSO) and high (0.2 % DMSO) % controls were averaged and the data obtained from the test compounds expressed as a % of 100 % using the below formulae:

$$\% \text{ value} = 100 - (100 * ((\text{high control} - \text{unknown}) / (\text{high control} - \text{low control})))$$

% data was fitted to a non-linear regression equation (log inhibitor vs response-variable slope 4-parameters) to obtain IC₅₀ values.

The IC₅₀ values for a variety of test compounds are shown in Table 1.

Activation DNA sequence:

Duplex Sequences

5'-ACCCTGCTGTGGGC/ideoxyU/GGAGAACAAGGTGAT-3'

5'-ATCACCTTGTCTCCAHGCCCACAGCAGGGT-3'

```

5' - ACCCTGCTGTGGGCGGAGAACAAGGTGAT -3'
      |   | | | | | | | | | | | | | |
3' - TGGGACGACACCCGHACCTCTTGTTCCTACTA -5'

```

PARP1 probe displacement homogeneous time-resolved fluorescence assay (HTRF assay)

10 nM full length N-terminally FLAG-tagged PARP1 was incubated with 2 nM Anti-FLAG Tb-cryptate antibody and PARP1/2 Cy5 fluorescent dye-labelled binding probe (10-fold probe K_d = 270 nM) in 20 mM HEPES (pH 7.5), 100 mM NaCl, 2 mM DTT, 0.1 % BSA (w/v), 0.02 % Tween (v/v) assay buffer for 40 min at room temperature. A Cy5-labelled binding probe is shown below and described in Papeo, G. *et al. J. Biomol. Screen.* 2014; 19:1212-1219. 6 μ l of this reaction mixture was then transferred to each well of a black non-binding surface 384-well plate and 35 nl of compound solution in DMSO was then added using pintool technology. Following incubation for 1 h at room temperature, fluorescence was measured on a Pherastar

FS (Ex 337 nm, Em620 nm, em665 nm; integration start 60µs; integration time 400µs) using the HTRF module.

Typically compounds were tested from 58.5 µM at factor 3 dilution intervals in 12-point concentration-response curves to determine IC₅₀ values. Data was analysed using ActivityBase software and replicate values for the low (without enzyme but with probe and Tb-cryptate antibody, 0.6% DMSO) and high (0.6 % DMSO) % controls were averaged and the data obtained from the test compounds expressed as a % of 100 % using the below formulae:

$$\% \text{activity} = 100 * (\text{value} - \text{low control}) / (\text{high control} - \text{low control})$$

%activity data was fitted to a non-linear regression equation to obtain IC₅₀ values

K_d values were calculated using Cheng-Prusoff formula:

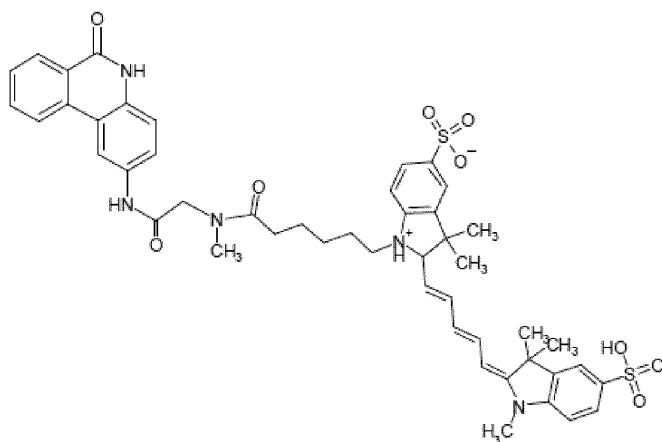
$$\text{IC}_{50} = (1 + ([\text{probe concentration}] / [\text{K}_{\text{mprobe}}])) * \text{K}_{\text{d}}$$

Therefore K_d = IC₅₀ / (1 + ([probe concentration] / [K_{mprobe}])); using probe at 10 x K_m, this equated to K_d = IC₅₀/11

PARP2 probe displacement homogeneous time-resolved fluorescence assay (HTRF assay)

This assay was performed under identical conditions as for PARP1, except that N-terminally FLAG-tagged PARP2 (amino acids 1-583) was used instead of PARP1, and PARP1/2 binding probe was used at 10-fold probe K_d = 540 nM. Data analysis was performed identical as for PARP1.

Cy5 probe structure:



NanoBRET cellular target occupancy assay

NanoBRET assays were employed to demonstrate cellular target engagement and selectivity at PARP1 and PARP2. These assays are based on bioluminescence resonance energy transfer (BRET) between a Nano-luc-tagged protein (eg PARP1 or PARP2) and a fluorescent group on a high affinity NAD⁺ competitive binding probe. Such cellular probe displacement assays can be utilised to measure inhibitor affinities and selectivity ratios at PARP1 and 2.

Frozen HEK293 cells transiently transfected with either PARP1-NanoLuc® fusion or PARP2-NanoLuc® fusion constructs (Promega) were thawed and dispensed as a suspension in 384-well microplates each at a density of 1750 cells per well. NanoBRET™ TE PARP Tracer-01 was then added to final concentrations of 11 and 2 nM for PARP1 and PARP2 assays, respectively. Compounds were added from 25 µM at factor 3 dilution intervals in 12-point concentration-response curves and plates were incubated for 2 hours at 37°C. BRET ratios were then measured using a NanoBRET module (LUM 610-LP 450-80) and PHERAstar FS or FSX reader following addition of NanoBRET™ Nano-Glo® Substrate and Extracellular NanoLuc® Inhibitor according to manufacturer's instructions. K_d values were calculated using Cheng-Prussoff formula:

$$IC_{50} = (1 + ([\text{tracer concentration}]/[K_{m_{\text{tracer}}}])) * K_d$$

Binned potency, affinity and selectivity data for a variety of test compounds are shown in Table 1 where DELFIA and Probe Displacement HTRF assays were used. Binned potency, affinity and selectivity data for a subset of test compounds where the NanoBRET assay was used are shown in Table 2.

TABLE 1*Results of Parp 1/2 assays for selected compounds (DELFA and Probe Displacement HTRF)*

Compound	PARP1 DELFIA	PARP1 HTRF	PARP2 HTRF	Selectivity
1	++	NT	NT	NT
2	++++	++++	+	+++
3a	++	NT	NT	NT
3b	++	NT	NT	NT
4a	++	++	++	-
4b	++	NT	NT	NT
5	+	NT	NT	NT
6a	++++	++++	-	+++
6b	++	++	+	+
7a	+++	++++	++	+++
7b	++	NT	NT	NT
8	++++	++++	-	+++
9a	+++	+++	+	+++
9b	+++	+++	++	-
10a	+++	++++	++	+++
10b	++++	++++	++	+++
11a	+	++	-	-
11b	++	++	+	-
12	++	NT	NT	NT
13a	+	NT	NT	NT
13b	+	NT	NT	NT
14a	+	NT	NT	NT
14b	+++	+++	-	+++
15	++	NT	NT	NT
16a	++	NT	NT	NT
16b	++	NT	NT	NT
17	+++	+++	-	+++
18	++	NT	NT	NT
19	+	NT	NT	NT
20	+++	+++	-	++
21	+	NT	NT	NT
22	+	NT	NT	NT
23a	++	NT	NT	NT
23b	+	+	-	-
24a	+	NT	NT	NT
24b	+	NT	NT	NT
25	++	NT	NT	NT
26rac	+++	+++	++	+
27	+++	+++	+	+

28	++	NT	NT	NT
29	+	NT	NT	NT
30	++	NT	NT	NT
31a	+	NT	NT	NT
31b	+++	+++	-	+++
32a	+++	+++	+	+
32b	++	NT	NT	NT
33a	-	NT	NT	NT
33b	+++	+++	-	++
34a	+++	+++	++	-
34b	++++	++++	+	+++
35a	++	NT	NT	NT
35b	+++	+++	-	+++
36	++++	++++	-	+++
37rac	++	NT	NT	NT
38a	+	+	+	-
38b	+	+	-	-
39rac	++	++	-	+
40	++++	++++	++	++
41	++	++	-	+
42rac	++++	++++	+	+++
43a	++	+++	++	-
43b	++++	++++	++	+
44a	++++	++++	-	+++
44b	+++	+++	+	+
45	++++	++++	++	+++
46a	++++	+++	+	+++
46b	++	++	++	-
47	++	++	-	-
48	++++	++++	++	+++
49rac	++++	++++	++	+++
50a	+++	+++	+	+
50b	+++	+++	-	+++
51a	++	++	-	+
51b	+	+	+	-
52a	+++	+++	++	-
52b	++++	++++	++	+++
53a	++++	++++	+	+++
53b	++	++	-	+
54	++++	++++	++	+++
55a	++++	++++	+	+++
55b	+++	+++	++	-
10rac	++++	++++	++	+++
56a	++	+++	-	++

56b	+	++	-	-
57a	++++	+++	-	+++
57b	++	++	-	+
58a	++++	++++	-	+++
58b	+++	+++	-	++
59	+	++	-	-
60a	++++	++++	-	+++
60b	++	+++	-	++
61a	++	+++	+	+
61b	++++	++++	+	+++
62a	+++	+++	+	++
62b	++	++	+	-
63	++++	+++	+	++
64a	++++	++++	++	+
64b	++++	++++	++	+++
65a	++++	++++	++	+++
65b	++	++	+	+
66a	+	+	-	-
66b	+	+	-	-
67a	++	++	+	+
67b	++	++	+	+
68a	++++	++++	++	+++
68b	+++	++++	++	+
69a	++++	+++	++	++
69b	+++	+++	++	-
70a	+++	++	+	+
70b	+++	++	++	-
71a	+	+	-	-
71b	+++	+++	-	+++
72a	+++	+++	+	+++
72b	++++	++++	++	+++
73a	++	++	-	-
73b	+++	+++	-	++
74a	++	++	+	+
74b	+++	+++	+	++
75	NT	+	-	-
76a	NT	+++	++	-
76b	NT	+++	++++	-
77a	NT	++	-	+
77b	NT	+++	-	+++
78a	NT	++++	+	+++
78b	NT	+++	++	+
79a	NT	+++	++	+
79b	NT	+++	++	+

80a	NT	++++	++	+++
80b	NT	++	++	-
81a	NT	++	-	+
81b	NT	+++	-	+++
82a	NT	+++	++	-
82b	NT	+++	-	++
83a	NT	++	+	-
83b	NT	++	-	+
84a	NT	+	-	-
84b	NT	+++	-	++
85a	NT	+++	++	+
85b	++++	++++	+++	++
86a	+++	+++	++	+
86b	++++	++++	++++	+
87a	NT	++	+	+
87b	NT	++++	+	+++
88a	NT	++	++	-
88b	NT	++++	+	+++
89a	NT	-	-	-
89b	NT	++	-	+
90a	NT	++	-	+
90b	NT	++	+	+
91a	++++	++++	++	+++
91b	++++	++++	++	+++
92a	++	++	-	+
92b	+++	++++	+	+++
93a	++	++	-	+
93b	+	+	-	-
94a	+++	+++	+	+
94b	++++	++++	-	+++
95rac	++	+	+	-
96a	+++	+++	+	+
96b	++	++	++	-
97a	-	-	-	-
97b	++	++	-	-
98a	+++	+++	-	+++
98b	++	++	-	+
99a	+	+	-	-
99b	+++	++	++	-
100a	++++	++++	++	+++
100b	+++	+++	+	+++
101a	+++	+++	++	+
101b	++++	++++	++	+++
102rac	++++	++++	+	+++

103rac	++++	++++	+	+++
104rac	++++	++++	+	+++
105rac	++	++	+	-
106a	++	++	-	+
106b	+	-	-	-
107a	+++	+++	+	+
107b	++	++	++	-
108a	++	++	-	-
108b	++	++	-	+
109a	+++	++++	-	+++
109b	+++	++	+	+
110a	++++	++++	-	+++
110b	++	+++	++	-
111a	+++	+++	++	+
111b	++++	++++	++	+++
112a	++	++	+	-
112b	+++	+++	-	+++
113a	++	++	++	-
113b	++	++	-	+
114a	++++	++++	-	+++
114b	++	++	+	+
115a	++	++	+	+
115b	+++	+++	+	+++
116a	+++	+++	-	+++
116b	++	++	+	-
117a	+++	+++	++	+
117b	++++	++++	++	+++
118a	++++	++++	-	+++
118b	+++	+++	-	++
119rac	++++	++++	+	+++
120rac	++	++	-	+
121a	+++	+++	++	+
121b	++++	++++	++	+++
122a	++++	+++	-	+++
122b	+++	++	+	-
123a	+++	+++	++	+
123b	++++	++++	+	+++
124rac	++++	++++	++	+++
125a	++++	++++	+	+++
125b	++++	++++	+	+++
126a	++++	++++	+	+++
126b	++	++	-	+
127rac	+++	+++	-	+++
128a	+++	+++	+	+++

128b	++++	++++	+++	++
129a	++++	++++	+	+++
129b	++++	++++	+++	+++
130a	++++	++++	++	+
130b	++++	++++	++	+++
131a	+++	++	+	+
131b	++++	++++	-	+++
132rac	+++	+++	-	+++
133a	++++	++++	+	+++
133b	+++	+++	-	+++
134rac	++++	++++	-	+++
135rac	++++	++++	+++	+
136rac	++++	++++	+++	+++
137a	++++	++++	++	+++
137b	++++	++++	+++	+
138rac	+++	+++	+	++
139a	++++	++++	+	+++
139b	+++	+++	+	+++
140a	++	+++	-	++
140b	+++	+++	+	+++
141rac	++++	++++	+	+++
142rac	++++	++++	+	+++
143rac	+++	++++	+	+++
144rac	++++	++++	+	+++
136a	++++	++++	++	+++
136b	++++	++++	+++	+++
145a	++++	++++	+	+++
145b	++++	++++	+	+++
146a	++	++	+	-
146b	+++	+++	-	+++
147a	+	+	-	-
147b	+	+	-	-
148a	+	-	-	-
148b	+	+	-	-
149a	++	++	-	+
149b	+	+	-	-
150rac	++++	++++	++++	-
151a	++++	++++	++	+++
151b	++++	++++	-	+++
152a	++++	++++	+	+++
152b	+++	+++	-	++
153rac	++++	++++	++	++
154rac	++++	++++	+++	+
155a	+++	+++	++	+

155b	++++	++++	++	+++
156rac	+++	+++	-	++
157rac	++++	++++	+	+++
158a	++++	++++	+	+++
158b	+++	+++	+	+++
159a	-	-	-	-
159b	++	++	-	+
160rac	++++	++++	+	+++
161a	++	++	-	-
161b	++++	++++	+	+++
162a	+++	+++	++	-
162b	++++	++++	+++	++
163rac	++++	++++	++	+++
164a	++++	++++	+	+++
164b	+++	+++	-	+++
165a	++++	++++	++	+++
165b	+++	+++	+	+++
154a	++++	++++	++	+++
154b	++++	++++	+++	+
166rac	++++	++++	+	+++
167a	+++	+++	-	++
167b	++++	++++	++	+++
168	++++	++++	-	+++
169a	+	-	-	-
169b	++++	+++	-	+++
170rac	++++	++++	++++	-
171rac	++++	++++	++	+++
172a	++++	++++	+	+++
172b	++++	++++	+++	+++
173	++	+	-	-
174rac	++++	++++	++	+++
174a	++++	++++	++	+++
174b	++++	++++	+++	+++
175rac	++++	++++	++	+++
176rac	NT	++	-	+
177rac	NT	++++	-	+++
178a	NT	++	+	-
178b	NT	++++	+	+++
179	NT	+++	-	+++
180a	++++	++++	+	+++
180b	++++	++++	+++	++
181a	+++	+++	++	+
181b	++++	++++	++	+++
182a	+++	+++	++	+
182b	++++	++++	++	+++

183a	++++	++++	+	+++
183b	++++	++++	++	+++
184a	++++	++++	+	+++
184b	++++	++++	++	+++
176a	++	++	-	+
176b	+++	++	-	++
170a	++++	++++	++++	-
170b	++++	++++	++++	-
185a	++++	++++	++	+++
185b	+++	++	+	+
186a	++++	++++	++	+++
186b	++++	++++	+++	+
187a	+++	+++	++	-
187b	++++	++++	++++	-
188a	++	++	-	+
188b	++++	++++	++	+++
189a	+++	+++	++	-
189b	++++	++++	+++	++
190a	++	++	+	+
190b	++++	++++	+++	++
191rac	++	++	-	+
192	++++	++++	+	+++
193	+++	+++	+	+++
194a	+++	+++	+	+
194b	++++	++++	+++	+
195rac	++++	++++	++	+++
196a	++++	++++	++	+++
196b	++++	++++	+	+++
197a	++++	++++	++	+++
197b	+++	+++	+	+++
198rac	++++	++++	+++	+
199a	++++	++++	++	+++
199b	++	++	-	+
200rac	+++	+++	-	+++
201a	++	++	-	+
201b	++++	++++	+	+++
202a	+++	+++	++	+
202b	++++	++++	+++	+
203rac	++++	++++	-	+++
204rac	++++	++++	-	+++
205a	++	++	-	+
205b	+++	+++	+	+
206a	++++	++++	++	+++
206b	++++	++++	+	+++
207a	++++	++++	-	+++
207b	++	++	-	-

208a	++++	+++	++	+
208b	++++	++++	+++	++
209a	++++	++++	++	+++
209b	+++	+++	+	+++
210a	++	++	-	+
210b	++++	++++	+	+++
211rac	++++	++++	++	+++
212a	++	++	-	+
212b	-	-	-	-
213a	+++	+++	-	+++
213b	++++	++++	++	+++
214a	+++	+++	++	++
214b	++++	++++	++	+++
215rac	+++	+++	++	-
216rac	++	++	-	-
217a	++	++	-	-
217b	++++	++++	++	++
218a	+++	+++	-	+++
218b	++++	++++	++	+++
219a	++++	++++	+++	++
219b	++++	++++	++	+++
220a	++	++	+	-
220b	+++	+++	+	+
221a	+++	+++	++	+
221b	++++	++++	+++	++
222a	++++	++++	++	+
222b	++++	++++	+++	+++
223a	++++	++++	++	+++
223b	++++	++++	++	+++
224a	++	+	+	-
224b	++	++	+	-
225rac	++++	++++	+	+++
226rac	+++	+++	-	++
227	++++	++++	++	+++
228	++++	++++	+	+++
229rac	+++	++++	++	+++
230rac	++++	++++	+	+++
231rac	++++	++++	+	+++
232a	+++	+++	++	-
232b	++++	++++	++	+++
233rac	++++	++++	++	+++
234rac	++++	++++	++	+++
235rac	++++	++++	+++	+
236a	+++	+++	++	+
236b	++++	++++	+++	+
237rac	++++	++++	+++	++
238	++++	++++	++	+++
239a	++++	++++	-	+++

239b	++++	++++	+	+++
240a	+++	+++	-	++
240b	+	+	-	-
241rac	++++	++++	++	+++
242rac	++++	++++	++	++
243rac	+++	+++	-	++
244rac	++++	++++	++++	-
245a	++++	++++	++	+++
245b	+++	+++	-	+++
246a	++	++	-	+
246b	++++	++++	+	+++
247rac	++++	++++	+++	+
248rac	++++	++++	++	+++
249a	+	+	-	-
249b	++	++	-	+
250a	++	++	+	-
250b	+++	+++	++	+
251a	++	++	+	-
251b	+++	+++	++	+
252a	++	++	+	-
252b	+++	+++	++	+
253rac	+++	+++	-	+
254rac	+++	++	+	+
255rac	++++	++++	++	++
256rac	++++	++++	+	+++
257rac	++++	++++	+	+++
258rac	++++	++++	++	+++
259	++++	++++	++	+++
260	++++	++++	+	+++
261a	++	+	-	-
261b	++++	++++	+	+++
262a	++	+	+	-
262b	++	++	+	+
263rac	+++	++	++	-
264rac	++++	++++	++	+++
265a	++++	++++	+	+++
265b	++++	++++	++	+++
266a	++++	++++	++	+++
266b	+++	+++	-	+++
267a	+++	+++	++	+
267b	++++	++++	+++	+++
268rac	++++	++++	++	+++
269a	++++	++++	+	+++
269b	++	++	-	+
270a	+++	+++	+++	-
270b	++++	++++	+++	+
271rac	++++	++++	++	+++
272a	-	-	-	-

272b	++	++	-	+
273a	++	++	+	-
274a	++	++	+	-
274b	+++	++	+	+
275rac	++++	++++	++	+
276rac	++++	++++	++	+++
277a	++++	++++	+	+++
277b	+++	+++	-	++
278rac	+++	+++	-	+++
279a	++	++	-	+
279b	+	+	-	-
280a	+++	+++	+	++
280b	++++	++++	+++	++
281a	++++	++++	+++	+
281b	++	++	++	-
282rac	+++	+++	++	+
283a	++	++	-	+
283b	++++	++++	+	+++
284	++++	++++	-	+++
285a	++++	++++	++	+++
285b	++++	++++	-	+++
286rac	+++	+++	-	+++
287a	+++	+++	-	++
287b	+	+	-	-
288rac	+++	+++	+	+++
273b	+++	+++	++	+
289a	++	++	+	-
289b	++++	+++	++	+
290rac	+++	++	+	+
291a	+++	++	+	+
291b	++	++	+	-
292a	+++	++	+	-
292b	++++	++++	++	+++
293a	-	-	-	-
293b	++	++	+	-
294rac	++	++	-	-
295	++++	++++	-	+++
296rac	++++	++++	++	+
297rac	+++	+++	++	-
298a	+	+	-	-
298b	+++	+++	+	+++
299	++++	++++	-	+++
300	++++	++++	+	+++
301rac	++	++	+	-
302	++++	++++	-	+++
303	++++	++++	-	+++
304	++++	+++	-	+++
305	++++	++++	-	+++

306a	++	++	+	+
306b	++++	++++	++	+++
307rac	+++	+++	++	-
308a	++	++	+	+
308b	++++	++++	++	+++
309a	++++	++++	-	+++
309b	+++	+++	-	++
310	+++	++++	-	+++
311	++++	++++	+	+++
312	++++	++++	++	+++
313a	+++	+++	-	+++
313b	++++	++++	+	+++
314a	++++	++++	++	+
314b	++++	++++	++	+++
315rac	++++	++++	++	+++
316a	++++	++++	++	+++
316b	+++	+++	++	+
317a	+++	++	+	-
317b	++++	++++	++	+++
318rac	+++	+++	++	+
319rac	+	+	+	-
320rac	++	++	+	-
321rac	++	++	++	-
322a	++++	++++	-	+++
322b	++++	++++	++	+++
323a	++++	++++	-	+++
323b	++++	++++	+++	+++
324rac	++++	++++	++	+++
325rac	++++	++++	+	+++
326a	++	++	+	+
326b	+++	++++	+	+++
327a	++	++	-	+
327b	++	++	-	-
328a	++	++	-	+
328b	+++	+++	-	+++
329rac	++++	++++	++	+++
330	++++	++++	+++	+
331a	++++	++++	++	+++
331b	+++	+++	+	+++
332a	++	++	+	+
332b	++++	++++	+	+++
333b	+++	+++	+	+++
334rac	++++	+++	+	++
335rac	++	++	-	+
336rac	++++	++++	+++	++
337a	++++	++++	++	+++
337b	++++	++++	++	+++
338a	++++	++++	++	+++

338b	+++	+++	+	++
339a	++++	++++	+++	+
339b	++++	++++	++	+++
340a	++++	++++	++	+++
340b	+++	+++	++	+
341a	++++	++++	++	+++
341b	+++	+++	++	+
342a	++	++	++	-
342b	++++	++++	+++	+
333a	++++	++++	++	+++
343a	++++	++++	++	+++
343b	++++	++++	+	+++
344a	++++	++++	-	+++
344b	++++	++++	+	+++
345a	++++	++++	++	+++
345b	+++	+++	+	+
346a	++++	++++	+	+++
346b	++	++	-	+
347a	++++	++++	++	+++
347b	+++	+++	+	+++
348a	+++	+++	++	-
348b	++	++	++	-
349a	++++	++++	-	+++
349b	++++	++++	++	+++
350a	++++	++++	++	+++
350b	++++	++++	+++	++
351a	++++	++++	+	+++
351b	++++	++++	++	+++
352a	++++	++++	+++	+++
352b	++++	++++	++	++
353a	++++	++++	++	+++
353b	+++	+++	+	+++
354a	++++	++++	+++	+
354b	++++	++++	++	+++
355a	++	++	+	-
355b	++++	++++	++	+++
356a	++++	++++	+	+++
356b	++	++	+	+
357a	++++	++++	++	+++
357b	+++	++++	+	+++
358rac	++++	++++	++	+++
359a	+++	+++	+	++
359b	+++	++	-	+
360rac	++++	++++	++	+++
361	++++	++++	++	+++
362rac	++++	++++	+	+++
363a	++++	++++	+	+++
363b	++++	++++	+	+++

364a	++	++	-	+
364b	++++	++++	++	++
365rac	++++	++++	++	+++
315a	++++	++++	++	+++
315b	++++	++++	++	+++
366a	+++	+++	-	+++
366b	++++	++++	++	++
367a	++++	++++	++	+++
367b	++++	++++	+	+++
368	++++	++++	-	+++
369	++++	++++	+	+++
370a	++++	++++	++	+++
370b	++++	++++	+++	++
371a	++++	++++	+++	+++
371b	+++	+++	+	++
372a	++++	++++	++	+
372b	++++	++++	+++	+++
324a	++++	++++	-	+++
324b	++++	++++	++	+++
373	++++	++++	+	+++
374a	+++	+++	++	+
374b	++++	++++	+++	++
375	++++	++++	++	+
376	++++	++++	++	+++
377a	+++	+++	-	+++
377b	++++	++++	+	+++
378a	++++	++++	++	+++
378b	++++	++++	+	+++
379	++++	++++	++	+++
380	++++	++++	-	+++
381	++++	++++	+	+++
382a	++	++	-	+
382b	++++	++++	++	+++
383	++++	++++	++	+
384	++++	++++	++	+
385a	++++	++++	+	+++
385b	++++	++++	+++	+++
386a	++++	++++	++	+++
386b	++++	++++	+	+++
387	++++	++++	++	+++
388	++++	++++	++	+++
389	++++	++++	++	+++
390a	++++	++++	++	+++
390b	++++	++++	+++	++
391rac	++++	++++	+	+++
392rac	++	++	-	+
393rac	++++	++++	+	+++
394	++++	++++	+++	+

395a	++++	++++	++	+
395b	++++	++++	+++	++
396a	++++	++++	++	+++
396b	++++	++++	++	+++
397a	++++	++++	++	+++
397b	++++	++++	+++	+++
398a	++++	++++	+	+++
398b	++++	++++	++	+++
399a	++++	++++	++	+++
399b	++++	++++	+++	+
400rac	++++	++++	++	+++
401a	++++	++++	+++	+++
401b	++++	++++	+++	+
402a	++++	++++	++	+++
402b	++++	++++	+++	+++
403rac	++++	++++	+++	+++
404a	+++	+++	+	+++
404b	++++	++++	+	+++
405rac	++++	++++	++	+++
415rac	+++	++++	-	+++
406rac	++++	++++	-	+++
407a	+++	++++	++	++
407b	++++	++++	++++	+
408a	++++	++++	++	+++
408b	+++	+++	+	+
409a	++++	++++	+	+++
409b	++++	++++	++	+++
410a	++++	++++	++	+++
410b	++++	++++	++	+++
411	++++	++++	++	+++
412rac	++	++	-	+
413rac	++++	++++	++	+++
414rac	+++	+++	++	++

TABLE 2*Results of Parp 1/2 assays for selected compounds (NanoBRET)*

Compound	PARP1 NanoBRET	PARP2 NanoBRET	Selectivity
10b	++++	+	+++
64b	++++	++	+++
68a	++++	+	+++
72b	++++	+	+++

86b	++++	+++	+
129b	++++	++	+++
137b	++++	++	+++
144rac	++++	-	+++
136b	++++	++	+++
150rac	+++	++	+
151a	++++	-	+++
157rac	++++	-	+++
154b	++++	++	+++
170rac	++++	+++	+
174rac	++++	+	+++
174a	++++	+	+++
174b	++++	++	+++
175rac	++++	+	+++
180b	++++	++	+++
183b	++++	+	+++
184b	++++	++	+++
186b	++++	+++	+++
192	++++	+	+++
196a	++++	++	+++
197a	++++	++	+++
198rac	++++	++	+
223b	++++	++	+++
228	++++	-	+++
239b	++++	+	+++
255rac	++++	+	+++
258rac	++++	++	+++
259	++++	+	+++
260	++++	-	+++
285a	++++	++	+++
295	+++	-	++
299	+++	-	+++

300	++++	-	+++
302	+++	-	+++
312	++	+	++
313b	++++	+	+++
314b	++++	++	+++
315rac	++++	++	+++
316a	++++	++	+++
322b	++++	++	+++
323a	++++	-	+++
323b	++++	++	+++
324rac	++++	+	+++
329rac	++++	+	+++
330	+++	++	+
337a	++++	+	+++
337b	++++	++	+++
339a	++++	+++	+
343a	++++	+	+++
344b	++++	-	+++
350b	++++	+++	+++
352a	++++	++	+++
353a	++++	++	+++
354a	++++	+++	++
354b	++++	++	+++
357a	++++	+	+++

Key

DELFI, Probe Displacement HTRF and NanoBRET assay categories:

- indicates IC₅₀ or K_d value above 10 μ M

+ indicates IC₅₀ or K_d value above 1 μ M up to 10 μ M

++ indicates IC₅₀ or K_d value above 100 nM up to 1 μ M

+++ indicates IC₅₀ or K_d value above 10 nM up to 100 nM

++++ indicates IC₅₀ or K_d value of 10 nM or less

Selectivity categories:

- indicates a value of less than 10

+ indicates a value of 10 to less than 50

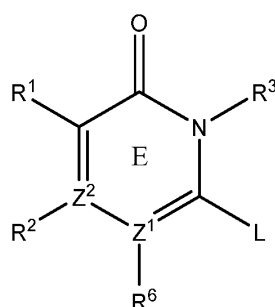
++ indicates a value of 50 to less than 100

+++ indicate a value of at least 100

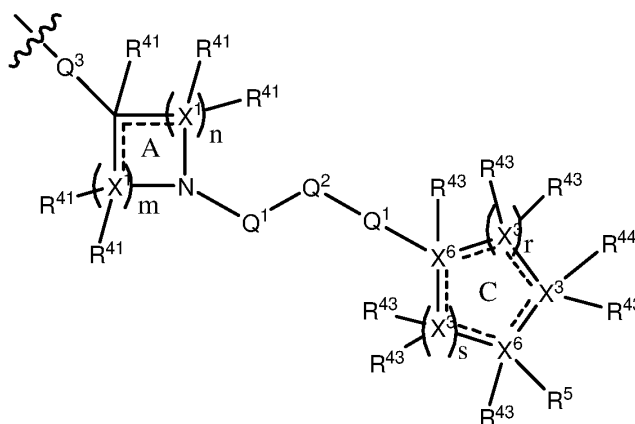
The selectivity values relate to the selectivity preference of PARP1 over PARP2. They are calculated from the ratio of K_d values for PARP1 and PARP2 inhibition as K_d (PARP2) / K_d (PARP1).

CLAIMS:

1. A PARP1 inhibitor compound for use in medicine, which compound comprises the following structure:



wherein R¹ is selected from H and a substituted or unsubstituted organic group; R² may be present or absent and is independently selected from H and a substituted or unsubstituted organic group; R¹ and R² may together form a ring; R³ is independently selected from H and a substituted or unsubstituted organic group; R⁶ may be present or absent and is independently selected from H and a substituted or unsubstituted organic group; Z¹ and Z² are independently selected from C and N; and L comprises a group having the following structure:



wherein, n is a number independently selected from 0, 1, 2, 3, 4, 5 and 6; m is a number independently selected from 0, 1, 2, 3, 4, 5 and 6; and m + n is a number selected from 2, 3, 4, 5, and 6; preferably wherein both n and m are at least 1;

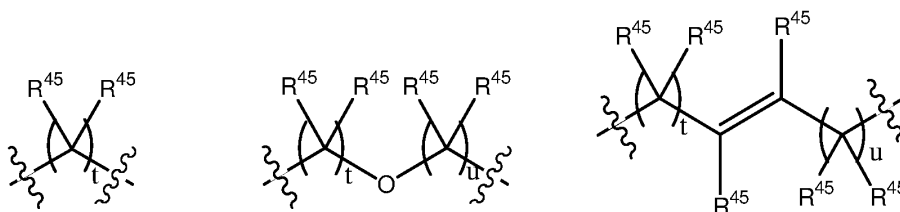
wherein, r is a number independently selected from 0, 1, 2, 3, 4, and 5; s is a number independently selected from 0, 1, 2, 3, 4, and 5; and $r + s$ is a number selected from 1, 2, 3, 4, and 5; preferably wherein both r and s are at least 1;

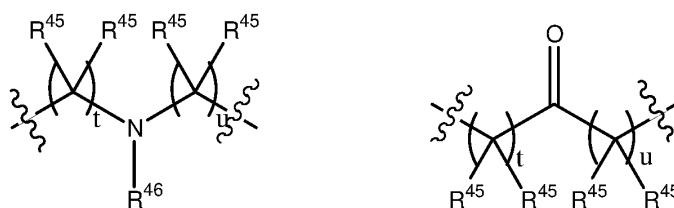
and wherein, each X^1 may be the same or different and is independently selected from C, N, O and S; each X^3 may be the same or different and is independently selected from C, N, O and S; each X^6 may be the same or different and is independently selected from C and N; each R^{41} may be the same or different, and may be present or absent, and is selected from H and a substituted or unsubstituted organic group; each R^{43} may be the same or different, and may be present or absent, and is selected from H and a substituted or unsubstituted organic group; and R^{44} may be present or absent, and is selected from H and a substituted or unsubstituted organic group;

and wherein, the dotted lines indicate that: the ring A may comprise single bonds, or a combination of both single and double bonds, and may be aliphatic or aromatic; and independently the ring C may comprise single bonds, or a combination of both single and double bonds, and may be aliphatic or aromatic;

and wherein, R^5 is selected from H and a substituted or unsubstituted organic group;

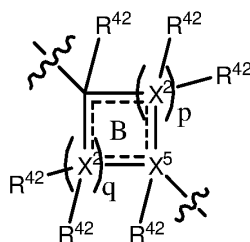
and wherein each Q^1 may be the same or different, and may be present or absent, and comprises a group independently selected from the following structures:





wherein t is independently a number selected from 0, 1, 2, 3, 4 and 5; u is independently a number selected from 0, 1, 2, 3, 4 and 5; and $t + u$ is a number selected from 0, 1, 2, 3, 4, 5 and 6 (preferably a number selected from 0, 1, 2, and 3); each R^{45} may be the same or different and is independently selected from H and a substituted or unsubstituted organic group; and R^{46} is selected from H and a substituted or unsubstituted organic group;

and wherein Q^2 may be present or absent and is a group having the following structure:

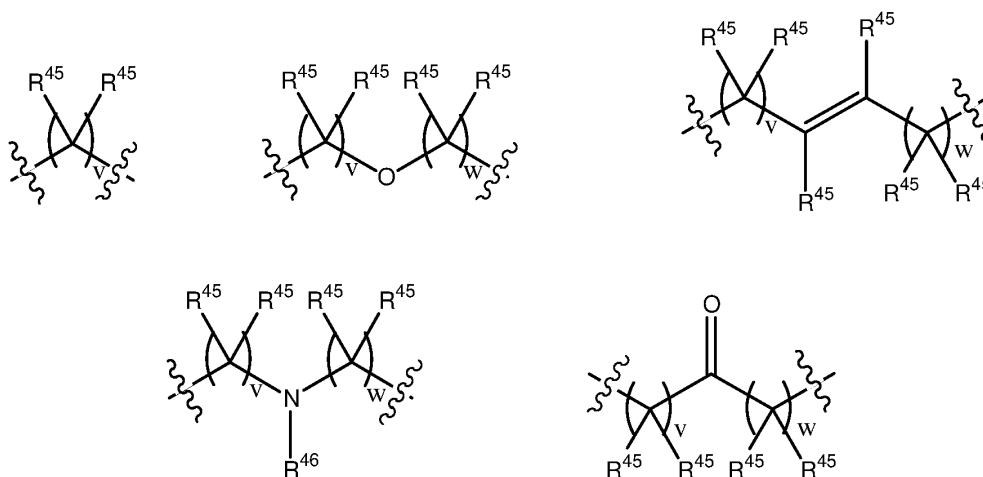


wherein, p is a number independently selected from 0, 1, 2, 3, 4, 5 and 6; q is a number independently selected from 0, 1, 2, 3, 4, 5 and 6; and $p + q$ is a number selected from 2, 3, 4, 5, and 6;

and wherein, each X^2 may be the same or different and is independently selected from C, N, O and S; X^5 is independently selected from C and N; each R^{42} may be the same or different, and may be present or absent, and is selected from H and a substituted or unsubstituted organic group;

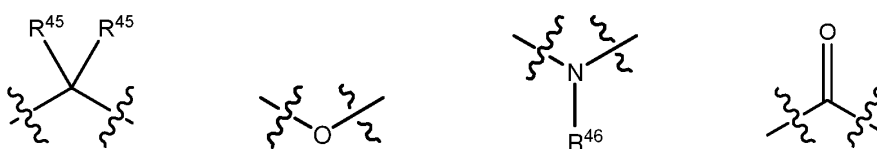
and wherein, the dotted lines indicate that: the ring B may comprise single bonds, or a combination of both single and double bonds, and may be aliphatic or aromatic;

and wherein Q^3 may be present or absent and comprises a group independently selected from the following structures:



wherein v is independently a number selected from 0, 1, 2, 3, 4 and 5; w is independently a number selected from 0, 1, 2, 3, 4 and 5; and $v + w$ is a number selected from 0, 1, 2, 3, 4, 5 and 6 (preferably a number selected from 0, 1, and 2).

2. A compound according to claim 1, wherein Q^3 is absent or is a group independently selected from the following structures:



wherein each R^{45} may be the same or different and is independently selected from H and a substituted or unsubstituted organic group; and R^{46} is selected from H and a substituted or unsubstituted organic group.

3. A compound according to any preceding claim, wherein R^{41} , R^{42} , R^{43} , R^{44} and R^{45} are each independently selected from H and a group selected from the following groups:

- deuterium;
- a halogen (such as -F, -Cl, -Br and -I);
- a nitrile group;
- a substituted or unsubstituted linear or branched C₁-C₆ alkyl group (such as Me, Et, Pr, i-Pr, n-Bu, i-Bu, t-Bu, pentyl and hexyl);
- a substituted or unsubstituted linear or branched C₁-C₆ alkyl-aryl group (such as -CH₂Ph, -CH₂(2,3 or 4)F-Ph, -CH₂(2,3 or 4)Cl-Ph, -CH₂(2,3 or 4)Br-Ph, -CH₂(2,3 or 4)I-Ph, -CH₂CH₂Ph, -CH₂CH₂CH₂Ph, -CH₂CH₂CH₂CH₂Ph, -CH₂CH₂CH₂CH₂CH₂Ph, and -CH₂CH₂CH₂CH₂CH₂CH₂Ph);
- a substituted or unsubstituted linear or branched C₁-C₆ halogenated alkyl group (such as -CH₂F, -CH₂Cl, -CH₂Br, -CH₂I, -CHF₂, -CF₃, -CCl₃, -CBr₃, -CI₃, -CH₂CH₂F, -CH₂CF₃, -CH₂CCl₃, -CH₂CBr₃, and -CH₂CI₃);
- -NH₂ or a substituted or unsubstituted linear or branched primary secondary or tertiary C₁-C₆ amine group (such as -NMeH, -NMe₂, -NEtH, -NEtMe, -NEt₂, -NPrH, -NPrMe, -NPrEt, -NPr₂, -NBuH, -NBuMe, -NBuEt, -CH₂-NH₂, -CH₂-NMeH, -CH₂-NMe₂, -CH₂-NEtH, -CH₂-NEtMe, -CH₂-NEt₂, -CH₂-NPrH, -CH₂-NPrMe, and -CH₂-NPrEt);
- a substituted or unsubstituted amino-aryl group (such as -NH-Ph, -NH-(2,3 or 4)F-Ph, -NH-(2,3 or 4)Cl-Ph, -NH-(2,3 or 4)Br-Ph, -NH-(2,3 or 4)I-Ph, -NH-(2,3 or 4)Me-Ph, -NH-(2,3 or 4)Et-Ph, -NH-(2,3 or 4)Pr-Ph, -NH-(2,3 or 4)Bu-Ph, -NH-(2,3 or 4)OMe-Ph, -NH-(2,3 or 4)OEt-Ph, -NH-(2,3 or 4)OPr-Ph, -NH-(2,3 or 4)OBu-Ph, -NH-2,(3,4,5 or 6)F₂-Ph, -NH-2,(3,4,5 or 6)Cl₂-Ph, -NH-2,(3,4,5 or 6)Br₂-Ph, -NH-2,(3,4,5 or 6)I₂-Ph, -NH-2,(3,4,5 or 6)Me₂-Ph, -NH-2,(3,4,5 or 6)Et₂-Ph, -NH-2,(3,4,5 or 6)Pr₂-Ph, -NH-2,(3,4,5 or 6)Bu₂-Ph,
- a substituted or unsubstituted cyclic amine or amido group (such as pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, 2-keto-pyrrolidinyl, 3-keto-pyrrolidinyl, 2-keto-piperidinyl, 3-keto-piperidinyl, and 4-keto-piperidinyl);
- a substituted or unsubstituted cyclic C₃-C₈ alkyl group (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl);
- an -OH group or a substituted or unsubstituted linear or branched C₁-C₆ alcohol group (such as -CH₂OH, -CH₂CH₂OH, -CH(CH₃)CH₂OH, -C(CH₃)₂OH, -CH₂CH₂CH₂OH, -CH₂CH₂CH₂CH₂OH, -CH(CH₃)CH₂CH₂OH, -CH(CH₃)CH(CH₃)OH, -CH(CH₂CH₃)CH₂OH, -C(CH₃)₂CH₂OH, -CH₂CH₂CH₂CH₂CH₂OH, and -CH₂CH₂CH₂CH₂CH₂CH₂OH);
- a substituted or unsubstituted linear or branched C₁-C₆ carboxylic acid group (such as -COOH,

-CH₂COOH, -CH₂CH₂COOH, -CH₂CH₂CH₂COOH, -CH₂CH₂CH₂CH₂COOH, and -CH₂CH₂CH₂CH₂CH₂COOH);

- a substituted or unsubstituted linear or branched carbonyl group (such as -(CO)Me, -(CO)Et, -(CO)Pr, -(CO)iPr, -(CO)nBu, -(CO)iBu, -(CO)tBu, -(CO)Ph, -(CO)CH₂Ph, -(CO)CH₂OH, -(CO)CH₂OCH₃, -(CO)CH₂NH₂, -(CO)CH₂NHMe, -(CO)CH₂NMe₂, -(CO)-cyclopropyl, -(CO)-1,3-epoxypropan-2-yl, -(CO)NH₂, -(CO)NHMe, -(CO)NMe₂, -(CO)NH₂Et, -(CO)NEt₂, -(CO)-pyrrolidine-N-yl, -(CO)-morpholine-N-yl, -(CO)-piperazine-N-yl, -(CO)-N-methyl-piperazine-N-yl, -(CO)NHCH₂CH₂OH, -(CO)NHCH₂CH₂OMe, -(CO)NHCH₂CH₂NH₂, -(CO)NHCH₂CH₂NHMe, and -(CO)NHCH₂CH₂NMe₂;

- a substituted or unsubstituted linear or branched C₁-C₆ carboxylic acid ester group (such as -COOMe, -COOEt, -COOPr, -COO-i-Pr, -COO-n-Bu, -COO-i-Bu, -COO-t-Bu, -CH₂COOMe, -CH₂CH₂COOMe, -CH₂CH₂CH₂COOMe, and -CH₂CH₂CH₂CH₂COOMe);

- a substituted or unsubstituted linear or branched C₁-C₆ amide group (such as -CO-NH₂, -CO-NMeH, -CO-NMe₂, -CO-NEtH, -CO-NEtMe, -CO-NEt₂, -CO-NPrH, -CO-NPrMe, and -CO-NPrEt);

- a substituted or unsubstituted linear or branched C₁-C₇ amino carbonyl group (such as -NH-CO-Me, -NH-CO-Et, -NH-CO-Pr, -NH-CO-Bu, -NH-CO-pentyl, -NH-CO-hexyl, -NH-CO-Ph, -NMe-CO-Me, -NMe-CO-Et, -NMe-CO-Pr, -NMe-CO-Bu, -NMe-CO-pentyl, -NMe-CO-hexyl, -NMe-CO-Ph;

- a substituted or unsubstituted linear or branched C₁-C₇ alkoxy or aryloxy group (such as -OMe, -OEt, -OPr, -O-i-Pr, -O-n-Bu, -O-i-Bu, -O-t-Bu, -O-pentyl, -O-hexyl, -OCH₂F, -OCHF₂, -OCF₃, -OCH₂Cl, -OCHCl₂, -OCCl₃, -O-Ph, -O-CH₂-Ph, -O-CH₂-(2,3 or 4)-F-Ph, -O-CH₂-(2,3 or 4)-Cl-Ph, -CH₂OMe, -CH₂OEt, -CH₂OPr, -CH₂OBu, -CH₂CH₂OMe, -CH₂CH₂CH₂OMe, -CH₂CH₂CH₂CH₂OMe, and -CH₂CH₂CH₂CH₂CH₂OMe);

- a substituted or unsubstituted linear or branched aminoalkoxy group (such as -OCH₂NH₂, -OCH₂NHMe, -OCH₂NMe₂, -OCH₂NHEt, -OCH₂NEt₂, -OCH₂CH₂NH₂, -OCH₂CH₂NHMe, -OCH₂CH₂NMe₂, -OCH₂CH₂NHEt, and -OCH₂CH₂NEt₂;

- a substituted or unsubstituted sulphonyl group (such as -SO₂Me, -SO₂Et, -SO₂Pr, -SO₂iPr, -SO₂Ph, -SO₂-(2,3 or 4)-F-Ph, -SO₂-cyclopropyl, -SO₂CH₂CH₂OCH₃, -SO₂NH₂, -SO₂NHMe, -SO₂NMe₂, -SO₂NHEt, -SO₂NEt₂, -SO₂-pyrrolidine-N-yl, -SO₂-morpholine-N-yl, -SO₂NHCH₂OMe, and -SO₂NHCH₂CH₂OMe);

- a substituted or unsubstituted aminosulphonyl group (such as -NHSO₂Me, - NHSO₂Et, - NHSO₂Pr, - NHSO₂iPr, - NHSO₂Ph, - NHSO₂-(2,3 or 4)-F-Ph, - NHSO₂-cyclopropyl, - NHSO₂CH₂CH₂OCH₃);

- a substituted or unsubstituted aromatic group (such as Ph-, 2-F-Ph-, 3-F-Ph-, 4-F-Ph-, 2-Cl-Ph-, 3-Cl-Ph-, 4-Cl-Ph-, 2-Br-Ph-, 3-Br-Ph-, 4-Br-Ph-, 2-I-Ph-, 3-I-Ph-, 4-I-Ph-, 2,(3,4,5 or 6)-F₂-Ph-, 2,(3,4,5 or 6)-Cl₂-Ph-, 2,(3,4,5 or 6)-Br₂-Ph-, 2,(3,4,5 or 6)-I₂-Ph-, 2,(3,4,5 or 6)-Me₂-Ph-, 2,(3,4,5 or 6)-Et₂-Ph-, 2,(3,4,5 or 6)-Pr₂-Ph-, 2,(3,4,5 or 6)-Bu₂-Ph-, 2,(3,4,5 or 6)-(CN)₂-Ph-, 2,(3,4,5 or 6)-(NO₂)₂-Ph-, 2,(3,4,5 or 6)-(NH₂)₂-Ph-, 2,(3,4,5 or 6)-(MeO)₂-Ph-, 2,(3,4,5 or 6)-(CF₃)₂-Ph-, 3,(4 or 5)-F₂-Ph-, 3,(4 or 5)-Cl₂-Ph-, 3,(4 or 5)-Br₂-Ph-, 3,(4 or 5)-I₂-Ph-, 3,(4 or 5)-Me₂-Ph-, 3,(4 or 5)-Et₂-Ph-, 3,(4 or 5)-Pr₂-Ph-, 3,(4 or 5)-Bu₂-Ph-, 3,(4 or 5)-(CN)₂-Ph-, 3,(4 or 5)-(NO₂)₂-Ph-, 3,(4 or 5)-(NH₂)₂-Ph-, 3,(4 or 5)-(MeO)₂-Ph-, 3,(4 or 5)-(CF₃)₂-Ph-, 2-Me-Ph-, 3-Me-Ph-, 4-Me-Ph-, 2-Et-Ph-, 3-Et-Ph-, 4-Et-Ph-, 2-Pr-Ph-, 3-Pr-Ph-, 4-Pr-Ph-, 2-Bu-Ph-, 3-Bu-Ph-, 4-Bu-Ph-, 2-(CN)-Ph-, 3-(CN)-Ph-, 4-(CN)-Ph-, 2-(NO₂)-Ph-, 3-(NO₂)-Ph-, 4-(NO₂)-Ph-, 2-(NH₂)-Ph-, 3-(NH₂)-Ph-, 4-(NH₂)-Ph-, 2-MeO-Ph-, 3-MeO-Ph-, 4-MeO-Ph-, 2-(NH₂-CO)-Ph-, 3-(NH₂-CO)-Ph-, 4-(NH₂-CO)-Ph-, 2-CF₃-Ph-, 3-CF₃-Ph-, 4-CF₃-Ph-, 2-CF₃O-Ph-, 3-CF₃O-Ph-, and 4-CF₃O-Ph-);

- a saturated or unsaturated, substituted or unsubstituted, heterocyclic group including an aromatic heterocyclic group and/or a non-aromatic heterocyclic group (such as pyrrole-1-yl, pyrrole-2-yl, pyrrole-3-yl, pyrazole-1-yl, pyrazole-3-yl, pyrazole-4-yl, pyrazole-5-yl, imidazole-1-yl, imidazole-2-yl, imidazole-4-yl, imidazole-5-yl, 1,2,3-triazole-1-yl, 1,2,3-triazole-4-yl, 1,2,3-triazole-5-yl, 1,2,4-triazole-1-yl, 1,2,4-triazole-3-yl, 1,2,4-triazole-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazine-3-yl, pyridazine-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-6-yl, pyrazine-2-yl, pyrrolidine-1-yl, pyrrolidine-2-yl, pyrrolidine-3-yl, piperidine-1-yl, piperidine-2-yl, piperidine-3-yl, piperidine-4-yl, 2-azapiperidine-1-yl, 2-azapiperidine-3-yl, 2-azapiperidine-4-yl, 3-azapiperidine-1-yl, 3-azapiperidine-2-yl, 3-azapiperidine-4-yl, 3-azapiperidine-5-yl, piperazine-1-yl, piperazine-2-yl, furan-2-yl, furan-3-yl, pyran-2-yl, pyran-3-yl, pyran-4-yl, 2-azapyran-2-yl, 2-azapyran-3-yl, 2-azapyran-4-yl, 2-azapyran-5-yl, 2-azapyran-6-yl, 3-azapyran-2-yl, 3-azapyran-4-yl, 3-azapyran-5-yl, 3-azapyran-6-yl, 4-azapyran-2-yl, 4-azapyran-3-yl, 4-azapyran-4-yl, 4-azapyran-5-yl, 4-azapyran-6-yl, oxetan-2-yl, oxetan-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-2-yl, 2-aza-tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-4-yl, 2-aza-tetrahydrofuran-5-yl, 3-aza-tetrahydrofuran-2-yl, 3-aza-tetrahydrofuran-3-yl, 3-aza-tetrahydrofuran-4-yl, 3-aza-tetrahydrofuran-5-yl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, 2-aza-tetrahydropyran-2-yl, 2-aza-

tetrahydropyran-3-yl, 2-aza-tetrahydropyran-4-yl, 2-aza-tetrahydropyran-5-yl, 2-aza-tetrahydropyran-6-yl, 3-aza-tetrahydropyran-2-yl, 3-aza-tetrahydropyran-3-yl, 3-aza-tetrahydropyran-4-yl, 3-aza-tetrahydropyran-5-yl, 3-aza-tetrahydropyran-6-yl, morpholine-2-yl, morpholine-3-yl, morpholine-4-yl, thiophen-2-yl, thiophen-3-yl, isothiazole-3-yl, isothiazole-4-yl, isothiazole-5-yl, thiazole-2-yl, thiazole-4-yl, thiazole-5-yl, thiopyran-2-yl, thiopyran-3-yl, thiopyran-4-yl, 2-azathiopyran-2-yl, 2-azathiopyran-3-yl, 2-azathiopyran-4-yl, 2-azathiopyran-5-yl, 2-azathiopyran-6-yl, 3-azathiopyran-2-yl, 3-azathiopyran-4-yl, 3-azathiopyran-5-yl, 3-azathiopyran-6-yl, 4-azathiopyran-2-yl, 4-azathiopyran-3-yl, 4-azathiopyran-4-yl, 4-azathiopyran-5-yl, 4-azathiopyran-6-yl, thiolane-2-yl, thiolane-3-yl, thiane-2-yl, thiane-3-yl, thiane-4-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, furazan-3-yl, (1,3,4-oxadiazol)-2-yl, (1,3,4-oxadiazol)-5-yl, (1,2,4-oxadiazol)-3-yl, (1,2,4-oxadiazol)-5-yl; and tetrazole-1-yl, tetrazole-2-yl, tetrazole-5-yl);

- where there are two R groups attached to the same atom, they may together form a group which is double bonded to that atom, (such as a carbonyl group (=O) or an alkene group (=C(R')₂) wherein each R' group is the same or different and is H or an organic group, preferably H or a straight or branched C₁-C₆ alkyl group);

- wherein, a pair of R⁴¹ groups attached to different atoms may together form a ring with ring A atoms, and/or a pair of R⁴² groups attached to different atoms may together form a ring with ring B atoms, optionally wherein each of the pair of R⁴¹ groups and/or pair of R⁴² groups independently comprises (X⁷)_{1 or 2}, wherein each X⁷ may be the same or different and is independently selected from C, N, O and S; and wherein each X⁷ is independently unsubstituted or (i) independently substituted with H or an organic group selected from a C₁-C₆ alkyl group, a C₁-C₆ halogenated alkyl group, a halogen such as F, or hydroxyl, when X⁷ is C; and (ii) independently substituted with H or an organic group selected from a C₁-C₆ alkyl group, a C₁-C₆ halogenated alkyl group, or a C₁-C₆ amide group, when X⁷ is N; and

-wherein groups R⁵ and R⁴⁴ may together form a ring with atoms X⁶ and X³ of ring C to which they are attached, optionally wherein the R⁵ and R⁴⁴ groups together comprise (X⁸)_{3, 4 or 5}, wherein each X⁸ may be the same or different and is independently selected from C, N, O and S; and wherein each X⁸ is independently unsubstituted or (i) independently substituted with H or an organic group selected from a C₁-C₆ alkyl group, a C₁-C₆ halogenated alkyl group, a halogen such as F, or hydroxyl, when X⁸ is C; and (ii) independently substituted with H or

an organic group selected from a C₁-C₆ alkyl group, a C₁-C₆ halogenated alkyl group, or a C₁-C₆ amide group, when X⁸ is N.

4. A compound according to claim 3, wherein R⁴¹, R⁴², R⁴³ and R⁴⁴ are each independently selected from H, deuterium, a halogen (such as -F, -Cl, -Br, and -I, preferably F or Cl), a nitrile group, a substituted or unsubstituted C₁-C₆ alkyl group, a substituted or unsubstituted linear or branched C₁-C₆ halogenated alkyl group (preferably CF₃ or CHF₂), a cyclopropyl group, an -OH group or a substituted or unsubstituted linear or branched C₁-C₆ alcohol group, a substituted or unsubstituted linear or branched C₁-C₇ amino carbonyl group (such as -NH-CO-Me), an -NH₂ group or a substituted or unsubstituted C₁-C₆ amino group and a substituted or unsubstituted C₁-C₆ alkoxy group; wherein, when a pair of R⁴¹ groups attached to different atoms together forms a ring with ring A atoms, and/or a pair of R⁴² groups attached to different atoms together forms a ring with ring B atoms, each of the pair of R⁴¹ groups and/or pair of R⁴² groups independently comprises -CH₂- or -CH₂CH₂-; and wherein when groups R⁵ and R⁴⁴ together form a ring with atoms of ring C, R⁵ and R⁴⁴ together comprise -CH=CH-CH=CH- or -NH-CO-NH-.

5. A compound according to claim 3 or claim 4, wherein R⁴⁵ is selected from H, a halogen (such as -F, -Cl, -Br, and -I, preferably -F), a substituted or unsubstituted C₁-C₆ alkyl group, a substituted or unsubstituted linear or branched C₁-C₆ halogenated alkyl group (preferably CF₃), an -NH₂ group or a substituted or unsubstituted C₁-C₆ amino group, an -OH group or a substituted or unsubstituted linear or branched C₁-C₆ alcohol group and a substituted or unsubstituted C₁-C₆ alkoxy group.

6. A compound according to any preceding claim, wherein R⁴⁶ is selected from H and a group selected from the following groups:

- a substituted or unsubstituted linear or branched C₁-C₆ alkyl group (such as Me, Et, Pr, i-Pr, n-Bu, i-Bu, t-Bu, pentyl and hexyl);
- a substituted or unsubstituted linear or branched C₁-C₆ alkyl-aryl group (such as -CH₂Ph, -CH₂(2,3 or 4)F-Ph, -CH₂(2,3 or 4)Cl-Ph, -CH₂(2,3 or 4)Br-Ph, -CH₂(2,3 or 4)I-Ph, -

CH₂CH₂Ph, -CH₂CH₂CH₂Ph, -CH₂CH₂CH₂CH₂Ph, -CH₂CH₂CH₂CH₂CH₂Ph, and -CH₂CH₂CH₂CH₂CH₂CH₂Ph);

- a substituted or unsubstituted linear or branched C₁-C₆ halogenated alkyl group (such as -CH₂F, -CF₃, -CH₂CH₂F and -CH₂CF₃);

- a substituted or unsubstituted cyclic amine or amido group (such as pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, 2-keto-pyrrolidinyl, 3-keto-pyrrolidinyl, 2-keto-piperidinyl, 3-keto-piperidinyl, and 4-keto-piperidinyl);

- a substituted or unsubstituted cyclic C₃-C₈ alkyl group (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl);

- a substituted or unsubstituted linear or branched C₂-C₆ alcohol group (such as -CH₂CH₂OH, -CH(CH₃)CH₂OH, -C(CH₃)₂OH, -CH₂CH₂CH₂OH, -CH₂CH₂CH₂CH₂OH, -CH(CH₃)CH₂CH₂OH, -CH(CH₃)CH(CH₃)OH, -CH(CH₂CH₃)CH₂OH, -C(CH₃)₂CH₂OH, -CH₂CH₂CH₂CH₂CH₂OH, and -CH₂CH₂CH₂CH₂CH₂CH₂OH);

- a substituted or unsubstituted linear or branched C₂-C₆ carboxylic acid group (such as -CH₂COOH, -CH₂CH₂COOH, -CH₂CH₂CH₂COOH, -CH₂CH₂CH₂CH₂COOH, and -CH₂CH₂CH₂CH₂CH₂COOH);

- a substituted or unsubstituted linear or branched carbonyl group (such as -(CO)Me, -(CO)Et, -(CO)Pr, -(CO)-i-Pr, -(CO)-n-Bu, -(CO)-i-Bu, -(CO)-t-Bu, -(CO)Ph, -(CO)CH₂Ph, -(CO)CH₂OH, -(CO)CH₂OCH₃, -(CO)CH₂NH₂, -(CO)CH₂NHMe, -(CO)CH₂NMe₂, -(CO)-cyclopropyl, -(CO)-1,3-epoxypropan-2-yl, -(CO)NH₂, -(CO)NHMe, -(CO)NMe₂, -(CO)NHEt, -(CO)NEt₂, -(CO)-pyrrolidine-N-yl, -(CO)-morpholine-N-yl, -(CO)-piperazine-N-yl, -(CO)-N-methyl-piperazine-N-yl, -(CO)NHCH₂CH₂OH, -(CO)NHCH₂CH₂OMe, -(CO)NHCH₂CH₂NH₂, -(CO)NHCH₂CH₂NHMe, and -(CO)NHCH₂CH₂NMe₂;

- a substituted or unsubstituted linear or branched C₁-C₆ carboxylic acid ester group (such as -COOMe, -COOEt, -COOPr, -COO-i-Pr, -COO-n-Bu, -COO-i-Bu, -COO-t-Bu, -CH₂COOMe, -CH₂CH₂COOMe, -CH₂CH₂CH₂COOMe, and -CH₂CH₂CH₂CH₂COOMe);

- a substituted or unsubstituted linear or branched C₁-C₆ amide group (such as -CO-NH₂, -CO-NMeH, -CO-NMe₂, -CO-NEtH, -CO-NEtMe, -CO-NEt₂, -CO-NPrH, -CO-NPrMe, and -CO-NPrEt);

- a substituted or unsubstituted sulphonyl group (such as -SO₂Me, -SO₂Et, -SO₂Pr, -SO₂iPr, -SO₂Ph, -SO₂-(2,3 or 4)-F-Ph, -SO₂-cyclopropyl, -SO₂CH₂CH₂OCH₃, -SO₂NH₂, -SO₂NHMe, -SO₂NMe₂,

-SO₂NHEt, -SO₂NEt₂, -SO₂-pyrrolidine-N-yl, -SO₂-morpholine-N-yl, -SO₂NHCH₂OMe, and -SO₂NHCH₂CH₂OMe;

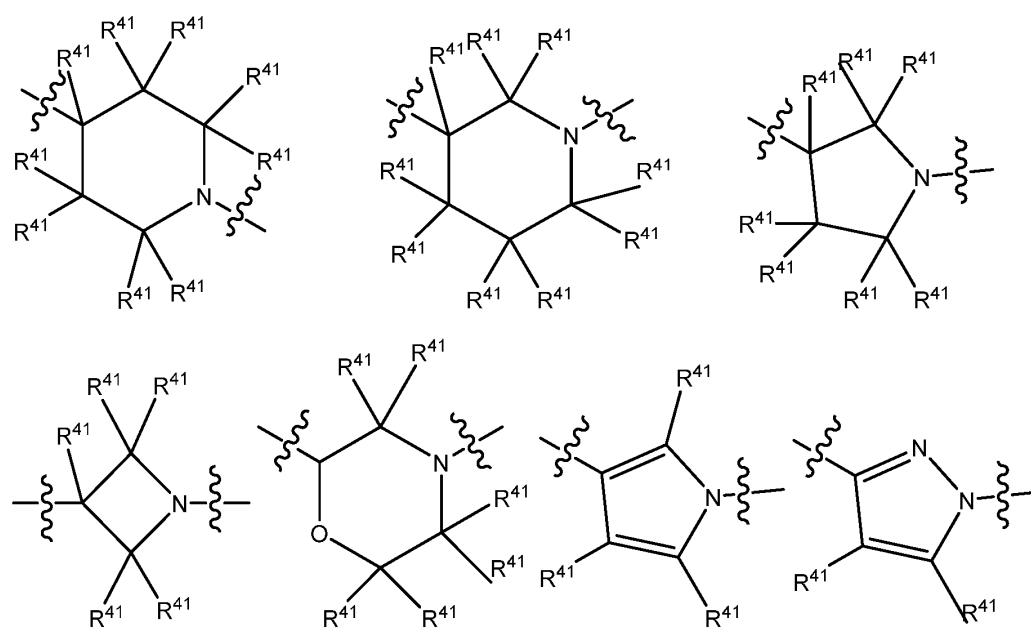
- a substituted or unsubstituted aromatic group (such as Ph-, 2-F-Ph-, 3-F-Ph-, 4-F-Ph-, 2-Cl-Ph-, 3-Cl-Ph-, 4-Cl-Ph-, 2-Br-Ph-, 3-Br-Ph-, 4-Br-Ph-, 2-I-Ph-, 3-I-Ph-, 4-I-Ph-, 2,(3,4,5 or 6)-F₂-Ph-, 2,(3,4,5 or 6)-Cl₂-Ph-, 2,(3,4,5 or 6)-Br₂-Ph-, 2,(3,4,5 or 6)-I₂-Ph-, 2,(3,4,5 or 6)-Me₂-Ph-, 2,(3,4,5 or 6)-Et₂-Ph-, 2,(3,4,5 or 6)-Pr₂-Ph-, 2,(3,4,5 or 6)-Bu₂-Ph-, 2,(3,4,5 or 6)-(CN)₂-Ph-, 2,(3,4,5 or 6)-(NO₂)₂-Ph-, 2,(3,4,5 or 6)-(NH₂)₂-Ph-, 2,(3,4,5 or 6)-(MeO)₂-Ph-, 2,(3,4,5 or 6)-(CF₃)₂-Ph-, 3,(4 or 5)-F₂-Ph-, 3,(4 or 5)-Cl₂-Ph-, 3,(4 or 5)-Br₂-Ph-, 3,(4 or 5)-I₂-Ph-, 3,(4 or 5)-Me₂-Ph-, 3,(4 or 5)-Et₂-Ph-, 3,(4 or 5)-Pr₂-Ph-, 3,(4 or 5)-Bu₂-Ph-, 3,(4 or 5)-(CN)₂-Ph-, 3,(4 or 5)-(NO₂)₂-Ph-, 3,(4 or 5)-(NH₂)₂-Ph-, 3,(4 or 5)-(MeO)₂-Ph-, 3,(4 or 5)-(CF₃)₂-Ph-, 2-Me-Ph-, 3-Me-Ph-, 4-Me-Ph-, 2-Et-Ph-, 3-Et-Ph-, 4-Et-Ph-, 2-Pr-Ph-, 3-Pr-Ph-, 4-Pr-Ph-, 2-Bu-Ph-, 3-Bu-Ph-, 4-Bu-Ph-, 2-(CN)-Ph-, 3-(CN)-Ph-, 4-(CN)-Ph-, 2-(NO₂)-Ph-, 3-(NO₂)-Ph-, 4-(NO₂)-Ph-, 2-(NH₂)-Ph-, 3-(NH₂)-Ph-, 4-(NH₂)-Ph-, 2-MeO-Ph-, 3-MeO-Ph-, 4-MeO-Ph-, 2-(NH₂-CO)-Ph-, 3-(NH₂-CO)-Ph-, 4-(NH₂-CO)-Ph-, 2-CF₃-Ph-, 3-CF₃-Ph-, 4-CF₃-Ph-, 2-CF₃O-Ph-, 3-CF₃O-Ph-, and 4-CF₃O-Ph-); and

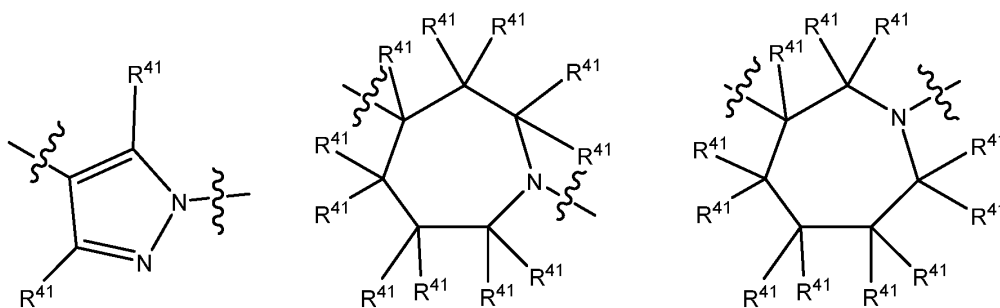
- a substituted or unsubstituted saturated or unsaturated, substituted or unsubstituted, heterocyclic group including an aromatic heterocyclic group and/or a non-aromatic heterocyclic group (such as pyrrole-2-yl, pyrrole-3-yl, pyrazole-3-yl, pyrazole-4-yl, pyrazole-5-yl, imidazole-2-yl, imidazole-4-yl, imidazole-5-yl, 1,2,3-triazole-4-yl, 1,2,3-triazole-5-yl, 1,2,4-triazole-3-yl, 1,2,4-triazole-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazine-3-yl, pyridazine-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrimidin-6-yl, pyrazine-2-yl, pyrrolidine-2-yl, pyrrolidine-3-yl, piperidine-2-yl, piperidine-3-yl, piperidine-4-yl, 2-azapiperidine-3-yl, 2-azapiperidine-4-yl, 3-azapiperidine-2-yl, 3-azapiperidine-4-yl, 3-azapiperidine-5-yl, piperazine-2-yl, furan-2-yl, furan-3-yl, pyran-2-yl, pyran-3-yl, pyran-4-yl, 2-azapyran-3-yl, 2-azapyran-4-yl, 2-azapyran-5-yl, 2-azapyran-6-yl, 3-azapyran-2-yl, 3-azapyran-4-yl, 3-azapyran-5-yl, 3-azapyran-6-yl, 4-azapyran-2-yl, 4-azapyran-3-yl, 4-azapyran-5-yl, 4-azapyran-6-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-3-yl, 2-aza-tetrahydrofuran-4-yl, 2-aza-tetrahydrofuran-5-yl, 3-aza-tetrahydrofuran-2-yl, 3-aza-tetrahydrofuran-4-yl, 3-aza-tetrahydrofuran-5-yl, tetrahydropyran-2-yl, oxetan-3-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, 2-aza-tetrahydropyran-3-yl, 2-aza-tetrahydropyran-4-yl, 2-aza-tetrahydropyran-5-yl, 2-aza-tetrahydropyran-6-yl, 3-aza-tetrahydropyran-2-yl, 3-aza-tetrahydropyran-4-yl, 3-aza-tetrahydropyran-5-yl, 3-aza-tetrahydropyran-6-yl, morpholine-2-yl, morpholine-3-yl, thiophen-2-yl, thiophen-3-yl, isothiazole-3-yl, isothiazole-4-yl, isothiazole-5-yl, thiazole-2-yl, thiazole-4-yl, thiazole-5-yl,

thiopyran-2-yl, thiopyran-3-yl, thiopyran-4-yl, 2-azathiopyran-3-yl, 2-azathiopyran-4-yl, 2-azathiopyran-5-yl, 2-azathiopyran-6-yl, 3-azathiopyran-2-yl, 3-azathiopyran-4-yl, 3-azathiopyran-5-yl, 3-azathiopyran-6-yl, 4-azathiopyran-2-yl, 4-azathiopyran-3-yl, 4-azathiopyran-5-yl, 4-azathiopyran-6-yl, thiolane-2-yl, thiolane-3-yl, thiane-2-yl, thiane-3-yl, thiane-4-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, furazan-3-yl, (1,3,4-oxadiazol)-2-yl, (1,3,4-oxadiazol)-5-yl, (1,2,4-oxadiazol)-3-yl, (1,2,4-oxadiazol)-5-yl; and tetrazole-5-yl).

7. A compound according to claim 6, wherein R^{46} is selected from H, a substituted or unsubstituted C_1 - C_6 alkyl group or a substituted or unsubstituted linear or branched C_1 - C_6 halogenated alkyl group.

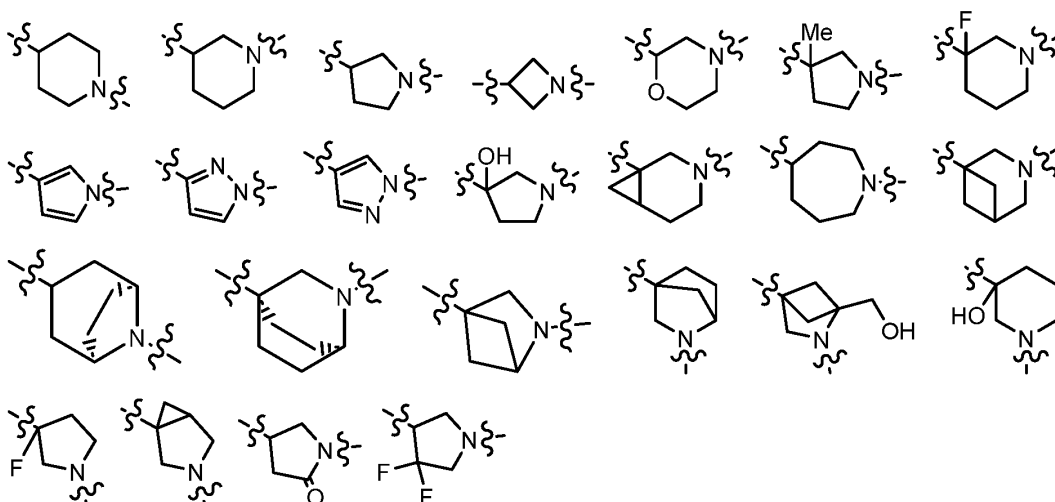
8. A compound according to any preceding claim, wherein ring A of the group L comprises any of the following structures:



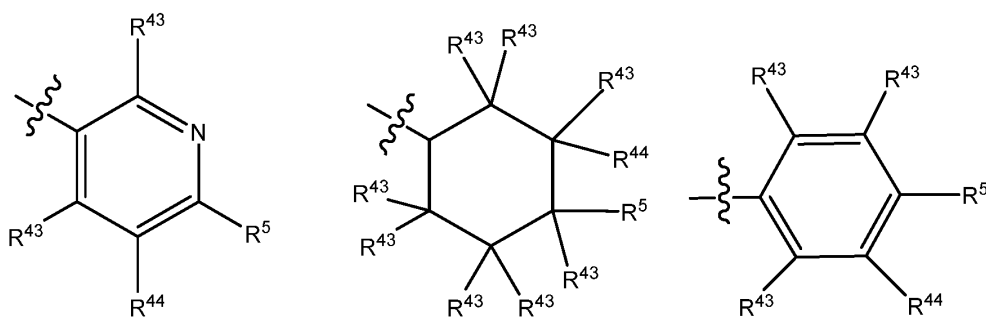


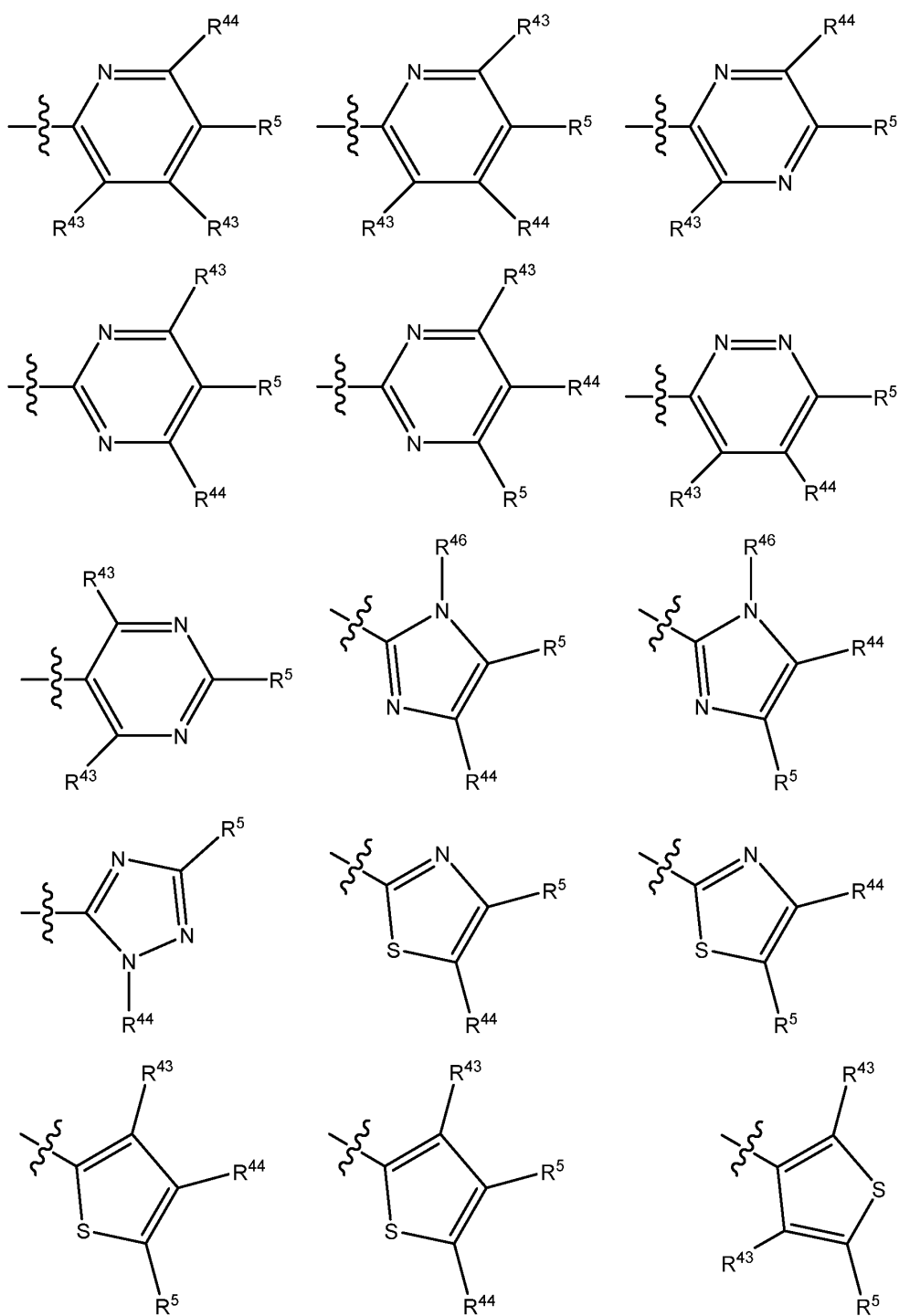
wherein R^{41} is as defined in any preceding claim.

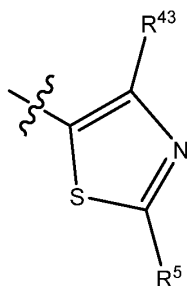
9. A compound according to claim 8, wherein ring A of the group L comprises any of the following structures:



10. A compound according to any preceding claim, wherein ring C of the group L comprises any of the following structures:

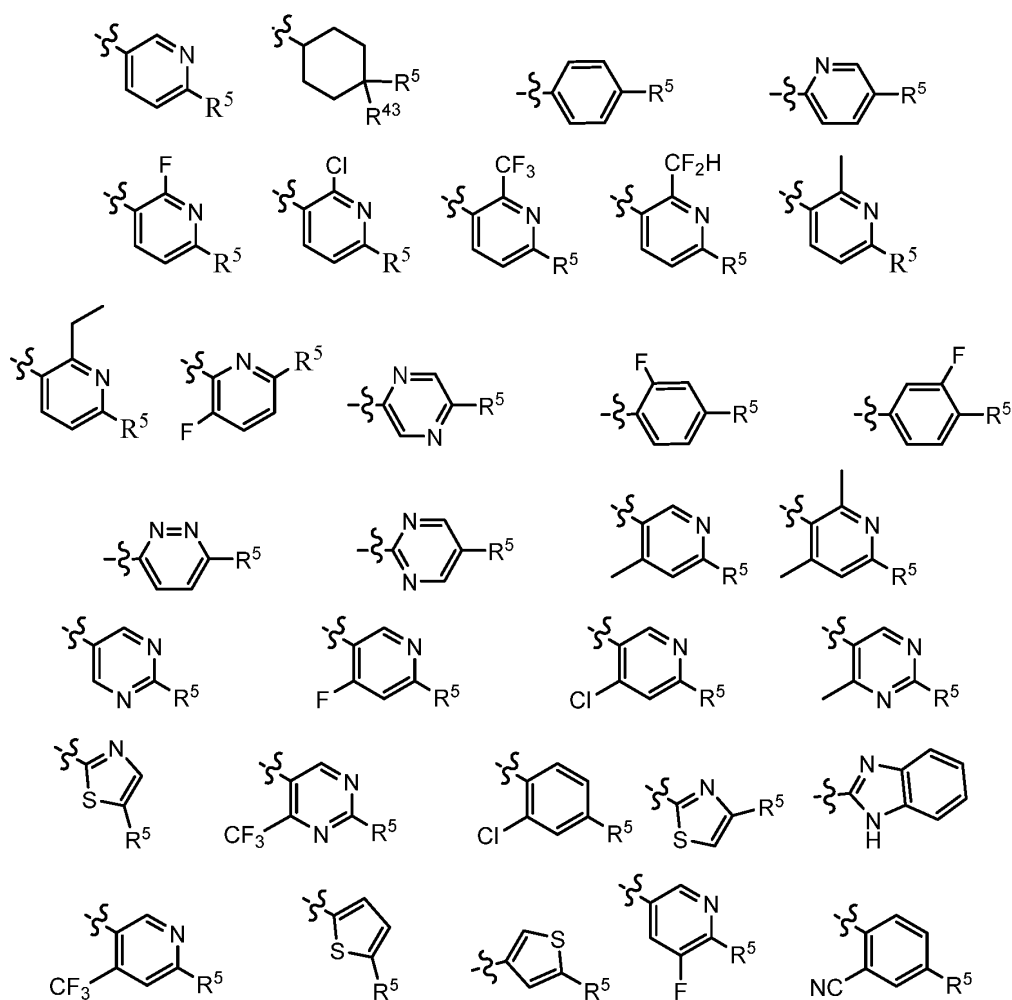


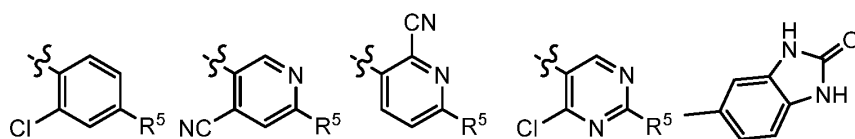




wherein R⁵, R⁴³, R⁴⁴ and R⁴⁶ are as defined in any preceding claim.

11. A compound according to claim 10, wherein ring C of the group L comprises any of the following structures:

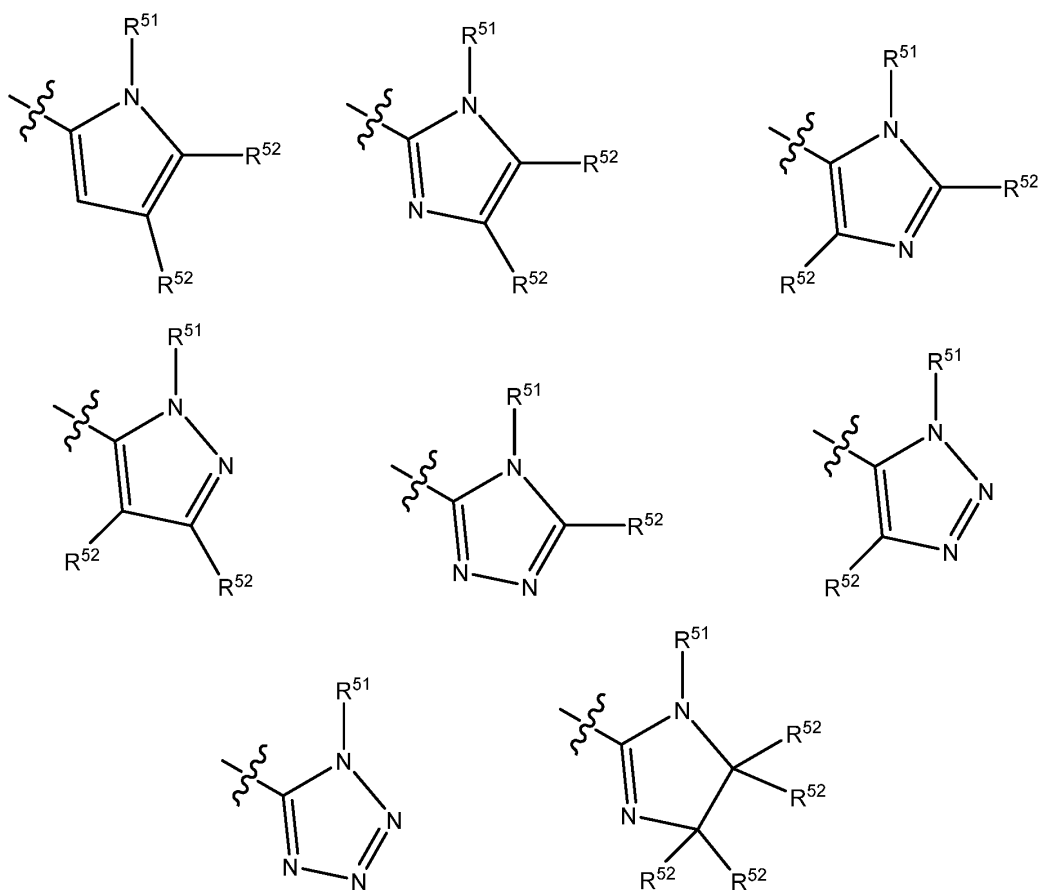




wherein R^5 and R^{43} are as defined in claim 10.

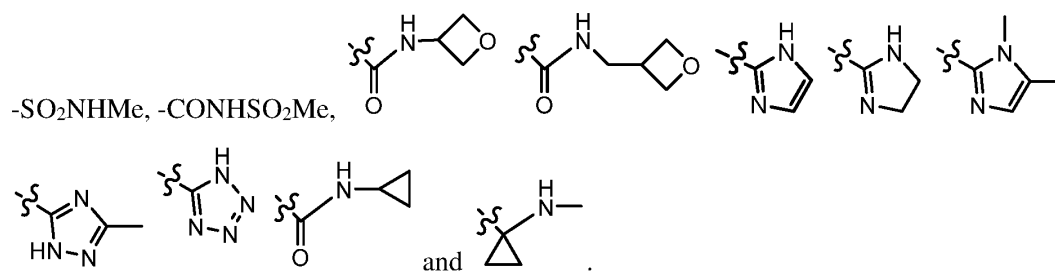
12. A compound according to any preceding claim, wherein R^5 is a substituted or unsubstituted organic group.

13. A compound according to any of claims 1 to 11, wherein the group R^5 is selected from H, -F, -Cl, -Br, -I, -CN, -CONR⁵¹R⁵¹, -NR⁵¹COR⁵², -SO₂NR⁵¹R⁵¹, -NR⁵¹SO₂R⁵³, -O-CR⁵²R⁵²R⁵², -CR⁵²R⁵²NR⁵¹R⁵¹ and any of the following structures:

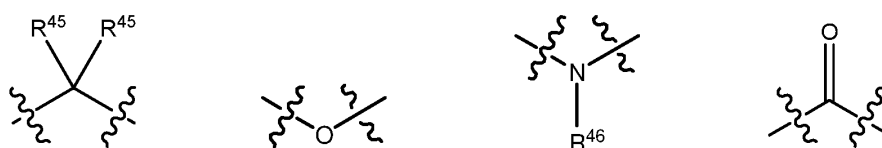


wherein, each of R⁵¹, R⁵² and R⁵³ may be the same or different and are independently selected from H and a substituted or unsubstituted organic group.

14. A compound according to claim 13, wherein the group R⁵ is selected from -F, -Cl, -CN, -CONH₂, -CONHMe, -CONHEt, -CONMe₂, -CONHCOMe, -CONHCH₂-CH₂OMe, -CONH-CH₂-CH₂F, -CONH-CH₂-CF₃, -CONH-CH₂-CHF₂, -OCHF₂, -NHCOMe, -NHSO₂Me,



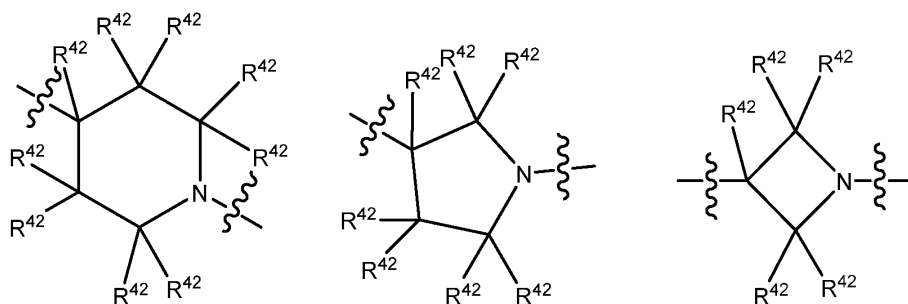
15. A compound according to any preceding claim, wherein Q² is present and each Q¹ is independently absent or is a group independently selected from the following structures:



wherein each R⁴⁵ may be the same or different and is independently selected from H and a substituted or unsubstituted organic group; and R⁴⁶ is selected from H and a substituted or unsubstituted organic group.

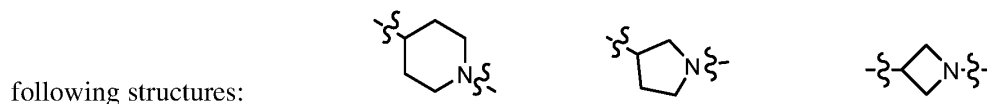
16. A compound according to claim 15, wherein group Q² of the group L is present in which X⁵ is N.

17. A compound according to claim 16, wherein Q² of the group L comprises any of the following structures:

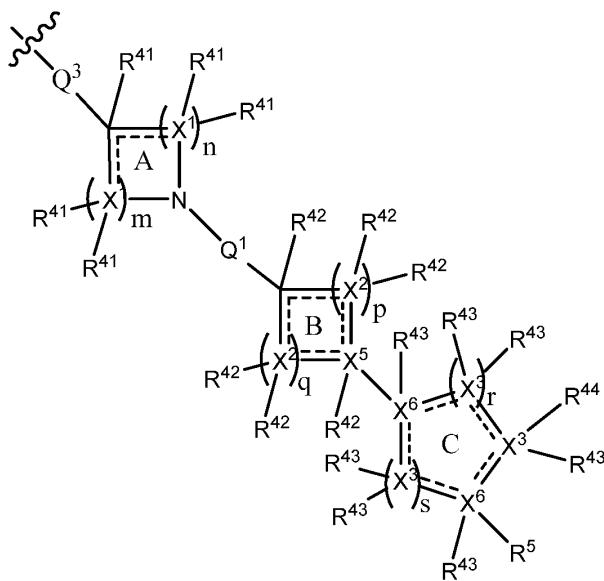


wherein R⁴² is as defined in any preceding claim.

18. A compound according to claim 17, wherein Q² of the group L comprises any of the

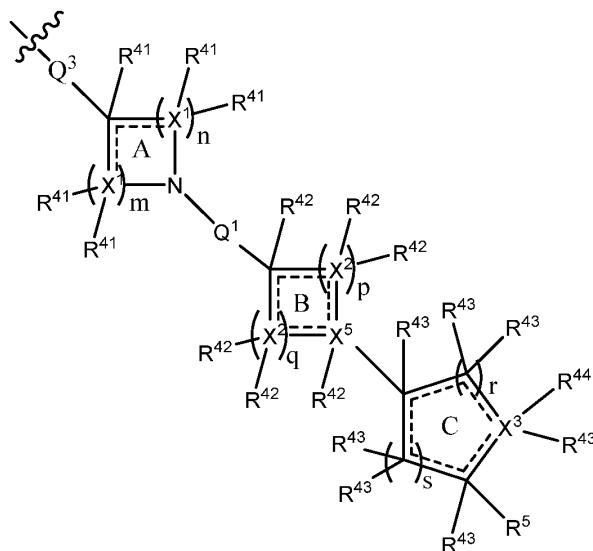


19. A compound according to any of claims 15 to 18, wherein the group L comprises a group having the following structure:



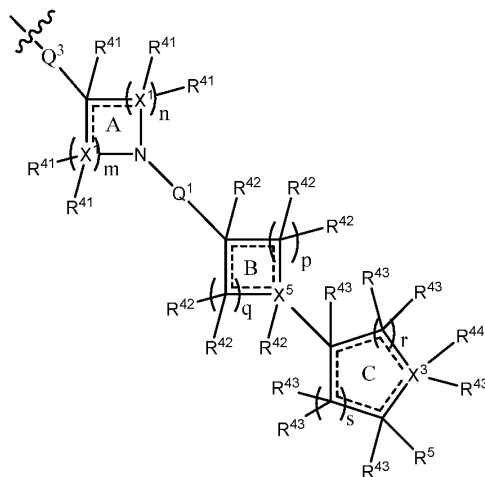
wherein Q¹ is absent or is a group as defined in claim 3, Q³ is absent or is a group as defined in claim 2, and n, m, p, q, r, s, X¹, X², X³, X⁵, X⁶, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁵, and rings A, B, and C are as defined in any preceding claim.

20. A compound according to claim 19, wherein the group L comprises a group having the following structure:



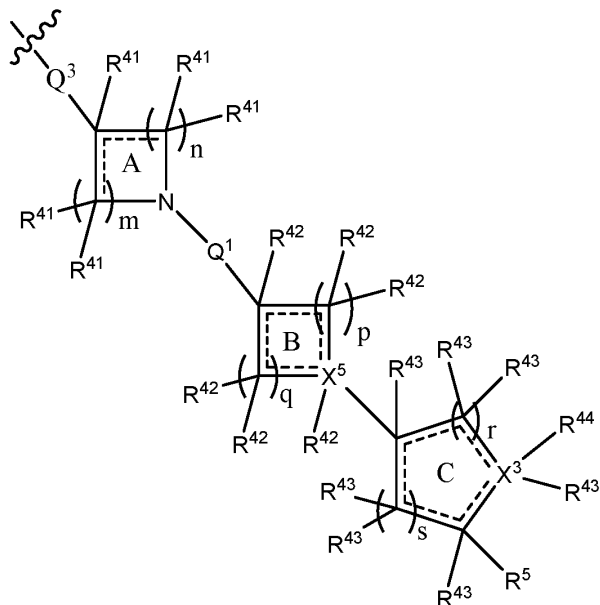
wherein n, m, p, q, r, s, X¹, X², X³, X⁵, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁵, Q¹, Q³ and rings A, B, and C are as defined in claim 19.

21. A compound according to claim 20, wherein the group L comprises a group having the following structure:



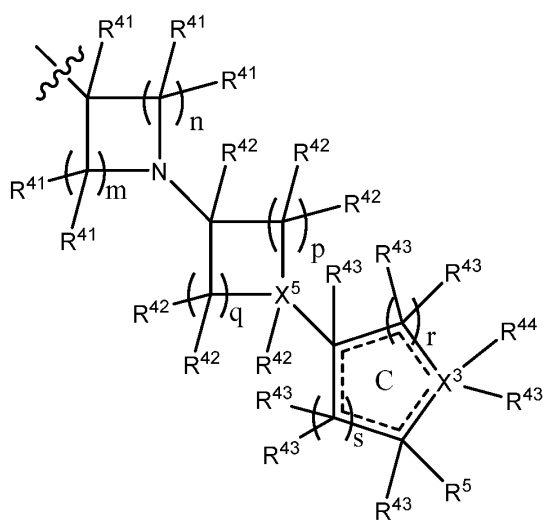
wherein n, m, p, q, r, s, X¹, X³, X⁵, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁵, Q¹, Q³ and rings A, B, and C are as defined in claim 20.

22. A compound according to claim 21, wherein the group L comprises a group having the following structure:



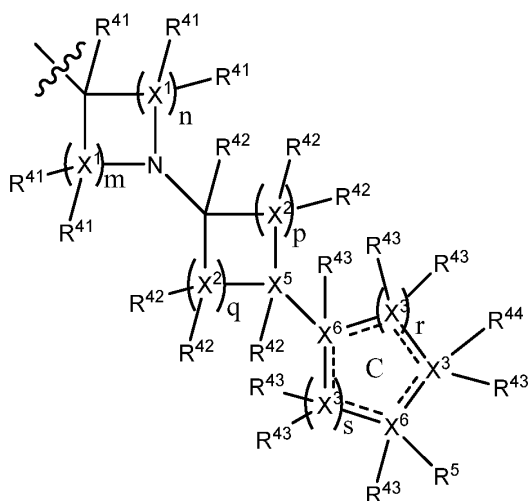
wherein n , m , p , q , r , s , X^3 , X^5 , R^{41} , R^{42} , R^{43} , R^{44} , R^5 , and rings A, B, and C are as defined in claim 21.

23. A compound according to claim 22, wherein the group L comprises a group having the following structure:



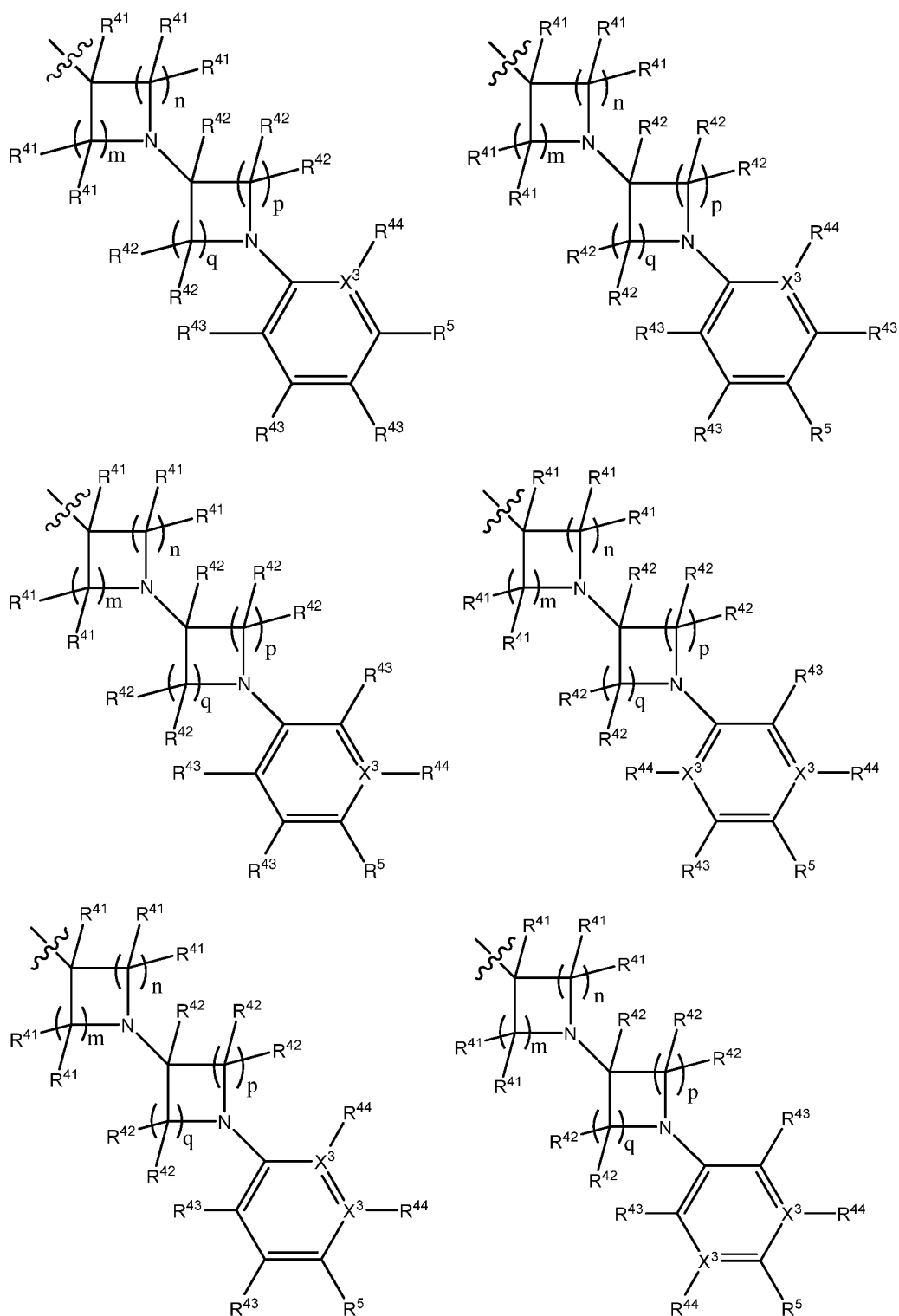
wherein n , m , p , q , r , s , X^3 , X^5 , R^{41} , R^{42} , R^{43} , R^{44} , R^5 , and ring C, are as defined in claim 22.

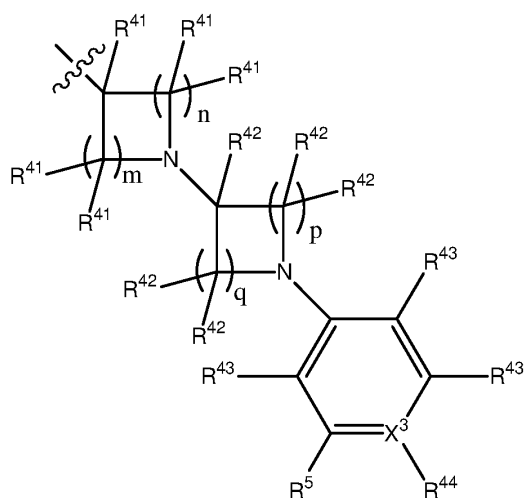
24. A compound according to claim 19, wherein the group L comprises a group having the following structure:



wherein n , m , p , q , r , s , X^1 , X^2 , X^3 , X^5 , X^6 , R^{41} , R^{42} , R^{43} , R^{44} , R^5 , and ring C, are as defined in claim 19.

25. A compound according to claim 24, wherein the group L comprises a group selected from the following structures:

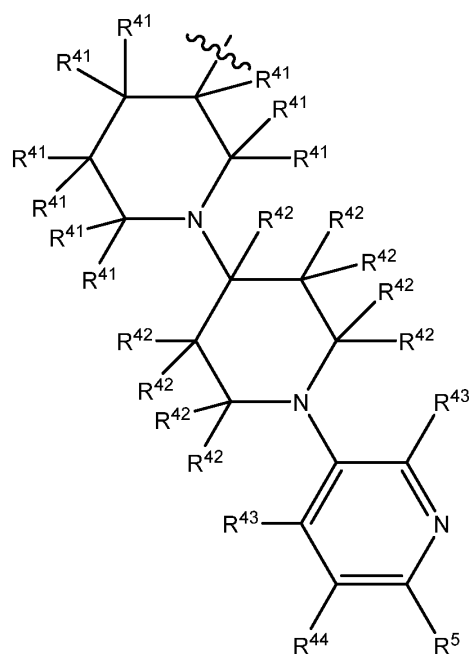
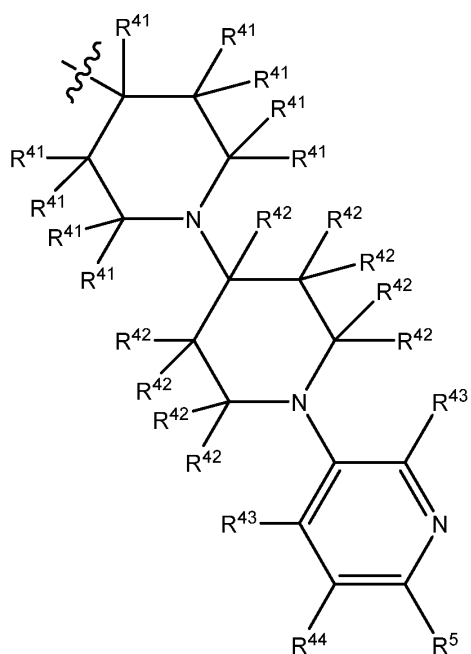


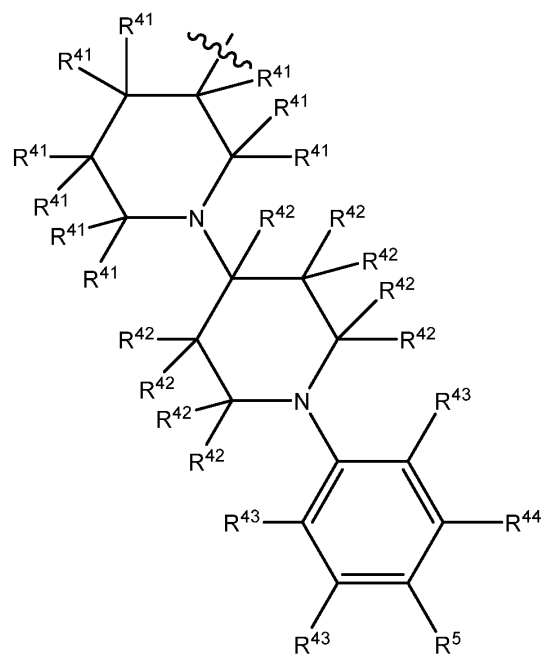
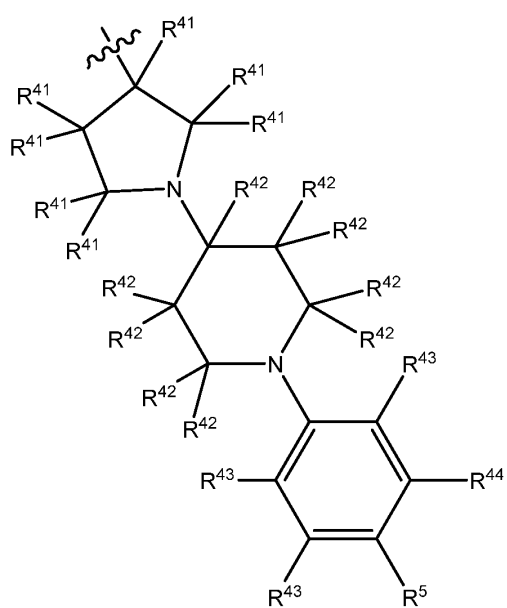
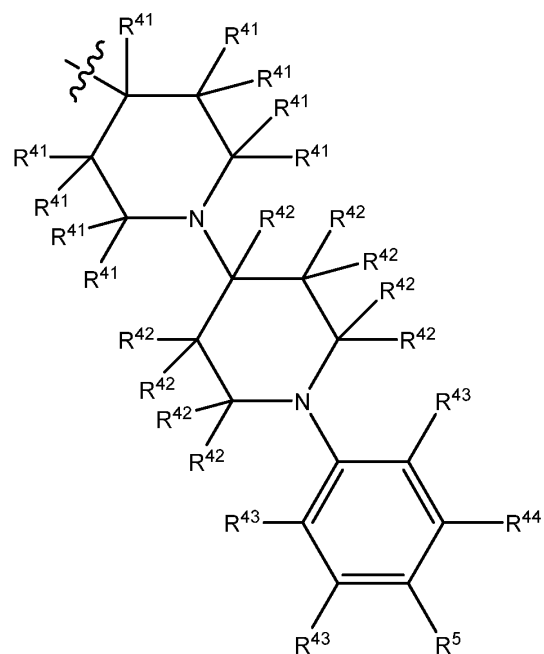
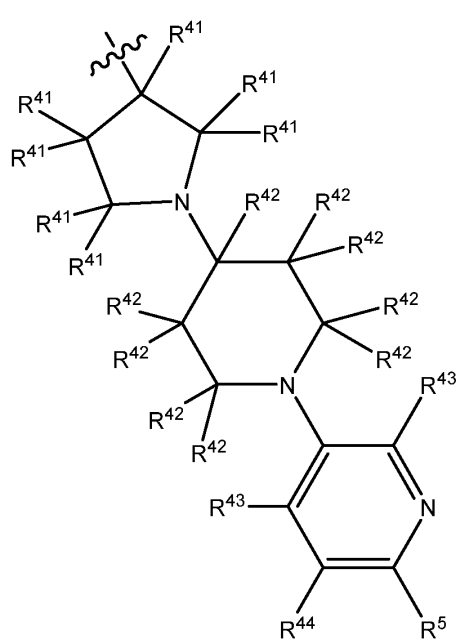


wherein n , m , p , q , X^3 , R^{41} , R^{42} , R^{43} , R^{44} , and R^5 , are as defined in claim 24.

26. A compound according to any of claims 15 to 25, wherein m is selected from 1 or 2, n is selected from 2 or 3, p is selected from 1, 2 or 3 and q is selected from 1 or 2.

27. A compound according to claim 25 or claim 26, wherein the group L comprises a group having any the following structures:

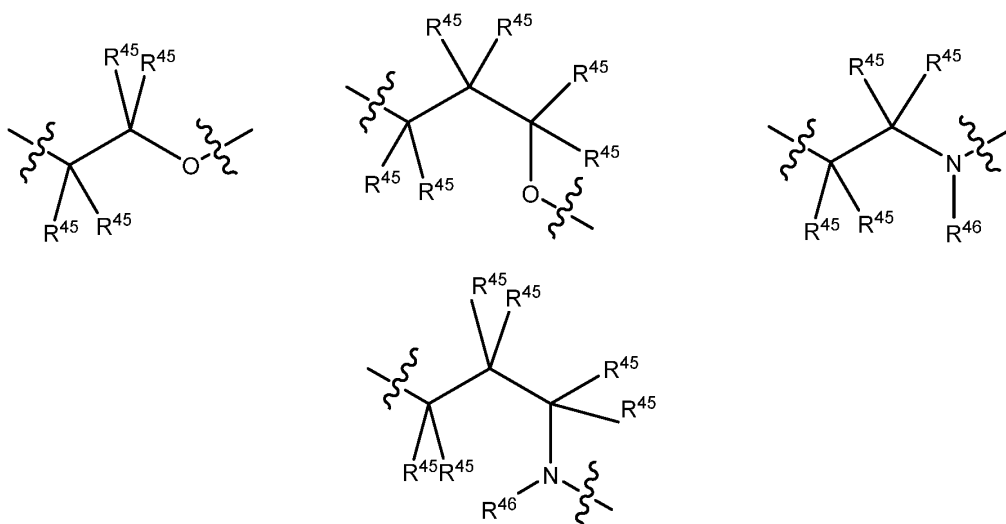




wherein, R^{41} , R^{42} , R^{43} , R^{44} and R^5 are as defined in claim 25.

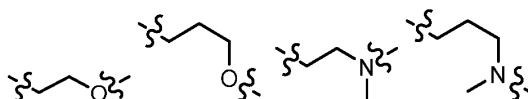
28. A compound according to any of claims 1 to 14, wherein group Q^2 of the group L is absent and only one Q^1 group is present, and wherein the Q^1 group separates ring A from ring C by 3 or 4 atoms in the linear direction.

29. A compound according to claim 28, wherein the Q^1 group comprises any of the following structures:

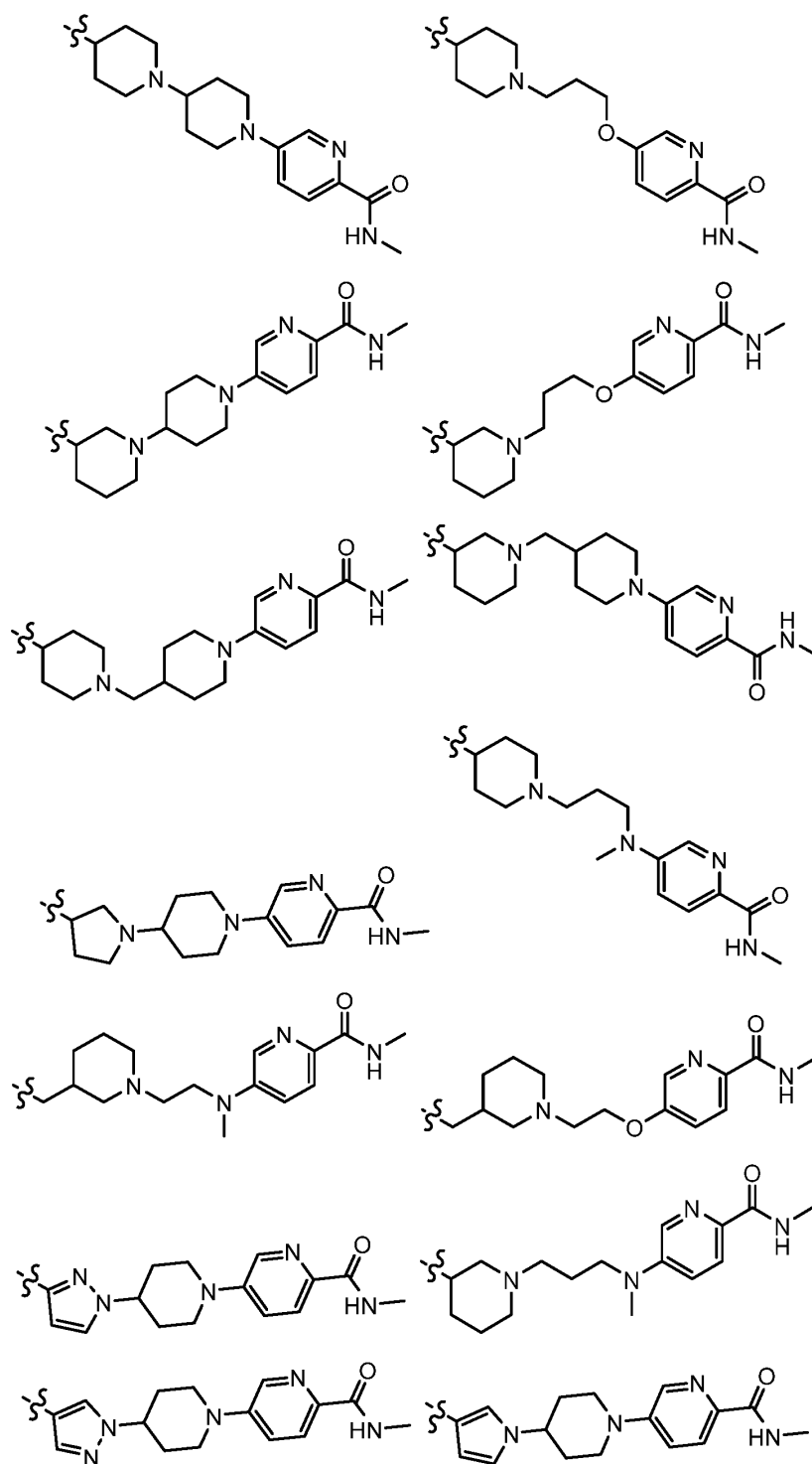


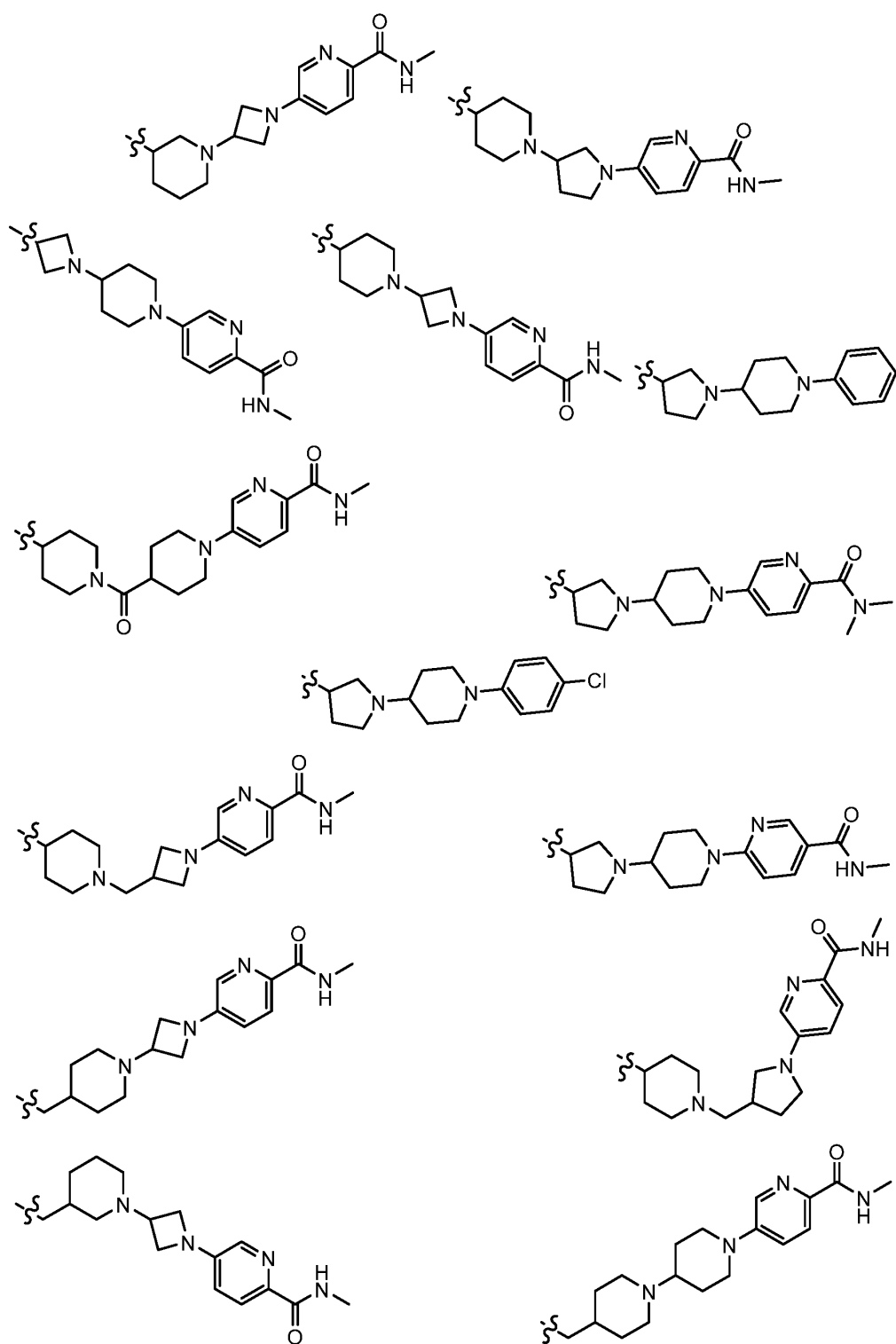
wherein R^{45} and R^{46} are as defined in any preceding claim.

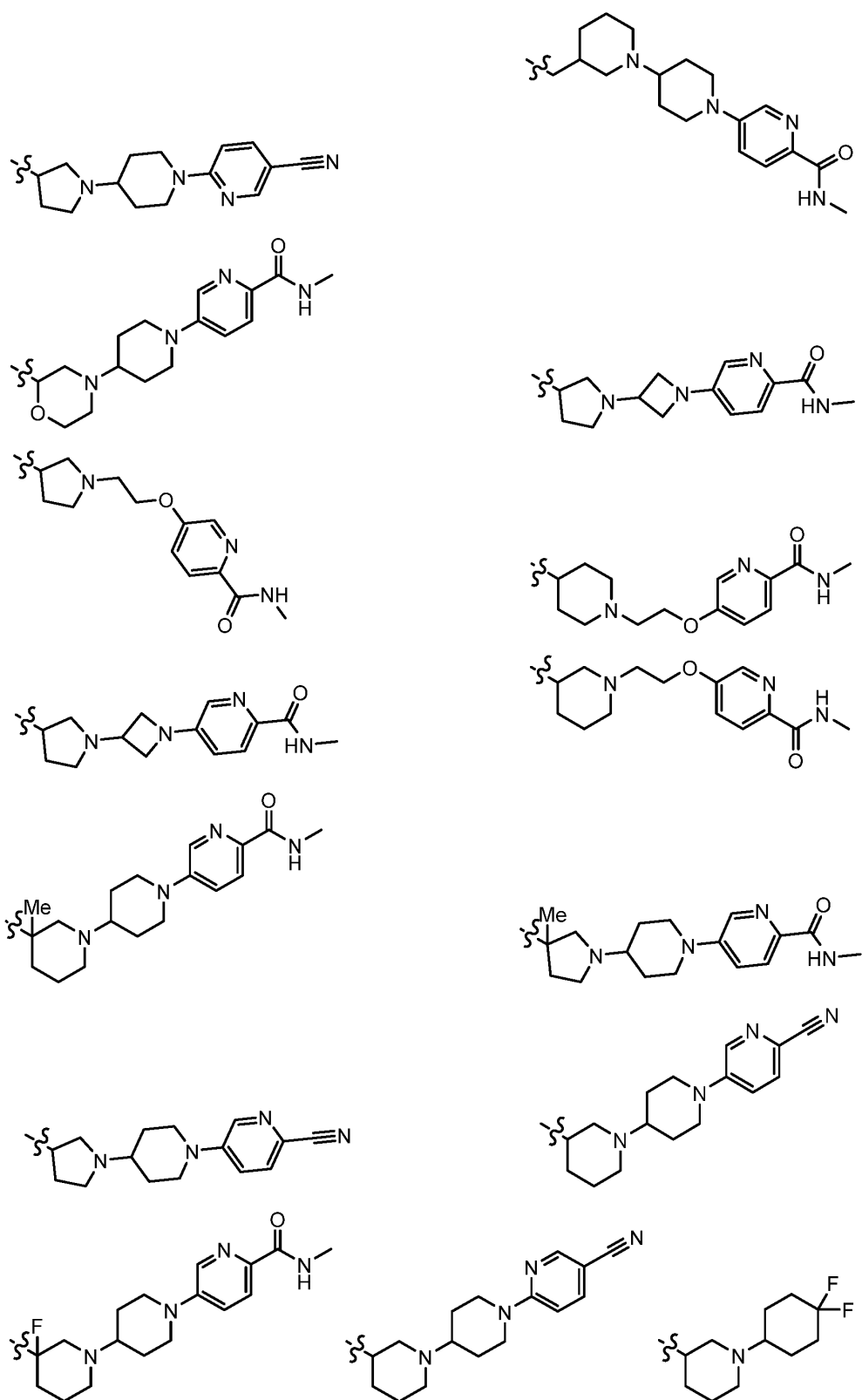
30. A compound according to claim 29, wherein the Q^1 group comprises any of the following structures:

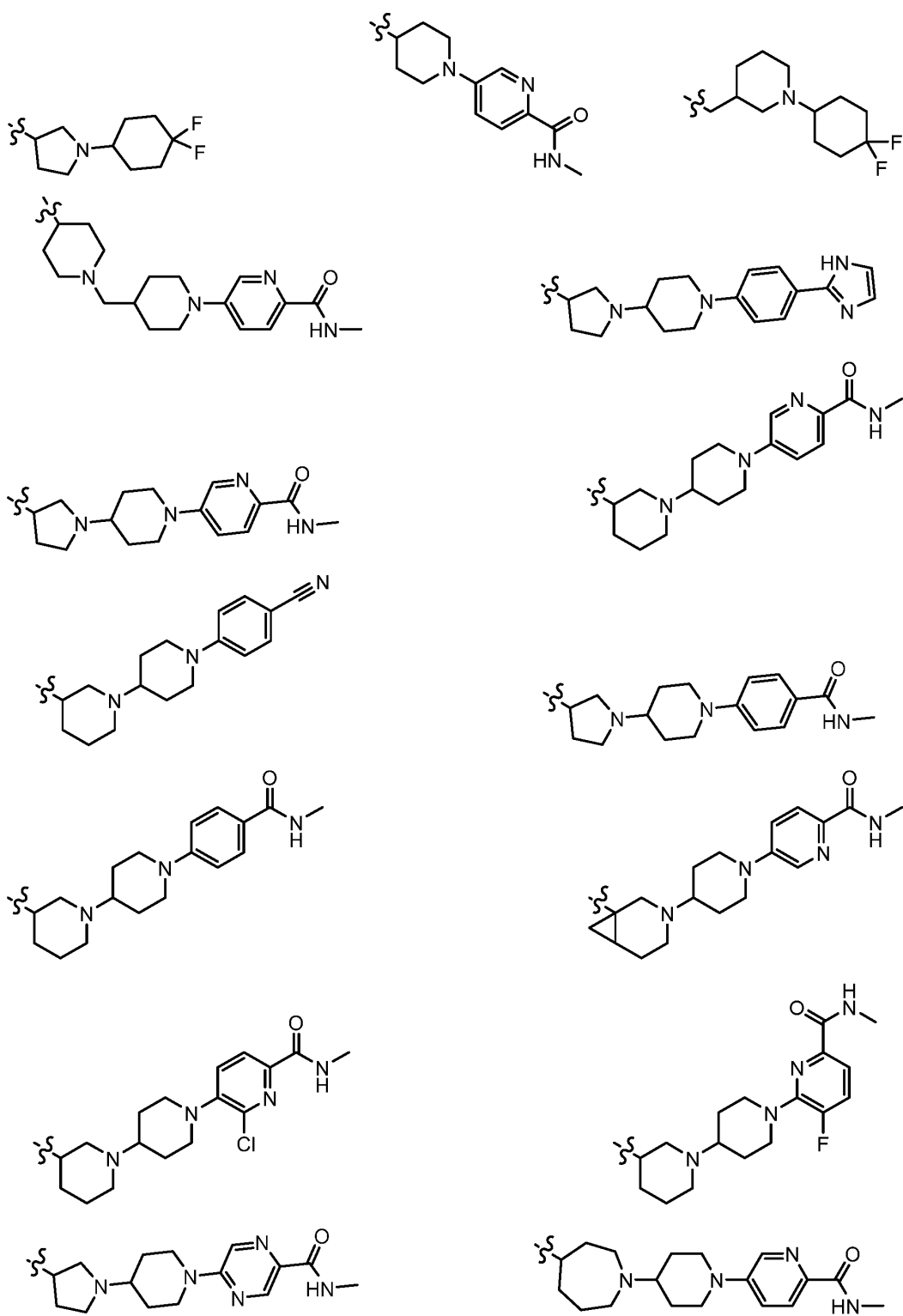


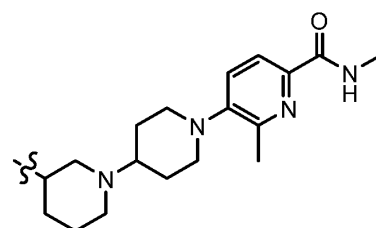
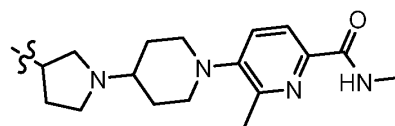
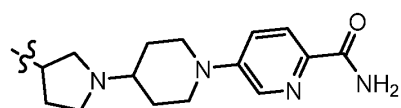
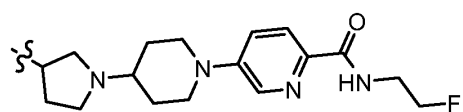
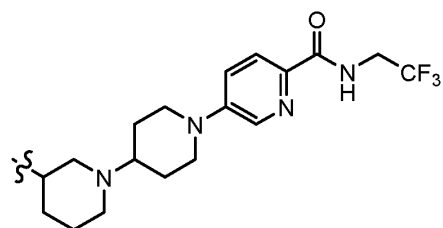
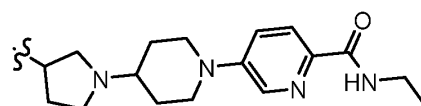
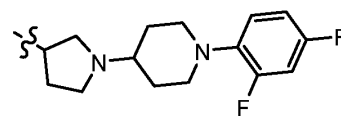
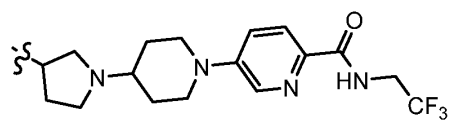
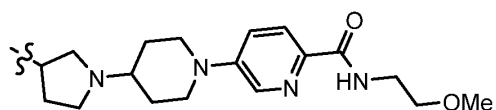
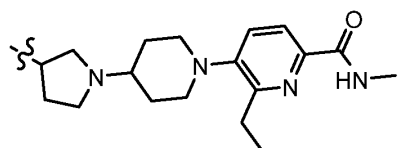
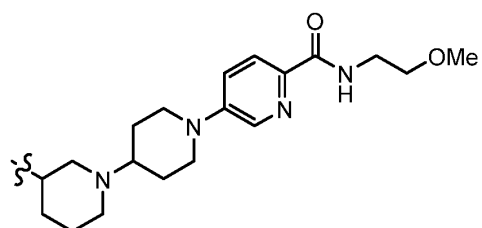
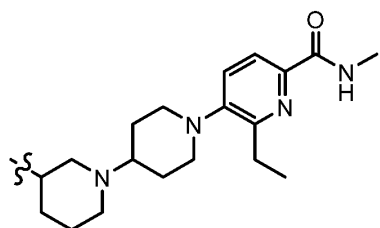
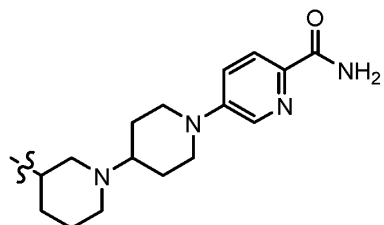
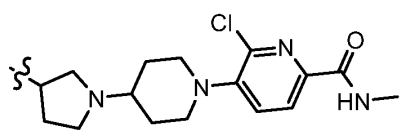
31. A compound according to any of claims 1 to 11, or 13 to 14, wherein the group L comprises a group having any the following structures:

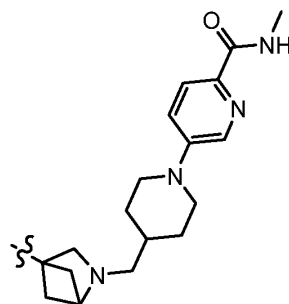
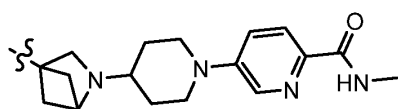
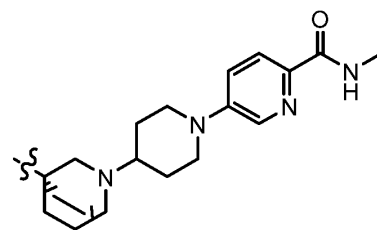
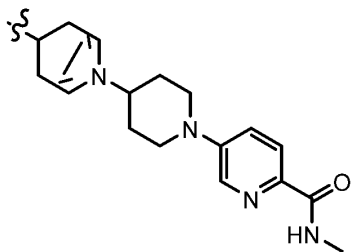
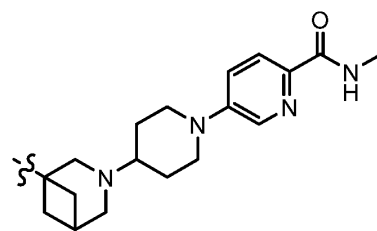
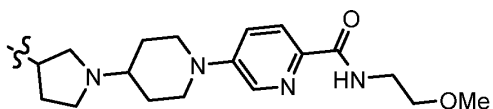
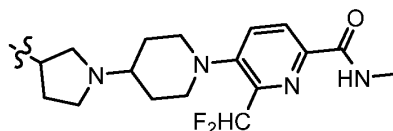
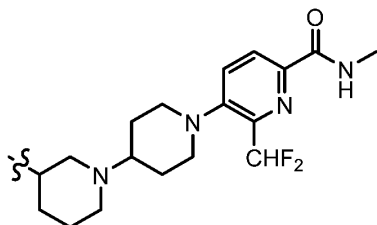
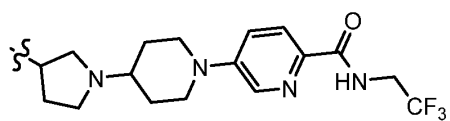
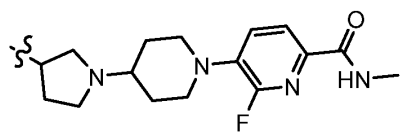
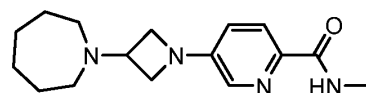
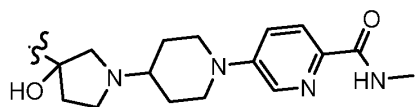
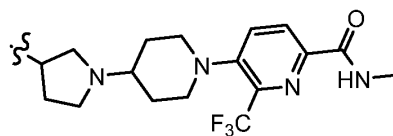
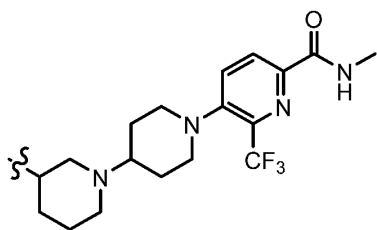


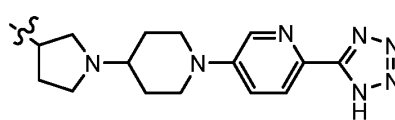
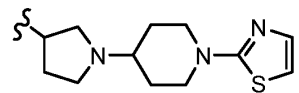
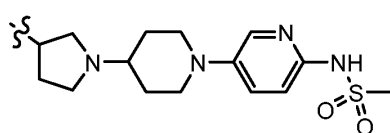
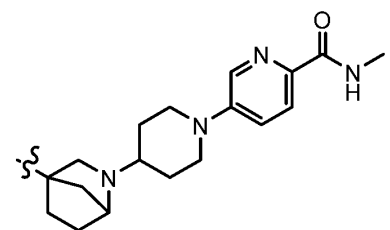
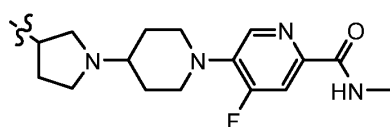
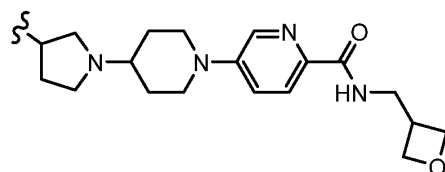
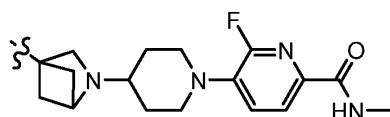
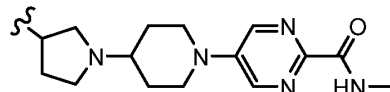
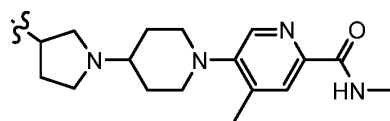
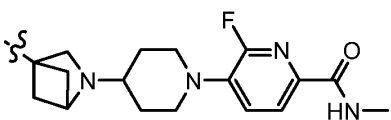
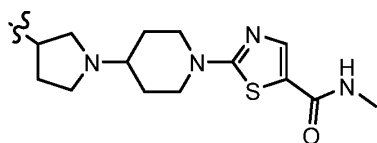
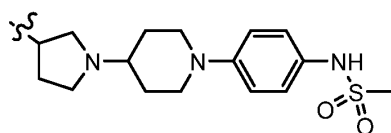
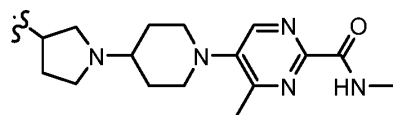
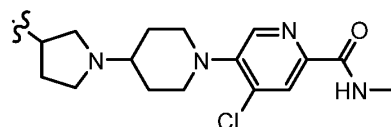
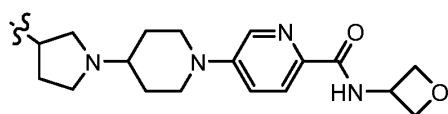
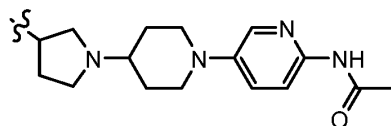
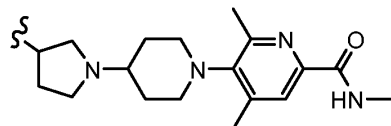
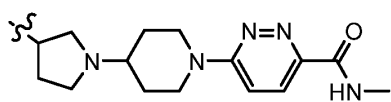


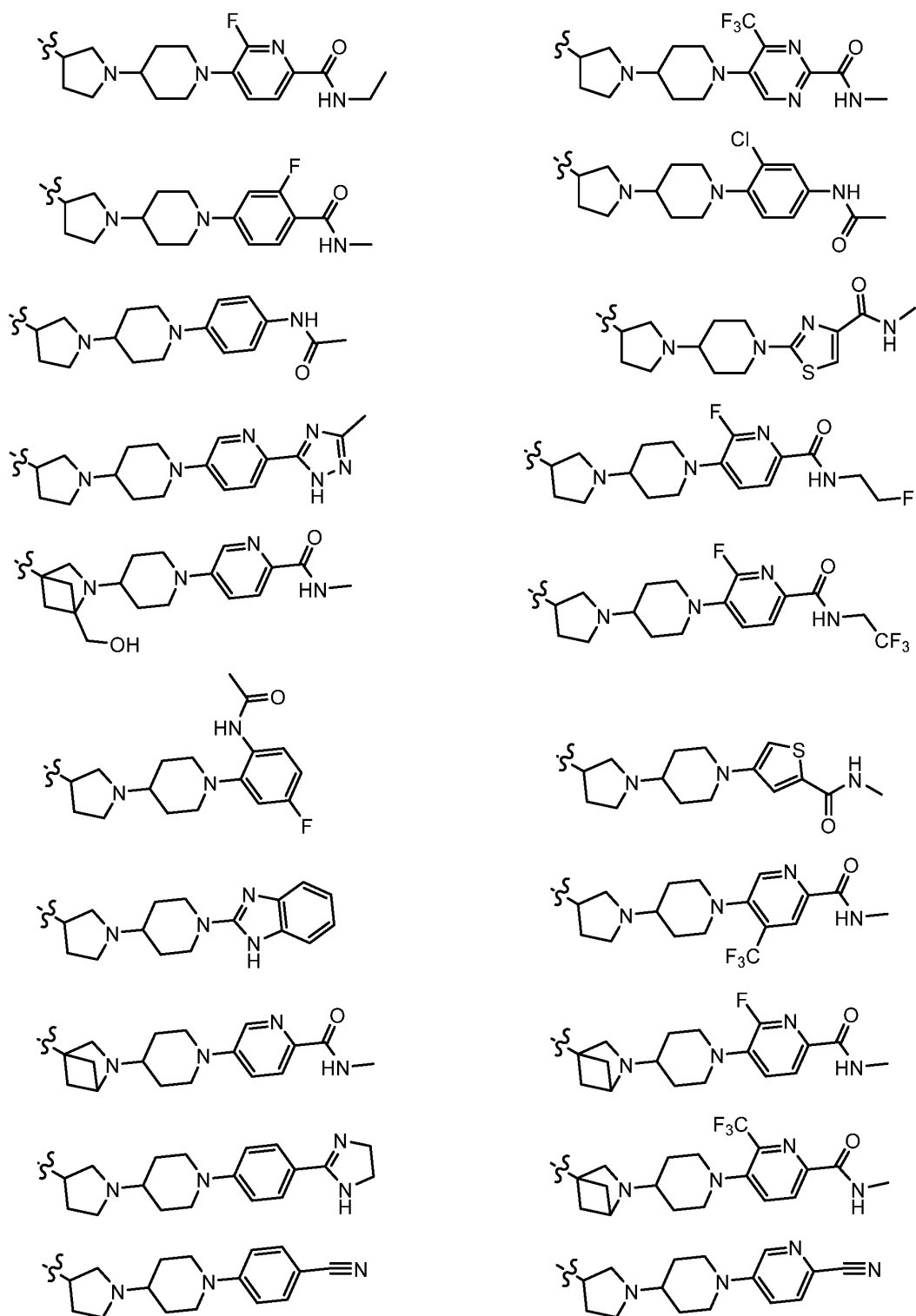


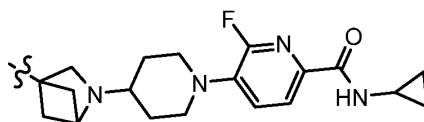
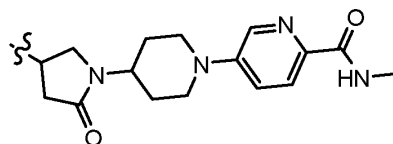
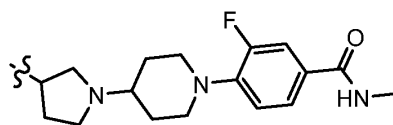
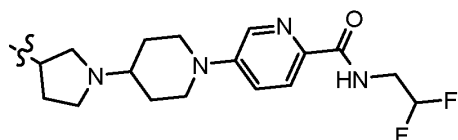
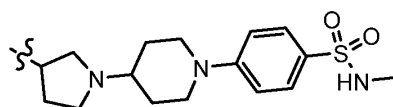
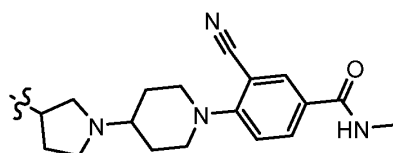
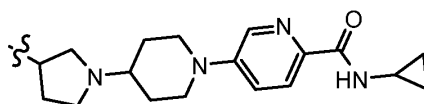
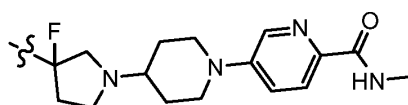
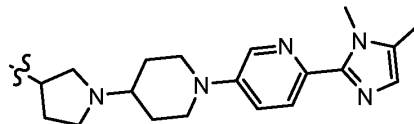
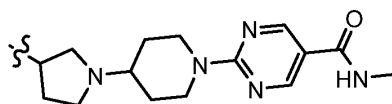
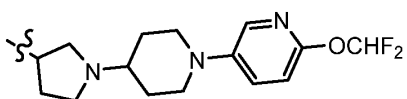
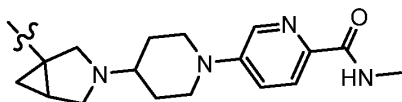
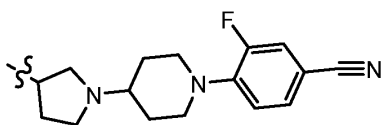
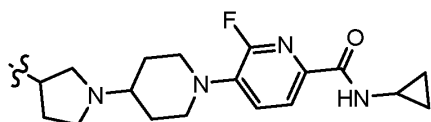
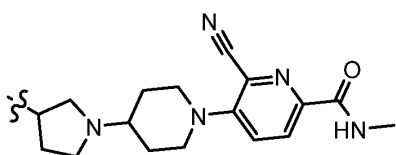
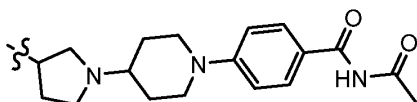
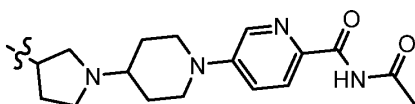
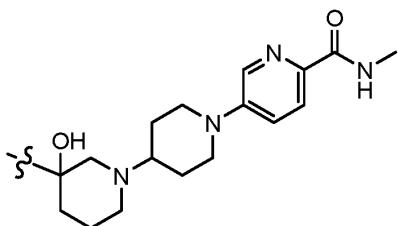
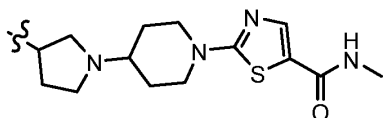
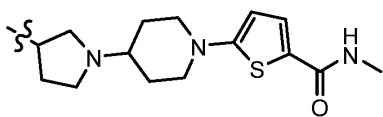


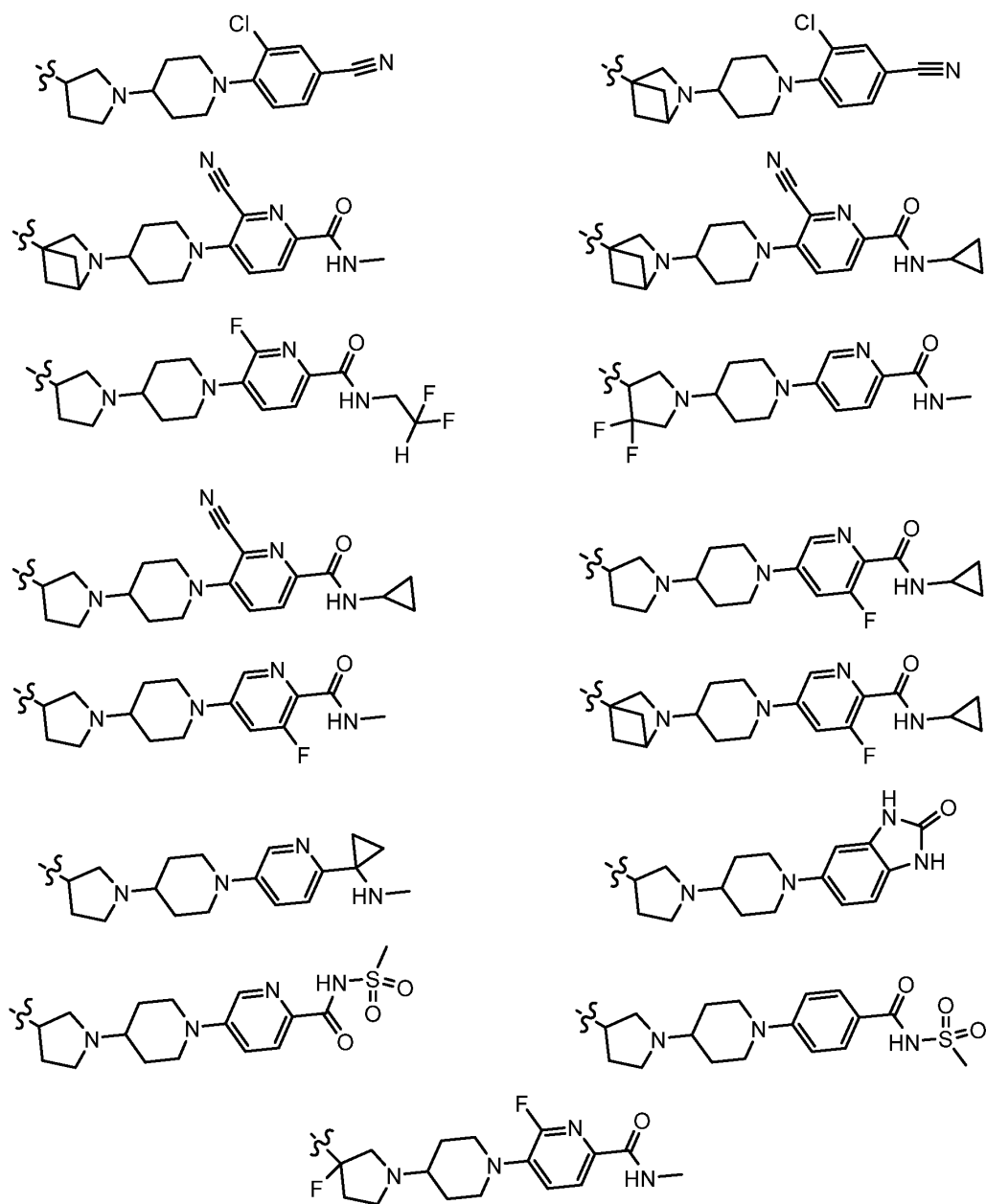




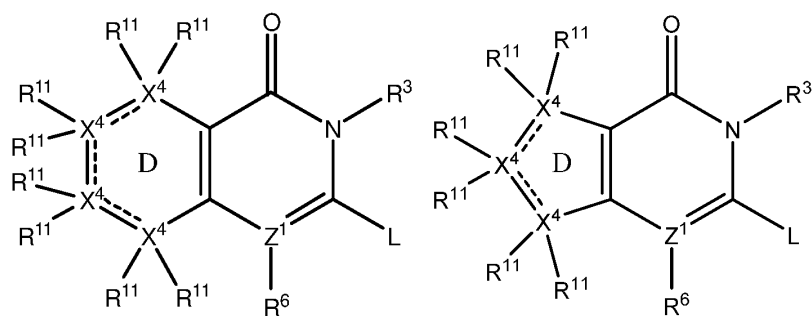






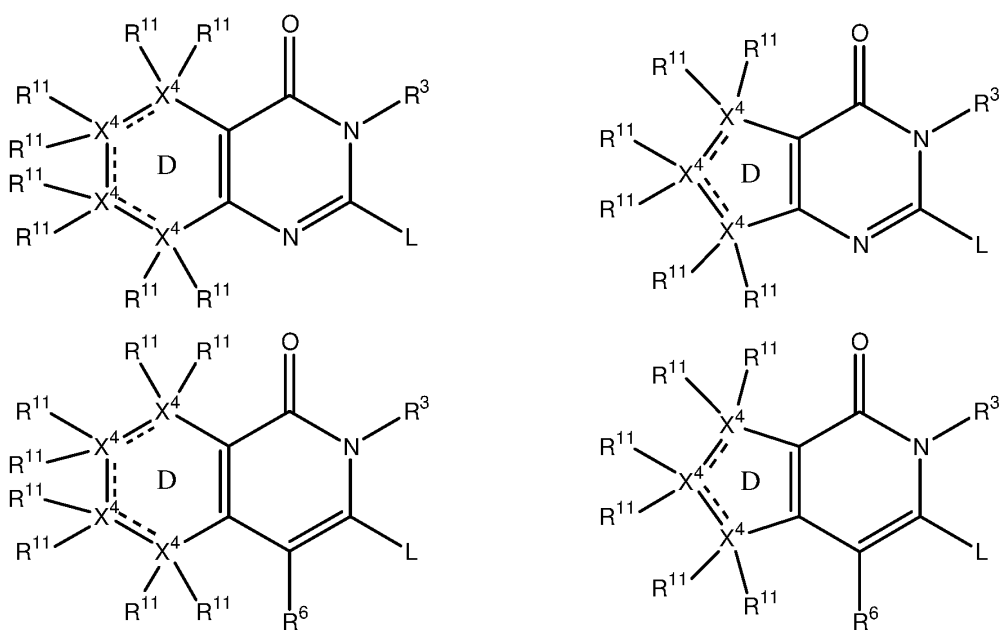


32. A compound according to any preceding claim, which compound comprises any of the following structures:



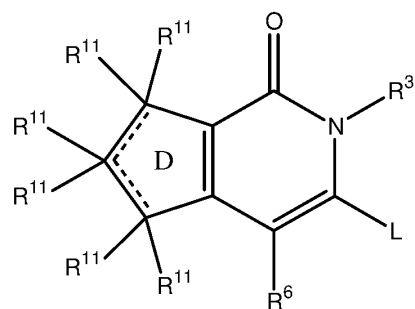
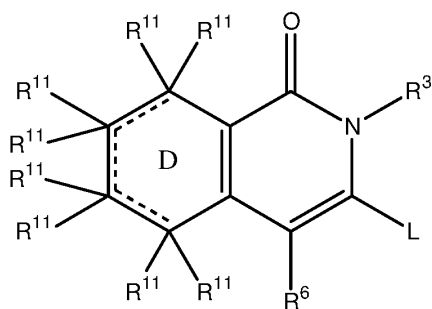
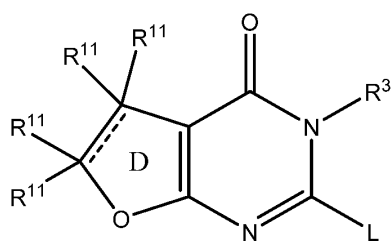
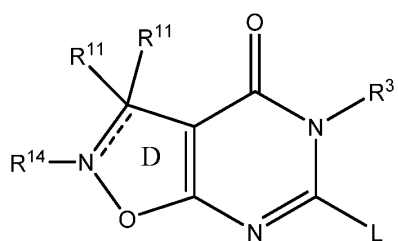
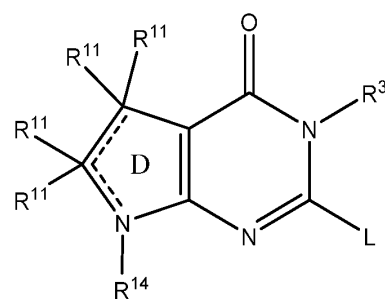
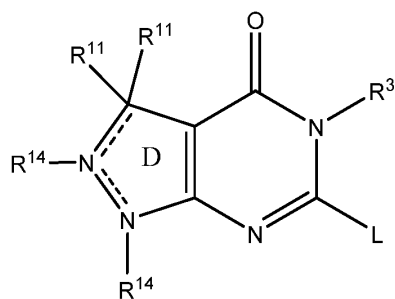
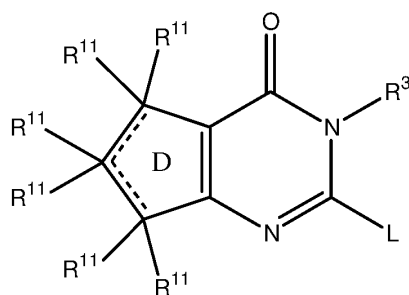
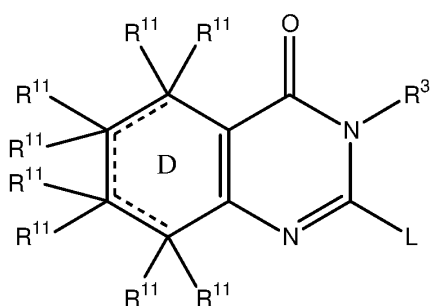
wherein, the dotted lines indicate that the ring D may comprise single bonds, or a combination of both single and double bonds, and may be aliphatic or aromatic; each X^4 may be the same or different and is independently selected from C, N, O and S; each R^{11} may be the same or different and is independently selected from H and a substituted or unsubstituted organic group; and wherein Z^1 , R^3 , R^6 , and L are as defined in any preceding claim.

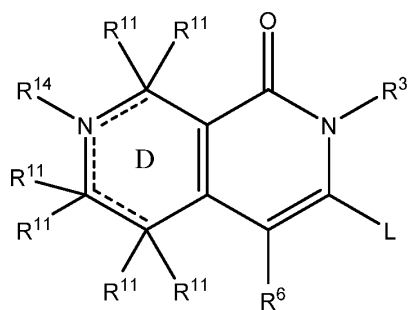
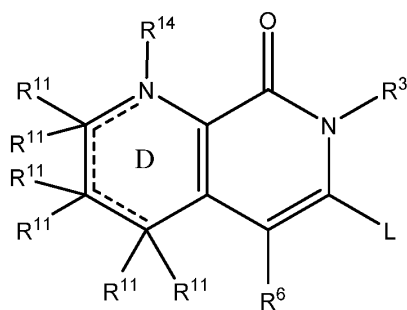
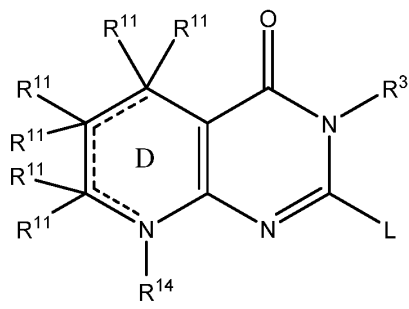
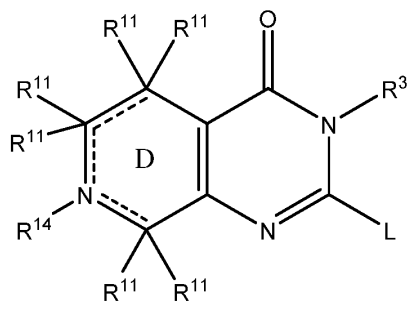
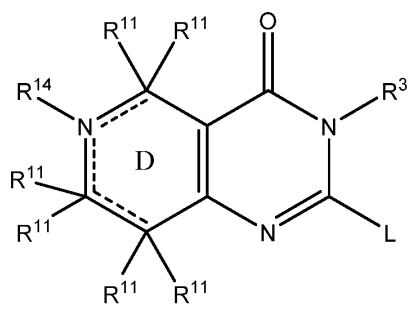
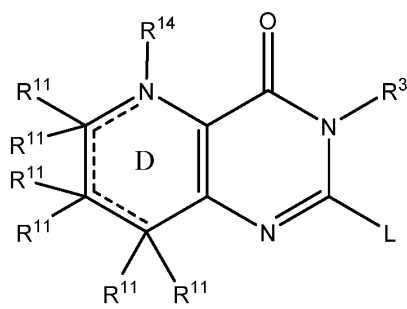
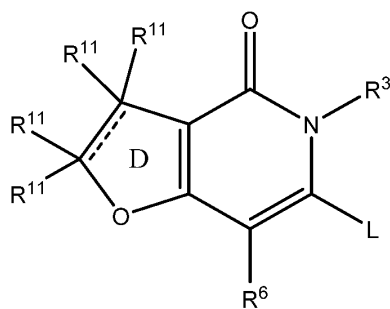
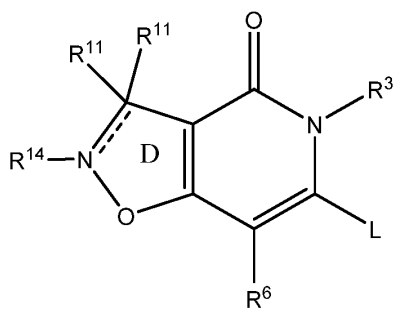
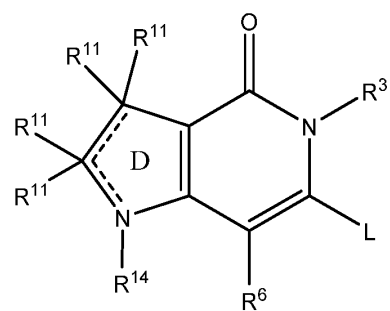
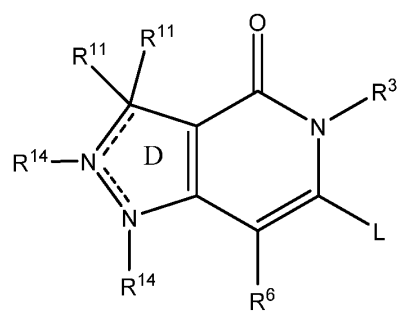
33. A compound according to claim 32, which compound comprises any of the following structures:

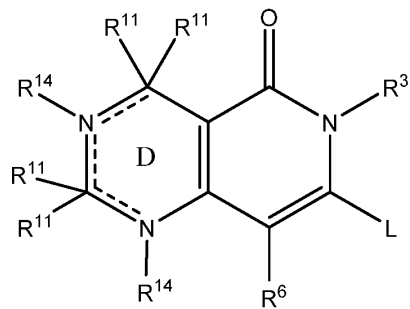
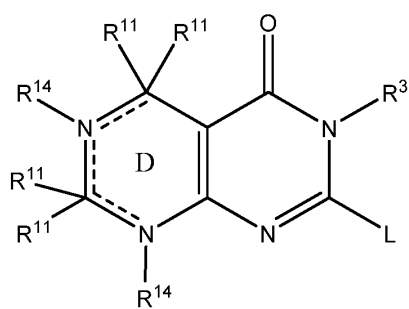
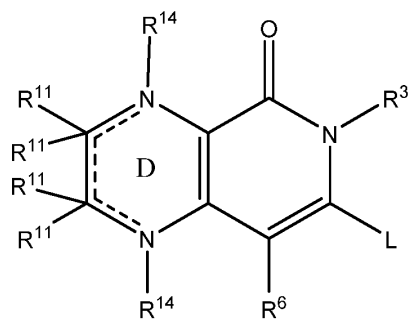
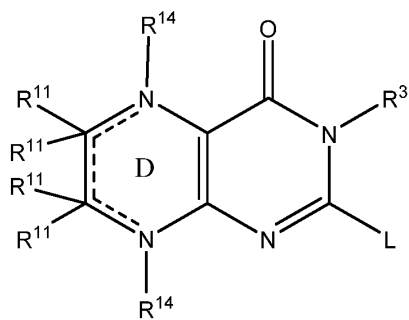
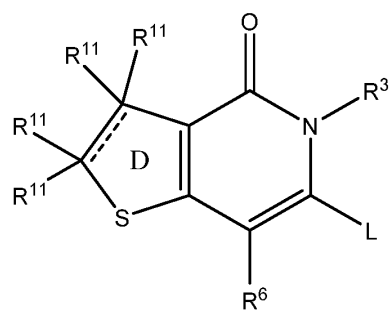
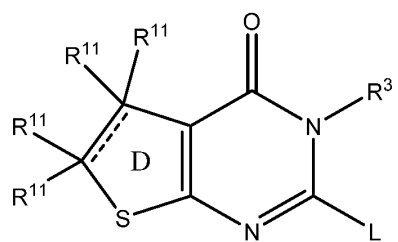
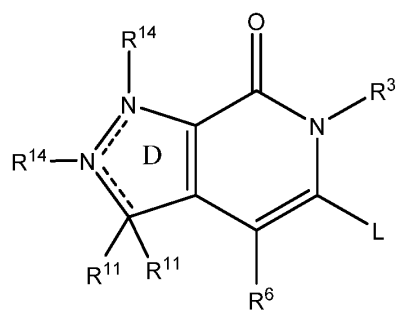
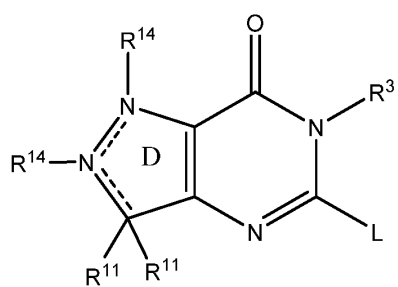
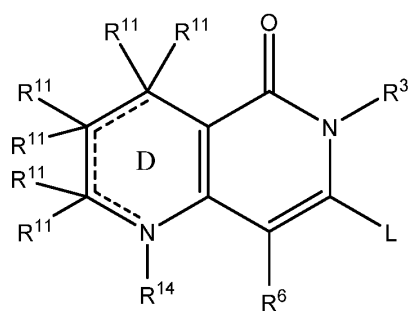
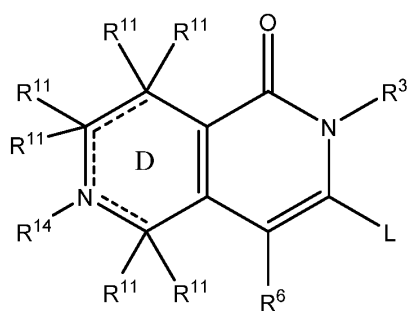


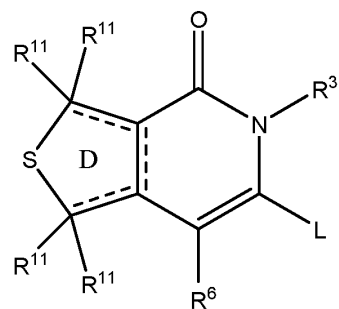
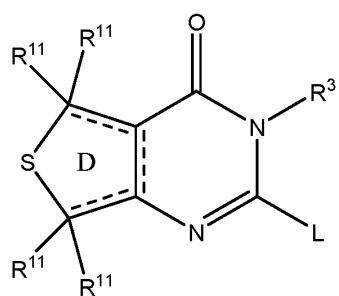
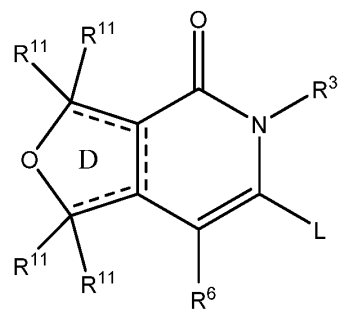
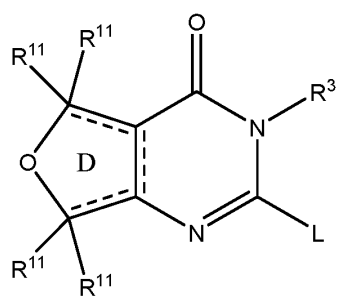
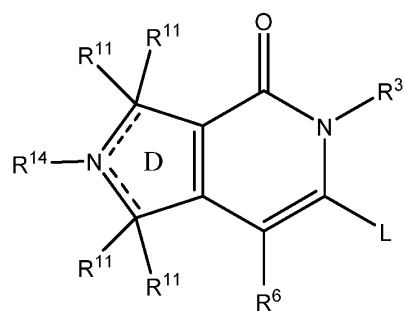
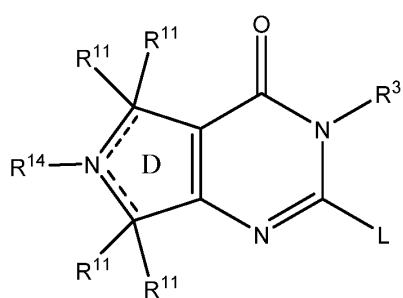
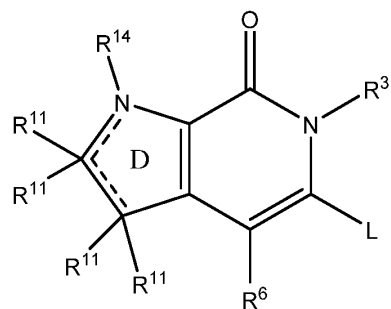
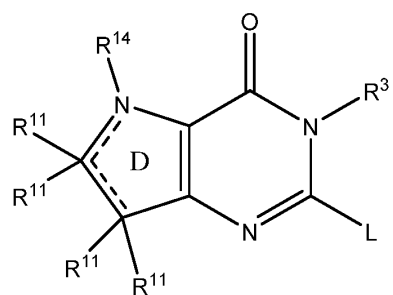
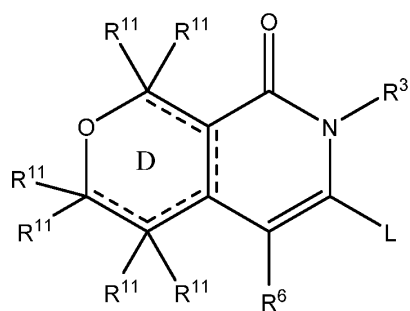
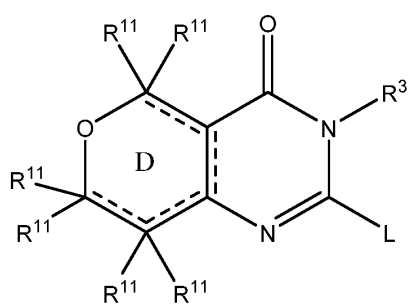
wherein the ring D, X^4 , R^{11} , R^3 , R^6 , and L are as defined in claim 32, preferably wherein at least one X^4 is C.

34. A compound according to claim 33, which compound comprises any of the following structures:



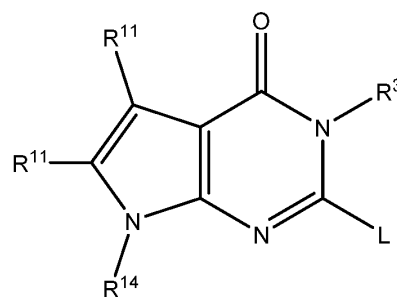
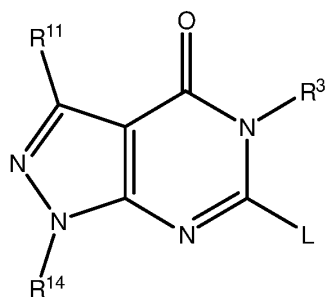
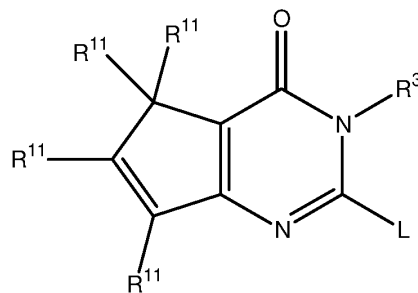
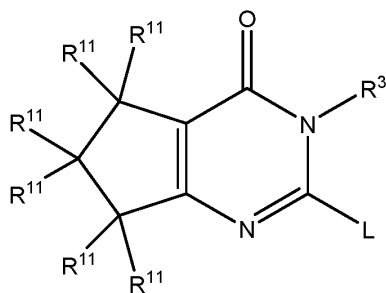
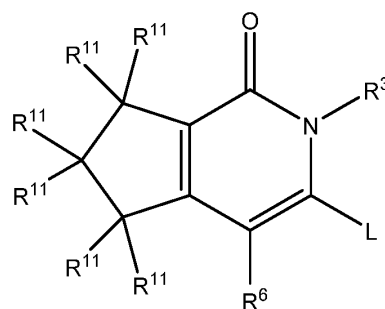
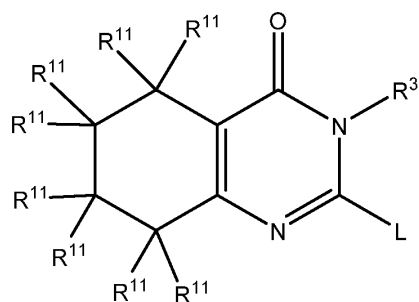
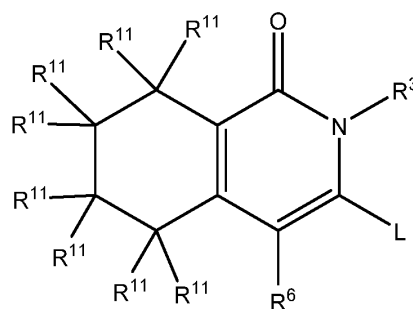
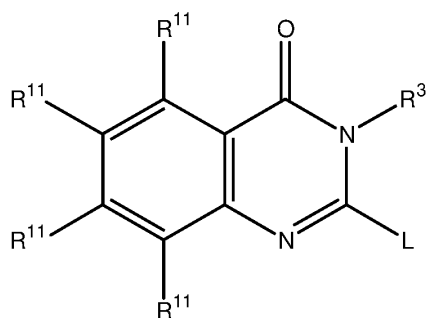


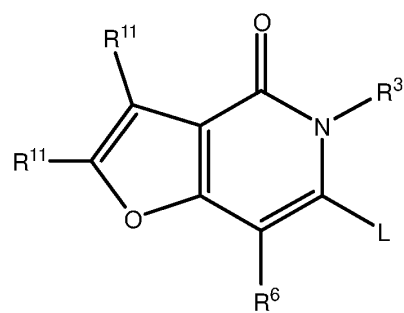
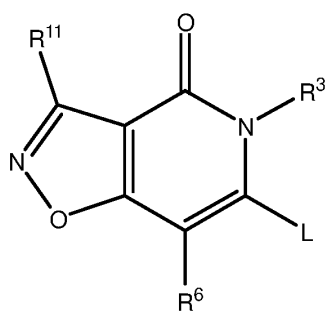
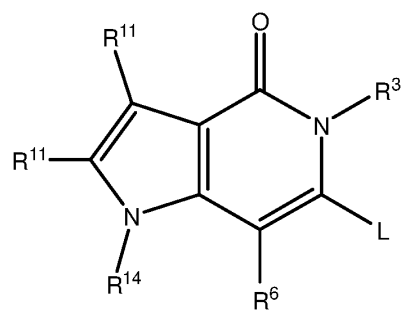
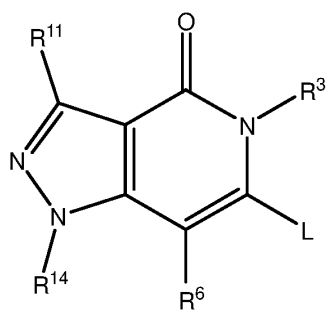
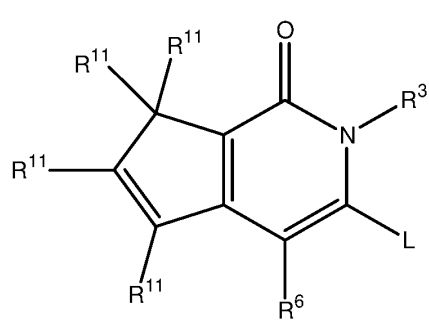
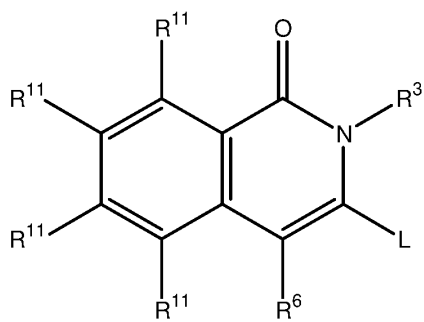
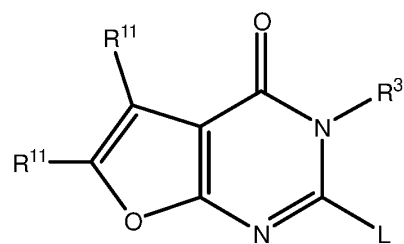
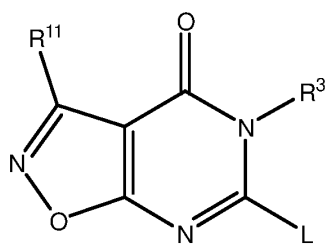


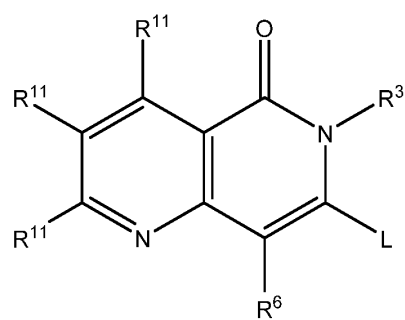
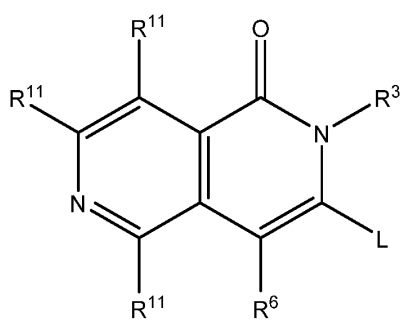
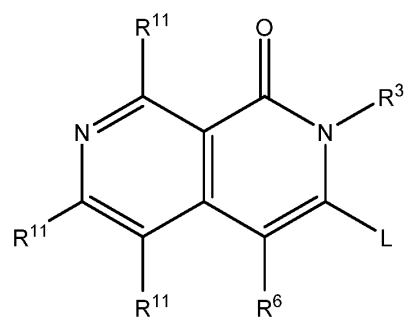
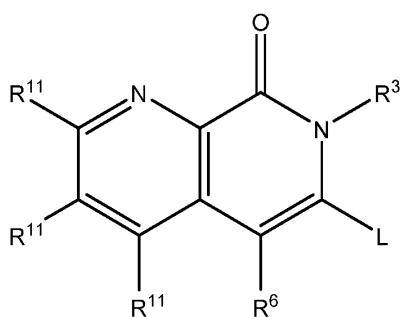
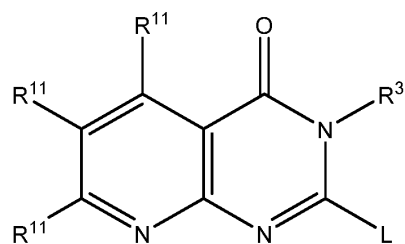
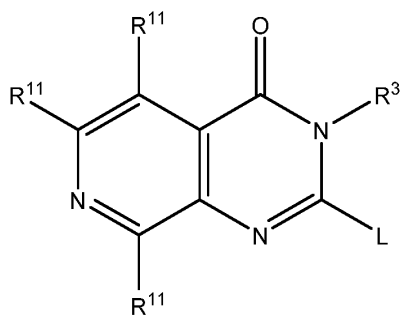
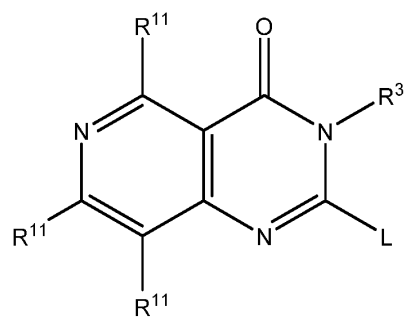
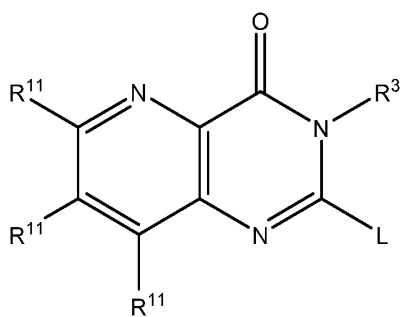


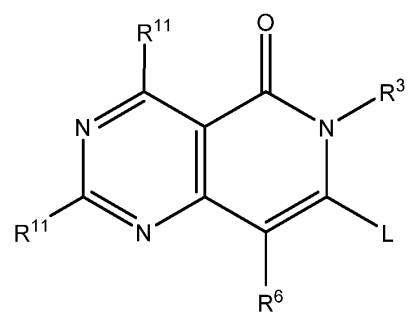
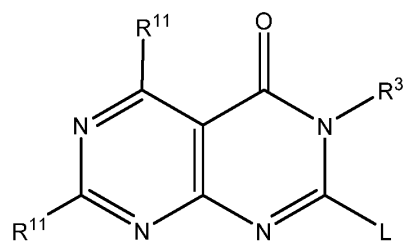
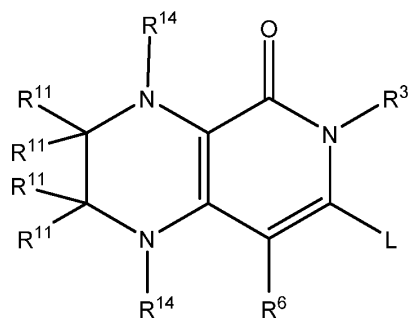
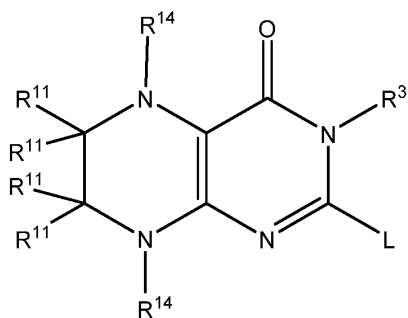
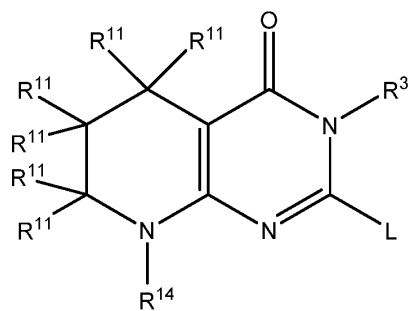
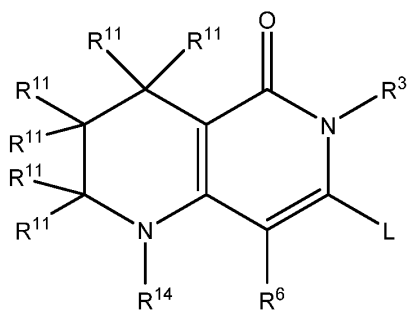
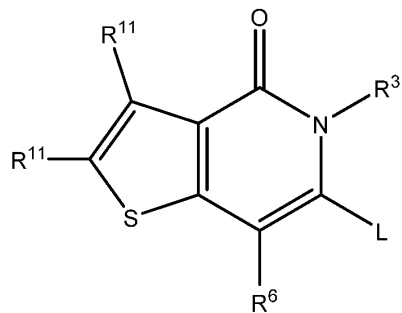
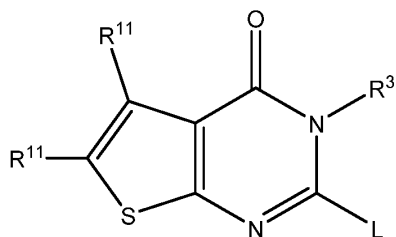
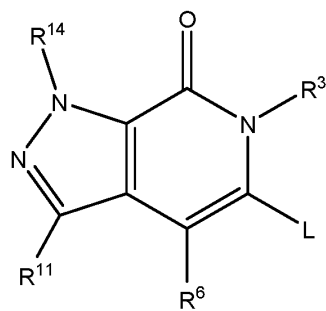
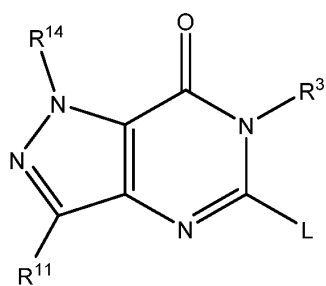
wherein R^{14} may be present or absent and if present is selected from H, C_1 to C_3 alkyl or C_1 to C_3 fluoroalkyl; and R^{11} , ring D, R^3 , R^6 , and L are as defined in claim 33.

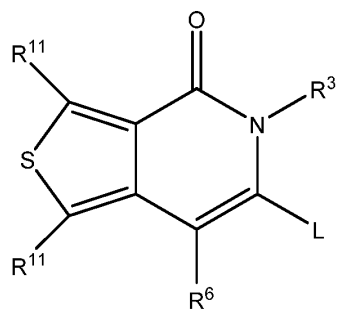
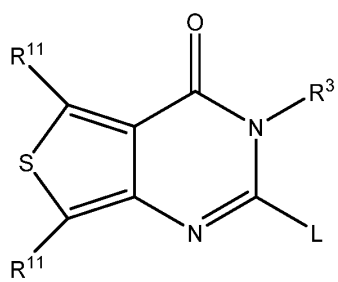
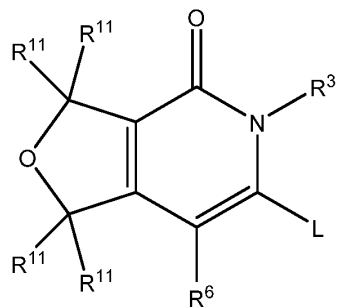
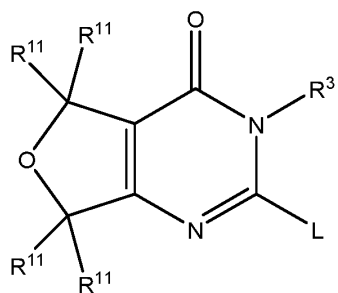
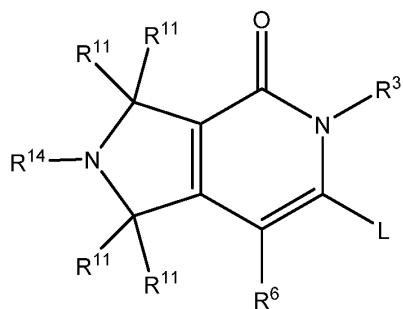
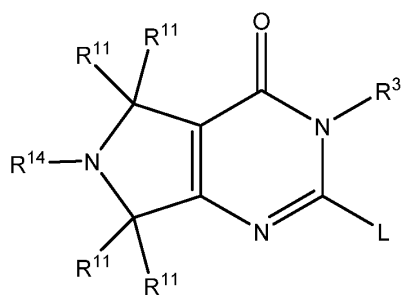
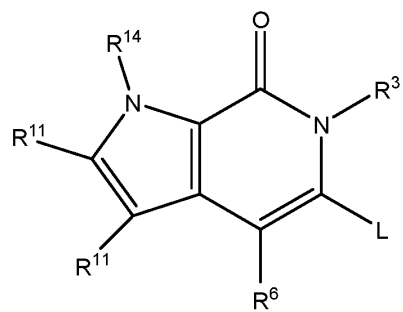
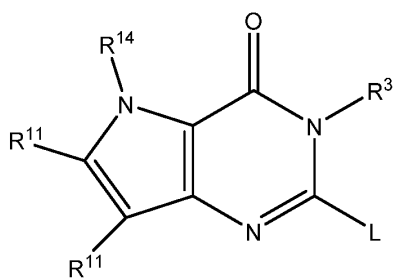
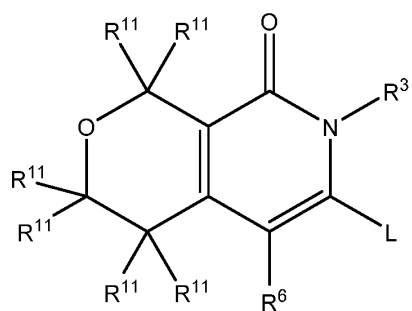
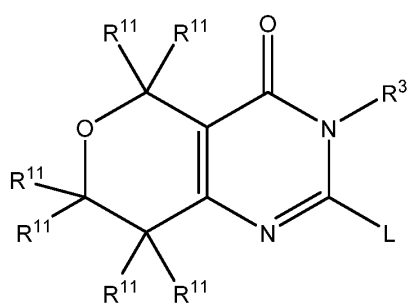
35. A compound according to claim 34, which compound comprises any of the following structures:









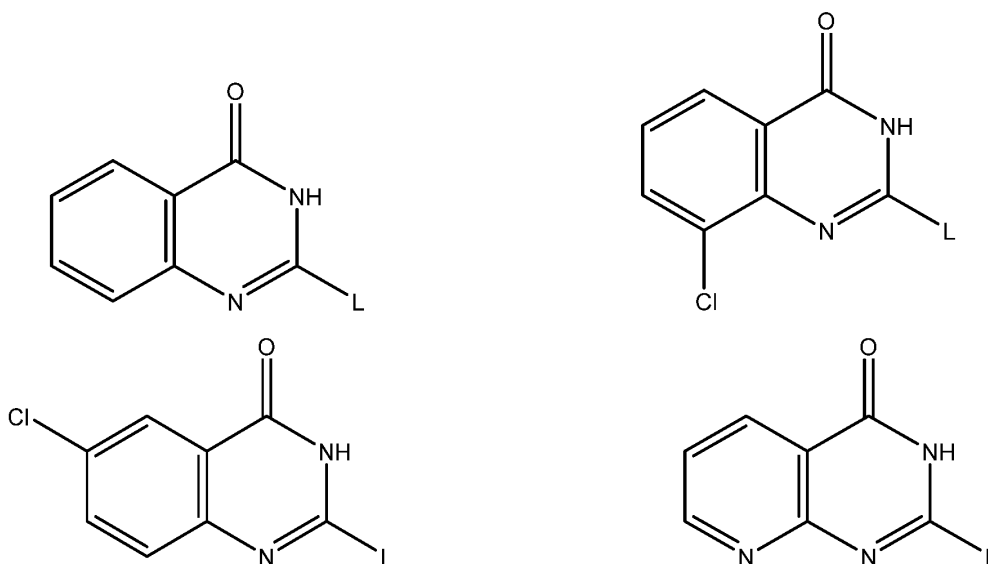


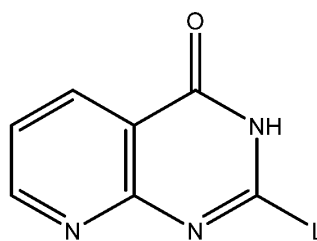
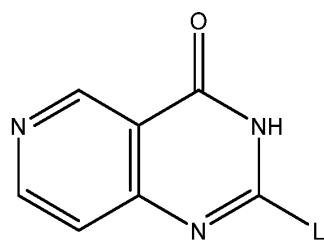
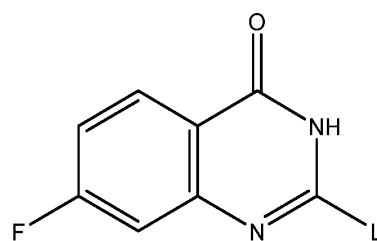
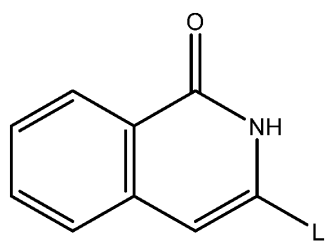
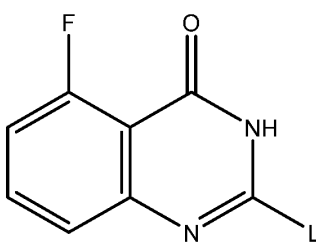
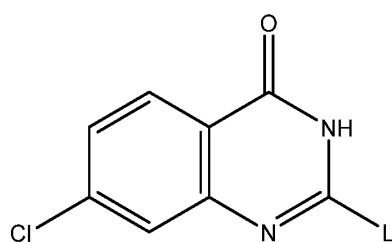
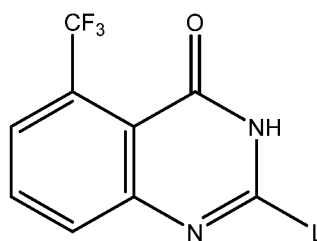
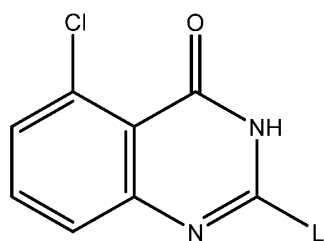
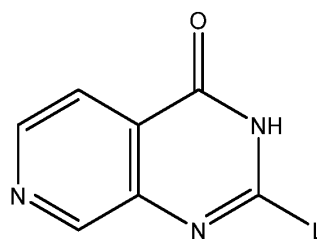
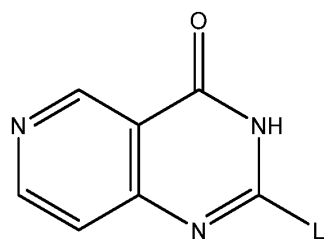
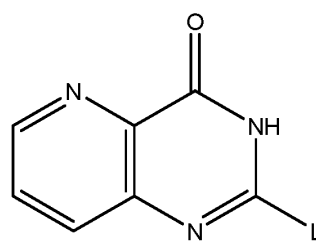
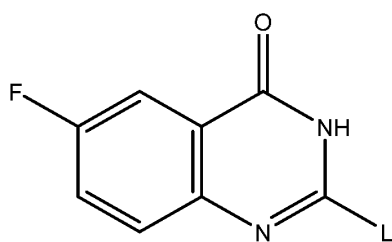
wherein R³, R¹¹, R¹⁴, R⁶, and L are as defined in claim 34.

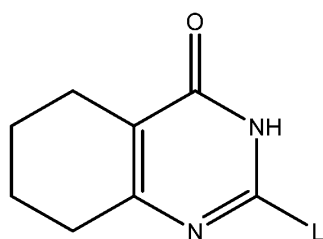
36. A compound according to any of claims 32 to 35, wherein each R¹¹ is independently selected from H, a halogen, a nitrile group, a linear or branched C₁-C₃ alkyl group, a linear or branched C₁-C₃ halogenated alkyl group (preferably fluoroalkyl), an -OH group, a linear or branched C₁-C₃ alcohol group, a halogenated (preferably fluoro-) linear or branched C₁-C₃ alcohol group, -NH₂, a linear or branched primary secondary or tertiary C₁-C₃ amine group, a halogenated (preferably fluoro-) linear or branched primary, secondary or tertiary C₁-C₃ amine group, a linear or branched C₁-C₃ alkoxy group, a linear or branched C₁-C₃ halogenated alkoxy group (preferably fluoroalkoxy), and/or a pair of R¹¹ groups attached to the same atom forming =O; and independently, and/or when a pair of R¹¹ groups attached to different atoms together forms a ring with ring D atoms, the pair of R¹¹ groups comprises -CH₂CH₂CH₂-.

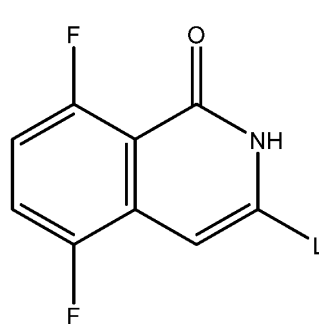
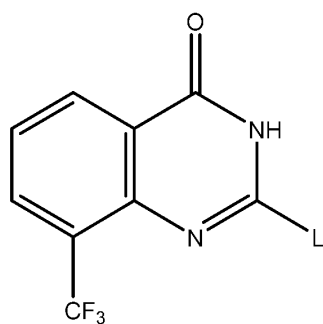
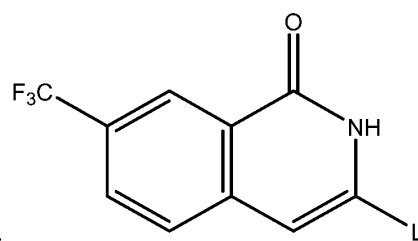
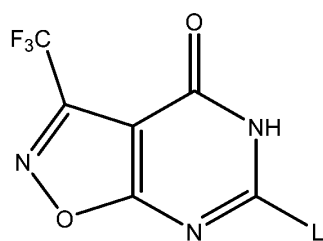
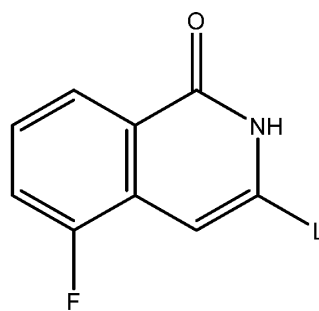
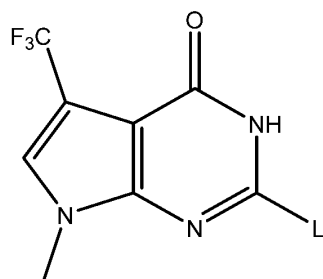
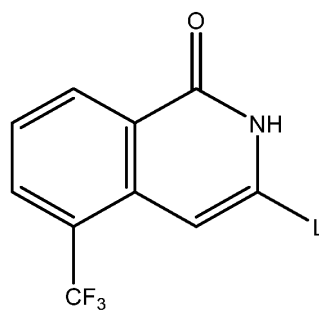
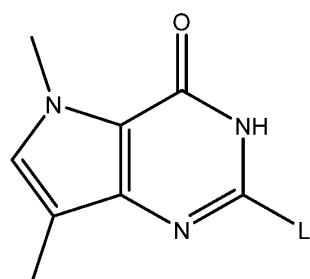
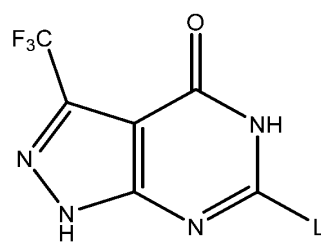
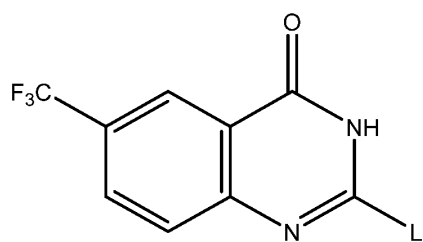
37. A compound according to claim 36, wherein each R¹¹ is independently selected from H, Cl, F, CHF₂, CF₃, CH₃, OH, CH₃O, and NH₂, and/or a pair of R¹¹ groups attached to the same atom forming =O; and independently, when a pair of R¹¹ groups attached to different atoms together forms a ring with ring D atoms, the pair of R¹¹ groups comprises -CH₂CH₂CH₂-.

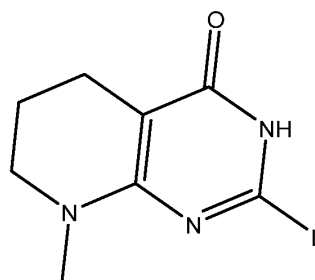
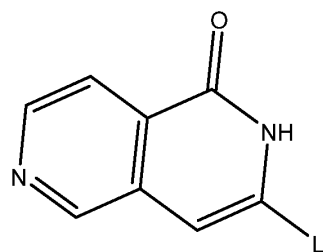
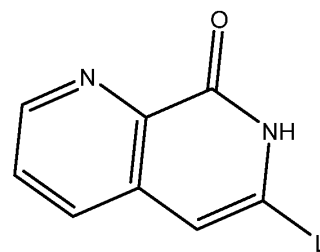
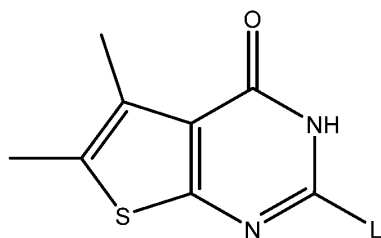
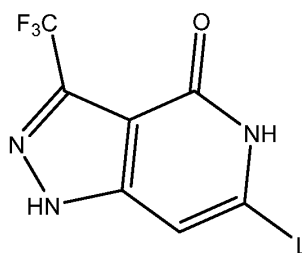
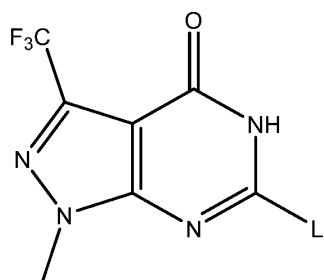
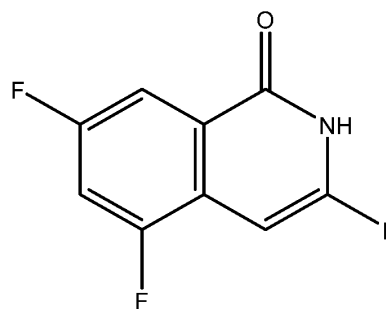
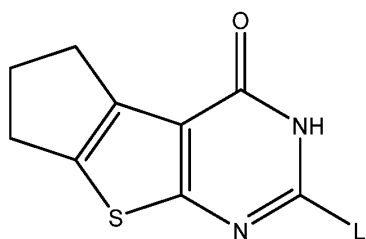
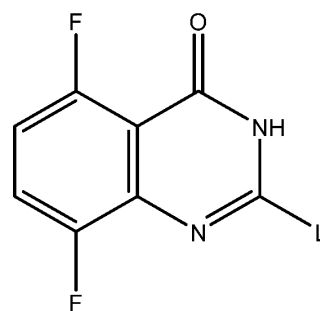
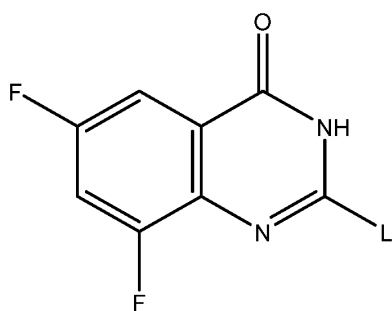
38. A compound according to claim 37, which compound comprises any of the following structures:

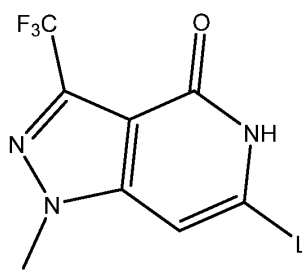
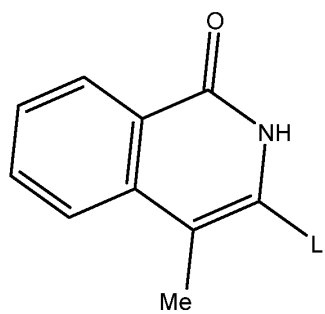
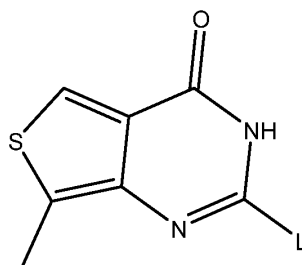
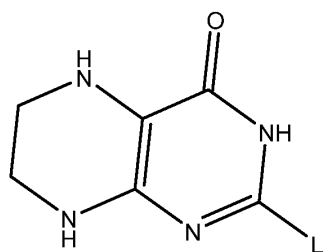
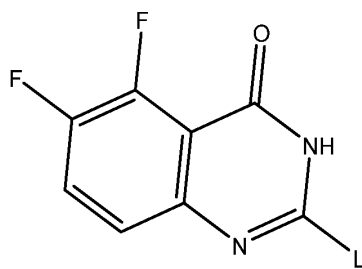
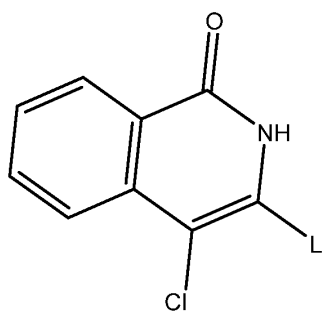
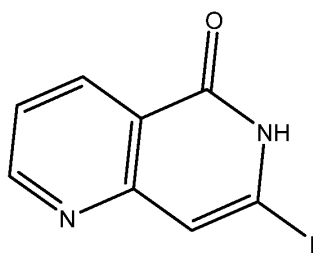
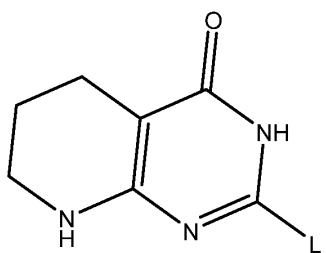
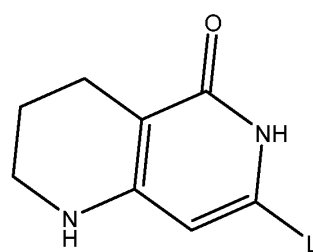
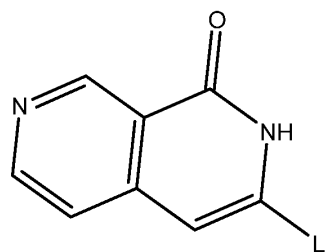


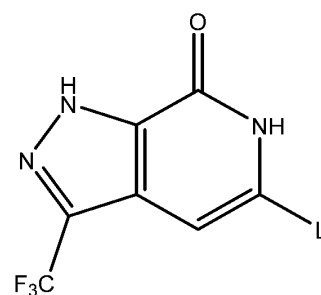
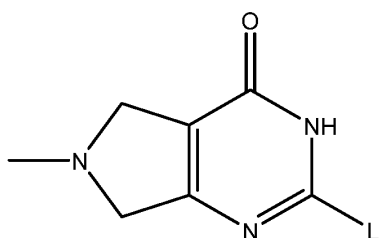
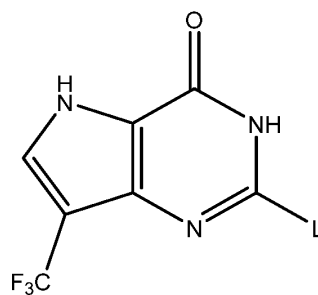
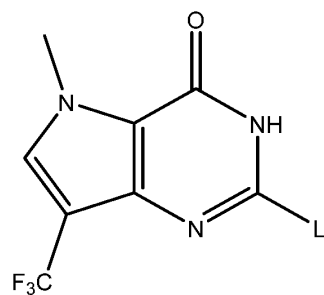
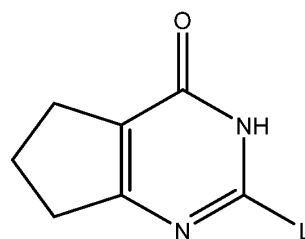
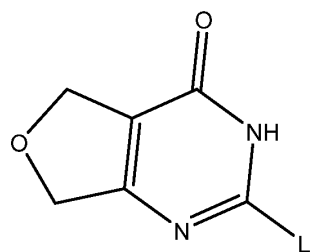
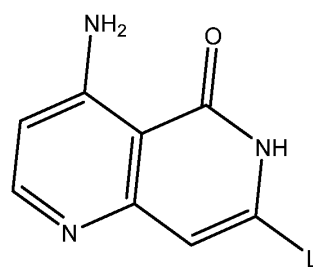
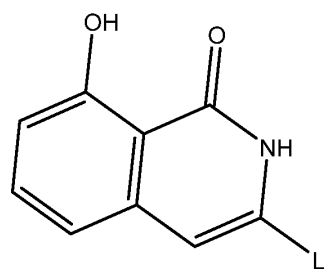
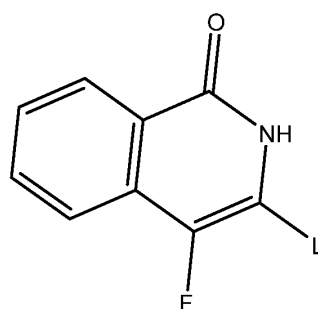
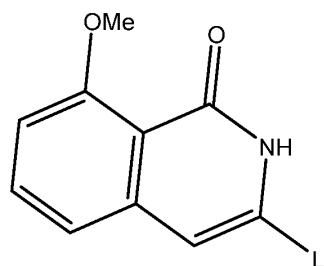


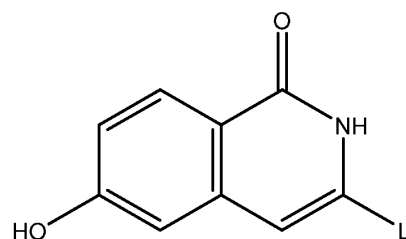
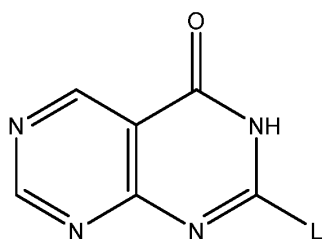
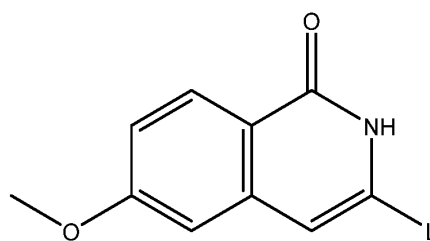
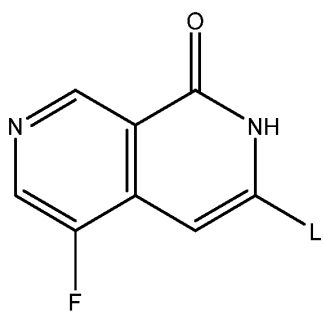
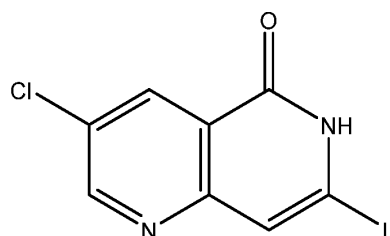
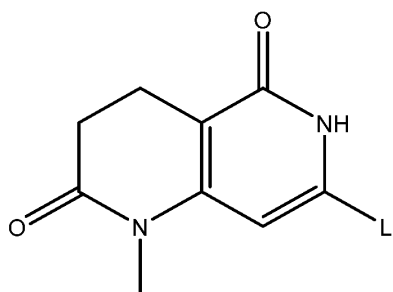
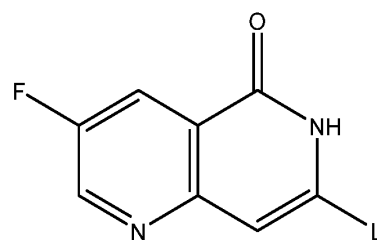
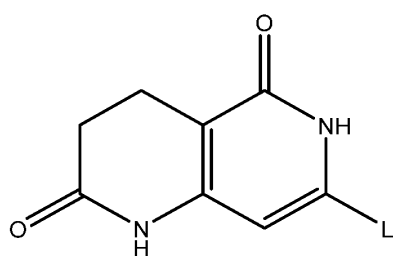
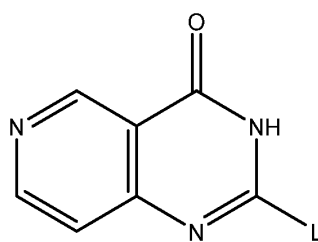
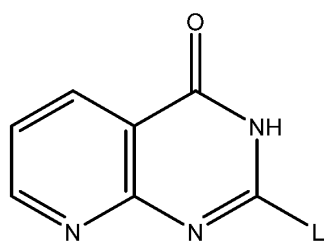


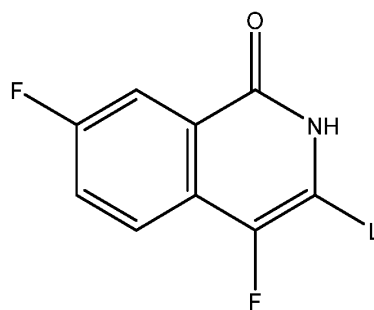
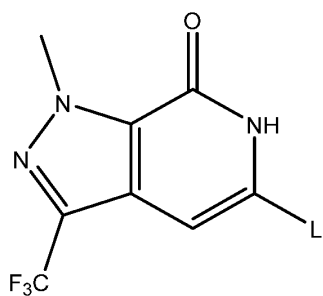
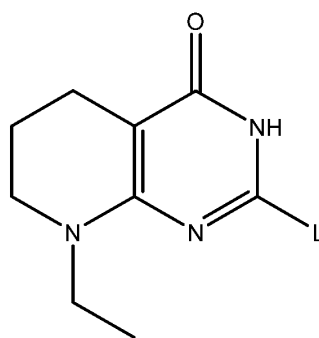
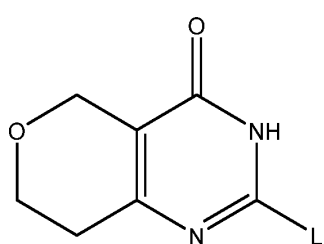
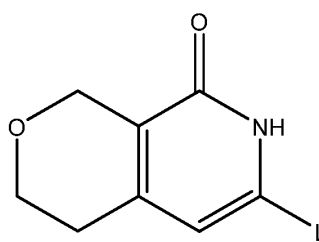
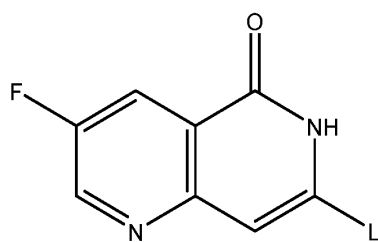
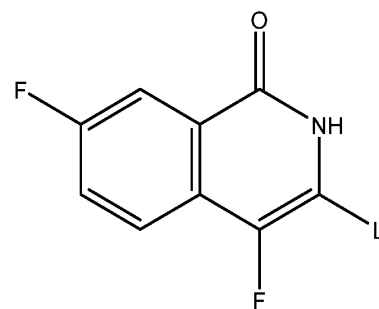
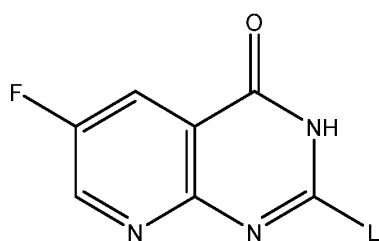
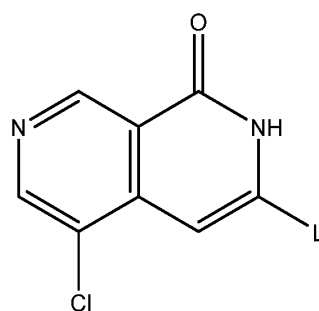
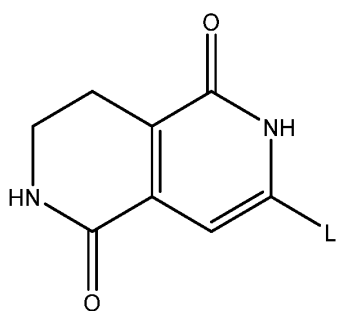


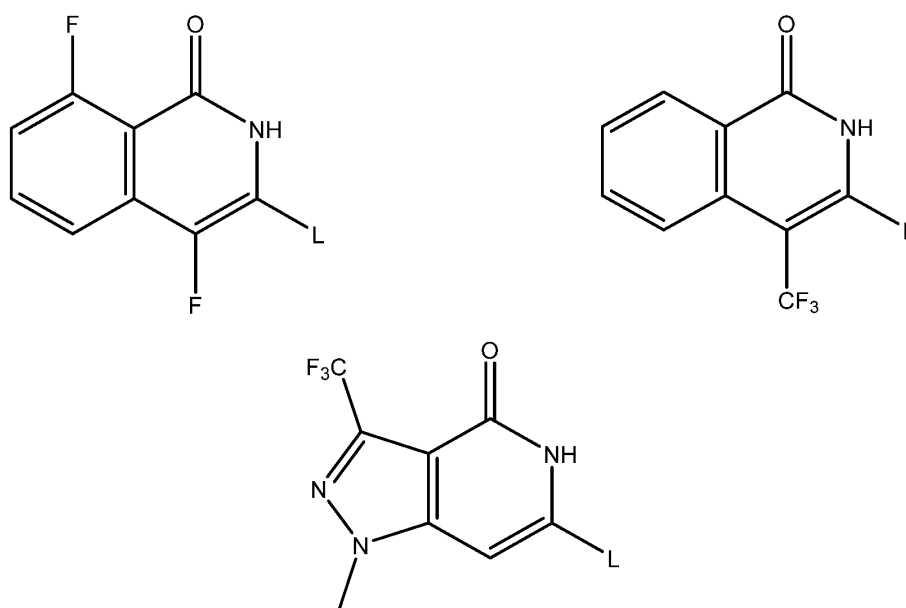




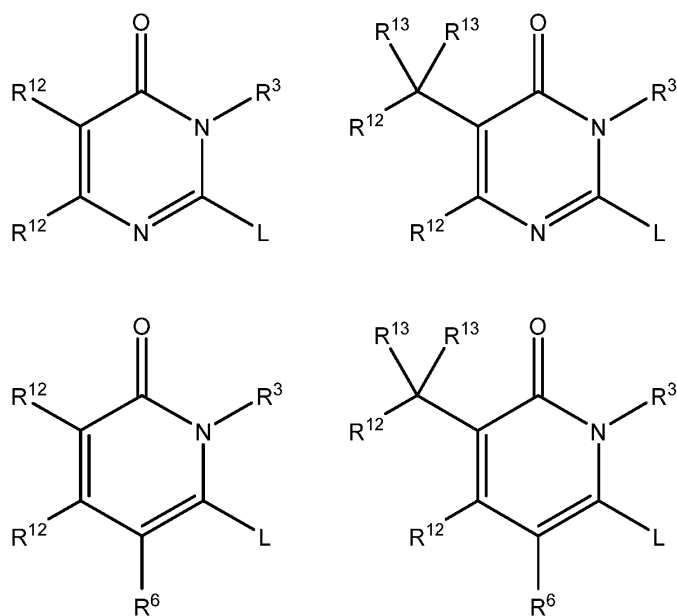


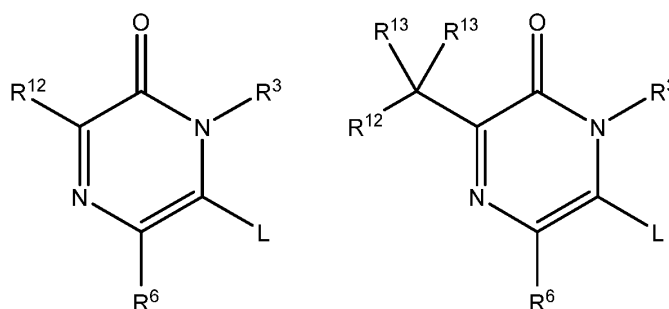






39. A compound according to any of claims 1 to 31, which compound comprises any of the following structures:



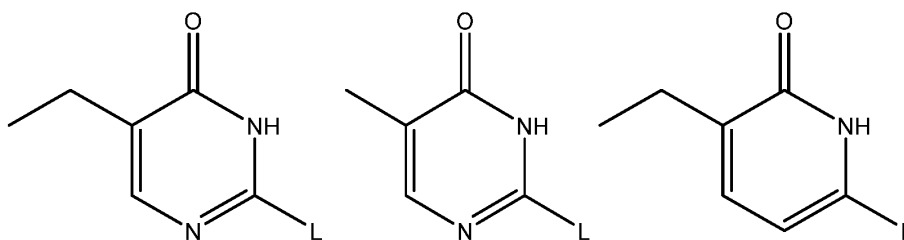


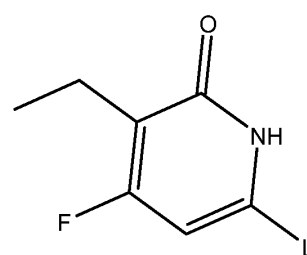
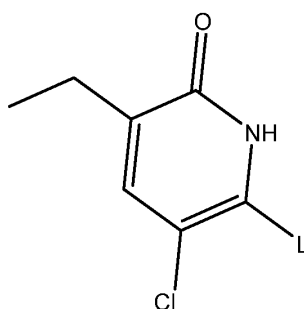
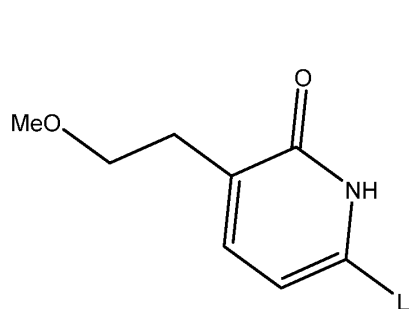
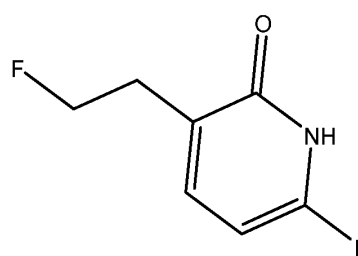
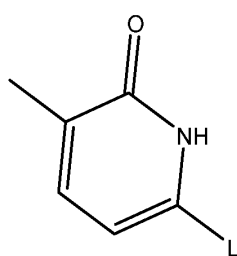
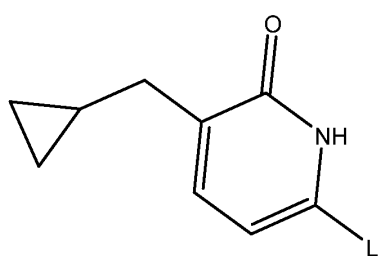
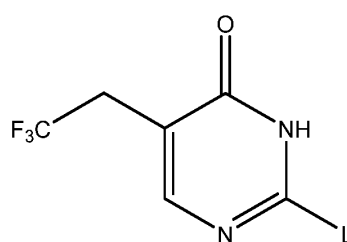
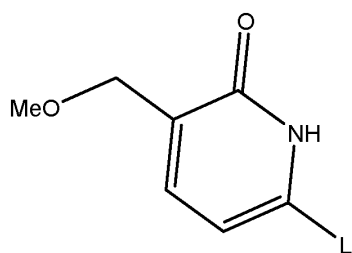
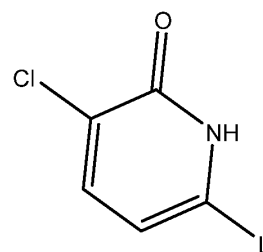
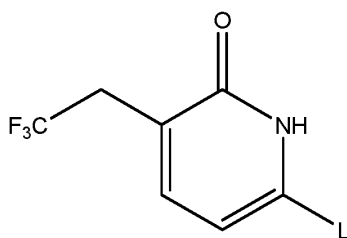
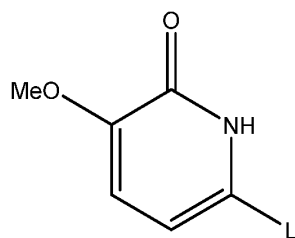
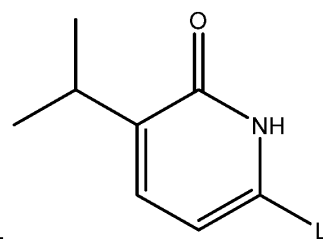
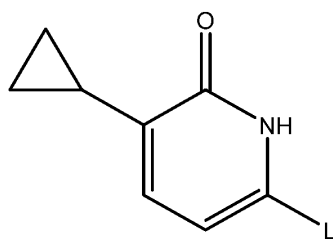
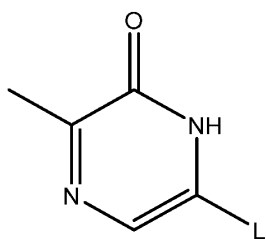
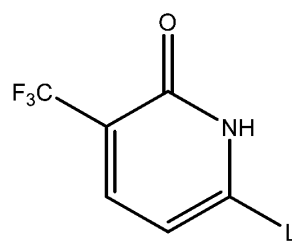
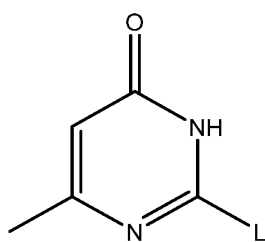
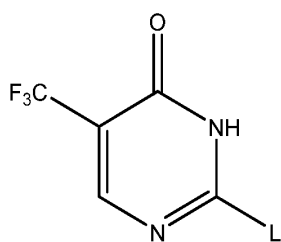
wherein each R^{12} is independently selected from H and a substituted or unsubstituted organic group, preferably a lower (C_1 to C_6) alkyl, alkoxy or haloalkyl group, a substituted or unsubstituted C_3 to C_6 cycloalkyl or heterocyclic group, and a halogen group, wherein at least one R^{12} is not H; and wherein each R^{13} may be the same or different and is independently selected from H and a substituted or unsubstituted organic group; and wherein R^3 , R^6 , and L are as defined in any preceding claim.

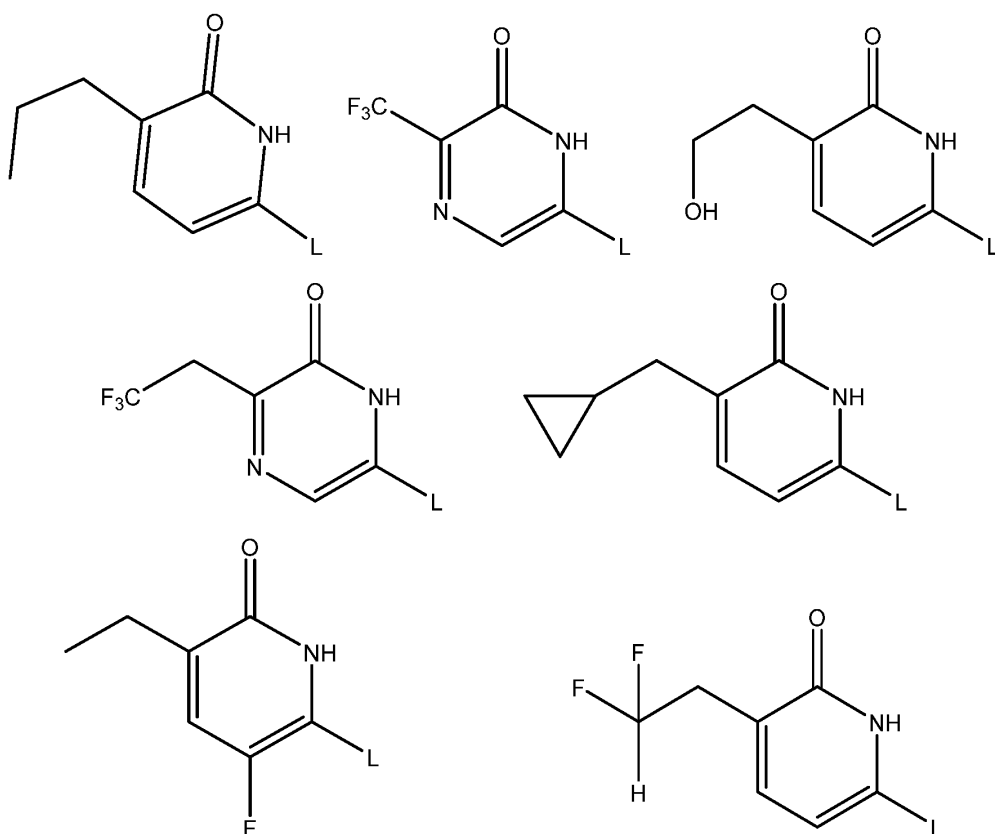
40. A compound according to claim 39, wherein at least one R^{12} is selected from $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-F$, $-Cl$, $-CH_2CF_3$, $-CH_2CH_2F$, $-CH_2CH_2OH$, methoxy, methoxymethyl, methoxyethyl, isopropyl, cyclopropyl or cyclopropylmethyl.

41. A compound according to claim 39 or claim 40, wherein R^{13} is selected from H, F, C_1 to C_3 alkyl or C_1 to C_3 fluoroalkyl.

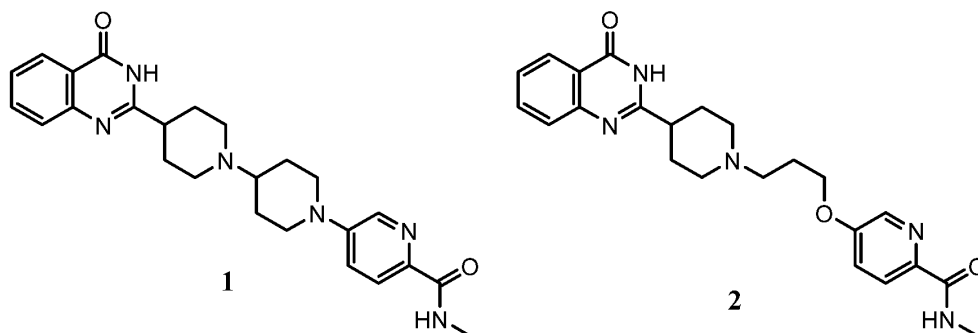
42. A compound according to any of claims 39 to 41, which compound comprises any of the following structures:

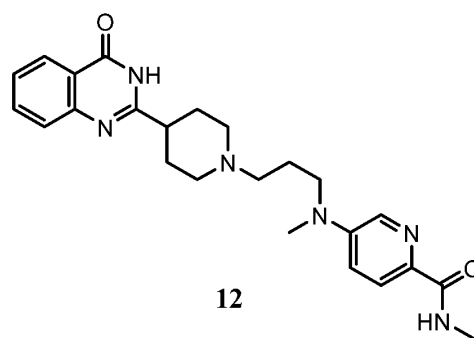
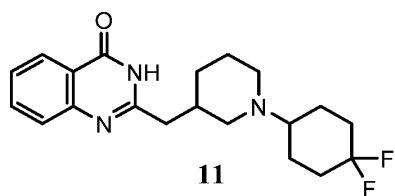
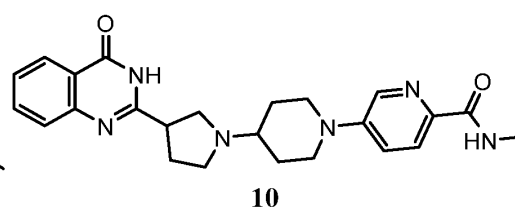
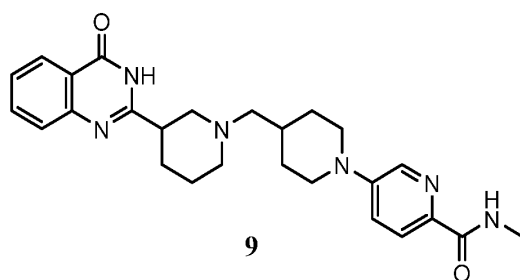
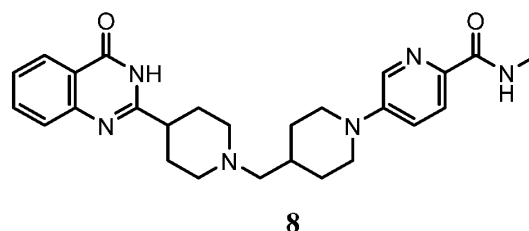
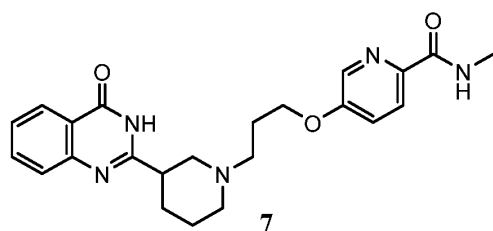
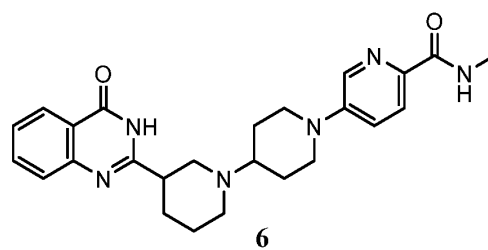
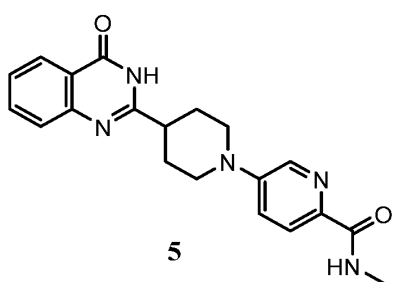
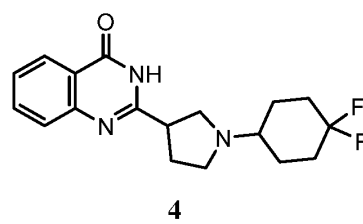
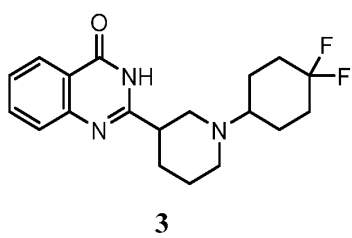


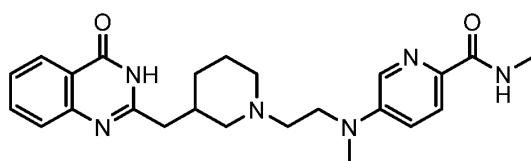




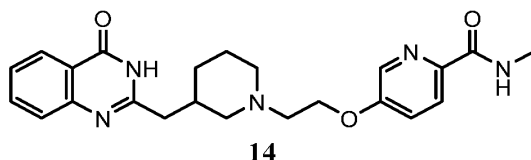
43. A compound according to any of claims 32 to 37 or 39 to 41, wherein R^3 is H.
44. A compound according to any of claims 32 to 37 or 39 to 41, wherein R^6 is selected from H, halogen, C_1 to C_3 alkyl, C_1 to C_3 haloalkyl, C_1 to C_3 alcohol or C_1 to C_3 aminoalkyl.
45. A compound for use in medicine according to any preceding claim, which compound comprises a formula selected from one of the following:



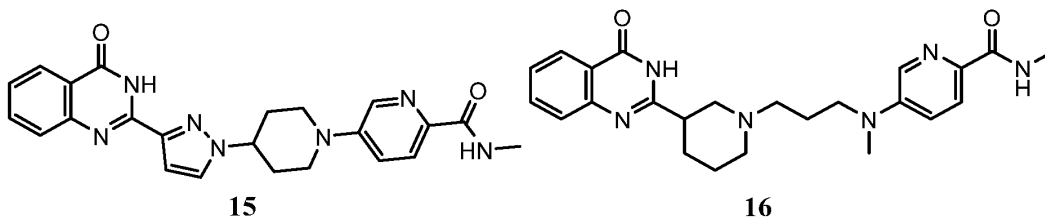




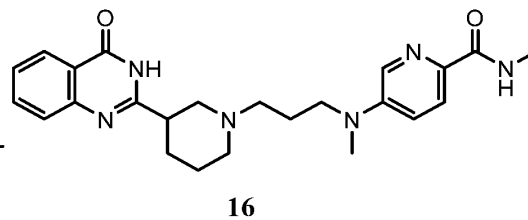
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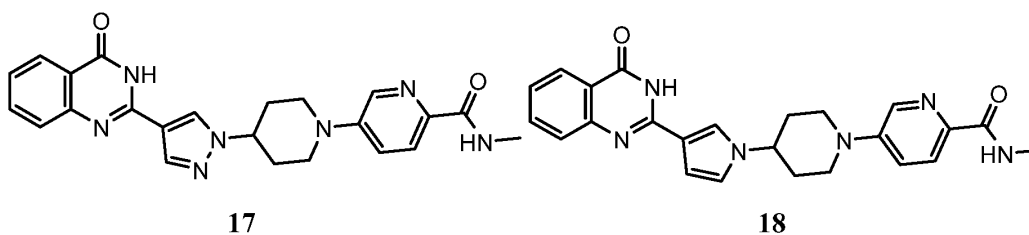
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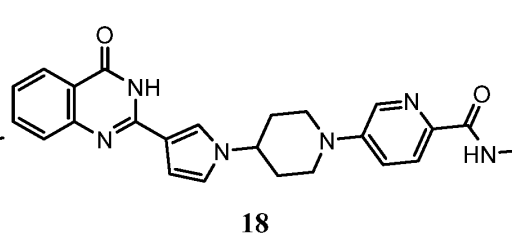
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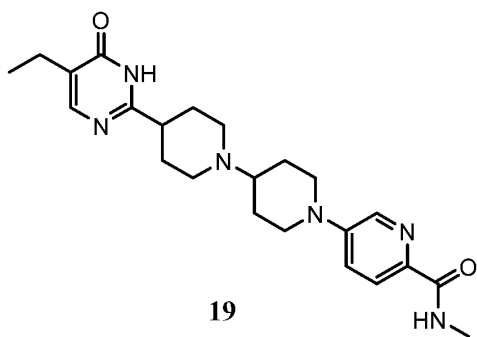
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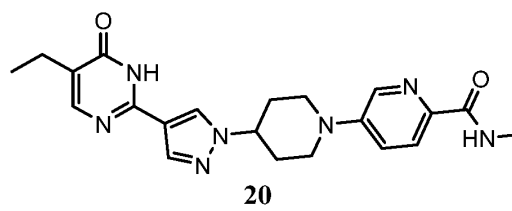
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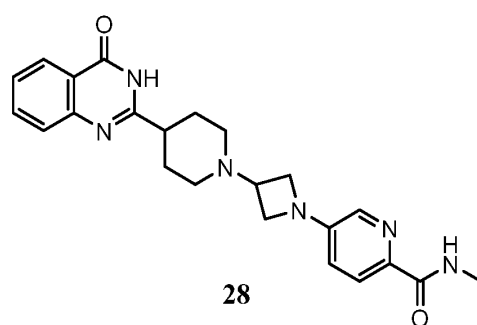
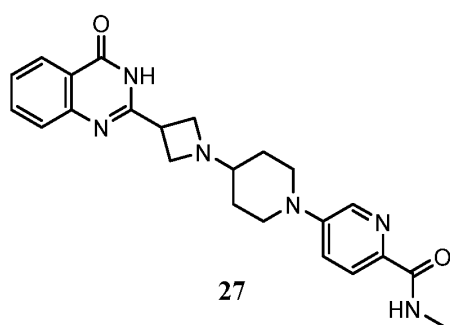
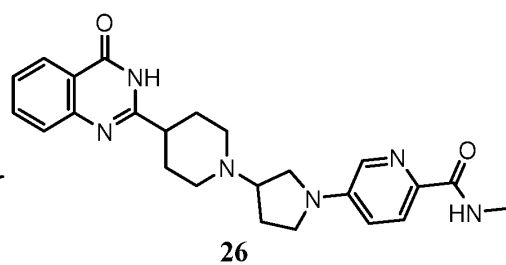
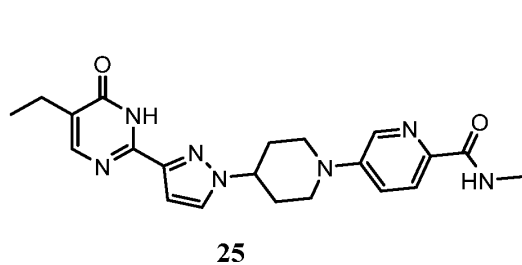
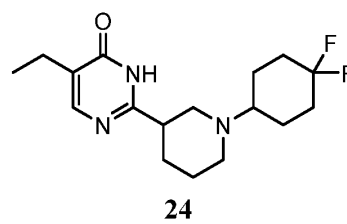
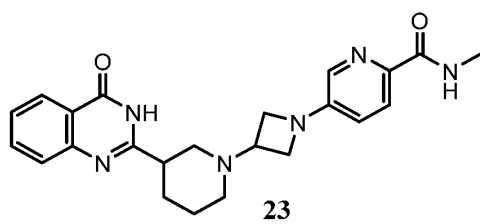
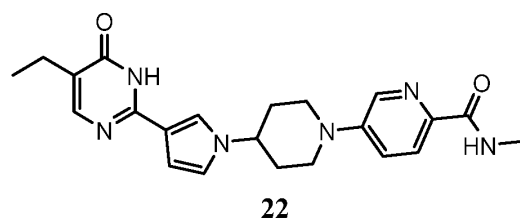
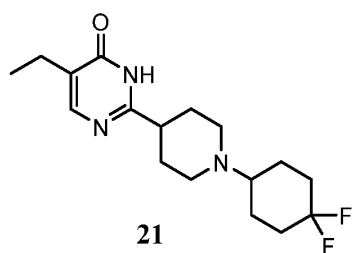
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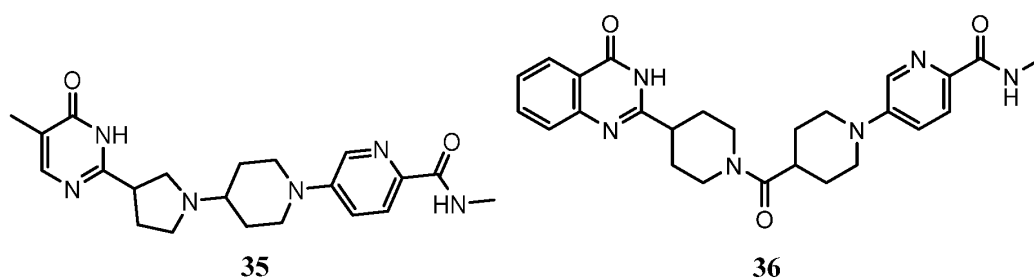
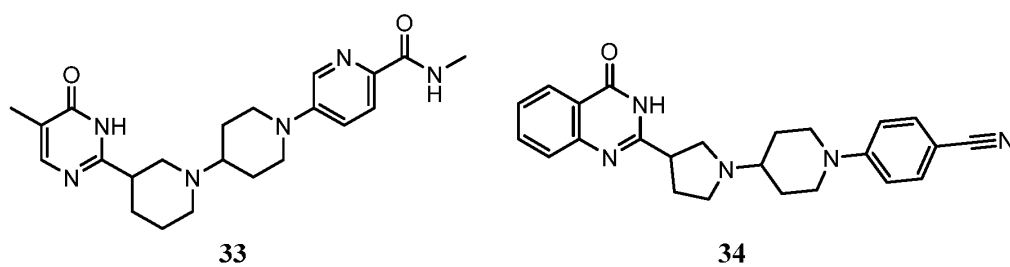
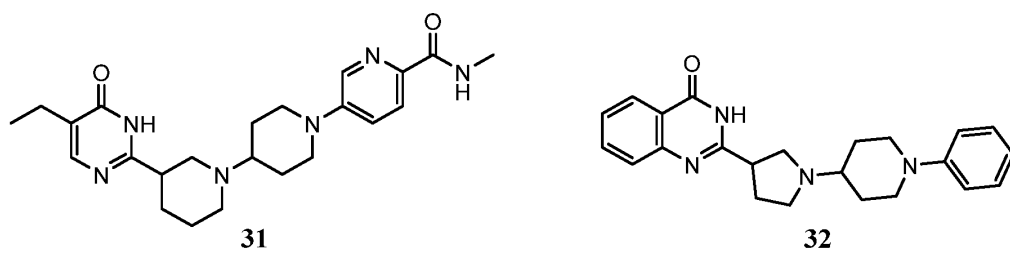
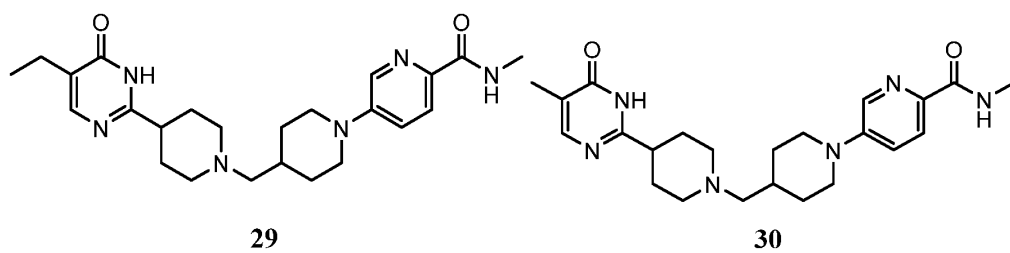


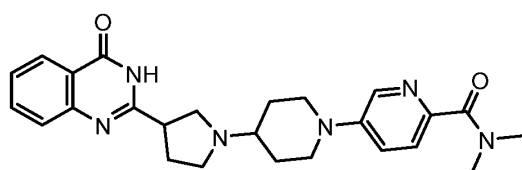
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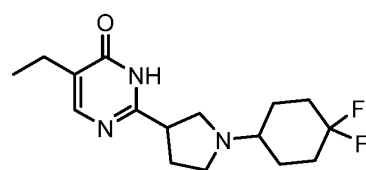
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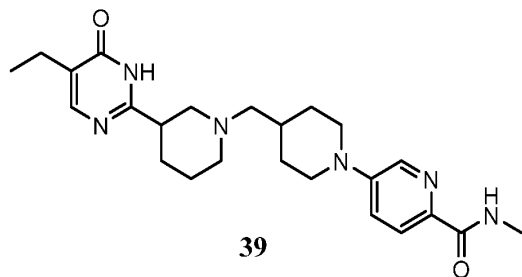




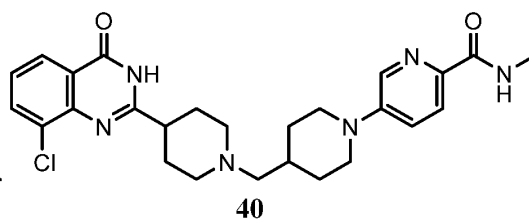
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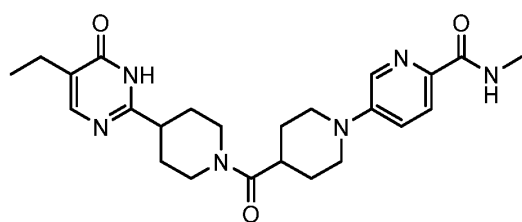
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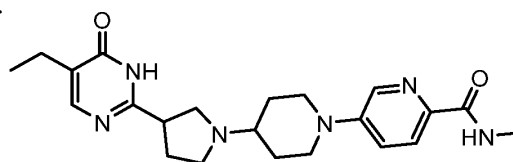
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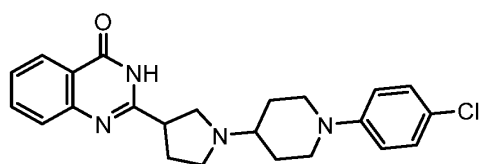
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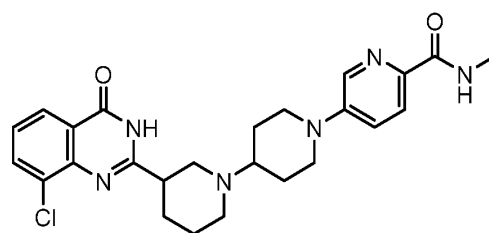
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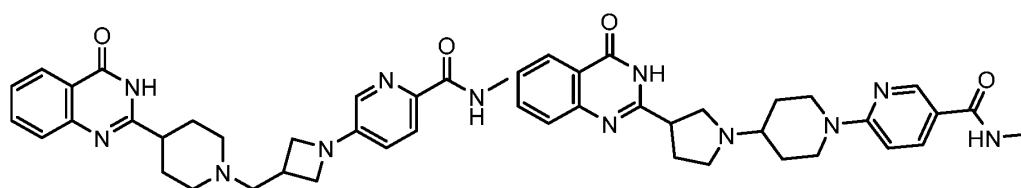
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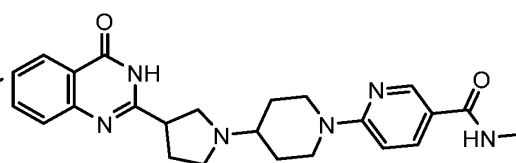
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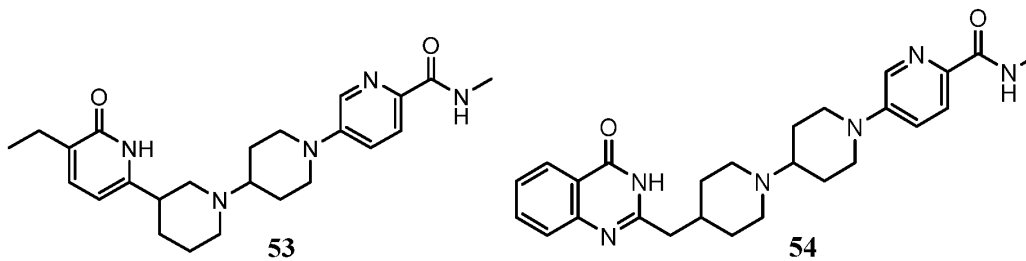
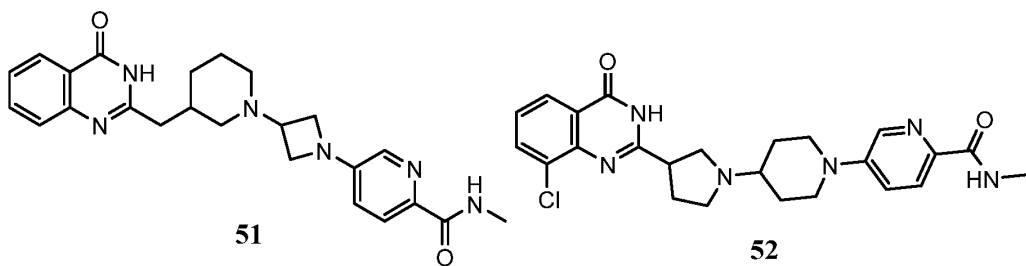
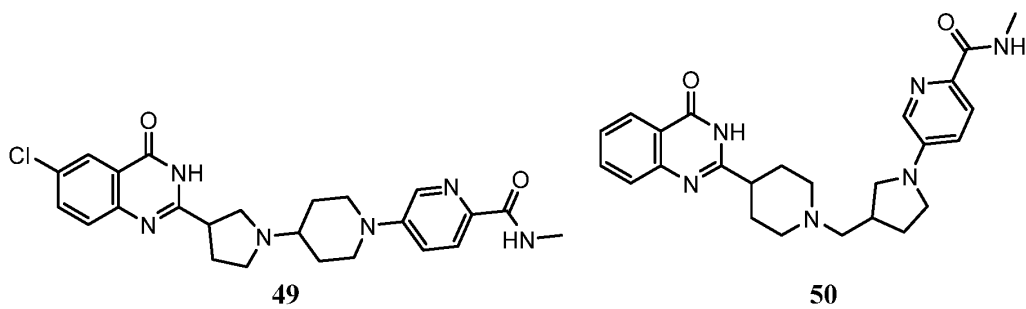
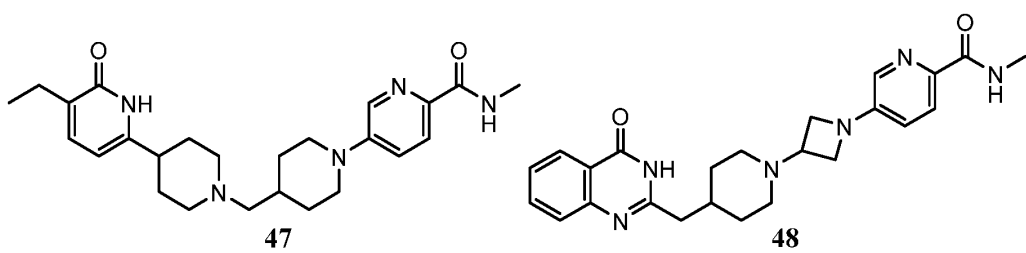
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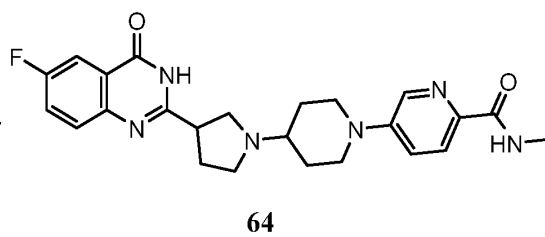
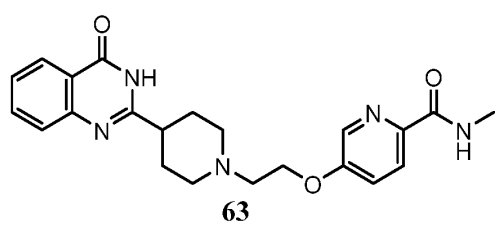
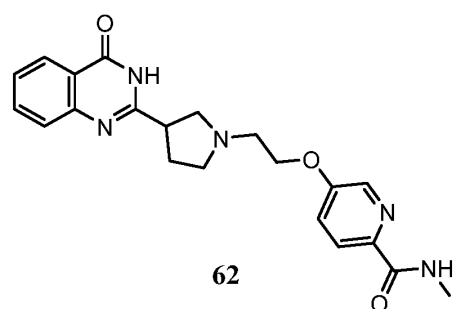
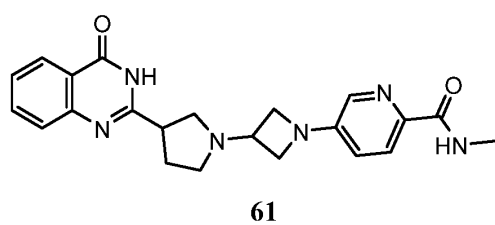
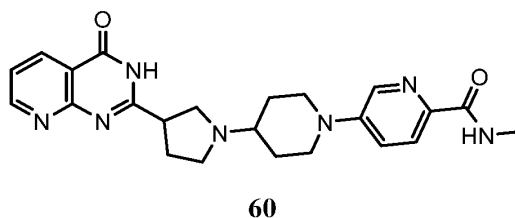
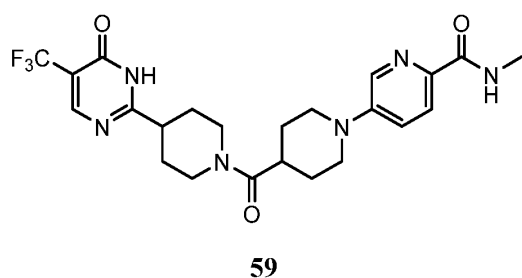
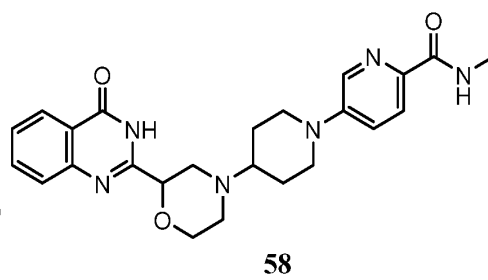
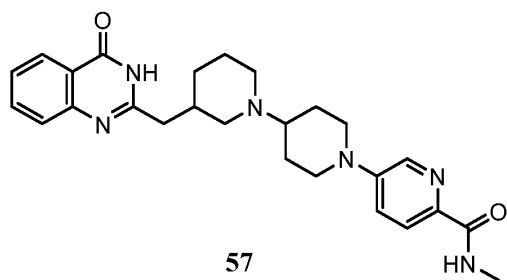
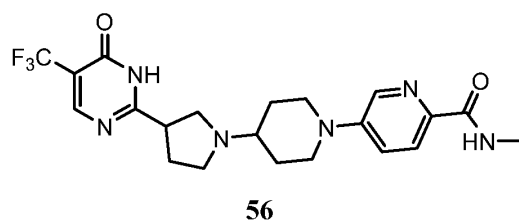
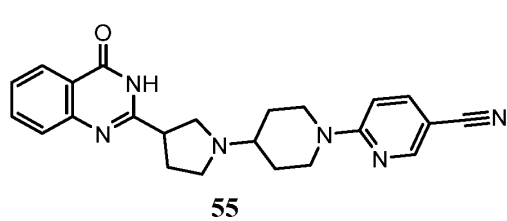


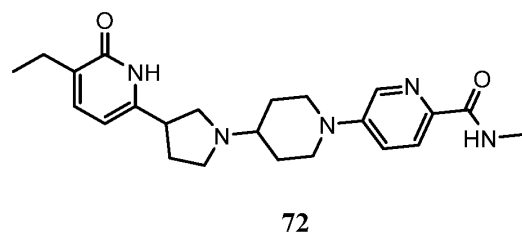
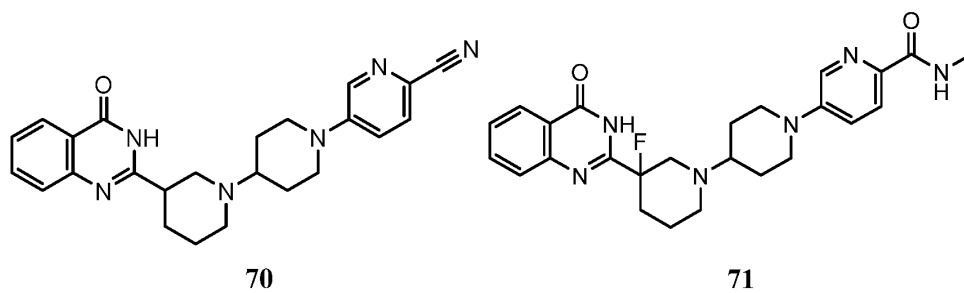
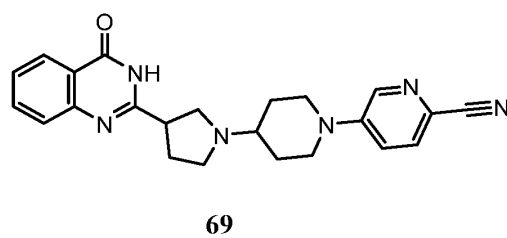
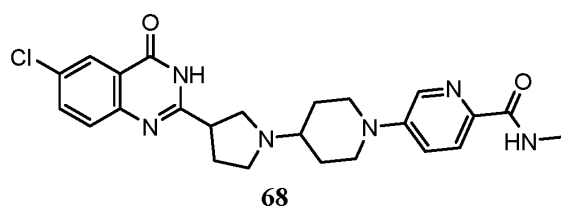
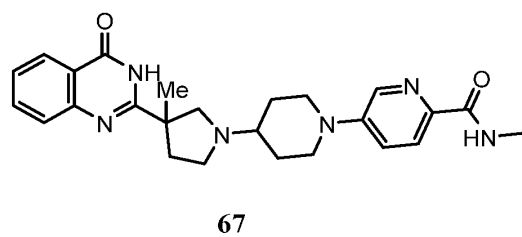
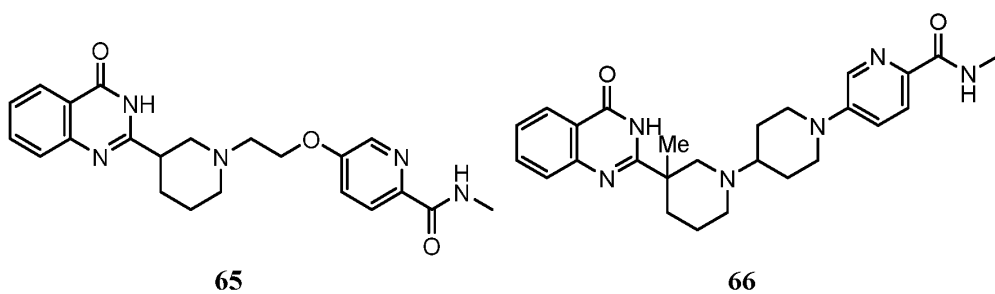
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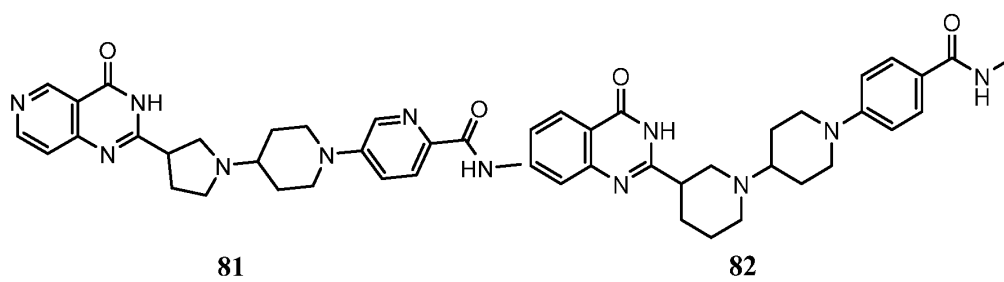
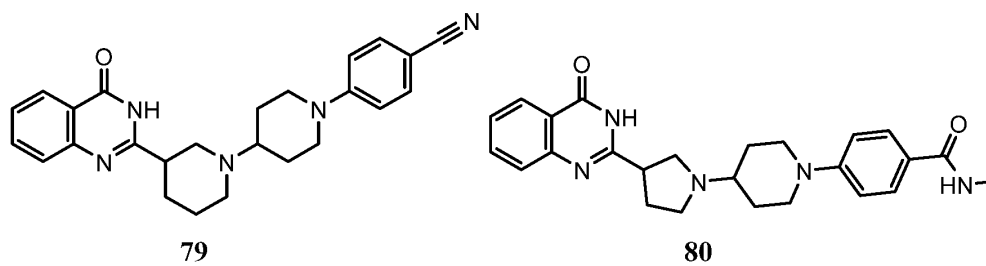
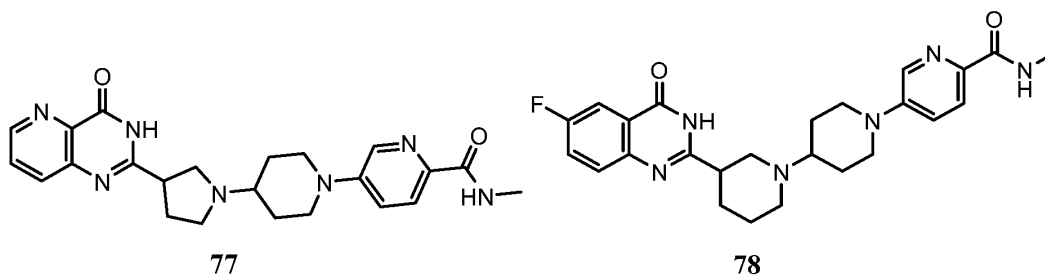
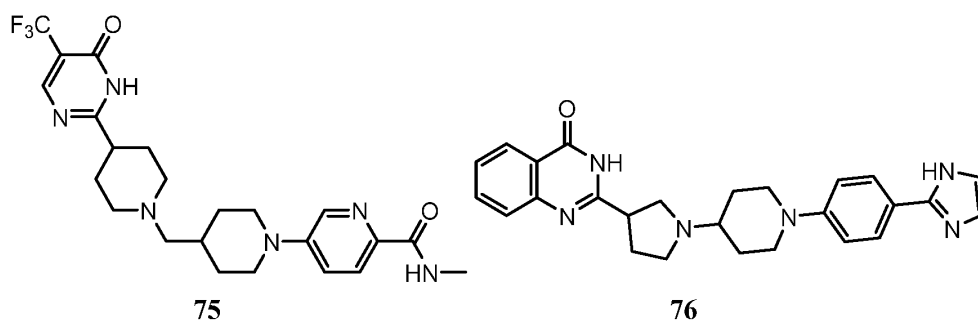
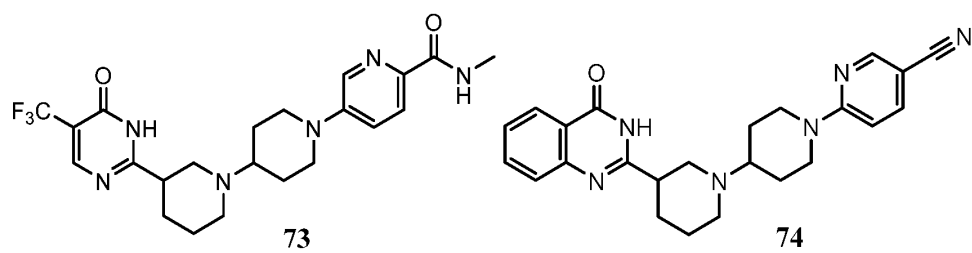


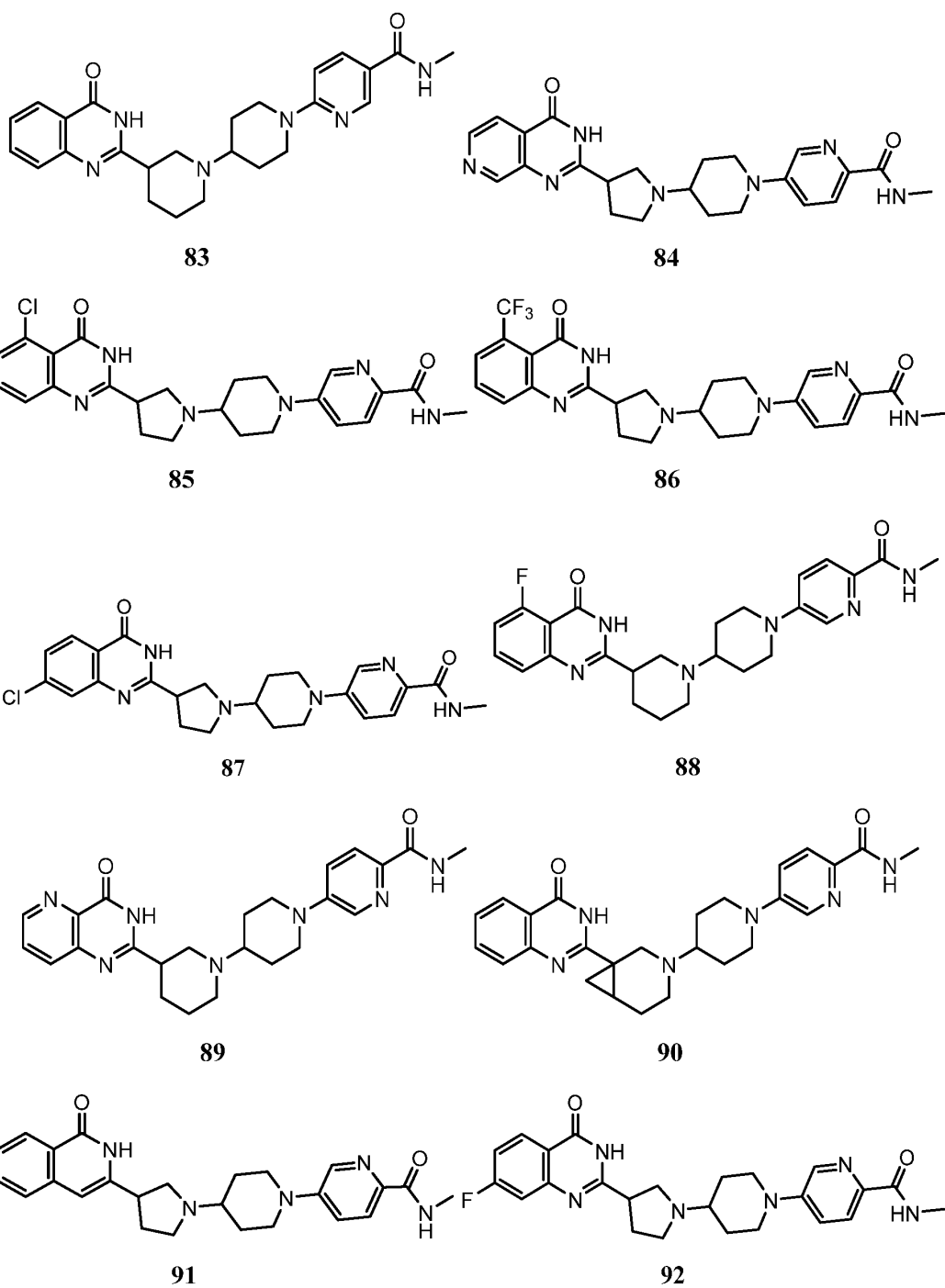
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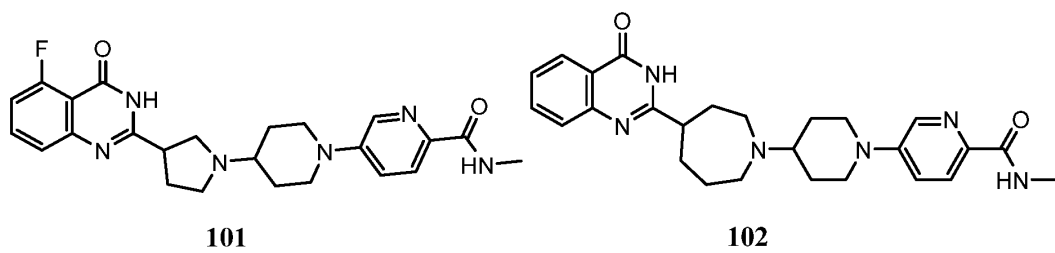
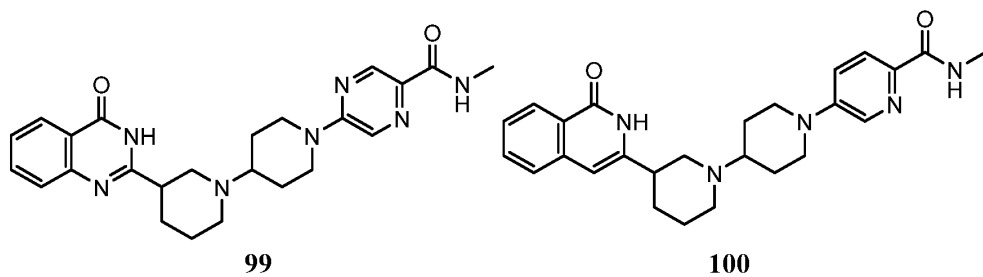
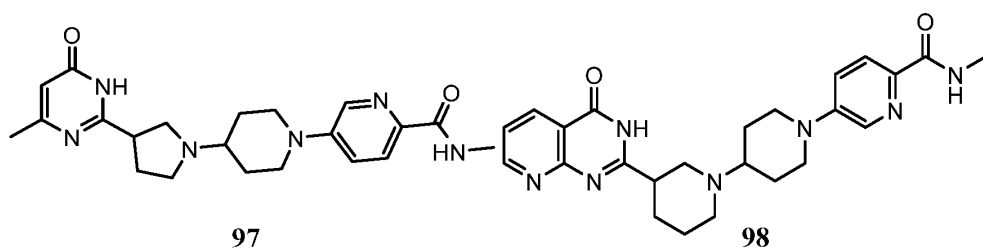
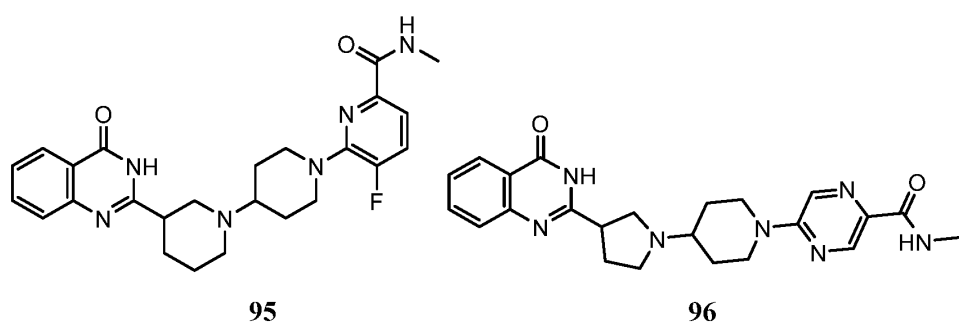
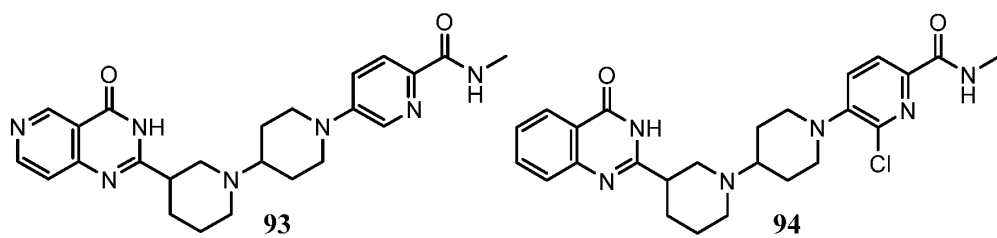


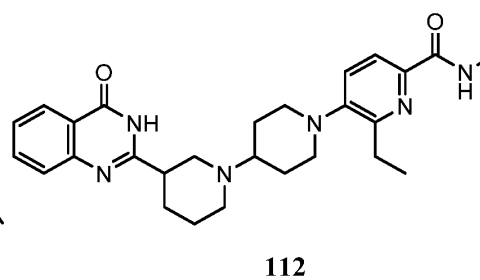
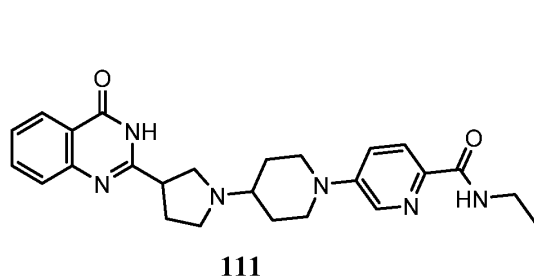
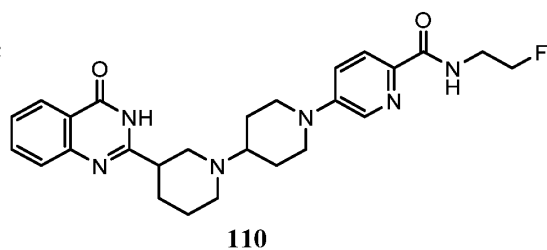
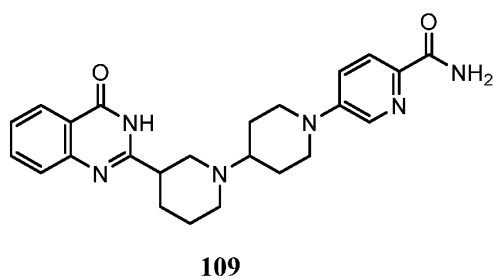
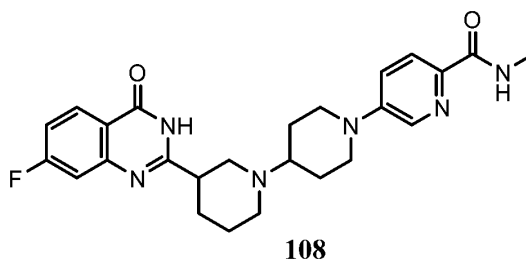
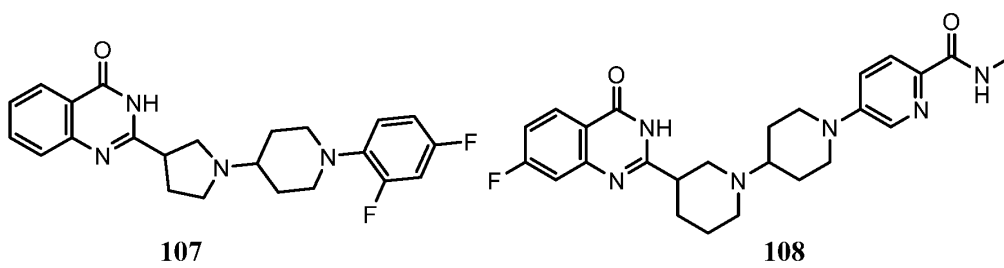
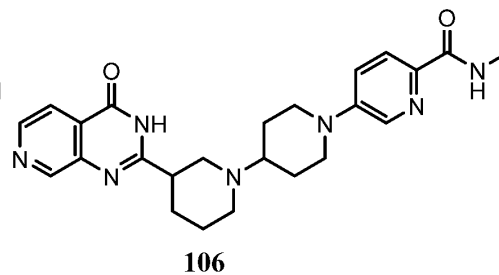
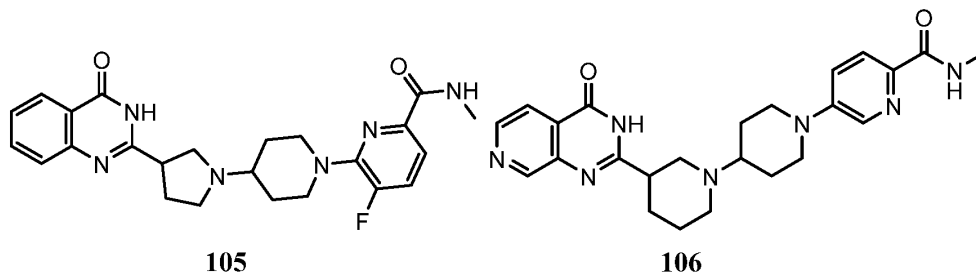
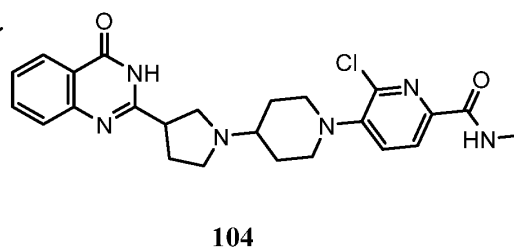
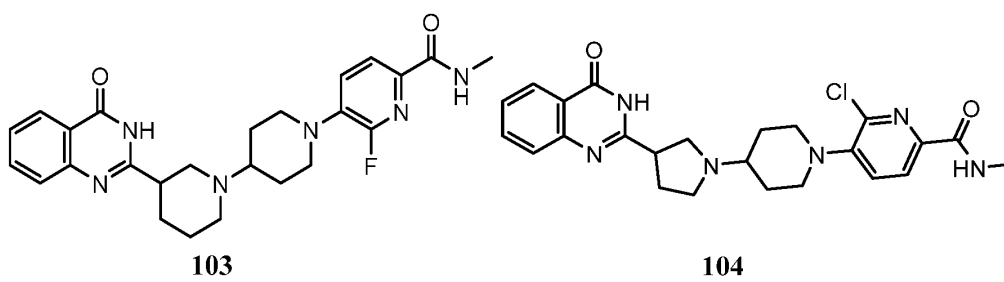


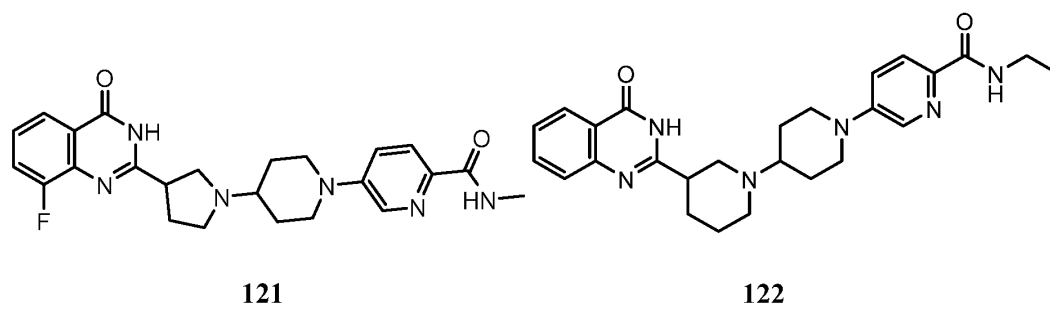
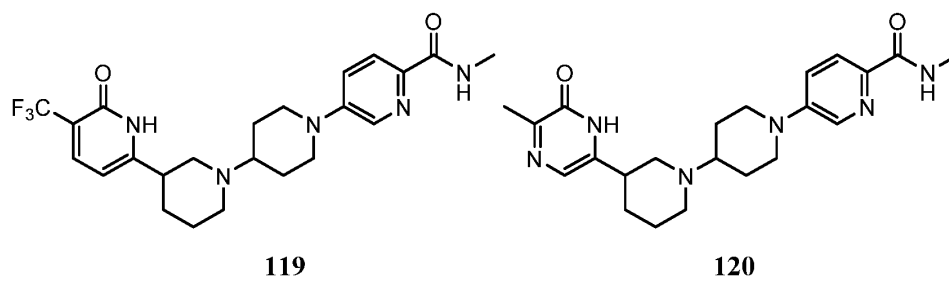
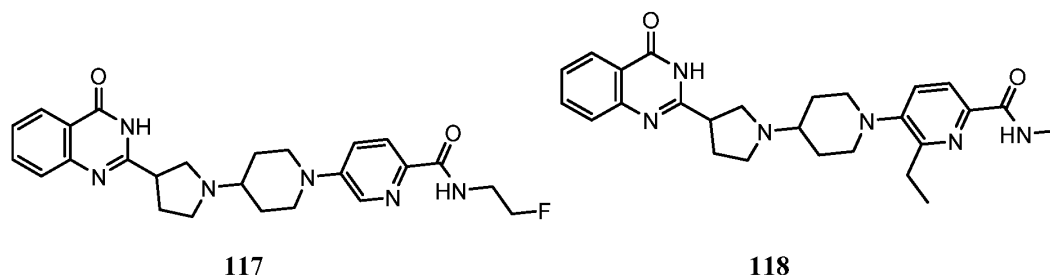
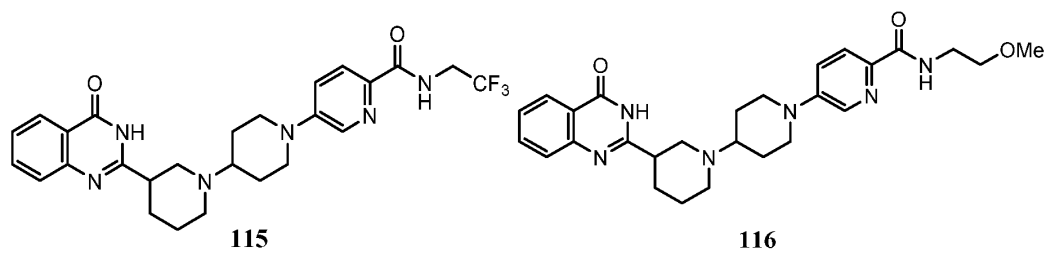
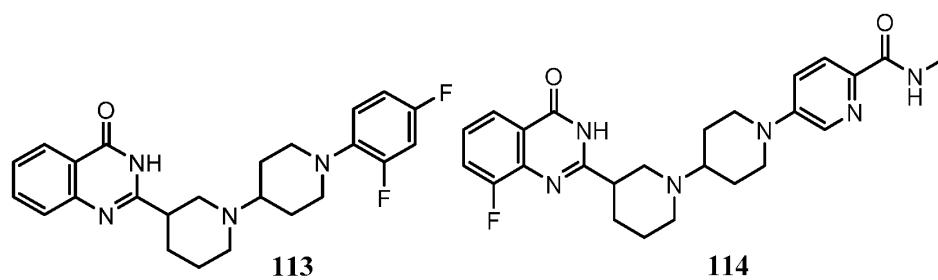


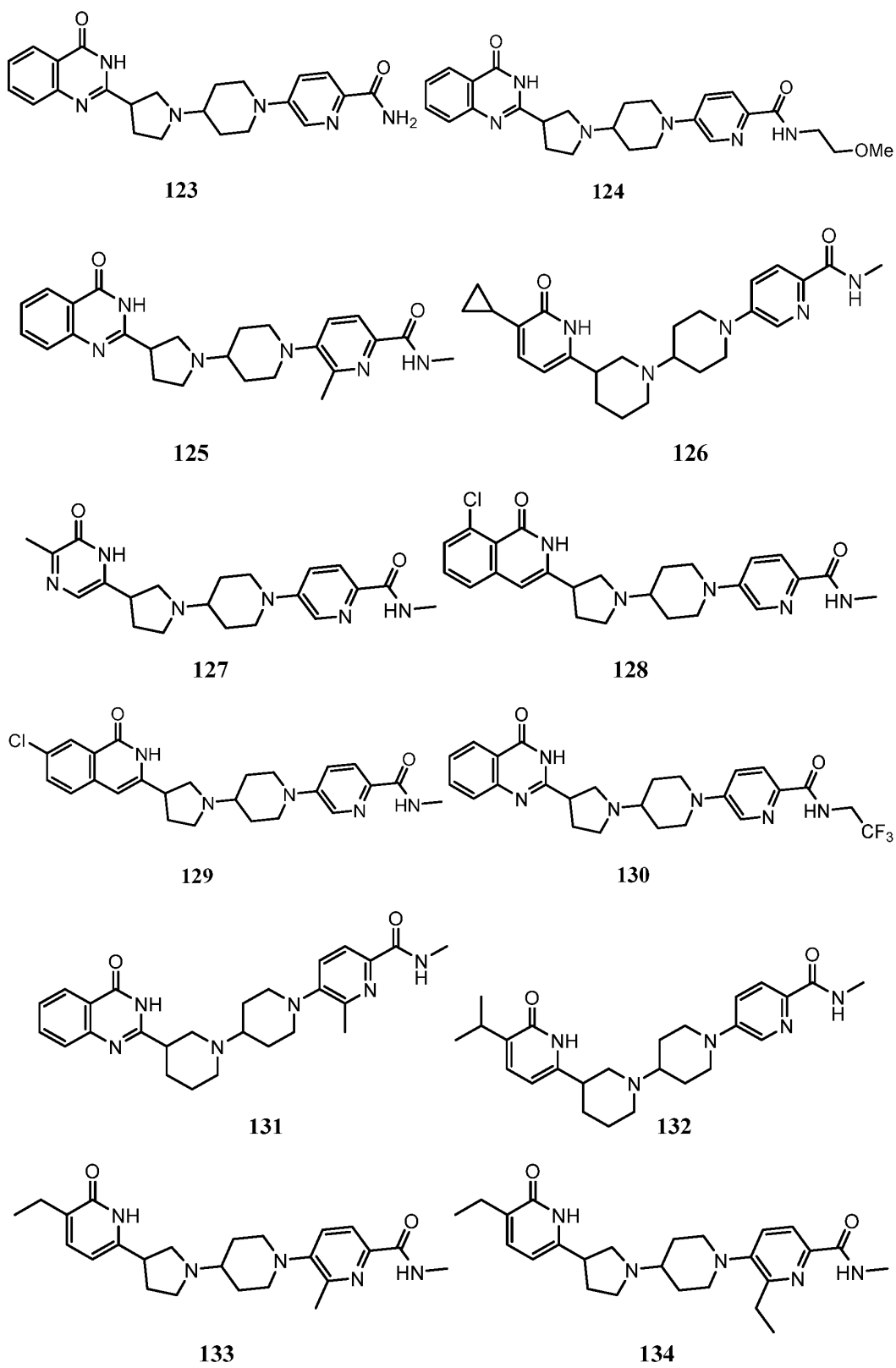


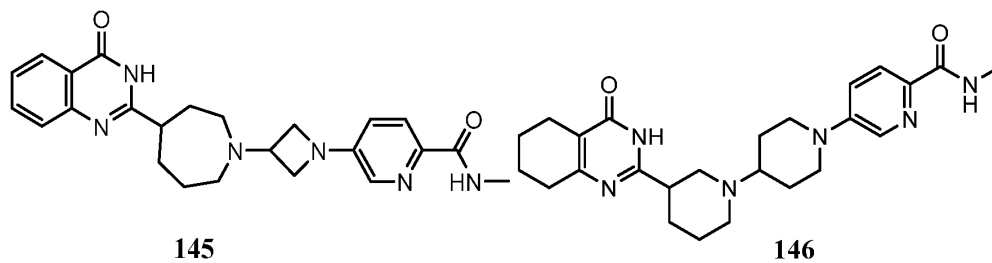
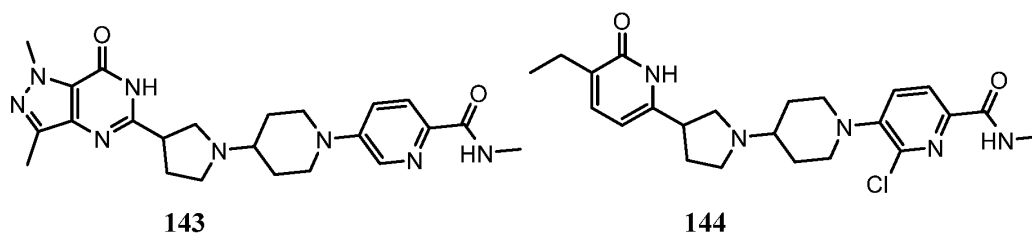
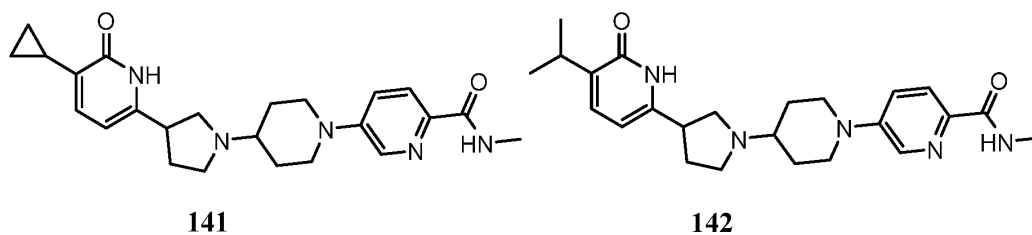
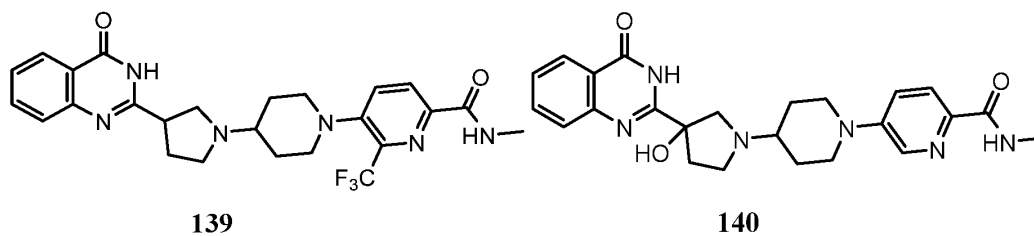
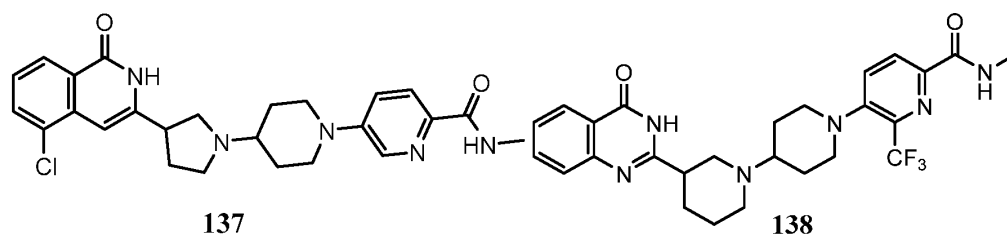
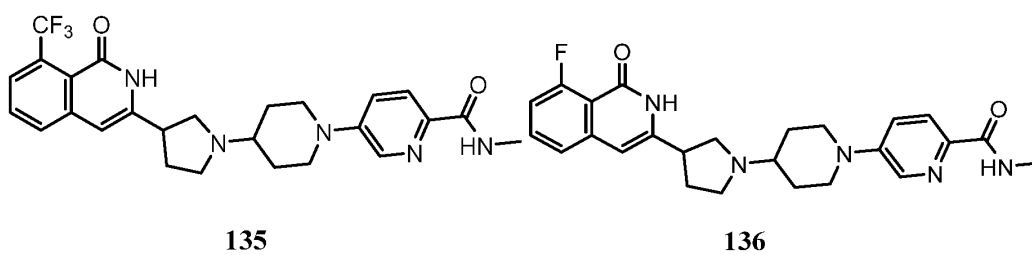


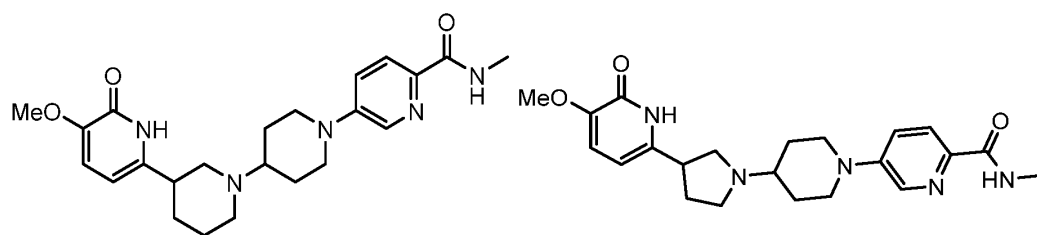






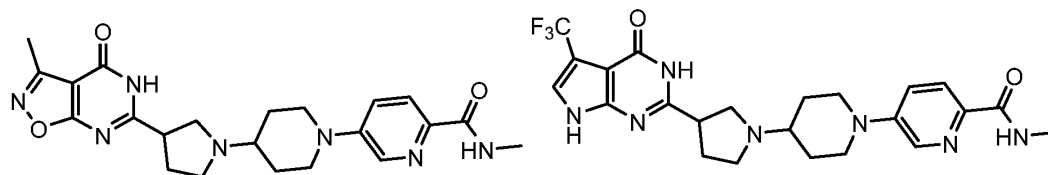






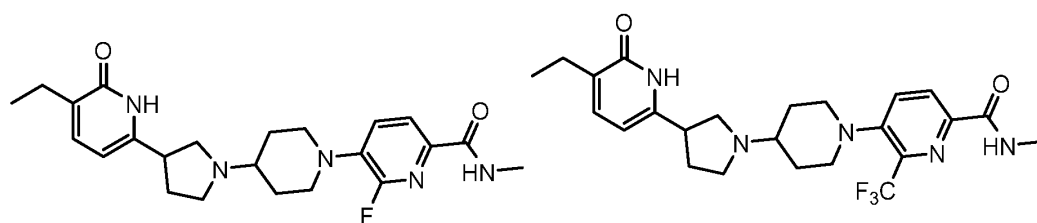
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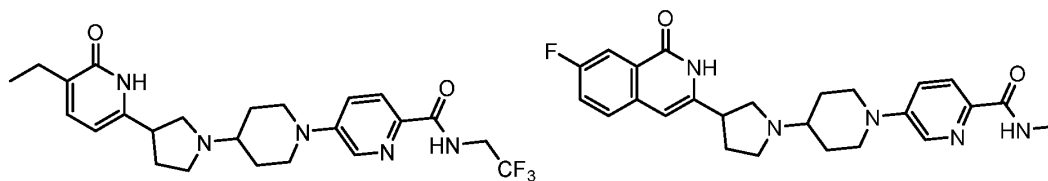
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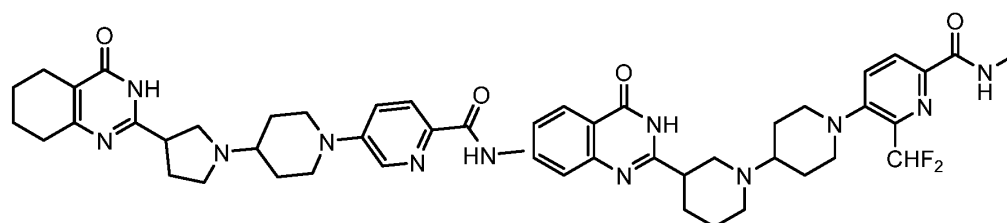
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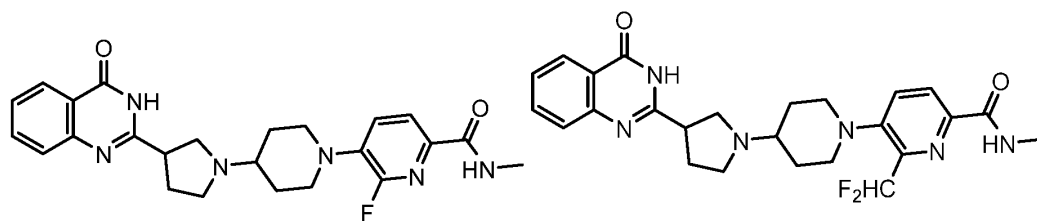
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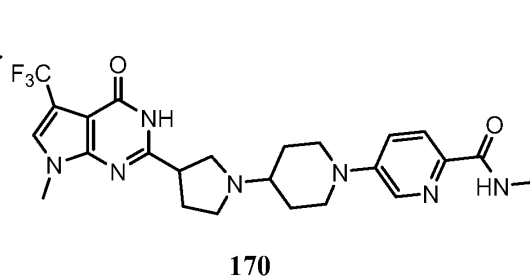
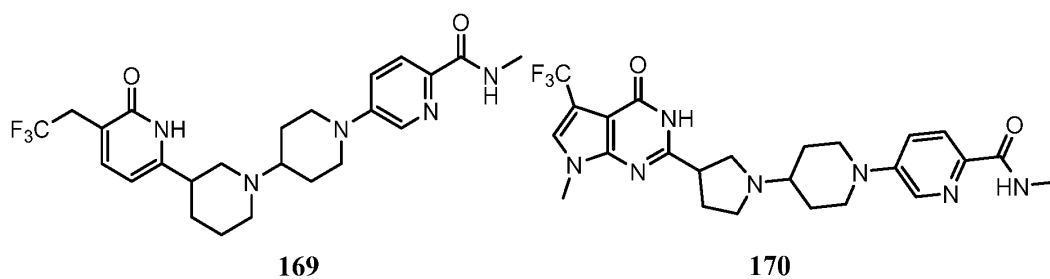
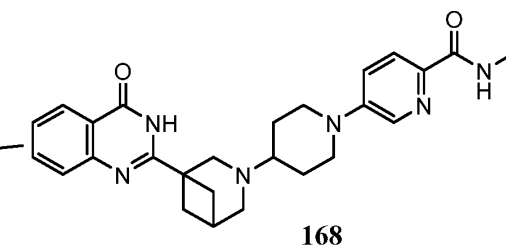
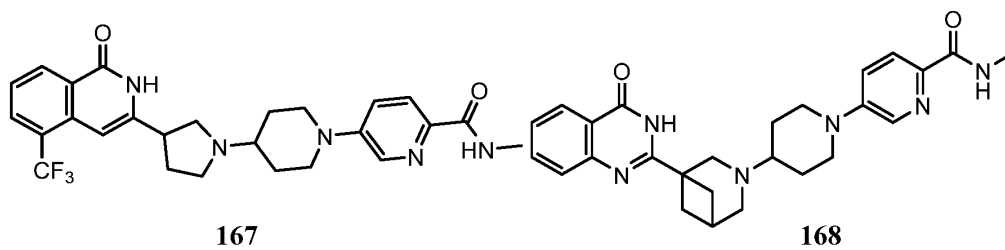
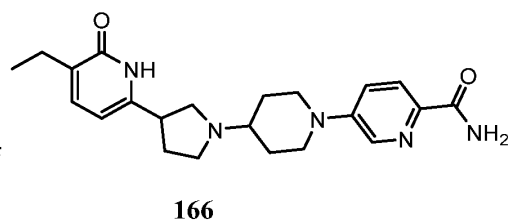
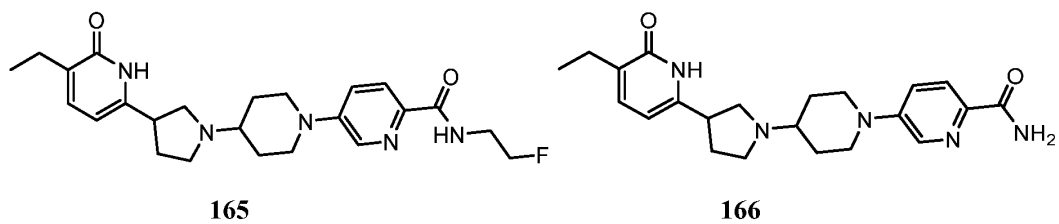
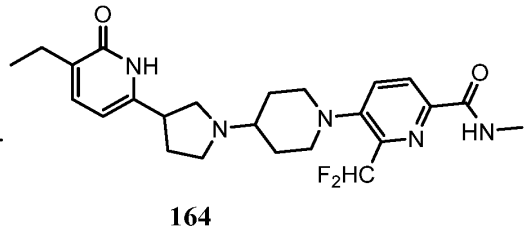
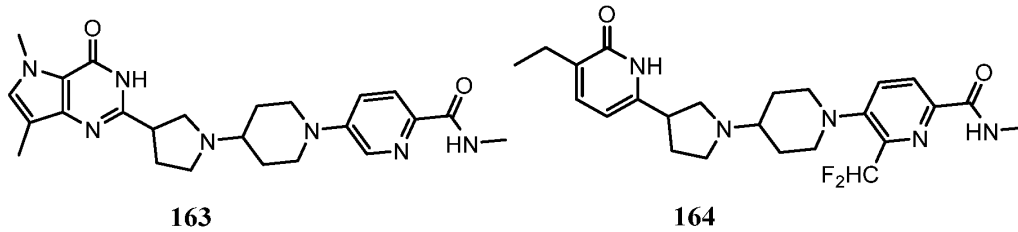
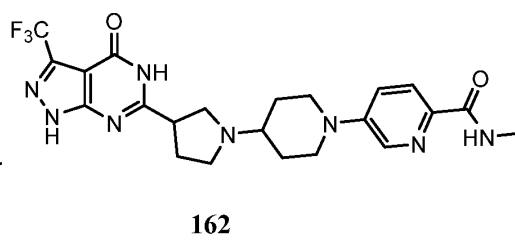
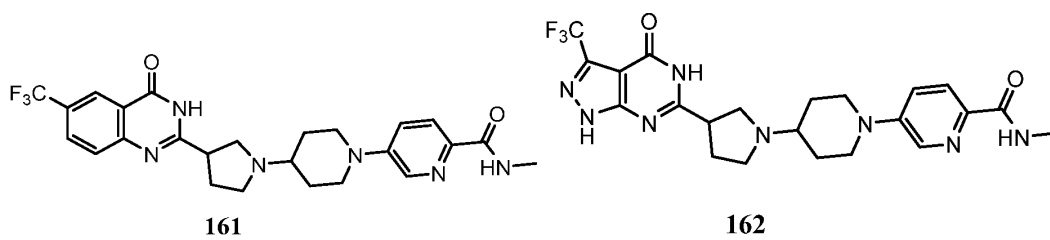
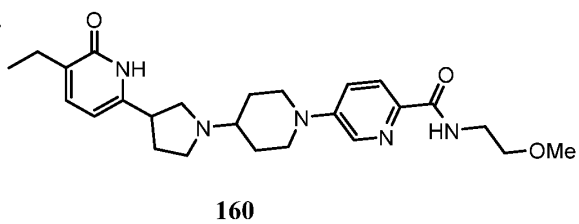
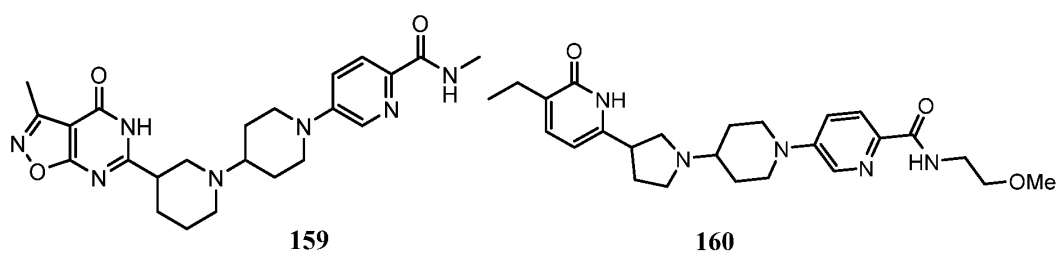
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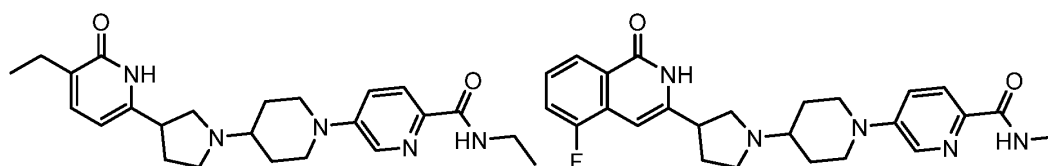
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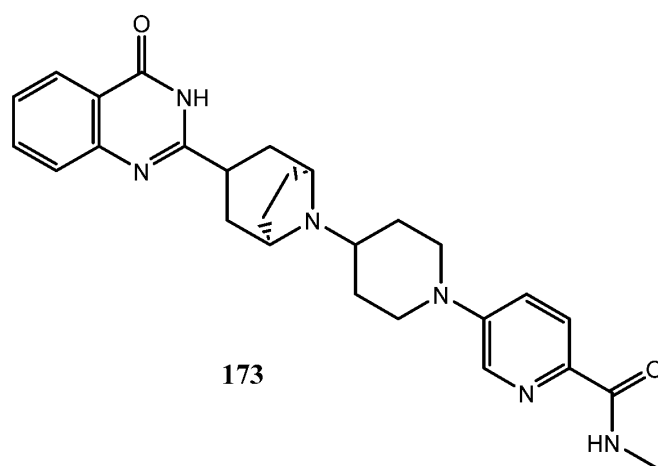
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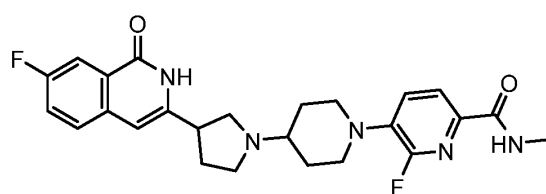


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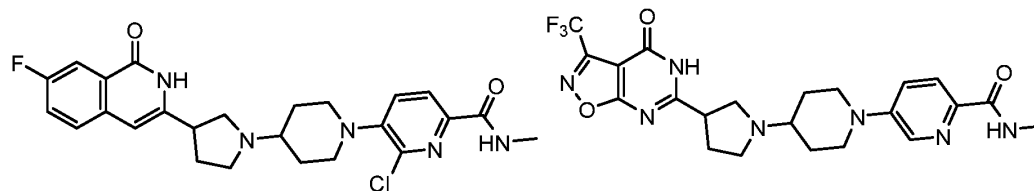
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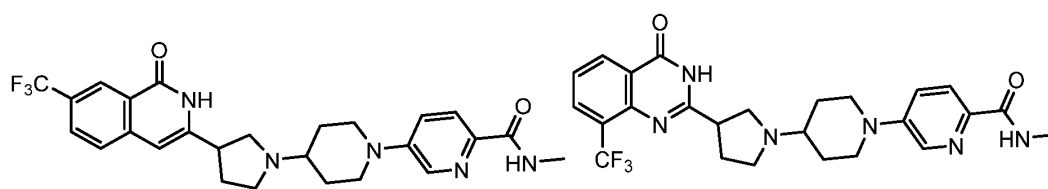


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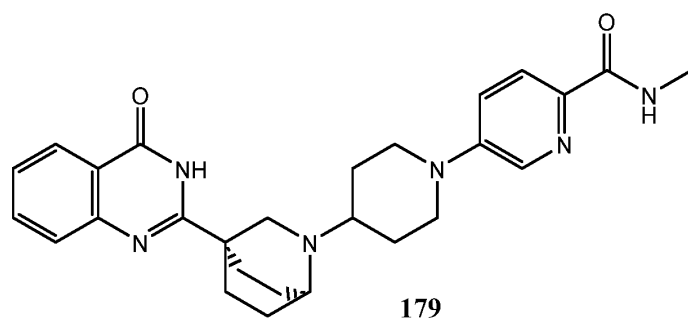
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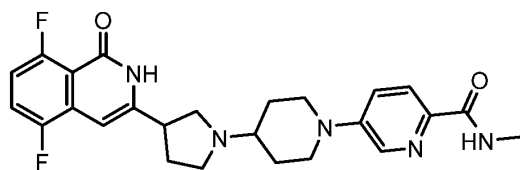


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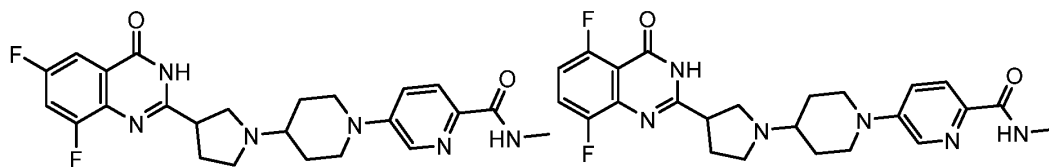
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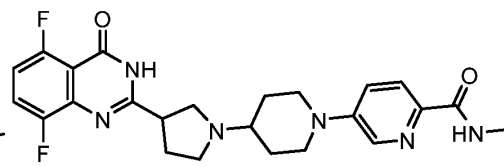
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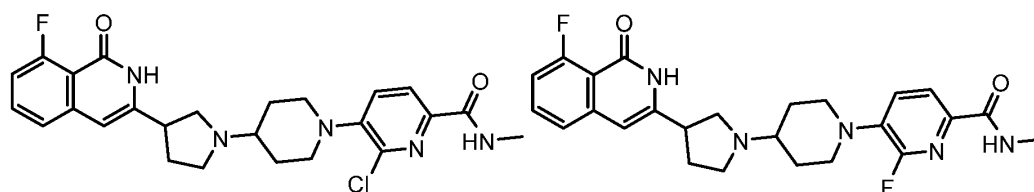
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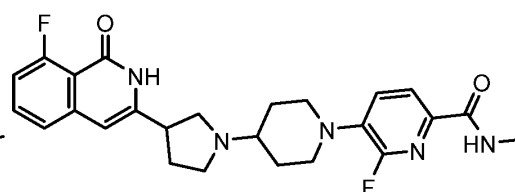
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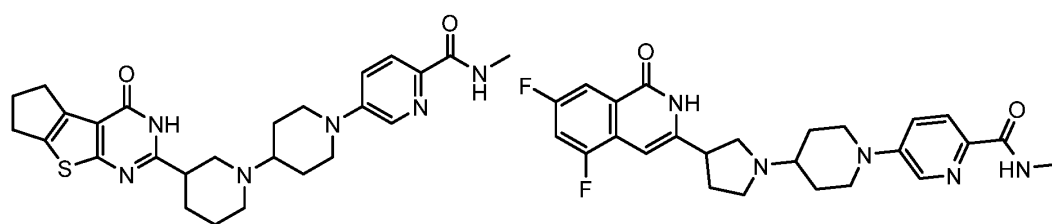
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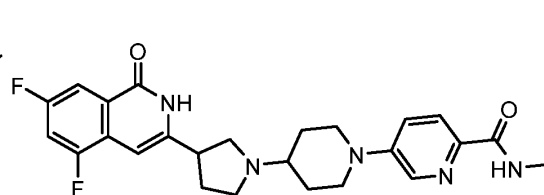
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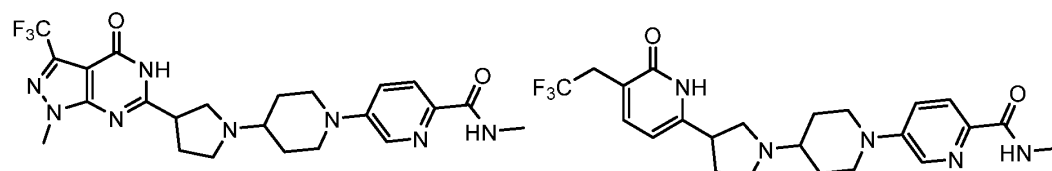
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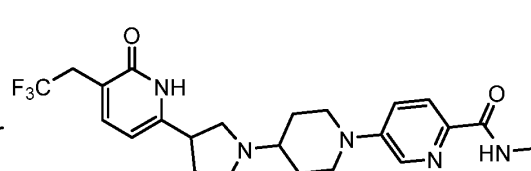
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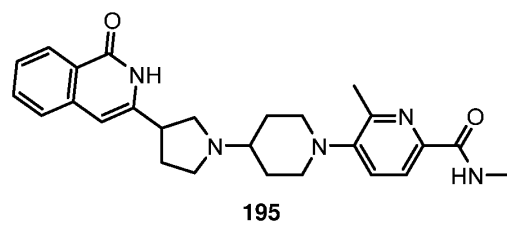
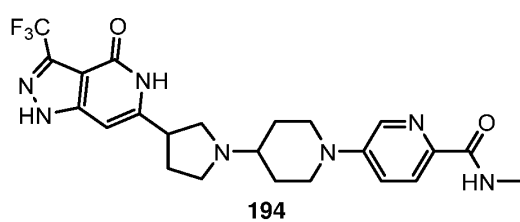
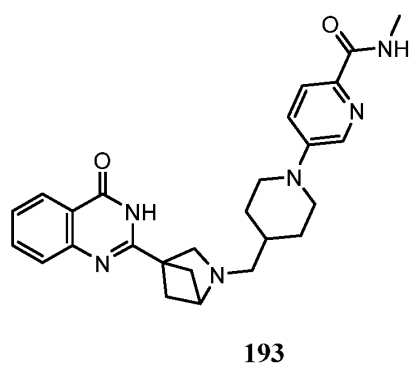
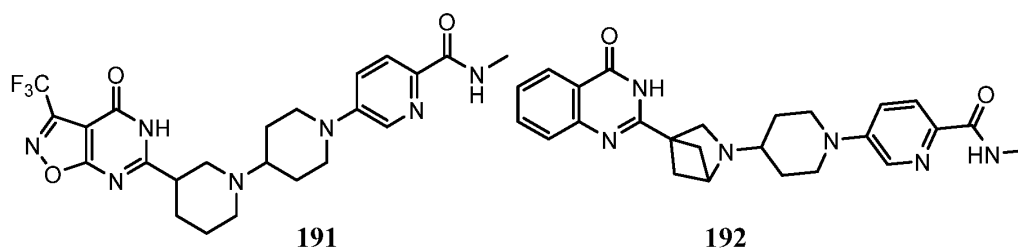
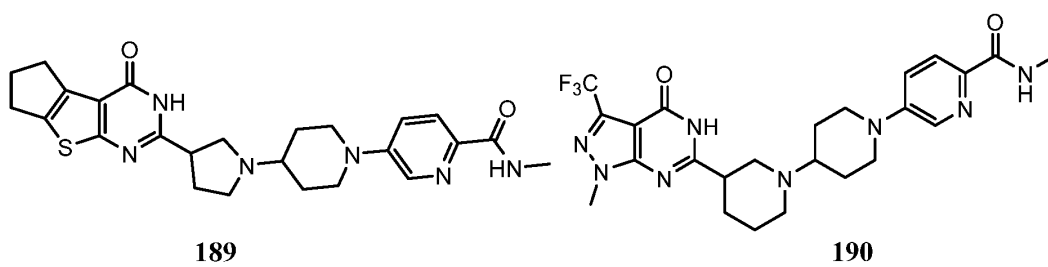
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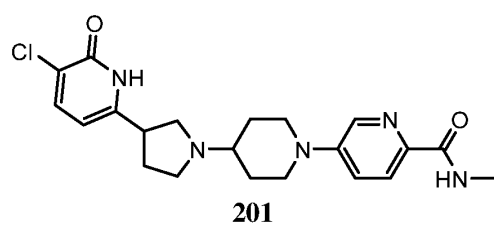
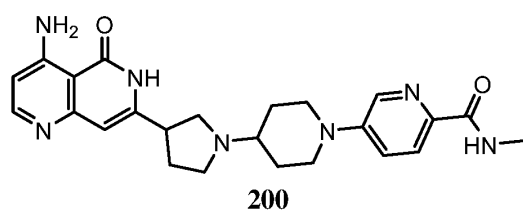
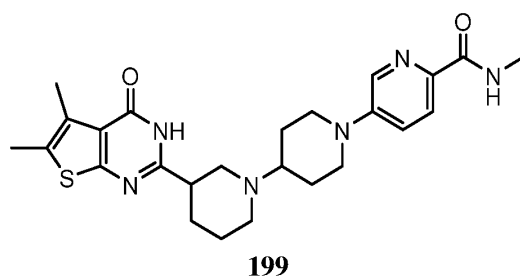
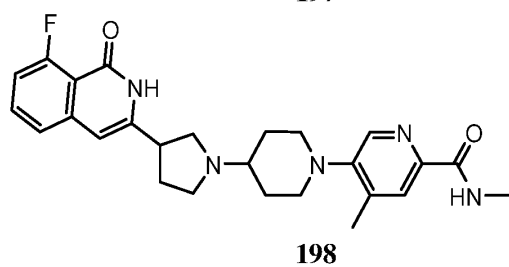
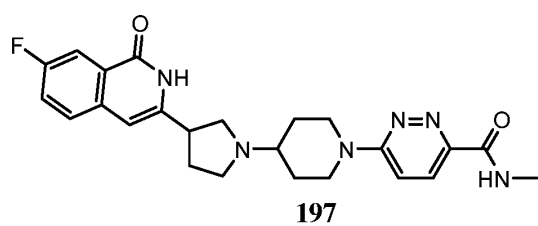
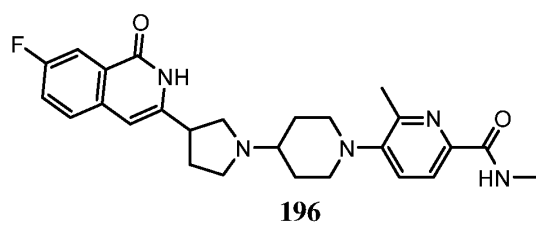


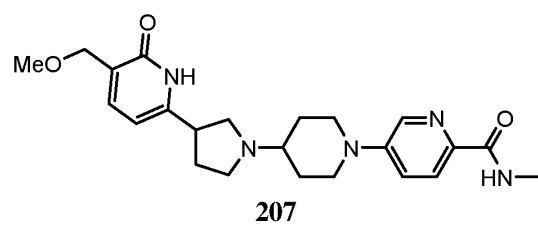
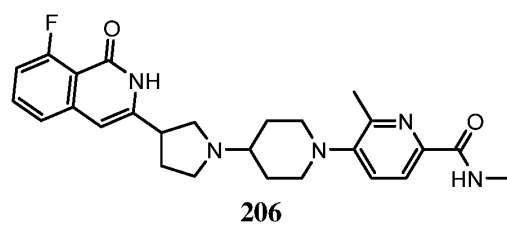
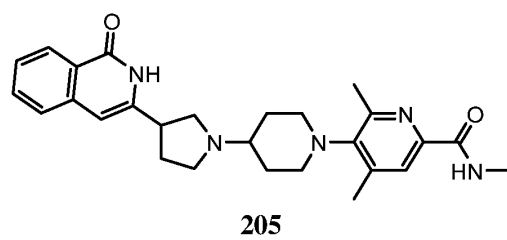
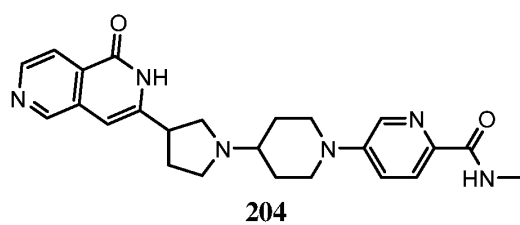
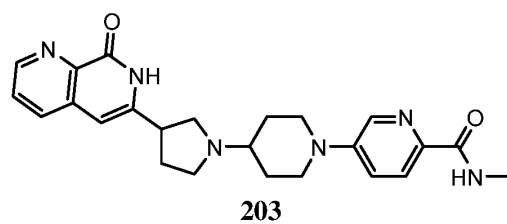
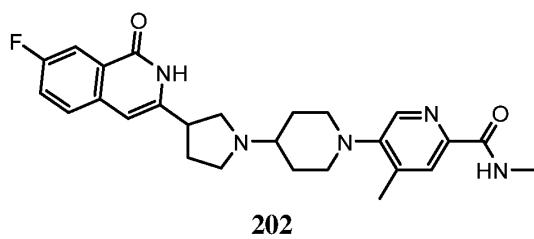
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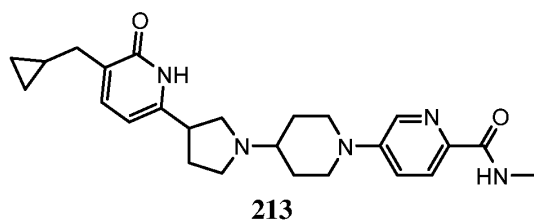
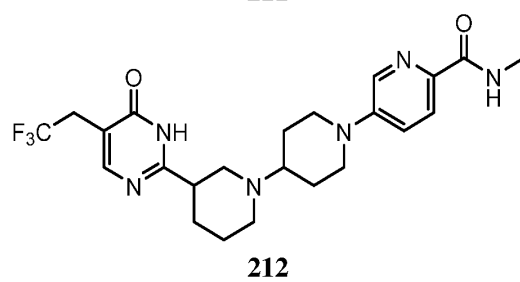
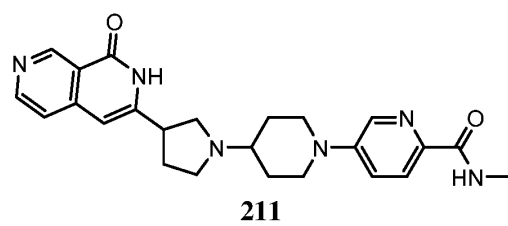
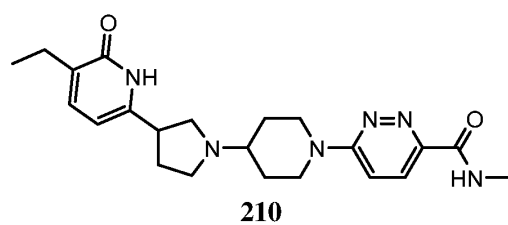
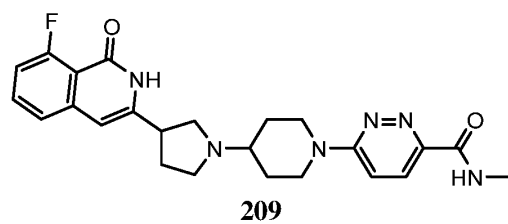
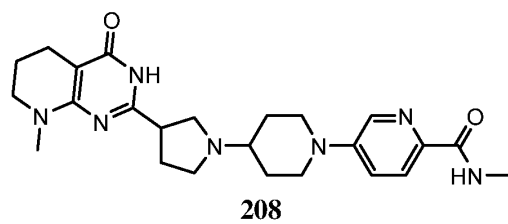


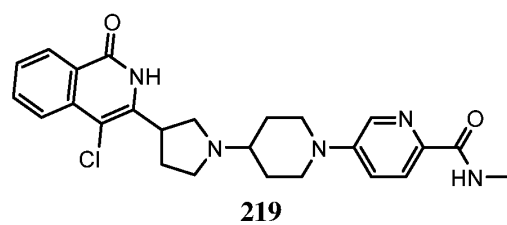
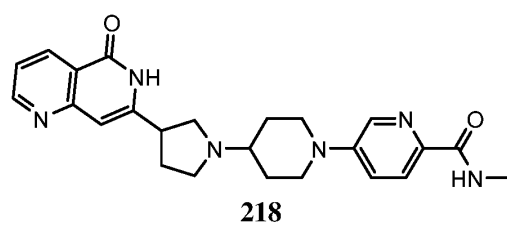
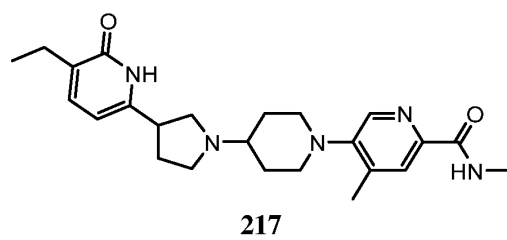
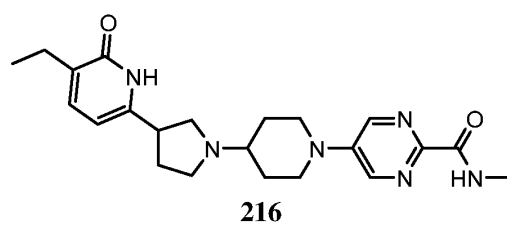
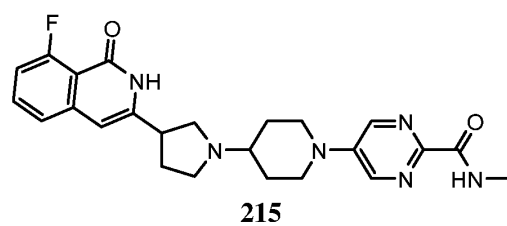
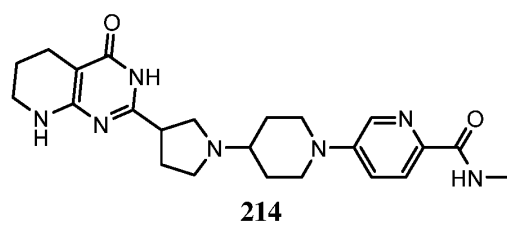
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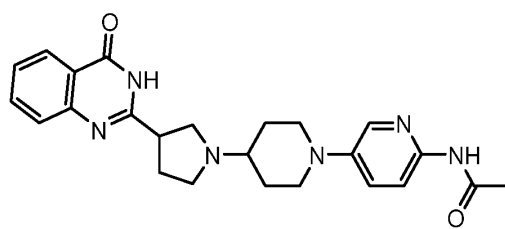




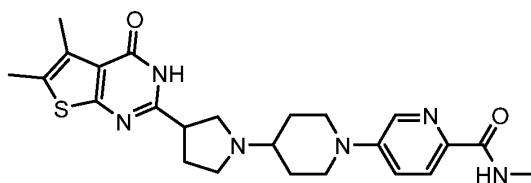




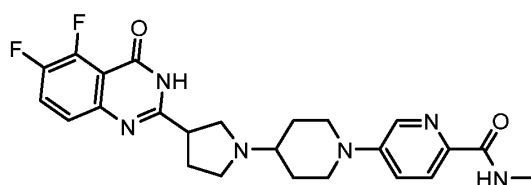




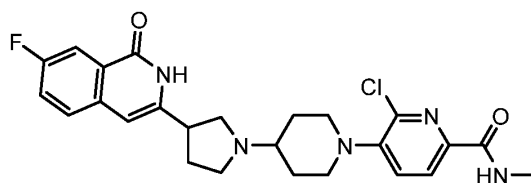
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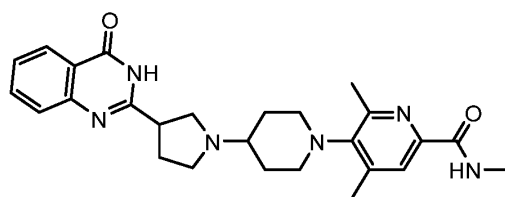
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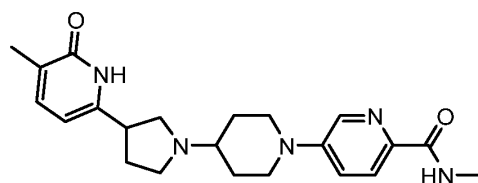
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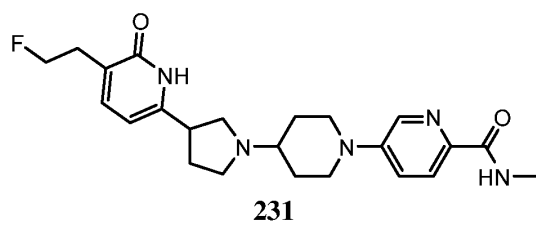
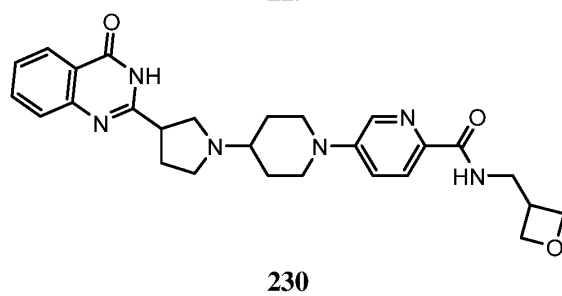
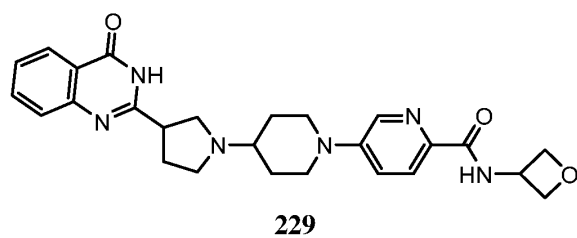
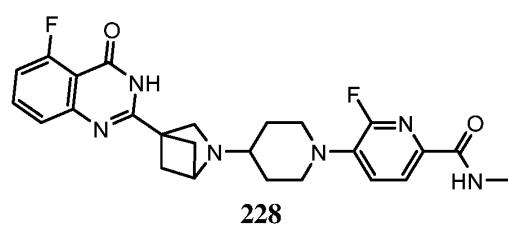
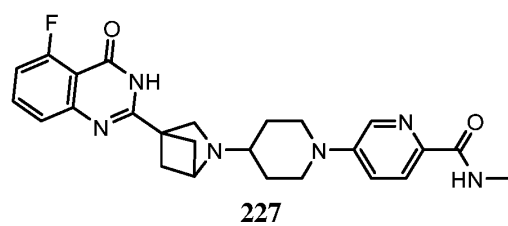
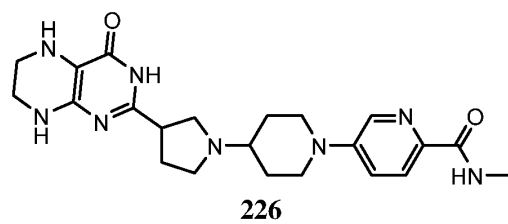
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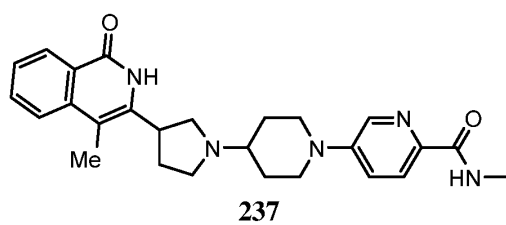
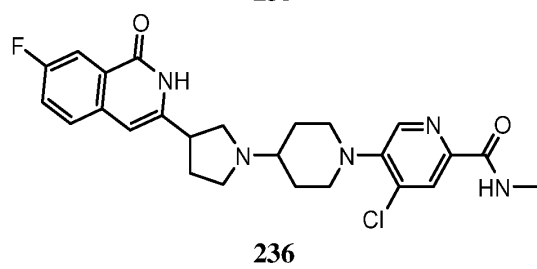
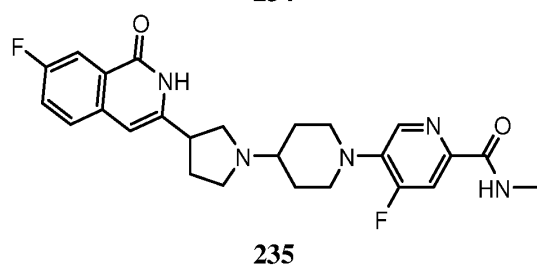
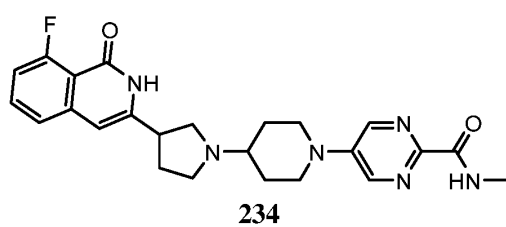
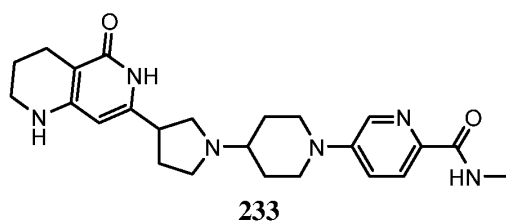
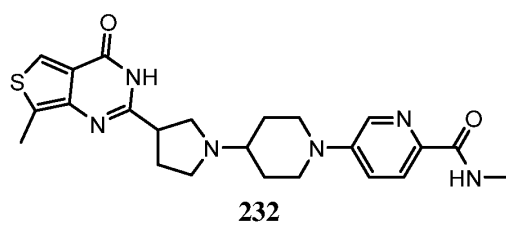


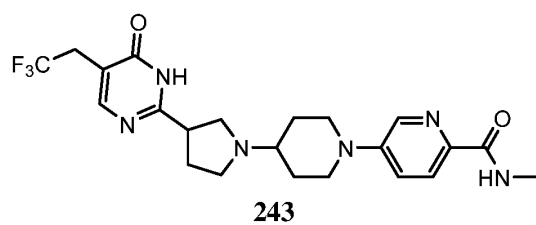
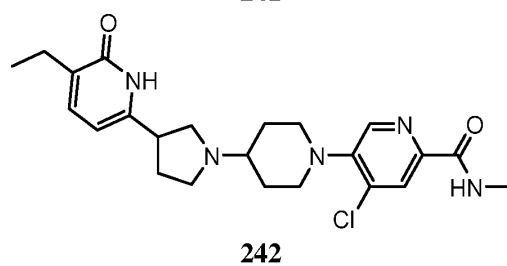
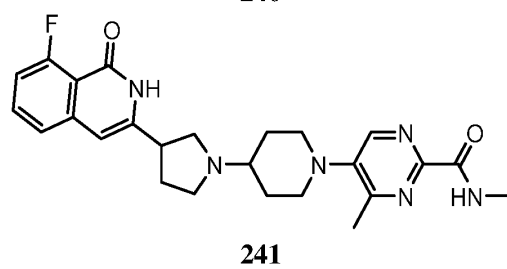
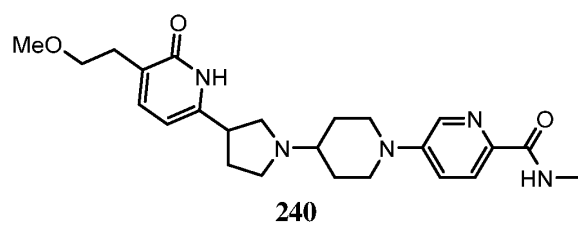
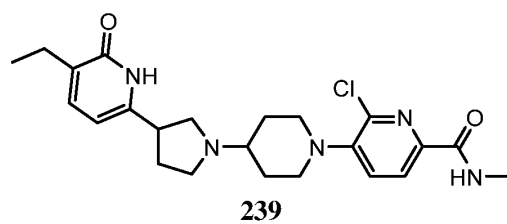
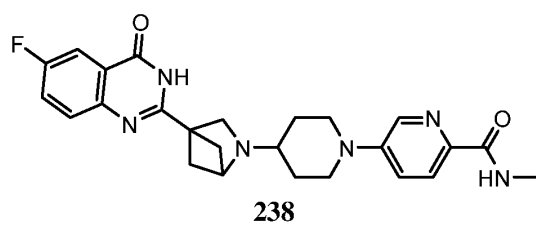
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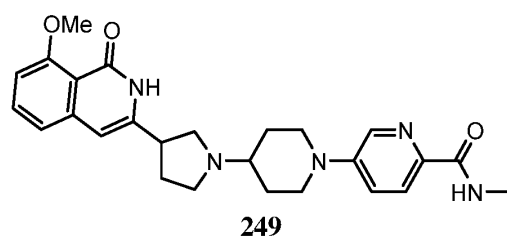
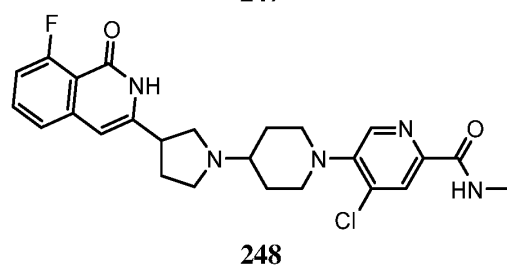
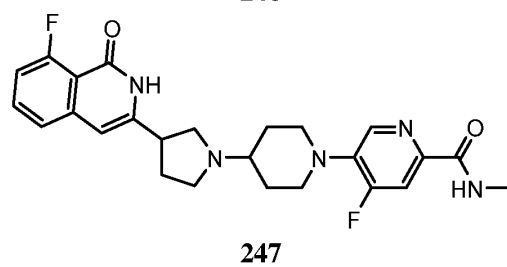
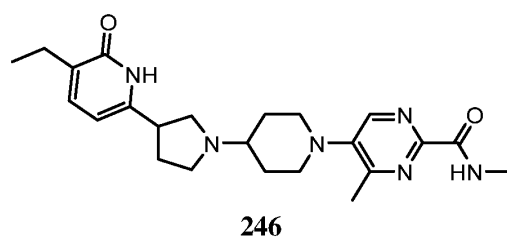
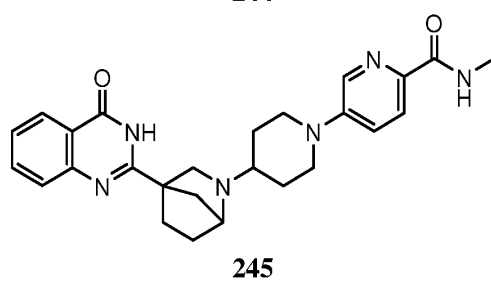
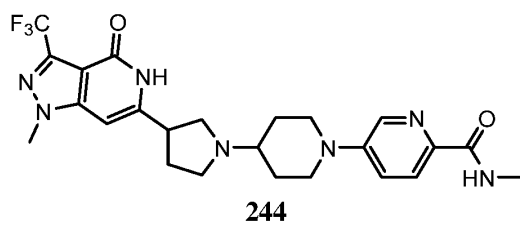


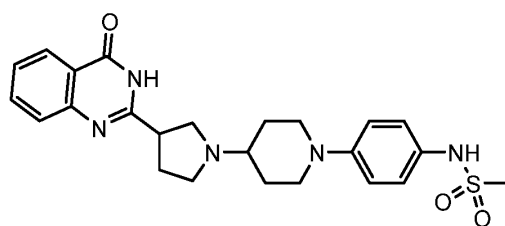
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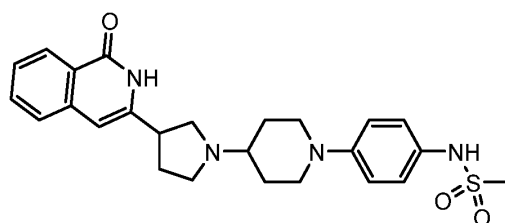




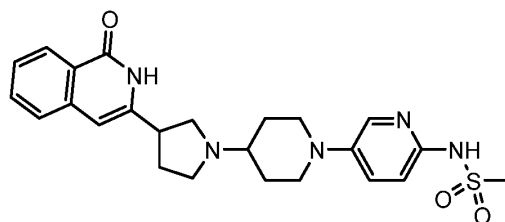




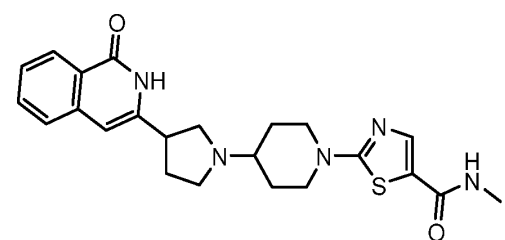
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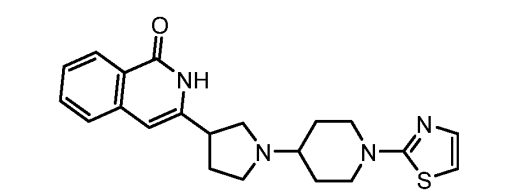
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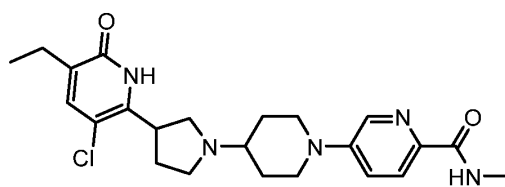
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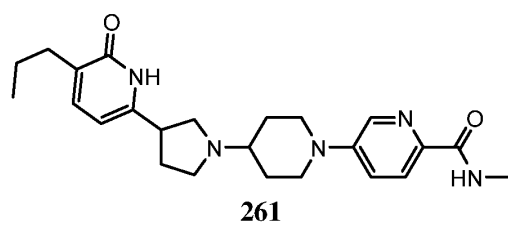
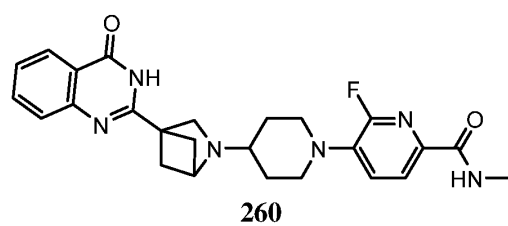
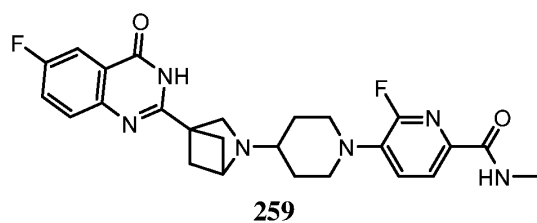
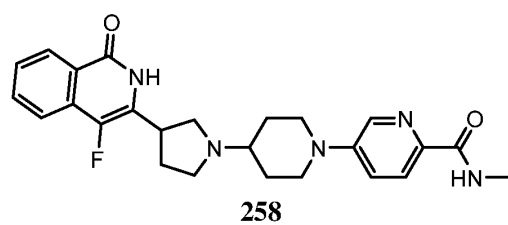
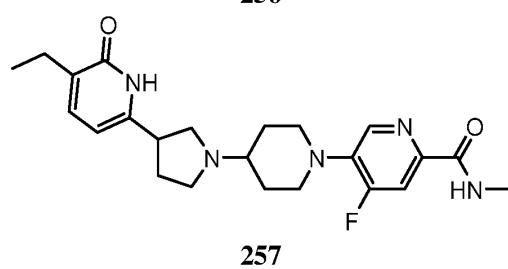
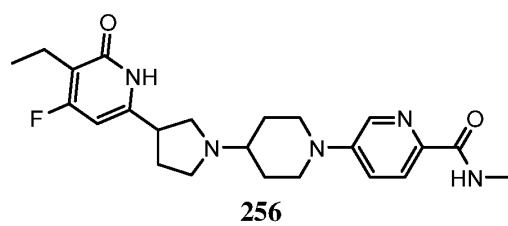
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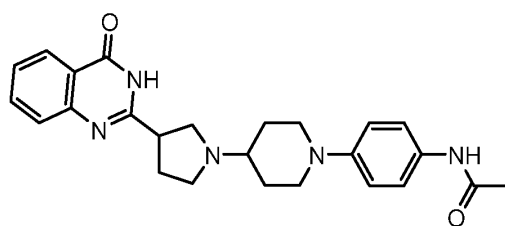


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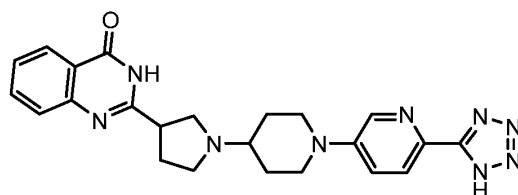


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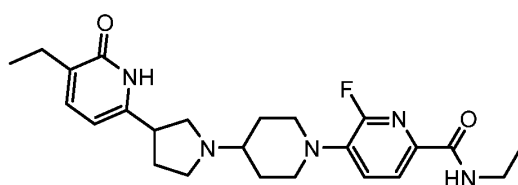




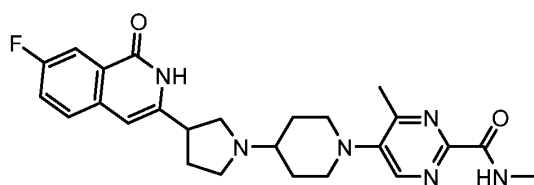
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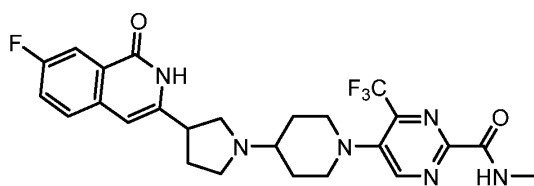
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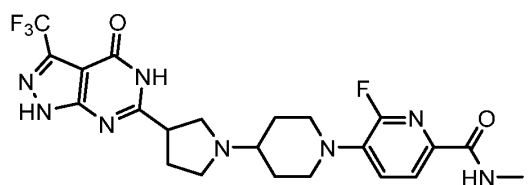
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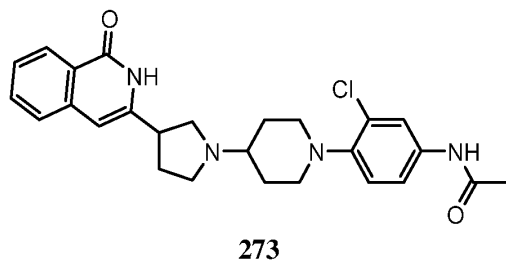
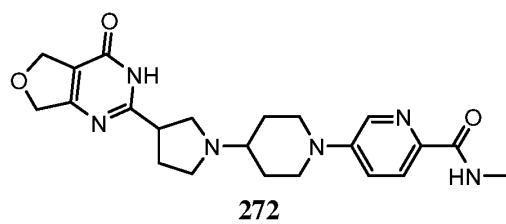
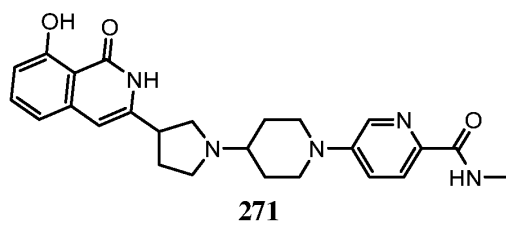
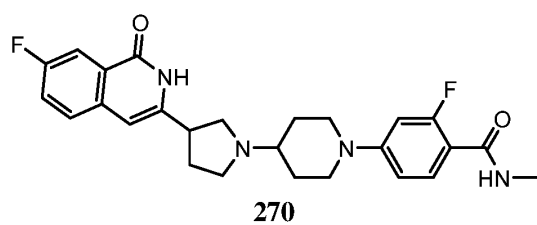
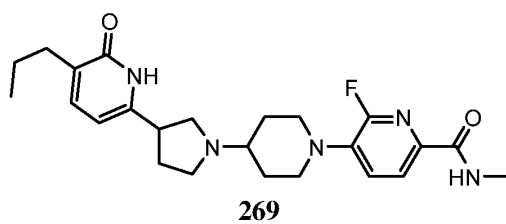
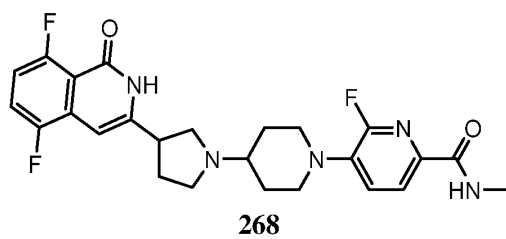
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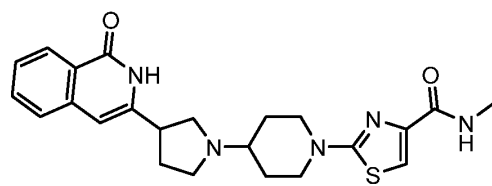


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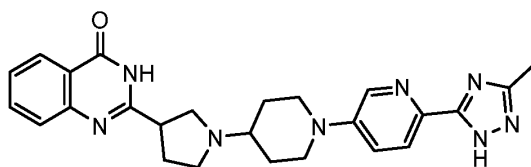


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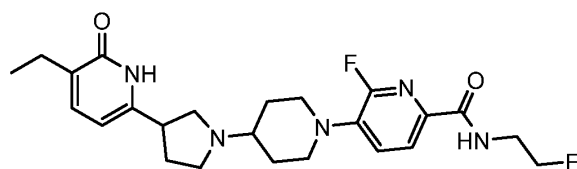




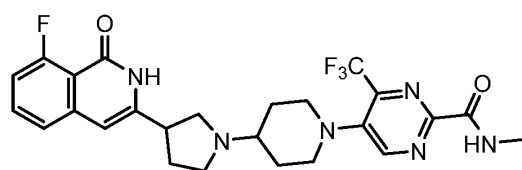
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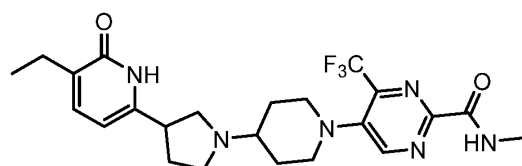
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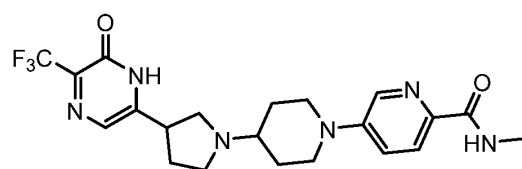
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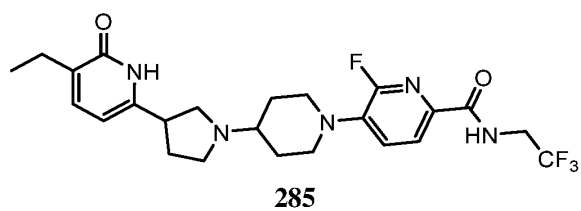
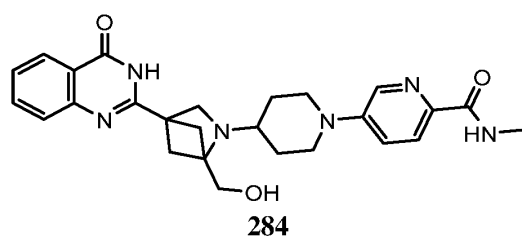
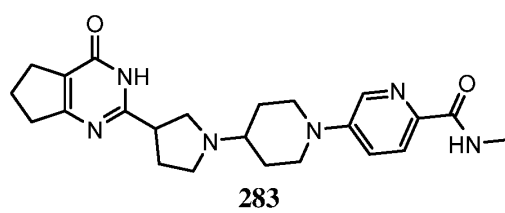
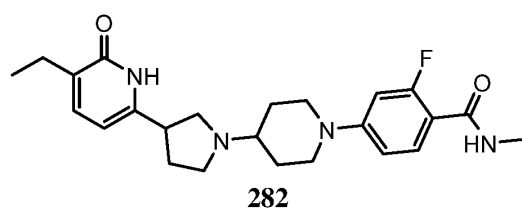
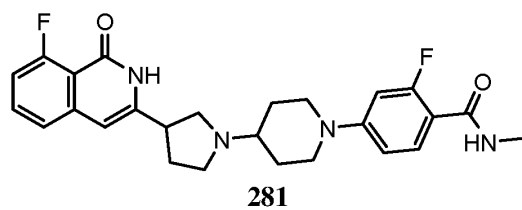
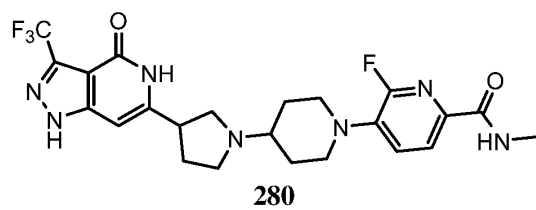
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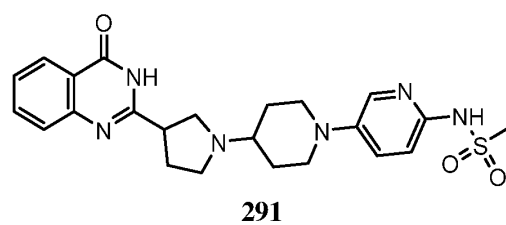
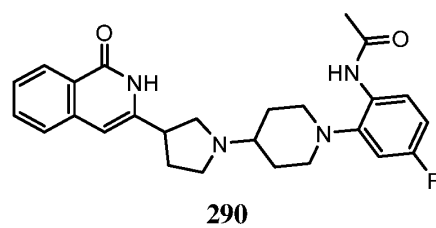
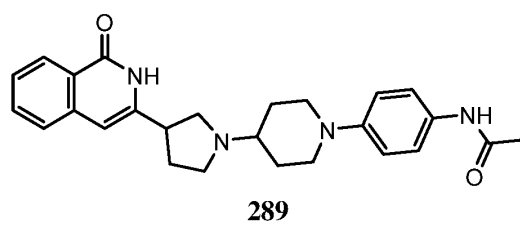
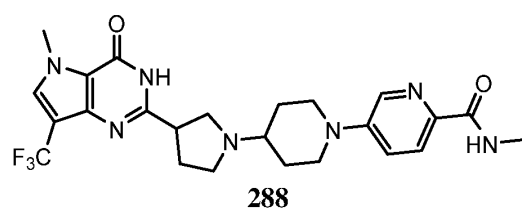
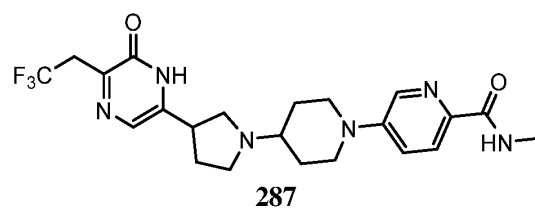
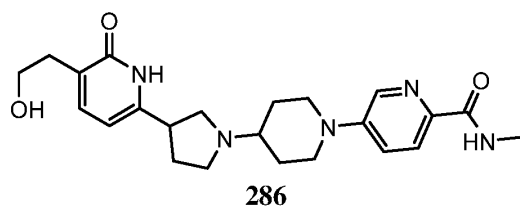


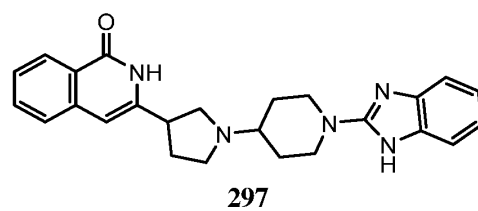
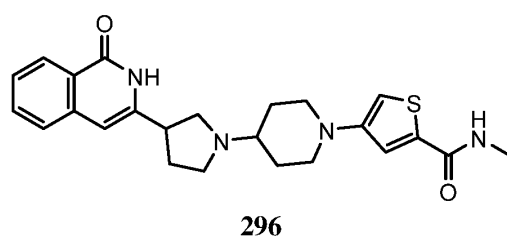
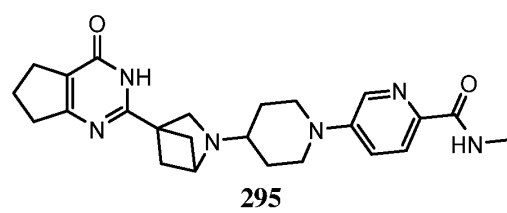
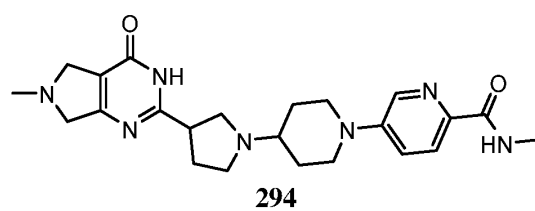
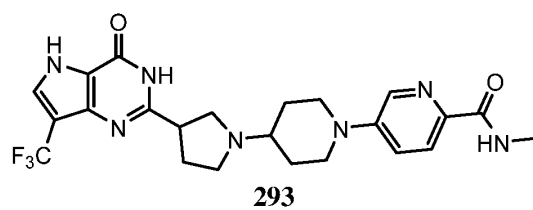
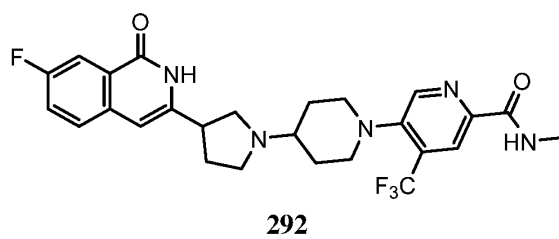
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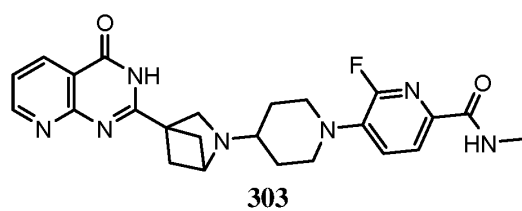
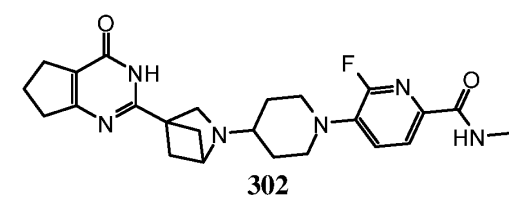
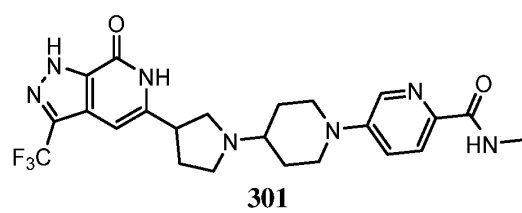
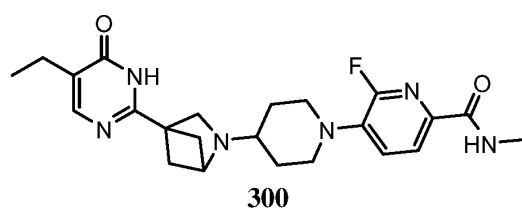
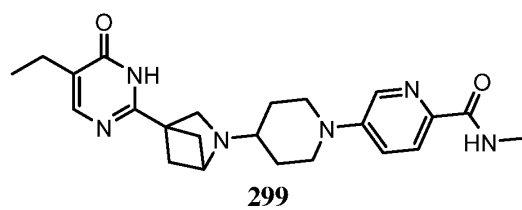
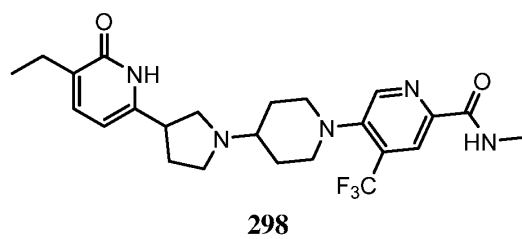


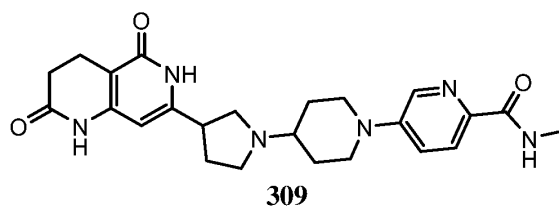
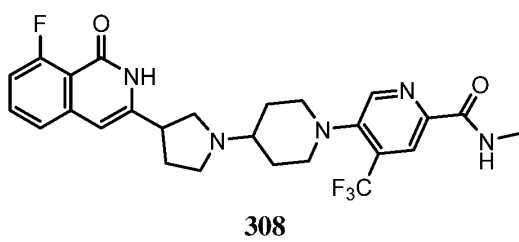
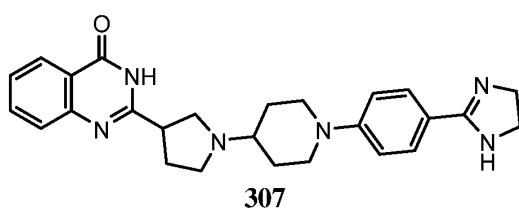
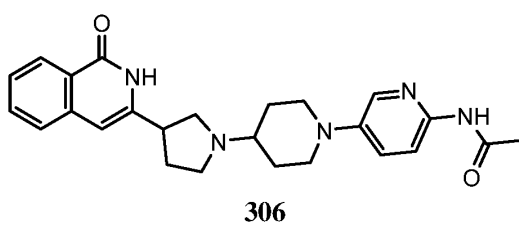
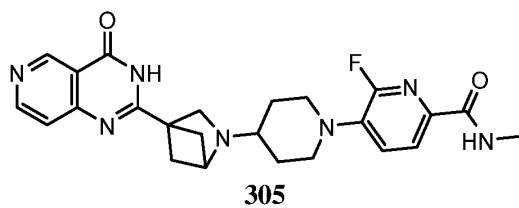
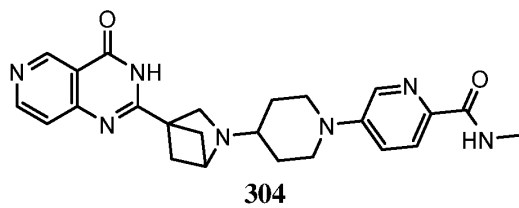
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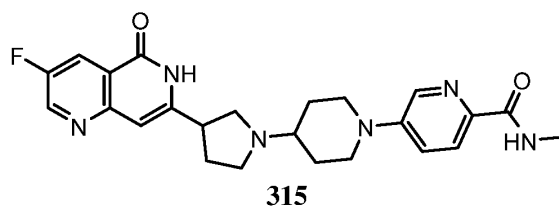
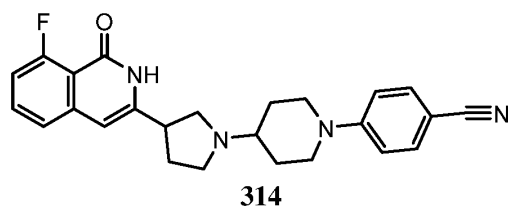
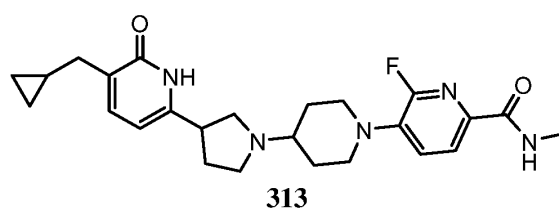
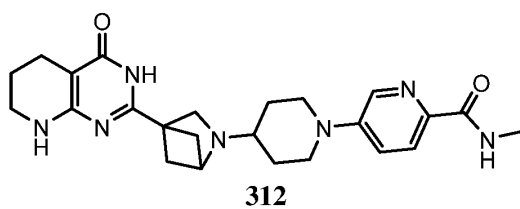
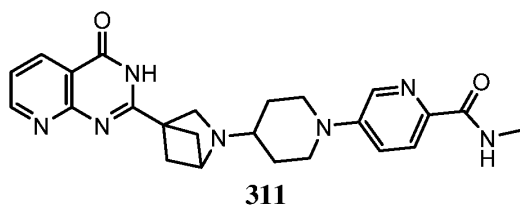
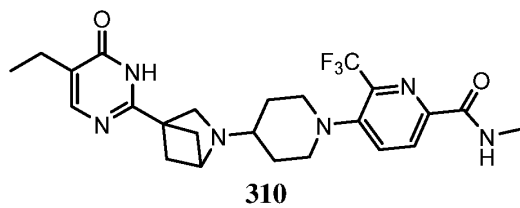


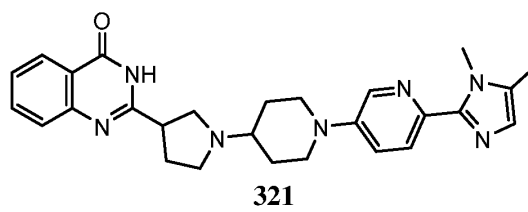
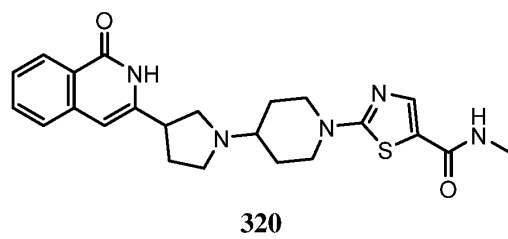
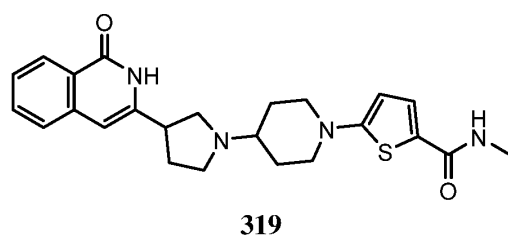
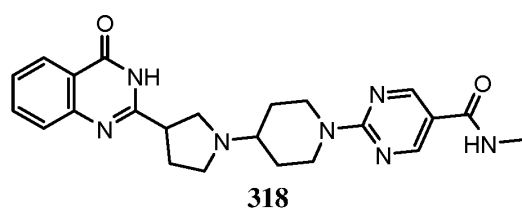
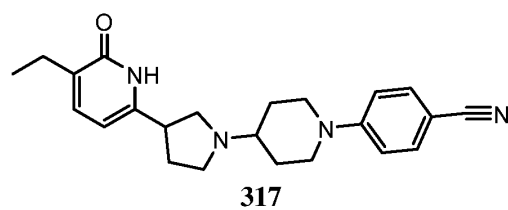
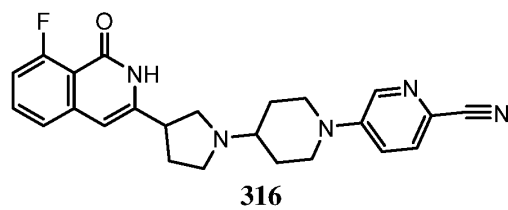


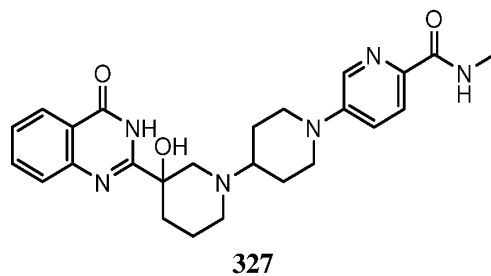
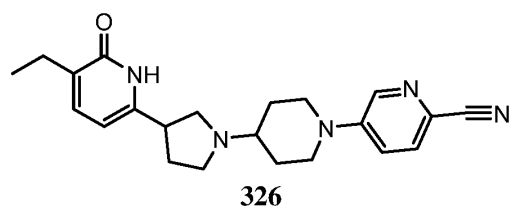
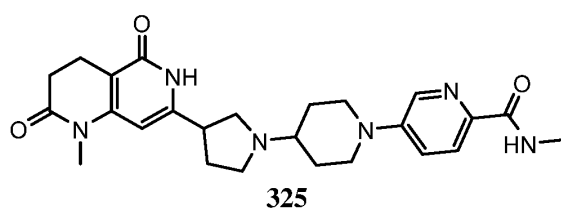
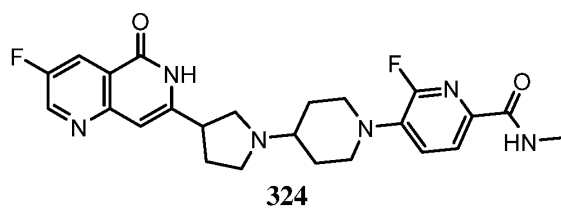
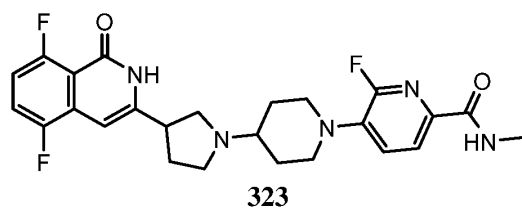
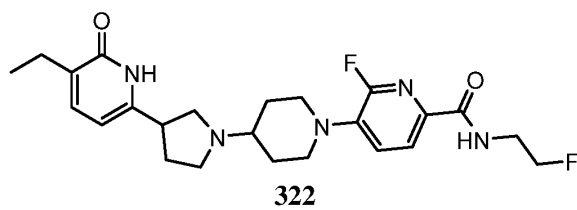


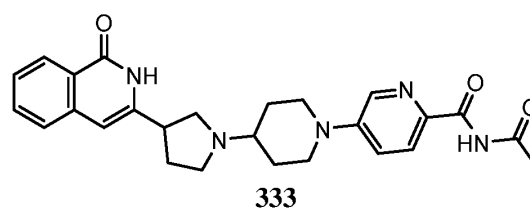
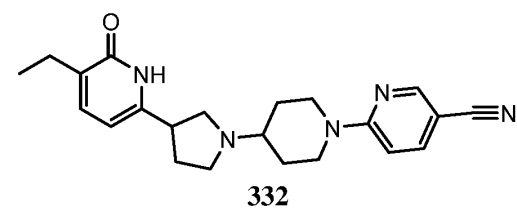
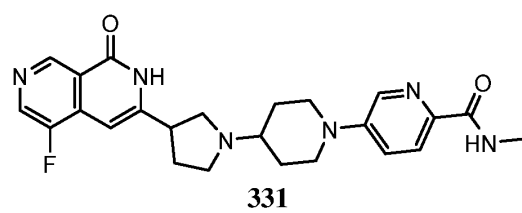
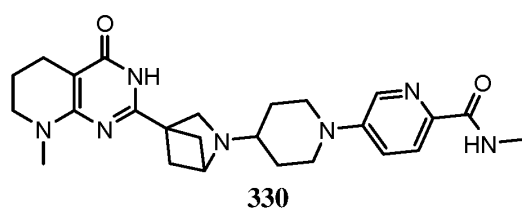
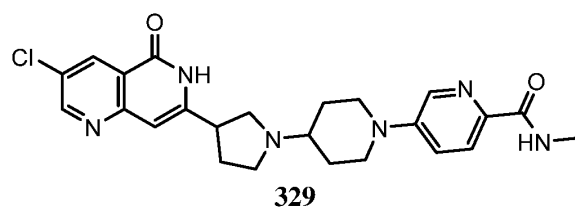
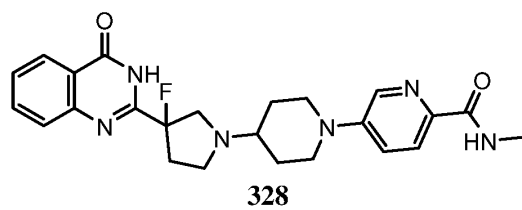


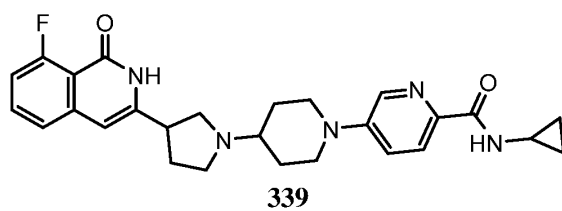
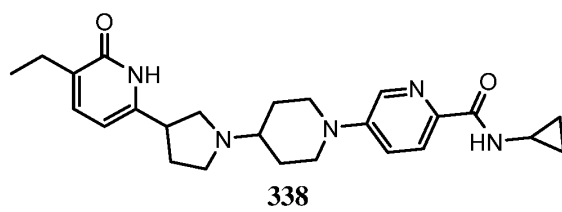
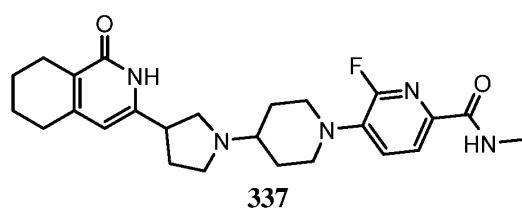
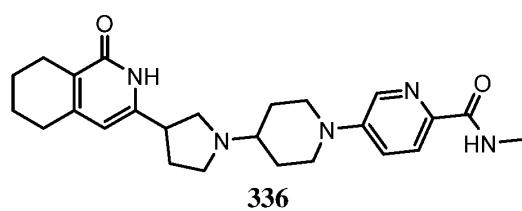
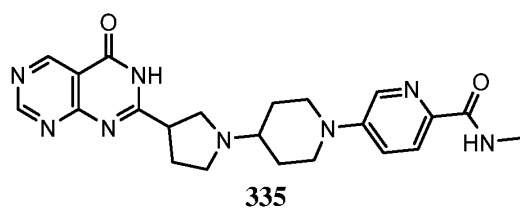
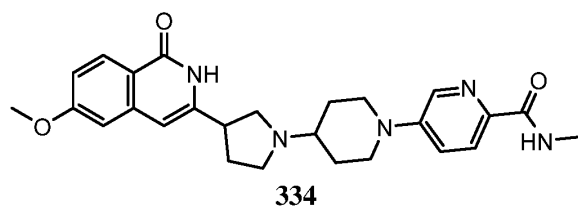


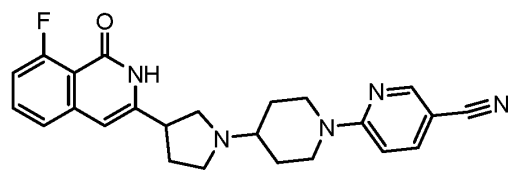




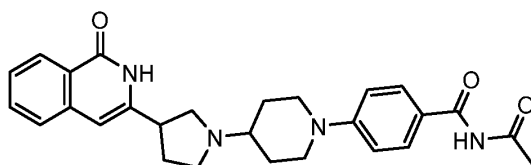




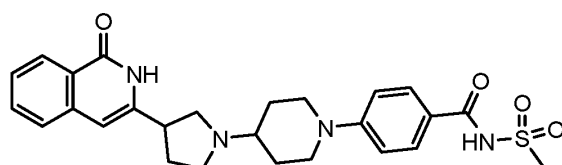




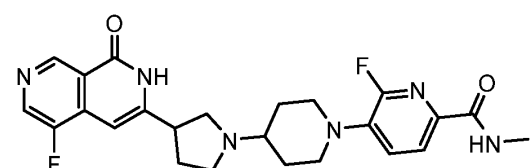
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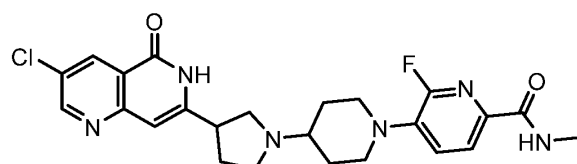
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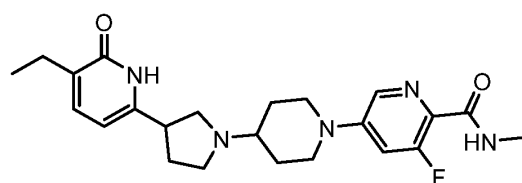
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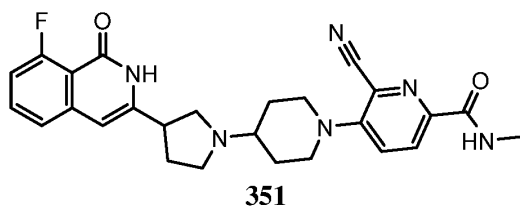
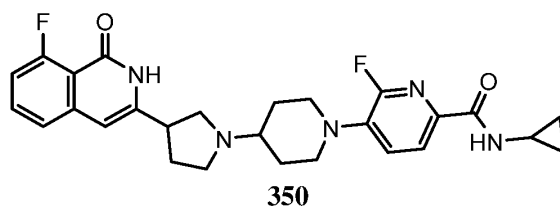
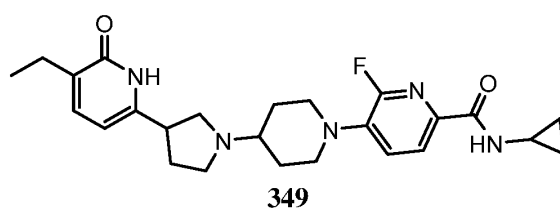
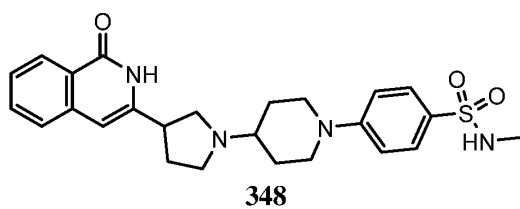
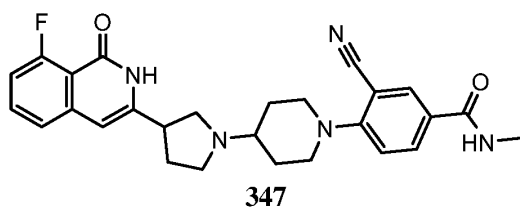
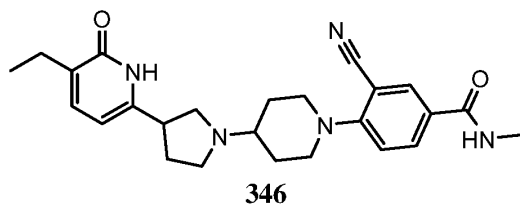
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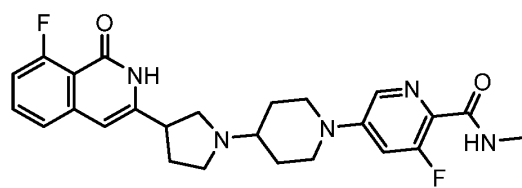


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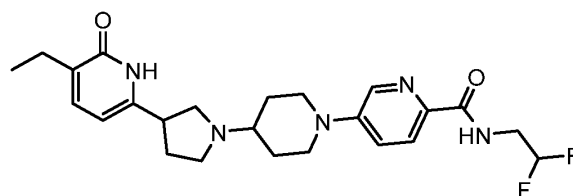


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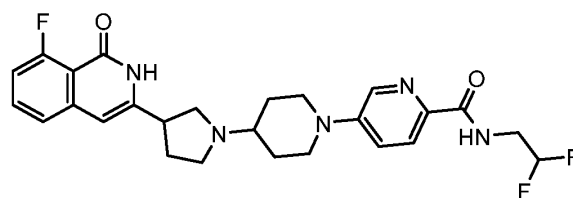




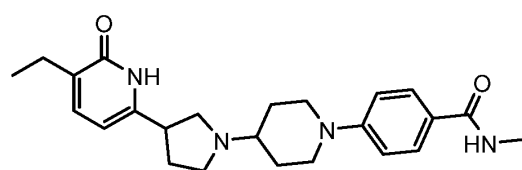
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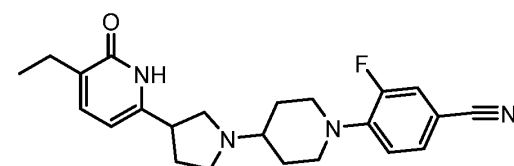
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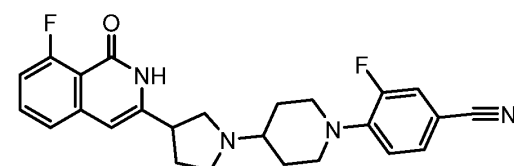
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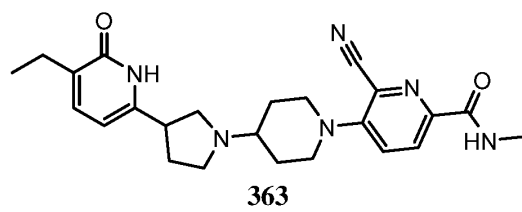
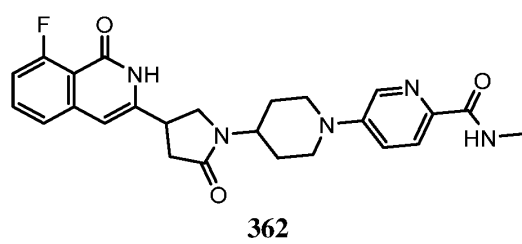
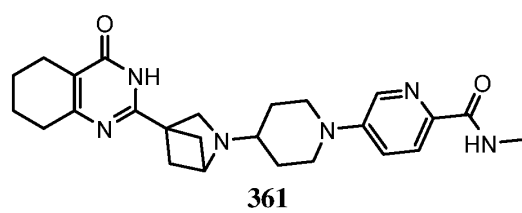
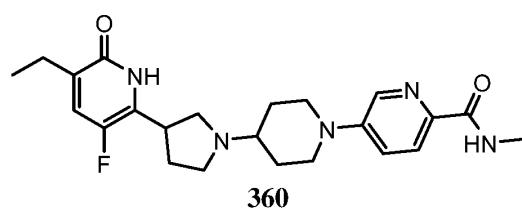
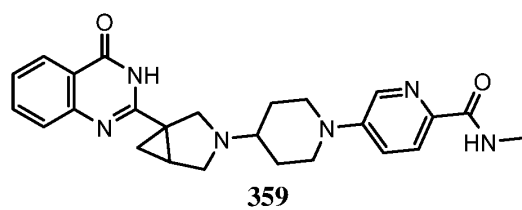
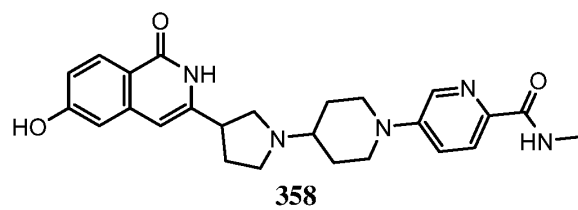
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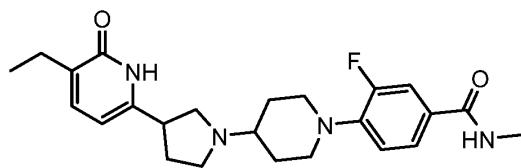


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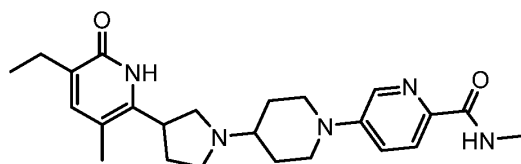


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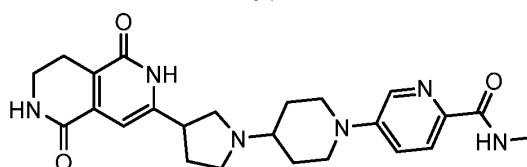




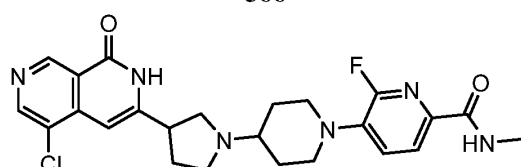
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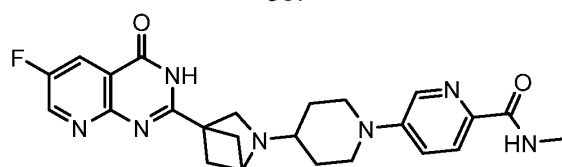
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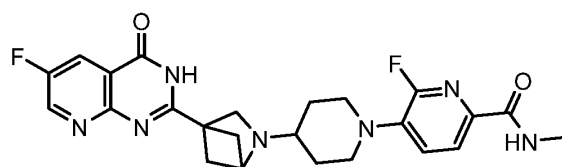
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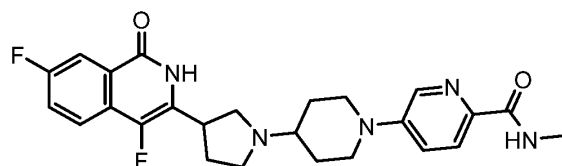
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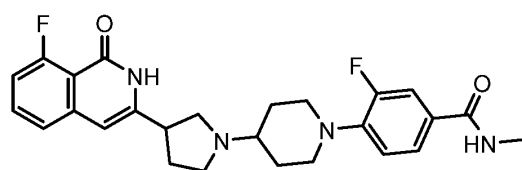
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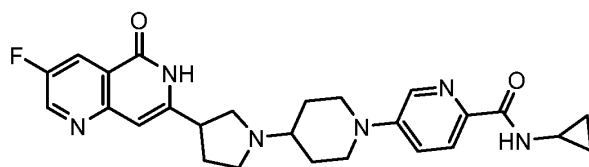
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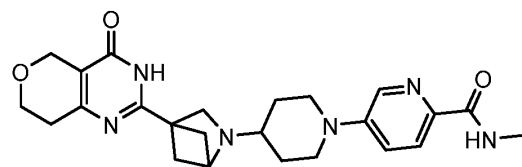
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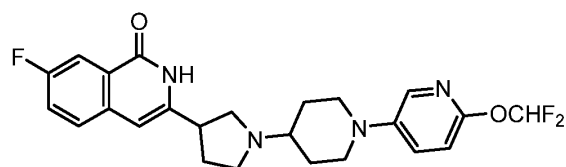
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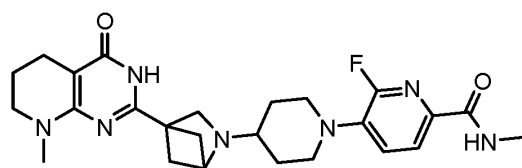
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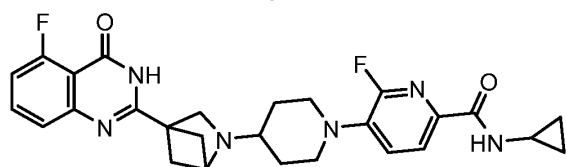
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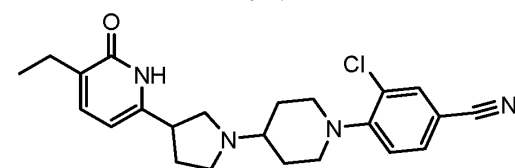
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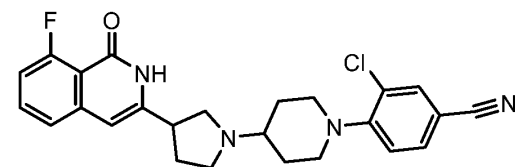
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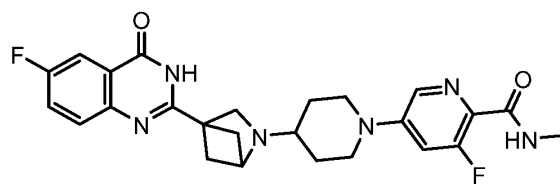
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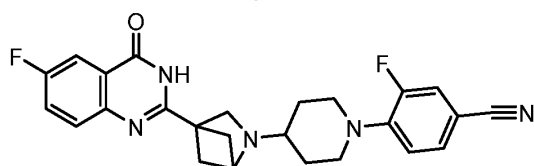
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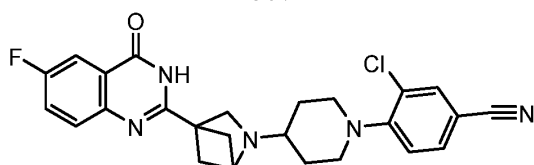
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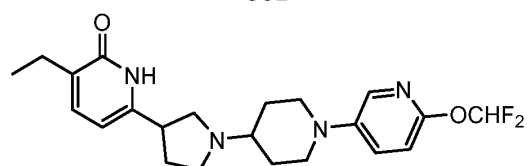
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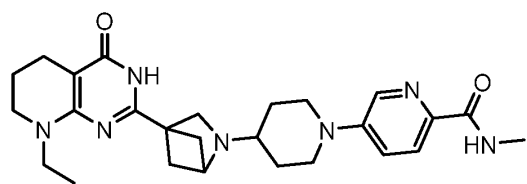
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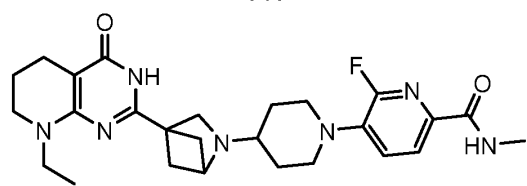
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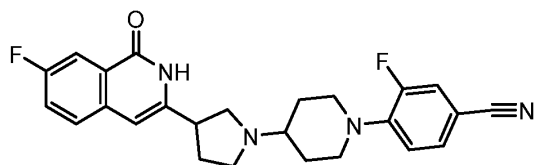
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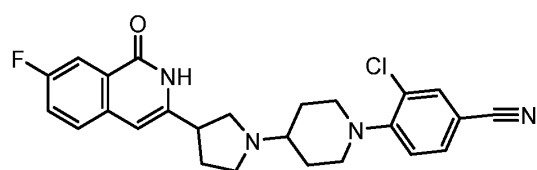
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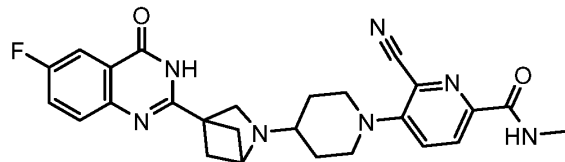
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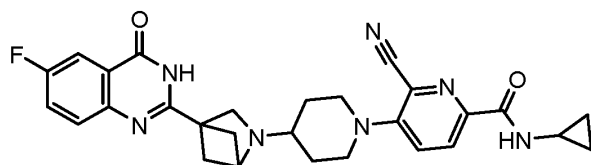
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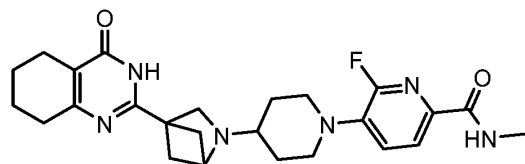
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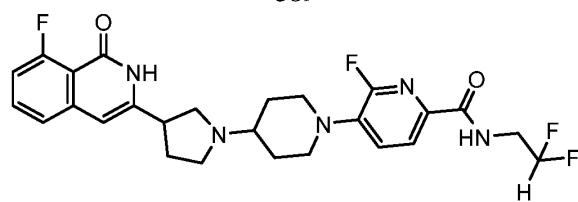
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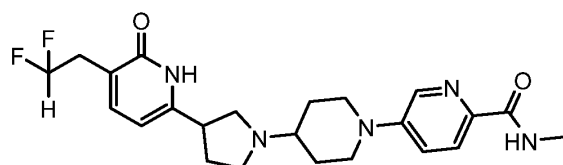
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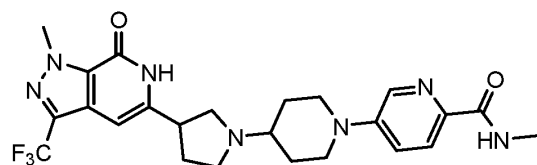
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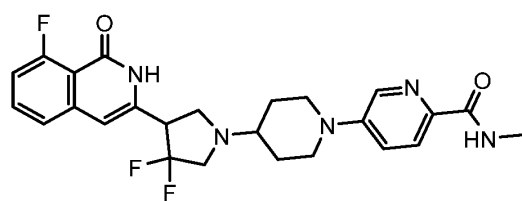
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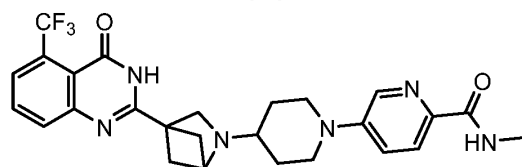
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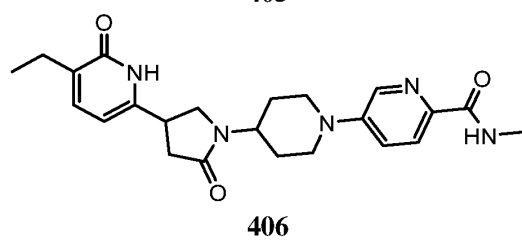
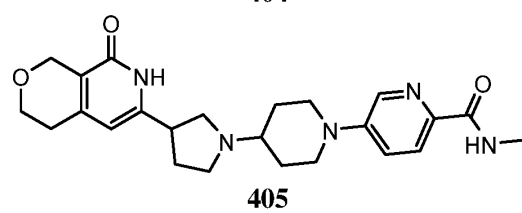
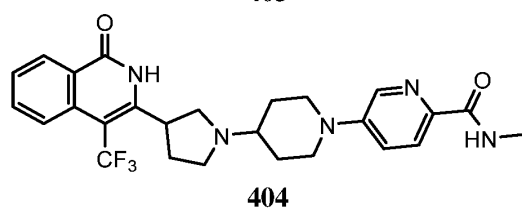
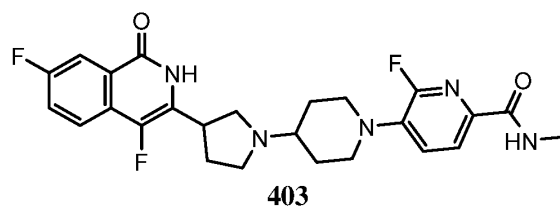
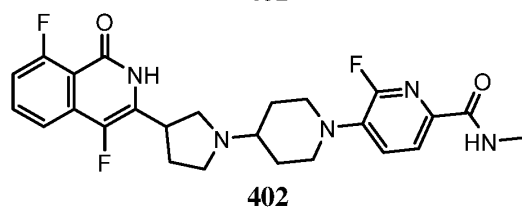
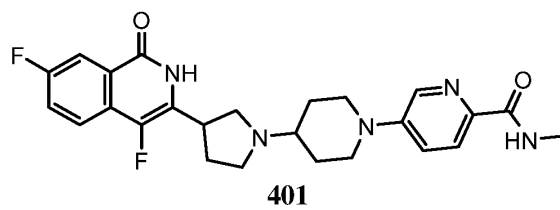
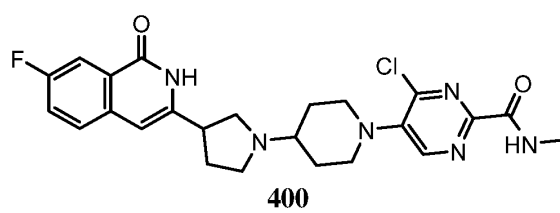


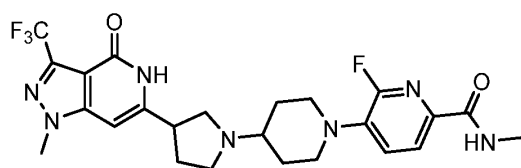
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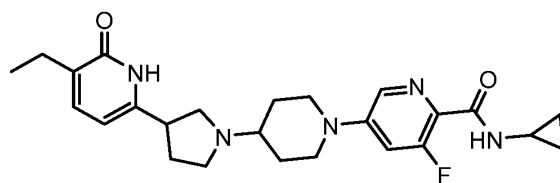
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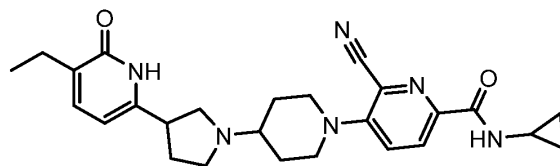




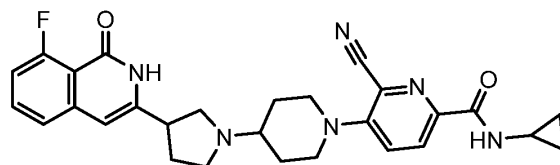
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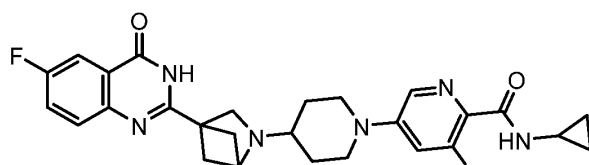
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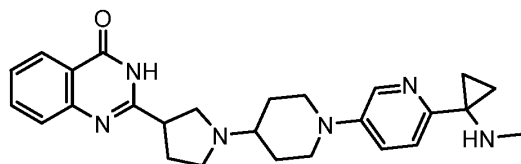
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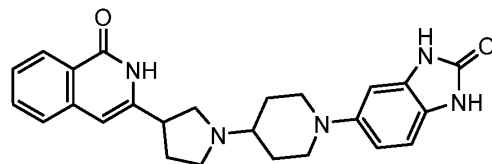
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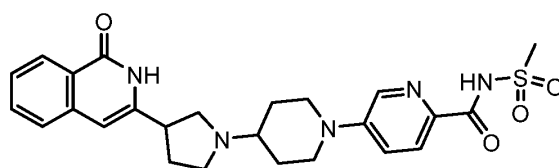
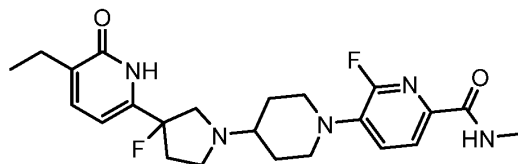
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46. A compound for use in medicine according to any preceding claim, which compound comprises:

- an isolated enantiomer, or
- a mixture of two or more enantiomers, or
- a mixture of two or more diastereomers, and/or epimers, or
- a racemic mixture, or
- a tautomer of the compound.

47. A compound according to any preceding claim which is selective for PARP1 over PARP2.

48. A compound for use in treating a cancer, which compound is a compound as defined in any preceding claim.

49. A compound according to claim 48, wherein the cancer is a cancer selected from: a solid or liquid tumour including cancer of the eye, brain (such as gliomas, glioblastomas, medullablastomas, craniopharyngioma, ependymoma, and astrocytoma), spinal cord, kidney, mouth, lip, throat, oral cavity, nasal cavity, small intestine, colon, parathyroid gland, gall bladder, head and neck, breast, bone, bile duct, cervix, heart, hypopharyngeal gland, lung, bronchus, liver, skin, ureter, urethra, testicles, vagina, anus, laryngeal gland, ovary, thyroid, oesophagus, nasopharyngeal gland, pituitary gland, salivary gland, prostate, pancreas, adrenal glands; an endometrial cancer, oral cancer, melanoma, neuroblastoma, gastric cancer, an

angiomatosis, a hemangioblastoma, a pheochromocytoma, a pancreatic cyst, a renal cell carcinoma, Wilms' tumour, squamous cell carcinoma, sarcoma, osteosarcoma, Kaposi sarcoma, rhabdomyosarcoma, hepatocellular carcinoma, PTEN Hamartoma-Tumor Syndromes (PHTS) (such as Lhermitte-Duclos disease, Cowden syndrome, Proteus syndrome, and Proteus-like syndrome), leukaemias and lymphomas (such as acute lymphoblastic leukaemia, chronic lymphocytic leukaemia, acute myelogenous leukaemia, chronic myelogenous leukaemia, hairy cell leukaemia, T-cell prolymphocytic leukemia (T-PLL), large granular lymphocytic leukemia, adult T-cell leukemia, juvenile myelomonocytic leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, mantle lymphoma, follicular lymphoma, primary effusion lymphoma, AIDS-related lymphoma, diffuse B cell lymphoma, Burkitt lymphoma, cutaneous T-cell lymphoma, nasopharyngeal and gastrointestinal cancers.

50. A compound according to claim 48 or claim 49, wherein the cancer is deficient in a DNA damage response repair pathway, such as Homologous Recombination dependent DNA Double Strand Break DNA repair activity.

51. A compound according to any of claims 48 to 50, wherein the cancer is deficient in BRCA1 and/or BRCA2 function.

52. A pharmaceutical composition comprising a compound as defined in any of claims 1 to 47.

53. A pharmaceutical composition according to claim 52, further comprising a pharmaceutically acceptable additive and/or excipient, and/or wherein the compound is in the form of a pharmaceutically acceptable salt, hydrate, acid, ester, or other alternative form of the compound.

54. A pharmaceutical composition according to claim 52 or claim 53, which composition is for treating a cancer as defined in any of claims 48 to 51.

55. A pharmaceutical composition according to claim 54 for treating a cancer, further comprising a further agent for treating cancer; preferably wherein the further agent for treating cancer is selected from anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I

inhibitors, senolytic agents, hormones and hormone analogues, signal transduction pathway inhibitors, other DNA damage repair pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, antibody-drug conjugates, immunotherapeutic agents, hormone-deprivation therapy, proapoptotic agents and cell cycle signalling inhibitors.

56. A pharmaceutical composition according to claim 55 for treating a cancer, wherein the further agent is an immunotherapeutic agent selected from an anti-tumour vaccine, an oncolytic virus, an immune stimulatory antibody such as anti-CTLA4, anti-PD1, anti-PDL-1, anti-OX40, anti-41BB, anti-CD27, anti-CD40, anti-LAG3, anti-TIM3, and anti-GITR, a pattern recognition receptor agonist such as a STING, TLR-9 or RIG-I Helicase agonist, an IDO or TDO inhibitor, a novel adjuvant, a peptide, a cytokine, a chimeric antigen receptor T cell therapy (CAR-T), a small molecule immune modulator, tumour microenvironment modulators, and anti-angiogenic agents.

57. A pharmaceutical kit for treating a cancer, which pharmaceutical kit comprises:

(a) a compound as defined in any of claims 1 to 47; and

(b) a further agent for treating cancer; preferably wherein the further agent for treating cancer is selected from anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, senolytic agents, hormones and hormone analogues, signal transduction pathway inhibitors, other DNA damage repair pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, antibody-drug conjugates, hormone-deprivation therapy, immunotherapeutic agents (such as selected from an anti-tumour vaccine, an oncolytic virus, an immune stimulatory antibody such as anti-CTLA4, anti-PD1, anti-PDL-1, anti-OX40, anti-41BB, anti-CD27, anti-CD40, anti-LAG3, anti-TIM3, and anti-GITR, a pattern recognition receptor agonist such as a STING, TLR-9 or RIG-I Helicase agonist, an IDO or TDO inhibitor, a novel adjuvant, a peptide, a cytokine, a chimeric antigen receptor T cell therapy (CAR-T), a small molecule immune modulator, tumour microenvironment modulators, and anti-angiogenic agents), proapoptotic agents and cell cycle signalling inhibitors; wherein the compound and the further agent are suitable for administration simultaneously, sequentially or separately.

58. A method of treating a disease and/or a condition and/or a disorder, which method comprises administering to a patient a compound or a composition or a kit as defined in any preceding claim.

59. A method according to claim 58, wherein the disease or condition or disorder is a disease or condition or disorder as defined in any of claims 48 to 51.

60. A method according to claim 59 for treating a cancer, which method comprises administering to a patient a compound or a composition as defined in any of claims 1 to 50 and a further agent for treating a cancer as defined in claim 55 or claim 56; preferably wherein the compound or composition and the further agent are administered simultaneously, sequentially or separately.

61. A method according to any of claims 58 to 60, wherein the patient is an animal, preferably a mammal, including canines, equines and felines, and more preferably a human.

62. A compound, which is selected from any of the compounds defined in claim 45.

63. A compound according to claim 62, which compound comprises:

- an isolated enantiomer, or
- a mixture of two or more enantiomers, or
- a mixture of two or more diastereomers, and/or epimers, or
- a racemic mixture, or
- a tautomer of the compound.

64. A method of synthesis of a PARP1 inhibitor compound as defined in any of claims 1 to 47, which method comprises conducting a reaction between (i) a first reactant comprising ring E bearing a portion of substituent group L and (ii) a second reactant comprising the remainder of substituent group L, so as to form the PARP1 inhibitor compound.

65. A method according to claim 64, wherein the first reactant comprises ring E and ring A, and the second reactant comprises a Q1 or Q2 precursor bearing a reactive group, which method comprises joining the N atom of ring A to the Q1 or Q2 precursor.

66. A method according to claim 65, wherein the reactive group of the Q1 or Q2 precursor comprises a carbonyl group, an alkyl halide or an alkyl sulfonate.
67. A method according to any of claims 64 to 66, wherein the reaction comprises alkylation, reductive amination or amide formation so as to form group L.
68. A method according to claim 64, wherein the first reactant comprises ring E, ring A, and at least one of Q1 and Q2, and the second reactant comprises a ring C derivative bearing a leaving group such as a halide or sulfonate.
69. A method according to claim 68, wherein the reaction comprises a nucleophilic substitution reaction, such as a nucleophilic aromatic substitution reaction, so as to form group L.