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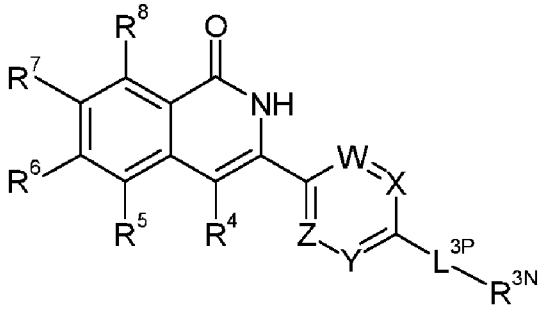
(54) Title: 3-ARYL-5-SUBSTITUTED-ISOQUINOLIN-1-ONE COMPOUNDS AND THEIR THERAPEUTIC USE



(57) Abstract: The present invention pertains generally to the field of therapeutic compounds. More specifically the present invention pertains to certain 3-aryl-5-substituted- 2H-isoquinolin-1-one compounds that, inter alia, inhibit PARP (e.g., PARP1, TNKS1, TNKS2, etc.) and/or Wnt signalling. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both in vitro and in vivo, to inhibit PARP (e.g., PARP1, TNKS1, TNKS2, etc.); to inhibit Wnt signalling; to treat disorders that are ameliorated by the inhibition of PARP (e.g., PARP1, TNKS1, TNKS2, etc.); to treat disorders that are ameliorated by the inhibition of Wnt signalling; to treat proliferative conditions such as cancer, etc.

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3-ARYL-5-SUBSTITUTED-ISOQUINOLIN-1-ONE COMPOUNDS AND THEIR THERAPEUTIC USE

TECHNICAL FIELD

The present invention pertains generally to the field of therapeutic compounds. More specifically the present invention pertains to certain 3-aryl-5-substituted-2H-isoquinolin-1-one compounds that, *inter alia*, inhibit PARP (e.g., PARP1, TNKS1, TNKS2, *etc.*) and/or Wnt signalling. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both *in vitro* and *in vivo*, to inhibit PARP (e.g., PARP1, TNKS1, TNKS2, *etc.*); to inhibit Wnt signalling; to treat disorders that are ameliorated by the inhibition of PARP (e.g., PARP1, TNKS1, TNKS2, *etc.*); to treat disorders that are ameliorated by the inhibition of Wnt signalling; to treat proliferative conditions such as cancer, *etc.*

BACKGROUND

A number of publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Each of these references is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference.

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word “comprise,” and variations such as “comprises” and “comprising,” will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a pharmaceutical carrier” includes mixtures of two or more such carriers, and the like.

Ranges are often expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent “about,” it will be understood that the particular value forms another embodiment.

This disclosure includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

Cancer

Cancer is the second largest cause of death worldwide. Cancer accounts for 13% of global mortality with more than 70% of cancer deaths occurring in low and middle-income countries where the prevalence of cancer is expected to increase as mortality from other diseases decreases. In the UK alone, a disease such as breast cancer kills over 12,000 women each year.

One approach to this problem has been to identify novel targets for cancer therapies and to use these to tailor the treatment of each patient according to the molecular make-up of their particular disease, rather than their overt clinical characteristics. While this has been in part successful, there are still a significant number of tumour types for which there are no targeted therapies and few treatment options other than surgery and cytotoxic chemotherapy.

PARP

There is now a significant body of evidence to suggest that inhibition of poly ADP ribose polymerase (PARP) superfamily proteins, such as PARP1, PARP2, Tankyrase 1 (also known as TNKS1, PARP5a) and Tankyrase 2 (also known as TNKS2, PARP5B) could have clinical utility. See, e.g., Krishnakumar *et al.*, 2010. PARP superfamily members use beta-NAD^+ as a substrate to generate ADP-ribose polymers on amino acid residues of protein acceptors. The result is a dramatic post-translational modification that can significantly alter the properties of the protein acceptor. See, e.g., Krishnakumar *et al.*, 2010.

Although much of the focus has been on PARP1, studies over the past decade have identified a family of as many as 17 proteins that share homology to the catalytic domain of PARP1. In addition to the PARP-like domain, the PARP family members are "functionalized" with a wide variety of other structural and functional domains (e.g., DBDs, RNA-binding domains, subcellular localization signals, macrodomains, BRCT motifs, ankyrin repeats, zinc fingers) that determine their overall biological activities. Recently, a unified nomenclature referring to this family of proteins as ADP-ribosyl transferases (ARTs) has been proposed to recognize that fact that (1) PARPs catalyze a transferase reaction, not a template-dependent polymerization reaction; and (2) not all family members have PARP activity; some are likely to function as mono(ADP-ribosyl)

transferases (mARTs). This new nomenclature is reflected in a recent structure-based classification of PARP family members into three groups based on their catalytic domains: (1) PARPs 1-5, which are bona fide PARPs containing a conserved glutamate (Glu 988 in PARP1) that defines the PARP catalytic activity; (2) PARPs 6–8, 10–12, and 14–16, which are confirmed or putative mARTs; and (3) PARPs 9 and 13, which lack key NAD-binding residues and the catalytic glutamate, and are likely inactive. See, e.g., Krishnakumar *et al.*, 2010.

PARP family members localize to various cellular compartments, including the nucleus, cytoplasm, mitochondria, and vault particles, although the subcellular localization and function of many of the PARPs are unknown. The known functions of the PARP family members span a wide range of cellular processes, including DNA repair, transcription, cellular signalling, cell-cycle regulation, and mitosis. This diverse array of processes plays key roles in a wide variety of biological outcomes, including differentiation, development, stress responses, inflammation, and cancer. See, e.g., Krishnakumar *et al.*, 2010.

The primary nuclear PARPs are PARP1, PARP2 (the closest paralog to PARP1), PARP3, and tankyrases 1 and 2. PARP1 is a very well studied protein and has a well-established role in DNA repair. See, e.g., Lord *et al.*, 2008. Tankyrase 1 encompasses four distinct domains; the N terminal HPS domain (homopolymeric stretches of His, Pro and Ser); the ankyrin domain, containing 24 ANK repeats; a SAM (sterile alpha module) domain; and a C terminal PARP catalytic domain. See, e.g., Hsiao *et al.*, 2008.

The best characterised function of tankyrase 1 is in telomere maintenance. The cellular machinery that normally replicates genomic DNA is unable to synthesise DNA at the telomere, the structure that caps the end of each chromosome. DNA synthesis at the telomere is instead carried out by telomerase. This enzyme complex consists of a RNA template and a DNA polymerase catalytic subunit. However, the activity of telomerase in most human somatic cells is relatively low and as such, attrition of the DNA at the telomere gradually occurs. This attrition of telomeric DNA is one of the factors that can lead to replicative senescence in somatic cells and this shortening of telomeres is often referred to as a “mitotic clock” that predetermines the replicative capacity of most cells. However, the situation in cancer cells is considerably different from that in somatic cells; up to 90% of all human cancer cells have a high level of telomerase activity. This increased level of telomere maintenance is one of the factors that enables tumour cells to avoid senescence and perpetually replicate. See, e.g., Harley, 2008.

The length of telomeric DNA is determined by a “protein counting” mechanism in which a series of telomere-bound proteins negatively regulate the access of telomerase to the telomere. For example, longer telomeres bind a larger number of DNA double strand-

binding Telomeric Repeat Binding Factor (TRF1) proteins. Together with the TIN2-TPP1-POT1 protein complex, TRF1 blocks the access of telomerase to the 3' DNA overhang at the end of chromosomes, thus limiting further extension of the telomere. Regulation of this process is controlled by tankyrase 1 which promotes telomeric extension by poly(ADP-ribosyl)ating TRF1, causing its release from the telomere and eventual proteasomal destruction. This release and degradation of TRF1 allows an enhanced level of telomerase access to the chromosome end and extension of the telomere. See, e.g., Harley, 2008.

Tankyrase 1 is also required after DNA replication in the S/G_2 phase of the cell cycle to resolve sister chromatid cohesion before mitosis ensues. Depletion of tankyrase 1 in HeLa cells results in mitotic arrest. Persistent sister chromatid cohesion in tankyrase 1 depleted cells results in sister chromatid fusion. See, e.g., Hsiao *et al.*, 2009. The mitotic defect in tankyrase-depleted cells may, in part, be determined by the tankyrase 1-mediated poly(ADP ribosyl)ation of the protein NuMA, which plays an essential role in organising microtubules at spindle pores. See, e.g., Chang *et al.*, 2005.

Recent work has also suggested a role for Tankyrase 1 in the control of oncogenic Wnt signalling, most likely via a mechanism that involves the stabilisation of the Wnt signalling component, Axin. See, e.g., Huang *et al.*, 2009. In this latter work and subsequent work (see, e.g., James et al., 2012; Bao et al., 2012; Casás-Selves et al., 2012; Waaler et al., 2012; Riffell et al., 2012) a number of investigators have shown that toolbox, non-drug like small molecule inhibitors of tankyrase can inhibit oncogenic Wnt signalling and can inhibit tumour cells that are addicted to Wnt signalling.

Wnt Signalling

Wnt signalling is an intracellular protein signalling network that transduces signals from cell surface bound receptors to a series of gene transcription events. In canonical Wnt signalling, Wnt ligands bind to cell-surface receptors of the Frizzled family; Frizzled bound receptors activate Dishevelled family proteins. In turn, activated Dishevelled proteins inhibit the function of a complex of proteins including Axin 1 and 2, GSK-3, and the protein APC. This Axin/GSK-3/APC complex normally promotes the proteolytic degradation of the β-catenin intracellular signalling molecule. When Wnt signalling is stimulated and Dishevelled proteins are active, the "β-catenin destruction complex" is inhibited, β-catenin degradation is reduced and β-catenin is able to enter the nucleus and interact with TCF/LEF family transcription factors. This latter act drives a series of specific gene expression events that ultimately mediate Wnt signalling.

The association of dysregulated Wnt/β-catenin signalling with cancer has been well documented. Constitutively activated β-catenin signalling, caused either by APC

deficiency or activating β-catenin mutations can lead to tumourigenesis. Furthermore, tankyrase is directly involved in the Wnt signalling cascade. Tankyrase PARylates both Axin 1 and Axin 2 and causes their degradation, driving β-catenin stabilisation/nuclear translocation and TCF/LEF mediated transcription. See, e.g., Huang *et al.*, 2009. When tankyrase is inhibited, either genetically or with small molecules, Axin1 and 2 levels are stabilized and β-catenin degradation is enhanced, ultimately suppressing Wnt signalling, even in situations where Wnt signalling is usually constitutively elevated, such as APC deficiency. See, e.g., Huang *et al.*, 2009. These data suggest that tankyrase inhibition could be used in order to modulate Wnt signalling, both in cancer, but also in other, non-cancer, pathologies where Wnt signalling is aberrant.

In addition to its effects on Wnt signally, it has also recently been demonstrated that silencing of tankyrase 1 by RNA interference is lethal in tumour cells with deficiencies in either of the breast cancer susceptibility proteins, BRCA1 and BRCA2, but not in wild type cells. *BRCA* mutation carriers with cancer still retain functional BRCA protein function in their normal cells, whilst it is lacking in tumour cells, suggesting that a tankyrase 1 inhibitor could be used to selectively target tumour cells in *BRCA* patients. See, e.g., McCabe *et al.*, 2009b. This approach of combining tumour-specific genetic deficiencies with inhibition of a drug target to elicit a therapeutic window is an example of a "synthetic lethal" approach to the design of cancer therapies. See, e.g., Kaelin, 2009. This BRCA selective effect of tankyrase 1 inhibition may be caused by telomere attrition (caused by tankyrase 1 inhibition) and stalled replication forks (caused by BRCA deficiency) acting in concert to cause a threshold of DNA damage that is inconsistent with cell viability. Alternatively, synergistic defects in cytokinesis and sister chromatid segregation caused by BRCA deficiency and tankyrase 1 inhibition may also underlie the BRCA selective effect. See, e.g., Daniels, 2004. The use of tankyrase 1 inhibition in this context is described in McCabe *et al.*, 2009a and McCabe *et al.*, 2009b.

It has been shown that a proportion of patients without *BRCA* mutations have clinical characteristics, tumour morphologies and tumour molecular profiles that are reminiscent of *BRCA* mutation-associated cancer, a property termed BRCAness. See, e.g., Turner *et al.*, 2004. This BRCAness phenotype is most well described in a significant number of patients with triple negative breast tumours. See, e.g., Turner *et al.*, 2004. It has been shown that BRCA1 deficient, triple-negative breast cancer cell lines such as HCC1937 are particularly sensitive to tankyrase 1 inhibition. See, e.g., McCabe *et al.*, 2009a and McCabe *et al.*, 2009b. Inhibiting tankyrase 1 therefore, may be very effective in patients with germ-line *BRCA* mutations as well as patients whose tumours exhibit a BRCAness phenotype.

Non-Tumourigenic Mechanisms Modulated by Tankyrase

In addition to tankyrase inhibitors having potential as cancer therapeutics, a number of other studies suggest tankyrase inhibitors could be used in a number of other non-cancer related pathologies, the majority of which are driven by aberrant Wnt signalling, of which tankyrase activity is a rate limiting step (see, e.g., Riffell et al., 2012).

For example:

Recent work has indicated that inhibition of tankyrase can stabilize Axin2 levels in immature oligodendrocyte progenitor cells (OLPs) (see, e.g., Fancy *et al.*, 2011). On the basis that Axin2 function is essential for normal kinetics of remyelination, tankyrase inhibition has been shown to accelerate OLP myelination after hypoxic and demyelinating injury (see, e.g., Fancy *et al.*, 2011). This data suggest that small molecule tankyrase inhibitors might serve as pharmacological agents that could aid remyelination in neuropathies such as multiple sclerosis, neonatal hypoxic ischemic encephalopathy (HIE), and neonatal periventricular leukomalacia (PVL) (see, e.g., Fancy *et al.*, 2011).

Other studies have also shown that tankyrase is essential for Herpes Simplex Virus replication (HSV). Efficient HSV-1 replication requires tankyrase PARP activity (see, e.g., Li *et al.*, 2011). Further support for this hypothesis comes from the observation that HSV did not replicate efficiently in cells depleted of tankyrase 1. Moreover, tankyrase and the tankyrase substrate TRF2 (telomeric repeat binding factor 2) control the degradation of Ebstein-Barr Virus (EBV) DNA (see, e.g., Deng *et al.*, 2002), suggesting tankyrase inhibitors could have utility as antiviral agents.

In addition, tankyrase inhibition is known to modulate glucose uptake (see, e.g., Yeh *et al.*, 2007), suggesting that a small molecule tankyrase inhibitor could have utility in the treatment of metabolic diseases such as type 2 diabetes. In this case, tankyrase inhibition is thought to modulate glucose uptake by altering the function and cellular localisation of the glucose transporter type 4 (GLUT4) and the aminopeptidase IRAP (insulin-responsive aminopeptidase).

In addition, tankyrase inhibition is known to induce cardiomyocyte differentiation (see, e.g., Wang *et al.*, 2011), suggesting that small molecule tankyrase inhibitors could have some ability in the treatment of cardiac disorders, such as cardiac repair after cardiac infarction.

In addition, tankyrase inhibition is know to minimise the pathological effects of lung fibrosis and tankyrase inhibitors can improve the survival of mice with bleomycin induced lung fibrosis (see, e.g., Distler *et al.*, 2012) suggesting that small molecule tankyrase

inhibitors could have some usefuleness in the treatment of lung disorders and fibrotic disorders such as pulmonary fibrosis, cystic fibrosis, cirrhosis, endomyocardial fibrosis, mediastinal fibrosis, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, nephrogenic systemic fibrosis, Crohn's disease, keloid, scleroderma/systemic sclerosis and arthrofibrosis.

In addition to these pathologies, Wnt signalling and its modulation are also involved in a number of other pathogenic conditions suggesting that small molecules tankyrase inhibitors could have utility in these other Wnt related diseases, including:

Alzheimer's disease, where the Wnt mediator B-catenin activity is aberrant (see, e.g., Caricasole *et al.*, 2003; Moon *et al.*, 2004; Mudher and Lovestone, 2002);

Dupuytren skin disease, where the Wnt mediator B-catenin activity is also aberrant (see, e.g., Varallo *et al.*, 2003);

tooth agenesis, where the Wnt mediator Axin2 activity is aberrant (see, e.g., Lammi *et al.*, 2004);

osteoarthritis, where the Wnt mediator secreted frizzled-related protein 3 (FRP3) activity is aberrant (see, e.g., Loughlin *et al.*, 2004);

exudative vitreoretinopathy, where the Wnt mediators frizzled family receptor 4 (FZD4) (see, e.g., Robitaille *et al.*, 2002) and Norrie disease protein (see, e.g., Xu *et al.*, 2004) activities are aberrant;

schizophrenia, where the Wnt mediators glycogen synthase kinase 3 beta (GSK3b) and wingless-type MMTV integration site family member 1 (Wnt1) are aberrant (see, e.g., Kozlovsky *et al.*, 2002; Miyaoka *et al.*, 1999);

osteoporosis, where the Wnt mediator low density lipoprotein receptor-related protein 5 (LRP5) activity is aberrant (see, e.g., Gong *et al.*, 2001);

dermal hypoplasia, where the Wnt mediator porcupine homolog (PORCN) activity is aberrant (see, e.g., Grzeschik *et al.*, 2007);

XX sex reversal, where the Wnt mediator R-spondin 1 (RSPO1) activity is aberrant (see, e.g., Parma *et al.*, 2006);

anonychia and hyponychia, were the Wnt mediator R-spondin 4 (RSPO4) is aberrant (see, e.g., Bergmann *et al.*, 2006; Blaydon *et al.*, 2006);

sclerosteosis and Van Buchem disease, where the Wnt mediator sclerostin (SOST) activity is aberrant (see, e.g., Balemans *et al.*, 2001; Balemans *et al.*, 2002);

Fuhrmann syndrome, were the Wnt mediator wingless-related MMTV integration site 7A (Wnt7a) activity is aberrant (see, e.g., Woods *et al.*, 2006);

Odonto-onchyo-dermal hypoplasia, where Wnt mediator wingless related MMTV integration site 10a (Wnt10a) activity is aberrant (see, e.g., Adaimy *et al.*, 2007); and

early onset obesity, where the Wnt mediator wingless related MMTV integration site 10b (Wnt10b) activity is aberrant (see, e.g., Christodoulides *et al.*, 2006).

Moreover, aberrant telomerase protein component TERT expression and aberrant Wnt signalling are implicated in nephropathy, including HIV-associated nephropathy (see, e.g., Shkreli *et al.*, 2011). Given the strong link between tankyrase inhibitors and modulation of both Wnt signalling and TERT function, it is likely that small molecule tankyrase inhibitors could be used in the treatment of these pathologies.

The inventors have identified a class of small molecule inhibitors of PARP superfamily members including PARP1 and Tankyrase 1 which are useful in the treatment of conditions, including proliferative conditions such as cancer. In some cases, these inhibitors are able to elicit biochemical inhibition of these targets as well as eliciting cellular activity including one or more or all of: (i) inhibition of Wnt signalling; (ii) inhibition of cell survival/proliferation; (iii) stabilisation of Axin and tankyrase levels; and (iv) formation of markers of DNA damage such as γH2AX foci.

It appears that the following 3-aryl-5-*substituted*-2H-isoquinolin-1-ones are known.

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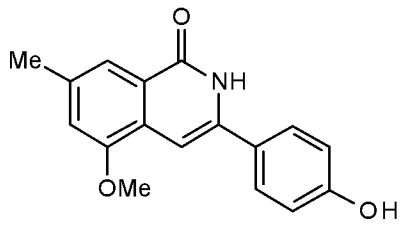
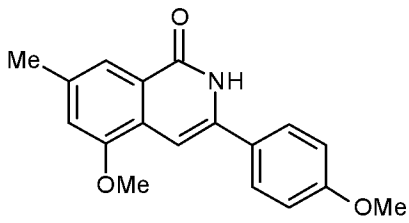
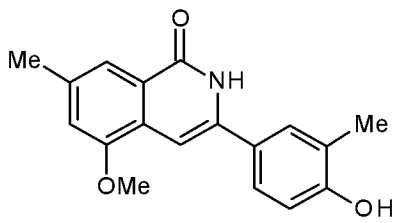
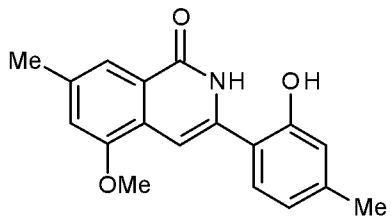
P01		70351-69-8
P02		70351-70-1
P03		70351-71-2
P04		70351-72-3

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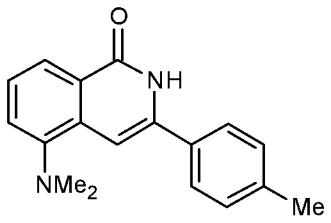
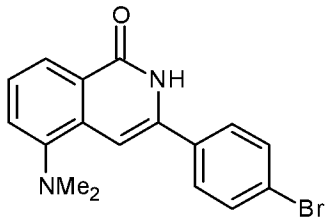
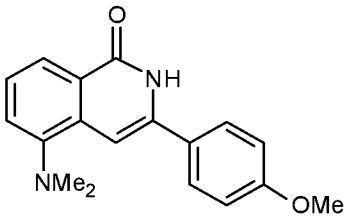
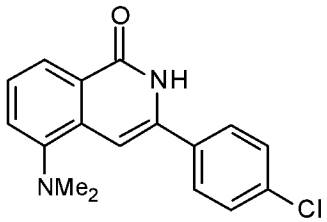
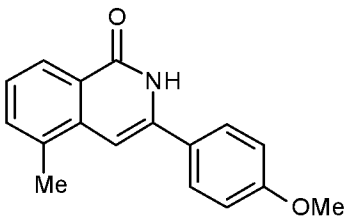
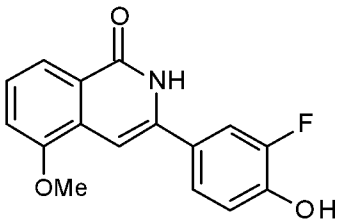
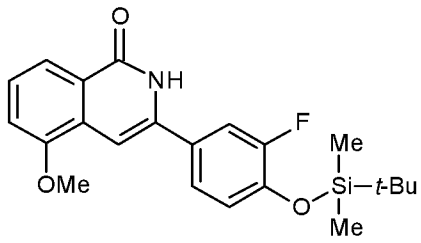
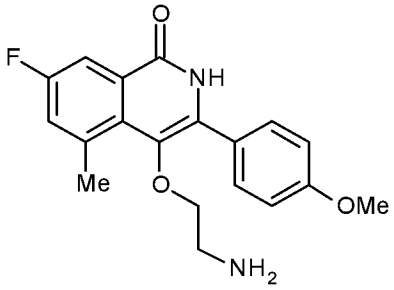
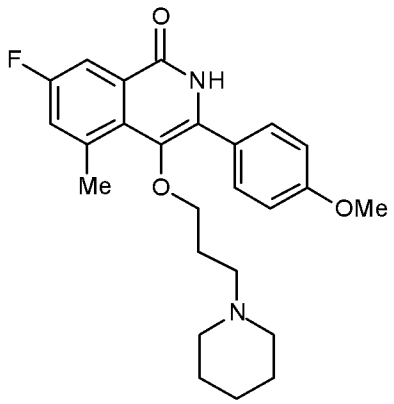
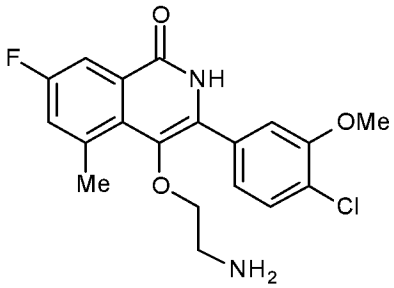
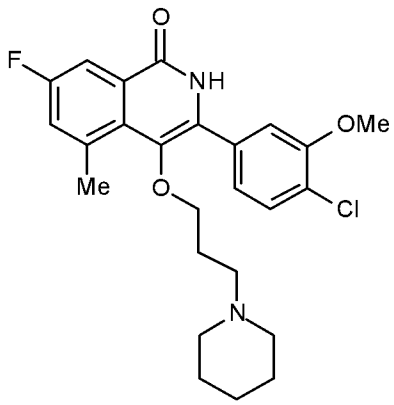
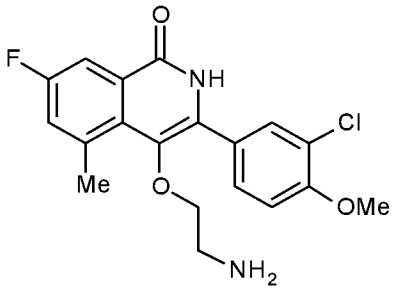
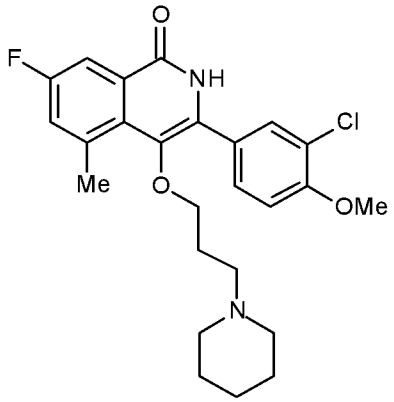
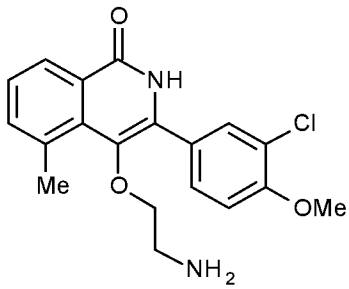
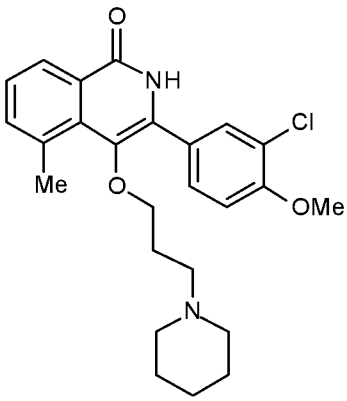
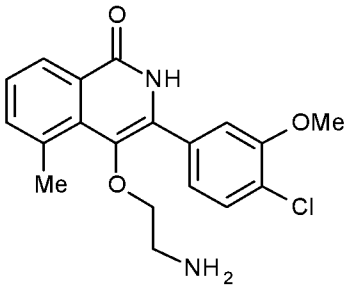
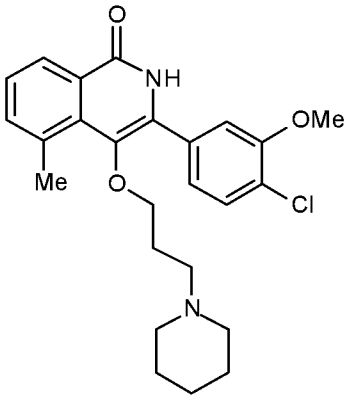
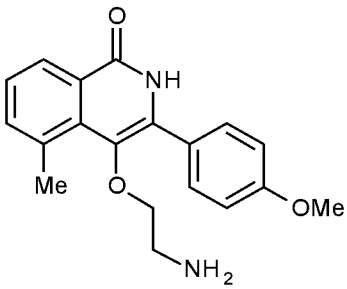
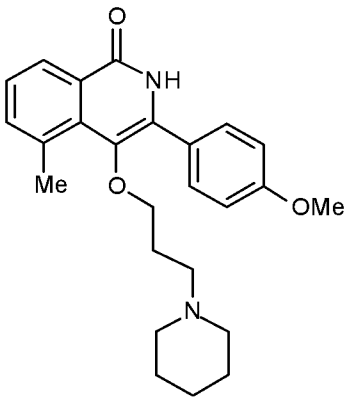
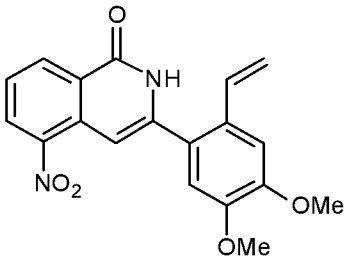
P05		203628-15-3
P06		203628-17-5
P07		203628-19-7
P08		220630-92-2
P09		223553-35-3
P10		884500-93-0

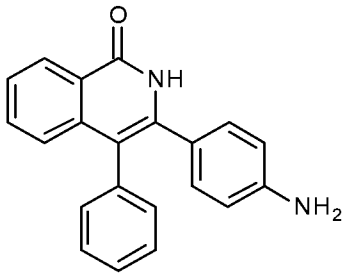
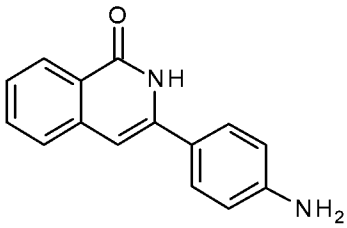
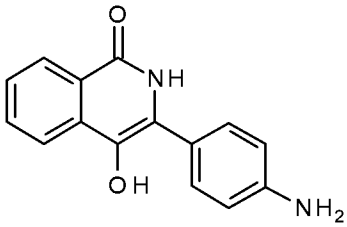
#	Structure	Registry No.
P11		884501-99-9
P12		1256940-02-9
P13		1256940-03-0
P14		1256940-06-3

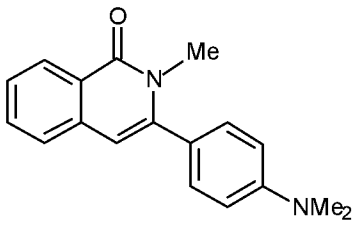
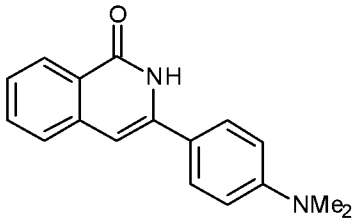
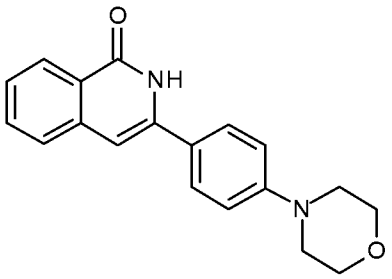
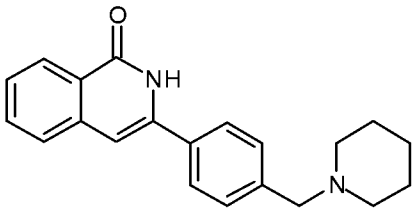
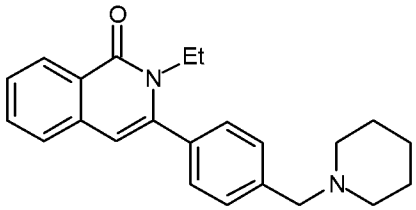
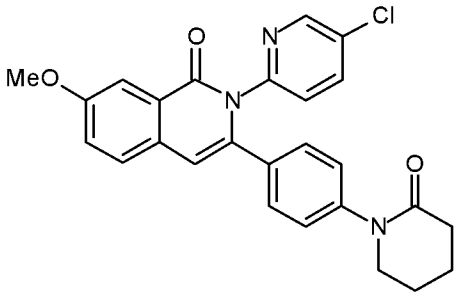
#	Structure	Registry No.
P15		1256940-07-4
P16		1256940-08-5
P17		1256940-09-6
P18		1256940-10-9

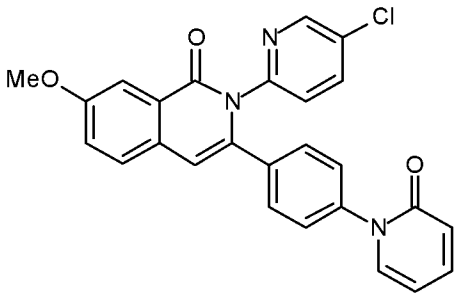
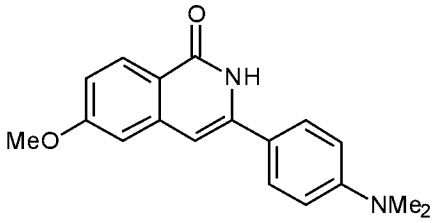
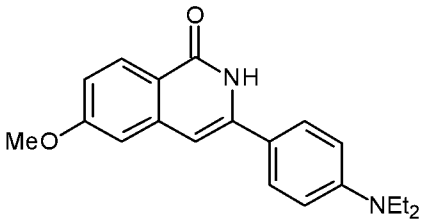
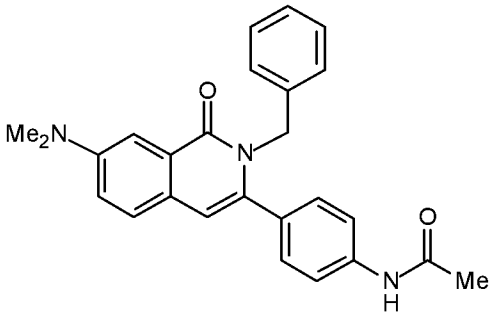
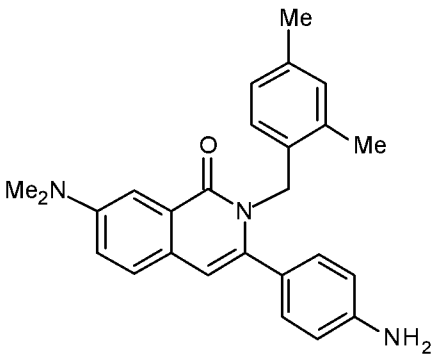
#	Structure	Registry No.
P19		1256940-11-0
P20		1256940-12-1
P21		1256940-13-2
P22		1256940-16-5

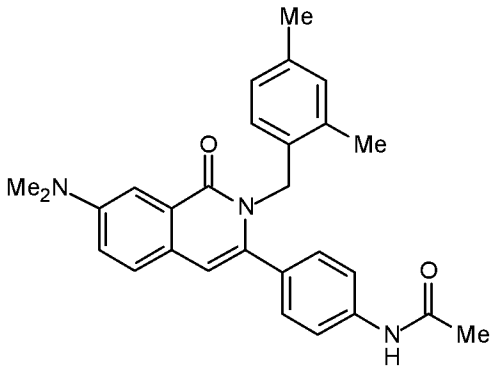
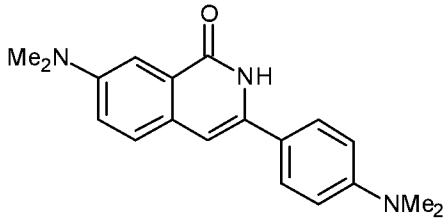
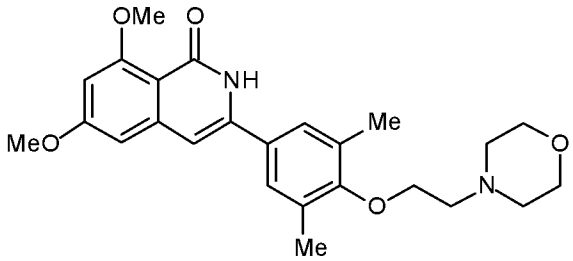
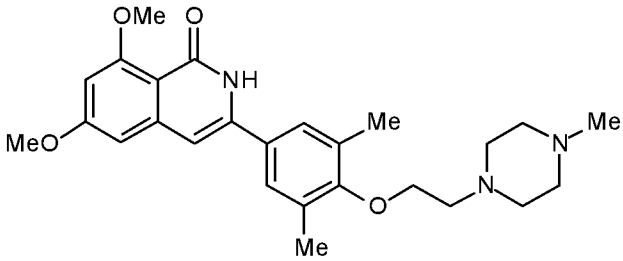
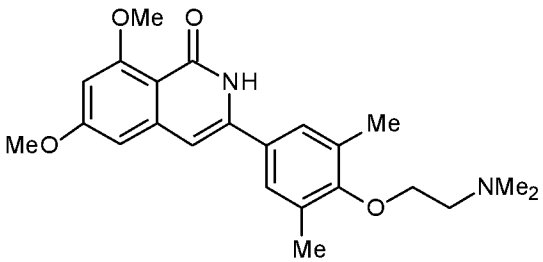
#	Structure	Registry No.
P23		1256940-17-6
P24		1262335-24-9

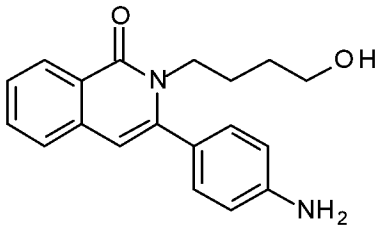
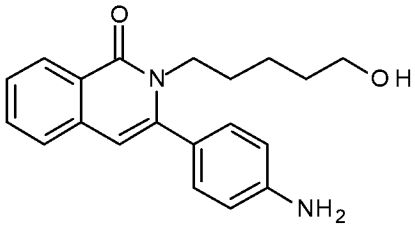
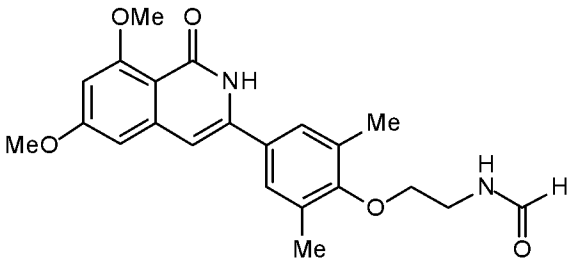
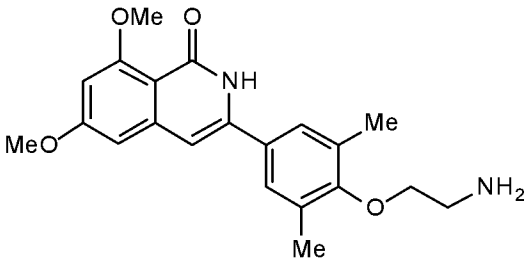
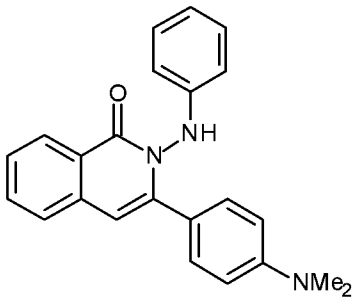
It appears that the following 3-aryl-5-*unsubstituted*-2H-isoquinolin-1-ones are known.

#	Structure	Registry No.
P25		19069-81-9
P26		98659-53-1
P27		98659-55-3

#	Structure	Registry No.
P28		145104-33-2
P29		223552-86-1
P30		223553-20-6
P31		376354-94-8
P32		376354-97-1
P33		503613-43-2

#	Structure	Registry No.
P34		503613-44-3
P35		630423-61-9
P36		630423-64-2
P37		721960-58-3
P38		721960-60-7

#	Structure	Registry No.
P39		721960-73-2
P40		862469-72-5
P41		924299-93-4
P42		1044871-80-8
P43		1044871-83-1

#	Structure	Registry No.
P44		1193268-39-1
P45		1193268-40-4
P46		1253733-07-1
P47		1253733-10-6
P48		1417652-57-3

SUMMARY OF THE INVENTION

One aspect of the invention pertains to certain 3-aryl-5-substituted-2H-isoquinolin-1-one compounds (referred to herein as IQ compounds), as described herein.

Another aspect of the invention pertains to a composition (e.g., a pharmaceutical composition) comprising an IQ compound, as described herein, and a pharmaceutically acceptable carrier or diluent.

Another aspect of the invention pertains to a method of preparing a composition (e.g., a pharmaceutical composition) comprising the step of mixing an IQ compound, as described herein, and a pharmaceutically acceptable carrier or diluent.

Another aspect of the present invention pertains to a method of inhibiting PARP (e.g., PARP1, TNKS1, TNKS2, *etc.*) function (e.g., in a cell), *in vitro* or *in vivo,* comprising contacting the cell with an effective amount of an IQ compound, as described herein.

Another aspect of the present invention pertains to a method of inhibiting Wnt signalling (e.g., in a cell), *in vitro* or *in vivo,* comprising contacting the cell with an effective amount of an IQ compound, as described herein.

Another aspect of the present invention pertains to a method of treatment comprising administering to a subject in need of treatment a therapeutically-effective amount of an IQ compound, as described herein, preferably in the form of a pharmaceutical composition.

Another aspect of the present invention pertains to an IQ compound as described herein for use in a method of treatment of the human or animal body by therapy.

Another aspect of the present invention pertains to use of an IQ compound, as described herein, in the manufacture of a medicament for use in treatment.

In one embodiment, the treatment is treatment of a proliferative condition.

In one embodiment, the treatment is treatment of cancer.

In one embodiment, the treatment is treatment of head cancer; neck cancer; nervous system cancer; lung/mediastinum cancer; breast cancer; oesophagus cancer; stomach cancer; liver cancer; biliary tract cancer; pancreatic cancer; small bowel cancer; large bowel cancer; gynaecological cancer; genito-urinary cancer; thyroid gland cancer; adrenal gland cancer; skin cancer; bone sarcoma; soft tissue sarcoma; paediatric malignancy; Hodgkin's disease; non-Hodgkin's lymphoma; myeloma; leukaemia; or metastasis from an unknown primary site.

In one embodiment, the treatment is treatment of: a neurodegenerative disorder, such as multiple sclerosis (MS); a neurological disorder associated with demyelination; neonatal hypoxic ischemic encephalopathy (HIE); neonatal periventricular leukomalacia (PVL); a cardiac related pathology, such as myocardial infarction; cardiac damage (e.g., to repair cardiac damage); an infectious disease, such as a pathology related to Herpes Simplex Virus (HSV); a pathology related to Epstein-Barr Virus (EBV); a metabolic disease, such as a metabolic disease where glucose uptake is dysfunctional, such as diabetes, such as type 2 diabetes; or fibrosis (e.g., lung fibrosis).

In one embodiment, the treatment is treatment of: a neurodegenerative disorder, such as multiple sclerosis (MS); neonatal hypoxic ischemic encephalopathy (HIE); neonatal periventricular leukomalacia (PVL); a cardiac related pathology, such as myocardial infarction; a pathology related to Herpes Simplex Virus (HSV); a pathology related to Epstein-Barr Virus (EBV); or a metabolic disease such as type 2 diabetes.

In one embodiment, the treatment is treatment of: Alzheimer's disease; late onset Alzheimer's disease; Dupuytren skin disease; tooth agenesis; vascular defects in the eye; Osteoperosis-pseudoglioma Syndrome (OPPG); exudative vitreoretinopathy; familial exudative vitreoretinopathy; retinal angiogenesis; schizophrenia; osteoporosis; dermal hypoplasia; XX sex reversal; Mullerian-duct regression and virilization; SERKAL syndrome; anonychia; hyponychia; sclerosteosis; van Buchem disease; Fuhrmann syndrome; odonto-onchyo-dermal hypoplasia; Type 2 diabetes; obesity; early onset obesity; a nephropathy, such as HIV-associated nephropathy; early coronary disease; bone density defects; tetra-amelia syndrome; split-hand/foot malformation; caudal duplication; Fuhrmann syndrome; odonto-onycho-dermal dysplasia; skeletal dysplasia; focal dermal hypoplasia; autosomal recessive anonychia; or neural tube defects.

In one embodiment, the treatment is treatment of: Alzheimer's disease; Dupuytren skin disease; tooth agenesis; exudative vitreoretinopathy; schizophrenia; osteoporosis; dermal hypoplasia; XX sex reversal; anonychia; hyponychia; sclerosteosis; van Buchem disease; Fuhrmann syndrome; odonto-onchyo-dermal hypoplasia; early onset obesity; or a nephropathy, such as HIV-associated nephropathy.

Another aspect of the present invention pertains to a kit comprising (a) an IQ compound, as described herein, preferably provided as a pharmaceutical composition and in a suitable container and/or with suitable packaging; and (b) instructions for use, for example, written instructions on how to administer the compound.

Another aspect of the present invention pertains to an IQ compound *obtainable* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

Another aspect of the present invention pertains to an IQ compound *obtained* by a method of synthesis as described herein, or a method comprising a method of synthesis as described herein.

Another aspect of the present invention pertains to novel intermediates, as described herein, which are suitable for use in the methods of synthesis described herein.

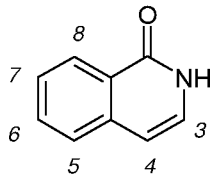
Another aspect of the present invention pertains to the use of such novel intermediates, as described herein, in the methods of synthesis described herein.

As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspects of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Compounds

One aspect of the present invention relates to certain compounds which are structurally related to 2H-isoquinolin-1-one.



2H-Isoquinolin-1-one

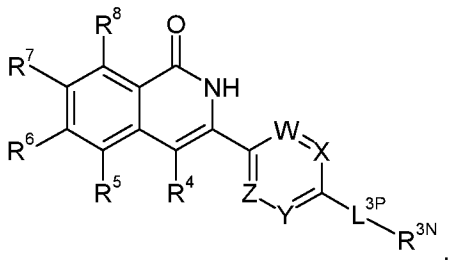
More particularly, the present invention relates to certain 3-aryl-5-substituted-2H-isoquinolin-1-one compounds, as defined herein.

Yet more particularly, the present invention relates to certain 2H-isoquinolin-1-one compounds which have both:

(a) a *particular* substituent (denoted herein as R^5) at the 5-position; and

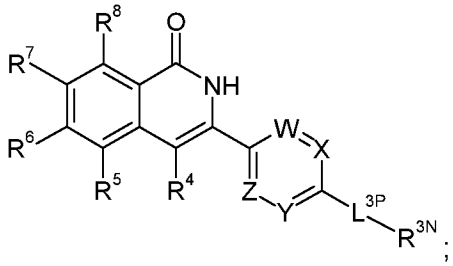
(b) a *particular* six-membered carboaryl or heteroaryl substituent (denoted herein as the ring containing W, X, Y, and Z) at the 3-position having a *particular* para-substituent (denoted herein as $-L^{3P}-R^{3N}$).

Thus, one aspect of the present invention pertains to compounds selected from compounds of the following formula, and pharmaceutically acceptable salts, N-oxides, hydrates, and solvates thereof, wherein $-R^{3N}$, $-L^{3P}-$, W, X, Y, Z, $-R^4$, $-R^5$, $-R^6$, $-R^7$, and $-R^8$ are as defined herein (for convenience, collectively referred to herein as "3-aryl-5-substituted-2H-isoquinolin-1-one compounds" or "IQ compounds"):



Some embodiments of the invention include the following:

(1) A compound selected from compounds of the following formula, and pharmaceutically acceptable salts, N-oxides, hydrates, and solvates thereof:



;

wherein:

W is CR^W, X is CR^X, Y is CR^Y, and Z is CR^Z ("phenyl"); or
W is N, X is CR^X, Y is CR^Y, and Z is CR^Z ("pyrid-2-yl"); or
W is CR^W, X is N, Y is CR^Y, and Z is CR^Z ("pyrid-3-yl"); or
W is N, X is CR^X, Y is CR^Y, and Z is N ("pyrimidin-2-yl"); or
W is CR^W, X is N, Y is N, and Z is CR^Z ("pyrimidin-5-yl"); or
W is N, X is CR^X, Y is N, and Z is CR^Z ("pyrazin-2-yl"); or
W is N, X is N, Y is CR^Y, and Z is CR^Z ("pyridazin-3-yl");

wherein:

$-R^W$ is independently -H or $-R^{WW}$;
$-R^X$ is independently -H or $-R^{XX}$;
$-R^Y$ is independently -H or $-R^{YY}$; and
$-R^Z$ is independently -H or $-R^{ZZ}$;

wherein:

$-R^{WW}$ is independently $-X^1$, $-R^1$, -OH, $-OR^1$, $-CF_3$, or $-OCF_3$;
$-R^{XX}$ is independently $-X^1$, $-R^1$, -OH, $-OR^1$, $-CF_3$, or $-OCF_3$;
$-R^{YY}$ is independently $-X^1$, $-R^1$, -OH, $-OR^1$, $-CF_3$, or $-OCF_3$; and
$-R^{ZZ}$ is independently $-X^1$, $-R^1$, -OH, $-OR^1$, $-CF_3$, or $-OCF_3$;

wherein:

each $-X^1$ is independently -F, -Cl, -Br, or -I; and
each $-R^1$ is independently linear or branched saturated C_{1-4}alkyl;

and wherein:

$-L^{3P}-$ is independently a single covalent bond or $-L^{3PL}-$;

wherein:

$-L^{3PL}-$ is independently $-L^{3PR1}-$, $-C(=O)-$, $-L^{3PR2}-C(=O)-$, $-S(=O)_2-$, $-L^{3PR3}-S(=O)_2-$, or $-O-L^{3PR4}-$;

wherein:

each $-L^{3PR1}-$ is linear or branched saturated C_{1-4}alkylene;

each $-L^{3PR2}-$ is linear or branched saturated C_{1-4}alkylene;

each $-L^{3PR3}-$ is linear or branched saturated C_{1-4}alkylene;

each $-L^{3PR4}-$ is linear or branched saturated C_{1-4}alkylene;

and wherein:

$-R^{3N}$ is independently $-NH_2$, $-NHR^A$, $-NR^AR^B$, or $-NR^CR^D$;

wherein:

each $-R^A$ is independently:

$-R^{A1}$, $-R^{A2}$, $-R^{A3}$, $-R^{A4}$, $-R^{A5}$, $-L^A-R^{A2}$, $-L^A-R^{A3}$, $-L^A-R^{A4}$, or $-L^A-R^{A5}$;

each $-R^{A1}$ is linear or branched saturated C_{1-6}alkyl,

and is optionally substituted with one or more groups $-R^{S1}$;

each $-R^{A2}$ is saturated C_{3-6}cycloalkyl,

and is optionally substituted with one or more groups $-R^{S2C}$;

each $-R^{A3}$ is non-aromatic C_{3-7}heterocyclyl,

and is optionally substituted *on carbon* with one or more groups $-R^{S2C}$,

and is optionally substituted *on secondary nitrogen, if present,* with a group $-R^{SN}$;

each $-R^{A4}$ is independently phenyl or naphthyl,

and is optionally substituted with one or more groups $-R^{S3C}$;

each $-R^{A5}$ is C_{5-10}heteroaryl,

and is optionally substituted *on carbon* with one or more groups $-R^{S3C}$,

and is optionally substituted *on secondary nitrogen, if present,* with a group $-R^{SN}$;

each $-L^A-$ is linear or branched saturated C_{1-4}alkylene;

and wherein:

each $-R^{S1}$ is independently:

$-F$, $-Cl$, $-Br$, $-I$,

$-OH$, $-OR^{TT}$,

$-OCF_3$,

$-NH_2$, $-NHR^{TT}$, $-NR^{TT}_2$, $-R^{TM}$,

$-C(=O)OH$, $-C(=O)OR^{TT}$, $-OC(=O)R^{TT}$,

$-C(=O)NH_2$, $-C(=O)NHR^{TT}$, $-C(=O)NR^{TT}_2$, $-C(=O)R^{TM}$,
$-NHC(=O)R^{TT}$, $-NR^{TN}C(=O)R^{TT}$,
$-NHC(=O)NH_2$, $-NHC(=O)NHR^{TT}$, $-NHC(=O)NR^{TT}_2$, $-NHC(=O)R^{TM}$,
$-NR^{TN}C(=O)NH_2$, $-NR^{TN}C(=O)NHR^{TT}$, $-NR^{TN}C(=O)NR^{TT}_2$, $-NR^{TN}C(=O)R^{TM}$,
$-NHC(=O)OR^{TT}$, $-NR^{TN}C(=O)OR^{TT}$,
$-OC(=O)NH_2$, $-OC(=O)NHR^{TT}$, $-OC(=O)NR^{TT}_2$, $-OC(=O)R^{TM}$,
$-C(=O)R^{TT}$,
$-S(=O)_2NH_2$, $-S(=O)_2NHR^{TT}$, $-S(=O)_2NR^{TT}_2$, $-S(=O)_2R^{TM}$,
$-NHS(=O)_2R^{TT}$, $-NR^{TN}S(=O)_2R^{TT}$,
$-S(=O)_2R^{TT}$,
$-CN$, $-NO_2$, $-SR^{TT}$, or $=O$;

each $-R^{S2C}$ is independently:

$-R^{TT}$,
$-F$, $-Cl$, $-Br$, $-I$,
$-OH$, $-OR^{TT}$,
$-L^T-OH$, $-L^T-OR^{TT}$,
$-CF_3$, $-OCF_3$,
$-NH_2$, $-NHR^{TT}$, $-NR^{TT}_2$, $-R^{TM}$,
$-L^T-NH_2$, $-L^T-NHR^{TT}$, $-L^T-NR^{TT}_2$, $-L^T-R^{TM}$,
$-C(=O)OH$, $-C(=O)OR^{TT}$, $-OC(=O)R^{TT}$,
$-C(=O)NH_2$, $-C(=O)NHR^{TT}$, $-C(=O)NR^{TT}_2$, $-C(=O)R^{TM}$,
$-NHC(=O)R^{TT}$, $-NR^{TN}C(=O)R^{TT}$,
$-NHC(=O)NH_2$, $-NHC(=O)NHR^{TT}$, $-NHC(=O)NR^{TT}_2$, $-NHC(=O)R^{TM}$,
$-NR^{TN}C(=O)NH_2$, $-NR^{TN}C(=O)NHR^{TT}$, $-NR^{TN}C(=O)NR^{TT}_2$, $-NR^{TN}C(=O)R^{TM}$,
$-NHC(=O)OR^{TT}$, $-NR^{TN}C(=O)OR^{TT}$,
$-OC(=O)NH_2$, $-OC(=O)NHR^{TT}$, $-OC(=O)NR^{TT}_2$, $-OC(=O)R^{TM}$,
$-C(=O)R^{TT}$,
$-S(=O)_2NH_2$, $-S(=O)_2NHR^{TT}$, $-S(=O)_2NR^{TT}_2$, $-S(=O)_2R^{TM}$,
$-NHS(=O)_2R^{TT}$, $-NR^{TN}S(=O)_2R^{TT}$,
$-S(=O)_2R^{TT}$,
$-CN$, $-NO_2$, $-SR^{TT}$, or $=O$;

each $-R^{S3C}$ is independently:

$-R^{TT}$,
$-F$, $-Cl$, $-Br$, $-I$,
$-OH$, $-OR^{TT}$,
$-L^T-OH$, $-L^T-OR^{TT}$,
$-CF_3$, $-OCF_3$,

-NH_2, -NHR^{TT}, -NR^{TT}_2, -R^{TM},
-L^T-NH_2, -L^T-NHR^{TT}, -L^T-NR^{TT}_2, -L^T-R^{TM},
-C(=O)OH, -C(=O)OR^{TT}, -OC(=O)R^{TT},
-C(=O)NH_2, -C(=O)NHR^{TT}, -C(=O)NR^{TT}_2, -C(=O)R^{TM},
-NHC(=O)R^{TT}, -NR^{TN}C(=O)R^{TT},
-NHC(=O)NH_2, -NHC(=O)NHR^{TT}, -NHC(=O)NR^{TT}_2, -NHC(=O)R^{TM},
-NR^{TN}C(=O)NH_2, -NR^{TN}C(=O)NHR^{TT}, -NR^{TN}C(=O)NR^{TT}_2, -NR^{TN}C(=O)R^{TM},
-NHC(=O)OR^{TT}, -NR^{TN}C(=O)OR^{TT},
-OC(=O)NH_2, -OC(=O)NHR^{TT}, -OC(=O)NR^{TT}_2, -OC(=O)R^{TM},
-C(=O)R^{TT},
-S(=O)$_2NH_2$, -S(=O)$_2NHR^{TT}$, -S(=O)$_2NR^{TT}_2$, -S(=O)$_2R^{TM}$,
-NHS(=O)$_2R^{TT}$, -NR^{TN}S(=O)$_2R^{TT}$,
-S(=O)$_2R^{TT}$,
-CN, -NO_2, or -SR^{TT};

and additionally, two adjacent groups -R^{S3C}, if present, may together form: -O-CH_2-O- or -O-CH_2CH_2-O-;

each -R^{SN} is independently:

-R^{TT},
-L^T-OH, -L^T-OR^{TT},
-L^T-NH_2, -L^T-NHR^{TT}, -L^T-NR^{TT}_2, -L^T-R^{TM},
-C(=O)R^{TT},
-C(=O)OR^{TT},
-C(=O)NH_2, -C(=O)NHR^{TT}, -C(=O)NR^{TT}_2, -C(=O)R^{TM}, or
-S(=O)$_2R^{TT}$;

wherein:

each -L^T- is linear or branched saturated C_{1-4}alkylene;

each -R^{TT} is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl; wherein said linear or branched saturated C_{1-4}alkyl is optionally substituted with -OH or -OR^{TTT}, wherein -R^{TTT} is linear or branched saturated C_{1-4}alkyl;

each -R^{TN} is linear or branched saturated C_{1-4}alkyl;

each -R^{TM} is independently azetidino, pyrrolidino, piperidino, piperazino, morpholino, azepano, or diazepano, and is:

optionally substituted *on carbon* with one or more groups selected from: -R^{TMM}, -C(=O)R^{TMM}, -S(=O)$_2R^{TMM}$, -F, -NH_2, -NHR^{TMM}, -NR^{TMM}_2, -OH, and -OR^{TMM}; and

optionally substituted *on secondary nitrogen, if present,* with a group selected from: $-R^{TMM}$, $-C(=O)R^{TMM}$, $-C(=O)OR^{TMM}$, and $-S(=O)_2R^{TMM}$;

wherein each $-R^{TMM}$ is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl;

and wherein:

$-R^B$ is independently $-R^{B1}$, $-R^{B2}$, or $-L^B-R^{B2}$;

$-R^{B1}$ is linear or branched saturated C_{1-6}alkyl, and is optionally substituted with -OH or $-OR^{BB}$, wherein $-R^{BB}$ is linear or branched saturated C_{1-4}alkyl;

$-R^{B2}$ is saturated C_{3-6}cycloalkyl; and

$-L^B-$ is linear or branched saturated C_{1-4}alkylene;

and wherein:

$-NR^CR^D$ is independently $-NR^{C1}R^{D1}$, $-NR^{C2}R^{D2}$, $-NR^{C3}R^{D3}$, $-NR^{C4}R^{D4}$, or $-NR^{C5}R^{D5}$;

wherein:

$-NR^{C1}R^{D1}$ is a monocyclic non-aromatic heterocyclyl group having from 4 to 8 ring atoms, wherein exactly 1 of said ring atoms is a ring heteroatom, and is N, or exactly 2 of said ring atoms are ring heteroatoms, and are both N, or exactly 2 of said ring atoms are ring heteroatoms, and are N and O, or exactly 2 of said ring atoms are ring heteroatoms, and are N and S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$;

and wherein said monocyclic non-aromatic heterocyclyl group is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

optionally substituted *on secondary nitrogen, if present,* with a group $-R^{NN}$;

$-NR^{C2}R^{D2}$ is a fused bicyclic non-aromatic heterocyclyl group having from 7 to 12 ring atoms, wherein exactly 1 of said ring atoms is a ring heteroatom, and is N, or exactly 2 of said ring atoms are ring heteroatoms, and are both N, or exactly 2 of said ring atoms are ring heteroatoms, and are N and O, or exactly 2 of said ring atoms are ring heteroatoms, and are N and S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$, or exactly 3 of said ring atoms are ring heteroatoms, one of which is N, and each of the other two is independently N, O, or S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$;

and wherein said fused bicyclic non-aromatic heterocyclyl group is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

optionally substituted *on secondary nitrogen, if present,* with a group $-R^{NN}$;

$-NR^{C3}R^{D3}$ is a bridged non-aromatic heterocyclyl group having from 7 to 11 ring atoms, wherein exactly 1 of said ring atoms is a ring heteroatom, and is N, or exactly 2 of said ring atoms are ring heteroatoms, and are both N, or exactly 2 of said ring atoms are ring heteroatoms, and are N and O, or exactly 2 of said ring atoms are ring heteroatoms, and are N and S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$, or exactly 3 of said ring atoms are ring heteroatoms, one of which is N, and each of the other two is independently N, O, or S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$;

and wherein said bridged non-aromatic heterocyclyl group is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

optionally substituted *on secondary nitrogen, if present,* with a group $-R^{NN}$;

$-NR^{C4}R^{D4}$ is a spiro non-aromatic heterocyclyl group having from 6 to 12 ring atoms, wherein exactly 1 of said ring atoms is a ring heteroatom, and is N, or exactly 2 of said ring atoms are ring heteroatoms, and are both N, or exactly 2 of said ring atoms are ring heteroatoms, and are N and O, or exactly 2 of said ring atoms are ring heteroatoms, and are N and S, or exactly 3 of said ring atoms are ring heteroatoms, one of which is N, and each of the other two is independently N, O, or S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$;

and wherein said spiro non-aromatic heterocyclyl group is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

optionally substituted *on secondary nitrogen, if present,* with a group $-R^{NN}$;

wherein:

each $-R^{NC}$ is independently:

$-R^{QQ}$,
-F, -Cl, -Br, -I,
-OH, $-OR^{QQ}$,
$-L^{Q}$-OH, $-L^{Q}$-OR^{QQ},
$-CF_3$, $-OCF_3$,
$-NH_2$, $-NHR^{QQ}$, $-NR^{QQ}{}_2$, $-R^{QM}$,
$-L^{Q}$-NH_2, $-L^{Q}$-NHR^{QQ}, $-L^{Q}$-$NR^{QQ}{}_2$, $-L^{Q}$-R^{QM},
-C(=O)OH, $-C(=O)OR^{QQ}$, $-OC(=O)R^{QQ}$,
$-C(=O)NH_2$, $-C(=O)NHR^{QQ}$, $-C(=O)NR^{QQ}{}_2$, $-C(=O)R^{QM}$,
$-NHC(=O)R^{QQ}$, $-NR^{QN}C(=O)R^{QQ}$,
$-NHC(=O)NH_2$, $-NHC(=O)NHR^{QQ}$, $-NHC(=O)NR^{QQ}{}_2$, $-NHC(=O)R^{QM}$,
$-NR^{QN}C(=O)NH_2$, $-NR^{QN}C(=O)NHR^{QQ}$,
$-NR^{QN}C(=O)NR^{QQ}{}_2$, $-NR^{QN}C(=O)R^{QM}$,
$-NHC(=O)OR^{QQ}$, $-NR^{QN}C(=O)OR^{QQ}$,
$-OC(=O)NH_2$, $-OC(=O)NHR^{QQ}$, $-OC(=O)NR^{QQ}{}_2$, $-OC(=O)R^{QM}$,

$-C(=O)R^{QQ}$,
$-S(=O)_2NH_2$, $-S(=O)_2NHR^{QQ}$, $-S(=O)_2NR^{QQ}{}_2$, $-S(=O)_2R^{QM}$,
$-NHS(=O)_2R^{QQ}$, $-NR^{QN}S(=O)_2R^{QQ}$,
$-S(=O)_2R^{QQ}$,
$-CN$, $-NO_2$, $-SR^{QQ}$, or $=O$;

each $-R^{NN}$ is independently:

$-R^{QQ}$,
$-L^{Q}$-OH, $-L^{Q}$-OR^{QQ},
$-L^{Q}$-NH_2, $-L^{Q}$-NHR^{QQ}, $-L^{Q}$-$NR^{QQ}{}_2$, $-L^{Q}$-R^{QM},
$-C(=O)R^{QQ}$,
$-C(=O)OR^{QQ}$,
$-C(=O)NH_2$, $-C(=O)NHR^{QQ}$, $-C(=O)NR^{QQ}{}_2$, $-C(=O)R^{QM}$, or
$-S(=O)_2R^{QQ}$;

wherein:

each $-L^{Q}-$ is linear or branched saturated C_{1-4}alkylene;

each $-R^{QQ}$ is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl or benzyl; wherein said linear or branched saturated C_{1-4}alkyl is optionally substituted with -OH or $-OR^{QQQ}$, and said phenyl and benzyl are optionally substituted with $-R^{QQQ}$, wherein each $-R^{QQQ}$ is linear or branched saturated C_{1-4}alkyl;

each $-R^{QN}$ is linear or branched saturated C_{1-4}alkyl;

each $-R^{QM}$ is independently azetidino, pyrrolidino, piperidino, piperazino, morpholino, azepano, or diazepano, and is:

optionally substituted *on carbon* with one or more groups selected from: $-R^{QMM}$, $-C(=O)R^{QMM}$, $-S(=O)_2R^{QMM}$, -F, $-NH_2$, $-NHR^{QMM}$, $-NR^{QMM}{}_2$, -OH, and $-OR^{QMM}$; and

optionally substituted *on secondary nitrogen, if present,* with a group selected from: $-R^{QMM}$, $-C(=O)R^{QMM}$, $-C(=O)OR^{QMM}$, and $-S(=O)_2R^{QMM}$;

wherein each $-R^{QMM}$ is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl;

and wherein:

$-NR^{C5}R^{D5}$ is independently: 1H-pyrrol-1-yl; 2H-isoindol-2-yl; 1H-indol-1-yl; 1H-pyrazol-1-yl; 1H-benzoimidazol-1-yl; 1H-imidazol-1-yl; 2H-indazol-2-yl; 1H-indazol-1-yl; 4H-[1,2,4]triazol-4-yl; 1H-[1,2,3]triazol-1-yl; 1H-[1,2,4]triazol-1-yl; 1H-benzotriazol-1-yl; or 1H-tetrazol-1-yl; and is optionally substituted with one or more groups $-R^{H}$;

wherein each -R^H is independently:

-R^{HH},
-F, -Cl, -Br, -I,
-OH, -OR^{HH},
-L^H-OH, -L^H-OR^{HH},
-CF_3, -OCF_3,
-NH_2, -NHR^{HH}, -NR^{HH}_2, -R^{HM},
-L^H-NH_2, -L^H-NHR^{HH}, -L^H-NR^{HH}_2, -L^H-R^{HM},
-C(=O)OH, -C(=O)OR^{HH}, -OC(=O)R^{HH},
-C(=O)NH_2, -C(=O)NHR^{HH}, -C(=O)NR^{HH}_2, -C(=O)R^{HM},
-NHC(=O)R^{HH}, -NR^{HN}C(=O)R^{HH},
-NHC(=O)NH_2, -NHC(=O)NHR^{HH}, -NHC(=O)NR^{HH}_2, -NHC(=O)R^{HM},
-NR^{HN}C(=O)NH_2, -NR^{HN}C(=O)NHR^{HH}, -NR^{HN}C(=O)NR^{HH}_2, -NR^{HN}C(=O)R^{HM},
-NHC(=O)OR^{HH}, -NR^{HN}C(=O)OR^{HH},
-OC(=O)NH_2, -OC(=O)NHR^{HH}, -OC(=O)NR^{HH}_2, -OC(=O)R^{HM},
-C(=O)R^{HH},
-$S(=O)_2NH_2$, -$S(=O)_2NHR^{HH}$, -$S(=O)_2NR^{HH}_2$, -$S(=O)_2R^{HM}$,
-$NHS(=O)_2R^{HH}$, -$NR^{HN}S(=O)_2R^{HH}$,
-$S(=O)_2R^{HH}$,
-CN, -NO_2, or -SR^{HH};

wherein:

each -L^H- is linear or branched saturated C_{1-4}alkylene;

each -R^{HH} is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl; wherein said linear or branched saturated C_{1-4}alkyl is optionally substituted with -OH or -OR^{HHH}, wherein -R^{HHH} is linear or branched saturated C_{1-4}alkyl;

each -R^{HN} is linear or branched saturated C_{1-4}alkyl;

each -R^{HM} is independently azetidino, pyrrolidino, piperidino, piperazino, morpholino, azepano, or diazepano, and is:

optionally substituted *on carbon* with one or more groups selected from: -R^{HMM}, -C(=O)R^{HMM}, -$S(=O)_2R^{HMM}$, -F, -NH_2, -NHR^{HMM}, -NR^{HMM}_2, -OH, and -OR^{HMM}; and

optionally substituted *on secondary nitrogen, if present,* with a group selected from: -R^{HMM}, -C(=O)R^{HMM}, -C(=O)OR^{HMM}, and -$S(=O)_2R^{HMM}$;

wherein each -R^{HMM} is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl;

and wherein:

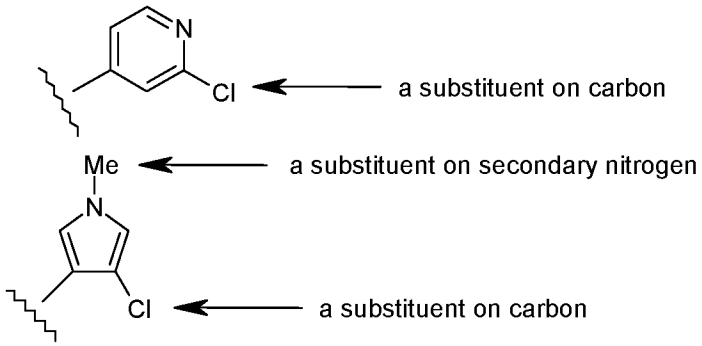
-R^5 is independently -R^{5A}, -R^{5B}, -R^{5C}, -R^{5D}, or -R^{5E};
-R^{5A} is linear or branched saturated C_{1-4}alkyl;
-R^{5B} is saturated C_{3-6}cycloalkyl;
-R^{5C} is independently -F, -Cl, -Br, or -I;
-R^{5D} is -CF_3; and
-R^{5E} is independently -C≡CH or C_{3-6}alkynyl optionally substituted with one or more groups -R^{EE}; wherein each -R^{EE} is independently selected from -OH, -OR^{EEE}, -NH_2, -NHR^{EEE}, and -NR^{EEE}_2; wherein each -R^{EEE} is linear or branched saturated C_{1-4}alkyl;

and wherein:

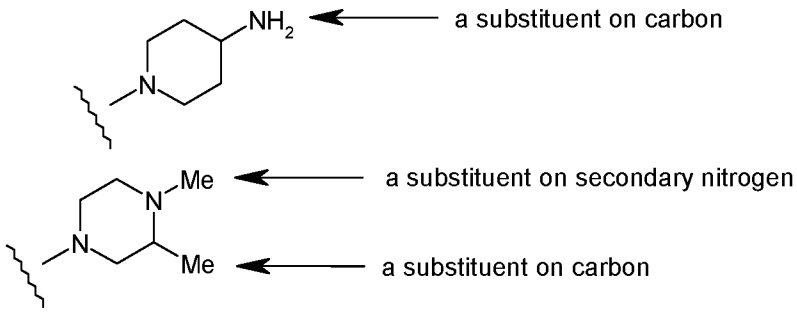
-R^4 is -H;
-R^6 is independently -H or -F; and
-R^7 is independently -H or -F; and
-R^8 is independently -H or -F.

For the avoidance of doubt, it is not intended that any two or more of -R^{3N}, -L^{3P}, W, X, Y, Z, -R^4, -R^5, -R^6, -R^7, and -R^8 together form a ring fused to the ring(s) to which they are attached. For example, it is not intended that -R^4 and -R^5 together form a ring fused to the ring to which they are attached. Similarly, it is not intended that -R^4 and Z together form a ring fused to the rings to which they are attached. Similarly, it is not intended that -R^4 and W together form a ring fused to the rings to which they are attached.

For the avoidance of doubt, the phrase “substituent on carbon” is intended to refer to a substituent which is attached to a carbon ring atom. Similarly, the phrase “substituent on secondary nitrogen” is intended to refer to a substituent which is attached to a nitrogen ring atom which, in the absence of the substituent, would be a secondary nitrogen ring atom (i.e., -NH-). Consequently, a pyridyl group may only have “substituents on carbon”, whereas 1H-pyrrole may have both “substituents on carbon” and a “substituent on secondary nitrogen”, as illustrated below.



Similarly, a piperidino group may only have "substituents on carbon", whereas piperizino may have both "substituents on carbon" and a "substituent on secondary nitrogen", as illustrated below.



The Groups W, X, Y, and Z

(2) A compound according to (1), wherein:
W is CR^W, X is CR^X, Y is CR^Y, and Z is CR^Z ("phenyl"); or
W is N, X is CR^X, Y is CR^Y, and Z is CR^Z ("pyrid-2-yl"); or
W is CR^W, X is N, Y is CR^Y, and Z is CR^Z ("pyrid-3-yl"); or
W is N, X is CR^X, Y is CR^Y, and Z is N ("pyrimidin-2-yl"); or
W is CR^W, X is N, Y is N, and Z is CR^Z ("pyrimidin-5-yl").

(3) A compound according to any (1), wherein:
W is CR^W, X is CR^X, Y is CR^Y, and Z is CR^Z ("phenyl"); or
W is CR^W, X is N, Y is CR^Y, and Z is CR^Z ("pyrid-3-yl"); or
W is CR^W, X is N, Y is N, and Z is CR^Z ("pyrimidin-5-yl").

(4) A compound according to (1), wherein:
W is CR^W, X is CR^X, Y is CR^Y, and Z is CR^Z ("phenyl").

(5) A compound according to (1), wherein:
W is CR^W, X is N, Y is CR^Y, and Z is CR^Z ("pyrid-3-yl").

(6) A compound according to (1), wherein:

W is CR^W, X is N, Y is N, and Z is CR^Z ("pyrimidin-5-yl").

The Group $-R^W$

(7) A compound according to any one of (1) to (6), wherein $-R^W$, if present, is -H.

(8) A compound according to any one of (1) to (6), wherein $-R^W$, if present, is $-R^{WW}$.

The Group $-R^X$

(9) A compound according to any one of (1) to (8), wherein $-R^X$, if present, is -H.

(10) A compound according to any one of (1) to (8), wherein $-R^X$, if present, is $-R^{XX}$.

The Group $-R^Y$

(11) A compound according to any one of (1) to (10), wherein $-R^Y$, if present, is -H.

(12) A compound according to any one of (1) to (10), wherein $-R^Y$, if present, is $-R^{YY}$.

The Group $-R^Z$

(13) A compound according to any one of (1) to (12), wherein $-R^Z$, if present, is -H.

(14) A compound according to any one of (1) to (12), wherein $-R^Z$, if present, is $-R^{ZZ}$.

The Group $-R^{WW}$

(15) A compound according to any one of (1) to (14), wherein $-R^{WW}$, if present, is independently $-X^1$, $-R^1$, or $-CF_3$.

(16) A compound according to any one of (1) to (14), wherein $-R^{WW}$, if present, is independently $-X^1$ or $-R^1$.

(17) A compound according to any one of (1) to (14), wherein $-R^{WW}$, if present, is independently $-X^1$.

(18) A compound according to any one of (1) to (14), wherein $-R^{WW}$, if present, is independently $-R^1$.

The Group -R^{XX}

(19) A compound according to any one of (1) to (18), wherein -R^{XX}, if present, is independently -X^1, -R^1, or -CF_3.

(20) A compound according to any one of (1) to (18), wherein -R^{XX}, if present, is independently -X^1 or -R^1.

(21) A compound according to any one of (1) to (18), wherein -R^{XX}, if present, is independently -X^1.

(22) A compound according to any one of (1) to (18), wherein -R^{XX}, if present, is independently -R^1.

The Group -R^{YY}

(23) A compound according to any one of (1) to (22), wherein -R^{YY}, if present, is independently -X^1, -R^1, or -CF_3.

(24) A compound according to any one of (1) to (22), wherein -R^{YY}, if present, is independently -X^1 or -R^1.

(25) A compound according to any one of (1) to (22), wherein -R^{YY}, if present, is independently -X^1.

(26) A compound according to any one of (1) to (22), wherein -R^{YY}, if present, is independently -R^1.

The Group -R^{ZZ}

(27) A compound according to any one of (1) to (26), wherein -R^{ZZ}, if present, is independently -X^1, -R^1, or -CF_3.

(28) A compound according to any one of (1) to (26), wherein -R^{ZZ}, if present, is independently -X^1 or -R^1.

(29) A compound according to any one of (1) to (26), wherein -R^{ZZ}, if present, is independently -X^1.

(30) A compound according to any one of (1) to (26), wherein -R^{ZZ}, if present, is independently -R^1.

The Group -X^1

(31) A compound according to any one of (1) to (30), wherein each -X^1, if present, is independently -F, -Cl, or -Br.

(32) A compound according to any one of (1) to (30), wherein each -X^1, if present, is independently -F or -Cl.

(33) A compound according to any one of (1) to (30), wherein each -X^1, if present, is -F.

(34) A compound according to any one of (1) to (30), wherein each -X^1, if present, is -Cl.

(35) A compound according to any one of (1) to (30), wherein each -X^1, if present, is -Br.

(36) A compound according to any one of (1) to (30), wherein each -X^1, if present, is -I.

The Group -R^1

(37) A compound according to any one of (1) to (36), wherein each -R^1, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(38) A compound according to any one of (1) to (36), wherein each -R^1, if present, is independently -Me, -Et, -nPr, or -iPr.

(39) A compound according to any one of (1) to (36), wherein each -R^1, if present, is independently -Me or -Et.

(40) A compound according to any one of (1) to (36), wherein each -R^1, if present, is -Me.

The Group -L^{3P}-

(41) A compound according to any one of (1) to (40), wherein -L^{3P}- is a single covalent bond.

(42) A compound according to any one of (1) to (40), wherein -L^{3P}- is -L^{3PL}-.

The Group -L^{3PL}-

(43) A compound according to any one of (1) to (42), wherein -L^{3PL}-, if present, is independently -L^{3PR1}-, -C(=O)-, -L^{3PR2}-C(=O)-, -O-L^{3PR4}-, or -$S(=O)_2$-.

(44) A compound according to any one of (1) to (42), wherein -L^{3PL}-, if present, is independently -L^{3PR1}-, -C(=O)-, -O-L^{3PR4}-, or -$S(=O)_2$-.

(45) A compound according to any one of (1) to (42), wherein -L^{3PL}-, if present, is -L^{3PR1}-.

(46) A compound according to any one of (1) to (42), wherein -L^{3PL}-, if present, is -C(=O)-.

(47) A compound according to any one of (1) to (42), wherein -L^{3PL}-, if present, is -L^{3PR2}-C(=O)-.

(48) A compound according to any one of (1) to (42), wherein -L^{3PL}-, if present, is -$S(=O)_2$-.

(49) A compound according to any one of (1) to (42), wherein -L^{3PL}-, if present, is -L^{3PR3}-$S(=O)_2$-.

(50) A compound according to any one of (1) to (42), wherein -L^{3PL}-, if present, is -O-L^{3PR4}-.

The Group -L^{3PR1}-

(51) A compound according to any one of (1) to (50), wherein each -L^{3PR1}-, if present, is independently -CH_2-, -CH(Me)-, -$C(Me)_2$-, -CH_2CH_2-, -$CH(Me)CH_2$-, -$CH_2CH(Me)$-, -$C(Me)_2CH_2$-, -$CH_2C(Me)_2$-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(52) A compound according to any one of (1) to (50), wherein each -L^{3PR1}-, if present, is independently -CH_2-, -CH(Me)-, -$C(Me)_2$-, -CH(Et)-, or -CH_2CH_2-.

(53) A compound according to any one of (1) to (50), wherein each -L^{3PR1}-, if present, is independently -CH_2-, -CH(Me)-, or -$C(Me)_2$-.

(54) A compound according to any one of (1) to (50), wherein each -L^{3PR1}-, if present, is independently -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(55) A compound according to any one of (1) to (50), wherein each -L^{3PR1}-, if present, is independently -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(56) A compound according to any one of (1) to (50), wherein each -L^{3PR1}-, if present, is independently -CH_2- or -CH_2CH_2-.

(57) A compound according to any one of (1) to (50), wherein each -L^{3PR1}-, if present, is -CH_2-.

(58) A compound according to any one of (1) to (50), wherein each -L^{3PR1}-, if present, is independently -CH(Me)-.

(59) A compound according to any one of (1) to (50), wherein each -L^{3PR1}-, if present, is independently -$C(Me)_2$-.

(60) A compound according to any one of (1) to (50), wherein each -L^{3PR1}-, if present, is -CH_2CH_2-.

The Group -L^{3PR2}-

(61) A compound according to any one of (1) to (60), wherein each -L^{3PR2}-, if present, is independently -CH_2-, -CH(Me)-, -$C(Me)_2$-, -CH_2CH_2-, -$CH(Me)CH_2$-, -$CH_2CH(Me)$-, -$C(Me)_2CH_2$-, -$CH_2C(Me)_2$-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(62) A compound according to any one of (1) to (60), wherein each -L^{3PR2}-, if present, is independently -CH_2-, -CH(Me)-, -$C(Me)_2$-, -CH(Et)-, or -CH_2CH_2-.

(63) A compound according to any one of (1) to (60), wherein each -L^{3PR2}-, if present, is independently -CH_2-, -CH(Me)-, or -$C(Me)_2$-.

(64) A compound according to any one of (1) to (60), wherein each -L^{3PR2}-, if present, is independently -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(65) A compound according to any one of (1) to (60), wherein each -L^{3PR2}-, if present, is independently -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(66) A compound according to any one of (1) to (60), wherein each -L^{3PR2}-, if present, is independently -CH_2- or -CH_2CH_2-.

(67) A compound according to any one of (1) to (60), wherein each -L^{3PR2}-, if present, is -CH_2-.

(68) A compound according to any one of (1) to (60), wherein each -L^{3PR2}-, if present, is independently -CH(Me)-.

(69) A compound according to any one of (1) to (60), wherein each -L^{3PR2}-, if present, is independently -$C(Me)_2$-.

(70) A compound according to any one of (1) to (60), wherein each -L^{3PR2}-, if present, is -CH_2CH_2-.

The Group -L^{3PR3}-

(71) A compound according to any one of (1) to (70), wherein each -L^{3PR3}-, if present, is independently -CH_2-, -CH(Me)-, -$C(Me)_2$-, -CH_2CH_2-, -CH(Me)CH_2-, -CH_2CH(Me)-, -$C(Me)_2CH_2$-, -$CH_2C(Me)_2$-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(72) A compound according to any one of (1) to (70), wherein each -L^{3PR3}-, if present, is independently -CH_2-, -CH(Me)-, -$C(Me)_2$-, -CH(Et)-, or -CH_2CH_2-.

(73) A compound according to any one of (1) to (70), wherein each -L^{3PR3}-, if present, is independently -CH_2-, -CH(Me)-, or -$C(Me)_2$-.

(74) A compound according to any one of (1) to (70), wherein each -L^{3PR3}-, if present, is independently -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(75) A compound according to any one of (1) to (70), wherein each -L^{3PR3}-, if present, is independently -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(76) A compound according to any one of (1) to (70), wherein each -L^{3PR3}-, if present, is independently -CH_2- or -CH_2CH_2-.

(77) A compound according to any one of (1) to (70), wherein each -L^{3PR3}-, if present, is -CH_2-.

(78) A compound according to any one of (1) to (70), wherein each -L^{3PR3}-, if present, is -CH_2CH_2-.

The Group -L^{3PR4}-

(79) A compound according to any one of (1) to (78), wherein each -L^{3PR4}-, if present, is independently -CH_2-, -CH(Me)-, -$C(Me)_2$-, -CH_2CH_2-, -CH(Me)CH_2-, -CH_2CH(Me)-, -$C(Me)_2CH_2$-, -$CH_2C(Me)_2$-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(80) A compound according to any one of (1) to (78), wherein each -L^{3PR4}-, if present, is independently -CH_2-, -CH(Me)-, -$C(Me)_2$-, -CH(Et)-, or -CH_2CH_2-.

(81) A compound according to any one of (1) to (78), wherein each -L^{3PR4}-, if present, is independently -CH_2-, -CH(Me)-, or -$C(Me)_2$-.

(82) A compound according to any one of (1) to (78), wherein each -L^{3PR4}-, if present, is independently -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(83) A compound according to any one of (1) to (78), wherein each -L^{3PR4}-, if present, is independently -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(84) A compound according to any one of (1) to (78), wherein each -L^{3PR4}-, if present, is independently -CH_2- or -CH_2CH_2-.

(85) A compound according to any one of (1) to (78), wherein each -L^{3PR4}-, if present, is -CH_2-.

(86) A compound according to any one of (1) to (78), wherein each -L^{3PR4}-, if present, is -CH_2CH_2-.

The Group -R^{3N}

(87) A compound according to any one of (1) to (86), wherein -R^{3N} is independently -NHR^A, -NR^AR^B, or -NR^CR^D.

(88) A compound according to any one of (1) to (86), wherein -R^{3N} is independently -NR^AR^B or -NR^CR^D.

(89) A compound according to any one of (1) to (86), wherein -R^{3N} is -NH_2.

(90) A compound according to any one of (1) to (86), wherein -R^{3N} is -NHR^A.

(91) A compound according to any one of (1) to (86), wherein -R^{3N} is -NR^AR^B.

(92) A compound according to any one of (1) to (86), wherein -R^{3N} is -NR^CR^D.

The Group -R^A

(93) A compound according to any one of (1) to (92), wherein each -R^A, if present, is independently: -R^{A1}, -R^{A2}, -R^{A3}, -L^A-R^{A2}, or -L^A-R^{A3}.

(94) A compound according to any one of (1) to (92), wherein each -R^A, if present, is independently: -R^{A1}, -R^{A3}, or -L^A-R^{A3}.

(95) A compound according to any one of (1) to (92), wherein each -R^A, if present, is -R^{A1}.

(96) A compound according to any one of (1) to (92), wherein each -R^A, if present, is -R^{A2}.

(97) A compound according to any one of (1) to (92), wherein each -R^A, if present, is -R^{A3}.

(98) A compound according to any one of (1) to (92), wherein each -R^A, if present, is -R^{A4}.

(99) A compound according to any one of (1) to (92), wherein each -R^A, if present, is -R^{A5}.

(100) A compound according to any one of (1) to (92), wherein each -R^A, if present, is -L^A-R^{A2}.

(101) A compound according to any one of (1) to (92), wherein each -R^A, if present, is -L^A-R^{A3}.

(102) A compound according to any one of (1) to (92), wherein each -R^A, if present, is -L^A-R^{A4}.

(103) A compound according to any one of (1) to (92), wherein each -R^A, if present, is -L^A-R^{A5}.

The Group -R^{A1}

(104) A compound according to any one of (1) to (103), wherein each -R^{A1}, if present, is independently linear or branched saturated C_{1-4}alkyl, and is optionally substituted with one or more groups -R^{S1}.

(105) A compound according to any one of (1) to (103), wherein each -R^{A1}, if present, is independently linear or branched saturated C_{1-4}alkyl, and is optionally substituted with one or more groups selected from: -OH, -OR^{TT}, -NH_2, -NHR^{TT}, and -NR^{TT}_2.

(106) A compound according to any one of (1) to (xx), wherein each -R^{A1}, if present, is independently linear or branched saturated C_{1-4}alkyl, and is optionally substituted with one or more groups selected from: -OH and -OR^{TT}.

(107) A compound according to any one of (1) to (103), wherein each -R^{A1}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu, and is optionally substituted with one or more groups -R^{S1}.

(108) A compound according to any one of (1) to (103), wherein each -R^{A1}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu, and is optionally substituted with one or more groups selected from: -OH, -OR^{TT}, -NH_2, -NHR^{TT}, and -NR^{TT}_2.

(109) A compound according to any one of (1) to (103), wherein each -R^{A1}, if present, is independently -Me, -Et, -nPr, or -iPr, and is optionally substituted with one or more groups -R^{S1}.

(110) A compound according to any one of (1) to (103), wherein each -R^{A1}, if present, is independently -Me, -Et, -nPr, or -iPr, and is optionally substituted with one or more groups selected from: -OH, -OR^{TT}, -NH_2, -NHR^{TT}, and -NR^{TT}_2.

(111) A compound according to any one of (1) to (103), wherein each -R^{A1}, if present, is independently -Me or -Et, and is optionally substituted with one or more groups -R^{S1}.

(112) A compound according to any one of (1) to (103), wherein each -R^{A1}, if present, is independently linear or branched saturated C_{1-4}alkyl.

(113) A compound according to any one of (1) to (103), wherein each -R^{A1}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(114) A compound according to any one of (1) to (103), wherein each -R^{A1}, if present, is independently -Me, -Et, -nPr, or -iPr.

(115) A compound according to any one of (1) to (103), wherein each -R^{A1}, if present, is independently -Me or -Et.

(116) A compound according to any one of (1) to (103), wherein each -R^{A1}, if present, is -Me.

The Group -R^{A2}

(117) A compound according to any one of (1) to (116), wherein each -R^{A2}, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, and is optionally substituted with one or more groups -R^{S2C}.

(118) A compound according to any one of (1) to (116), wherein each -R^{A2}, if present, is independently cyclopropyl, cyclobutyl, or cyclopentyl, and is optionally substituted with one or more groups -R^{S2C}.

(119) A compound according to any one of (1) to (116), wherein each -R^{A2}, if present, is independently cyclopropyl or cyclobutyl, and is optionally substituted with one or more groups -R^{S2C}.

The Group -R^{A3}

(120) A compound according to any one of (1) to (119), wherein each -R^{A3}, if present, is independently oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, dioxanyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, azepanyl, or diazepanyl,
and is optionally substituted *on carbon* with one or more groups -R^{S2C},
and is optionally substituted *on secondary nitrogen, if present,* with a group -R^{SN}.

(121) A compound according to any one of (1) to (119), wherein each -R^{A3}, if present, is independently tetrahydrofuranyl, tetrahydropyranyl, dioxanyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl,
and is optionally substituted *on carbon* with one or more groups -R^{S2C},
and is optionally substituted *on secondary nitrogen, if present,* with a group -R^{SN}.

(122) A compound according to any one of (1) to (119), wherein each -R^{A3}, if present, is independently tetrahydropyranyl or piperidinyl,
and is optionally substituted *on carbon* with one or more groups -R^{S2C},
and is optionally substituted *on secondary nitrogen, if present,* with a group -R^{SN}.

(123) A compound according to any one of (1) to (119), wherein each -R^{A3}, if present, is tetrahydropyranyl, and is optionally substituted *on carbon* with one or more groups -R^{S2C}.

(124) A compound according to any one of (1) to (119), wherein each -R^{A3}, if present, is piperidinyl,
and is optionally substituted *on carbon* with one or more groups -R^{S2C},
and is optionally substituted *on secondary nitrogen* with a group -R^{SN}.

(125) A compound according to any one of (1) to (119), wherein each $-R^{A3}$, if present, is pyrrolidinyl,

and is optionally substituted *on carbon* with one or more groups $-R^{S2C}$,

and is optionally substituted *on secondary nitrogen* with a group $-R^{SN}$.

(126) A compound according to any one of (1) to (119), wherein each $-R^{A3}$, if present, is azetidinyl,

and is optionally substituted *on carbon* with one or more groups $-R^{S2C}$,

and is optionally substituted *on secondary nitrogen* with a group $-R^{SN}$.

The Group $-R^{A4}$

(127) A compound according to any one of (1) to (126), wherein each $-R^{A4}$, if present, is phenyl, and is optionally substituted with one or more groups $-R^{S3C}$.

(128) A compound according to any one of (1) to (126), wherein each $-R^{A4}$, if present, is naphthyl, and is optionally substituted with one or more groups $-R^{S3C}$.

The Group $-R^{A5}$

(129) A compound according to any one of (1) to (128), wherein each $-R^{A5}$, if present, is independently furanyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, benzoimidazolyl, indazolyl, benzofuranyl, benzothienyl, benzooxazolyl, benzothiazolyl, benzoisoxazolyl, benzoisothiazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, quinazolinyl, or phthalazinyl,

and is optionally substituted *on carbon* with one or more groups $-R^{S3C}$,

and is optionally substituted *on secondary nitrogen, if present,* with a group $-R^{SN}$.

(130) A compound according to any one of (1) to (128), wherein each $-R^{A5}$, if present, is independently furanyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, or pyrazinyl,

and is optionally substituted *on carbon* with one or more groups $-R^{S3C}$,

and is optionally substituted *on secondary nitrogen, if present,* with a group $-R^{SN}$.

(131) A compound according to any one of (1) to (128), wherein each $-R^{A5}$, if present, is independently furanyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, or isothiazolyl,

and is optionally substituted *on carbon* with one or more groups $-R^{S3C}$,

and is optionally substituted *on secondary nitrogen, if present,* with a group $-R^{SN}$.

(132) A compound according to any one of (1) to (128), wherein each $-R^{A5}$, if present, is imidazolyl,

and is optionally substituted *on carbon* with one or more groups $-R^{S3C}$,

and is optionally substituted *on secondary nitrogen* with a group $-R^{SN}$.

(133) A compound according to any one of (1) to (128), wherein each $-R^{A5}$, if present, is independently pyridyl, pyridazinyl, pyrimidinyl, or pyrazinyl,

and is optionally substituted *on carbon* with one or more groups $-R^{S3C}$.

The Group $-L^{A}-$

(134) A compound according to any one of (1) to (133), wherein each $-L^{A}-$, if present, is independently $-CH_2-$, $-CH(Me)-$, $-C(Me)_2-$, $-CH_2CH_2-$, $-CH(Me)CH_2-$, $-CH_2CH(Me)-$, $-C(Me)_2CH_2-$, $-CH_2C(Me)_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

(135) A compound according to any one of (1) to (133), wherein each $-L^{A}-$, if present, is independently $-CH_2-$, $-CH(Me)-$, $-C(Me)_2-$, $-CH(Et)-$, or $-CH_2CH_2-$.

(136) A compound according to any one of (1) to (133), wherein each $-L^{A}-$, if present, is independently $-CH_2-$, $-CH(Me)-$, or $-C(Me)_2-$.

(137) A compound according to any one of (1) to (133), wherein each $-L^{A}-$, if present, is independently $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

(138) A compound according to any one of (1) to (133), wherein each $-L^{A}-$, if present, is independently $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

(139) A compound according to any one of (1) to (133), wherein each $-L^{A}-$, if present, is independently $-CH_2-$ or $-CH_2CH_2-$.

(140) A compound according to any one of (1) to (133), wherein each $-L^{A}-$, if present, is $-CH_2-$.

(141) A compound according to any one of (1) to (133), wherein each $-L^{A}-$, if present, is $-CH_2CH_2-$.

The Group $-R^{S1}$

(142) A compound according to any one of (1) to (141), wherein each $-R^{S1}$, if present, is independently:

-F, -Cl, -Br, -I,

-OH, -OR^{TT},
-OCF_3,
-NH_2, -NHR^{TT}, -NR^{TT}_2, -R^{TM},
-C(=O)OH, -C(=O)OR^{TT}, -OC(=O)R^{TT},
-$C(=O)NH_2$, -C(=O)NHR^{TT}, -C(=O)NR^{TT}_2, -C(=O)R^{TM},
-C(=O)R^{TT},
-$S(=O)_2NH_2$, -$S(=O)_2NHR^{TT}$, -$S(=O)_2NR^{TT}_2$, -$S(=O)_2R^{TM}$,
-$NHS(=O)_2R^{TT}$, -$NR^{TN}S(=O)_2R^{TT}$,
-$S(=O)_2R^{TT}$,
-CN, -NO_2, -SR^{TT}, or =O.

(143) A compound according to any one of (1) to (141), wherein each -R^{S1}, if present, is independently:
-F, -Cl, -Br, -I,
-OH, -OR^{TT},
-OCF_3,
-NH_2, -NHR^{TT}, -NR^{TT}_2, -R^{TM},
-C(=O)OH, -C(=O)OR^{TT}, -OC(=O)R^{TT},
-$C(=O)NH_2$, -C(=O)NHR^{TT}, -C(=O)NR^{TT}_2, -C(=O)R^{TM},
-$NHC(=O)R^{TT}$, -$NR^{TN}C(=O)R^{TT}$,
-C(=O)R^{TT},
-$S(=O)_2NH_2$, -$S(=O)_2NHR^{TT}$, -$S(=O)_2NR^{TT}_2$, -$S(=O)_2R^{TM}$,
-$NHS(=O)_2R^{TT}$, -$NR^{TN}S(=O)_2R^{TT}$, or
-$S(=O)_2R^{TT}$.

(144) A compound according to any one of (1) to (141), wherein each -R^{S1}, if present, is independently:
-F, -Cl, -Br, -I,
-OH, -OR^{TT},
-OCF_3,
-NH_2, -NHR^{TT}, -NR^{TT}_2, -R^{TM},
-C(=O)OH, -C(=O)OR^{TT}, -OC(=O)R^{TT},
-$C(=O)NH_2$, -C(=O)NHR^{TT}, -C(=O)NR^{TT}_2, -C(=O)R^{TM},
-$NHC(=O)R^{TT}$, -$NR^{TN}C(=O)R^{TT}$, or
-C(=O)R^{TT}.

(145) A compound according to any one of (1) to (141), wherein each -R^{S1}, if present, is independently:
-F,
-OH, -OR^{TT},
-NH_2, -NHR^{TT}, -NR^{TT}_2, or -R^{TM}.

(146) A compound according to any one of (1) to (141), wherein each $-R^{S1}$, if present, is independently:

$-OH$, $-OR^{TT}$,

$-NH_2$, $-NHR^{TT}$, $-NR^{TT}_2$, or $-R^{TM}$.

(147) A compound according to any one of (1) to (141), wherein each $-R^{S1}$, if present, is independently $-OH$ or $-OR^{TT}$.

The Group $-R^{S2C}$

(148) A compound according to any one of (1) to (148), wherein each $-R^{S2C}$, if present, is independently:

$-R^{TT}$,

$-F$, $-Cl$, $-Br$, $-I$,

$-OH$, $-OR^{TT}$,

$-L^{T}-OH$, $-L^{T}-OR^{TT}$,

$-CF_3$, $-OCF_3$,

$-NH_2$, $-NHR^{TT}$, $-NR^{TT}_2$, $-R^{TM}$,

$-L^{T}-NH_2$, $-L^{T}-NHR^{TT}$, $-L^{T}-NR^{TT}_2$, $-L^{T}-R^{TM}$,

$-C(=O)OH$, $-C(=O)OR^{TT}$, $-OC(=O)R^{TT}$,

$-C(=O)NH_2$, $-C(=O)NHR^{TT}$, $-C(=O)NR^{TT}_2$, $-C(=O)R^{TM}$,

$-NHC(=O)R^{TT}$, $-NR^{TN}C(=O)R^{TT}$,

$-C(=O)R^{TT}$,

$-S(=O)_2NH_2$, $-S(=O)_2NHR^{TT}$, $-S(=O)_2NR^{TT}_2$, $-S(=O)_2R^{TM}$,

$-NHS(=O)_2R^{TT}$, $-NR^{TN}S(=O)_2R^{TT}$,

$-S(=O)_2R^{TT}$,

$-CN$, $-NO_2$, $-SR^{TT}$, or $=O$.

(149) A compound according to any one of (1) to (148), wherein each $-R^{S2C}$, if present, is independently:

$-R^{TT}$,

$-F$, $-Cl$, $-Br$, $-I$,

$-OH$, $-OR^{TT}$,

$-L^{T}-OH$, $-L^{T}-OR^{TT}$,

$-CF_3$, $-OCF_3$,

$-NH_2$, $-NHR^{TT}$, $-NR^{TT}_2$, $-R^{TM}$,

$-L^{T}-NH_2$, $-L^{T}-NHR^{TT}$, $-L^{T}-NR^{TT}_2$, $-L^{T}-R^{TM}$,

$-C(=O)OH$, $-C(=O)OR^{TT}$, $-OC(=O)R^{TT}$,

$-C(=O)NH_2$, $-C(=O)NHR^{TT}$, $-C(=O)NR^{TT}_2$, $-C(=O)R^{TM}$,

$-NHC(=O)R^{TT}$, $-NR^{TN}C(=O)R^{TT}$,

$-C(=O)R^{TT}$,
$-S(=O)_2NH_2$, $-S(=O)_2NHR^{TT}$, $-S(=O)_2NR^{TT}{}_2$, $-S(=O)_2R^{TM}$,
$-NHS(=O)_2R^{TT}$, $-NR^{TN}S(=O)_2R^{TT}$,
$-S(=O)_2R^{TT}$, or
=O.

(150) A compound according to any one of (1) to (148), wherein each $-R^{S2C}$, if present, is independently:
$-R^{TT}$,
-F, -Cl, -Br, -I,
$-OR^{TT}$,
$-L^T-OR^{TT}$,
$-OCF_3$,
$-NH_2$, $-NHR^{TT}$, $-NR^{TT}{}_2$, $-R^{TM}$,
$-L^T-NH_2$, $-L^T-NHR^{TT}$, $-L^T-NR^{TT}{}_2$, $-L^T-R^{TM}$, or
=O.

(151) A compound according to any one of (1) to (148), wherein each $-R^{S2C}$, if present, is independently:
$-R^{TT}$,
-F,
$-OR^{TT}$,
$-L^T-OR^{TT}$,
$-OCF_3$,
$-NH_2$, $-NHR^{TT}$, $-NR^{TT}{}_2$, $-R^{TM}$,
$-L^T-NH_2$, $-L^T-NHR^{TT}$, $-L^T-NR^{TT}{}_2$, $-L^T-R^{TM}$, or
=O.

(152) A compound according to any one of (1) to (148), wherein each $-R^{S2C}$, if present, is independently:
$-R^{TT}$,
-F,
$-OR^{TT}$,
$-L^T-OR^{TT}$,
$-NH_2$, $-NHR^{TT}$, $-NR^{TT}{}_2$, $-R^{TM}$,
$-L^T-NH_2$, $-L^T-NHR^{TT}$, $-L^T-NR^{TT}{}_2$, $-L^T-R^{TM}$, or
=O.

(153) A compound according to any one of (1) to (148), wherein each $-R^{S2C}$, if present, is independently:

$-R^{TT}$,
$-OH$, $-OR^{TT}$,
$-L^{T}-OH$, $-L^{T}-OR^{TT}$,
$-NH_2$, $-NHR^{TT}$, $-NR^{TT}_2$, $-R^{TM}$,
$-L^{T}-NH_2$, $-L^{T}-NHR^{TT}$, $-L^{T}-NR^{TT}_2$, $-L^{T}-R^{TM}$, or
$=O$.

(154) A compound according to any one of (1) to (148), wherein each $-R^{S2C}$, if present, is independently:

$-R^{TT}$,
$-OH$, $-OR^{TT}$,
$-NH_2$, $-NHR^{TT}$, $-NR^{TT}_2$, $-R^{TM}$, or
$=O$.

The Group $-R^{S3C}$

(155) A compound according to any one of (1) to (154), wherein each $-R^{S3C}$, if present, is independently:

$-R^{TT}$,
$-F$, $-Cl$, $-Br$, $-I$,
$-OH$, $-OR^{TT}$,
$-L^{T}-OH$, $-L^{T}-OR^{TT}$,
$-CF_3$, $-OCF_3$,
$-NH_2$, $-NHR^{TT}$, $-NR^{TT}_2$, $-R^{TM}$,
$-L^{T}-NH_2$, $-L^{T}-NHR^{TT}$, $-L^{T}-NR^{TT}_2$, $-L^{T}-R^{TM}$,
$-C(=O)OH$, $-C(=O)OR^{TT}$, $-OC(=O)R^{TT}$,
$-C(=O)NH_2$, $-C(=O)NHR^{TT}$, $-C(=O)NR^{TT}_2$, $-C(=O)R^{TM}$,
$-NHC(=O)R^{TT}$, $-NR^{TN}C(=O)R^{TT}$,
$-C(=O)R^{TT}$,
$-S(=O)_2NH_2$, $-S(=O)_2NHR^{TT}$, $-S(=O)_2NR^{TT}_2$, $-S(=O)_2R^{TM}$,
$-NHS(=O)_2R^{TT}$, $-NR^{TN}S(=O)_2R^{TT}$,
$-S(=O)_2R^{TT}$,
$-CN$, $-NO_2$, or $-SR^{TT}$.

(156) A compound according to any one of (1) to (154), wherein each $-R^{S3C}$, if present, is independently:

$-R^{TT}$,
$-F$, $-Cl$, $-Br$, $-I$,
$-OH$, $-OR^{TT}$,

$-L^T-OH$, $-L^T-OR^{TT}$,
$-CF_3$, $-OCF_3$,
$-NH_2$, $-NHR^{TT}$, $-NR^{TT}_2$, $-R^{TM}$,
$-L^T-NH_2$, $-L^T-NHR^{TT}$, $-L^T-NR^{TT}_2$, $-L^T-R^{TM}$,
$-C(=O)OH$, $-C(=O)OR^{TT}$, $-OC(=O)R^{TT}$,
$-C(=O)NH_2$, $-C(=O)NHR^{TT}$, $-C(=O)NR^{TT}_2$, $-C(=O)R^{TM}$,
$-NHC(=O)R^{TT}$, $-NR^{TN}C(=O)R^{TT}$, or
$-C(=O)R^{TT}$.

(157) A compound according to any one of (1) to (154), wherein each $-R^{S3C}$, if present, is independently:
$-R^{TT}$,
-F, -Cl, -Br, -I,
-OH, $-OR^{TT}$,
$-L^T-OH$, $-L^T-OR^{TT}$,
$-NH_2$, $-NHR^{TT}$, $-NR^{TT}_2$, $-R^{TM}$,
$-L^T-NH_2$, $-L^T-NHR^{TT}$, $-L^T-NR^{TT}_2$, or $-L^T-R^{TM}$.

(158) A compound according to any one of (1) to (154), wherein each $-R^{S3C}$, if present, is independently:
$-R^{TT}$,
-F, -Cl, -Br, -I,
-OH, $-OR^{TT}$,
$-NH_2$, $-NHR^{TT}$, $-NR^{TT}_2$, or $-R^{TM}$.

<u>The Group $-R^{SN}$</u>

(159) A compound according to any one of (1) to (158), wherein each $-R^{SN}$, if present, is independently:
$-R^{TT}$,
$-L^T-OH$, $-L^T-OR^{TT}$,
$-L^T-NH_2$, $-L^T-NHR^{TT}$, $-L^T-NR^{TT}_2$, $-L^T-R^{TM}$,
$-C(=O)R^{TT}$,
$-C(=O)OR^{TT}$,
$-C(=O)NH_2$, $-C(=O)NHR^{TT}$, $-C(=O)NR^{TT}_2$, or $-C(=O)R^{TM}$.

(160) A compound according to any one of (1) to (158), wherein each $-R^{SN}$, if present, is independently:
$-R^{TT}$,
$-L^T-OH$, $-L^T-OR^{TT}$,
$-L^T-NH_2$, $-L^T-NHR^{TT}$, $-L^T-NR^{TT}_2$, $-L^T-R^{TM}$,

$-C(=O)R^{TT}$, or
$-C(=O)OR^{TT}$.

(161) A compound according to any one of (1) to (158), wherein each $-R^{SN}$, if present, is independently:
$-R^{TT}$,
$-L^{T}$-OH, $-L^{T}$-OR^{TT},
$-L^{T}$-NH_2, $-L^{T}$-NHR^{TT}, $-L^{T}$-NR^{TT}_2, $-L^{T}$-R^{TM}, or
$-C(=O)R^{TT}$.

(162) A compound according to any one of (1) to (158), wherein each $-R^{SN}$, if present, is independently:
$-R^{TT}$,
$-L^{T}$-OH, $-L^{T}$-OR^{TT},
$-L^{T}$-NH_2, $-L^{T}$-NHR^{TT}, $-L^{T}$-NR^{TT}_2, or
$-C(=O)R^{TT}$.

(163) A compound according to any one of (1) to (158), wherein each $-R^{SN}$, if present, is independently:
$-R^{TT}$,
$-C(=O)R^{TT}$, or
$-C(=O)OR^{TT}$.

(164) A compound according to any one of (1) to (158), wherein each $-R^{SN}$, if present, is independently $-R^{TT}$ or $-C(=O)R^{TT}$.

(165) A compound according to any one of (1) to (158), wherein each $-R^{SN}$, if present, is independently $-R^{TT}$.

<u>The Group $-L^{T}$-</u>

(166) A compound according to any one of (1) to (165), wherein each $-L^{T}$-, if present, is independently $-CH_2$-, -CH(Me)-, $-C(Me)_2$-, $-CH_2CH_2$-, $-CH(Me)CH_2$-, $-CH_2CH(Me)$-, $-C(Me)_2CH_2$-, $-CH_2C(Me)_2$-, $-CH_2CH_2CH_2$-, or $-CH_2CH_2CH_2CH_2$-.

(167) A compound according to any one of (1) to (165), wherein each $-L^{T}$-, if present, is independently $-CH_2$-, -CH(Me)-, $-C(Me)_2$-, -CH(Et)-, or $-CH_2CH_2$-.

(168) A compound according to any one of (1) to (165), wherein each $-L^{T}$-, if present, is independently $-CH_2$-, -CH(Me)-, or $-C(Me)_2$-.

(169) A compound according to any one of (1) to (165), wherein each $-L^T-$, if present, is independently $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

(170) A compound according to any one of (1) to (165), wherein each $-L^T-$, if present, is independently $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

(171) A compound according to any one of (1) to (165), wherein each $-L^T-$, if present, is independently $-CH_2-$ or $-CH_2CH_2-$.

(172) A compound according to any one of (1) to (165), wherein each $-L^T-$, if present, is $-CH_2-$.

(173) A compound according to any one of (1) to (165), wherein each $-L^T-$, if present, is $-CH_2CH_2-$.

The Group $-R^{TT}$

(174) A compound according to any one of (1) to (173), wherein each $-R^{TT}$, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl.

(175) A compound according to any one of (1) to (173), wherein each $-R^{TT}$, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, phenyl, or benzyl.

(176) A compound according to any one of (1) to (173), wherein each $-R^{TT}$, if present, is independently linear or branched saturated C_{1-4}alkyl, phenyl, or benzyl.

(177) A compound according to any one of (1) to (173), wherein each $-R^{TT}$, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, or saturated C_{3-6}cycloalkyl-methyl; wherein said linear or branched saturated C_{1-4}alkyl is optionally substituted with -OH or $-OR^{TTT}$, wherein $-R^{TTT}$ is linear or branched saturated C_{1-4}alkyl.

(178) A compound according to any one of (1) to (173), wherein each $-R^{TT}$, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, or saturated C_{3-6}cycloalkyl-methyl.

(179) A compound according to any one of (1) to (173), wherein each -R^{TT}, if present, is independently linear or branched saturated C_{1-4}alkyl or saturated C_{3-6}cycloalkyl; wherein said linear or branched saturated C_{1-4}alkyl is optionally substituted with -OH or -OR^{TTT}, wherein -R^{TTT} is linear or branched saturated C_{1-4}alkyl.

(180) A compound according to any one of (1) to (173), wherein each -R^{TT}, if present, is independently linear or branched saturated C_{1-4}alkyl or saturated C_{3-6}cycloalkyl.

(181) A compound according to any one of (1) to (173), wherein each -R^{TT}, if present, is linear or branched saturated C_{1-4}alkyl, and is optionally substituted with -OH or -OR^{TTT}, wherein -R^{TTT} is linear or branched saturated C_{1-4}alkyl.

(182) A compound according to any one of (1) to (173), wherein each -R^{TT}, if present, is linear or branched saturated C_{1-4}alkyl.

(183) A compound according to any one of (1) to (173), wherein each -R^{TT}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(184) A compound according to any one of (1) to (173), wherein each -R^{TT}, if present, is independently -Me or -tBu.

(185) A compound according to any one of (1) to (173), wherein each -R^{TT}, if present, is -Me.

(186) A compound according to any one of (1) to (173), wherein each -R^{TT}, if present, is -tBu.

The Group -R^{TTT}

(187) A compound according to any one of (1) to (186), wherein each -R^{TTT}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(188) A compound according to any one of (1) to (186), wherein each -R^{TTT}, if present, is independently -Me or -Et.

(189) A compound according to any one of (1) to (186), wherein each -R^{TTT}, if present, is -Me.

The Group -R^{TN}

(190) A compound according to any one of (1) to (189), wherein each -R^{TN}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(191) A compound according to any one of (1) to (189), wherein each -R^{TN}, if present, is independently -Me or -Et.

(192) A compound according to any one of (1) to (189), wherein each -R^{TN}, if present, is -Me.

The Group -R^{TM}

(193) A compound according to any one of (1) to (192), wherein each -R^{TM}, if present, is independently pyrrolidino, piperidino, piperazino, or morpholino, and is:

optionally substituted *on carbon* with one or more groups selected from: -R^{TMM}, -C(=O)R^{TMM}, -S(=O)$_2R^{TMM}$, -F, -NH_2, -NHR^{TMM}, -NR^{TMM}_2, -OH, and -OR^{TMM}; and

optionally substituted *on secondary nitrogen, if present,* with a group selected from: -R^{TMM}, -C(=O)R^{TMM}, -C(=O)OR^{TMM}, and -S(=O)$_2R^{TMM}$;

wherein each -R^{TMM} is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl.

The Group -R^{TMM}

(194) A compound according to any one of (1) to (193), wherein each -R^{TMM}, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, phenyl, or benzyl.

(195) A compound according to any one of (1) to (193), wherein each -R^{TMM}, if present, is independently linear or branched saturated C_{1-4}alkyl, phenyl, or benzyl.

(196) A compound according to any one of (1) to (193), wherein each -R^{TMM}, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, or saturated C_{3-6}cycloalkyl-methyl.

(197) A compound according to any one of (1) to (193), wherein each -R^{TMM}, if present, is independently linear or branched saturated C_{1-4}alkyl or saturated C_{3-6}cycloalkyl.

(198) A compound according to any one of (1) to (193), wherein each -R^{TMM}, if present, is linear or branched saturated C_{1-4}alkyl.

(199) A compound according to any one of (1) to (193), wherein each -R^{TMM}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(200) A compound according to any one of (1) to (193), wherein each -R^{TMM}, if present, is independently -Me or -Et.

(201) A compound according to any one of (1) to (193), wherein each -R^{TMM}, if present, is -Me.

(202) A compound according to any one of (1) to (193), wherein each -R^{TMM}, if present, is independently saturated C_{3-6}cycloalkyl.

(203) A compound according to any one of (1) to (193), wherein each -R^{TMM}, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

(204) A compound according to any one of (1) to (193), wherein each -R^{TMM}, if present, is cyclopropyl.

The Group -R^{B}

(205) A compound according to any one of (1) to (204), wherein -R^{B}, if present, is -R^{B1}.

(206) A compound according to any one of (1) to (204), wherein -R^{B}, if present, is -R^{B2}.

(207) A compound according to any one of (1) to (204), wherein -R^{B}, if present, is -L^{B}-R^{B2}.

The Group -R^{B1}

(208) A compound according to any one of (1) to (207), wherein -R^{B1}, if present, is linear or branched saturated C_{1-6}alkyl.

(209) A compound according to any one of (1) to (207), wherein -R^{B1}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu, and is optionally substituted with -OH or -OR^{BB}, wherein -R^{BB} is linear or branched saturated C_{1-4}alkyl.

(210) A compound according to any one of (1) to (207), wherein -R^{B1}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(211) A compound according to any one of (1) to (207), wherein -R^{B1}, if present, is independently -Me, -Et, -nPr, or -iPr.

(212) A compound according to any one of (1) to (207), wherein -R^{B1}, if present, is independently: -Me; or -Et that is optionally substituted with -OH or -OR^{BB}, wherein -R^{BB} is linear or branched saturated C_{1-4}alkyl.

(213) A compound according to any one of (1) to (207), wherein -R^{B1}, if present, is independently -Me, -Et, -CH_2CH_2OH, or -CH_2CH_2OMe.

(214) A compound according to any one of (1) to (207), wherein -R^{B1}, if present, is independently -Me, -Et, or -CH_2CH_2OH.

(215) A compound according to any one of (1) to (207), wherein -R^{B1}, if present, is independently -Me or -Et.

(216) A compound according to any one of (1) to (207), wherein -R^{B1}, if present, is -Me.

The Group -R^{BB}

(217) A compound according to any one of (1) to (216), wherein -R^{BB}, if present, is independently -Me or -Et.

(218) A compound according to any one of (1) to (216), wherein -R^{BB}, if present, is -Me.

The Group -R^{B2}

(219) A compound according to any one of (1) to (218), wherein -R^{B2}, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

(220) A compound according to any one of (1) to (218), wherein -R^{B2}, if present, is independently cyclopropyl, cyclobutyl, or cyclopentyl.

(221) A compound according to any one of (1) to (218), wherein -R^{B2}, if present, is independently cyclopropyl or cyclobutyl.

(222) A compound according to any one of (1) to (218), wherein -R^{B2}, if present, is cyclopropyl.

The Group -L^{B}-

(223) A compound according to any one of (1) to (222), wherein each -L^{B}-, if present, is independently -CH_2-, -CH(Me)-, -$C(Me)_2$-, -CH_2CH_2-, -$CH(Me)CH_2$-, -$CH_2CH(Me)$-, -$C(Me)_2CH_2$-, -$CH_2C(Me)_2$-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(224) A compound according to any one of (1) to (222), wherein each -L^B-, if present, is independently -CH_2-, -CH(Me)-, -$C(Me)_2$-, -CH(Et), or -CH_2CH_2-.

(225) A compound according to any one of (1) to (222), wherein each -L^B-, if present, is independently -CH_2-, -CH(Me)-, or -$C(Me)_2$-.

(226) A compound according to any one of (1) to (222), wherein each -L^B-, if present, is independently -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(227) A compound according to any one of (1) to (222), wherein each -L^B-, if present, is independently -CH_2CH_2-, -$CH_2CH_2CH_2$-, or -$CH_2CH_2CH_2CH_2$-.

(228) A compound according to any one of (1) to (222), wherein each -L^B-, if present, is independently -CH_2- or -CH_2CH_2-.

(229) A compound according to any one of (1) to (222), wherein each -L^B-, if present, is -CH_2-.

(230) A compound according to any one of (1) to (222), wherein each -L^B-, if present, is -CH_2CH_2-.

The Group -NR^CR^D

(231) A compound according to any one of (1) to (230), wherein -NR^CR^D, if present, is -$NR^{C1}R^{D1}$.

(232) A compound according to any one of (1) to (230), wherein -NR^CR^D, if present, is -$NR^{C2}R^{D2}$.

(233) A compound according to any one of (1) to (230), wherein -NR^CR^D, if present, is -$NR^{C3}R^{D3}$.

(234) A compound according to any one of (1) to (230), wherein -NR^CR^D, if present, is -$NR^{C4}R^{D4}$.

(235) A compound according to any one of (1) to (230), wherein -NR^CR^D, if present, is -$NR^{C5}R^{D5}$.

The Group -$NR^{C1}R^{D1}$

(236) A compound according to any one of (1) to (235), wherein -$NR^{C1}R^{D1}$, if present, is a monocyclic non-aromatic heterocyclyl group having from 4 to 7 ring atoms.

(237) A compound according to any one of (1) to (235), wherein -$NR^{C1}R^{D1}$, if present, is a monocyclic non-aromatic heterocyclyl group having from 5 to 7 ring atoms.

(238) A compound according to any one of (1) to (235), wherein -$NR^{C1}R^{D1}$, if present, is a monocyclic non-aromatic heterocyclyl group having 5 ring atoms.

(239) A compound according to any one of (1) to (235), wherein -$NR^{C1}R^{D1}$, if present, is a monocyclic non-aromatic heterocyclyl group having 6 ring atoms.

(240) A compound according to any one of (1) to (235), wherein -$NR^{C1}R^{D1}$, if present, is a monocyclic non-aromatic heterocyclyl group having 7 ring atoms.

(241) A compound according to any one of (1) to (235), wherein, in -$NR^{C1}R^{D1}$, if present, exactly 1 of said ring atoms is a ring heteroatom, and is N.

(242) A compound according to any one of (1) to (235), wherein, in -$NR^{C1}R^{D1}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are both N.

(243) A compound according to any one of (1) to (235), wherein, in -$NR^{C1}R^{D1}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are N and O.

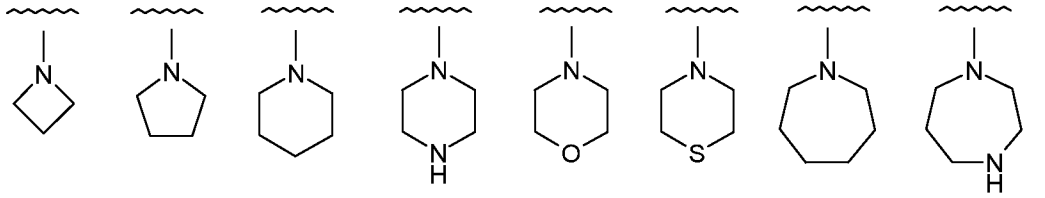
(244) A compound according to any one of (1) to (235), wherein, in -$NR^{C1}R^{D1}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are N and S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$.

(245) A compound according to any one of (1) to (235), wherein, in -$NR^{C1}R^{D1}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are N and S.

(246) A compound according to any one of (1) to (235), wherein, $-NR^{C1}R^{D1}$, if present, is independently selected from the following groups, wherein S, if present, is optionally in the form of S(=O) or $S(=O)_2$, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

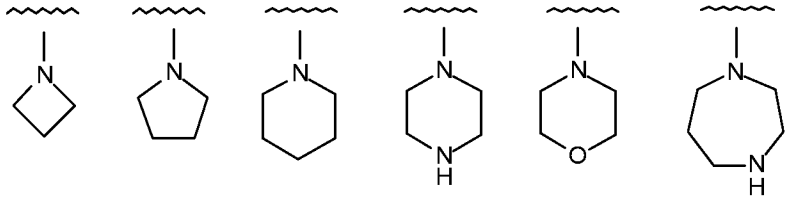
optionally substituted *on secondary nitrogen, if present,* with a group $-R^{NN}$:



(247) A compound according to any one of (1) to (235), wherein, $-NR^{C1}R^{D1}$, if present, is independently selected from the following groups, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

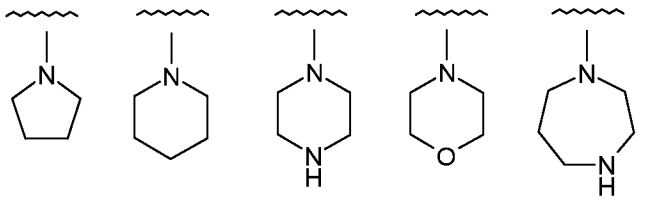
optionally substituted *on secondary nitrogen, if present,* with a group $-R^{NN}$:



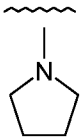
(248) A compound according to any one of (1) to (235), wherein, $-NR^{C1}R^{D1}$, if present, is independently selected from the following groups, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

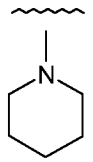
optionally substituted *on secondary nitrogen, if present,* with a group $-R^{NN}$:



(249) A compound according to any one of (1) to (235), wherein, $-NR^{C1}R^{D1}$, if present, is the following group, and is optionally substituted *on carbon* with one or more groups $-R^{NC}$:



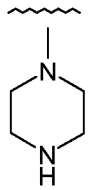
(250) A compound according to any one of (1) to (235), wherein, $-NR^{C1}R^{D1}$, if present, is the following group, and is optionally substituted *on carbon* with one or more groups $-R^{NC}$:



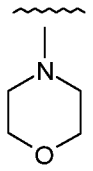
(251) A compound according to any one of (1) to (235), wherein, $-NR^{C1}R^{D1}$, if present, is the following group, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

optionally substituted *on secondary nitrogen* with a group $-R^{NN}$:



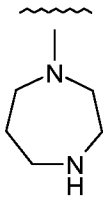
(252) A compound according to any one of (1) to (235), wherein, $-NR^{C1}R^{D1}$, if present, is the following group, and is optionally substituted *on carbon* with one or more groups $-R^{NC}$:



(253) A compound according to any one of (1) to (235), wherein, $-NR^{C1}R^{D1}$, if present, is the following group, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

optionally substituted *on secondary nitrogen* with a group $-R^{NN}$:



The Group -$NR^{C2}R^{D2}$

(254) A compound according to any one of (1) to (253), wherein -$NR^{C2}R^{D2}$, if present, is a fused bicyclic non-aromatic heterocyclyl group having from 7 to 12 ring atoms, wherein exactly 1 of said ring atoms is a ring heteroatom, and is N, or exactly 2 of said ring atoms are ring heteroatoms, and are both N, or exactly 2 of said ring atoms are ring heteroatoms, and are N and O, or exactly 2 of said ring atoms are ring heteroatoms, and are N and S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$;

and wherein said fused bicyclic non-aromatic heterocyclyl group is:

optionally substituted *on carbon* with one or more groups -R^{NC}, and

optionally substituted *on secondary nitrogen, if present,* with a group -R^{NN}.

(255) A compound according to any one of (1) to (253), wherein -$NR^{C2}R^{D2}$, if present, is a fused bicyclic non-aromatic heterocyclyl group having from 8 to 10 ring atoms.

(256) A compound according to any one of (1) to (253), wherein -$NR^{C2}R^{D2}$, if present, is a fused bicyclic non-aromatic heterocyclyl group having 8 ring atoms.

(257) A compound according to any one of (1) to (253), wherein -$NR^{C2}R^{D2}$, if present, is a fused bicyclic non-aromatic heterocyclyl group having 9 ring atoms.

(258) A compound according to any one of (1) to (253), wherein -$NR^{C2}R^{D2}$, if present, is a fused bicyclic non-aromatic heterocyclyl group having 10 ring atoms.

(259) A compound according to any one of (1) to (258), wherein, in -$NR^{C2}R^{D2}$, if present, exactly 1 of said ring atoms is a ring heteroatom, and is N.

(260) A compound according to any one of (1) to (258), wherein, in -$NR^{C2}R^{D2}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are both N.

(261) A compound according to any one of (1) to (258), wherein, in -$NR^{C2}R^{D2}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are N and O.

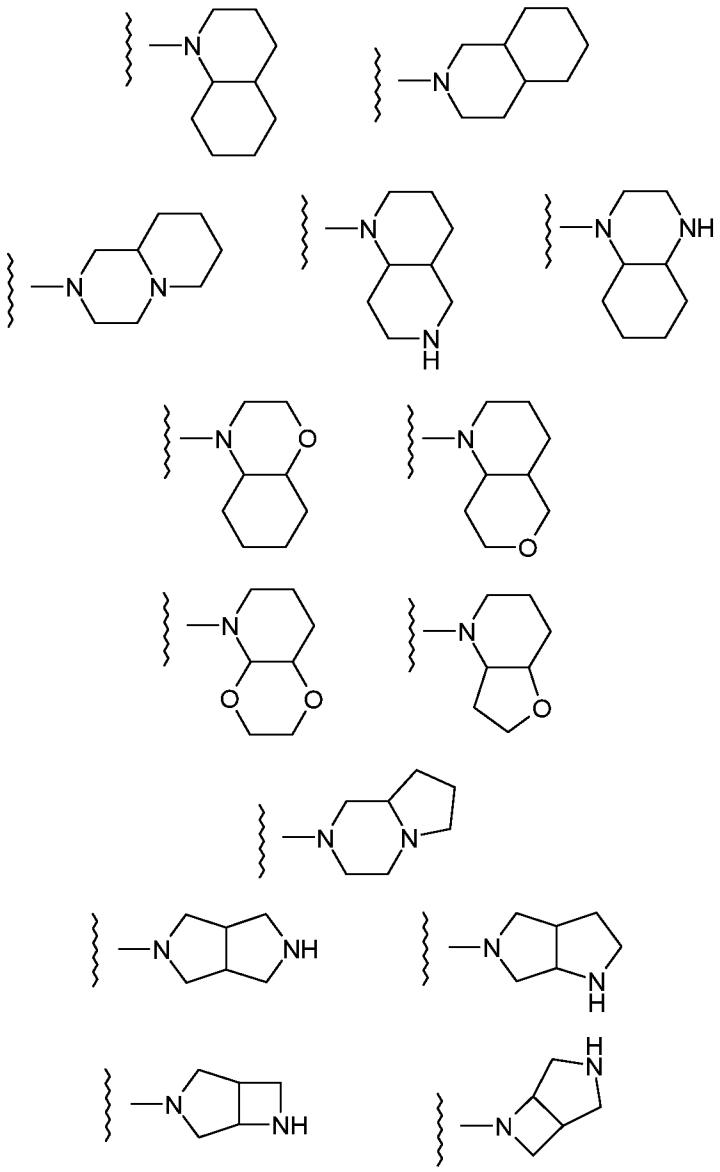
(262) A compound according to any one of (1) to (258), wherein, in -$NR^{C2}R^{D2}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are N and S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$.

(263) A compound according to any one of (1) to (258), wherein, in -$NR^{C2}R^{D2}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are N and S.

(264) A compound according to any one of (1) to (253), wherein, $-NR^{C2}R^{D2}$, if present, is independently selected from the following groups, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

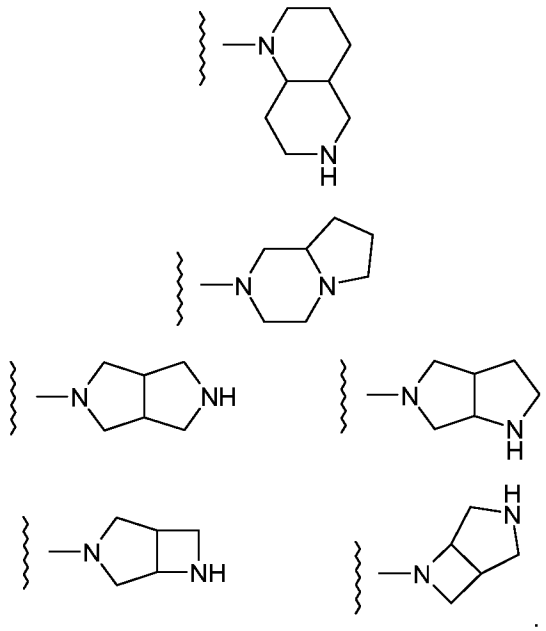
optionally substituted *on secondary nitrogen, if present,* with a group $-R^{NN}$:



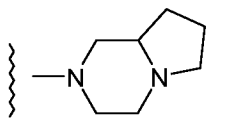
(265) A compound according to any one of (1) to (253), wherein, $-NR^{C2}R^{D2}$, if present, is independently selected from the following groups, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

optionally substituted *on secondary nitrogen, if present,* with a group $-R^{NN}$:



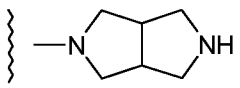
(266) A compound according to any one of (1) to (253), wherein, $-NR^{C2}R^{D2}$, if present, is the following group, and is optionally substituted *on carbon* with one or more groups $-R^{NC}$:



(267) A compound according to any one of (1) to (253), wherein, $-NR^{C2}R^{D2}$, if present, is the following group, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

optionally substituted *on secondary nitrogen* with a group $-R^{NN}$:



The Group -$NR^{C3}R^{D3}$

(268) A compound according to any one of (1) to (267), wherein -$NR^{C3}R^{D3}$, if present, is a bridged non-aromatic heterocyclyl group having from 7 to 11 ring atoms, wherein exactly 1 of said ring atoms is a ring heteroatom, and is N, or exactly 2 of said ring atoms are ring heteroatoms, and are both N, or exactly 2 of said ring atoms are ring heteroatoms, and are N and O;

and wherein said bridged non-aromatic heterocyclyl group is:

optionally substituted *on carbon* with one or more groups -R^{NC}, and

optionally substituted *on secondary nitrogen, if present,* with a group -R^{NN}.

(269) A compound according to any one of (1) to (267), wherein -$NR^{C3}R^{D3}$, if present, is a bridged non-aromatic heterocyclyl group having 7 ring atoms.

(270) A compound according to any one of (1) to (267), wherein -$NR^{C3}R^{D3}$, if present, is a bridged non-aromatic heterocyclyl group having 8 ring atoms.

(271) A compound according to any one of (1) to (267), wherein -$NR^{C3}R^{D3}$, if present, is a bridged non-aromatic heterocyclyl group having 9 ring atoms.

(272) A compound according to any one of (1) to (267), wherein -$NR^{C3}R^{D3}$, if present, is a bridged non-aromatic heterocyclyl group having 11 ring atoms.

(273) A compound according to any one of (1) to (272), wherein, in -$NR^{C3}R^{D3}$, if present, exactly 1 of said ring atoms is a ring heteroatom, and is N.

(274) A compound according to any one of (1) to (272), wherein, in -$NR^{C3}R^{D3}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are both N.

(275) A compound according to any one of (1) to (272), wherein, in -$NR^{C3}R^{D3}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are N and O.

(276) A compound according to any one of (1) to (272), wherein, in -$NR^{C3}R^{D3}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are N and S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$.

(277) A compound according to any one of (1) to (272), wherein, in -$NR^{C3}R^{D3}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are N and S.

(278) A compound according to any one of (1) to (272), wherein, in -$NR^{C3}R^{D3}$, if present, exactly 3 of said ring atoms are ring heteroatoms, one of which is N, and each of the

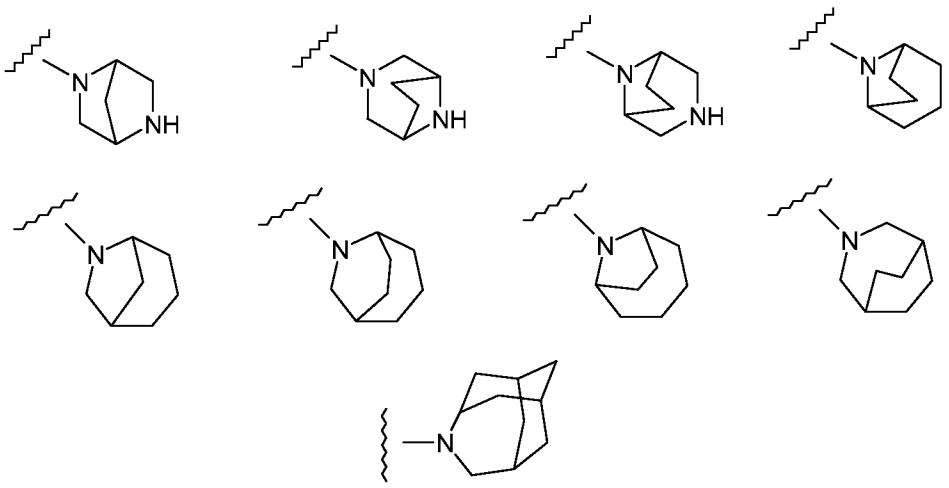
other two is independently N, O, or S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$.

(279) A compound according to any one of (1) to (272), wherein, in $-NR^{C3}R^{D3}$, if present, exactly 3 of said ring atoms are ring heteroatoms, one of which is N, and each of the other two is independently N, O, or S.

(280) A compound according to any one of (1) to (267), wherein, $-NR^{C3}R^{D3}$, if present, is independently selected from the following groups, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

optionally substituted *on secondary nitrogen, if present,* with groups $-R^{NN}$:



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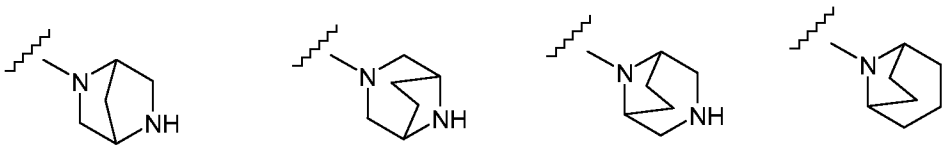
(281) A compound according to any one of (1) to (267), wherein, $-NR^{C3}R^{D3}$, if present, is independently selected from the following groups, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

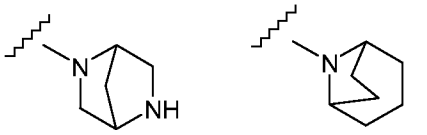
optionally substituted *on secondary nitrogen, if present,* with groups $-R^{NN}$:



(282) A compound according to any one of (1) to (267), wherein, $-NR^{C3}R^{D3}$, if present, is independently selected from the following groups, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

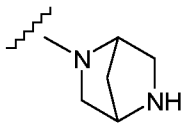
optionally substituted *on secondary nitrogen, if present,* with groups $-R^{NN}$:



(283) A compound according to any one of (1) to (267), wherein, $-NR^{C3}R^{D3}$, if present, is the following group, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

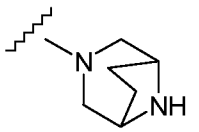
optionally substituted *on secondary nitrogen* with a group $-R^{NN}$:



(284) A compound according to any one of (1) to (267), wherein, $-NR^{C3}R^{D3}$, if present, is the following group, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

optionally substituted *on secondary nitrogen* with groups $-R^{NN}$:



The Group $-NR^{C4}R^{D4}$

(285) A compound according to any one of (1) to (284), wherein $-NR^{C4}R^{D4}$, if present, is a spiro non-aromatic heterocyclyl group having 7 ring atoms.

(286) A compound according to any one of (1) to (284), wherein $-NR^{C4}R^{D4}$, if present, is a spiro non-aromatic heterocyclyl group having 8 ring atoms.

(287) A compound according to any one of (1) to (284), wherein $-NR^{C4}R^{D4}$, if present, is a spiro non-aromatic heterocyclyl group having 9 ring atoms.

(288) A compound according to any one of (1) to (284), wherein $-NR^{C4}R^{D4}$, if present, is a spiro non-aromatic heterocyclyl group having 10 ring atoms.

(289) A compound according to any one of (1) to (284), wherein $-NR^{C4}R^{D4}$, if present, is a spiro non-aromatic heterocyclyl group having 11 ring atoms.

(290) A compound according to any one of (1) to (284), wherein $-NR^{C4}R^{D4}$, if present, is a spiro non-aromatic heterocyclyl group having 12 ring atoms.

(291) A compound according to any one of (1) to (290), wherein, in $-NR^{C4}R^{D4}$, if present, exactly 1 of said ring atoms is a ring heteroatom, and is N.

(292) A compound according to any one of (1) to (290), wherein, in $-NR^{C4}R^{D4}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are both N.

(293) A compound according to any one of (1) to (290), wherein, in $-NR^{C4}R^{D4}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are N and O.

(294) A compound according to any one of (1) to (290), wherein, in $-NR^{C4}R^{D4}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are N and S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$.

(295) A compound according to any one of (1) to (290), wherein, in $-NR^{C4}R^{D4}$, if present, exactly 2 of said ring atoms are ring heteroatoms, and are N and S.

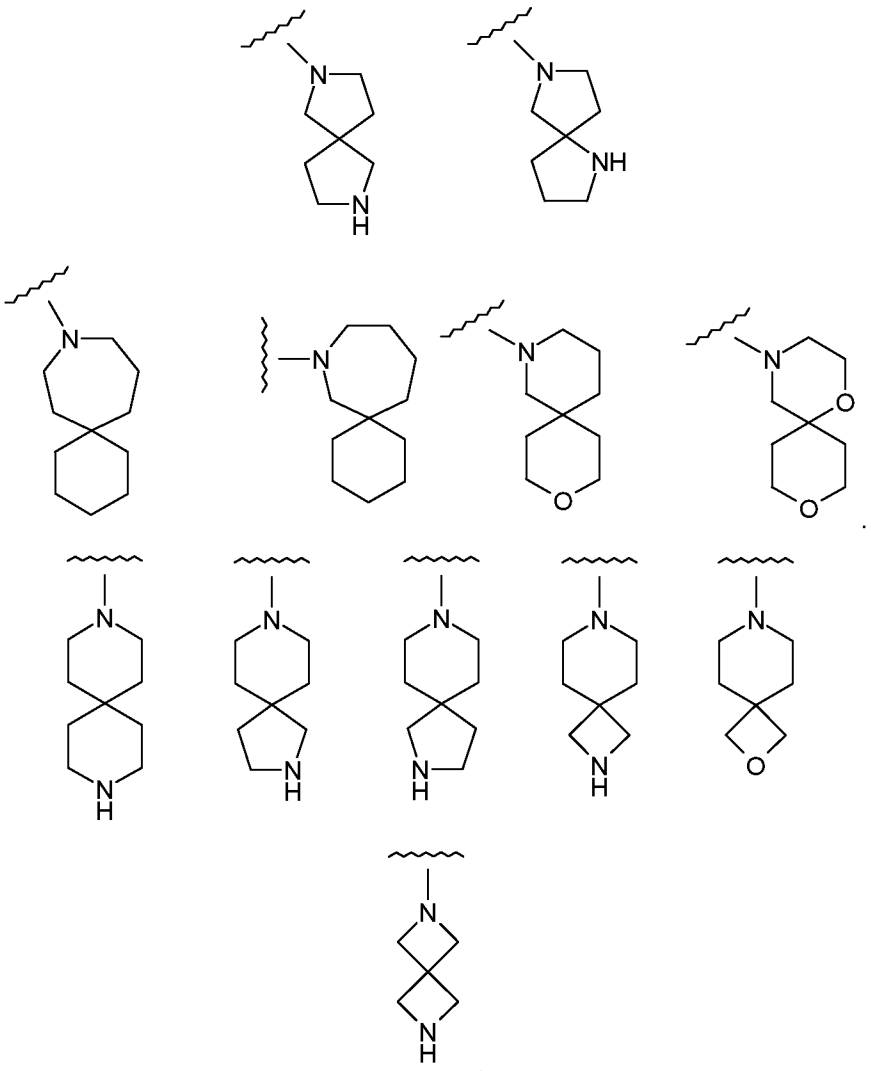
(296) A compound according to any one of (1) to (290), wherein, in $-NR^{C4}R^{D4}$, if present, exactly 3 of said ring atoms are ring heteroatoms, one of which is N, and each of the other two is independently N, O, or S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$.

(297) A compound according to any one of (1) to (290), wherein, in $-NR^{C4}R^{D4}$, if present, exactly 3 of said ring atoms are ring heteroatoms, one of which is N, and each of the other two is independently N, O, or S.

(298) A compound according to any one of (1) to (284), wherein, $-NR^{C4}R^{D4}$, if present, is independently selected from the following groups, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

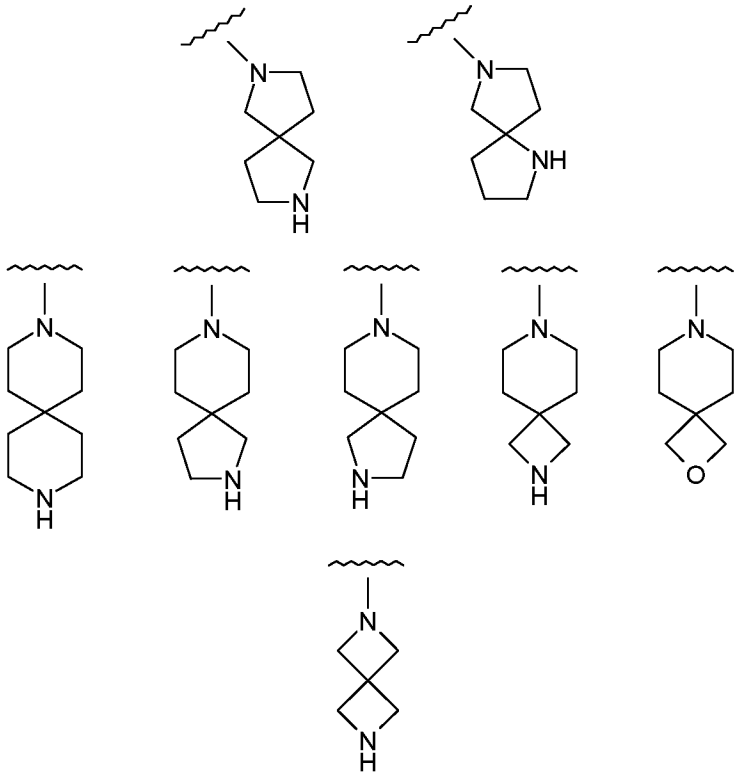
optionally substituted *on secondary nitrogen, if present,* with a group $-R^{NN}$:



(299) A compound according to any one of (1) to (284), wherein, $-NR^{C4}R^{D4}$, if present, is independently selected from the following groups, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

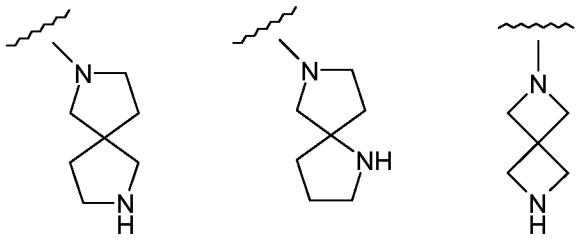
optionally substituted *on secondary nitrogen, if present,* with a group $-R^{NN}$:



(300) A compound according to any one of (1) to (284), wherein, $-NR^{C4}R^{D4}$, if present, is independently selected from the following groups, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

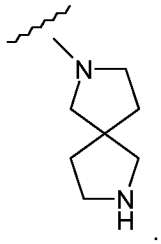
optionally substituted *on secondary nitrogen* with a group $-R^{NN}$:



(301) A compound according to any one of (1) to (284), wherein, $-NR^{C4}R^{D4}$, if present, is the following group, and is:

optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

optionally substituted *on secondary nitrogen* with a group $-R^{NN}$:



The Group $-R^{NC}$

(302) A compound according to any one of (1) to (301), wherein each $-R^{NC}$, if present, is independently:

$-R^{QQ}$,

-F, -Cl, -Br, -I,

-OH, $-OR^{QQ}$,

$-L^{Q}$-OH, $-L^{Q}-OR^{QQ}$,

$-NH_2$, $-NHR^{QQ}$, $-NR^{QQ}{}_2$, $-R^{QM}$,

$-L^{Q}-NH_2$, $-L^{Q}-NHR^{QQ}$, $-L^{Q}-NR^{QQ}{}_2$, $-L^{Q}-R^{QM}$, or

=O.

(303) A compound according to any one of (1) to (301), wherein each $-R^{NC}$, if present, is independently:

$-R^{QQ}$,

-OH, $-OR^{QQ}$,

$-NH_2$, $-NHR^{QQ}$, $-NR^{QQ}{}_2$, $-R^{QM}$, or

=O.

(304) A compound according to any one of (1) to (301), wherein each $-R^{NC}$, if present, is independently $-R^{QQ}$.

The Group $-R^{NN}$

(305) A compound according to any one of (1) to (304), wherein each $-R^{NN}$, if present, is independently:

$-R^{QQ}$,

$-L^{Q}$-OH, $-L^{Q}-OR^{QQ}$,

$-L^{Q}-NH_2$, $-L^{Q}-NHR^{QQ}$, $-L^{Q}-NR^{QQ}{}_2$, $-L^{Q}-R^{QM}$,

-C(=O)R^{QQ},
-C(=O)OR^{QQ},
-C(=O)NH_2, -C(=O)NHR^{QQ}, -C(=O)NR^{QQ}_2, or -C(=O)R^{QM}.

(306) A compound according to any one of (1) to (304), wherein each -R^{NN}, if present, is independently:
-R^{QQ},
-L^Q-OH, -L^Q-OR^{QQ},
-L^Q-NH_2, -L^Q-NHR^{QQ}, -L^Q-NR^{QQ}_2, -L^Q-R^{QM},
-C(=O)R^{QQ}, or
-C(=O)OR^{QQ}.

(307) A compound according to any one of (1) to (304), wherein each -R^{NN}, if present, is independently:
-R^{QQ},
-L^Q-OH, -L^Q-OR^{QQ},
-L^Q-NH_2, -L^Q-NHR^{QQ}, -L^Q-NR^{QQ}_2, -L^Q-R^{QM}, or
-C(=O)R^{QQ}.

(308) A compound according to any one of (1) to (304), wherein each -R^{NN}, if present, is independently:
-R^{QQ},
-L^Q-OH, -L^Q-OR^{QQ},
-L^Q-NH_2, -L^Q-NHR^{QQ}, -L^Q-NR^{QQ}_2, or
-C(=O)R^{QQ}.

(309) A compound according to any one of (1) to (304), wherein each -R^{NN}, if present, is independently:
-R^{QQ},
-C(=O)R^{QQ}, or
-C(=O)OR^{QQ}.

(310) A compound according to any one of (1) to (304), wherein each -R^{NN}, if present, is independently -R^{QQ} or -C(=O)R^{QQ}.

(311) A compound according to any one of (1) to (304), wherein each -R^{NN}, if present, is independently -R^{QQ}.

(312) A compound according to any one of (1) to (304), wherein each -R^{NN}, if present, is independently: -R^{QQ}, -L^Q-OH, or -L^Q-OR^{QQ}.

(313) A compound according to any one of (1) to (304), wherein each $-R^{NN}$, if present, is independently: $-L^{Q}$-OH or $-L^{Q}$-OR^{QQ}.

(314) A compound according to any one of (1) to (304), wherein each $-R^{NN}$, if present, is independently: $-L^{Q}$-OH.

The Group $-L^{Q}-$

(315) A compound according to any one of (1) to (314), wherein each $-L^{Q}-$, if present, is independently $-CH_2-$, $-CH(Me)-$, $-C(Me)_2-$, $-CH_2CH_2-$, $-CH(Me)CH_2-$, $-CH_2CH(Me)-$, $-C(Me)_2CH_2-$, $-CH_2C(Me)_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

(316) A compound according to any one of (1) to (314), wherein each $-L^{Q}-$, if present, is independently $-CH_2-$, $-CH(Me)-$, $-C(Me)_2-$, $-CH(Et)-$, or $-CH_2CH_2-$.

(317) A compound according to any one of (1) to (314), wherein each $-L^{Q}-$, if present, is independently $-CH_2-$, $-CH(Me)-$, or $-C(Me)_2-$.

(318) A compound according to any one of (1) to (314), wherein each $-L^{Q}-$, if present, is independently $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

(319) A compound according to any one of (1) to (314), wherein each $-L^{Q}-$, if present, is independently $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

(320) A compound according to any one of (1) to (314), wherein each $-L^{Q}-$, if present, is independently $-CH_2-$ or $-CH_2CH_2-$.

(321) A compound according to any one of (1) to (314), wherein each $-L^{Q}-$, if present, is $-CH_2-$.

(322) A compound according to any one of (1) to (314), wherein each $-L^{Q}-$, if present, is $-CH_2CH_2-$.

The Group $-R^{QQ}$

(323) A compound according to any one of (1) to (322), wherein each $-R^{QQ}$, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl; wherein said linear or branched saturated C_{1-4}alkyl is optionally substituted with -OH or $-OR^{QQQ}$, wherein $-R^{QQQ}$ is linear or branched saturated C_{1-4}alkyl.

(324) A compound according to any one of (1) to (322), wherein each $-R^{QQ}$, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl.

(325) A compound according to any one of (1) to (322), wherein each $-R^{QQ}$, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, phenyl, or benzyl.

(326) A compound according to any one of (1) to (322), wherein each $-R^{QQ}$, if present, is independently linear or branched saturated C_{1-4}alkyl, phenyl, or benzyl.

(327) A compound according to any one of (1) to (322), wherein each $-R^{QQ}$, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, or saturated C_{3-6}cycloalkyl-methyl; wherein said linear or branched saturated C_{1-4}alkyl is optionally substituted with -OH or $-OR^{QQ}$, wherein $-R^{QQ}$ is linear or branched saturated C_{1-4}alkyl.

(328) A compound according to any one of (1) to (322), wherein each $-R^{QQ}$, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, or saturated C_{3-6}cycloalkyl-methyl.

(329) A compound according to any one of (1) to (322), wherein each $-R^{QQ}$, if present, is independently linear or branched saturated C_{1-4}alkyl or saturated C_{3-6}cycloalkyl; wherein said linear or branched saturated C_{1-4}alkyl is optionally substituted with -OH or $-OR^{QQ}$, wherein $-R^{QQ}$ is linear or branched saturated C_{1-4}alkyl.

(330) A compound according to any one of (1) to (322), wherein each $-R^{QQ}$, if present, is independently linear or branched saturated C_{1-4}alkyl or saturated C_{3-6}cycloalkyl.

(331) A compound according to any one of (1) to (322), wherein each $-R^{QQ}$, if present, is linear or branched saturated C_{1-4}alkyl, and is optionally substituted with -OH or $-OR^{QQ}$, wherein $-R^{QQ}$ is linear or branched saturated C_{1-4}alkyl.

(332) A compound according to any one of (1) to (322), wherein each $-R^{QQ}$, if present, is linear or branched saturated C_{1-4}alkyl.

(333) A compound according to any one of (1) to (322), wherein each $-R^{QQ}$, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(334) A compound according to any one of (1) to (322), wherein each $-R^{QQ}$, if present, is independently -Me or -tBu.

(335) A compound according to any one of (1) to (322), wherein each -R^{QQ}, if present, is -Me.

(336) A compound according to any one of (1) to (322), wherein each -R^{QQ}, if present, is -tBu.

(337) A compound according to any one of (1) to (322), wherein each -R^{QQ}, if present, is saturated C_{3-6}cycloalkyl.

(338) A compound according to any one of (1) to (322), wherein each -R^{QQ}, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

(339) A compound according to any one of (1) to (322), wherein each -R^{QQ}, if present, is cyclopropyl.

(340) A compound according to any one of (1) to (322), wherein each -R^{QQ}, if present, is saturated C_{3-6}cycloalkyl-methyl.

(341) A compound according to any one of (1) to (322), wherein each -R^{QQ}, if present, is independently cyclopropyl-methyl, cyclobutyl-methyl, cyclopentyl-methyl, or cyclohexyl-methyl.

(342) A compound according to any one of (1) to (322), wherein each -R^{QQ}, if present, is cyclopropyl-methyl.

The Group -R^{QQQ}

(343) A compound according to any one of (1) to (342), wherein each -R^{QQQ}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(344) A compound according to any one of (1) to (342), wherein each -R^{QQQ}, if present, is independently -Me or -Et.

(345) A compound according to any one of (1) to (342), wherein each -R^{QQQ}, if present, is independently -Me.

The Group -R^{QN}

(346) A compound according to any one of (1) to (345), wherein each -R^{QN}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(347) A compound according to any one of (1) to (345), wherein each $-R^{QN}$, if present, is independently -Me or -Et.

(348) A compound according to any one of (1) to (345), wherein each $-R^{QN}$, if present, is independently -Me.

The Group $-R^{QM}$

(349) A compound according to any one of (1) to (348), wherein each $-R^{QM}$, if present, is independently pyrrolidino, piperidino, piperazino, or morpholino, and is:

optionally substituted *on carbon* with one or more groups selected from: $-R^{QMM}$, $-C(=O)R^{QMM}$, $-S(=O)_2R^{QMM}$, -F, $-NH_2$, $-NHR^{QMM}$, $-NR^{QMM}_2$, -OH, and $-OR^{QMM}$; and

optionally substituted *on secondary nitrogen, if present,* with a group selected from: $-R^{QMM}$, $-C(=O)R^{QMM}$, $-C(=O)OR^{QMM}$, and $-S(=O)_2R^{QMM}$;

wherein each $-R^{QMM}$ is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl.

The Group $-R^{QMM}$

(350) A compound according to any one of (1) to (349), wherein each $-R^{QMM}$, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, phenyl, or benzyl.

(351) A compound according to any one of (1) to (349), wherein each $-R^{QMM}$, if present, is independently linear or branched saturated C_{1-4}alkyl, phenyl, or benzyl.

(352) A compound according to any one of (1) to (349), wherein each $-R^{QMM}$, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, or saturated C_{3-6}cycloalkyl-methyl.

(353) A compound according to any one of (1) to (349), wherein each $-R^{QMM}$, if present, is independently linear or branched saturated C_{1-4}alkyl or saturated C_{3-6}cycloalkyl.

(354) A compound according to any one of (1) to (349), wherein each $-R^{QMM}$, if present, is linear or branched saturated C_{1-4}alkyl.

(355) A compound according to any one of (1) to (349), wherein each $-R^{QMM}$, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(356) A compound according to any one of (1) to (349), wherein each -R^{QMM}, if present, is independently -Me or -Et.

(357) A compound according to any one of (1) to (349), wherein each -R^{QMM}, if present, is -Me.

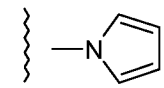
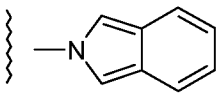
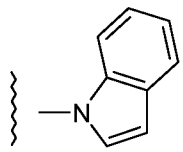
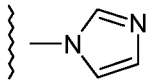
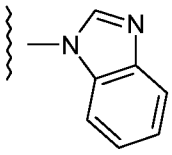
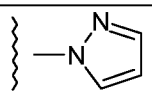
(358) A compound according to any one of (1) to (349), wherein each -R^{QMM}, if present, is independently saturated C_{3-6}cycloalkyl.

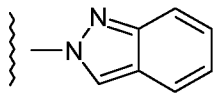
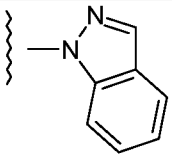
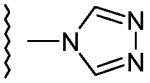
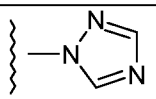
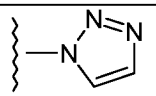
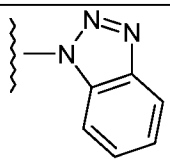
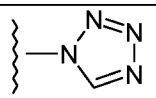
(359) A compound according to any one of (1) to (349), wherein each -R^{QMM}, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

(360) A compound according to any one of (1) to (349), wherein each -R^{QMM}, if present, is cyclopropyl.

The Group -$NR^{C5}R^{D5}$

(361) A compound according to any one of (1) to (360), wherein -$NR^{C5}R^{D5}$, if present, is independently: 1H-pyrrol-1-yl; 2H-isoindol-2-yl; 1H-indol-1-yl; 1H-pyrazol-1-yl; 1H-benzoimidazol-1-yl; 1H-imidazol-1-yl; 2H-indazol-2-yl; 1H-indazol-1-yl; 4H-[1,2,4]triazol-4-yl; 1H-[1,2,3]triazol-1-yl; 1H-[1,2,4]triazol-1-yl; 1H-benzotriazol-1-yl; or 1H-tetrazol-1-yl; and is optionally substituted with one or more groups -R^{H}.

	1H-pyrrol-1-yl
	2H-isoindol-2-yl
	1H-indol-1-yl
	1H-imidazol-1-yl
	1H-benzoimidazol-1-yl
	1H-pyrazol-1-yl

	2H-indazol-2-yl
	1H-indazol-1-yl
	4H-[1,2,4]triazol-4-yl
	1H-[1,2,4]triazol-1-yl
	1H-[1,2,3]triazol-1-yl
	1H-benzotriazol-1-yl
	1H-tetrazol-1-yl

(362) A compound according to any one of (1) to (360), wherein $-NR^{C5}R^{D5}$, if present, is independently: 1H-pyrrol-1-yl; 1H-pyrazol-1-yl; 1H-imidazol-1-yl; 4H-[1,2,4]triazol-4-yl; 1H-[1,2,3]triazol-1-yl; 1H-[1,2,4]triazol-1-yl; or 1H-tetrazol-1-yl; and is optionally substituted with one or more groups $-R^H$.

(363) A compound according to any one of (1) to (360), wherein $-NR^{C5}R^{D5}$, if present, is independently: 1H-pyrrol-1-yl; 1H-pyrazol-1-yl; or 1H-imidazol-1-yl; and is optionally substituted with one or more groups $-R^H$.

(364) A compound according to any one of (1) to (360), wherein $-NR^{C5}R^{D5}$, if present, is 1H-pyrrol-1-yl; and is optionally substituted with one or more groups $-R^H$.

(365) A compound according to any one of (1) to (360), wherein $-NR^{C5}R^{D5}$, if present, is 1H-pyrazol-1-yl; and is optionally substituted with one or more groups $-R^H$.

(366) A compound according to any one of (1) to (360), wherein $-NR^{C5}R^{D5}$, if present, is 1H-imidazol-1-yl; and is optionally substituted with one or more groups $-R^H$.

(367) A compound according to any one of (1) to (360), wherein $-NR^{C5}R^{D5}$, if present, is 1H-[1,2,4]triazol-1-yl; and is optionally substituted with one or more groups $-R^{H}$.

(368) A compound according to any one of (1) to (360), wherein $-NR^{C5}R^{D5}$, if present, is 1H-benzoimidazol-1-yl; and is optionally substituted with one or more groups $-R^{H}$.

(369) A compound according to any one of (1) to (360), wherein $-NR^{C5}R^{D5}$, if present, is 1H-indol-1-yl; and is optionally substituted with one or more groups $-R^{H}$.

The Group $-R^{H}$

(370) A compound according to any one of (1) to (369), wherein each $-R^{H}$, if present, is independently:

$-R^{HH}$,
-F, -Cl, -Br, -I,
-OH, $-OR^{HH}$,
$-L^{H}$-OH, $-L^{H}-OR^{HH}$,
$-CF_3$, $-OCF_3$,
$-NH_2$, $-NHR^{HH}$, $-NR^{HH}{}_2$, $-R^{HM}$,
$-L^{H}-NH_2$, $-L^{H}-NHR^{HH}$, $-L^{H}-NR^{HH}{}_2$, $-L^{H}-R^{HM}$,
$-C(=O)OH$, $-C(=O)OR^{HH}$, $-OC(=O)R^{HH}$,
$-C(=O)NH_2$, $-C(=O)NHR^{HH}$, $-C(=O)NR^{HH}{}_2$, $-C(=O)R^{HM}$,
$-NHC(=O)R^{HH}$, $-NR^{HN}C(=O)R^{HH}$, or
$-C(=O)R^{HH}$.

(371) A compound according to any one of (1) to (369), wherein each $-R^{H}$, if present, is independently:

$-R^{HH}$,
-F, -Cl, -Br, -I,
-OH, $-OR^{HH}$,
$-L^{H}$-OH, $-L^{HH}-OR^{HH}$,
$-NH_2$, $-NHR^{HH}$, $-NR^{HH}{}_2$, $-R^{HM}$,
$-L^{H}-NH_2$, $-L^{H}-NHR^{HH}$, $-L^{H}-NR^{HH}{}_2$, or $-L^{H}-R^{HM}$.

(372) A compound according to any one of (1) to (369), wherein each $-R^{H}$, if present, is independently:

$-R^{HH}$,
-OH, $-OR^{HH}$,
$-NH_2$, $-NHR^{HH}$, $-NR^{HH}{}_2$, or $-R^{HM}$.

(373) A compound according to any one of (1) to (369), wherein each $-R^{H}$, if present, is independently $-R^{HH}$.

The Group $-L^{H}-$

(374) A compound according to any one of (1) to (373), wherein each $-L^{H}-$, if present, is independently $-CH_2-$, $-CH(Me)-$, $-C(Me)_2-$, $-CH_2CH_2-$, $-CH(Me)CH_2-$, $-CH_2CH(Me)-$, $-C(Me)_2CH_2-$, $-CH_2C(Me)_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

(375) A compound according to any one of (1) to (373), wherein each $-L^{H}-$, if present, is independently $-CH_2-$, $-CH(Me)-$, $-C(Me)_2-$, $-CH(Et)-$, or $-CH_2CH_2-$.

(376) A compound according to any one of (1) to (373), wherein each $-L^{H}-$, if present, is independently $-CH_2-$, $-CH(Me)-$, or $-C(Me)_2-$.

(377) A compound according to any one of (1) to (373), wherein each $-L^{H}-$, if present, is independently $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

(378) A compound according to any one of (1) to (373), wherein each $-L^{H}-$, if present, is independently $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, or $-CH_2CH_2CH_2CH_2-$.

(379) A compound according to any one of (1) to (373), wherein each $-L^{H}-$, if present, is independently $-CH_2-$ or $-CH_2CH_2-$.

(380) A compound according to any one of (1) to (373), wherein each $-L^{H}-$, if present, is $-CH_2-$.

(381) A compound according to any one of (1) to (373), wherein each $-L^{H}-$, if present, is $-CH_2CH_2-$.

The Group $-R^{HH}$

(382) A compound according to any one of (1) to (381), wherein each $-R^{HH}$, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl.

(383) A compound according to any one of (1) to (381), wherein each $-R^{HH}$, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, phenyl, or benzyl.

(384) A compound according to any one of (1) to (381), wherein each -R^{HH}, if present, is independently linear or branched saturated C_{1-4}alkyl, phenyl, or benzyl.

(385) A compound according to any one of (1) to (381), wherein each -R^{HH}, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, or saturated C_{3-6}cycloalkyl-methyl; wherein said linear or branched saturated C_{1-4}alkyl is optionally substituted with -OH or -OR^{HHH}, wherein -R^{HHH} is linear or branched saturated C_{1-4}alkyl.

(386) A compound according to any one of (1) to (381), wherein each -R^{HH}, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, or saturated C_{3-6}cycloalkyl-methyl.

(387) A compound according to any one of (1) to (381), wherein each -R^{HH}, if present, is independently linear or branched saturated C_{1-4}alkyl or saturated C_{3-6}cycloalkyl; wherein said linear or branched saturated C_{1-4}alkyl is optionally substituted with -OH or -OR^{HHH}, wherein -R^{QQ} is linear or branched saturated C_{1-4}alkyl.

(388) A compound according to any one of (1) to (381), wherein each -R^{HH}, if present, is independently linear or branched saturated C_{1-4}alkyl or saturated C_{3-6}cycloalkyl.

(389) A compound according to any one of (1) to (381), wherein each -R^{HH}, if present, is linear or branched saturated C_{1-4}alkyl, and is optionally substituted with -OH or -OR^{HHH}, wherein -R^{HHH} is linear or branched saturated C_{1-4}alkyl.

(390) A compound according to any one of (1) to (381), wherein each -R^{HH}, if present, is linear or branched saturated C_{1-4}alkyl.

(391) A compound according to any one of (1) to (381), wherein each -R^{HH}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(392) A compound according to any one of (1) to (381), wherein each -R^{HH}, if present, is independently -Me or -tBu.

(393) A compound according to any one of (1) to (381), wherein each -R^{HH}, if present, is -Me.

(394) A compound according to any one of (1) to (381), wherein each -R^{HH}, if present, is -tBu.

(395) A compound according to any one of (1) to (381), wherein each -R^{HH}, if present, is saturated C_{3-6}cycloalkyl.

(396) A compound according to any one of (1) to (381), wherein each -R^{HH}, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

(397) A compound according to any one of (1) to (381), wherein each -R^{HH}, if present, is cyclopropyl.

The Group -R^{HHH}

(398) A compound according to any one of (1) to (397), wherein each -R^{HHH}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(399) A compound according to any one of (1) to (397), wherein each -R^{HHH}, if present, is independently -Me or -Et.

(400) A compound according to any one of (1) to (397), wherein each -R^{HH}, if present, is independently -Me.

The Group -R^{HN}

(401) A compound according to any one of (1) to (400), wherein each -R^{HN}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(402) A compound according to any one of (1) to (400), wherein each -R^{HN}, if present, is independently -Me or -Et.

(403) A compound according to any one of (1) to (400), wherein each -R^{HN}, if present, is independently -Me.

The Group -R^{HM}

(404) A compound according to any one of (1) to (403), wherein each -R^{HM}, if present, is independently pyrrolidino, piperidino, piperazino, or morpholino, and is:

optionally substituted *on carbon* with one or more groups selected from: -R^{HMM}, -C(=O)R^{HMM}, -S(=O)$_2R^{HMM}$, -F, -NH_2, -NHR^{HMM}, -NR^{HMM}_2, -OH, and -OR^{HMM}; and

optionally substituted *on secondary nitrogen, if present,* with a group selected from: -R^{HMM}, -C(=O)R^{HMM}, -C(=O)OR^{HMM}, and -S(=O)$_2R^{HMM}$;

wherein each -R^{HMM} is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl.

The Group -R^{HMM}

(405) A compound according to any one of (1) to (404), wherein each -R^{HMM}, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, phenyl, or benzyl.

(406) A compound according to any one of (1) to (404), wherein each -R^{HMM}, if present, is independently linear or branched saturated C_{1-4}alkyl, phenyl, or benzyl.

(407) A compound according to any one of (1) to (404), wherein each -R^{HMM}, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, or saturated C_{3-6}cycloalkyl-methyl.

(408) A compound according to any one of (1) to (404), wherein each -R^{HMM}, if present, is independently linear or branched saturated C_{1-4}alkyl or saturated C_{3-6}cycloalkyl.

(409) A compound according to any one of (1) to (404), wherein each -R^{HMM}, if present, is linear or branched saturated C_{1-4}alkyl.

(410) A compound according to any one of (1) to (404), wherein each -R^{HMM}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(411) A compound according to any one of (1) to (404), wherein each -R^{HMM}, if present, is independently -Me or -Et.

(412) A compound according to any one of (1) to (404), wherein each -R^{HMM}, if present, is -Me.

(413) A compound according to any one of (1) to (404), wherein each -R^{HMM}, if present, is independently saturated C_{3-6}cycloalkyl.

(414) A compound according to any one of (1) to (404), wherein each -R^{HMM}, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

(415) A compound according to any one of (1) to (404), wherein each -R^{HMM}, if present, is cyclopropyl.

The Group -R^5

(416) A compound according to any one of (1) to (415), wherein -R^5 is independently -R^{5A}, -R^{5B}, -R^{5C}, or -R^{5D}.

(417) A compound according to any one of (1) to (415), wherein -R^5 is -R^{5A}.

(418) A compound according to any one of (1) to (415), wherein -R^5 is -R^{5B}.

(419) A compound according to any one of (1) to (415), wherein -R^5 is -R^{5C}.

(420) A compound according to any one of (1) to (415), wherein -R^5 is -R^{5D}.

(421) A compound according to any one of (1) to (415), wherein -R^5 is -R^{5E}.

The Group -R^{5A}

(422) A compound according to any one of (1) to (421), wherein -R^{5A}, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(423) A compound according to any one of (1) to (421), wherein -R^{5A}, if present, is independently -Me, -Et, -nPr, or -iPr.

(424) A compound according to any one of (1) to (421), wherein -R^{5A}, if present, is independently -Me or -Et.

(425) A compound according to any one of (1) to (421), wherein -R^{5A}, if present, is -Me.

The Group -R^{5B}

(426) A compound according to any one of (1) to (425), wherein -R^{5B}, if present, is independently cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

(427) A compound according to any one of (1) to (425), wherein -R^{5B}, if present, is independently cyclopropyl, cyclobutyl, or cyclopentyl.

(428) A compound according to any one of (1) to (425), wherein -R^{5B}, if present, is independently cyclopropyl or cyclobutyl.

(429) A compound according to any one of (1) to (425), wherein -R^{5B}, if present, is cyclopropyl.

The Group -R^{5C}

(430) A compound according to any one of (1) to (429), wherein -R^{5C}, if present, is independently -F, -Cl, or -Br.

(431) A compound according to any one of (1) to (429), wherein -R^{5C}, if present, is independently -F or -Cl.

(432) A compound according to any one of (1) to (429), wherein -R^{5C}, if present, is -F.

(433) A compound according to any one of (1) to (429), wherein -R^{5C}, if present, is -Cl.

(434) A compound according to any one of (1) to (429), wherein -R^{5C}, if present, is -Br.

(435) A compound according to any one of (1) to (429), wherein -R^{5C}, if present, is -I.

The Group -R^{5E}

(436) A compound according to any one of (1) to (435), wherein -R^{5E}, if present, is independently -C≡CH or C_{3-4}alkynyl optionally substituted with one or more groups -R^{EE}; wherein each -R^{EE} is independently selected from -OH, -OR^{EEE}, -NH_2, -NHR^{EEE}, and -NR^{EEE}_2; wherein each -R^{EEE} is linear or branched saturated C_{1-4}alkyl.

(437) A compound according to any one of (1) to (435), wherein -R^{5E}, if present, is -C≡CH.

(438) A compound according to any one of (1) to (435), wherein -R^{5E}, if present, is C_{3-4}alkynyl optionally substituted with one or more groups -R^{EE}; wherein each -R^{EE} is independently selected from -OH, -OR^{EEE}, -NH_2, -NHR^{EEE}, and -NR^{EEE}_2; wherein each -R^{EEE} is linear or branched saturated C_{1-4}alkyl.

(439) A compound according to any one of (1) to (435), wherein -R^{5E}, if present, is independently -C≡CH, -C≡CH-CH_3, -C≡CH-CH_2R^{EE}, -C≡CH-CH_2CH_3 or -C≡CH-$CH_2CH_2R^{EE}$; wherein each -R^{EE} is independently selected from -OH, -OR^{EEE}, -NH_2, -NHR^{EEE}, and -NR^{EEE}_2; wherein each -R^{EEE} is linear or branched saturated C_{1-4}alkyl.

(440) A compound according to any one of (1) to (435), wherein -R^{5E}, if present, is independently -C≡CH-CH_3 or -C≡CH-CH_2R^{EE}; wherein each -R^{EE} is independently selected from -OH, -OR^{EEE}, -NH_2, -NHR^{EEE}, and -NR^{EEE}_2; wherein each -R^{EEE} is linear or branched saturated C_{1-4}alkyl.

(441) A compound according to any one of (1) to (435), wherein $-R^{5E}$, if present, is independently $-C\equiv CH-CH_2CH_3$ or $-C\equiv CH-CH_2CH_2R^{EE}$; wherein each $-R^{EE}$ is independently selected from -OH, $-OR^{EEE}$, $-NH_2$, $-NHR^{EEE}$, and $-NR^{EEE}_2$; wherein each $-R^{EEE}$ is linear or branched saturated C_{1-4}alkyl.

The Group $-R^{EE}$

(442) A compound according to any one of (1) to (441), wherein $-R^{EE}$, if present, is independently -OH or $-OR^{EEE}$.

(443) A compound according to any one of (1) to (441), wherein $-R^{EE}$, if present, is independently $-NH_2$, $-NHR^{EEE}$, or $-NR^{EEE}_2$.

The Group $-R^{EEE}$

(444) A compound according to any one of (1) to (443), wherein each $-R^{EEE}$, if present, is independently -Me, -Et, -nPr, -iPr, -nBu, -iBu, or -tBu.

(445) A compound according to any one of (1) to (443), wherein each $-R^{EEE}$, if present, is independently -Me, -Et, -nPr, or -iPr.

(446) A compound according to any one of (1) to (443), wherein each $-R^{EEE}$, if present, is independently -Me or -Et.

(447) A compound according to any one of (1) to (443), wherein each $-R^{EEE}$, if present, is -Me.

The Group $-R^6$

(448) A compound according to any one of (1) to (447), wherein $-R^6$ is -H.

(449) A compound according to any one of (1) to (447), wherein $-R^6$ is -F.

The Group $-R^7$

(450) A compound according to any one of (1) to (449), wherein $-R^7$ is -H.

(451) A compound according to any one of (1) to (449), wherein $-R^7$ is -F.

The Group -R^8

(452) A compound according to any one of (1) to (451), wherein -R^8 is -H.

(453) A compound according to any one of (1) to (451), wherein -R^8 is -F.

Specific Compounds

(454) A compound according to (1), selected from compounds of the following formulae and pharmaceutically acceptable salts, N-oxides, hydrates, and solvates thereof:

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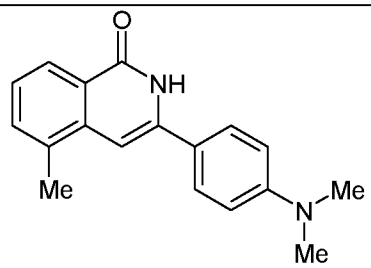
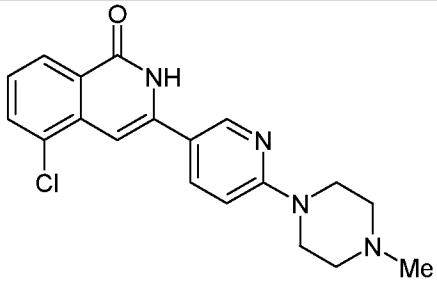
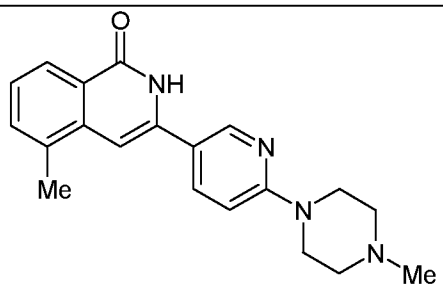
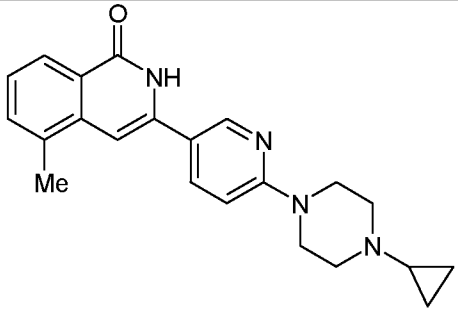
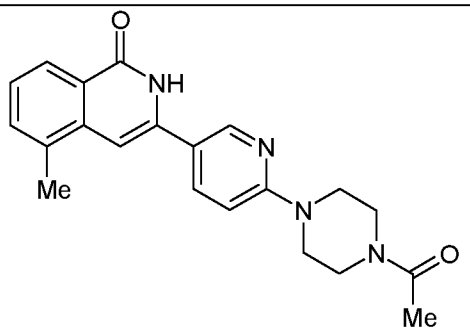
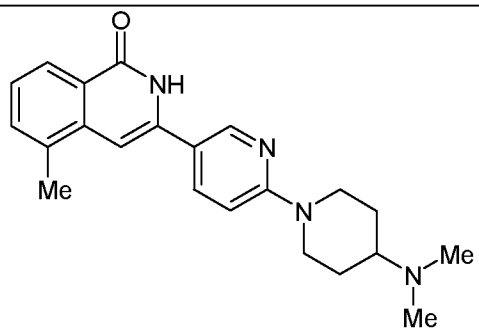
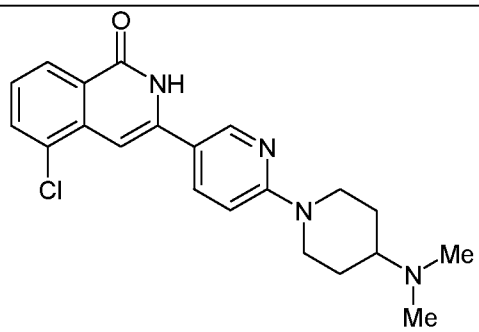
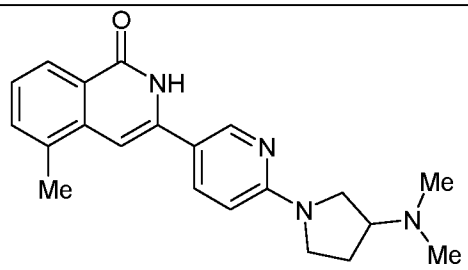
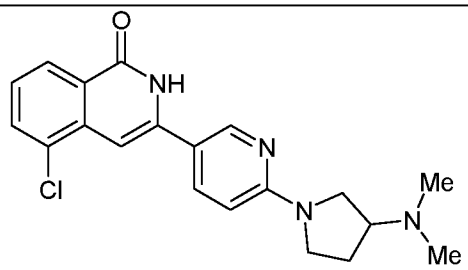
IQ-001	
IQ-002	
IQ-003	
IQ-004	

Pat. Code	Structure
IQ-005	
IQ-006	
IQ-007	
IQ-008	
IQ-009	

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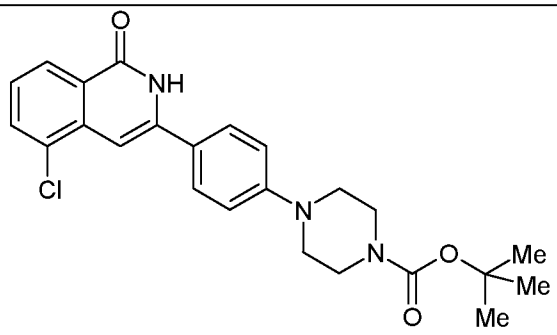
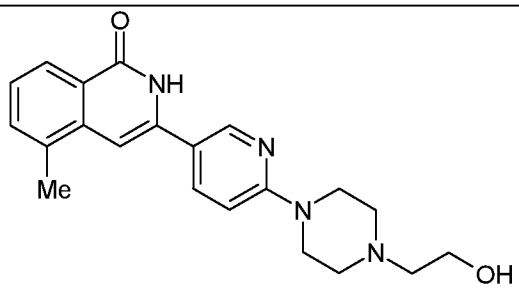
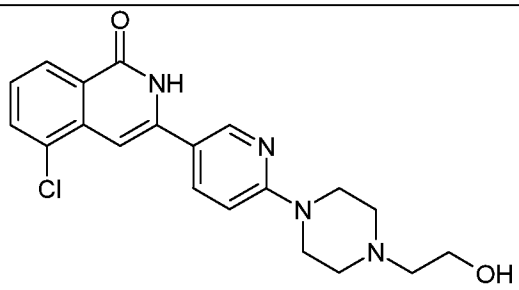
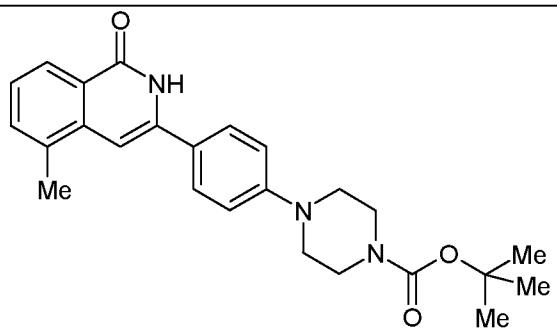
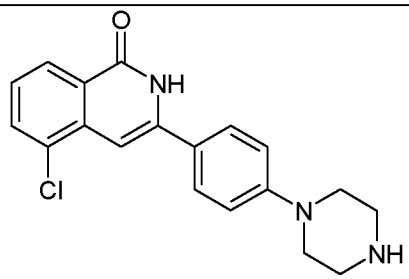
IQ-010	
IQ-011	
IQ-012	
IQ-013	
IQ-014	

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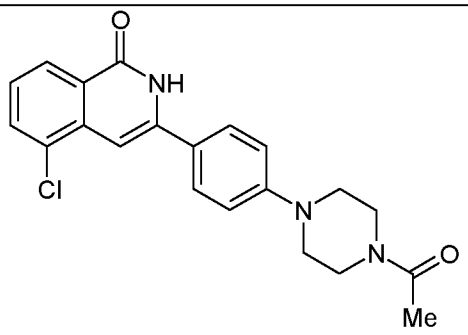
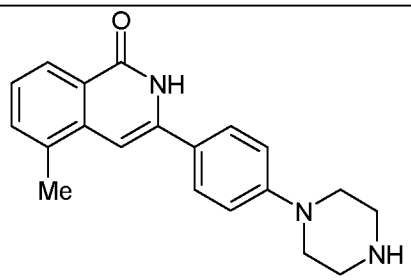
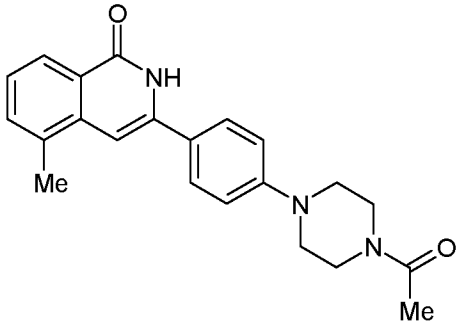
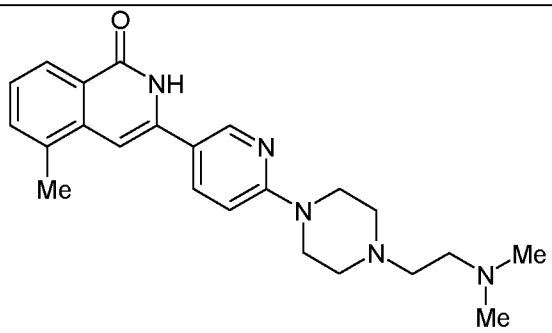
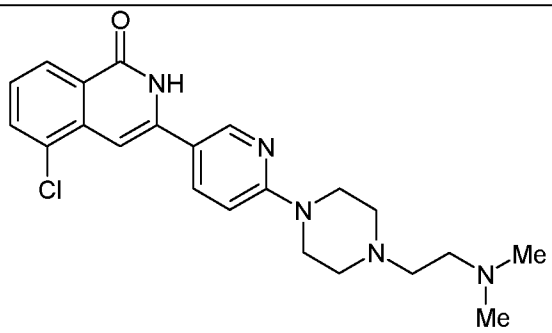
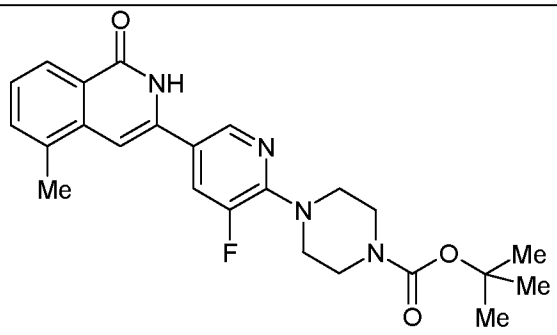
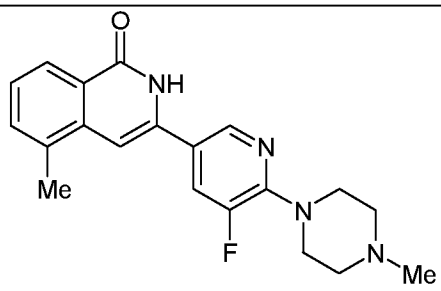
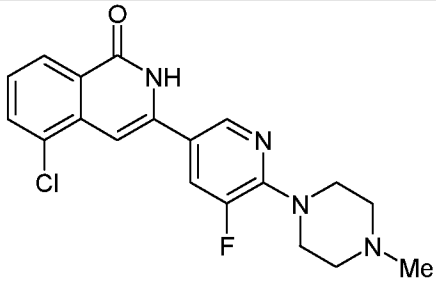
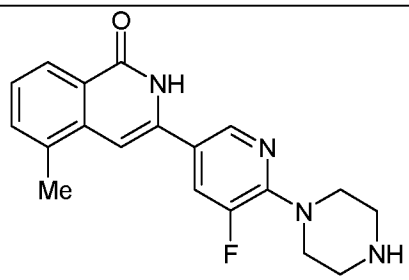
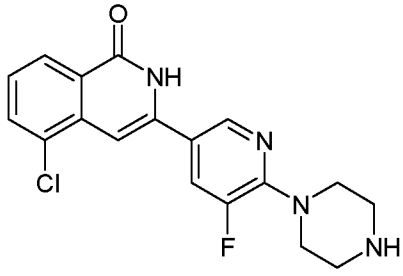
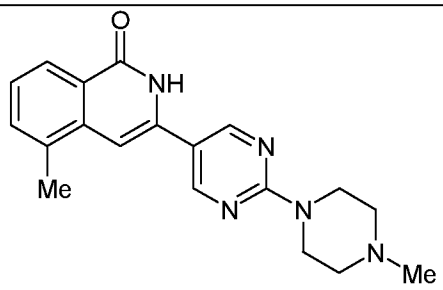
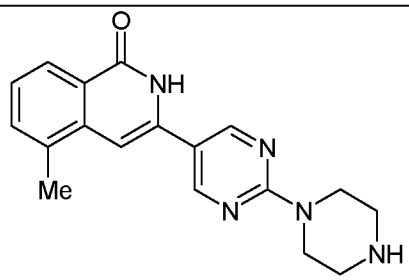
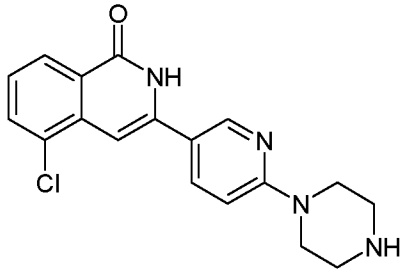
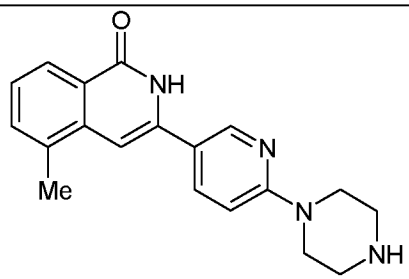
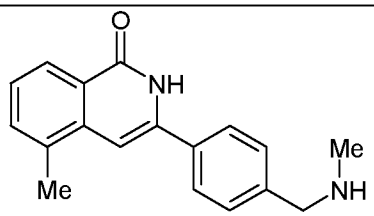
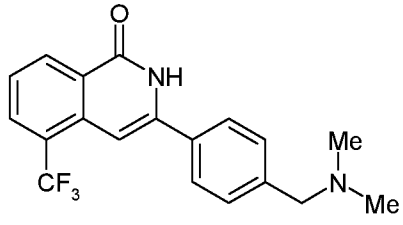
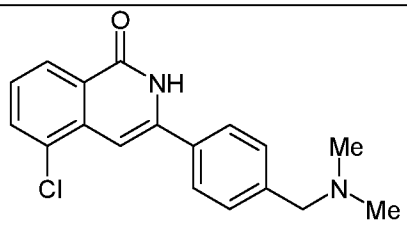
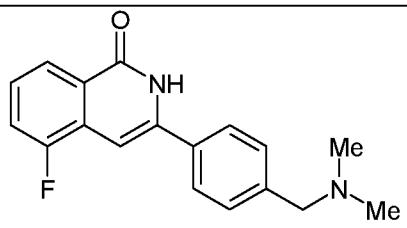
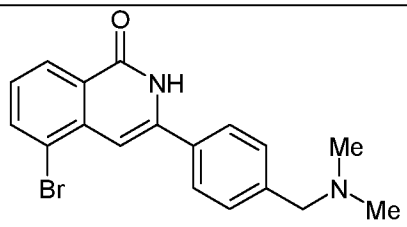
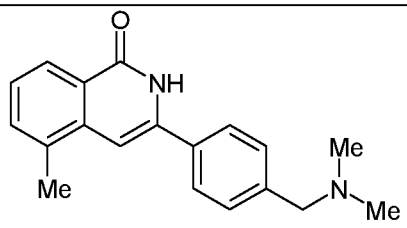
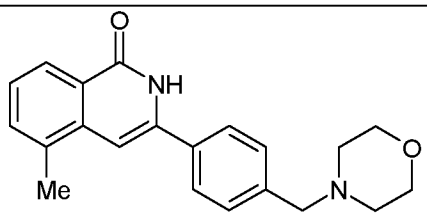
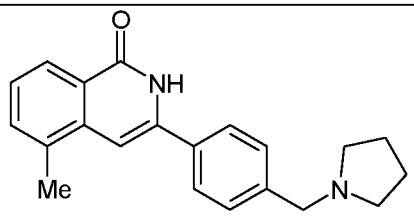
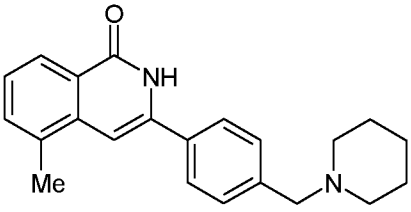
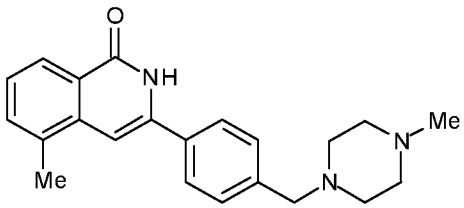
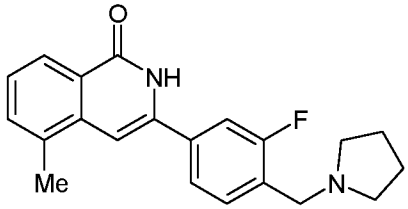
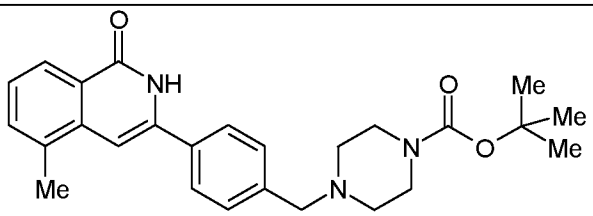
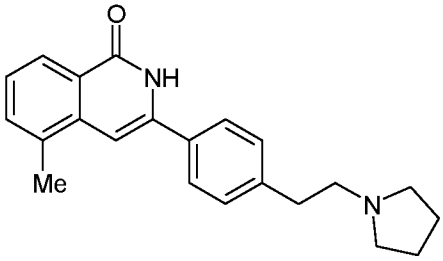
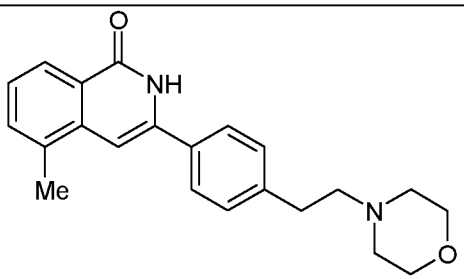
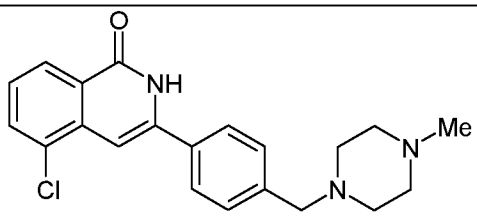
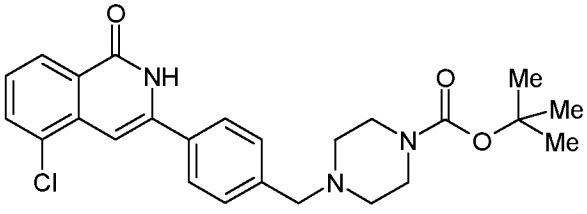
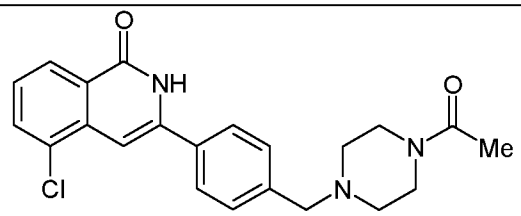
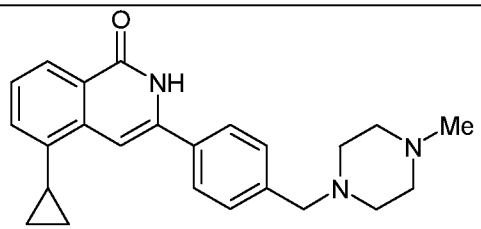
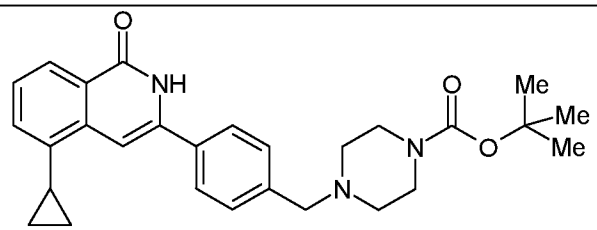
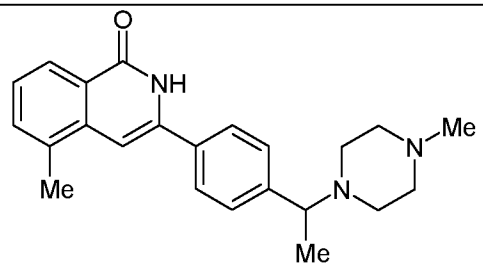
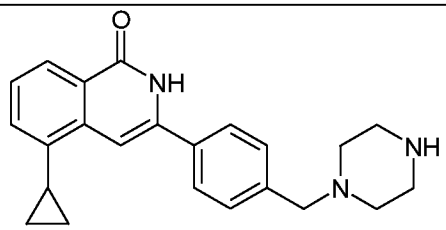
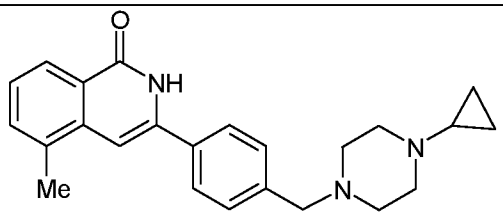
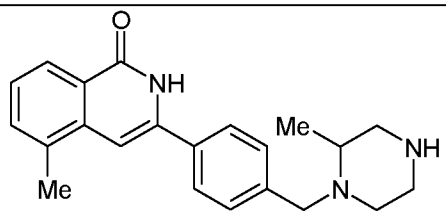
IQ-015	
IQ-016	
IQ-017	
IQ-018	
IQ-019	

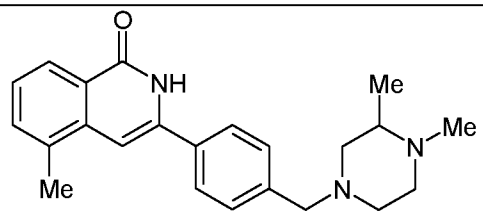
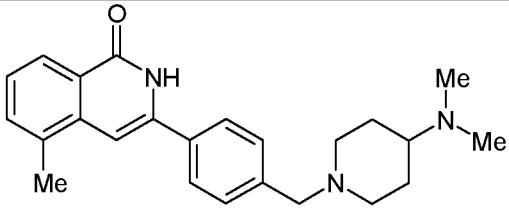
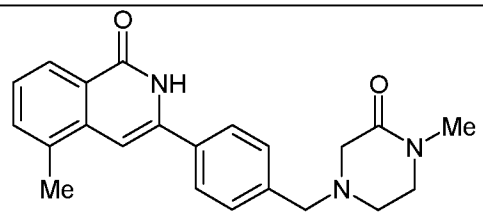
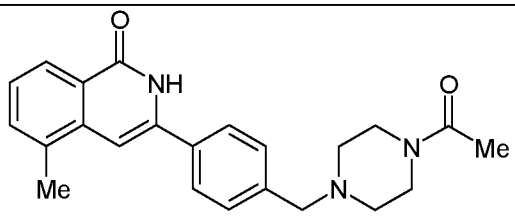
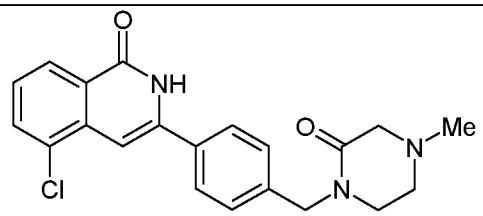
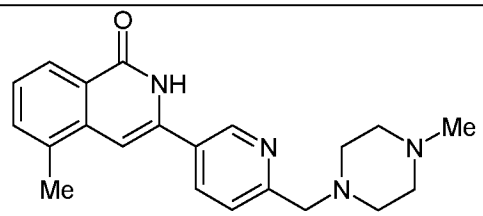
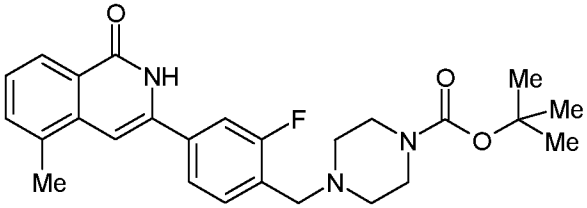
Pat. Code	Structure
IQ-020	
IQ-021	
IQ-022	
IQ-023	
IQ-024	

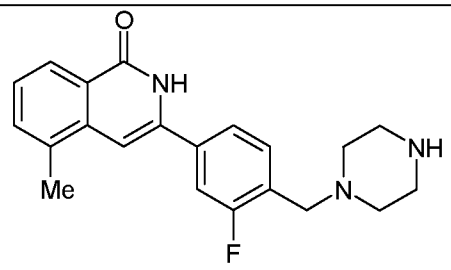
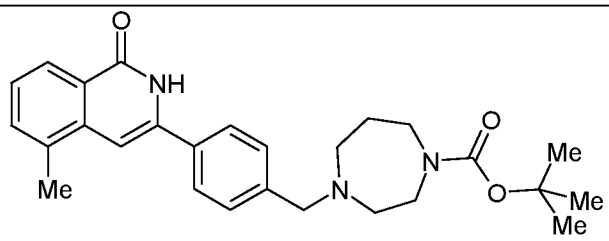
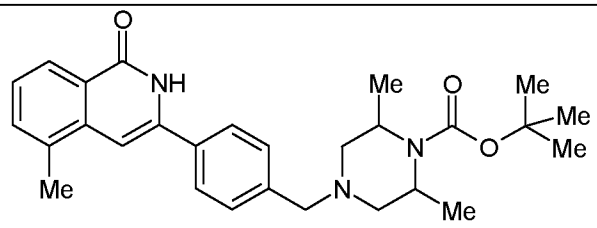
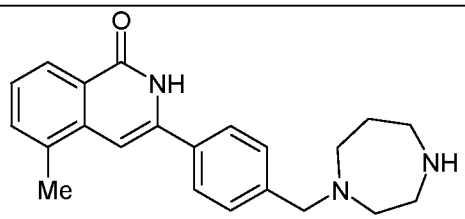
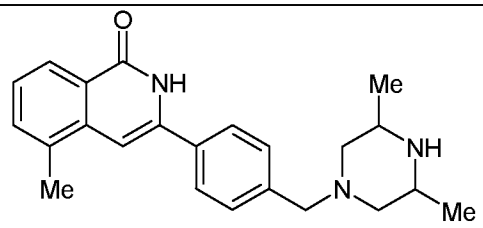
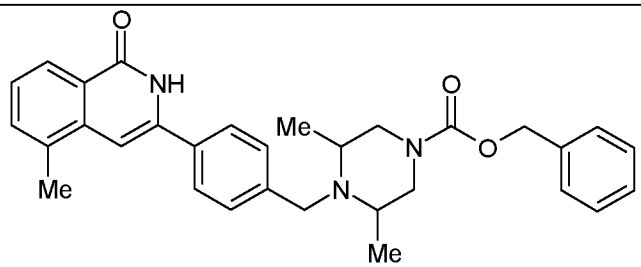
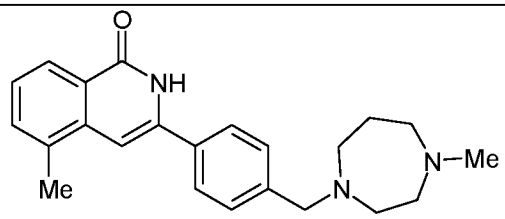
Pat. Code	Structure
IQ-025	
IQ-026	
IQ-027	
IQ-028	
IQ-029	
IQ-030	

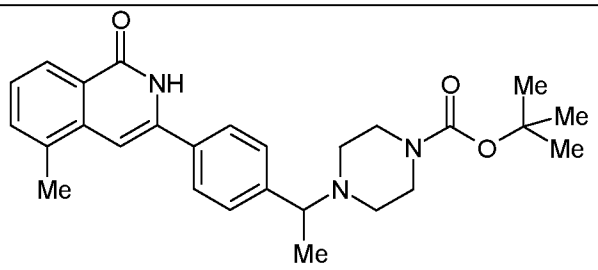
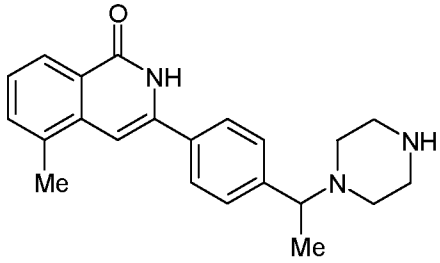
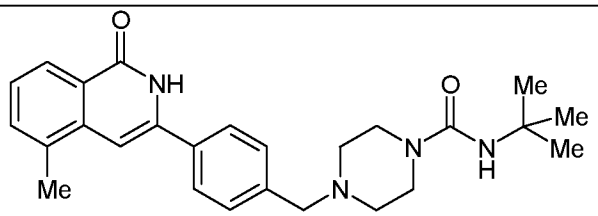
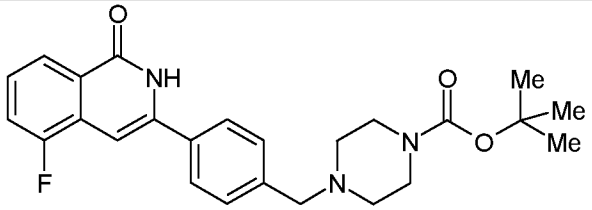
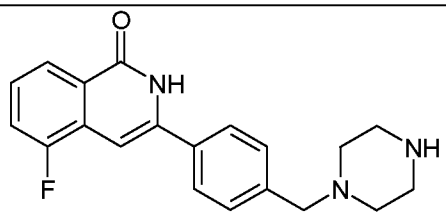
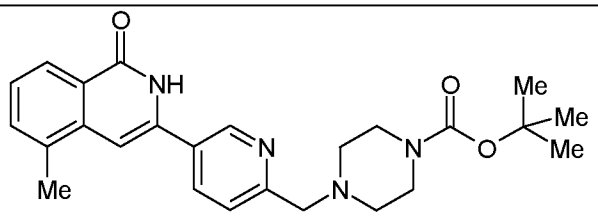
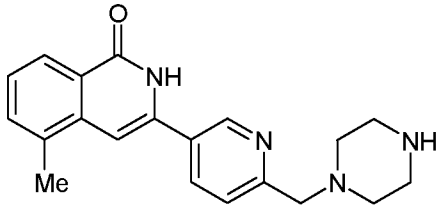
Pat. Code	Structure
IQ-031	
IQ-032	
IQ-033	
IQ-034	
IQ-035	
IQ-036	
IQ-037	

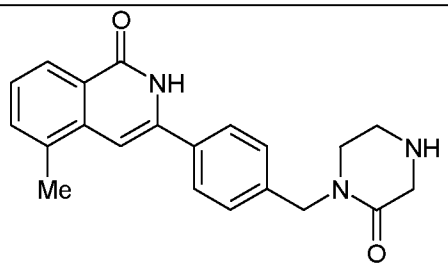
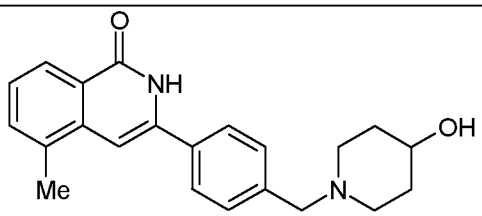
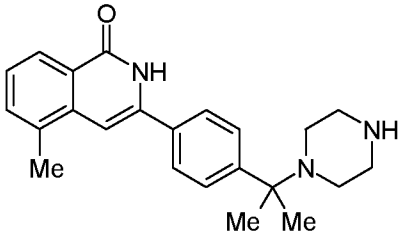
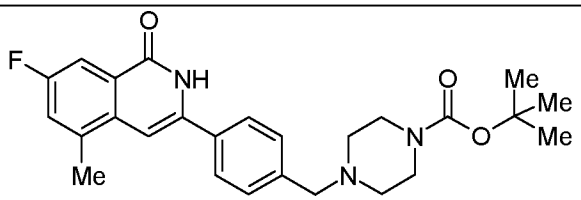
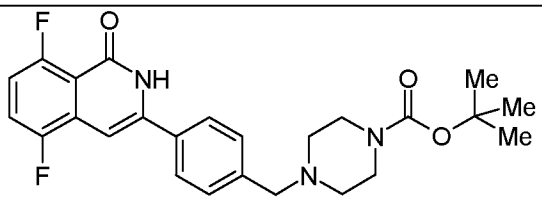
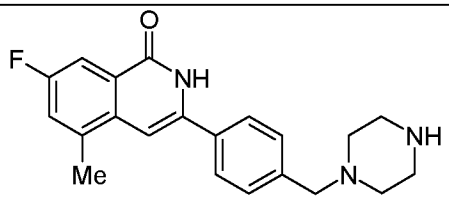
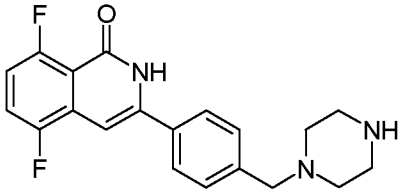
Pat. Code	Structure
IQ-038	
IQ-039	
IQ-040	
IQ-041	
IQ-042	
IQ-043	
IQ-044	

Pat. Code	Structure
IQ-045	
IQ-046	
IQ-047	
IQ-048	
IQ-049	
IQ-050	
IQ-051	

Pat. Code	Structure
IQ-052	
IQ-053	
IQ-054	
IQ-055	
IQ-056	
IQ-057	
IQ-058	

Pat. Code	Structure
IQ-059	
IQ-060	
IQ-061	
IQ-062	
IQ-063	
IQ-064	
IQ-065	

Pat. Code	Structure
IQ-066	
IQ-067	
IQ-068	
IQ-069	
IQ-070	
IQ-071	
IQ-072	

Pat. Code	Structure
IQ-073	
IQ-074	
IQ-075	
IQ-076	
IQ-077	
IQ-078	
IQ-079	

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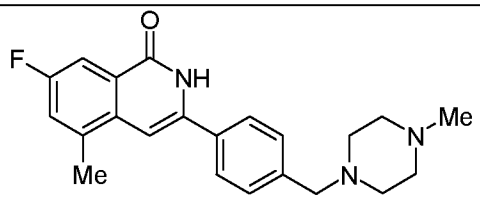
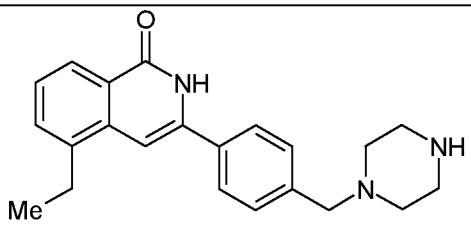
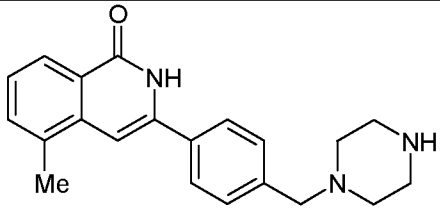
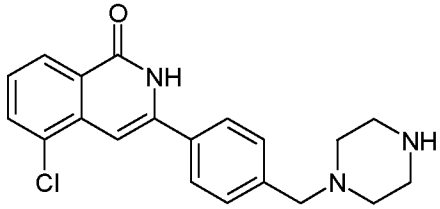
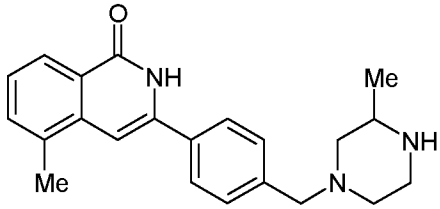
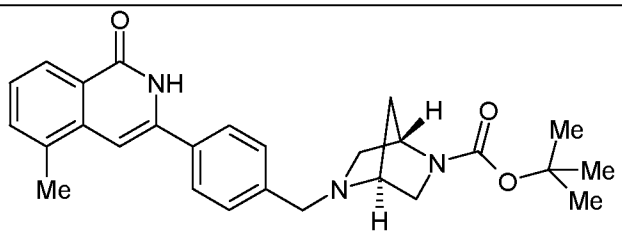
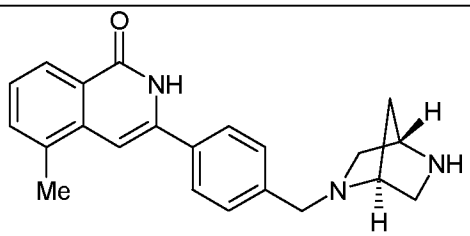
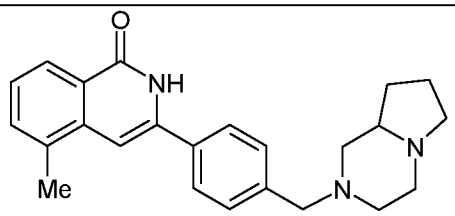
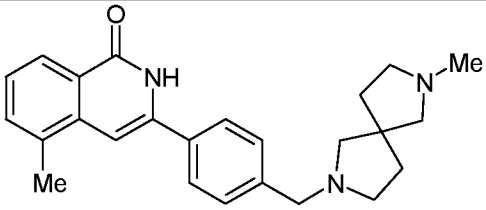
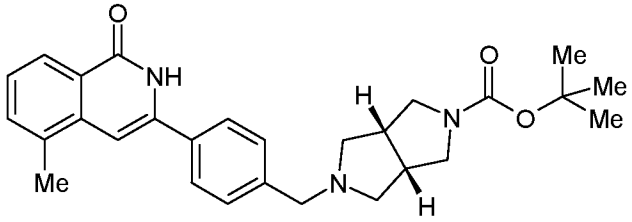
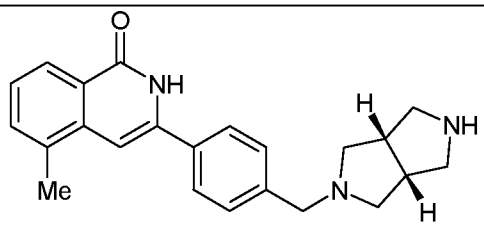
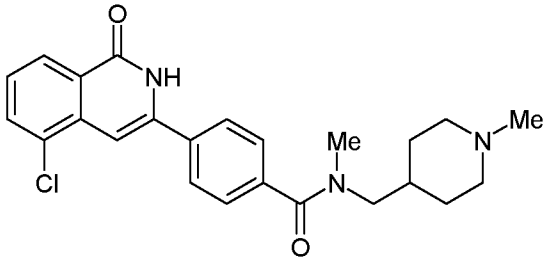
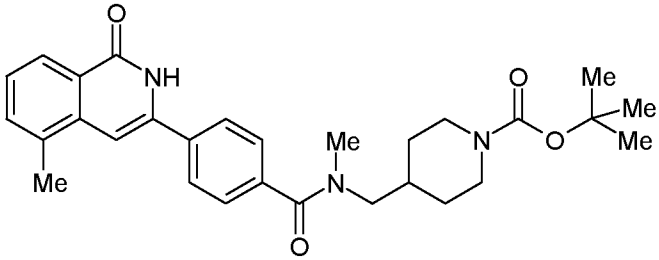
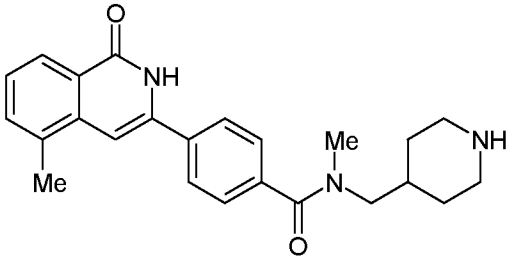
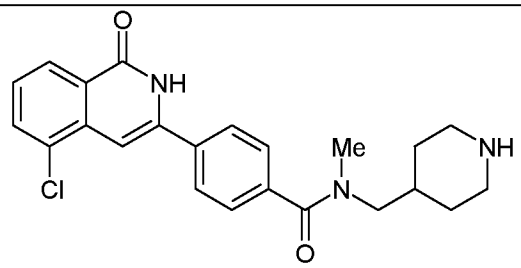
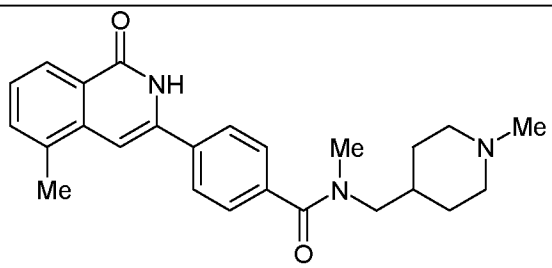
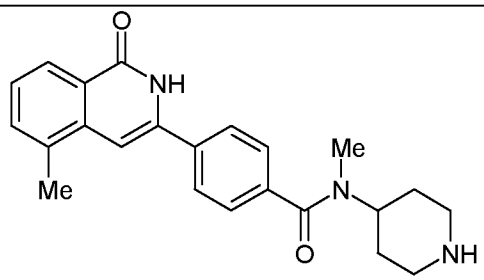
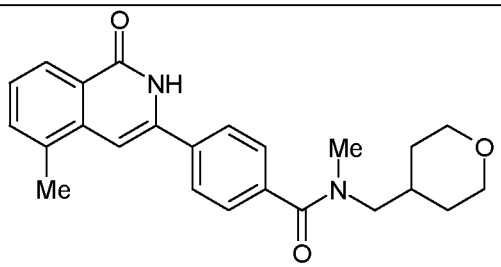
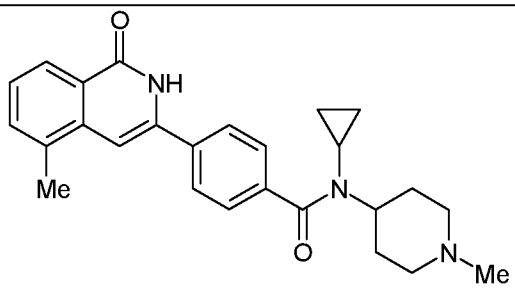
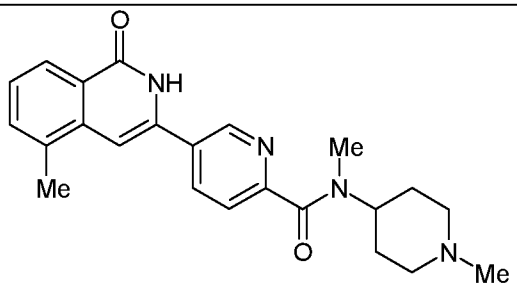
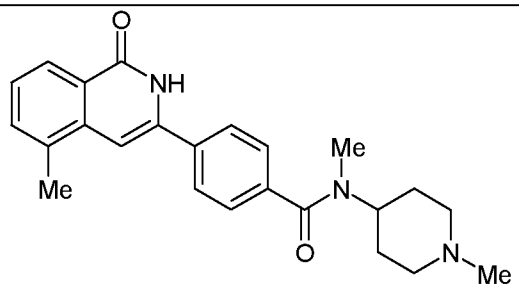
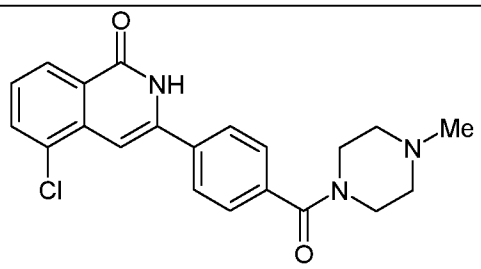
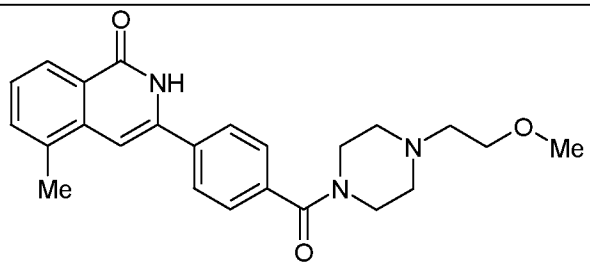
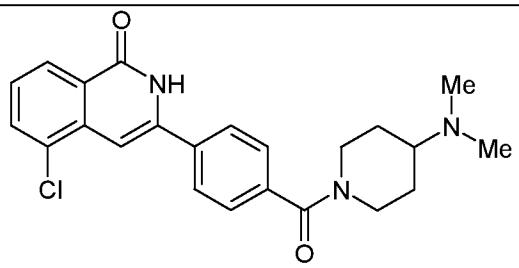
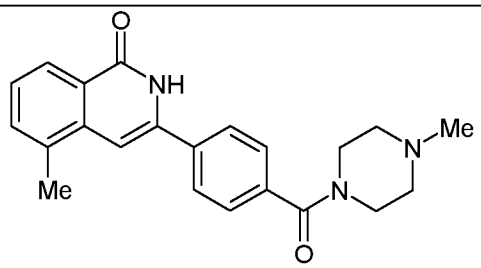
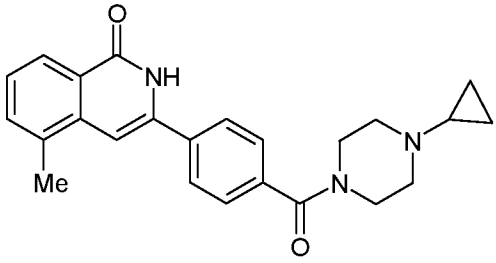
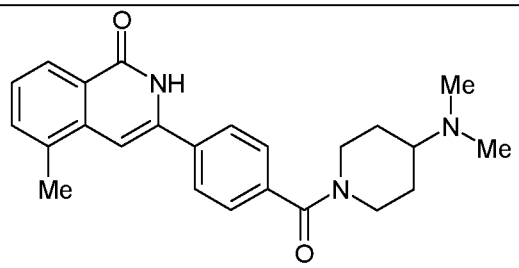
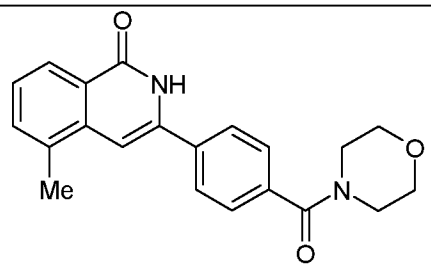
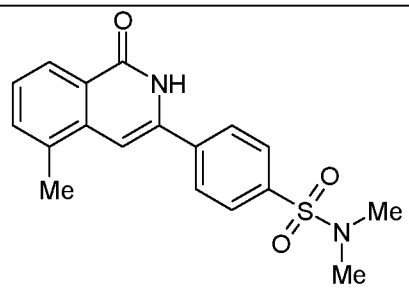
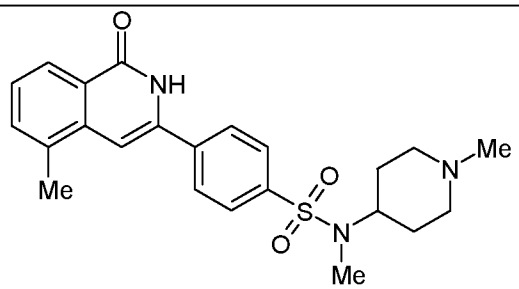
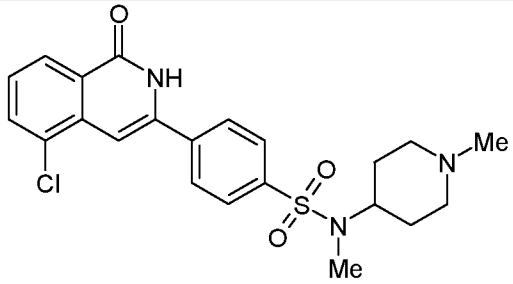
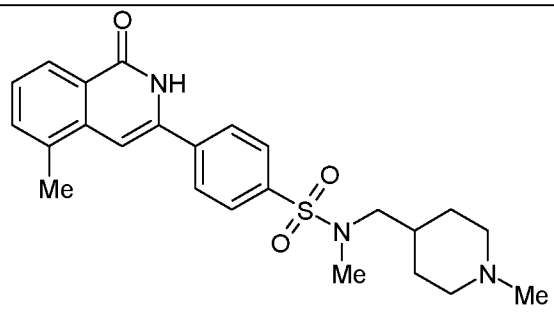
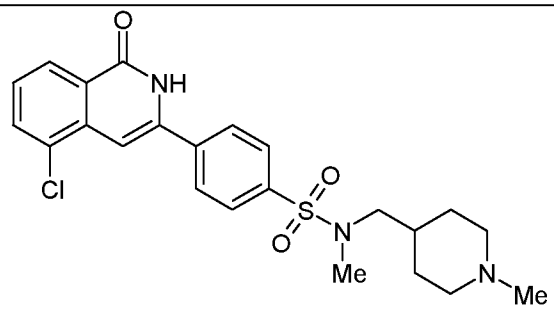
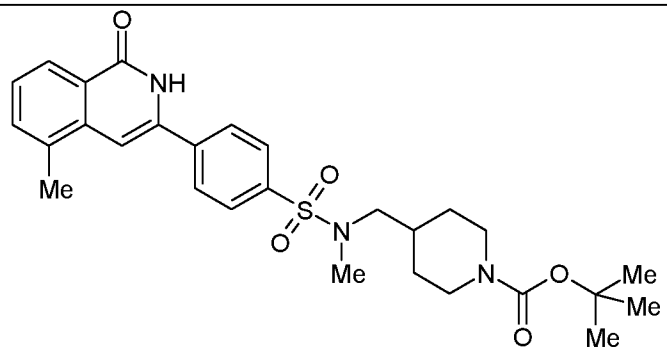
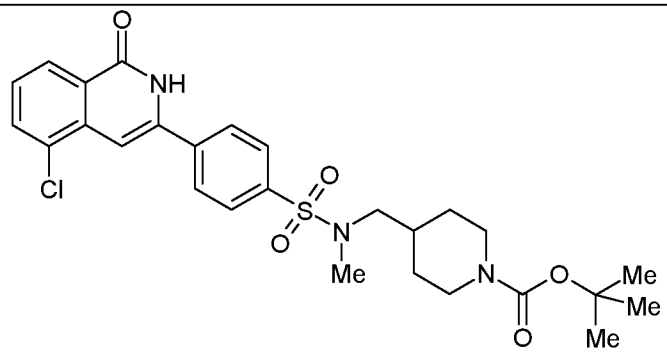
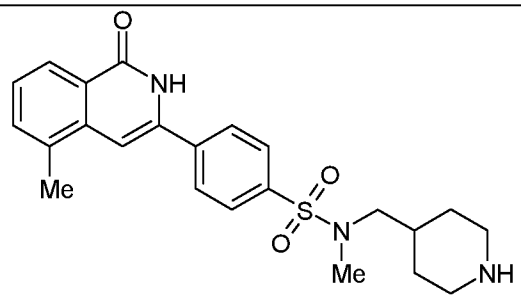
IQ-080	
IQ-081	
IQ-082	
IQ-083	
IQ-084	
IQ-085	
IQ-086	

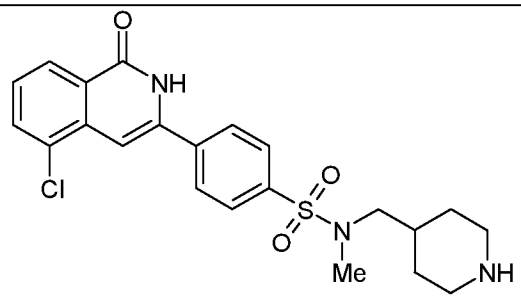
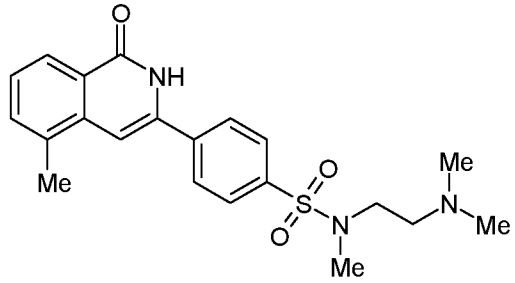
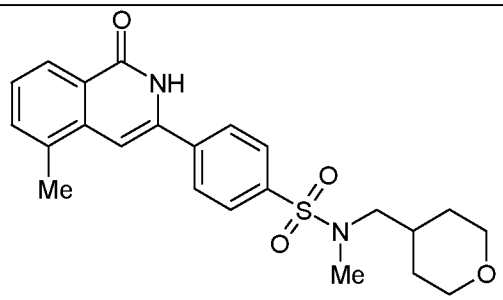
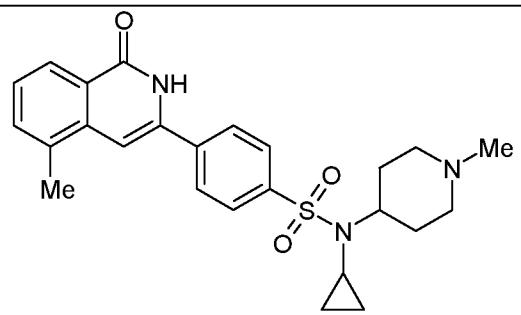
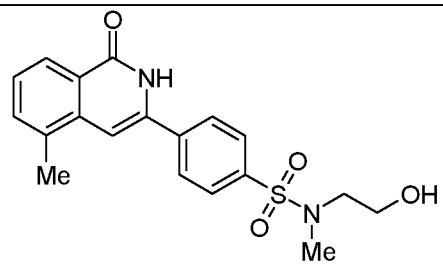
Pat. Code	Structure
IQ-087	
IQ-088	
IQ-089	
IQ-090	
IQ-091	
IQ-092	
IQ-093	

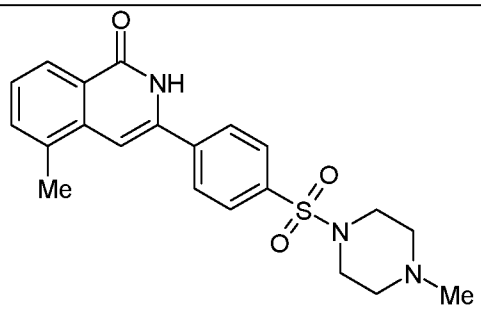
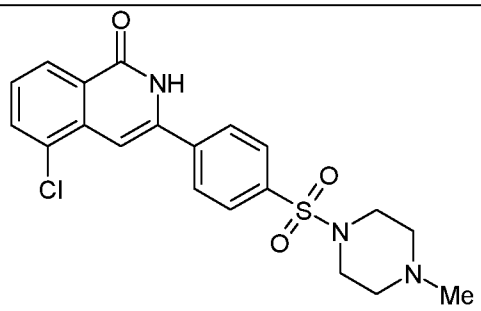
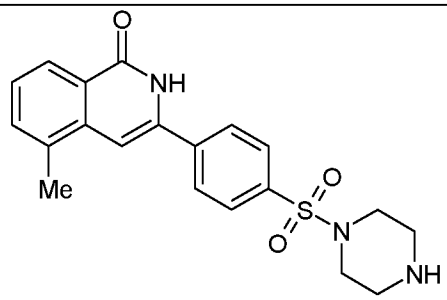
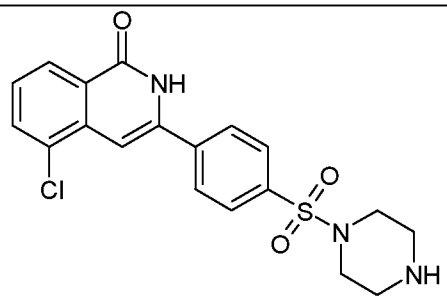
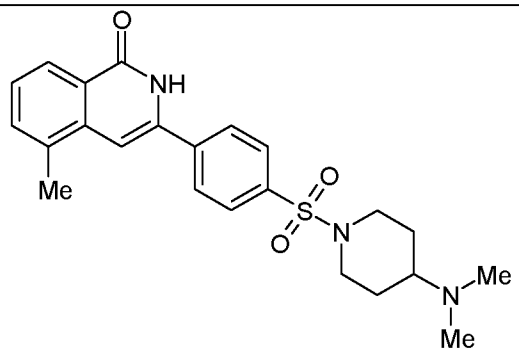
Pat. Code	Structure
IQ-094	
IQ-095	
IQ-096	
IQ-097	
IQ-098	
IQ-099	

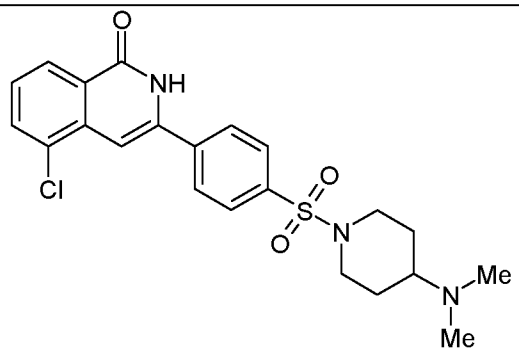
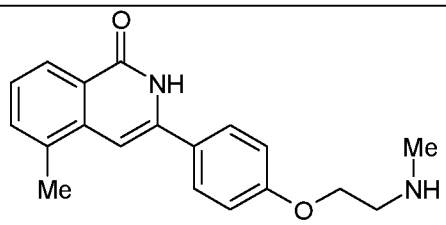
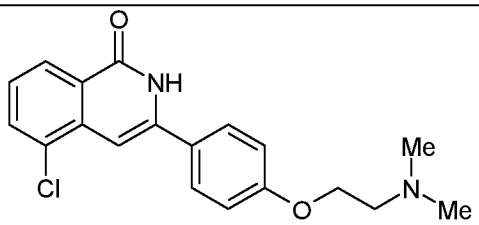
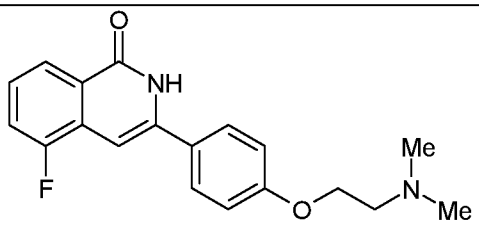
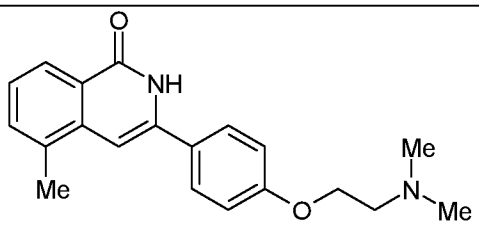
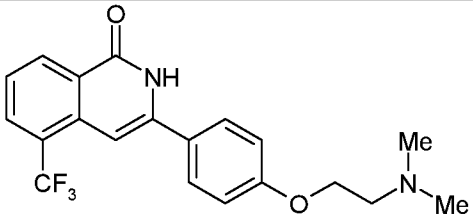
Pat. Code	Structure
IQ-100	
IQ-101	
IQ-102	
IQ-103	
IQ-104	
IQ-105	

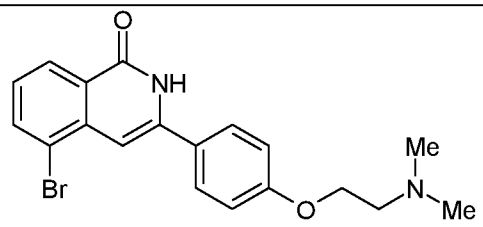
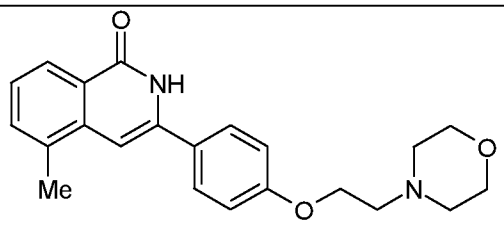
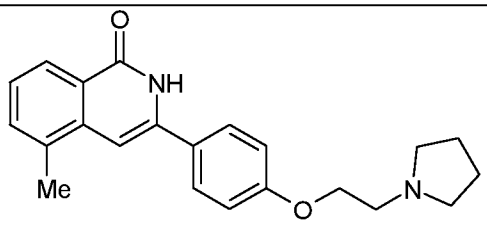
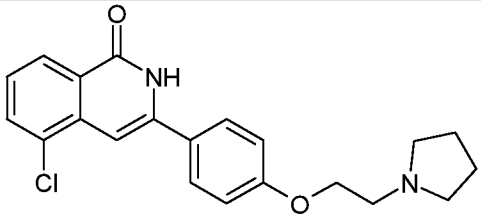
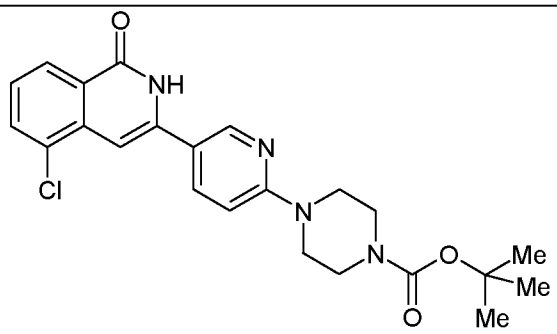
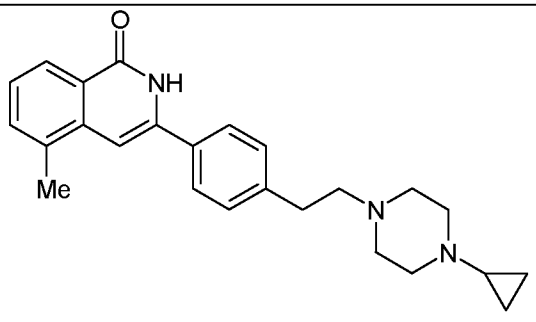
Pat. Code	Structure
IQ-106	
IQ-107	
IQ-108	
IQ-109	
IQ-110	

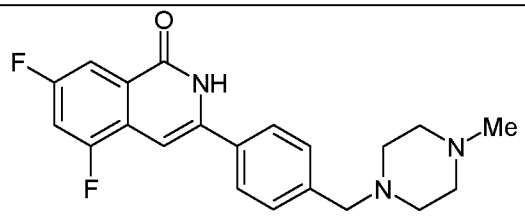
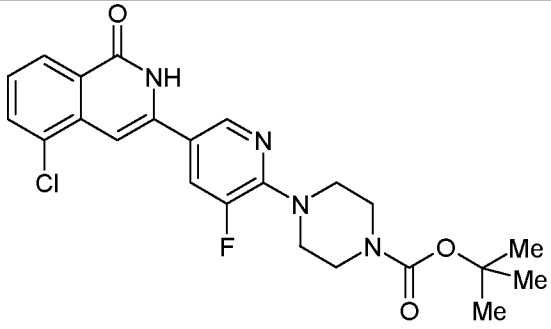
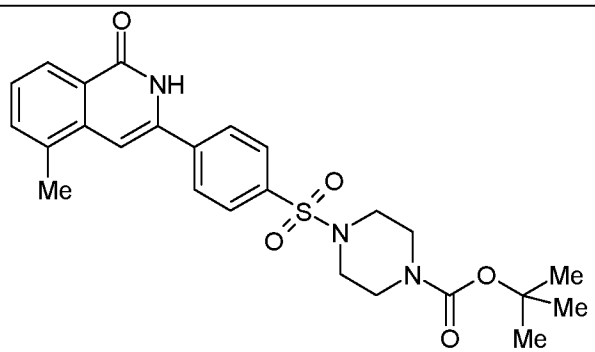
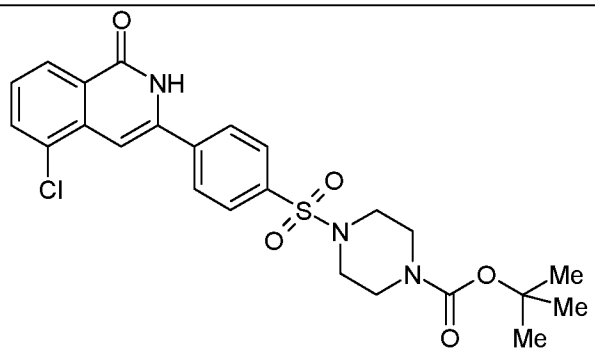
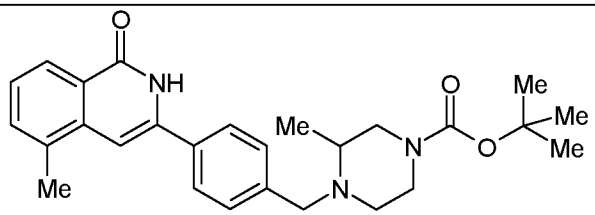
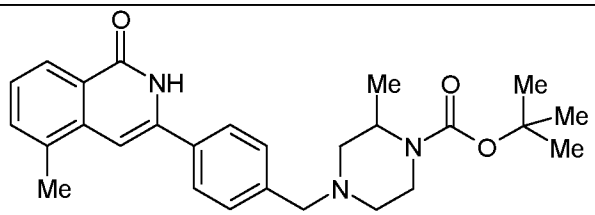
Pat. Code	Structure
IQ-111	
IQ-112	
IQ-113	
IQ-114	
IQ-115	

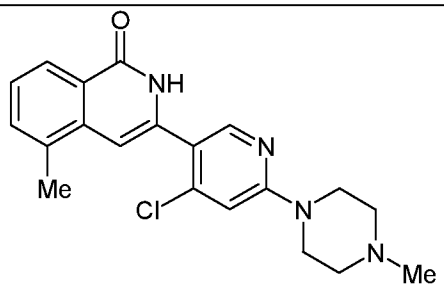
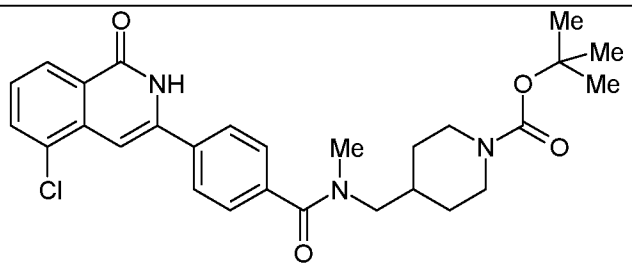
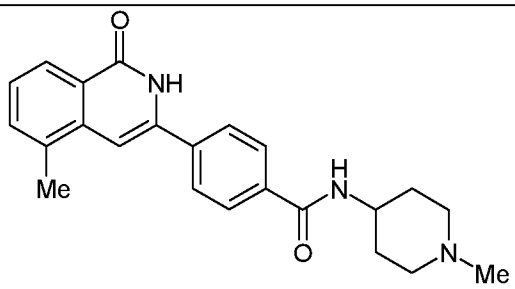
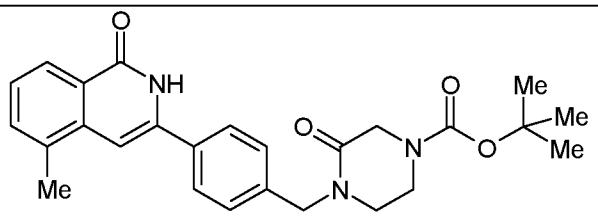
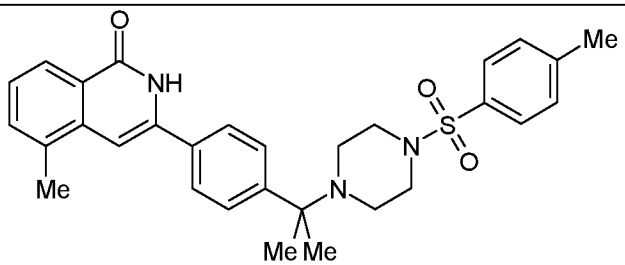
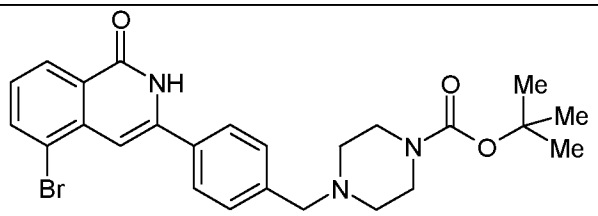
Pat. Code	Structure
IQ-116	
IQ-117	
IQ-118	
IQ-119	
IQ-120	

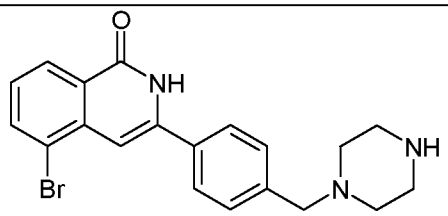
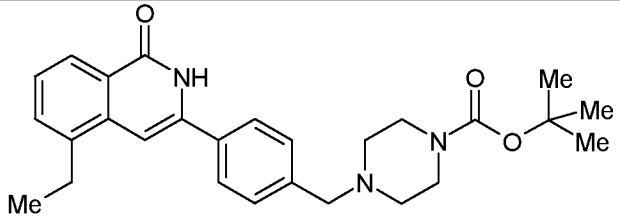
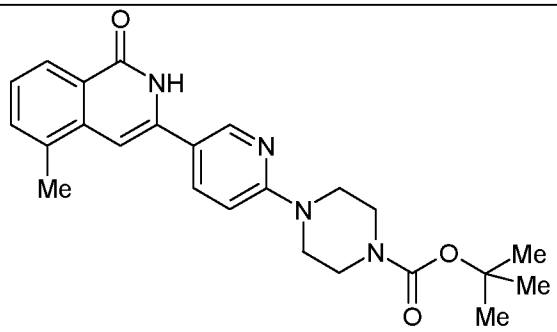
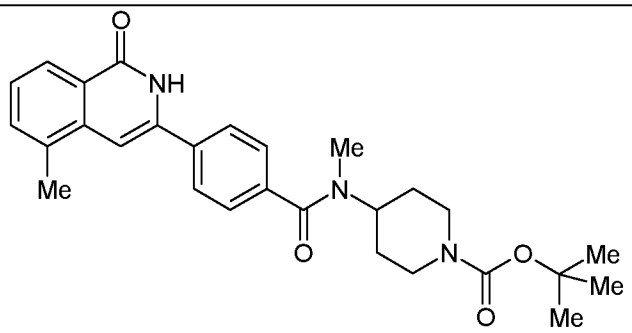
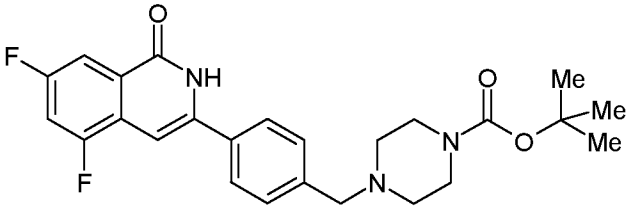
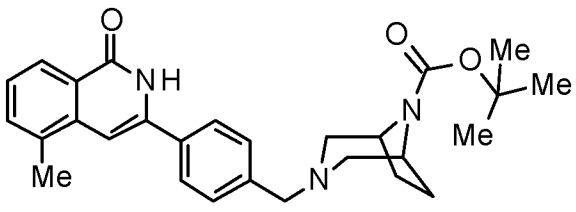
Pat. Code	Structure
IQ-121	
IQ-122	
IQ-123	
IQ-124	
IQ-125	

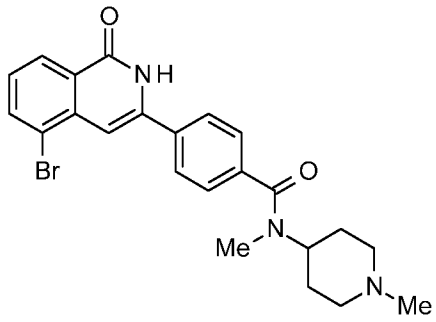
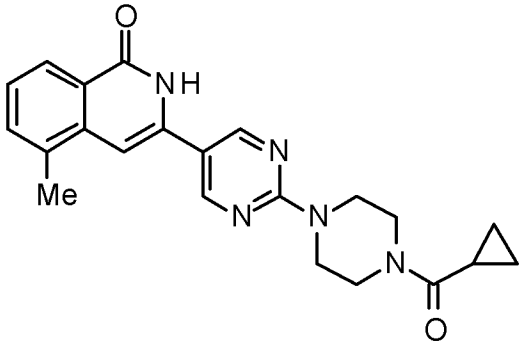
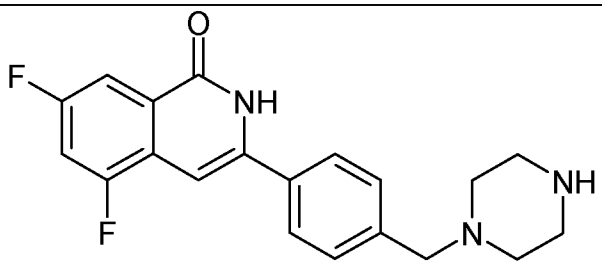
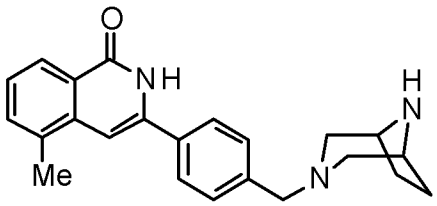
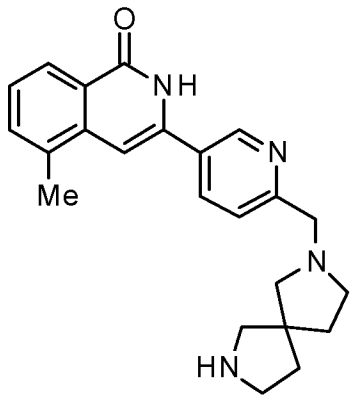
Pat. Code	Structure
IQ-126	
IQ-127	
IQ-128	
IQ-129	
IQ-130	
IQ-131	

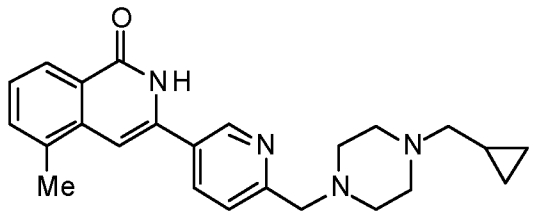
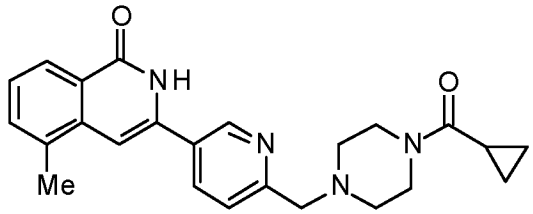
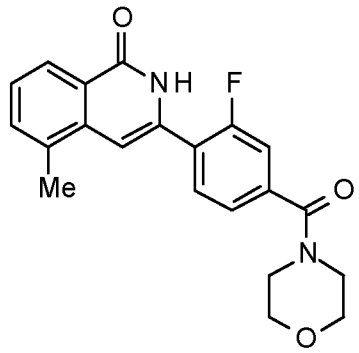
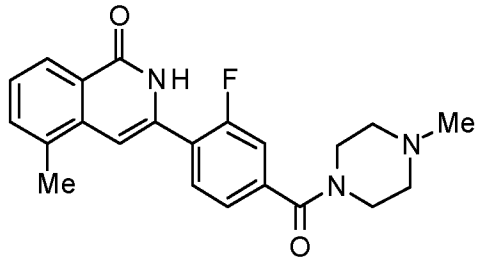
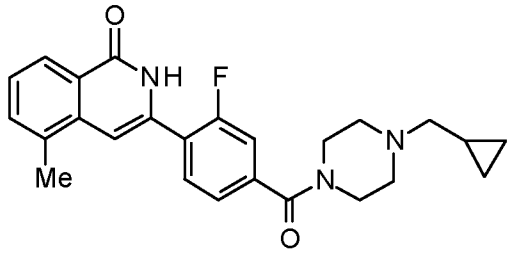
Pat. Code	Structure
IQ-132	
IQ-133	
IQ-134	
IQ-135	
IQ-136	
IQ-137	

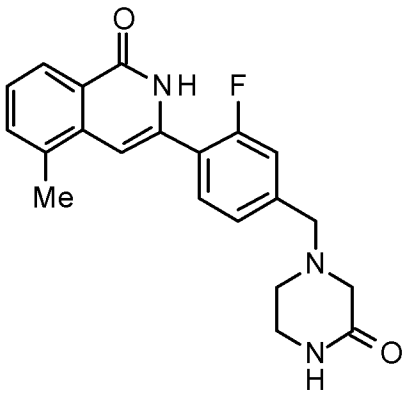
Pat. Code	Structure
IQ-138	
IQ-139	
IQ-140	
IQ-141	
IQ-142	
IQ-143	

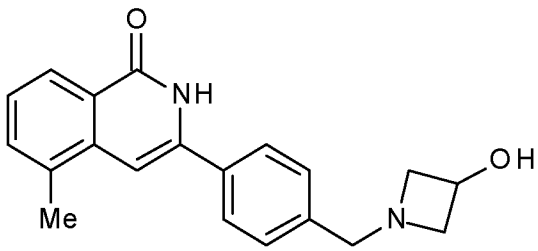
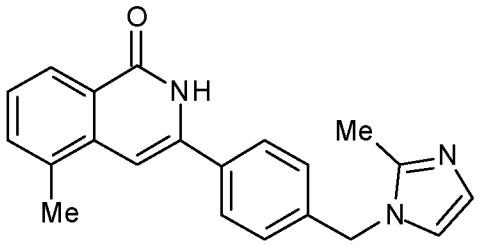
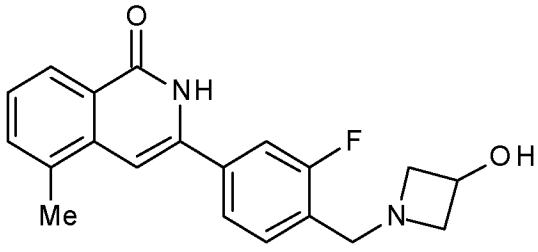
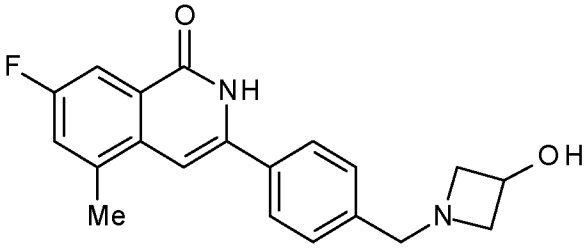
Pat. Code	Structure
IQ-144	
IQ-145	
IQ-146	
IQ-147	
IQ-148	
IQ-149	

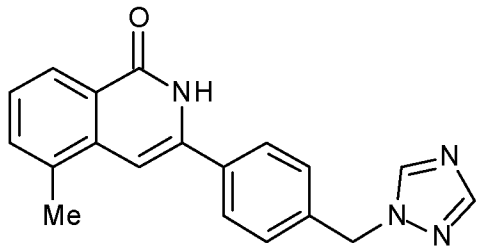
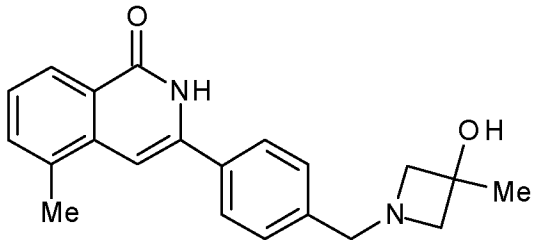
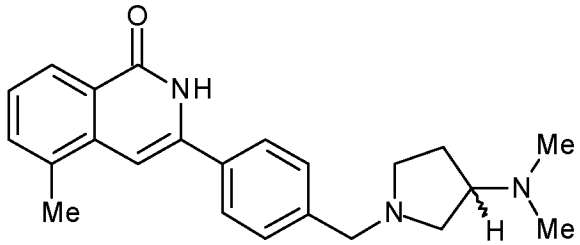
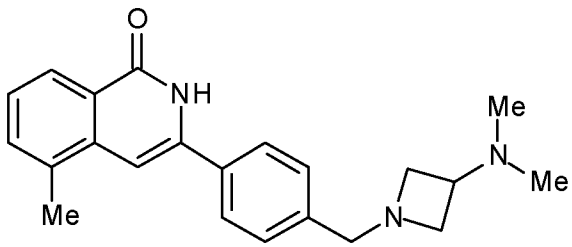
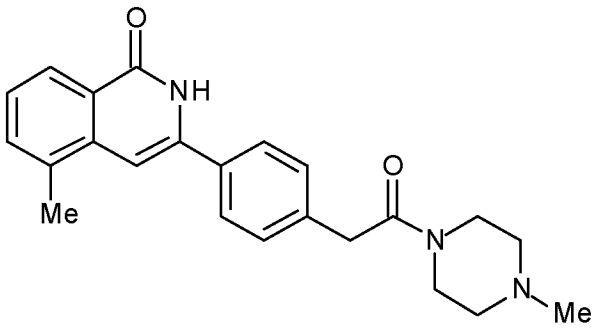
Pat. Code	Structure
IQ-150	
IQ-151	
IQ-152	
IQ-153	
IQ-154	
IQ-155	

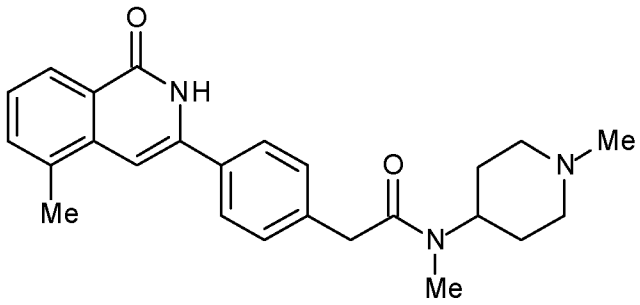
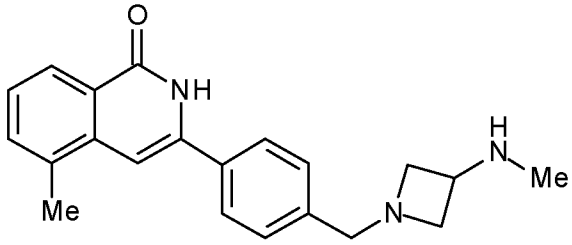
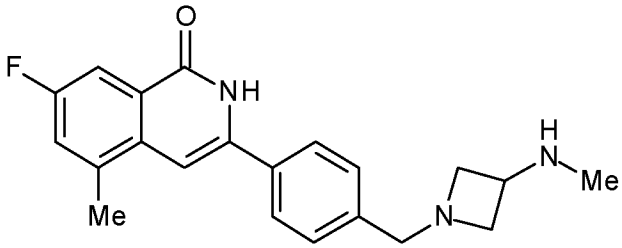
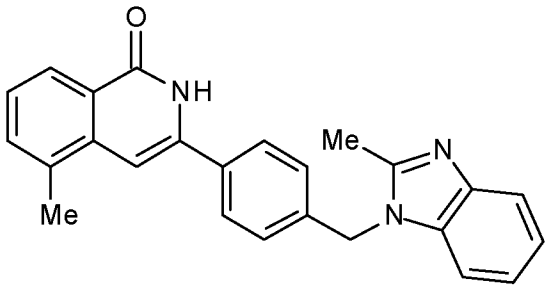
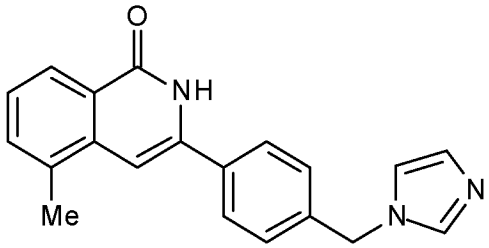
Pat. Code	Structure
IQ-156	
IQ-157	
IQ-158	
IQ-159	
IQ-160	

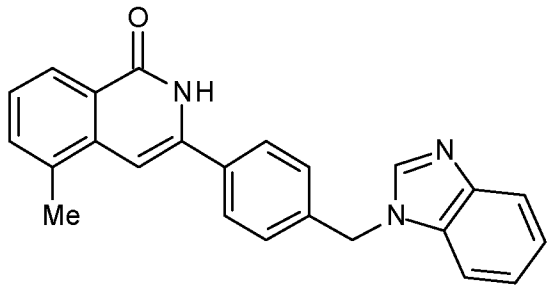
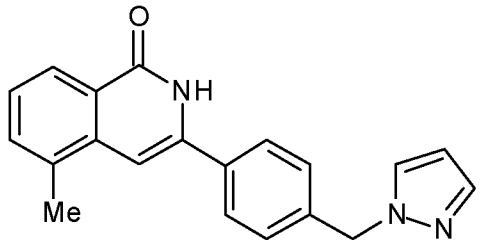
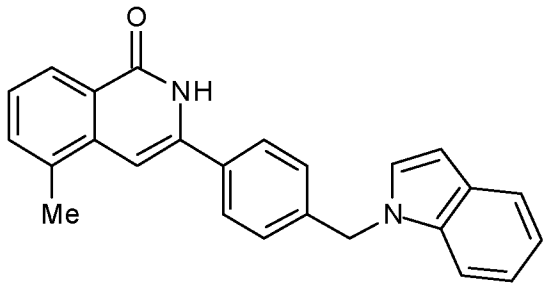
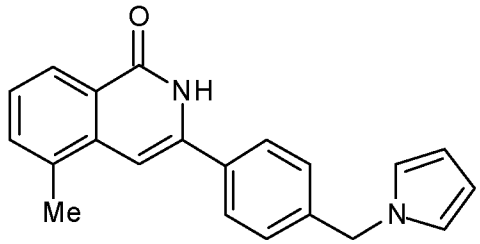
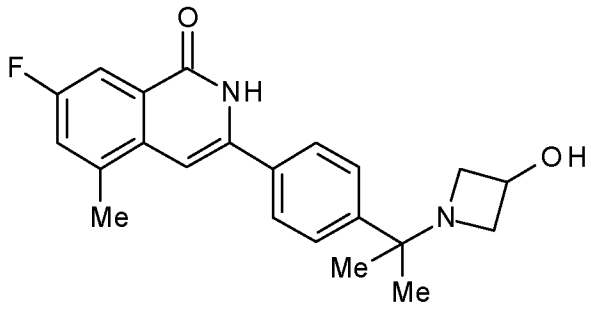
Pat. Code	Structure
IQ-161	
IQ-162	
IQ-163	
IQ-164	
IQ-165	

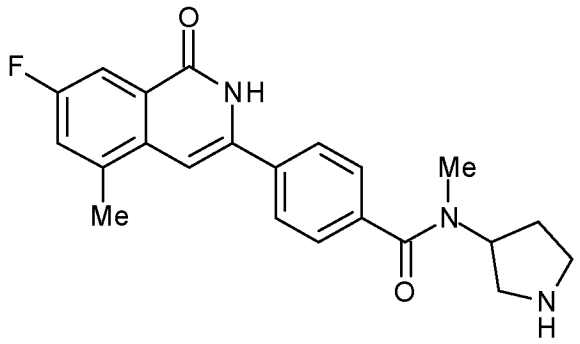
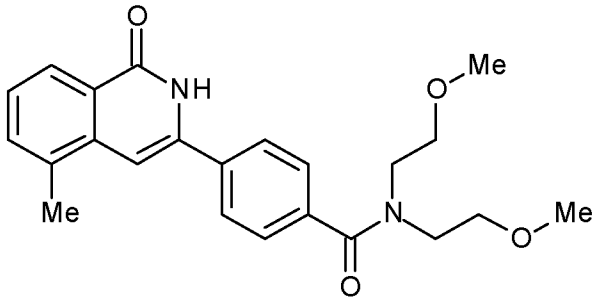
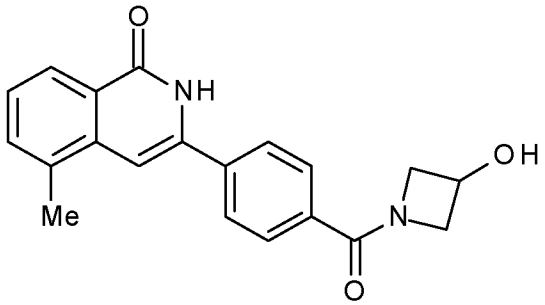
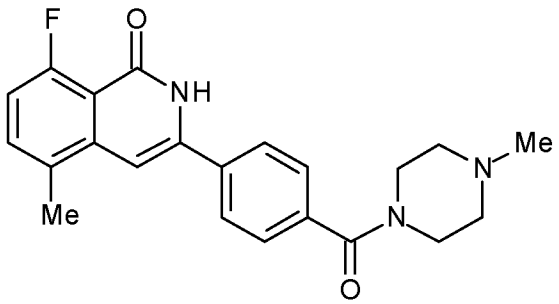
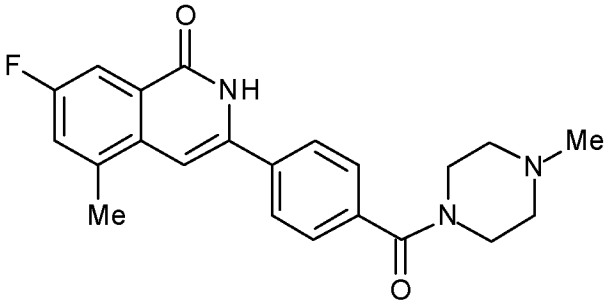
Pat. Code	Structure
IQ-166	

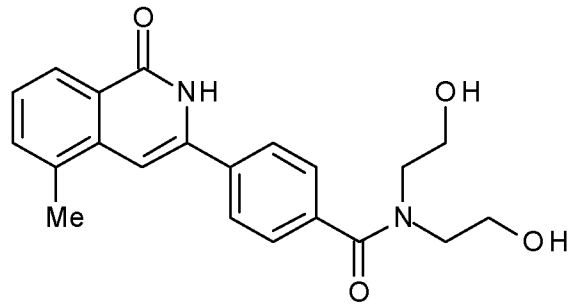
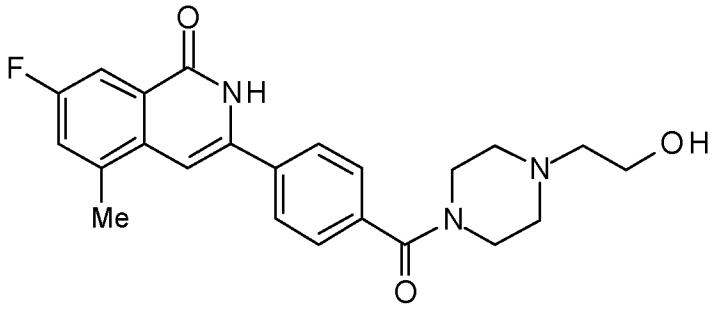
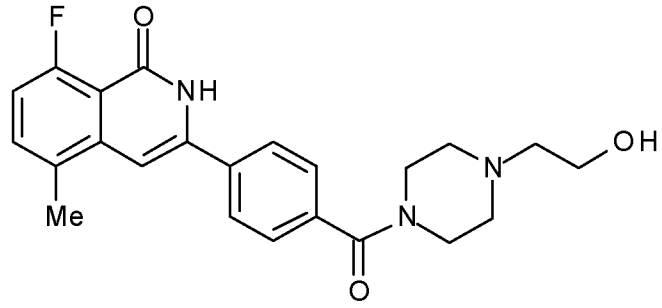
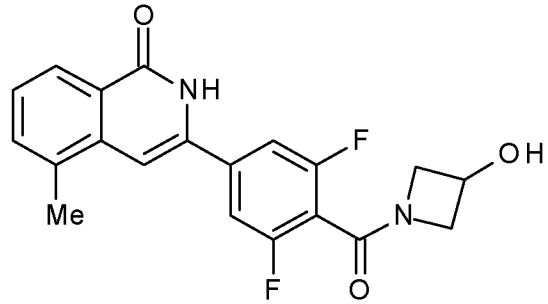
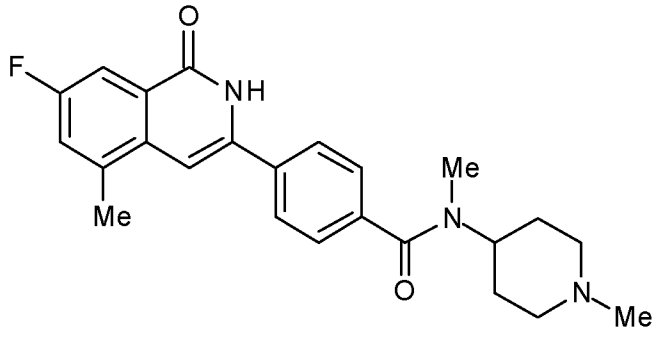
Pat. Code	Structure
IQ-167	
IQ-168	
IQ-169	
IQ-170	

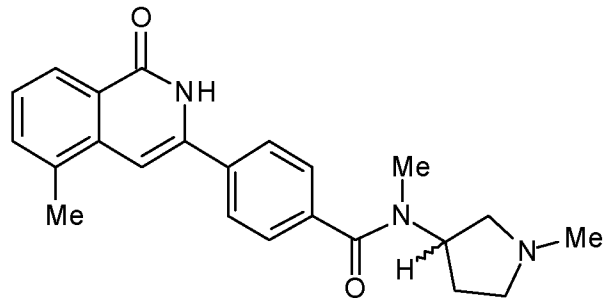
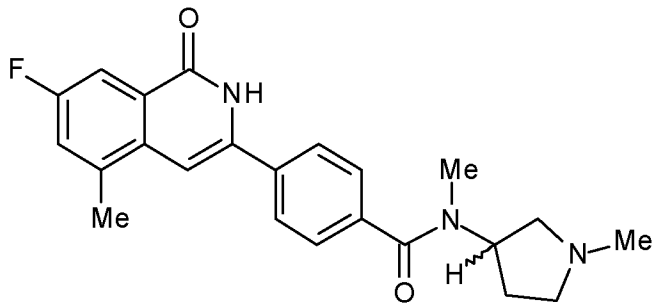
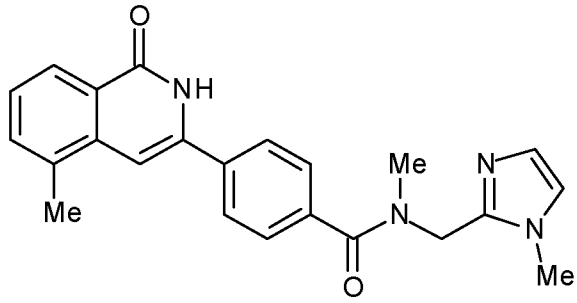
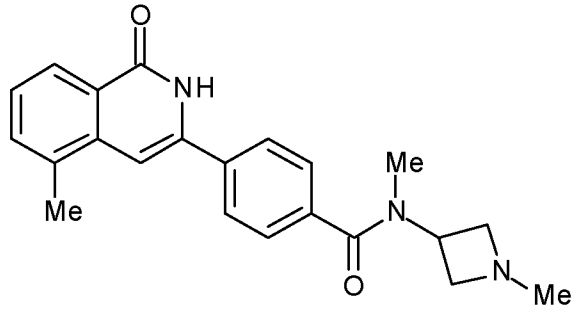
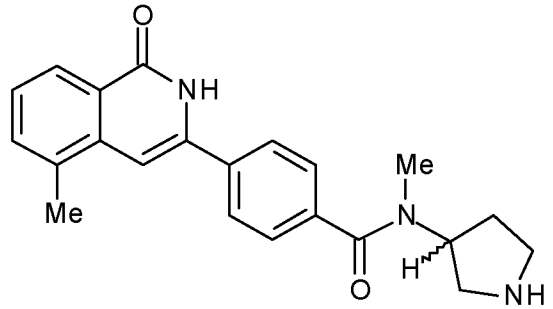
Pat. Code	Structure
IQ-171	
IQ-172	
IQ-173	
IQ-174	
IQ-175	

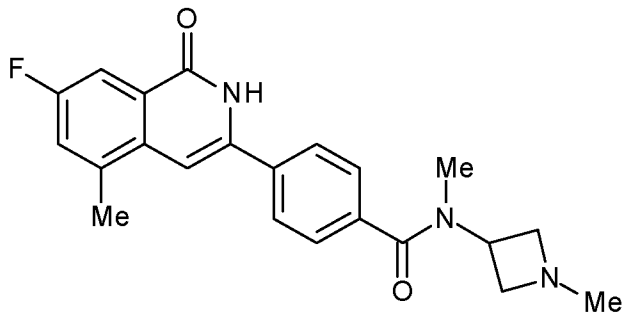
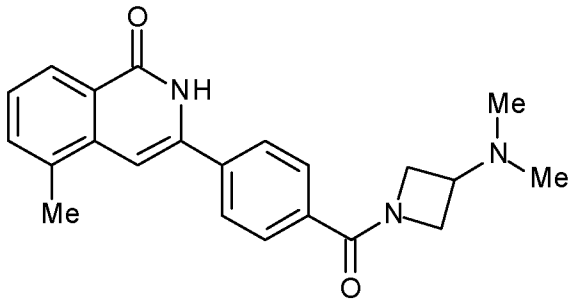
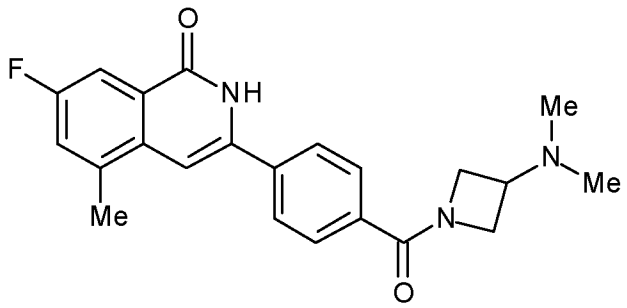
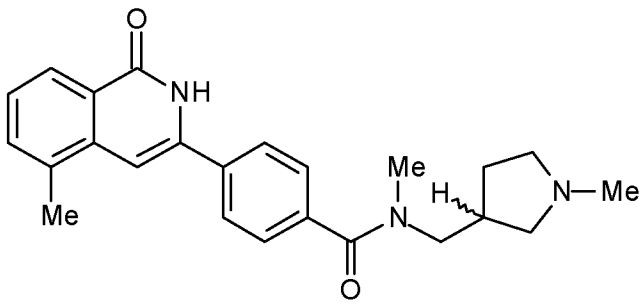
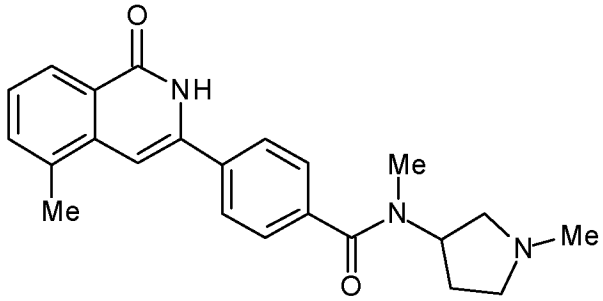
Pat. Code	Structure
IQ-176	
IQ-177	
IQ-178	
IQ-179	
IQ-180	

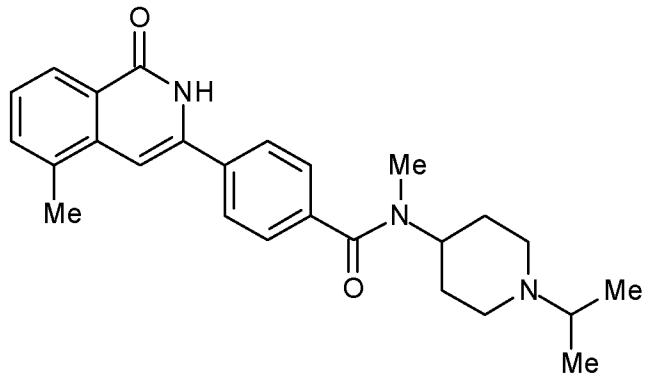
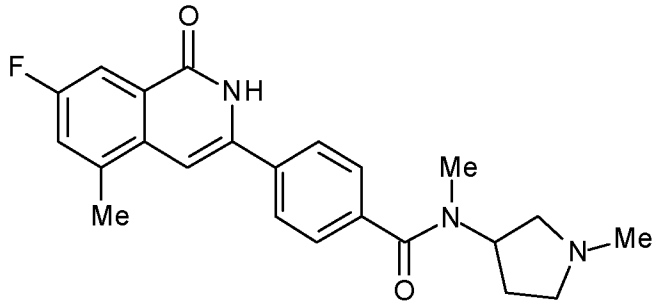
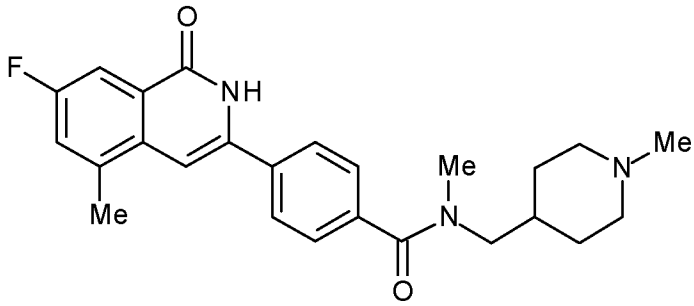
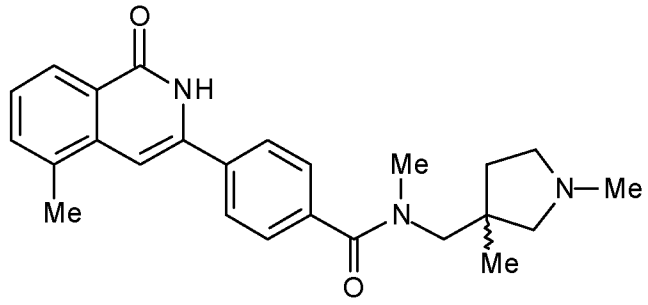
Pat. Code	Structure
IQ-181	
IQ-182	
IQ-183	
IQ-184	
IQ-185	

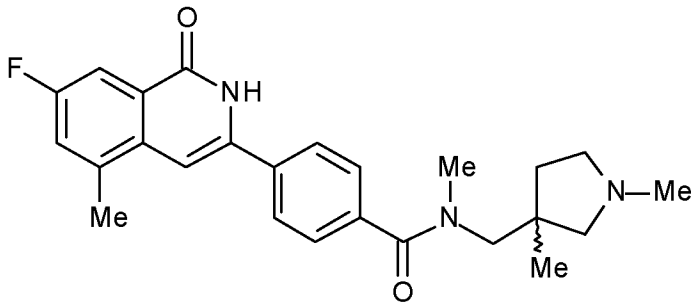
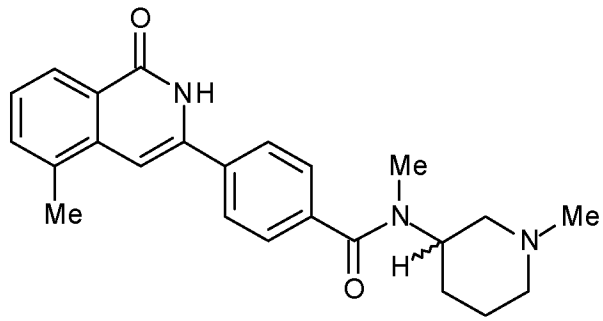
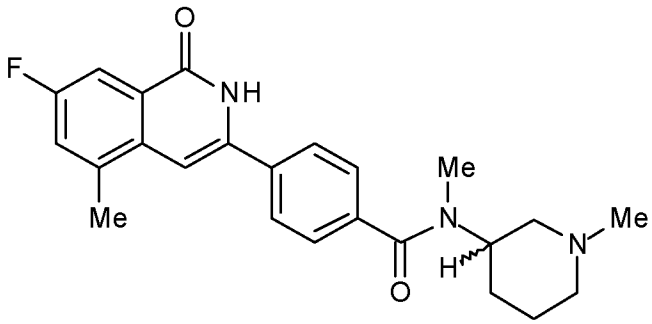
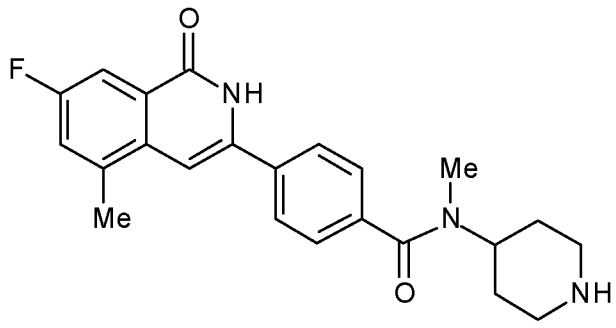
Pat. Code	Structure
IQ-186	
IQ-187	
IQ-188	
IQ-189	
IQ-190	

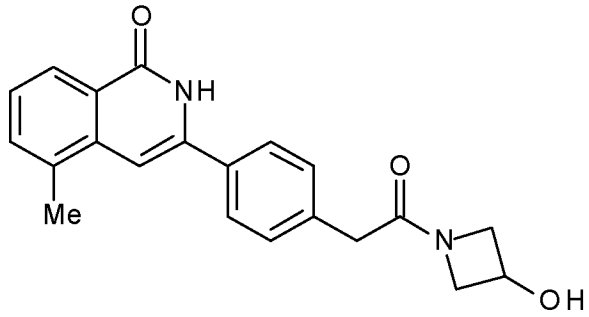
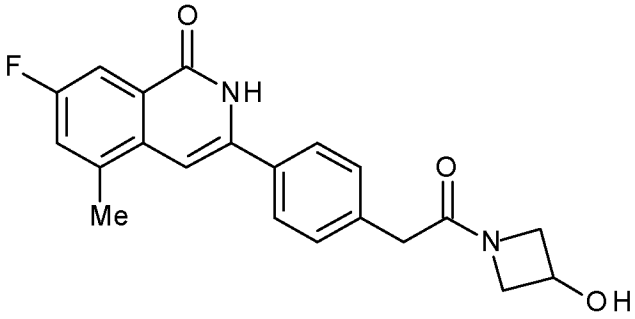
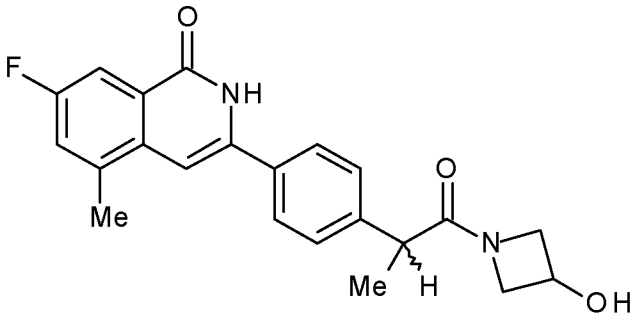
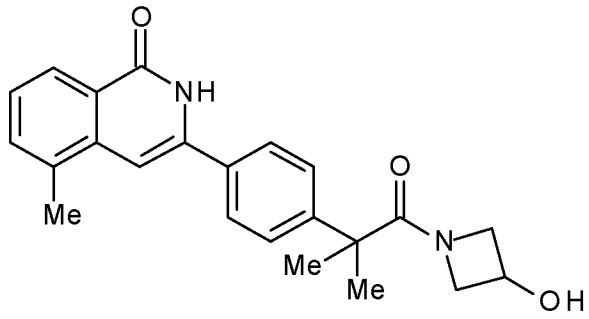
Pat. Code	Structure
IQ-191	
IQ-192	
IQ-193	
IQ-194	
IQ-195	

Pat. Code	Structure
IQ-196	
IQ-197	
IQ-198	
IQ-199	
IQ-200	

Pat. Code	Structure
IQ-201	
IQ-202	
IQ-203	
IQ-204	
IQ-205	

Pat. Code	Structure
IQ-206	
IQ-207	
IQ-208	
IQ-209	

Pat. Code	Structure
IQ-210	
IQ-211	
IQ-212	
IQ-213	

Pat. Code	Structure
IQ-214	
IQ-215	
IQ-216	
IQ-217	

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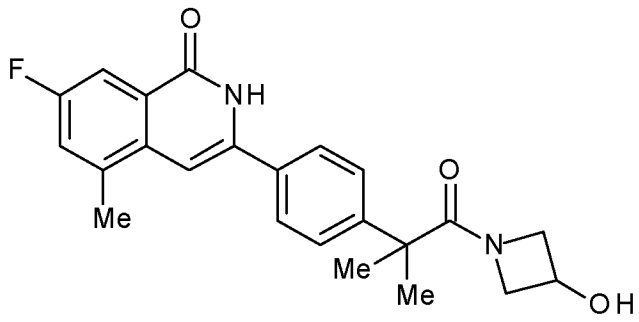
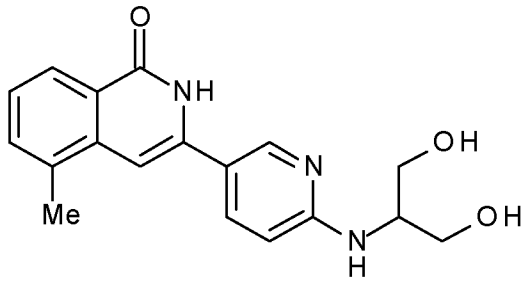
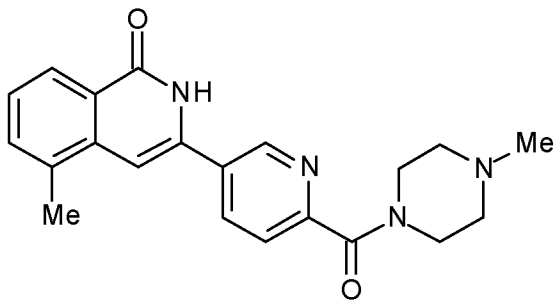
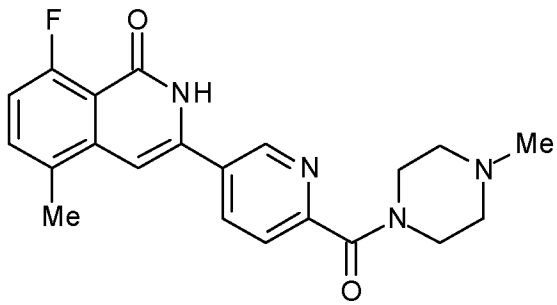
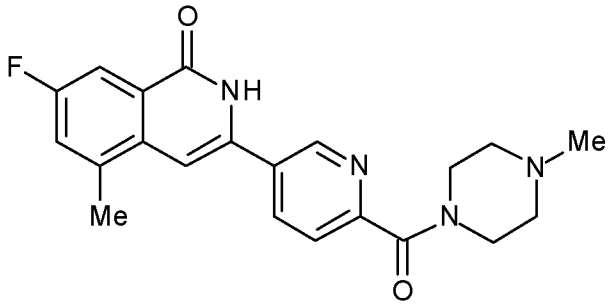
IQ-218	
IQ-219	
IQ-220	
IQ-221	
IQ-222	

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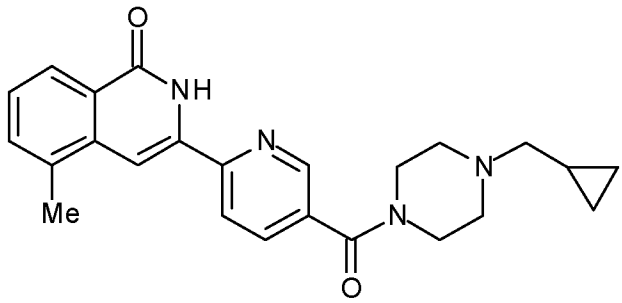
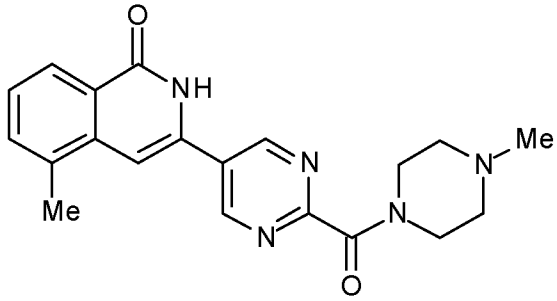
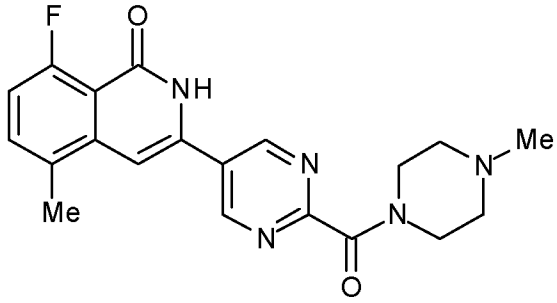
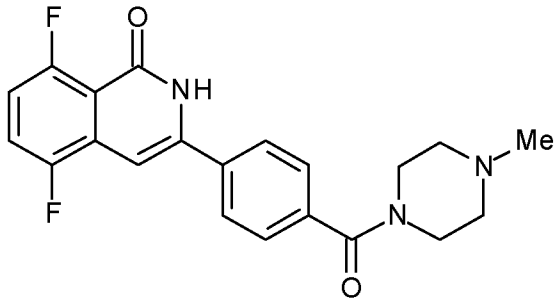
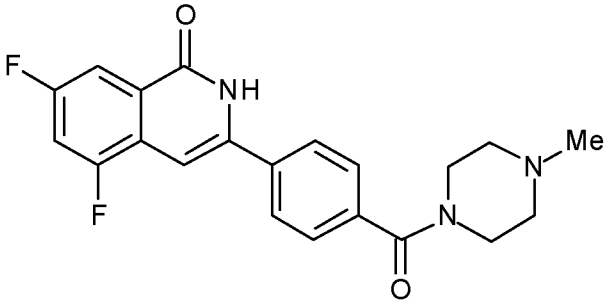
IQ-223	
IQ-224	
IQ-225	
IQ-226	
IQ-227	

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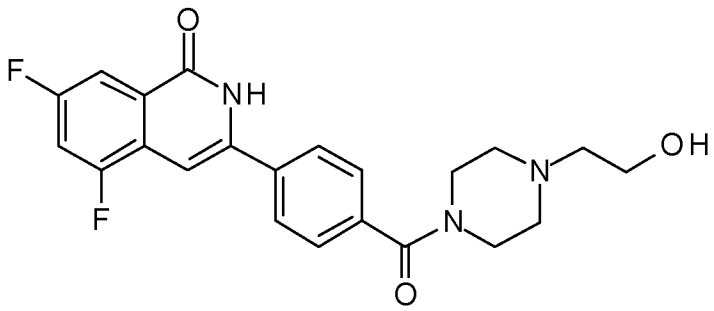
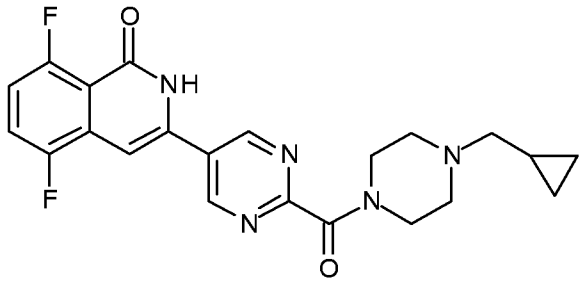
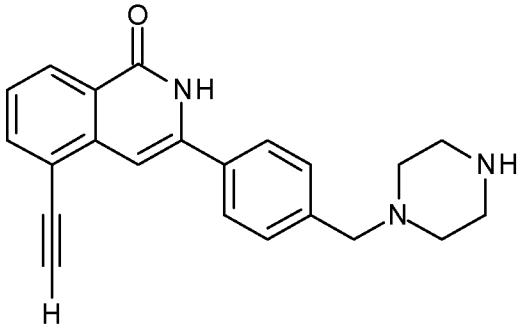
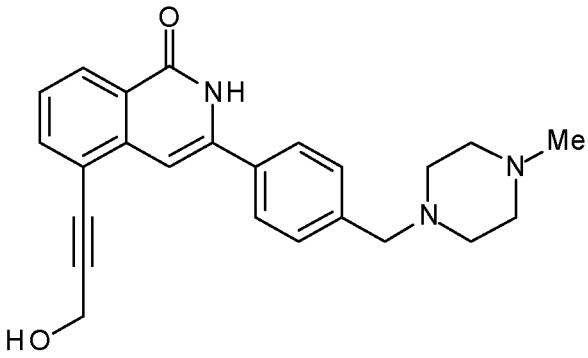
IQ-228	
IQ-229	
IQ-230	
IQ-231	

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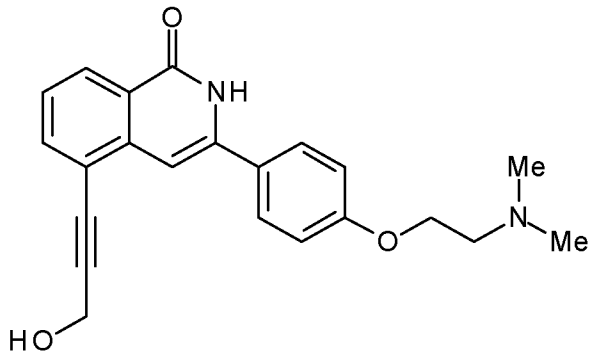
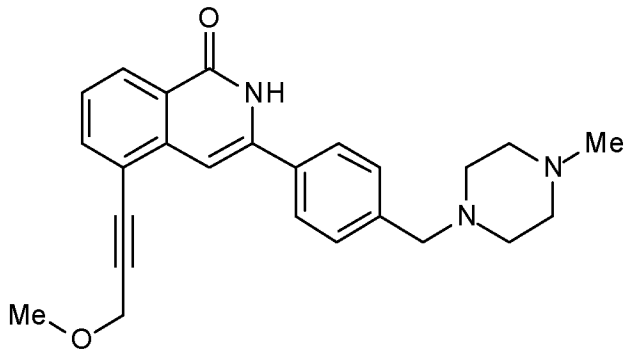
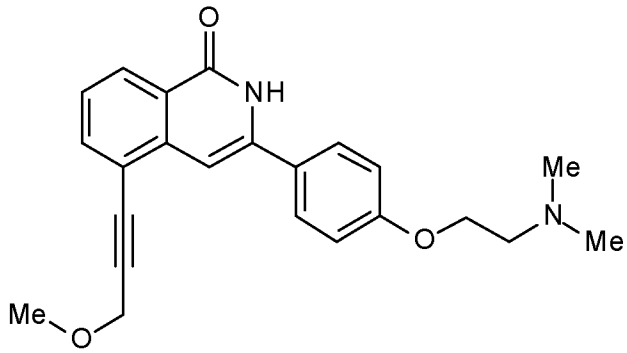
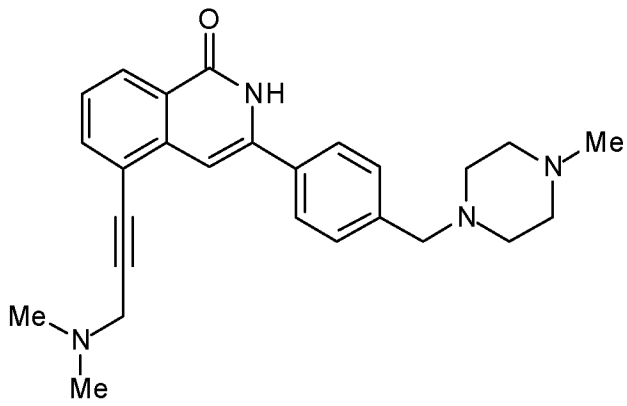
IQ-232	
IQ-233	
IQ-234	
IQ-235	

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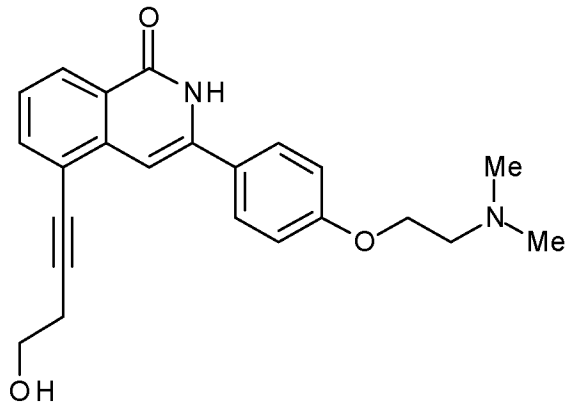
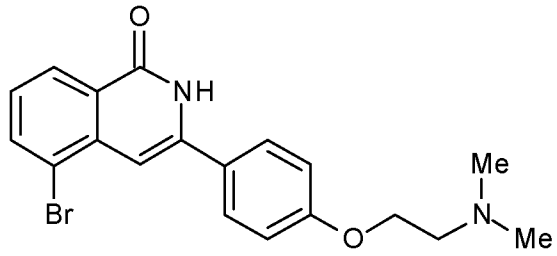
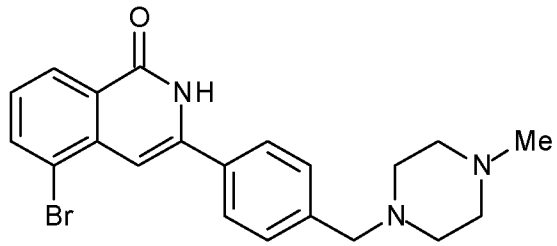
IQ-236	
IQ-237	
IQ-238	

Combinations

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the embodiments pertaining to the chemical groups represented by the variables (e.g., W, X, Y, Z, $-R^{W}$, $-R^{X}$, $-R^{Y}$, $-R^{Z}$, $-R^{WW}$, $-R^{XX}$, $-R^{YY}$, $-R^{ZZ}$, $-X^{1}$, $-R^{1}$, $-L^{3P}-$, $-L^{3PL}-$, $-L^{3PR1}-$, $-L^{3PR2}-$, $-L^{3PR3}-$, $-L^{3PR4}-$, $-R^{3N}$, $-R^{A}$, $-R^{A1}$, $-R^{A2}$, $-R^{A3}$, $-R^{A4}$, $-R^{A5}$, $-L^{A}-$, $-R^{S1}$, $-R^{S2C}$, $-R^{S3C}$, $-R^{SN}$, $-L^{T}-$, $-R^{TT}$, $-R^{TTT}$, $-R^{TN}$, $-R^{TM}$, $-R^{TMM}$, $-R^{B}$, $-R^{B1}$, $-R^{B2}$, $-L^{B}-$, $-R^{BB}$, $-NR^{C}R^{D}$, $-NR^{C1}R^{D1}$, $-NR^{C2}R^{D2}$, $-NR^{C3}R^{D3}$, $-NR^{C4}R^{D4}$, $-NR^{C5}R^{D5}$, $-R^{NC}$, $-R^{NN}$, $-L^{Q}-$, $-R^{QQ}$, $-R^{QN}$, $-R^{QM}$, $-R^{QMM}$, $-R^{H}$, $-L^{H}-$, $-R^{HH}$, $-R^{HN}$, $-R^{HM}$, $-R^{HMM}$, $-R^{5}$, $-R^{5A}$, $-R^{5B}$, $-R^{5C}$, $-R^{5D}$, $-R^{5E}$, $-R^{5EE}$, $-R^{5EEE}$, $-R^{4}$, $-R^{6}$, $-R^{7}$, $-R^{8}$, *etc.*) are specifically embraced by the present invention and are disclosed herein just as if each and every combination was individually and explicitly disclosed, to the extent that such combinations embrace compounds that are stable compounds (i.e., compounds that can be isolated, characterised, and tested for

biological activity). In addition, all sub-combinations of the chemical groups listed in the embodiments describing such variables are also specifically embraced by the present invention and are disclosed herein just as if each and every such sub-combination of chemical groups was individually and explicitly disclosed herein.

Substantially Purified Forms

One aspect of the present invention pertains to IQ compounds, as described herein, in substantially purified form and/or in a form substantially free from contaminants.

In one embodiment, the compound is in substantially purified form and/or in a form substantially free from contaminants.

In one embodiment, the compound is in a substantially purified form with a purity of least 50% by weight, e.g., at least 60% by weight, e.g., at least 70% by weight, e.g., at least 80% by weight, e.g., at least 90% by weight, e.g., at least 95% by weight, e.g., at least 97% by weight, e.g., at least 98% by weight, e.g., at least 99% by weight.

Unless specified, the substantially purified form refers to the compound in any stereoisomeric or enantiomeric form. For example, in one embodiment, the substantially purified form refers to a mixture of stereoisomers, i.e., purified with respect to other compounds. In one embodiment, the substantially purified form refers to one stereoisomer, e.g., optically pure stereoisomer. In one embodiment, the substantially purified form refers to a mixture of enantiomers. In one embodiment, the substantially purified form refers to an equimolar mixture of enantiomers (i.e., a racemic mixture, a racemate). In one embodiment, the substantially purified form refers to one enantiomer, e.g., optically pure enantiomer.

In one embodiment, the compound is in a form substantially free from contaminants wherein the contaminants represent no more than 50% by weight, e.g., no more than 40% by weight, e.g., no more than 30% by weight, e.g., no more than 20% by weight, e.g., no more than 10% by weight, e.g., no more than 5% by weight, e.g., no more than 3% by weight, e.g., no more than 2% by weight, e.g., no more than 1% by weight.

Unless specified, the contaminants refer to other compounds, that is, other than stereoisomers or enantiomers. In one embodiment, the contaminants refer to other compounds and other stereoisomers. In one embodiment, the contaminants refer to other compounds and the other enantiomer.

In one embodiment, the compound is in a substantially purified form with an optical purity of at least 60% (i.e., 60% of the compound, on a molar basis, is the desired stereoisomer

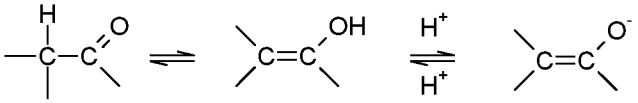
or enantiomer, and 40% is undesired stereoisomer(s) or enantiomer), e.g., at least 70%, e.g., at least 80%, e.g., at least 90%, e.g., at least 95%, e.g., at least 97%, e.g., at least 98%, e.g., at least 99%.

Isomers

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diasteriomeric, epimeric, atropic, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r-forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

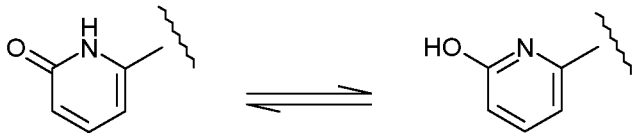
Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers," as used herein, are structural (or constitutional) isomers (i.e., isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-CH_2OH$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g., C_{1-7}alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hydroxyazo, and nitro/aci-nitro.



keto enol enolate

For example, 1H-pyridin-2-one-5-yl and 2-hydroxyl-pyridin-5-yl (shown below) are tautomers of one another. A reference herein to one is intended to encompass both.



1H-pyridin-2-one-6-yl 2-hydroxyl-pyridin-6-yl

Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including mixtures (e.g., racemic mixtures) thereof. Methods for the preparation (e.g., asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

Salts

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge *et al.*, 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be $-COO^{-}$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^{+} and K^{+}, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{3+}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^{+}) and substituted ammonium ions (e.g., NH_3R^{+}, $NH_2R_2^{+}$, NHR_3^{+}, NR_4^{+}). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^{+}$.

If the compound is cationic, or has a functional group which may be cationic (e.g., $-NH_2$ may be $-NH_3^{+}$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic

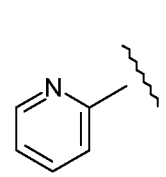
acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, formic, fumaric, glucheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

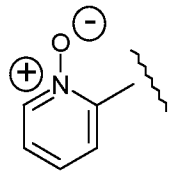
Unless otherwise specified, a reference to a particular compound also includes salt forms thereof.

N-Oxides

It may be convenient or desirable to prepare, purify, and/or handle a corresponding N-oxide of the compound. For example, a compound having a pyridyl group may be prepared, purified, and/or handled as the corresponding N-oxide.



pyrid-2-yl



pyrid-2-yl N-oxide

Unless otherwise specified, a reference to a particular compound also includes N-oxide forms thereof.

Hydrates and Solvates

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the compound. The term “solvate” is used herein in the conventional sense to refer to a complex of solute (e.g., compound, salt of compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, *etc.*

Unless otherwise specified, a reference to a particular compound also includes solvate and hydrate forms thereof.

Chemically Protected Forms

It may be convenient or desirable to prepare, purify, and/or handle the compound in a chemically protected form. The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g., pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Greene and P. Wuts; 4th Edition; John Wiley and Sons, 2006).

A wide variety of such "protecting," "blocking," or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore unreactive, under the specified conditions; so protected, the compound may be used as a reactant which has effectively only one reactive functional group. After the desired reaction (involving the other functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH_3, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal (R-CH$(OR)_2$) or ketal ($R_2C(OR)_2$), respectively, in which the carbonyl group (>C=O) is converted to a diether (>C$(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH_3); a benzyloxycarbonyl amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxycarbonyl amine

(-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxycarbonyl amine (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxycarbonyl amine (-NH-Fmoc), as a 6-nitroveratryloxycarbonyl amine (-NH-Nvoc), as a 2-trimethylsilylethyloxycarbonyl amine (-NH-Teoc), as a 2,2,2-trichloroethyloxycarbonyl amine (-NH-Troc), as an allyloxycarbonyl amine (-NH-Alloc), as a 2(-phenylsulfonyl)ethyloxycarbonyl amine (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O●).

For example, a carboxylic acid group may be protected as an ester for example, as: an C_{1-7}alkyl ester (e.g., a methyl ester; a t-butyl ester); a C_{1-7}haloalkyl ester (e.g., a C_{1-7}trihaloalkyl ester); a triC_{1-7}alkylsilyl-C_{1-7}alkyl ester; or a C_{5-20}aryl-C_{1-7}alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-$CH_2NHC(=O)CH_3$).

Prodrugs

It may be convenient or desirable to prepare, purify, and/or handle the compound in the form of a prodrug. The term “prodrug,” as used herein, pertains to a compound which, when metabolised (e.g., *in vivo*), yields the desired active compound. Typically, the prodrug is inactive, or less active than the desired active compound, but may provide advantageous handling, administration, or metabolic properties.

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in ADEPT, GDEPT, LIDEPT, *etc.*). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

General Chemical Synthesis

Several methods for the chemical synthesis of IQ compounds are described herein. These and/or other well known methods may be modified and/or adapted in known ways in order to facilitate the synthesis of additional compounds described herein.

All reagents were either purchased from common commercial sources or synthesised in accordance with known literature procedures. Commercial reagents were used without further purification unless otherwise stated. Microwave reactions were conducted using a CEM Discover. Flash column chromatography was conducted using pre-packed silica Biotage® SNAP (KP-Sil) cartiridges. Ion exchange chromatography was performed using Isolute® Flash SCX-2 cartridges.

Abbreviations

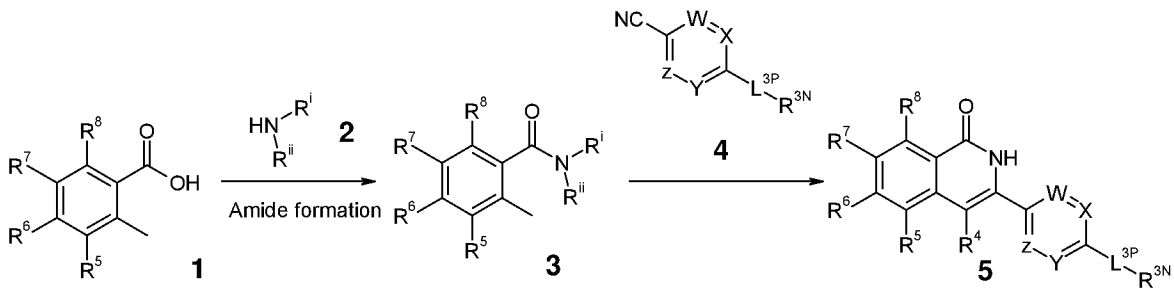
APCI : atmospheric pressure chemical ionisation.
BBr_3 : boron tribromide.
BINAP : 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.
Boc : *tert*-butyloxycarbonyl.
CH_2Cl_2 : dichloromethane.
CV : column volume.
DEAD : diethylazodicarboxylate.
DIAD : diisopropyl azodicarboxylate.
DIPEA: *N,N*-diisopropylamine
DMA : dimethyl acetamide.
DMAP : 4-dimethylaminopyridine
DME : dimethoxyethane.
DMF : *N,N*-dimethylformamide.
Dppf : 1,1'-Bis(diphenylphosphino)ferrocene.
EDCI : 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide.
ES : electrospray.
EtOAc : ethyl acetate.
h : hour(s).
HATU: 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.
IPA : isopropyl alcohol.
LDA : lithium diisopropylamide.
MCPBA : meta-Chloroperoxybenzoic acid
min : minute(s).
Ms/mesyl : methane sulfonyl
PFPA : perfluorophthalic anhydride.
PPh_3 : triphenyl phosphine.

PS : polymer supported.
Py : pyridine.
R_f : retention factor
Rt : retention time.
RT : room temperature.
SCX : strong cation exchange
SEM : 2-(trimethylsilyl)ethoxymethyl.
TBAF : tetra-n-butylammonium fluoride.
TBDMS : *tert*-butyldimethylsilyl.
TBDPS: *tert*-butyldiphenyllsilyl.
TBTU : *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate.
TFA : trifluoroacetic acid.
THF : tetrahydrofuran.
Ts/tosyl ; 4-toluenesulfonyl.

The general synthetic methods for the synthesis of 2H-isoquinolin-1-ones **5** are illustrated below:

*Route 1: Synthesis of 2H-isoquinolin-1-ones **5** via Cyclisation*

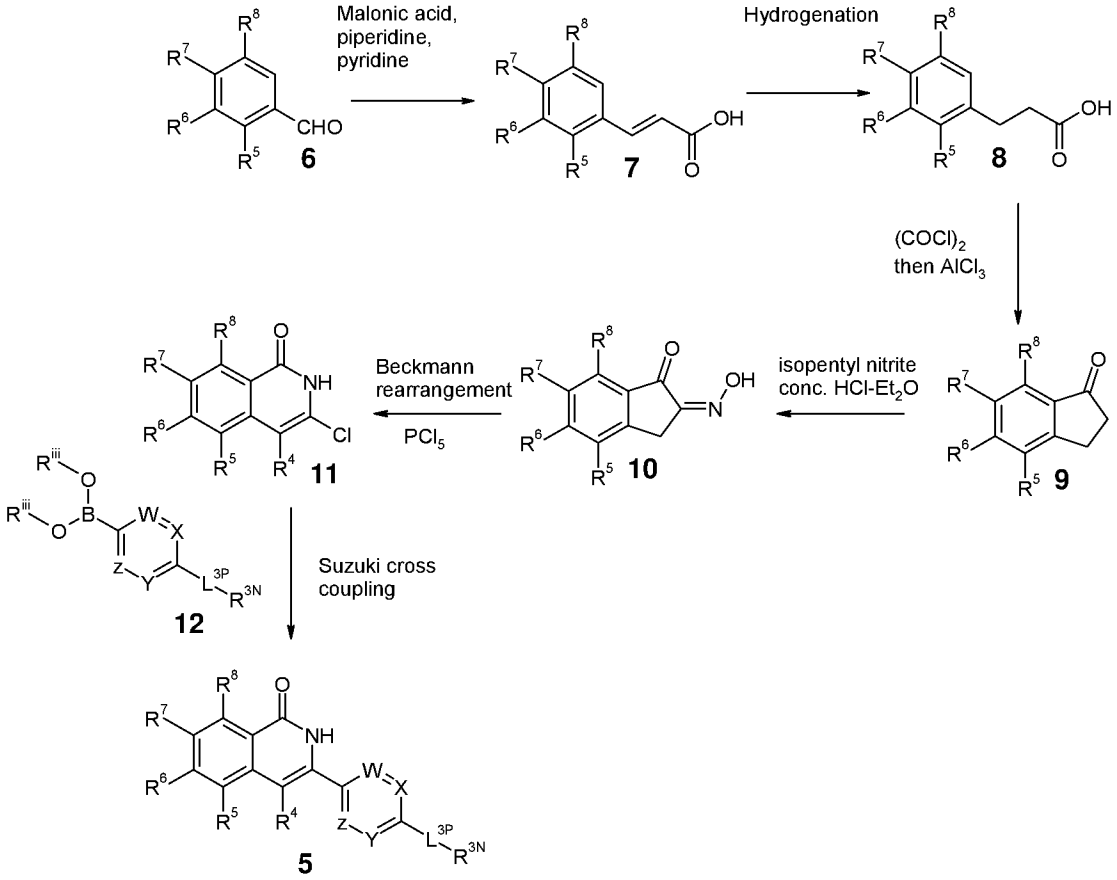
Scheme 1



Acid **1** can be reacted with amine **2** (e.g., *N,N*-diethylamine) to yield amide **3**, either by utilising standard amine coupling procedures (e.g., EDCI, HATU, *etc.*) or converting the acid **1** into the corresponding acid chloride (or mixed anhydride) and reacting with the amine **2** (see, e.g., Le *et al.*, 2004). The 2-*H*-isoquinolin-1-one **5** can be prepared by *in situ* deprotonation of 2-methyl-benzamide derivative **3** with a suitable base (e.g., *n*-BuLi, *sec*-BuLi, *t*-BuLi, LDA, *etc.*) in THF (or similar suitable aprotic solvent) at -78ºC, then reacting with the required nitrile **4** (see, e.g., Hattori *et al.*, 2006).

*Route 2: Synthesis of 2H-isoquinolin-1-ones **5** via Organopalladium Cross-Coupling*

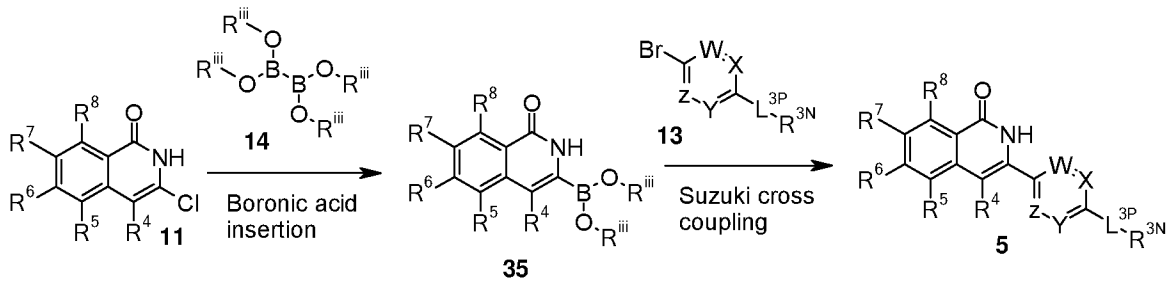
Scheme 2



The 2*H*-isoquinolin-1-one **5** can be synthesised by a palladium-mediated cross-coupling from the corresponding aryl halide **11** (e.g. chloride) and the corresponding boronic acid or ester (Suzuki cross-coupling).

*Route 2a: Alternative synthesis of 2H-isoquinolin-1-ones **5** via Organopalladium Cross-Coupling*

Scheme 2a



In an alternative route, the 2*H*-isoquinolin-1-one **5** can be synthesised by a palladium-mediated cross-coupling from the corresponding aryl or heteroaryl halides **13** (e.g., bromide) and the corresponding boronic ester **35** (Suzuki cross-coupling). The boronic ester **35** can be accessed by a palladium-mediated cross-coupling from the corresponding 3-halo-2*H*-isoquinolin-1-one **11** (e.g., chloride) with a suitable diboron reagent (e.g. bis (pinacolato) diboron), and a suitable source of palladium (e.g., $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$) in an appropriate solvent (e.g., THF, DMF, DME, DCE, toluene, *etc.*).

For the Suzuki cross-coupling, 3-halo-2*H*-isoquinolin-1-one (e.g chloride) **11** can be reacted with a suitable boronic acid or ester **12** in the presence of a suitable base (e.g., K_2CO_3, NaO*t*-Bu, K_3PO_4, *etc.*), a suitable source of palladium (e.g., $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, *etc.*) and a ligand (e.g., P(*t*-Bu)$_3$, BINAP, *etc.*) in an appropriate solvent (e.g., THF, DME, DCE, toluene, *etc.*).

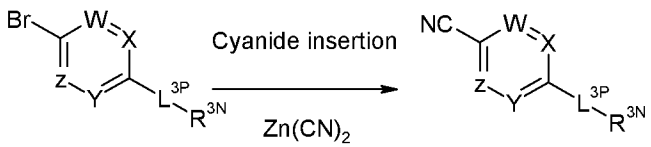
The 3-chloro-2*H*-isoquinolin-1-one **11** can be synthesised from indan-1,2-dione 2-oxime **10** (see, e.g., Merchant *et al.*, 1984) via Beckmann rearrangement followed by treatment with PCl_5.

Indan-1,2-dione 2-oxime **10** can be accessed from commercial sources or prepared from commercially available indanones **9** by nitrosation or from aldehyde **6** *via* chain extension, cyclisation and nitrosation (see, e.g., Musso *et al.*, 2003).

The general synthetic methods for the synthesis of nitrile intermediates **4** and boronic acid or boronic ester intermediates **12** are illustrated below:

*Synthesis of Aryl Nitrile **4** from Aryl Bromide **13***

Scheme 3

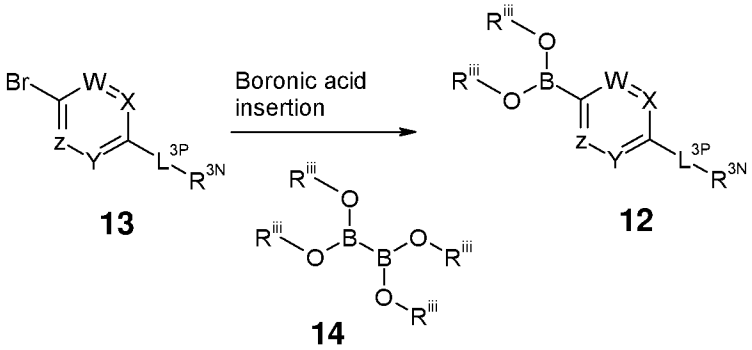


13 **4**

The nitrile **4** can be accessed by a palladium-mediated cyanide insertion from the corresponding carboaryl or heteroaryl halide **13** (e.g., iodide, bromide, chloride) with a source of cyanide e.g., $Zn(CN)_2$, $Cu(CN)_2$, and a suitable source of palladium (e.g., $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$) in an appropriate solvent (e.g., THF, DMF, DME, DCE, toluene, *etc.*).

*Synthesis of Boronic acid or Boronic ester intermediate **12** from Aryl Halide **13***

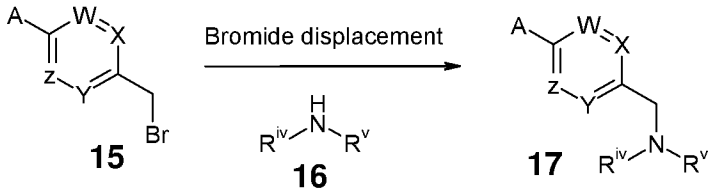
Scheme 4



The boronic acid or ester **12** can be accessed by a palladium-mediated cross-coupling from the corresponding aryl (heteroaryl) halide **13** (e.g., iodide, bromide, chloride) with bis (pinacolato) diboron, and a suitable source of palladium (e.g., $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$) in an appropriate solvent (e.g., THF, DMF, DME, DCE, toluene, *etc.*).

*Synthesis of Amine **17** from Alkyl Bromide **15***

Scheme 5



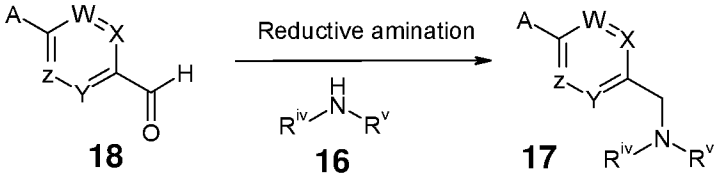
A = CN, Br, or $B(OR^{iii})_2$

The amine **17** can be accessed by bromide displacement from the corresponding halide **15** (e.g., iodide, bromide, chloride) and an appropriate amine **16** in an appropriate solvent (e.g., THF, DMF, CH_2Cl_2 *etc.*).

This method is exemplified in Scheme 5 with benzyl or heteroarylmethyl bromides, but it is understood that the same approach can be extended to other examples of A-aryl-L^{3PR1}-Br. The same method can be used for any amine **16** as defined in the claims, including aromatic heterocycles $HNR^{C5}R^{D5}$ (e.g., imidazole, pyrazole, etc.).

*Synthesis of Amine **17** from Aldehyde **18***

Scheme 6



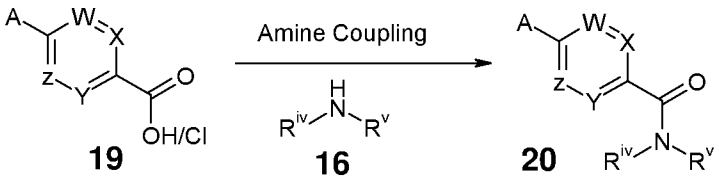
18 **16** **17**

A = CN, Br, or $B(OR^{iii})_2$

The amine **17** can be accessed by standard reductive amination conditions from the corresponding aldehyde **18** and an appropriate amine **16** in an appropriate solvent (e.g., DCE *etc.*), with the use a standard reducing reagent (e.g., sodium triacetoxy borohydride, sodium borohydride, *etc.*).

*Synthesis of Amide **20** from Acid **19***

Scheme 7



19 **16** **20**

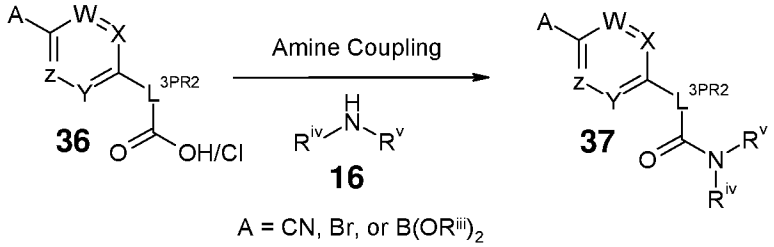
A = CN, Br, or $B(OR^{iii})_2$

The amide **20** can be accessed by standard amine coupling conditions from the corresponding acid (or acid chloride) **19** and an appropiate amine **16** in an appropriate solvent (e.g., THF, DMF, CH_2Cl_2 *etc.*), with a suitable base (e.g., DIPEA, Et_3N *etc.*) with the use a standard amine coupling reagent (e.g., HATU, TBTU, EDCI *etc.*).

Alternatively, the amide **20** can be accessed by standard amine coupling conditions from the corresponding acid chloride **19** and an appropiate amine **16** in an appropriate solvent (e.g., THF, DMF, CH_2Cl_2 *etc.*), with a suitable base (e.g., DIPEA, Et_3N *etc.*).

*Synthesis of Amide **20** from Acid **19***

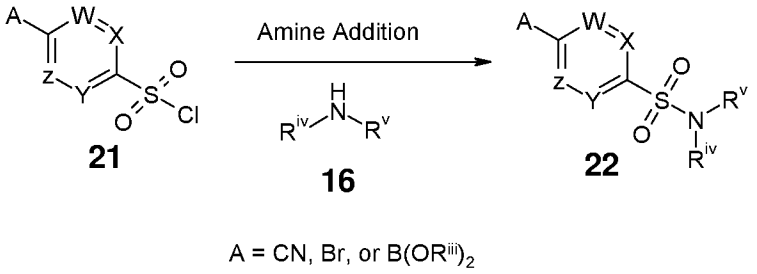
Scheme 7a



The same method from Scheme 7 can be applied using a carboxylic acid (or acid chloride) **36**, with an amine **16**, to afford amide **37**.

*Synthesis of Sulfonamide **22** from Sulfonyl chloride **21***

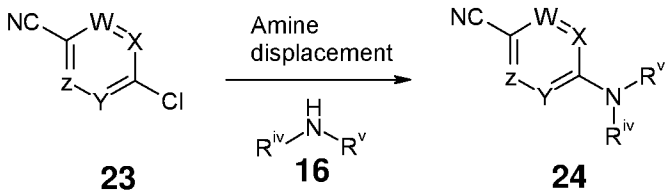
Scheme 8



The sulfonamide **22** can be prepared from the corresponding sulfonyl chloride **21** and an appropriate amine **16** in an appropriate solvent (e.g., THF, CH_2Cl_2 *etc.*), with a suitable base (e.g., DIPEA, Et_3N *etc.*).

*Synthesis of Amino-Heteroaryl Nitrile **24** from Halo-Heteroaryl Nitrile **23***

Scheme 9

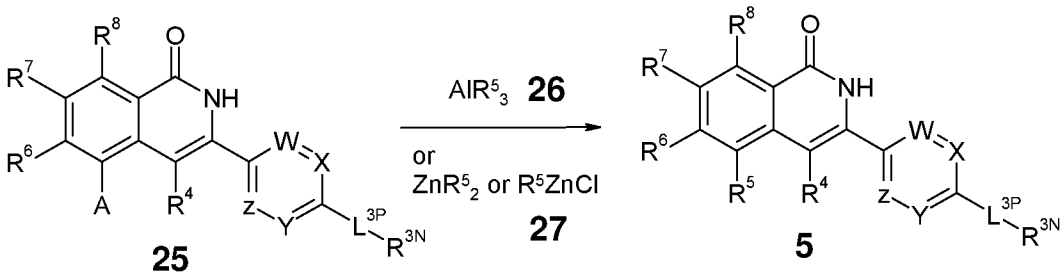


Halo-heteroaryl **23** can be reacted with amine **16** to yield amino-heteroaryl **24** (see, e.g., Nettekoven *et al.*, 2006) either by heating in acetonitrile (or other suitable solvent) or by irradiation using microwave heating in acetonitrile (or other suitable solvent).

The general synthetic methods for the synthesis of 2*H*-isoquinolin-1-ones **5** are illustrated below:

*Synthesis of 2H-isoquinolin-1-ones **5** via Organometal Cross-Coupling*

Scheme 10



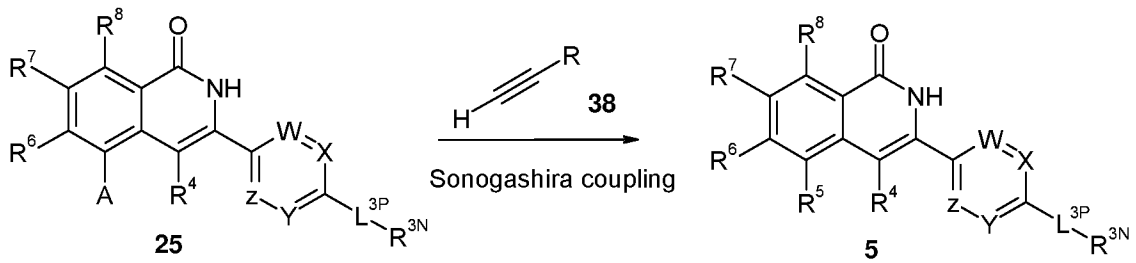
A = Cl, Br, I

The 2*H*-isoquinolin-1-one **5** can be synthesised by palladium-mediated cross-coupling of an aryl halide **25** and a suitable trialkylaluminium reagent **26** (see, e.g., Molander *et al.*, 2003) in the presence of a suitable source of palladium (e.g., $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, *etc.*) and $CeCl_3$ in an appropriate solvent (e.g., THF, DME, DCE, toluene, dioxane, *etc.*).

The aryl halide **25** can alternatively be reacted with a suitable organo-zinc halide or diorgano-zinc compound **27** (see, e.g., Hughes *et al.*, 2007) in the presence of a suitable source of palladium (e.g., $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, *etc.*), a ligand (e.g., $P(t\text{-}Bu)_3$, BINAP, *etc.*) in an appropriate solvent (e.g., THF, DME, DCE, toluene, dioxane, *etc.*).

*Synthesis of 2H-isoquinolin-1-ones **5** via Sonogashira coupling*

Scheme 10a



A = Cl, Br, I

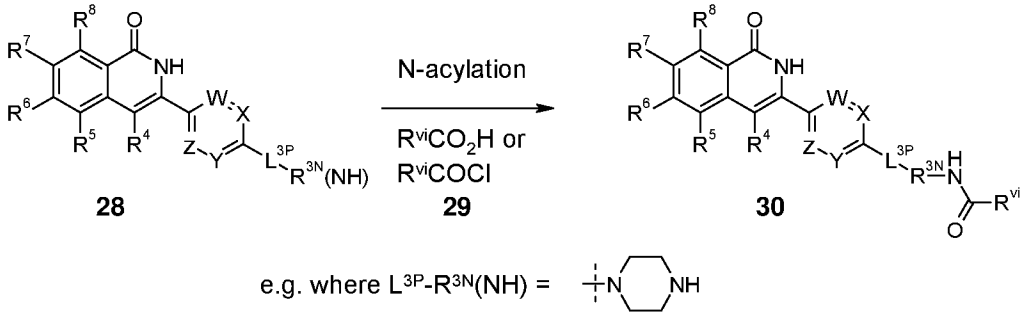
where $R^5 = R^{5E}$

The 2*H*-isoquinolin-1-one **5** can be synthesised by palladium/copper-mediated cross-coupling (Sonogashira coupling) of an aryl halide **25** and a suitable alkynyl reagent **38** in the presence of a base (e.g., DIPEA, triethylamine, pyrrolidine, piperidine, Cs_2CO_3, *etc.*), a suitable source of palladium (e.g., $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, *etc.*) and a ligand (e.g.,

PPh_3, $P(t\text{-}Bu)_3$, etc.) in an appropriate solvent (e.g., THF, DMF, DME, DCE, toluene, dioxane, *etc.*).

*Synthesis of 2H-isoquinolin-1-ones **30** via N-Acylation*

Scheme 11

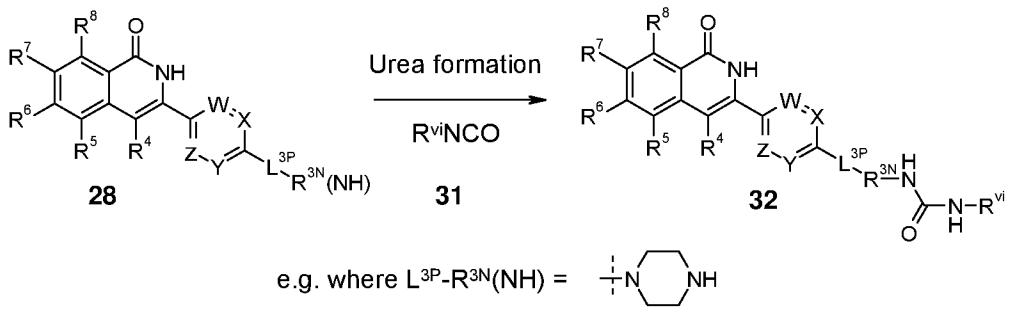


The amide **30** can be accessed by standard amine coupling conditions from the corresponding amine **28** and an appropiate acid **29** in an appropriate solvent (e.g., THF, DMF, CH_2Cl_2 *etc.*), with a suitable base (e.g., DIPEA, Et_3N *etc.*) with the use a standard amine coupling reagent (e.g., HATU, TBTU, EDCI *etc.*).

Alternatively, the amide **30** can be accessed by standard amine coupling conditions from the corresponding amine **28** and an appropiate acid chloride **29** in an appropriate solvent (e.g., THF, DMF, CH_2Cl_2 *etc.*), with a suitable base (e.g., DIPEA, Et_3N *etc.*).

*Synthesis of 2H-isoquinolin-1-ones **32** via Urea Formation*

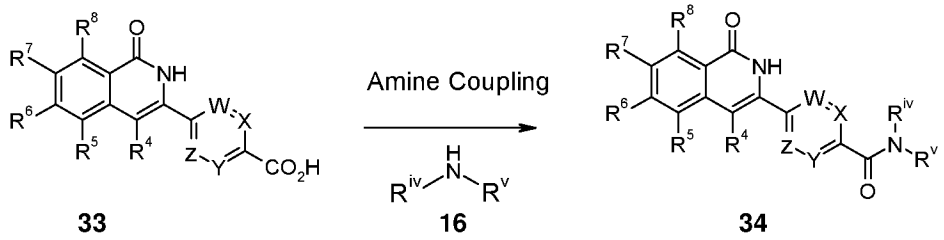
Scheme 12



The urea **32** can be accessed by standard urea formation conditions from the corresponding amine **28** and an appropiate isocyanate **31** in an appropriate solvent (e.g, DMF, CH_2Cl_2 *etc.*).

*Synthesis of 2H-isoquinolin-1-ones **34** via N-Acylation*

Scheme 13

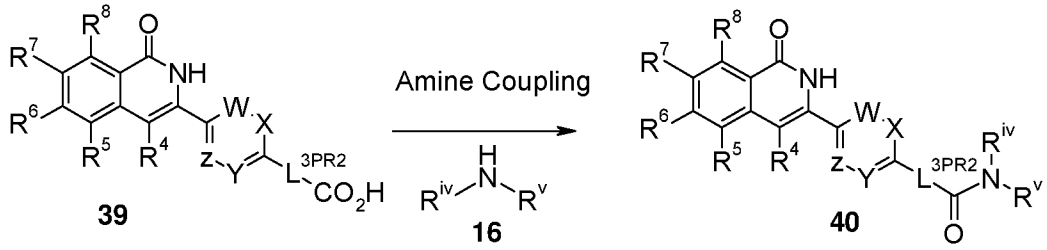


33 **16** **34**

The amide **34** can be accessed by standard amine coupling conditions from the corresponding acid **33** and an appropiate amine **16** in an appropriate solvent (e.g., THF, DMF, CH_2Cl_2 *etc.*), with a suitable base (e.g., DIPEA, Et_3N *etc.*) with the use a standard amine coupling reagent (e.g., HATU, TBTU, EDCI *etc.*).

*Synthesis of 2H-isoquinolin-1-ones **40** via N-Acylation*

Scheme 13a



39 **16** **40**

The same method from Scheme 13 can be applied using a carboxylic acid **39**, with an amine **16**, to afford amide **40**.

Compositions

One aspect of the present invention pertains to a composition (e.g., a pharmaceutical composition) comprising an IQ compound, as described herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

Another aspect of the present invention pertains to a method of preparing a composition (e.g., a pharmaceutical composition) comprising mixing an IQ compound, as described herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

Uses

The IQ compounds, as described herein, are useful, for example, in the treatment of disorders (e.g., diseases) that are ameliorated by the inhibition of PARP (e.g., PARP1, TNKS1, TNKS2, *etc.*) and/or the inhibition of Wnt signalling, as described herein.

Use in Methods of Inhibiting PARP (e.g., PARP1, TNKS1, TNKS2, *etc.*)

One aspect of the present invention pertains to a method of inhibiting PARP (e.g., PARP1, TNKS1, TNKS2, *etc.*) in a cell, *in vitro* or *in vivo,* comprising contacting the cell with an effective amount of an IQ compound, as described herein.

One aspect of the present invention pertains to a method of inhibiting TNKS1 and/or TNKS2 in a cell, *in vitro* or *in vivo,* comprising contacting the cell with an effective amount of an IQ compound, as described herein.

One of ordinary skill in the art is readily able to determine whether or not a candidate compound inhibits PARP (e.g., PARP1, TNKS1, TNKS2, *etc.*). For example, suitable assays are described herein or are known in the art.

In one embodiment, the method is performed *in vitro*.
In one embodiment, the method is performed *in vivo*.

In one embodiment, the IQ compound is provided in the form of a pharmaceutically acceptable composition.

Any type of cell may be treated, including but not limited to, adipose, lung, gastrointestinal (including, e.g., bowel, colon), breast (mammary), ovarian, prostate, liver (hepatic), kidney (renal), bladder, pancreas, brain, and skin.

For example, a sample of cells may be grown *in vitro* and a compound brought into contact with said cells, and the effect of the compound on those cells observed. As an example of "effect," the morphological status of the cells (e.g., alive or dead, *etc.*) may be determined. Where the compound is found to exert an influence on the cells, this may be used as a prognostic or diagnostic marker of the efficacy of the compound in methods of treating a patient carrying cells of the same cellular type.

Use in Methods of Inhibiting Wnt Signalling

One aspect of the present invention pertains to a method of inhibiting Wnt signalling in a cell, *in vitro* or *in vivo,* comprising contacting the cell with an effective amount of an IQ compound, as described herein.

One of ordinary skill in the art is readily able to determine whether or not a candidate compound inhibits Wnt signalling. For example, suitable assays are described herein or are known in the art.

In one embodiment, the method is performed *in vitro*.
In one embodiment, the method is performed *in vivo*.

In one embodiment, the IQ compound is provided in the form of a pharmaceutically acceptable composition.

Use in Methods of Inhibiting Cell Proliferation, *etc.*

The IQ compounds described herein, e.g., (a) regulate (e.g., inhibit) cell proliferation; (b) inhibit cell cycle progression; (c) promote apoptosis; or (d) a combination of one or more of these.

One aspect of the present invention pertains to a method of regulating (e.g., inhibiting) cell proliferation (e.g., proliferation of a cell), inhibiting cell cycle progression, promoting apoptosis, or a combination of one or more these, *in vitro* or *in vivo,* comprising contacting a cell with an effective amount of an IQ compound, as described herein.

In one embodiment, the method is a method of regulating (e.g., inhibiting) cell proliferation (e.g., proliferation of a cell), *in vitro* or *in vivo,* comprising contacting a cell with an effective amount of an IQ compound, as described herein.

In one embodiment, the method is performed *in vitro*.
In one embodiment, the method is performed *in vivo*.

In one embodiment, the IQ compound is provided in the form of a pharmaceutically acceptable composition.

Any type of cell may be treated, including but not limited to, lung, gastrointestinal (including, e.g., bowel, colon), breast (mammary), ovarian, prostate, liver (hepatic), kidney (renal), bladder, pancreas, brain, and skin.

One of ordinary skill in the art is readily able to determine whether or not a candidate compound regulates (e.g., inhibits) cell proliferation, *etc.* For example, assays which may conveniently be used to assess the activity offered by a particular compound are described herein.

For example, a sample of cells (e.g., from a tumour) may be grown *in vitro* and a compound brought into contact with said cells, and the effect of the compound on those cells observed. As an example of "effect," the morphological status of the cells (e.g., alive or dead, *etc.*) may be determined. Where the compound is found to exert an influence on the cells, this may be used as a prognostic or diagnostic marker of the efficacy of the compound in methods of treating a patient carrying cells of the same cellular type.

Use in Methods of Therapy

Another aspect of the present invention pertains to an IQ compound, as described herein, for use in a method of treatment of the human or animal body by therapy.

Use in the Manufacture of Medicaments

Another aspect of the present invention pertains to use of an IQ compound, as described herein, in the manufacture of a medicament for use in treatment.

In one embodiment, the medicament comprises the IQ compound.

Methods of Treatment

Another aspect of the present invention pertains to a method of treatment comprising administering to a patient in need of treatment a therapeutically effective amount of an IQ compound, as described herein, preferably in the form of a pharmaceutical composition.

Disorders Treated - Disorders Ameliorated by the Inhibition of PARP (e.g., PARP1, TNKS1, TNKS2, *etc.*)

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of a disorder (e.g., a disease) that is ameliorated by the inhibition of PARP.

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of a disorder (e.g., a disease) that is ameliorated by the inhibition of TNKS1 and/or TNKS2.

Disorders Treated - Proliferative Conditions

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of: a proliferative condition.

The term "proliferative condition," as used herein, pertains to an unwanted or uncontrolled cellular proliferation of excessive or abnormal cells which is undesired, such as neoplastic or hyperplastic growth.

In one embodiment, the treatment is treatment of: a proliferative condition characterised by benign, pre-malignant, or malignant cellular proliferation, including for example: neoplasms, hyperplasias, and tumours (e.g., histocytoma, glioma, astrocyoma, osteoma), cancers (see below), psoriasis, bone diseases, fibroproliferative disorders (e.g., of connective tissues), pulmonary fibrosis, atherosclerosis, smooth muscle cell proliferation in the blood vessels, such as stenosis or restenosis following angioplasty.

Disorders Treated - Cancer

In one embodiment (e.g., of use in methods of therapy, of use in the manufacture of medicaments, of methods of treatment), the treatment is treatment of cancer.

In one embodiment, the treatment is treatment of cancer characterised by, or further characterised by, cancer cells which overexpress PARP.

In one embodiment, the treatment is treatment of cancer characterised by, or further characterised by, cancer cells which overexpress TNKS1 and/or TNKS2.

In one embodiment, the treatment is treatment of lung cancer, small cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, stomach cancer, bowel cancer, colon

cancer, rectal cancer, colorectal cancer, thyroid cancer, breast cancer, ovarian cancer, endometrial cancer, prostate cancer, testicular cancer, liver cancer, kidney cancer, renal cell carcinoma, bladder cancer, pancreatic cancer, brain cancer, glioma, sarcoma, osteosarcoma, bone cancer, nasopharyngeal cancer (e.g., head cancer, neck cancer), skin cancer, squamous cancer, Kaposi's sarcoma, melanoma, malignant melanoma, lymphoma, or leukemia.

In one embodiment, the treatment is treatment of:

a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g., colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, epidermal, liver, lung (e.g., adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas), oesophagus, gall bladder, ovary, pancreas (e.g., exocrine pancreatic carcinoma), stomach, cervix, thyroid, prostate, skin (e.g., squamous cell carcinoma);

a hematopoietic tumour of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma;

a hematopoietic tumour of myeloid lineage, for example acute and chronic myelogenous leukemias, myelodysplastic syndrome, or promyelocytic leukemia;

a tumour of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma;

a tumour of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma;

melanoma; seminoma; teratocarcinoma; osteosarcoma; xenoderoma pigmentoum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

In one embodiment, the treatment is treatment of solid tumour cancer.

In one embodiment, the treatment is treatment of cancer head and neck cancer; nervous system cancer; lung/mediastinum cancer; breast cancer; oesophagus cancer; stomach cancer; liver cancer; biliary tract cancer; pancreatic cancer; small bowel cancer; large bowel cancer; gynaecological cancer; genito-urinary cancer; thyroid gland cancer; adrenal gland cancer; skin cancer; bone sarcoma; soft tissue sarcoma; paediatric malignancy; Hodgkin's disease; non-Hodgkin's lymphoma; myeloma; leukaemia; or metastasis from an unknown primary site.

In one embodiment, the treatment is treatment of cancer metastasis.

In one embodiment, the cancer is characterised by, or further characterised by, cancer stem cells.

The anti-cancer effect may arise through one or more mechanisms, including but not limited to, the regulation of cell proliferation, the inhibition of cell cycle progression, the

inhibition of angiogenesis (the formation of new blood vessels), the inhibition of metastasis (the spread of a tumour from its origin), the inhibition of cell migration (the spread of cancer cells to other parts of the body), the inhibition of invasion (the spread of tumour cells into neighbouring normal structures), or the promotion of apoptosis (programmed cell death). The compounds of the present invention may be used in the treatment of the cancers described herein, independent of the mechanisms discussed herein.

Disorders Treated - Non-Cancer Indications Related to tankyrase Inhibition

In one embodiment, the treatment is treatment of: a neurodegenerative disorder, such as multiple sclerosis (MS); a neurological disorder associated with demyelination; neonatal hypoxic ischemic encephalopathy (HIE); neonatal periventricular leukomalacia (PVL); a cardiac related pathology, such as myocardial infarction; cardiac damage (e.g., to repair cardiac damage); an infectious disease, such as a pathology related to Herpes Simplex Virus (HSV); a pathology related to Epstein-Barr Virus (EBV); a metabolic disease, such as a metabolic disease where glucose uptake is dysfunctional, such as diabetes, such as type 2 diabetes; or fibrosis (e.g., lung fibrosis).

In one embodiment, the treatment is treatment of: a neurodegenerative disorder, such as multiple sclerosis (MS); neonatal hypoxic ischemic encephalopathy (HIE); neonatal periventricular leukomalacia (PVL); a cardiac related pathology, such as myocardial infarction; a pathology related to Herpes Simplex Virus (HSV); a pathology related to Epstein-Barr Virus (EBV); or a metabolic disease such as type 2 diabetes.

Disorder Treated - Non-Cancer Indications Related to Wnt Signalling

In one embodiment, the treatment is treatment of: Alzheimer's disease; late onset Alzheimer's disease; Dupuytren skin disease; tooth agenesis; vascular defects in the eye; Osteoperosis-pseudoglioma Syndrome (OPPG); exudative vitreoretinopathy; familial exudative vitreoretinopathy; retinal angiogenesis; schizophrenia; osteoporosis; dermal hypoplasia; XX sex reversal; Mullerian-duct regression and virilization; SERKAL syndrome; anonychia; hyponychia; sclerosteosis; van Buchem disease; Fuhrmann syndrome; odonto-onchyo-dermal hypoplasia; Type 2 diabetes; obesity; early onset obesity; a nephropathy, such as HIV-associated nephropathy; early coronary disease; bone density defects; tetra-amelia syndrome; split-hand/foot malformation; caudal duplication; Fuhrmann syndrome; odonto-onycho-dermal dysplasia; skeletal dysplasia; focal dermal hypoplasia; autosomal recessive anonychia; or neural tube defects.

In one embodiment, the treatment is treatment of: Alzheimer's disease; Dupuytren skin disease; tooth agenesis; exudative vitreoretinopathy; schizophrenia; osteoporosis; dermal

hypoplasia; XX sex reversal; anonychia; hyponychia; sclerosteosis; van Buchem disease; Fuhrmann syndrome; odonto-onchyo-dermal hypoplasia; early onset obesity; or a nephropathy, such as HIV-associated nephropathy.

Treatment

The term "treatment," as used herein in the context of treating a disorder, pertains generally to treatment of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the disorder, and includes a reduction in the rate of progress, a halt in the rate of progress, alleviation of symptoms of the disorder, amelioration of the disorder, and cure of the disorder. Treatment as a prophylactic measure (i.e., prophylaxis) is also included. For example, use with patients who have not yet developed the disorder, but who are at risk of developing the disorder, is encompassed by the term "treatment."

For example, treatment includes the prophylaxis of cancer, reducing the incidence of cancer, alleviating the symptoms of cancer, *etc.*

The term "therapeutically-effective amount," as used herein, pertains to that amount of a compound, or a material, composition or dosage form comprising a compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

Combination Therapies

The term "treatment" includes combination treatments and therapies, in which two or more treatments or therapies are combined, for example, sequentially or simultaneously. For example, the compounds described herein may also be used in combination therapies, e.g., in conjunction with other agents. Examples of treatments and therapies include, but are not limited to, chemotherapy (the administration of active agents, including, e.g., drugs, antibodies (e.g., as in immunotherapy), prodrugs (e.g., as in photodynamic therapy, GDEPT, ADEPT, *etc.*); surgery; radiation therapy; photodynamic therapy; gene therapy; and controlled diets.

One aspect of the present invention pertains to a compound as described herein, in combination with one or more (e.g., 1, 2, 3, 4, *etc.*) additional therapeutic agents, as described below.

The particular combination would be at the discretion of the physician who would select dosages using his common general knowledge and dosing regimens known to a skilled practitioner.

The agents (i.e., the compound described herein, plus one or more other agents) may be administered simultaneously or sequentially, and may be administered in individually varying dose schedules and via different routes. For example, when administered sequentially, the agents can be administered at closely spaced intervals (e.g., over a period of 5-10 minutes) or at longer intervals (e.g., 1, 2, 3, 4 or more hours apart, or even longer periods apart where required), the precise dosage regimen being commensurate with the properties of the therapeutic agent(s).

The agents (i.e., the compound described here, plus one or more other agents) may be formulated together in a single dosage form, or alternatively, the individual agents may be formulated separately and presented together in the form of a kit, optionally with instructions for their use.

Examples of additional agents/therapies that may be co-administered/combined with treatment with the IQ compounds described herein include the following: antimetabolites; alkylating agents; spindle poisons; topoisomerase inhibitors; DNA binding agents; kinase inhibitors; therapeutic antibodies; PARP inhibitors; NAD metabolism inhibitors; metabolic inhibitors; targeted agents; endocrine agents; *etc.*

Other Uses

The IQ compounds described herein may also be used as cell culture additives to inhibit PARP (e.g., PARP1, TNKS1, TNKS2, *etc.*), to inhibit Wnt signalling, *etc.*

The IQ compounds described herein may also be used as part of an *in vitro* assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.

The IQ compounds described herein may also be used as a standard, for example, in an assay, in order to identify other active compounds, other PARP (e.g., PARP1, TNKS1, TNKS2, *etc.*) inhibitors, other Wnt signalling inhibitors, *etc.*

Kits

One aspect of the invention pertains to a kit comprising (a) an IQ compound as described herein, or a composition comprising an IQ compound as described herein, e.g., preferably provided in a suitable container and/or with suitable packaging; and (b) instructions for use, e.g., written instructions on how to administer the compound or composition.

The written instructions may also include a list of indications for which the active ingredient is a suitable treatment.

Routes of Administration

The IQ compound or pharmaceutical composition comprising the IQ compound may be administered to a subject by any convenient route of administration, whether systemically/peripherally or topically (i.e., at the site of desired action).

Routes of administration include, but are not limited to, oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, *etc.*); transmucosal (including, e.g., by a patch, plaster, *etc.*); intranasal (e.g., by nasal spray); ocular (e.g., by eyedrops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

The Subject/Patient

The subject/patient may be a chordate, a vertebrate, a mammal, a placental mammal, a marsupial (e.g., kangaroo, wombat), a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), a lagomorph (e.g., a rabbit), avian (e.g., a bird), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), porcine (e.g., a pig), ovine (e.g., a sheep), bovine (e.g., a cow), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutang, gibbon), or a human.

Furthermore, the subject/patient may be any of its forms of development, for example, a foetus.

In one preferred embodiment, the subject/patient is a human.

Formulations

While it is possible for an IQ compound to be administered alone, it is preferable to present it as a pharmaceutical formulation (e.g., composition, preparation, medicament) comprising at least one IQ compound, as described herein, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art,

including, but not limited to, pharmaceutically acceptable carriers, diluents, excipients, adjuvants, fillers, buffers, preservatives, anti-oxidants, lubricants, stabilisers, solubilisers, surfactants (e.g., wetting agents), masking agents, colouring agents, flavouring agents, and sweetening agents. The formulation may further comprise other active agents, for example, other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising mixing at least one IQ compound, as described herein, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, e.g., carriers, diluents, excipients, *etc.* If formulated as discrete units (e.g., tablets, *etc.*), each unit contains a predetermined amount (dosage) of the compound.

The term "pharmaceutically acceptable," as used herein, pertains to compounds, ingredients, materials, compositions, dosage forms, *etc.*, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of the subject in question (e.g., human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, diluent, excipient, *etc.* must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Suitable carriers, diluents, excipients, *etc.* can be found in standard pharmaceutical texts, for example, Remington's Pharmaceutical Sciences, 18th edition, Mack Publishing Company, Easton, Pa., 1990; and Handbook of Pharmaceutical Excipients, 5th edition, 2005.

The formulations may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the compound with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the compound with carriers (e.g., liquid carriers, finely divided solid carrier, *etc.*), and then shaping the product, if necessary.

The formulation may be prepared to provide for rapid or slow release; immediate, delayed, timed, or sustained release; or a combination thereof.

Formulations may suitably be in the form of liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), elixirs, syrups, electuaries, mouthwashes, drops, tablets (including, e.g., coated tablets), granules, powders, losenges, pastilles, capsules (including, e.g., hard

and soft gelatin capsules), cachets, pills, ampoules, boluses, suppositories, pessaries, tinctures, gels, pastes, ointments, creams, lotions, oils, foams, sprays, mists, or aerosols.

Formulations may suitably be provided as a patch, adhesive plaster, bandage, dressing, or the like which is impregnated with one or more compounds and optionally one or more other pharmaceutically acceptable ingredients, including, for example, penetration, permeation, and absorption enhancers. Formulations may also suitably be provided in the form of a depot or reservoir.

The compound may be dissolved in, suspended in, or mixed with one or more other pharmaceutically acceptable ingredients. The compound may be presented in a liposome or other microparticulate which is designed to target the compound, for example, to blood components or one or more organs.

Formulations suitable for oral administration (e.g., by ingestion) include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), elixirs, syrups, electuaries, tablets, granules, powders, capsules, cachets, pills, ampoules, boluses.

Formulations suitable for buccal administration include mouthwashes, losenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs. Losenges typically comprise the compound in a flavored basis, usually sucrose and acacia or tragacanth. Pastilles typically comprise the compound in an inert matrix, such as gelatin and glycerin, or sucrose and acacia. Mouthwashes typically comprise the compound in a suitable liquid carrier.

Formulations suitable for sublingual administration include tablets, losenges, pastilles, capsules, and pills.

Formulations suitable for oral transmucosal administration include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), mouthwashes, losenges, pastilles, as well as patches, adhesive plasters, depots, and reservoirs.

Formulations suitable for non-oral transmucosal administration include liquids, solutions (e.g., aqueous, non-aqueous), suspensions (e.g., aqueous, non-aqueous), emulsions (e.g., oil-in-water, water-in-oil), suppositories, pessaries, gels, pastes, ointments, creams, lotions, oils, as well as patches, adhesive plasters, depots, and reservoirs.

Formulations suitable for transdermal administration include gels, pastes, ointments, creams, lotions, and oils, as well as patches, adhesive plasters, bandages, dressings, depots, and reservoirs.

Tablets may be made by conventional means, e.g., compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (e.g., povidone, gelatin, acacia, sorbitol, tragacanth, hydroxypropylmethyl cellulose); fillers or diluents (e.g., lactose, microcrystalline cellulose, calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc, silica); disintegrants (*e.g.*, sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose); surface-active or dispersing or wetting agents (e.g., sodium lauryl sulfate); preservatives (e.g., methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sorbic acid); flavours, flavour enhancing agents, and sweeteners. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with a coating, for example, to affect release, for example an enteric coating, to provide release in parts of the gut other than the stomach.

Ointments are typically prepared from the compound and a paraffinic or a water-miscible ointment base.

Creams are typically prepared from the compound and an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

Emulsions are typically prepared from the compound and an oily phase, which may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and

the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulfate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for intranasal administration, where the carrier is a liquid, include, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the compound.

Formulations suitable for intranasal administration, where the carrier is a solid, include, for example, those presented as a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose.

Formulations suitable for pulmonary administration (e.g., by inhalation or insufflation therapy) include those presented as an aerosol spray from a pressurised pack, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichoro-tetrafluoroethane, carbon dioxide, or other suitable gases.

Formulations suitable for ocular administration include eye drops wherein the compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the compound.

Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols, for example, cocoa butter or a salicylate; or as a solution or suspension for treatment by enema.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the compound, such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration (e.g., by injection), include aqueous or non-aqueous, isotonic, pyrogen-free, sterile liquids (e.g., solutions, suspensions), in which the compound is dissolved, suspended, or otherwise provided (e.g., in a liposome or other microparticulate). Such liquids may additionally contain other pharmaceutically acceptable ingredients, such as anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, suspending agents, thickening agents, and solutes which render the formulation isotonic with the blood (or other relevant bodily fluid) of the intended recipient. Examples of excipients include, for example, water, alcohols, polyols, glycerol, vegetable oils, and the like. Examples of suitable isotonic carriers for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the compound in the liquid is from about 1 ng/mL to about 10 µg/mL, for example from about 10 ng/mL to about 1 µg/mL. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

Dosage

It will be appreciated by one of skill in the art that appropriate dosages of the IQ compounds, and compositions comprising the IQ compounds, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular IQ compound, the route of administration, the time of administration, the rate of excretion of the IQ compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, the severity of the disorder, and the species, sex, age, weight, condition, general health, and prior medical history of the patient. The amount of IQ compound and route of administration will ultimately be at the discretion of the physician, veterinarian, or clinician, although generally the dosage will be selected to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration can be effected in one dose, continuously or intermittently (e.g., in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to

those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell(s) being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician, veterinarian, or clinician.

In general, a suitable dose of the IQ compound is in the range of about 10 µg to about 250 mg (more typically about 100 µg to about 25 mg) per kilogram body weight of the subject per day. Where the compound is a salt, an ester, an amide, a prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

EXAMPLES

Chemical Synthesis

The following examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

Analytical Methods

Reverse Phase Preparative HPLC-MS: Mass-directed purification by preparative LC-MS using a preparative C-18 column (Phenomenex Luna C18 (2), 100 x 21.2 mm, 5 µm).

Analysis of products and intermediates has been carried out using reverse phase analytical HPLC-MS using the parameters set out below.

HPLC Analytical Methods:

AnalpH2_MeOH_4min: Phenomenex Luna C18 (2) 3 µm, 50 x 4.6 mm; A = water + 0.1% formic acid; B = MeOH; 45 °C; %B: 0 min 5%, 1 min 37.5%, 3 min 95%, 3.51 min 5%, 4.5 min 5%; 2.25 mL/min.

AnalpH2_MeOH_4min(1): Phenomenex Luna C18 (2) 3 µm, 50 x 4.6 mm; A = water + 0.1% formic acid; B = MeOH + 0.1% formic acid; 45 °C; %B: 0 min 5%, 1 min 37.5%, 3 min 95%, 3.51 min 5%, 4.5 min 5%; 2.25 mL/min.

AnalpH2_MeOH_4min(2): Phenomenex Luna C18 (2) 3 µm, 50 x 4.6 mm; A = water + 0.1% formic acid; B = MeOH + 0.1% formic acid; 40 °C; %B: 0 min 5%, 1 min 37.5%, 3 min 95%, 3.51 min 5%, 4.5 min 5%; 2.25 mL/min.

AnalpH2_MeOH_4min(3): Phenomenex Luna C18 (2) 3 µm, 50 x 4.6 mm; A = water + 0.1% formic acid; B = MeOH + 0.1% formic acid; 45 °C; %B: 0 min 5%, 1 min 37.5%, 3 min 95%, 3.51 min 5%, 4.0 min 5%; 2.25 mL/min.

AnalpH9_MeOH_4min: Phenomenex Luna C18 (2) 3 µm, 50 x 4.6 mm; A = water pH9 (Ammonium Bicarbonate 10 mM); B = MeOH; 45 °C; %B: 0 min 5%, 1 min 37.5%, 3 min 95%, 3.51 min 5%, 4.5 min 5%; 2.25 mL/min.

AnalpH9_MeOH_4min(1): Phenomenex Luna C18 (2) 3 µm, 50 x 4.6 mm; A = water pH9 (Ammonium Bicarbonate 10 mM); B = MeOH + 0.1% formic acid; 45 °C; %B: 0 min 5%, 1 min 37.5%, 3 min 95%, 3.51 min 5%, 4.5 min 5%; 2.25 mL/min.

AnalpH9_MeOH_4min(2): Phenomenex Luna C18 (2) 3 µm, 50 x 4.6 mm; A = water pH9 (Ammonium Bicarbonate 10 mM); B = MeOH; 45 °C; %B: 0 min 5%, 1 min 37.5%, 3 min 95%, 3.51 min 5%, 4.0 min 5%; 2.25 mL/min.

AnalpH2_MeCN_TFA_4min: Acquity UPLC BEH C18 1.7 µm, 50 x 2.1 mm; A = water + 0.025% TFA; B = Acetonitrile + 0.025% TFA; %B: 0 min 15%, 3 min 95%, 4 min 95%, 4.1 min 15%; 0.4 mL/min.

AnalpH2_MeCN_TFA_4min(1): Acquity UPLC BEH C18 1.7 µm, 50 x 2.1 mm; A = water + 0.025% TFA; B = Acetonitrile + 0.025% TFA; %B: 0 min 50%, 4 min 80%, 6 min 80%, 6.1 min 50%; 0.3 mL/min.

AnalpH2_MeCN_FA_7min(XTERRA1.m): Xterra C18 2.5 µm, 50 x 4.6 mm; A = water + 0.1% FA; B = Acetonitrile + 0.1% FA; %B: 0 min 20%, 4 min 90%, 7 min 90%, 7.1 min 20%; 1.0 mL/min.

AnalpH9_MeCN_AB_10min(Develosil): Develosil C18 2.7 µm, 150 x 4.6 mm; A = water + 0.01 M Ammonium bicarbonate; B = Acetonitrile; %B: 0 min 50%, 4 min 90%, 10 min 90%, 10.1 min 50%; 1.0 mL/min.

AnalpH2_MeOH_QC: Phenomenex Luna C18 (2) 3 µm, 150 x 4.6 mm; A = water + 0.1% formic acid; B = MeOH; 35 °C; %B: 0 min 5%, 7.5 min 95%, 10 min 95%, 10.10 min 5%,13.0 min 5%; 1.5 mL/min.

AnalpH2_MeOH_QC(1): Phenomenex Luna C18 (2) 3 µm, 150 x 4.6 mm; A = water + 0.1% formic acid; B = MeOH + 0.1% formic acid; 40 °C; %B: 0 min 5%, 7.5 min 95%, 10 min 95%, 10.10 min 5%,13.0 min 5%; 1.5 mL/min.

AnalpH2_MeOH_QC(2): Phenomenex Gemini C18 5 µm,150 x 4.6 mm; A = water + 0.1% formic acid; B = MeOH + 0.1% formic acid; 40 °C; %B: 0 min 5%, 7.5 min 95%, 10 min 95%, 10.10 min 5%,13.0 min 5%; 1.5 mL/min.

AnalpH2_MeOH_QC(3): Phenomenex Gemini C18 5 µm, 250 x 4.6 mm; A = water + 0.1% formic acid; B = MeOH + 0.1% formic acid; 40 °C; %B: 0 min 5%, 16 min 95%, 18 min 95%, 18.10 min 5%, 24.0 min 5%; 1.5 mL/min.

AnalpH9_MeOH_QC: Phenomenex Luna C18 (2)) 3 µm, 50 x 4.6 mm; A = water + pH9 (Ammonium Bicarbonate 10 mM); B = MeOH; 35 °C; %B: 0 min 5%, 7.5 min 95%, 10 min 95%, 10.10 min 5%,13.0 min 5%; 1.5 mL/min.

AnalpH9_MeOH_QC(1): Phenomenex Luna C18 (2) 3 µm, 50 x 4.6 mm; A = water + pH9 (Ammonium Bicarbonate 10 mM); B = MeOH + 0.1% formic acid; 35 °C; %B: 0 min 5%, 7.5 min 95%, 10 min 95%, 10.10 min 5%,13.0 min 5%; 1.5 mL/min.

AnalpH2_MeOH_QC(Sunfire): Waters Sunfire C18 (2) 5 µm, 100 x 4.6 mm; A = water + 0.1% formic acid; B = MeOH; 35 °C; %B: 0 min 5%, 7.5 min 95%, 10 min 95%, 10.10 min 5%,13.0 min 5%; 1.5 mL/min.

AnalpH2_MeOH_QC(Sunfire1): Waters Sunfire C18 (2) 5 µm, 100 x 4.6 mm; A = water + 0.1% formic acid; B = MeOH + 0.1% formic acid; 40 °C; %B: 0 min 5%, 7.5 min 95%, 10 min 95%, 10.10 min 5%,13.0 min 5%; 1.5 mL/min.

AnalpH9_MeOH_QC(Sunfire): Waters Sunfire C18 (2) 5 µm, 100 x 4.6 mm; A = water + pH9 (Ammonium Bicarbonate 10 mM); B = MeOH; 35 °C; %B: 0 min 5%, 7.5 min 95%, 10 min 95%, 10.10 min 5%,13.0 min 5%; 1.5 mL/min.

AnalpH9_MeOH_QC(Sunfire1): Waters Sunfire C18 (2) 5 µm, 100 x 4.6 mm; A = water + pH9 (Ammonium Bicarbonate 10 mM); B = MeOH + 0.1% formic acid; 35 °C; %B: 0 min 5%, 7.5 min 95%, 10 min 95%, 10.10 min 5%,13.0 min 5%; 1.5 mL/min.

Chiral HPLC Preparative Methods:

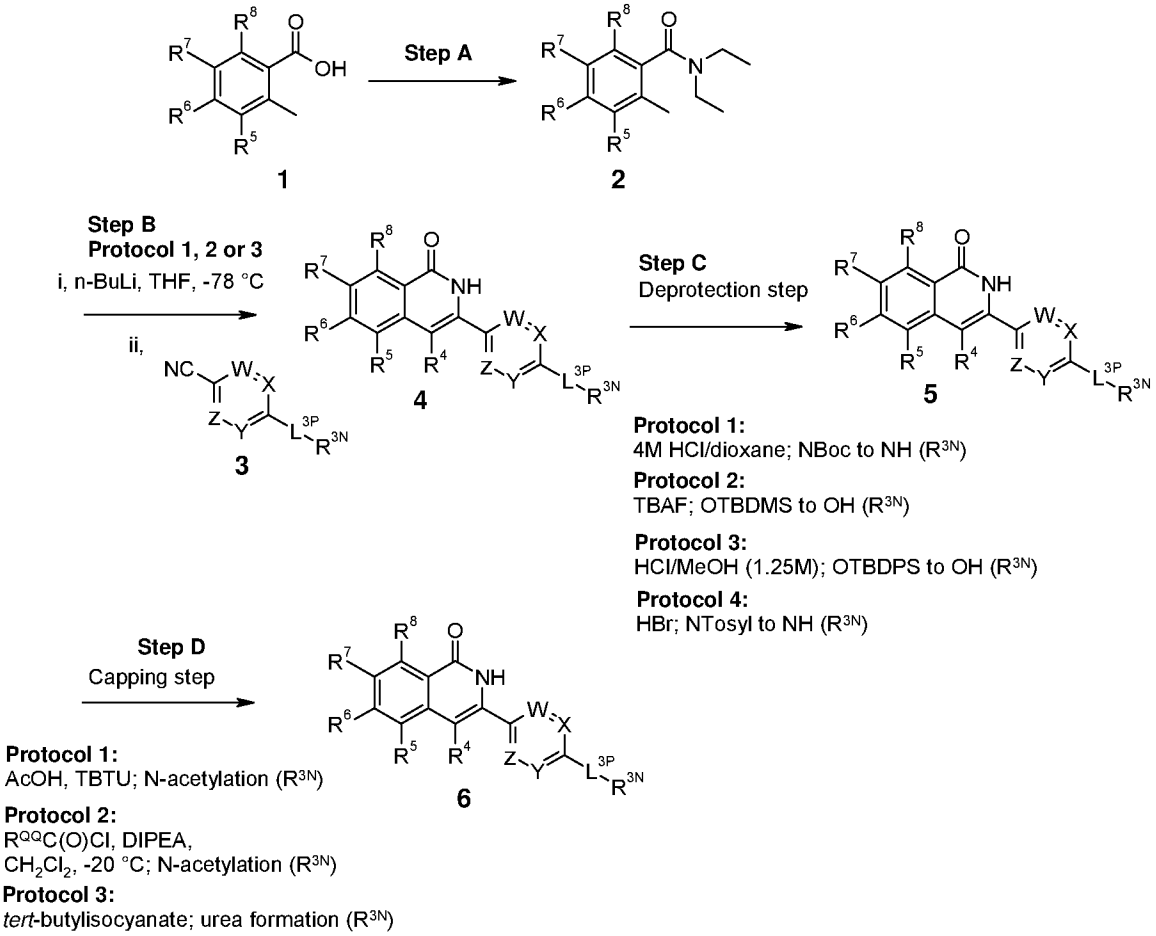
Chiral_Method_1: Daicel IA, 10 µm, 250 x 20 mm; MeOH + 0.2% diethylamine

Chiral_Method_2: Daicel IA, 10 µm, 250 x 20 mm; 50% (MeCN + 3% diethylamine) + 50% EtOH

Chiral_Method_3: Daicel IA, 10 µm, 250 x 20 mm; EtOH + 0.05% diethylamine

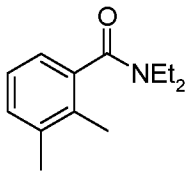
Synthesis of *2H*-isoquinolin-1-ones of Formula **4** - **6**

Scheme A (via Route 1)



Scheme A, Step A: Synthesis of *N,N*-Diethyl-benzamide Derivatives **2**

N,N-Diethyl-2,3-dimethyl-benzamide



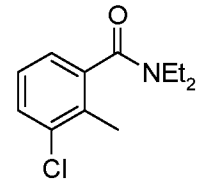
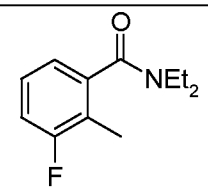
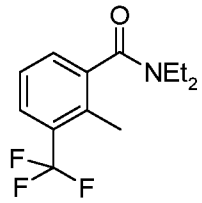
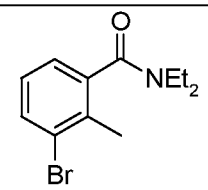
To a stirred solution of 2,3-dimethyl-benzoic acid (1.52 g, 10.1 mmol) in CH_2Cl_2/DMF (118 mL/ 12 mL) was added *N,N*-diisopropylethylamine (1.76 mL, 10.1 mmol) and TBTU (3.25 g, 10.1 mmol) and the reaction mixture stirred at RT for 50 min. *N,N*-diethylamine (1.58 mL, 15.2 mmol) was added and the reaction mixture stirred for 18 h. The reaction mixture was washed with 10% Na_2CO_3 solution (2 x 100 mL) and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography, eluting with isohexane and increasing the polarity to 30% EtOAc/isohexane to obtain *N,N*-diethyl-2,3-dimethyl-benzamide as a colourless liquid (1.48 g, 72%).

^{1}H NMR (400MHz, DMSO-d_6): δ 7.20-7.10 (m, 2H), 6.90 (d, J = 8 Hz, 1H), 3.70-3.55 (m, 1H), 3.35-3.20 (m, 1H), 3.15-2.90 (m, 2H), 2.25 (s, 3H), 2.07 (s, 3H), 1.17 (t, J = 7 Hz, 3H), 0.95 (t, J = 7 Hz, 3H).

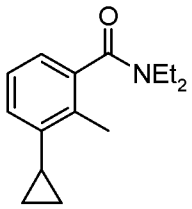
AnalpH2_MeOH_4min: Rt 2.75 min; m/z 206 $[M+1]^+$.

The following *N,N*-diethyl-benzamide derivatives are prepared using analogous procedures.

Table 1: *N,N*-Diethyl-benzamide Derivatives of Formula **2**

Compound	Reference	Analytical Data	Mass, %Yield, State
	Compound reported by Snieckus *et al.*, 1989	AnalpH2_MeOH_4min: Rt 2.84 min; m/z 226 $[M+1]^+$	10 g, 77%, colourless oil
	Compound reported by Fujio *et al.*, 2009	AnalpH2_MeOH_4min: Rt 2.63 min; m/z 210 $[M+1]^+$	1.15 g, 86%, colourless oil
		AnalpH2_MeOH_4min: Rt 2.94 min; m/z 260 $[M+1]^+$	1.17 g, 92%, colourless oil
	Compound reported by Naoto *et al.*, 2009	AnalpH2_MeOH_4min: Rt 2.80 min; m/z 269 $[M+1]^+$	4.93 g, 98%, colourless oil

3-Cyclopropyl-*N,N*-diethyl-2-methyl-benzamide **7**



7

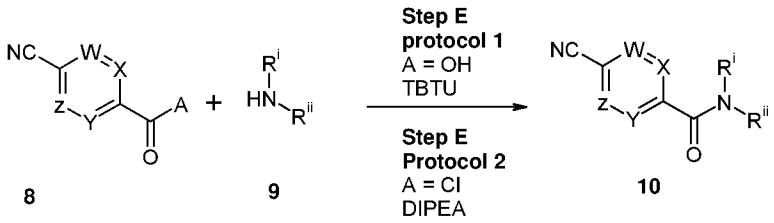
A solution of 3-bromo-*N*-*N*-diethyl-2-methylbenzamide (2.5 g, 9 mmol), cyclopropyl boronic acid (955 mg, 11 mmol), K_3PO_4 (9.81 g, 46 mmol) and water (10 mL) in toluene (40 mL) was de-gassed using N_2 for 1.5 h, $Pd(OAc)_2$ (207 mg, 0.9 mmol) and triphenyl phosphine (42 mg, 0.92 mmol) was added and the reaction mixture degassed for 1 h and heated at 90 °C for 16 h. The reaction mixture was cooled to RT, diluted with EtOAc (40 mL), washed with water (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude compound was purified by silica gel column chromatography eluting with 3% EtOAc/CH_2Cl_2 to obtain 3-cyclopropyl-*N,N*-diethyl-2-methyl-benzamide as a pale yellow liquid (1.3 g, 61%).

^{1}H NMR (400MHz, $CDCl_3$): δ 7.13-7.09 (m, 1H), 7.00-6.98 (m, 2H), 3.91-3.70 (m, 1H), 3.55-3.35 (m, 1H), 3.20-3.05 (m, 2H), 2.34 (s, 3H), 1.95-1.80 (m, 1H), 1.26 (t, *J* = 7 Hz, 3H), 1.02 (d, *J* = 7 Hz, 3H), 0.99-090 (m, 2H), 0.75-0.60 (m, 2H).

AnalpH2_MeOH_4min: Rt 2.92 min; m/z 232 $[M+1]^+$.

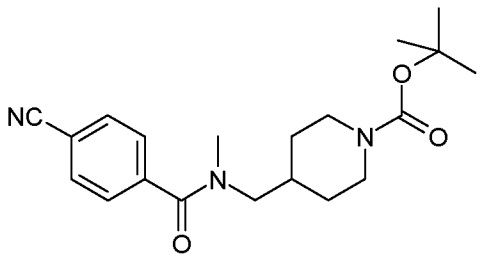
Synthesis of Nitrile Intermediates **3** of Formula **10** (required for Step B, Scheme A)

Scheme B



Scheme A, Step E (Protocol 1): Synthesis of Amide-Substituted Benzonitriles **10** (*via* acid coupling)

4-{[(4-Cyano-benzoyl)-methyl-amino]-methyl}-piperidine-1-carboxylic acid *tert*-butyl ester



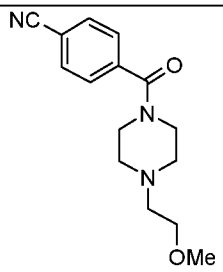
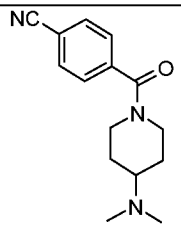
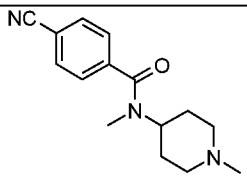
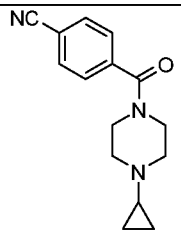
To a stirred solution of 4-cyanobenzoic acid (322 mg, 2.19 mmol) in CH_2Cl_2 (10 mL) was added TBTU (702 mg, 2.19 mmol) and *N,N*-diisopropylethylamine (1.14 mL, 6.54 mmol) and the reaction mixture stirred at RT for 10 min. 4-Methylaminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (500 mg, 2.19 mmol) in DMF (4 mL) was added and the reaction mixture was stirred at RT for 2 h. The crude material was concentrated *in vacuo* and purified by silica gel column chromatography, eluting with isohexane and increasing

the polarity to 100% EtOAc to afford 4-{[(4-cyano-benzoyl)-methyl-amino]-methyl}-piperidine-1-carboxylic acid *tert*-butyl ester as a orange solid (700 mg, 89%).

AnalpH2_MeOH_4min(1): Rt 2.73 min; m/z 358 $[M+1]^+$.

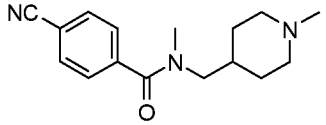
The following nitrile benzamide derivatives are prepared using analogous procedures.

Table 2: Amide-substituted Benzonitrile Intermediates **3** of Formula **10**

Compound	Analytical Data	Mass, %Yield, State
	AnalpH9_MeOH_4min: Rt 1.87 min; m/z 274 $[M+1]^+$	1.46 g (92%), yellow semi-solid
	AnalpH9_MeOH_4min: Rt 1.82 min; m/z 258 $[M+1]^+$	1.27 g (97%), white solid
	AnalpH9_MeOH_4min: Rt 1.89 min; m/z 258 $[M+1]^+$	1.0 g (99%), white solid
	AnalpH9_MeOH_4min: Rt 2.21 min; m/z 256 $[M+1]^+$	992 mg (99%), white solid

Scheme B, Step E (Protocol 2): Synthesis of Amide-Substituted Benzonitriles **10** (*via* Acid Chloride Coupling)

4-Cyano-*N*-methyl-*N*-(1-methyl-piperidin-4-ylmethyl)-benzamide

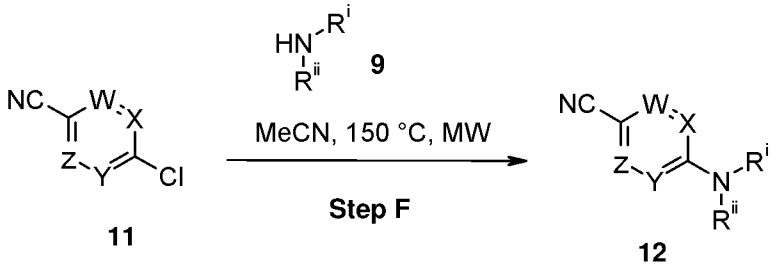


4-cyanobenzoylchloride (200 mg, 1.21 mmol) was dissolved in anhydrous CH_2Cl_2 (4 mL) and cooled to 0 °C. Methyl-(1-methyl-piperidin-4-ylmethyl)-amine (172 mg, 1.21 mmol) in anhydrous CH_2Cl_2 (1 mL) was added followed by *N,N*-diisopropylethylamine (0.63 mL, 3.62 mmol). The reaction mixture was allowed to warm to RT over 2 h. The reaction mixture was concentrated *in vacuo* and the crude product purified by reverse phase preparative HPLC-MS to obtain 4-cyano-*N*-methyl-*N*-(1-methyl-piperidin-4-ylmethyl)-benzamide as an off-white solid (213 mg, 65%).

AnalpH9_MeOH_4min(1): Rt 1.77 min; m/z 272 $[M+1]^+$.

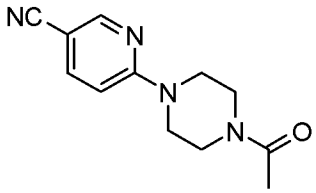
Synthesis of Nitrile intermediates **3** of Formula **12** (required for Step B – Scheme A)

Scheme C



Step F: Synthesis of Amino-Substituted Pyridine-Carbonitrile Derivatives **12**

6-(4-Acetyl-piperazin-1-yl)-nicotinonitrile

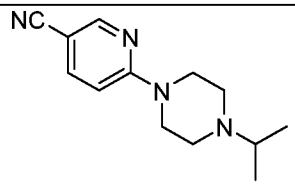
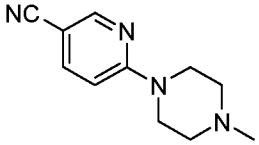
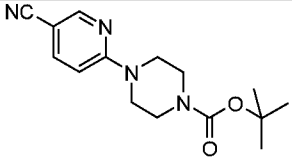
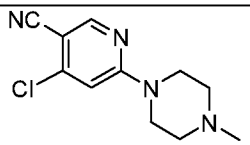
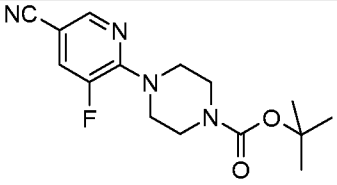
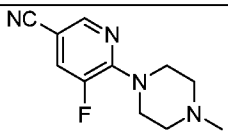
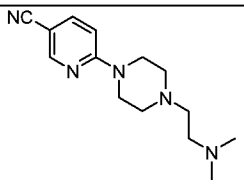
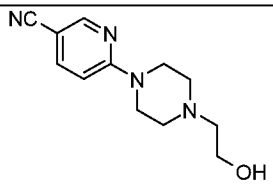
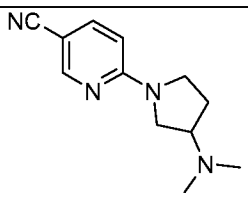


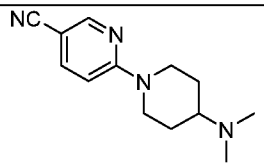
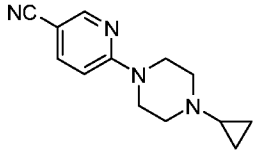
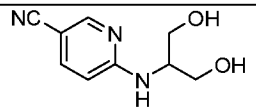
6-Chloropyridine-2-carbonitrile (104 mg, 0.75 mmol) and 1-acetylpiperazine (384 mg, 0.75 mmol) in acetonitrile (2.5 mL) were stirred and irradiated using a microwave reactor (300W, 150 °C, 60 min). The reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography, eluting with CH_2Cl_2 and increasing the polarity to 10% MeOH/CH_2Cl_2 to afford 6-(4-acetyl-piperazin-1-yl)-nicotinonitrile as an off-white solid (172 mg, quant.).

AnalpH2_MeOH_4min: Rt 1.77 min; m/z 231 $[M+1]^+$.

The following substituted pyridine-carbonitrile derivatives are prepared using analogous procedures.

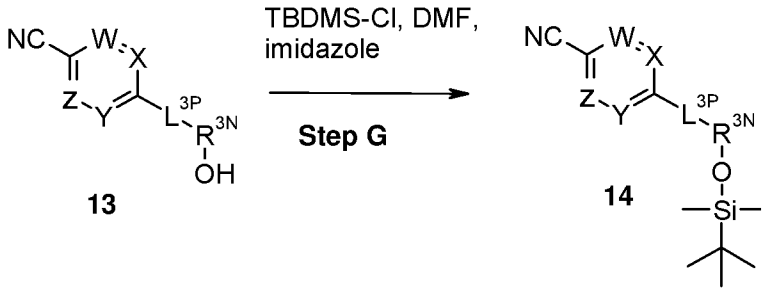
Table 3: Substituted Amino-Pyridine-Carbonitrile Derivatives **3** of formula **12**

Compound	Analytical Data	Mass, %Yield, State
	AnalpH9_MeOH_4min: Rt 2.55 min; m/z 231 $[M+1]^+$	157 mg, 91%, light brown crystalline solid
	Commercially available	N/A
	Commercially available	N/A
	AnalpH9_MeOH_4min: Rt 2.30 min; m/z 237 $[M+1]^+$	94 mg, 17%, yellow solid
	AnalpH2_MeOH_4min: Rt 3.10 min; m/z not observed	731 mg, 94%, yellow solid
	AnalpH9_MeOH_4min: Rt 1.80 min; m/z 221 $[M+1]^+$	496 mg, 88%, yellow solid
	AnalpH9_MeOH_4min: Rt 1.46 min; m/z 260 $[M+1]^+$	485 mg, 65%, yellow oil
	AnalpH9_MeOH_4min: Rt 1.85 min; m/z 233 $[M+1]^+$	350 mg, 70%, pale yellow solid
	AnalpH9_MeOH_4min: Rt 2.12 min; m/z 217 $[M+1]^+$	312 mg, 80%, light brown oil

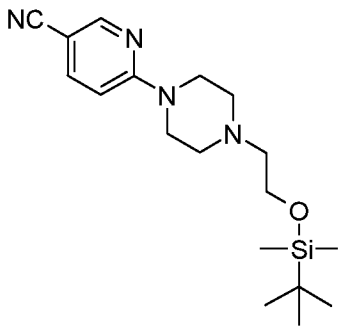
Compound	Analytical Data	Mass, %Yield, State
	AnalpH9_MeOH_4min: Rt 2.22 min; m/z 231 $[M+1]^+$	449 mg, 87%, cream solid
	AnalpH9_MeOH_4min: Rt 2.56 min; m/z 229 $[M+1]^+$	340 mg, 85%, beige solid
	AnalpH2_MeOH_4min(3): Rt 0.98 min; m/z 194 $[M+1]^+$	Used in next step as crude material

Synthesis of Nitrile Intermediates **3** of Formula **14** (required for Step B, Scheme A)

Scheme D



6-{4-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-piperazin-1-yl}-nicotinonitrile

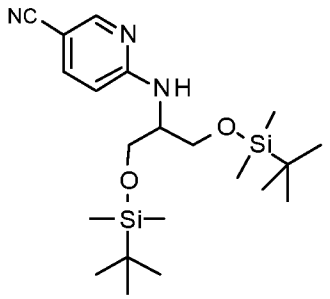


To a solution of 6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-nicotinonitrile (350 mg, 1.51 mmol) and imidazole (236 mg, 3.47 mmol) in anhydrous DMF (3 mL) was added TBDMS chloride (295 mg, 1.96 mmol) in anhydrous DMF (2 mL) and the reaction mixture stirred for 16 h at RT. The reaction mixture was diluted with EtOAc (5 mL) and washed with water (10 mL) and brine (10 mL). The organic phase was separated, passed through a phase separation cartridge and concentrated *in vacuo*. The crude residue was purified on silica gel column chromatography eluting with 30% EtOAc/isohexane, and increasing the polarity to 50% EtOAc/isohexane to afford 6-{4-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-piperazin-1-yl}-nicotinonitrile as a pale yellow solid (394 mg, 75%).

AnalpH2_MeOH_4min: Rt 2.17 min; m/z 347 $[M+1]^+$.

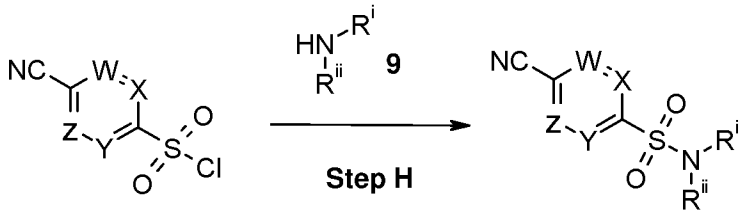
The following TBDMS-protected nicotinonitrile derivatives are prepared using analogous procedures.

Table 4: Nitrile Intermediates **3** of formula **14**

Compound	Reference	Analytical Data	Mass, %Yield, State
	Intermediate for IQ-219	AnalpH2_MeOH_4min(3): Rt 3.76 min; m/z 422 $[M+1]^+$	1.34 g, 88%, white solid

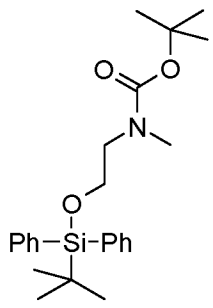
Synthesis of Nitrile intermediates **3** of Formula **16** (required for Step B, Scheme A)

Scheme E



Synthesis of Boc-protected Amine **9**

[2-(*tert*-Butyl-diphenyl-silanyloxy)-ethyl]-methyl-carbamic acid tert-butyl ester

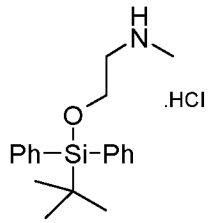


(2-Hydroxy-ethyl)-methyl-carbamic acid tert-butyl ester (400 mg, 2.28 mmol), TBDPS chloride (593 µL, 2.28 mmol) and imidazole (342 mg, 5.02 mmol) in DMF (2 mL) were

stirred at RT for 12 h. The reaction mixture was diluted with brine and extracted with CH_2Cl_2. The combined organics were passed through a phase separation cartridge and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography, eluting with isohexane and increasing the polarity to 50% EtOAc/ isohexane to obtain [2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-methyl-carbamic acid *tert*-butyl ester as a colourless oil (572 mg, 61%).

AnalpH2_MeOH_4min(1): Rt 3.74 min; m/z 414 $[M+1]^+$.

[2-(*tert*-Butyl-diphenyl-silanyloxy)-ethyl]-methyl-amine

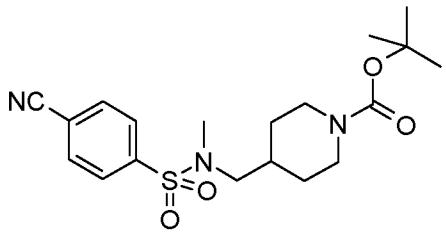


[2-(*tert*-Butyl-diphenyl-silanyloxy)-ethyl]-methyl-carbamic acid *tert*-butyl ester (572 mg, 1.38 mmol) and 4M HCl/dioxane (3 mL) in CH_2Cl_2 (5 mL) were stirred at RT for 3 h. The reaction mixture was concentrated *in vacuo* and the crude material was purified by silica gel column chromatography, eluting with CH_2Cl_2 and increasing the polarity to 10% MeOH/CH_2Cl_2 to obtain [2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-methyl-amine as a yellow solid (105 mg, 21%).

AnalpH2_MeOH_4min(1): Rt 2.41 min; m/z 314 $[M+1]^+$.

Step H: Synthesis of Sulfonamide Derivatives **16**

4-{[(4-Cyano-benzenesulfonyl)-methyl-amino]-methyl}-piperidine-1-carboxylic acid *tert* butyl ester

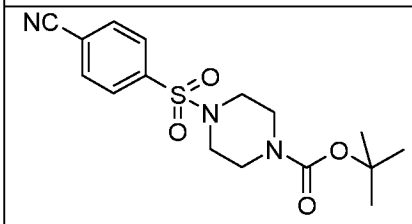
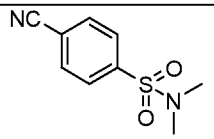
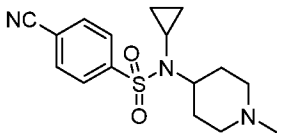
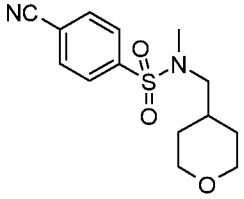
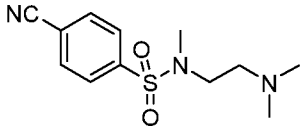
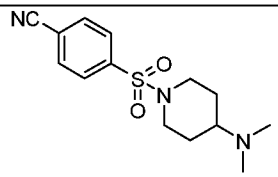


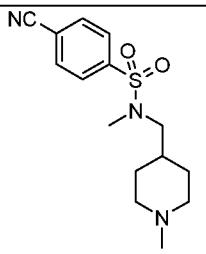
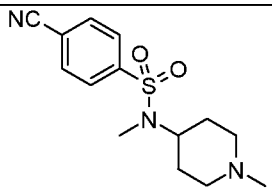
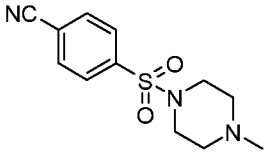
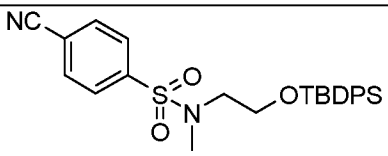
To a stirred solution of 4-cyanobenzenesulfonyl chloride (411 mg, 2.2 mmol) in CH_2Cl_2 (10 mL) was added 4-methylaminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (500 mg, 2.2 mmol) and triethylamine (0.91 mL, 6.5 mmol) and the reaction stirred at RT for 2 h after which time silica was added and solvent removed. The crude residue was purified by silica gel chromatography eluting with isohexane, and increasing the polarity to 100% EtOAc to afford 4{[4-cyano-benzenesulfonyl)-methyl-amino]-methyl}-piperidine-1-carboxylic acid *tert*-butyl ester as a white solid (750 mg, 87%).

AnalpH2_MeOH_4min(1): Rt 2.91 min; m/z 416 $[M+23]^+$.

The following substituted sulfonamide derivatives are prepared using analogous procedures.

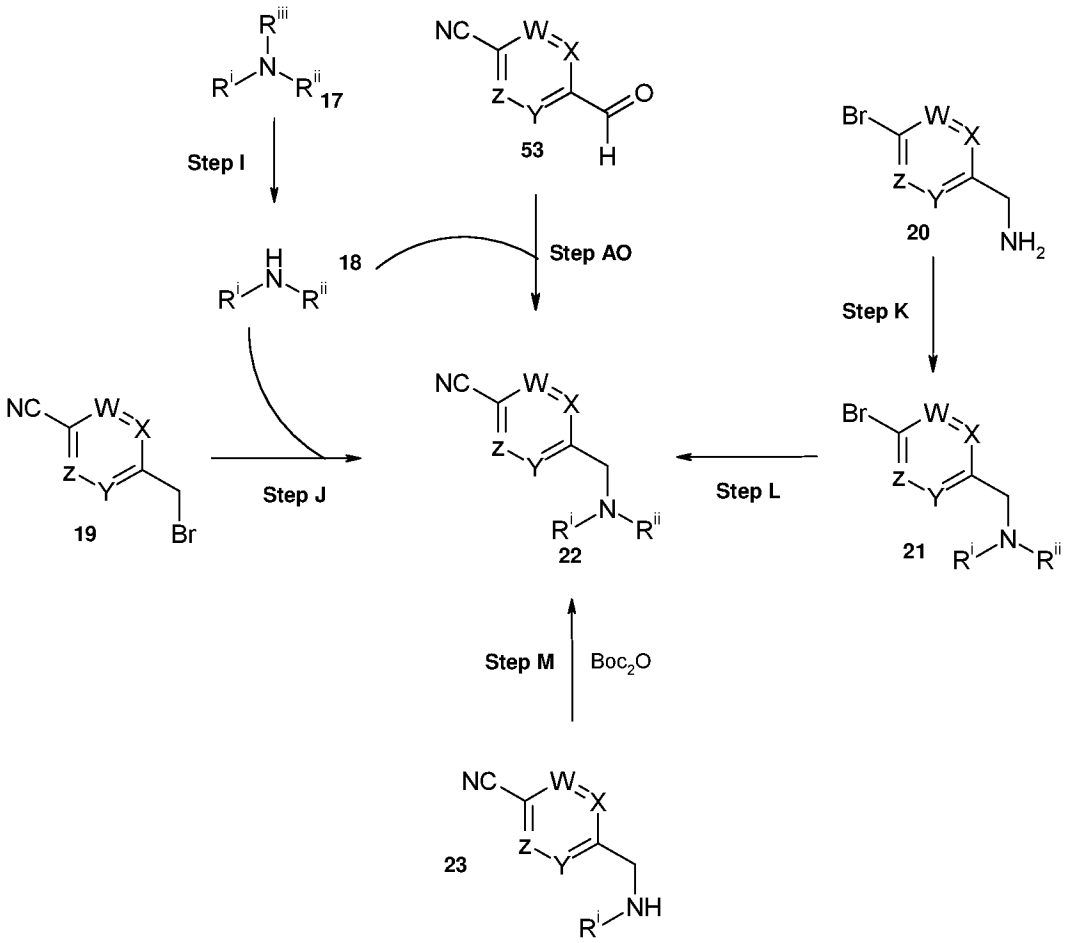
Table 5: Sulfonamide Derivatives **3** of formula **16**

Compound	Reference	Analytical Data	Mass, %Yield, State
		AnalpH2_MeOH_4min: Rt 2.72 min; m/z 374 $[M+23]^+$	669 mg, 96%, white solid
	Commercially available		N/A
		AnalpH2_MeOH_4min(1): Rt 1.24 min; m/z 320 $[M+1]^+$	300 mg, 94%, cream solid
		AnalpH2_MeOH_4min(1): Rt 2.29 min; m/z not observed	310 mg, quant., white solid
		AnalpH2_MeOH_4min(1): Rt 2.07 min; m/z 268 $[M+1]^+$	367 mg, quant., cream solid
		AnalpH2_MeOH_4min: Rt 1.80 min; m/z 294 $[M+1]^+$	560 mg, quant., white solid

Compound	Reference	Analytical Data	Mass, %Yield, State
		AnalpH2_MeOH_4min: Rt 1.05 min; m/z 308 $[M+1]^+$	669 mg, quant., white solid
		AnalpH9_MeOH_4min(1): Rt 1.86 min; m/z 294 $[M+1]^+$	129 mg, 65%, yellow solid
		AnalpH2_MeOH_4min: Rt 0.85 min; m/z 266 $[M+1]^+$	268 mg, quant., off-white solid
		AnalpH2_MeOH_4min(1): Rt 3.49 min; m/z 479 $[M+1]^+$	131 mg, 91%, yellow solid

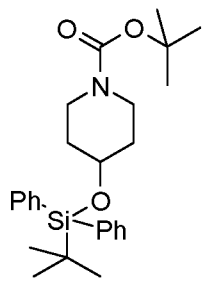
Synthesis of Nitriles **3** of Formula **22**

Scheme F



Scheme F, Step I: Synthesis of Amine Intermediates **18**

4-(*tert*-Butyl-diphenyl-silanyloxy)-piperidine-1-carboxylic acid *tert*-butyl ester



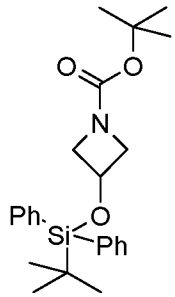
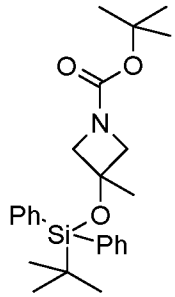
To a stirred solution of 4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (400 mg, 1.98 mmol) in DMF (2 mL) was added TBDPS chloride (0.52 mL, 1.98 mmol) and imidazole (297 mg, 4.47 mmol) and the reaction stirred at RT for 16 h afterwhich time the reaction mixture was diluted with brine (10 mL), washed with CH_2Cl_2 (3 x 25 mL) and the

organics combined and dried through a phase separation cartridge and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography, eluting with EtOAc and increasing the polarity to 30% EtOAc/isohexane to obtain 4-(*tert*-butyl-diphenyl-silanyloxy)-piperidine-1-carboxylic acid *tert*-butyl ester as a colourless oil (545 mg, 62%).

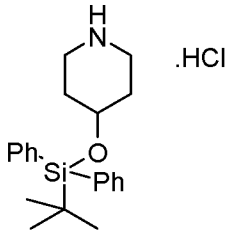
AnalpH2_MeOH_4min(1): Rt 3.92 min; m/z 440 $[M+1]^+$.

The following substituted amine derivatives are prepared using analogous procedures.

Table 6: Boc-protected Amine Intermediates **17**

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-167	AnalpH2_MeOH_4min(3): Rt 3.68 min; m/z 412 $[M+1]^+$	2.14 g, 90%, colourless oil
	IQ-172	AnalpH2_MeOH_4min(3): Rt 3.75 min; m/z 326 $[M-(Boc)]^+$	1.07 g, 95%, colourless oil

4-(*tert*-Butyl-diphenyl silanyloxy)-piperidine



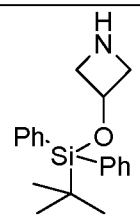
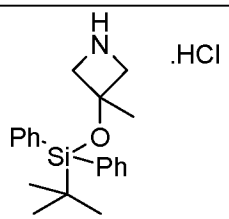
To 4-(*tert*-butyl-diphenyl-silanyloxy)-piperidine-1-carboxylic acid *tert*-butyl ester (54 mg, 0.124 mmol) was added 4M HCl/dioxane (2 mL) and CH_2Cl_2 (5 mL). The reaction mixture was stirred at RT for 2 h. 4M HCl/dioxane (3 mL) added and reaction stirred for a further 1 hr. The reaction mixture was concentrated *in vacuo*. The crude material was purified by

silica gel column chromatography eluting with CH_2Cl_2 and increasing the polarity to 10% MeOH/CH_2Cl_2 to obtain 4-(*tert*-butyl-diphenyl silanyloxy)-piperidine as a cream foam (370 mg, 79%).

AnalpH2_MeOH_4min(1): Rt 2.54 min; m/z 340 $[M+1]^+$.

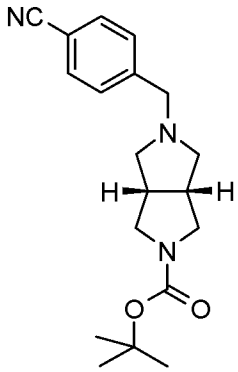
The following substituted amine derivatives are prepared using analogous procedures.

Table 7: Boc-deprotected Amine Intermediates **18**

Compound	Reference	Analytical Data	Mass, %Yield, State
	Intermediate for IQ-167 or IQ-169	AnalpH2_MeOH_4min(3): Rt 2.39 min; m/z 312 $[M+1]^+$	950 mg, 59%, pale oil
 .HCl	Intermediate for IQ-172	AnalpH2_MeOH_4min(3): Rt 2.46 min; m/z 326 $[M+1]^+$	188 mg, 21%, white solid

Scheme F, Step J: Synthesis of Nitrile Intermediates **3** of formula **22** (via Bromide displacement)

(3aS,6aR)-5-(4-Cyano-benzyl)-hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid *tert*-butyl ester



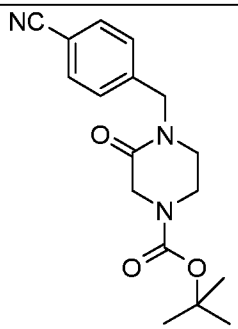
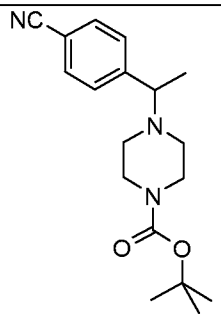
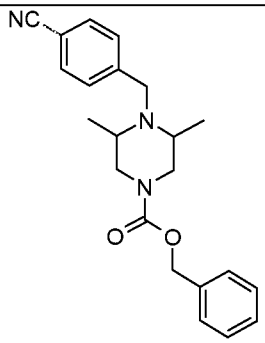
To 4-(bromomethyl)benzonitrile (277 mg, 1.41 mmol) was added hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid (300 mg, 1.41 mmol), potassium carbonate (215 mg, 1.55 mmol) and acetone (7 mL) and the reaction mixture stirred for 16 h. The reaction mixture was concentrated *in vacuo*, dissolved in CH_2Cl_2 (4 mL) and washed with water (4 mL).

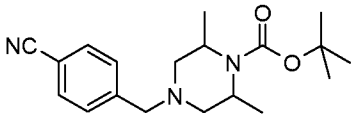
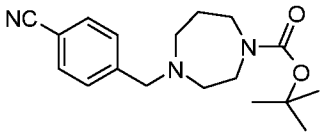
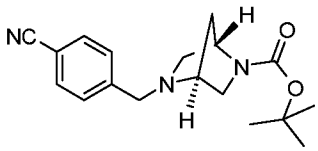
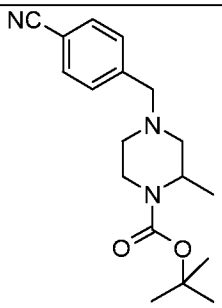
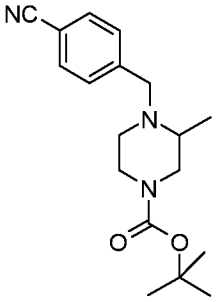
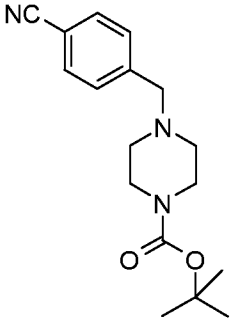
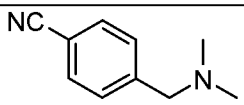
The organic phase was separated and the aqueous layer washed with CH_2Cl_2 (4 mL). The organic phases were combined, passed through a phase separation cartridge and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography, eluting with CH_2Cl_2 and increasing the polarity to 3.5% MeOH/ CH_2Cl_2 to obtain (3aS,6aR)-5-(4-cyano-benzyl)-hexahydro-pyrrolo[3,4-c]pyrrole-2-carboxylic acid *tert*-butyl ester as a yellow oil (278 mg, 60%).

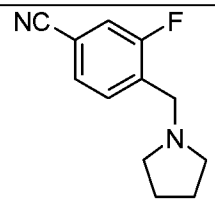
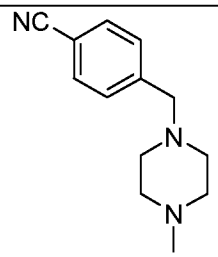
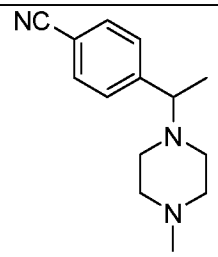
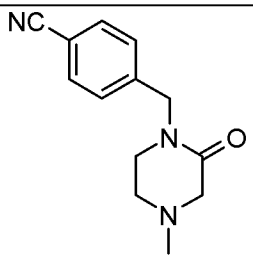
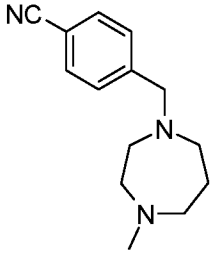
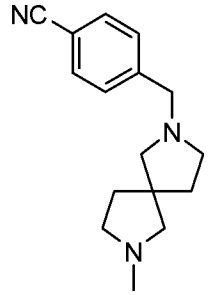
AnalpH2_MeOH_4min(1): Rt 1.54 min; m/z 328 $[M+1]^+$.

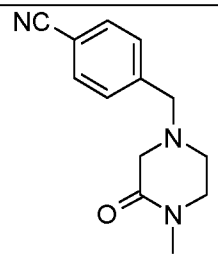
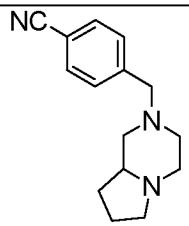
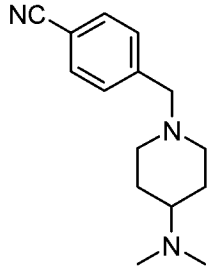
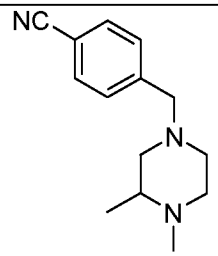
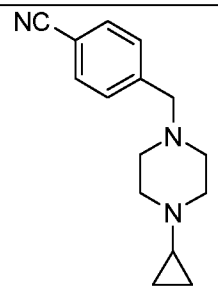
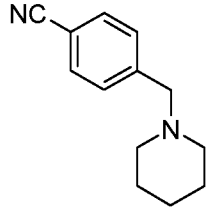
The following nitrile derivatives are prepared using analogous procedures.

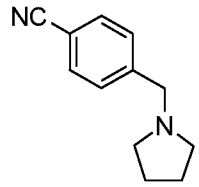
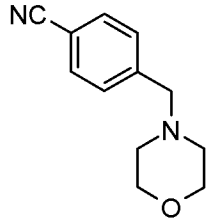
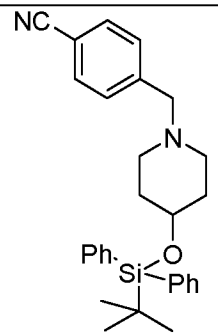
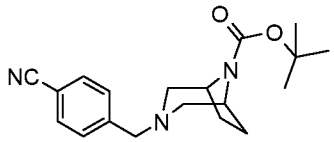
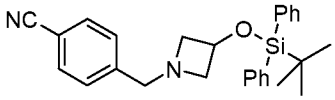
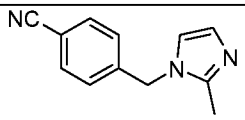
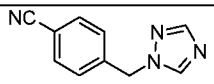
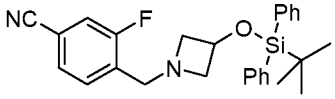
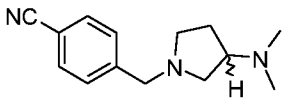
Table 8: Nitrile Intermediates **3** of formula **22**

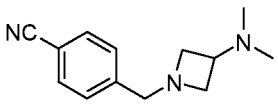
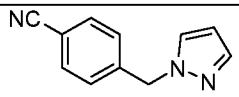
Compound	Reference	Analytical Data	Mass, %Yield, State
		AnalpH2_MeOH_4min(1): Rt 2.53 min; m/z 316 $[M+1]^+$	630 mg, 100%, white solid
		AnalpH2_MeOH_4min(1): Rt 1.82 min; m/z 316 $[M+1]^+$	220 mg, 73%, colourless oil
		AnalpH2_MeOH_4min(1): Rt 2.51 min; m/z 364 $[M+1]^+$	197 mg, 85%, colourless oil

Compound	Reference	Analytical Data	Mass, %Yield, State
		AnalpH2_MeOH_4min(1): Rt 3.20 min; m/z 330 $[M+1]^+$	280 mg, 83%, colourless oil
		AnalpH2_MeOH_4min(1): Rt 1.55 min; m/z 316 $[M+1]^+$	294 mg, 92%, colourless oil
		AnalpH2_MeOH_4min: Rt 1.43 min; m/z 314 $[M+1]^+$	445 mg, 69%, colourless oil
		AnalpH2_MeOH_4min: Rt 2.54 min; m/z 316 $[M+1]^+$	550 mg, 85%, colourless oil
		AnalpH2_MeOH_4min: Rt 1.85 min; m/z 316 $[M+1]^+$	420 mg, 65%, white solid
	Commercially available		N/A
	Commercially available		N/A

Compound	Reference	Analytical Data	Mass, %Yield, State
		AnalpH9_MeOH_4min: Rt 2.51 min; m/z 205 $[M+1]^+$	760 mg, 80%, pale yellow liquid
	Commercially available		N/A
		AnalpH9_MeCN_4min: Rt 1.83 min; m/z 230 $[M+1]^+$	189 mg, 89%, colourless oil
		AnalpH9_MeCN_4min(1): Rt 1.39 min; m/z 230 $[M+1]^+$	1.02 g, 85%, orange oil
		AnalpH9_MeOH_4min(1): Rt 1.81 min; m/z 230 $[M+1]^+$	150 mg, 64%, colourless oil
		AnalpH9_MeCN_4min(1): Rt 1.72 min; m/z 256 $[M+1]^+$	63 mg, 15%, brown oil

Compound	Reference	Analytical Data	Mass, %Yield, State
		AnalpH2_MeOH_4min(1): Rt 1.47 min; m/z 230 $[M+1]^+$	212 mg, 45%, orange glass
		AnalpH9_MeCN_4min: Rt 1.94 min; m/z 242 $[M+1]^+$	171 mg, 34%, pale orange oil
		AnalpH9_MeCN_4min: Rt 1.72 min; m/z 244 $[M+1]^+$	231 mg, 37%, white solid
		AnalpH2_MeOH_4min: Rt 0.95 min; m/z 230 $[M+1]^+$	110 mg, 23%, orange oil
		AnalpH9_MeCN_4min: Rt 2.19 min; m/z 242 $[M+1]^+$	68 mg, 13%, pale orange oil
		AnalpH2_MeOH_4min: Rt 0.34, 0.74 min; m/z 201 $[M+1]^+$	700 mg, 68%, pale yellow liquid

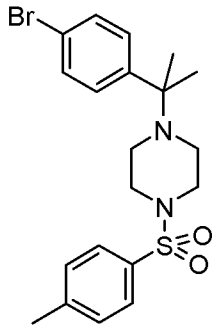
Compound	Reference	Analytical Data	Mass, %Yield, State
		AnalpH2_MeOH_4min: Rt 0.33, 0.57 min; m/z 187 $[M+1]^+$, 373 $[2M+1]^+$	700 mg, 73%, pale yellow liquid
	Commercially available		N/A
		AnalpH2_MeOH_4min(1): Rt 2.69 min; m/z 455 $[M+1]^+$	360 mg, 80%, yellow glass
		AnalpH2_MeOH_4min: Rt 2.82 min; m/z 328 $[M+1]^+$	194 mg, 100%, cream solid
	Intermediate for IQ-167	AnalpH2_MeOH_4min(3): Rt 2.56 min; m/z 427 $[M+1]^+$	180 mg, 28%, colourless glass
	Commercially available		N/A
	Commercially available		N/A
	Intermediate for IQ-169	AnalpH2_MeOH_4min(3): Rt 2.75 min; m/z 445 $[M+1]^+$	50 mg, 6%, yellow oil
	Intermediate for IQ-173	AnalpH2_MeOH_4min(3): Rt 0.39 min; m/z 230 $[M+1]^+$	414 mg, 51%, orange oil

Compound	Reference	Analytical Data	Mass, %Yield, State
	Intermediate for IQ-174	AnalpH9_MeOH_4min(2): Rt 0.39 min; m/z 230 $[M+1]^+$	469 mg, 65%, bright yellow oil
	Commercially available		N/A

Synthesis of Nitriles **3** of Formula **22**

Scheme F, Step K: Synthesis of Aryl Bromide Intermediates **21** (via amine dialkylation)

1-[1-(4-Bromo-phenyl)-1-methyl-ethyl]-4-(toluene-4-sulfonyl)-piperazine

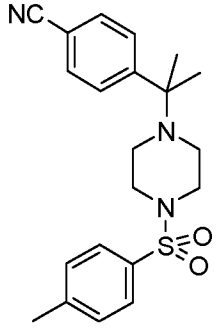


To a solution of 1-(4-bromo-phenyl)-1-methyl-ethylamine (400 mg, 1.84 mmol) in diisopropylethylamine (4 mL) was added *N,N*-bis(2-chloroethyl)-4-methylbenzene sulphonamide (500 mg, 1.68 mmol) and the reaction subjected to microwave irradiation at 150 °C for 9 h afterwhich time the reaction was concentrated *in vacuo* and the crude residue purified by reverse phase preparative HPLC-MS to afford 1-[1-(4-bromo-phenyl)-1-methyl-ethyl]-4-(toluene-4-sulfonyl)-piperazine as a peach solid (375 mg, 47%).

AnalpH2_MeOH_4min(1): RT 3.04 min; m/z 437/439 $[M+1]^+$.

Scheme F, Step L: Synthesis of Nitrile Intermediates **22**

4-{1-Methyl-1-[4-(toluene-4-sulfonyl)-piperazin-1-yl]-ethyl}-benzonitrile

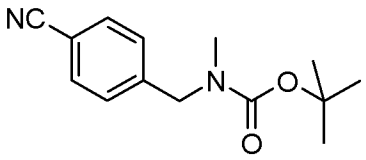


To a solution of 1-[1-(4-bromo-phenyl)-1-methyl-ethyl]-4-(toluene-4-sulfonyl)-piperazine (200 mg, 0.45 mmol) in DMF (3 mL) was added zinc cyanide (64.41 mg, 0.54 mmol) and tetrakis(triphenylphosphine)palladium(0) (52 mg, 0.045 mmol) and the reaction mixture degassed for 10 min under N_2. The reaction mixture was then subjected to microwave irradiation for 30 min at 180 °C, afterwhich time the reaction was diluted with 1:1 CH_2Cl_2/EtOAc (20 mL), washed with water (2 x 10 mL), passed through a phase separation cartridge and concentrated *in vacuo*. The crude residue was purified by reverse phase preparative HPLC-MS to afford 4-{1-methyl-1-[4-(toluene-4-sulfonyl)-piperazin-1-yl]-ethyl]-benzonitrile as a cream solid (70 mg, 47%).

AnalpH2_MeOH_4min(1): Rt 2.78 min; m/z 384 $[M+1]^+$.

Scheme F, Step M: Synthesis of Nitrile Intermediates **22** (via BOC protection)

(4-Cyano-benzyl)-methyl-carbamic acid *tert*-butyl ester

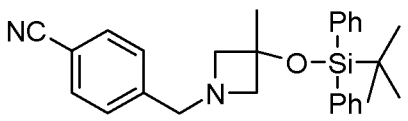


To 4-[(methylamine)methyl]benzonitrile (1g, 6.8 mmol) in CH_2Cl_2 (50 mL) was added DMAP (0.93 g, 7.6 mmol), di-*tert*-butyl dicarbonate (1.7 g, 7.6 mmol) and the reaction stirred for 48 h at RT. The reaction mixture was washed with saturated, aqueous $NaHCO_3$ and brine. The organic phase was separated and concentrated *in vacuo*. The crude residue was purified on silica gel chromatography eluting with isohexane, and increasing the polarity to 20% EtOAc/isohexane to afford (4-cyano-benzyl)-methyl-carbamic acid *tert*-butyl ester as a colourless oil (1.48 g, 89%).

AnalpH2_MeOH_4min: Rt 2.75 min; m/z 247 $[M+1]^+$.

Scheme F, Step AO: Synthesis of Nitrile Intermediates **22** (via Reductive Amination)

4-[3-(*tert*-Butyl-diphenyl-silanyloxy)-3-methyl-azetidin-1-ylmethyl]-benzonitrile



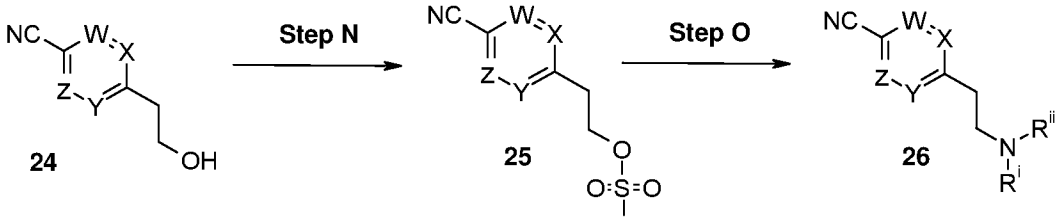
To a stirred solution of 4-formylbenzonitrile (68 mg, 0.51 mmol) and 3-(*tert*-Butyl-diphenyl-silanyloxy)-3-methyl-azetidine hydrochloride (188 mg, 0.51 mmol) in 1:1 MeOH/DMF (26 mL) was added acetic acid (catalytic). The reaction mixture was stirred under N_2 at 0 ºC for 1 h. Sodium cyanoborohydride (1M in THF, 0.6 mL, 0.57 mmol) was added and the reaction mixture stirred at RT, under N_2 for 18 h. The reacton mixture was concentrated in vacuo, the residue suspended in H_2O (10 mL), washed with CH_2Cl_2 (2 x 10 mL) and the

solution passed through a phase separation cartridge. The combined organic layers were concentrated *in vacuo* and the crude residue purified by silica gel chromatography eluting with 100% isohexane and increasing the polarity 100% EtOAc to afford 4-[3-(*tert*-butyl-diphenyl-silanyloxy)-3-methyl-azetidin-1-ylmethyl]-benzonitrile as a colourless oil (196 mg, 86%).

AnalpH2_MeOH_4min(3): Rt 2.71 min; m/z 441 $[M+1]^+$.

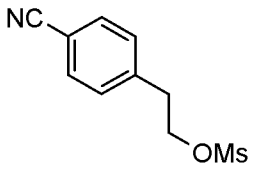
Synthesis of Nitrile intermediates **3** of Formula **26** (required for Step B, Scheme A)

Scheme G



Scheme G, Step N: Mesylation of Alcohol **24**

4-Cyano phenethyl methanesulfonate

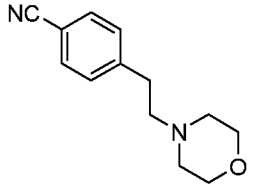


To a solution of 4-(2-hydroxy-ethyl)-benzonitrile (2 g, 13.6 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (6.8 mL, 47.52 mmol) and mesyl chloride (1.4 mL, 17.63 mmol) at 0 °C and stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with saturated $NaHCO_3$ solution (2 x 10 mL), the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain 4-cyano phenethyl methanesulfonate (3 g) as a pale yellow gummy liquid. The crude compound was used for the next step without further purification.

R_f: 0.6 (50% EtOAc/petroleum ether 60-80).

Scheme G, Step O: Synthesis of Amines (via Mesylate displacement)

4-(2-Morpholinoethyl) benzonitrile

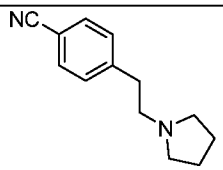
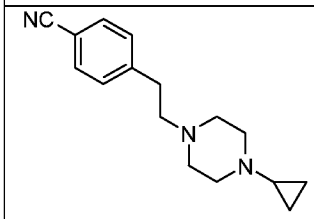


To a stirred solution of 4-cyano phenethyl methanesulfonate (6.04 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added morpholine (3.5g, 40.22 mmol) and heated 50 °C for 16 h.The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with saturated $NaHCO_3$ solution (2 x 10 mL), the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography, eluting with 3% MeOH/$CHCl_3$ to obtain 4-(2-morpholinoethyl) benzonitrile as a pale yellow solid (700 mg, 48%).

^{1}H NMR (400MHz, $CDCl_3$): δ 7.58 (d, *J* = 8 Hz, 2H), 7.30 (d, *J* = 8 Hz, 2H), 3.72 (t, *J* = 4.8 Hz, 4H), 2.85 (t, *J* = 8 Hz, 2H), 2.61-2.49 (6H, m).

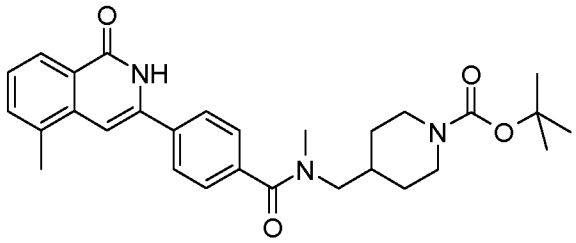
AnalpH9_MeOH_4min: Rt 2.20 min; m/z 217 $[M+1]^+$.
The following nitrile derivatives are prepared using analogous procedures.

Table 9: Nitrile Intermediates **3** of formula **26**

Compound	Analytical Data	Mass, %Yield, State
	AnalpH9_MeOH_4min: Rt 2.39 min; m/z 201 $[M+1]^+$	Pale yellow solid
	AnalpH9_MeOH_4min: Rt 2.62 min; m/z 256 $[M+1]^+$	Pale yellow solid

Scheme A, Step B (Protocol 1): Synthesis of Boc-protected *2H*-isoquinolin-1-one Derivatives of formula **4**

4-({Methyl-[4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzoyl]-amino}-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester (IQ-092)

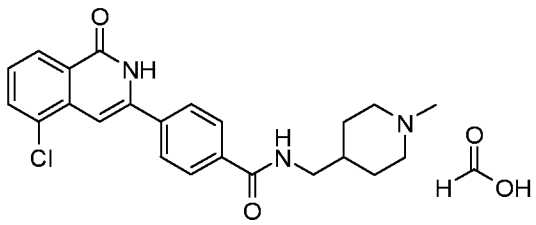


N,N-Diethyl-2,3-dimethyl-benzamide (200 mg, 0.97 mmol) was dissolved in anhydrous THF (4 mL) under a N_2 and cooled to -78 °C. *n*-BuLi (2.5M in n-hexanes, 0.82 mL, 2.04

mmol) was added dropwise to yield a deep red coloured solution and the reaction mixture was stirred at -78 °C for 30 minutes. 4-{[(4-Cyano-benzoyl)-methyl-amino]-methyl}-piperidine-1-carboxylic acid *tert*-butyl ester (348 mg, 0.97 mmol) was dissolved in anhydrous THF (4 mL) and added dropwise, and the reaction stirred at -78 °C for 2 h. The reaction mixture was quenched with ice/water, allowed to warm to RT and extracted with CH_2Cl_2 and EtOAc. The combined organic phase was passed through a phase separation cartridge and concentrated *in vacuo*. The crude compound was triturated with isohexane/diethyl ether (80:20), the solid filtered and dried *in vacuo* to give 4-({methyl-[4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzoyl]-amino}-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester as a light beige solid (171 mg, 36%).

AnalpH2_MeOH_QC(Sunfire1): Rt 7.81 min; m/z 490 $[M+1]^+$.

4-(5-Chloro-1-oxo-1,2-dihydro-isoquinolin-3-yl)-*N*-(1-methyl-piperidin-4-ylmethyl)-benzamide (IQ-091)

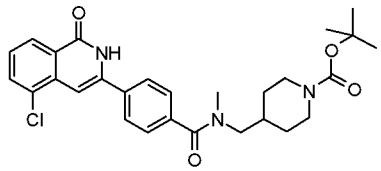
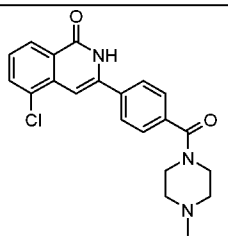
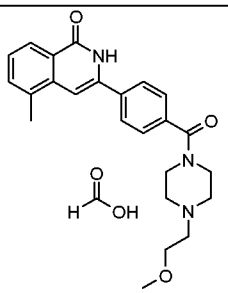
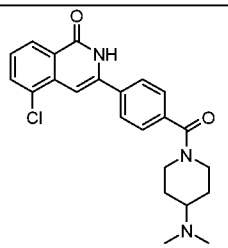


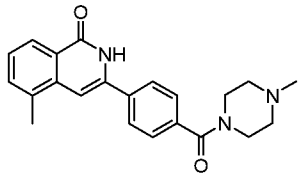
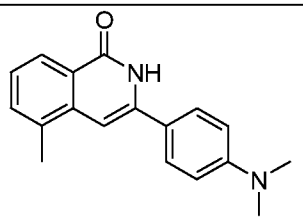
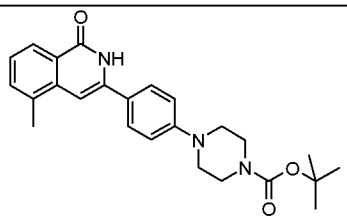
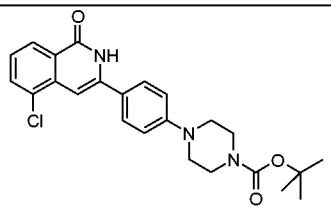
3-Chloro-*N,N*-diethyl-2-methyl-benzamide (150 mg, 0.66 mmol) was dissolved in anhydrous THF (2 mL) under N_2 and cooled to -78 °C. *n*-BuLi (2.5M in n-hexanes, 558 µL, 1.39 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 30 minutes. 4-Cyano-*N*-(1-methyl-piperidin-4-ylmethyl)-benzamide (180 mg, 0.66 mmol) in anhydrous THF (2 mL) was added dropwise to the reaction mixture and stirred at -78 °C continued for 1 h. The reaction mixture was poured into ice/water, allowed to warm to RT and extracted with CH_2Cl_2 (x3) and the organic phase dried ($MgSO_4$). The solution was filtered and concentrated *in vacuo*. The crude material was purified by reverse phase preparative HPLC-MS to afford 4-(5-chloro-1-oxo-1,2-dihydro-isoquinolin-3-yl)-*N*-(1-methyl-piperidin-4-ylmethyl)-benzamide as a white solid (37 mg, 13%).

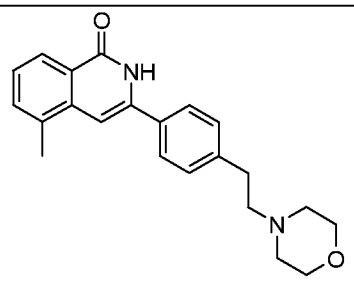
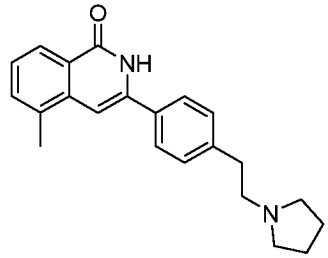
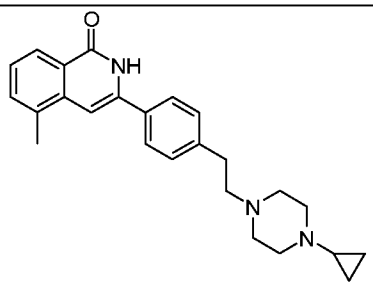
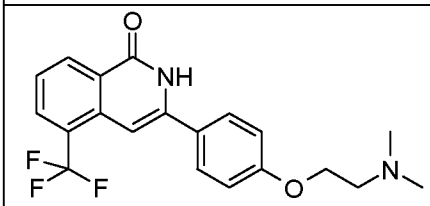
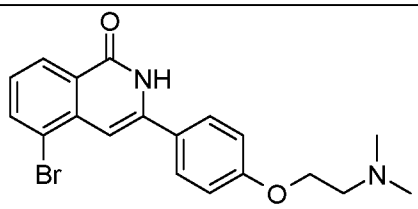
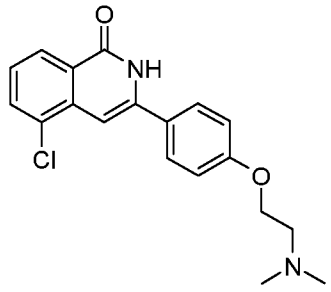
^{1}H NMR (400 MHz, DMSO-d_6): δ11.91 (br s, 1H), 8.25 (s, formic acid, 1H), 8.21 (d, J = 8. Hz, 1H), 7.9 (dd, J = 8 Hz, 1H), 7.85 (d, J = 8 Hz, 2H), 7.53 (d, J = 8 Hz, 1H), 7.51 (t, J = 8 Hz, 1H), 7.46 (d, J = 8 Hz, 1H), 6.97 (s, 1H), 3.42-3.38 (m, 1H), 3.20-3.12 (m, 1H), 2.95 (s, 1H), 2.90 (s, 2H), 2.82-2.78 (m, 1H), 2.68-2.64 (m, 1H), 2.18 (s, 2H), 2.09 (s, 1H), 1.86-1.92 (m, 1H), 1.79-1.81 (m, 1H), 1.68-1.65 (m, 2H), 1.49-1.42 (m, 1H), 1.30-1.23 (m, 1H), 0.90-0.79 (m, 1H).

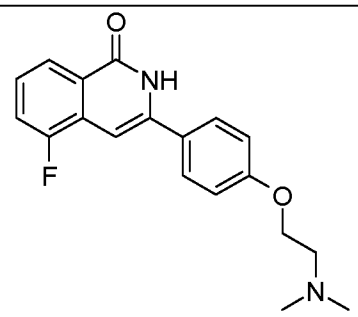
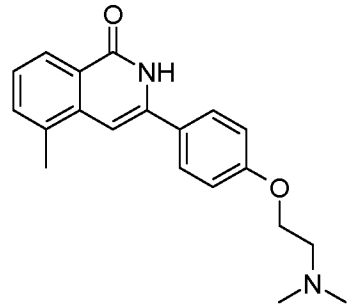
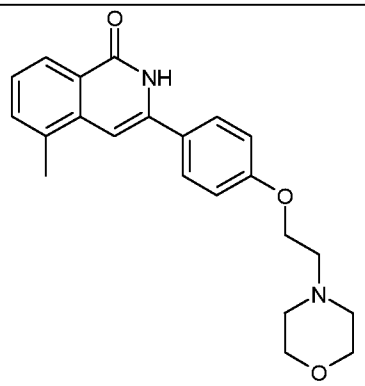
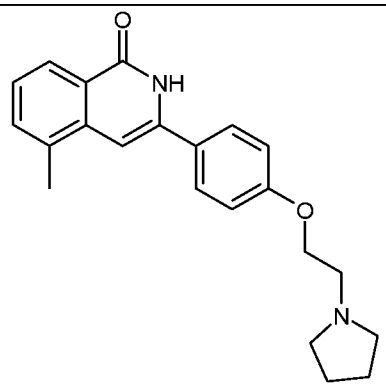
AnalpH2_MeOH_QC: Rt 5.70 min; m/z 424 $[M+1]^+$.

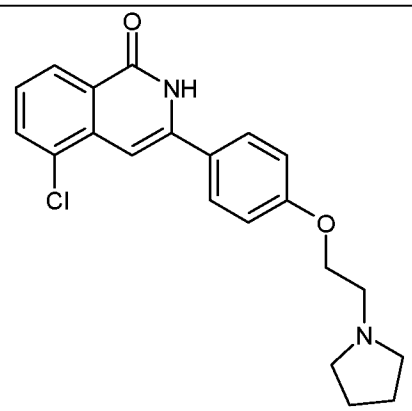
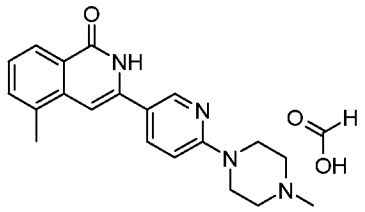
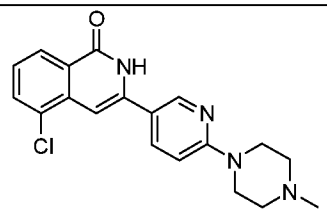
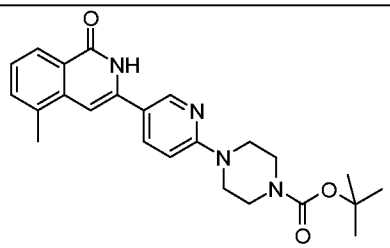
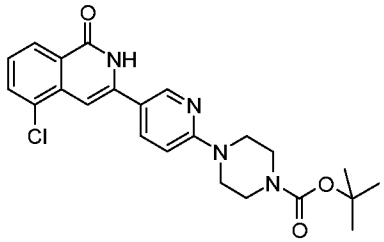
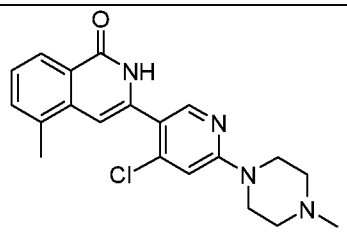
Table 10: *2H*-Isoquinolin-1-one Derivatives of Formula **4**

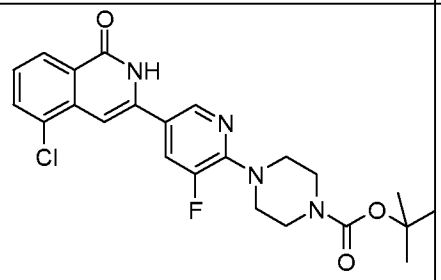
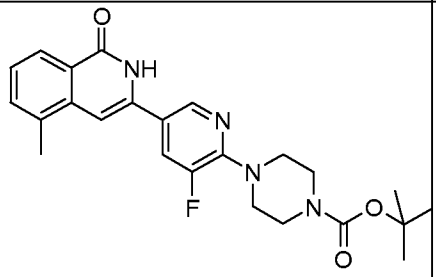
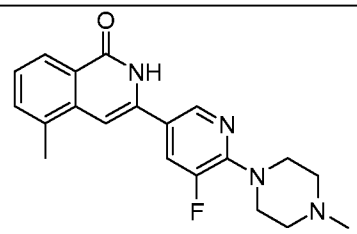
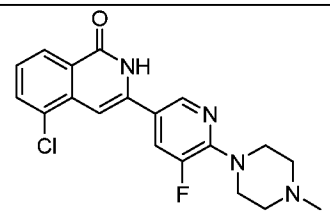
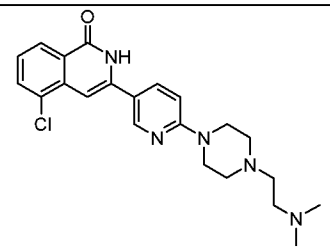
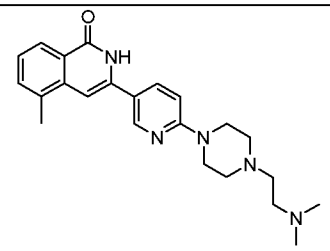
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-145	AnalpH2_MeOH_QC(Sunfire 1): Rt 8.08 min; m/z 510 $[M+1]^+$	142 mg, 31%, light beige solid
	IQ-101	AnalpH2_MeOH_QC: Rt 5.21 min; m/z 382 $[M+1]^+$	10 mg, 3 %, pale yellow solid
	IQ-102	AnalpH2_MeOH_QC: Rt 5.08 min; m/z 407 $[M+1]^+$	24 mg, 5%, beige solid
	IQ-103	AnalpH2_MeOH_QC: Rt 5.33 min; m/z 410 $[M+1]^+$	5 mg, 3%, white solid

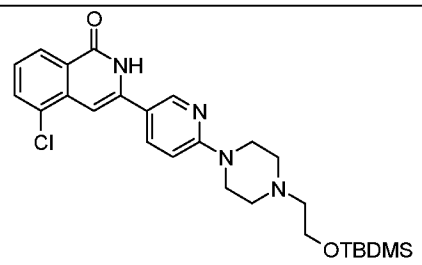
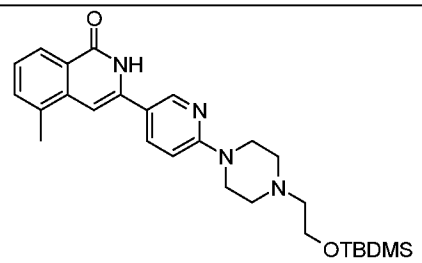
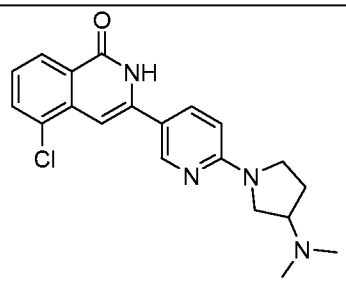
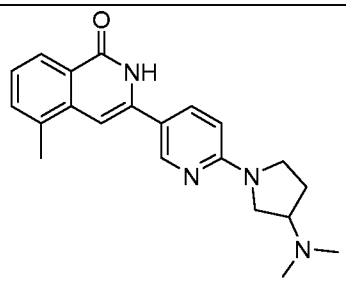
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-104	AnalpH2_MeOH_QC: Rt 4.93 min; m/z 362 $[M+1]^+$	27 mg, 9%, white solid ^{1}H NMR (400 MHz, DMSO-d_6): δ11.61 (br s, 1H), 8.09 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 7.3 Hz, 1H), 7.50 (d, J = 8.6 Hz, 2H), 7.4 (t, J = 7.8 Hz, 1H), 6.92 (s, 1H), 3.63 (br s, 2H), 3.38 (br s, 2H), 2.57 (s, 3H), 2.34 (br s, 4H), 2.21 (s, 3H).
	IQ-001	AnalpH2_MeOH_QC: Rt 8.49 min; m/z 279 $[M+1]^+$	143 mg, 64%, pale yellow solid
	IQ-013	AnalpH2_MeOH_QC: Rt 8.84 min; m/z 420 $[M+1]^+$	123 mg, 43%, yellow solid
	IQ-010	AnalpH2_MeOH_QC: Rt 9.14 min; m/z 440 $[M+1]^+$	231 mg, 60%, cream solid

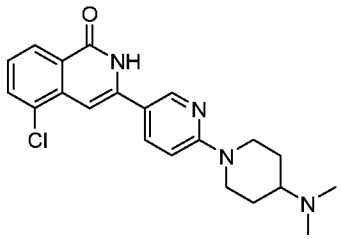
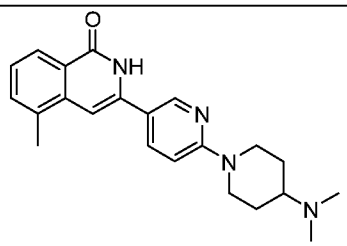
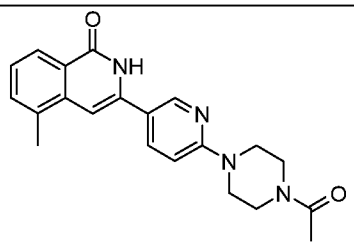
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-042	AnalpH2_MeOH_4min: Rt 5.21 min; m/z 349 $[M+1]^+$	46 mg, 26%, off-white solid
	IQ-041	AnalpH2_MeOH_4min: Rt 5.30 min; m/z 333 $[M+1]^+$	30 mg, 9%, off-white solid
	IQ-137	AnalpH2_MeOH_4min: Rt 5.55 min; m/z 388 $[M+1]^+$	12 mg, 6%, white solid
	IQ-131	AnalpH2_MeOH_QC: Rt 5.74 min; m/z 377 $[M+1]^+$	22 mg, 10%, pale brown gum
	IQ-132	AnalpH2_MeOH_QC: Rt 5.69 min; m/z 387 $[M+1]^+$	1.23 g, 86%, cream solid
	IQ-128	AnalpH2_MeOH_QC: Rt 5.59 min; m/z 343 $[M+1]^+$	86 mg, 32%, beige solid

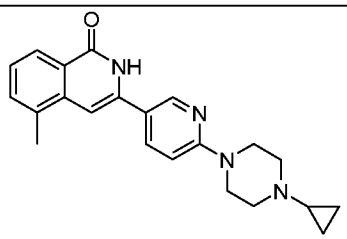
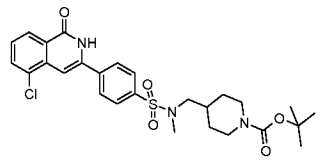
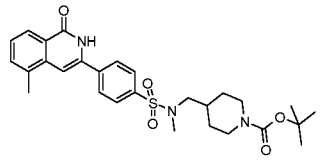
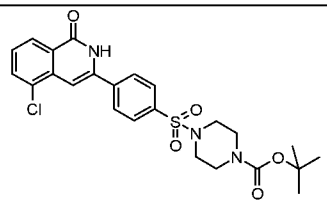
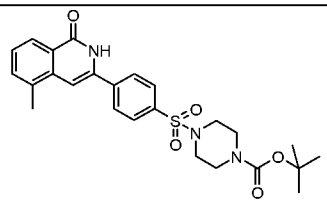
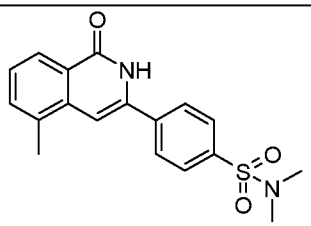
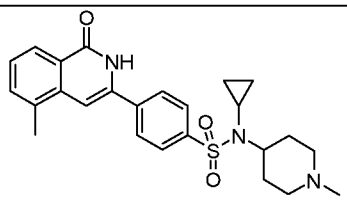
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-129	AnalpH2_MeOH_QC: Rt 5.21 min; m/z 327 $[M+1]^+$	135 mg, 52%, beige solid
	IQ-130	AnalpH2_MeOH_QC: Rt 5.27 min; m/z 323 $[M+1]^+$	101 mg, 40%, pale yellow solid
	IQ-133	AnalpH2_MeOH_QC: Rt 5.37 min; m/z 365 $[M+1]^+$	230 mg, 63%, white solid
	IQ-134	AnalpH2_MeOH_QC: Rt 5.53 min; m/z 349 $[M+1]^+$	42 mg, 24%, off-white solid

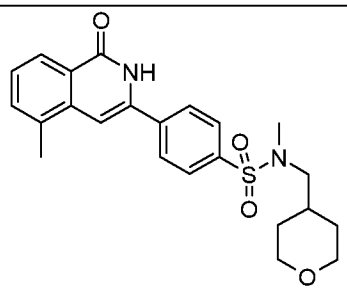
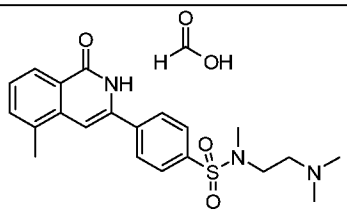
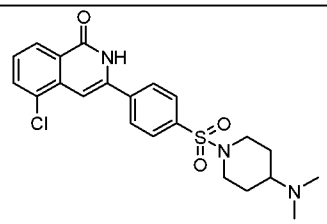
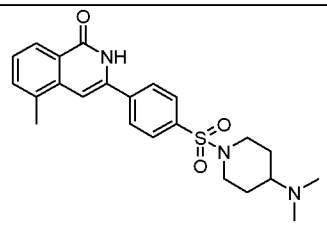
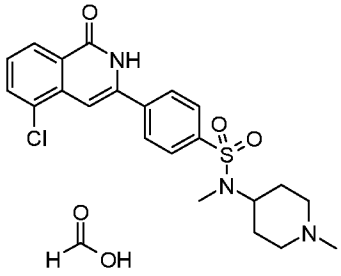
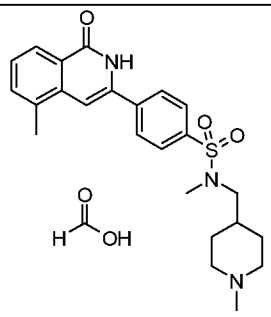
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-135	AnalpH2_MeOH_QC: Rt 8.84 min; m/z 369 $[M+1]^+$	40 mg, 22%, off-white solid
	IQ-003	AnalpH2_MeOH_QC: Rt 5.16 min; m/z 335 $[M+1]^+$	14 mg, 4%, off-white solid
	IQ-002-1	AnalpH2_MeOH_QC: Rt 5.45 min; m/z 355 $[M+1]^+$	196 mg, 84%, pale yellow solid
	IQ-153	AnalpH9_MeOH_QC: Rt 8.51 min; m/z 421 $[M+1]^+$	24 mg, 6%, yellow solid
	IQ-136	AnalpH2_MeOH_QC: Rt 8.79 min; m/z 441 $[M+1]^+$	126 mg, 29%, off-white solid
	IQ-144	AnalpH2_MeOH_QC: Rt 5.55 min; m/z 369 $[M+1]^+$	5.5 mg, 4%, white solid

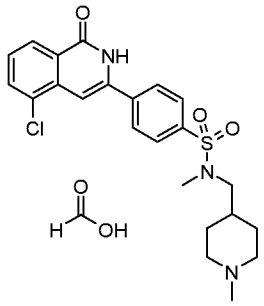
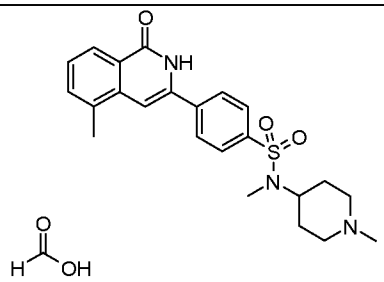
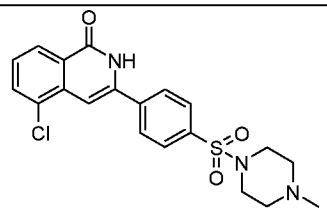
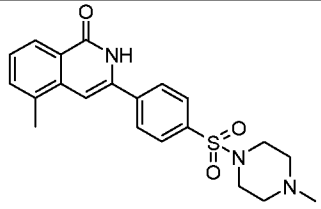
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-139	AnalpH2_MeOH_QC: Rt 9.37 min; m/z 459 $[M+1]^+$	139 mg, 34%, orange solid
	IQ-020	AnalpH2_MeOH_QC: Rt 9.03 min; m/z 439 $[M+1]^+$	63 mg, 15%, cream solid
	IQ-021	AnalpH2_MeOH_QC: Rt 5.37 min; m/z 353 $[M+1]^+$	8 mg, 3%, cream solid
	IQ-022	AnalpH2_MeOH_QC: Rt 5.69 min; m/z 373 $[M+1]^+$	56 mg, 23%, cream solid
	IQ-019	AnalpH2_MeOH_QC: Rt 5.59 min; m/z 412 $[M+1]^+$	49 mg, 26%, off-white solid
	IQ-018	AnalpH2_MeOH_QC: Rt 5.10 min; m/z 392 $[M+1]^+$	50 mg, 28%, pale yellow solid

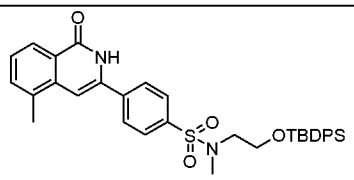
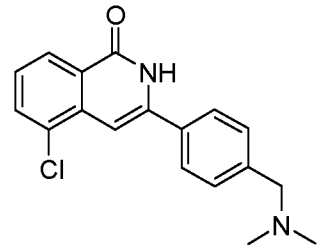
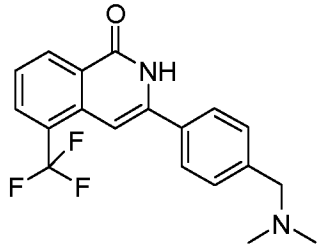
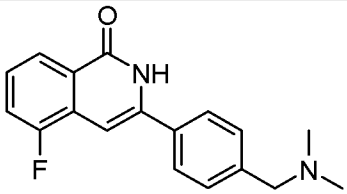
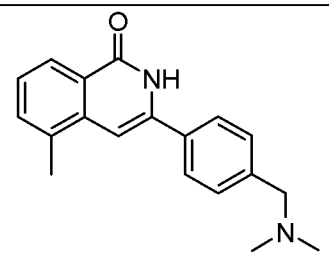
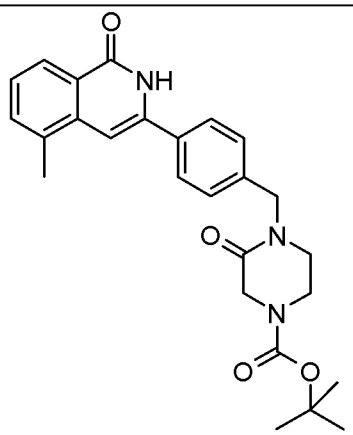
Compound	Code	Analytical Data	Mass, %Yield, State
		AnalpH2_MeOH_4min: Rt 2.68 min; m/z 499 $[M+1]^+$	222 mg, 99%, yellow solid
		AnalpH2_MeOH_4min: Rt 2.58 min; m/z 479 $[M+1]^+$	214 mg, 99%, orange solid
	IQ-009	AnalpH2_MeOH_QC: Rt 5.29 min; m/z 369 $[M+1]^+$	25.5 mg, 15%, tan solid
	IQ-008	AnalpH2_MeOH_QC: Rt 4.77 min; m/z 349 $[M+1]^+$	28 mg, 18%, pale yellow solid

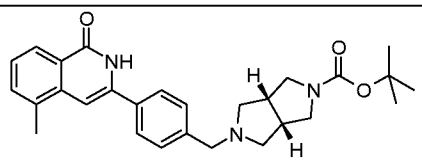
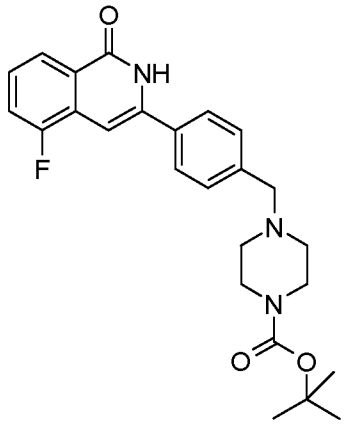
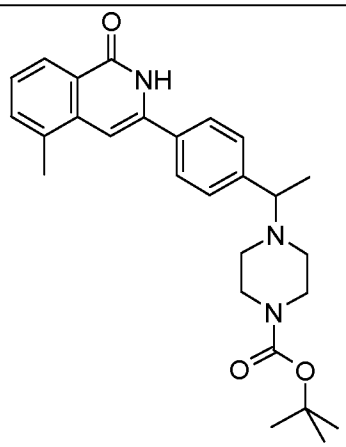
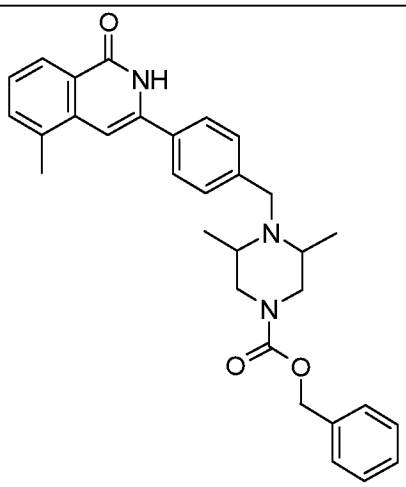
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-007	AnalpH2_MeOH_QC: Rt 5.51 min; m/z 384 $[M+1]^+$	72 mg, 42%, yellow solid ^{1}H NMR (400 MHz, DMSO-d_6): δ11.72 (br s, 1H), 8.54 (d, J = 2.8 Hz, 1H), 8.16 (dt, J = 7.6 Hz, 1H), 7.92 (dd, J = 9.1 Hz, 1H), 7.84 (dd, J = 7.6 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 6.82 (s, 1H), 4.4 (br d, J = 13.1 Hz, 2H), 2.91 (t, J = 11.9 Hz, 2H), 2.39-2.38 (m, 1H), 2.19 (s, 6H), 1.83 (br d, J = 12.6 Hz, 2H), 1.39-1.29 (m, 2H).
	IQ-006	AnalpH2_MeOH_QC: Rt 5.09 min; m/z 364 $[M+1]^+$	26 mg, 16%, pale yellow solid
	IQ-005	AnalpH2_MeOH_QC: Rt 7.39 min; m/z 363 $[M+1]^+$	24.5 mg, 8%, pale yellow solid

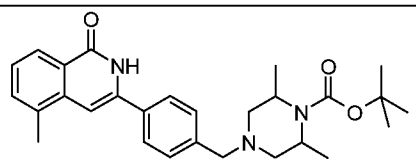
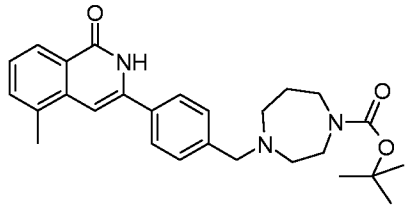
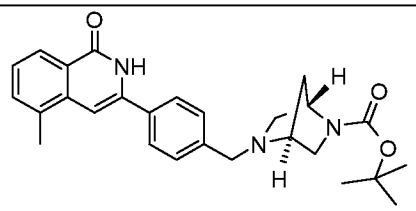
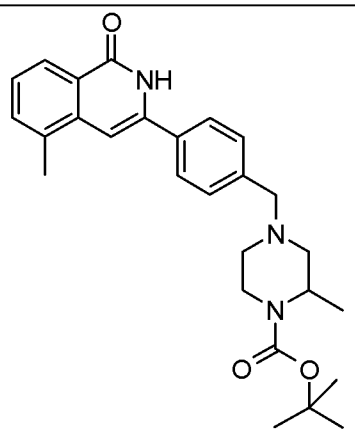
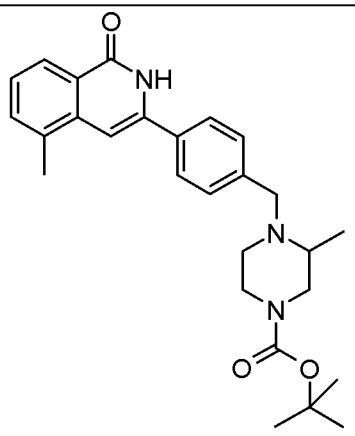
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-004	AnalpH2_MeOH_QC: Rt 5.45 min; m/z 362 $[M+1]^+$	53 mg, 33%, pale yellow solid
	IQ-114	AnalpH2_MeOH_QC(Sunfire 1): Rt 8.21 min; m/z 546 $[M+1]^+$	210 mg, 43%, white solid
	IQ-113	AnalpH2_MeOH_QC(Sunfire): Rt 7.98 min; m/z 526 $[M+1]^+$	230 mg, 45%, cream solid
	IQ-141	AnalpH2_MeOH_QC: Rt 8.71 min; m/z 504 $[M+1]^+$	189 mg, 57%, yellow solid
	IQ-140	AnalpH2_MeOH_QC: Rt 8.42 min; m/z 484 $[M+1]^+$	107 mg, 31%, yellow solid
	IQ-108	AnalpH2_MeOH_QC: Rt 7.56 min; m/z 343 $[M+1]^+$	32.5 mg, 12%, cream solid
	IQ-119	AnalpH2_MeOH_QC(1): Rt 5.71 min; m/z 452 $[M+1]^+$	83 mg, 20%, cream solid

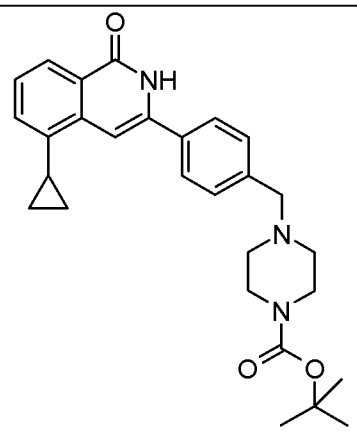
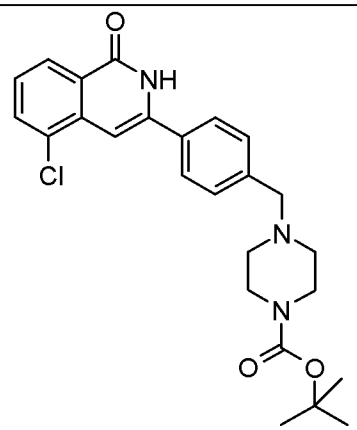
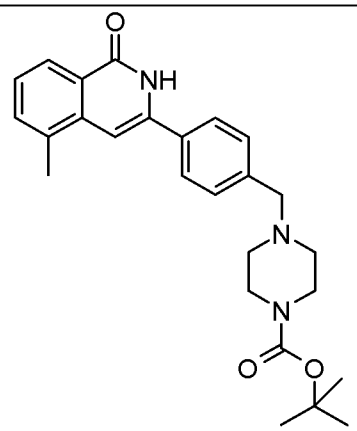
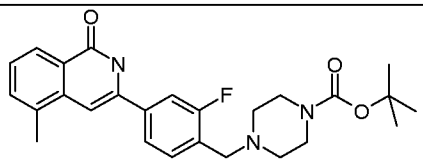
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-118	AnalpH2_MeOH_QC(1): Rt 7.98 min; m/z 427 $[M+1]^+$	120 mg, 28%, pale yellow solid
	IQ-117	AnalpH2_MeOH_QC(1): Rt 5.38 min; m/z 400 $[M+1]^+$	193 mg, 43%, pale yellow solid
	IQ-126	AnalpH2_MeOH_QC: Rt 5.85 min; m/z 446 $[M+1]^+$	163 mg, 56%, yellow yellow solid
	IQ-125	AnalpH2_MeOH_QC: Rt 5.55 min; m/z 426 $[M+1]^+$	104 mg, 33%, yellow yellow solid
	IQ-110	AnalpH2_MeOH_QC: Rt 5.87 min; m/z 446 $[M+1]^+$	130 mg, 48%, white solid
	IQ-111	AnalpH2_MeOH_QC: Rt 5.72 min; m/z 440 $[M+1]^+$	47 mg, 15%, white solid

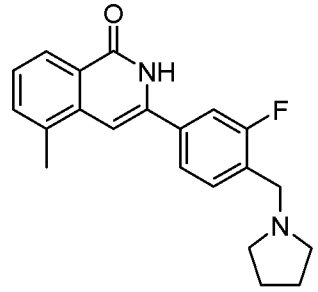
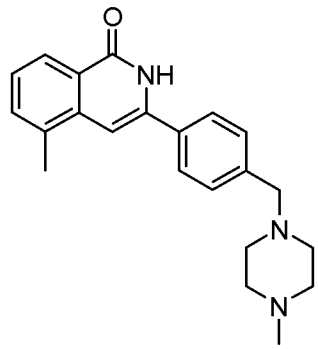
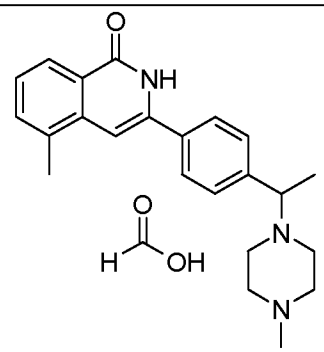
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-112	AnalpH2_MeOH_QC: Rt 6.02 min; m/z 461 $[M+1]^+$	52 mg, 18%, white solid ^{1}H NMR (400 MHz, DMSO-d_6): δ11.99 (br s, 1H), 8.23-8.21 (m, 1H), 8.21 (s, formic acid CHO, 0.4H), 8.06-8.03 (m, 2H), 7.92-7.88 (m, 3H), 7.54 (t, J = 7.6 Hz, 1H), 7.02 (s, 1H), 2.84 (d, J = 7.6 Hz, 2H), 2.80-2.74 (m, 2H), 2.70 (s, 3H), 2.18 (s, 3H), 1.92-1.86 (m, 2H), 1.65-1.50 (m, 2H), 1.59-1.50 (m, 1H), 1.21-1.10 (m, 2H).
	IQ-109	AnalpH2_MeOH_QC: Rt 5.58 min; m/z 426 $[M+1]^+$	10 mg, 4%, white solid
	IQ-122	AnalpH2_MeOH_QC: Rt 5.80 min; m/z 418 $[M+1]^+$	142 mg, 68%, cream solid
	IQ-121	AnalpH2_MeOH_QC: Rt 5.49 min; m/z 398 $[M+1]^+$	77 mg, 39%, cream solid

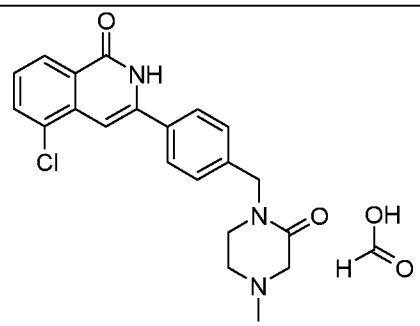
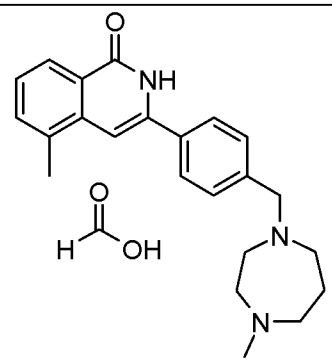
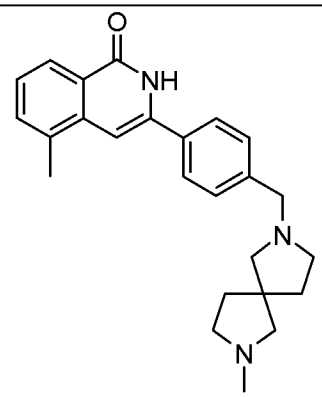
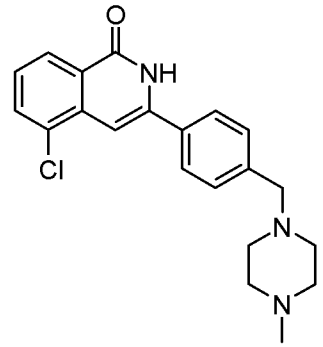
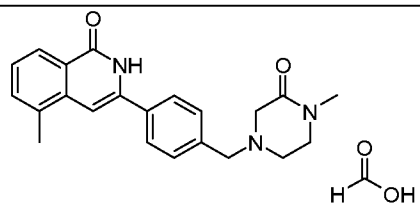
Compound	Code	Analytical Data	Mass, %Yield, State
		AnalpH2_MeOH_QC(1): Rt 9.80 min; m/z 611 $[M+1]^+$	3.8 mg, 2%, white solid
	IQ-031	AnalpH2_MeOH_QC: Rt 5.44 min; m/z 313 $[M+1]^+$	138 mg, 67%, cream solid
	IQ-030	AnalpH2_MeOH_QC: Rt 4.83 min; m/z 347 $[M+1]^+$	2 mg, 1% yellow solid
	IQ-032	AnalpH2_MeOH_QC: Rt 4.90 min; m/z 297 $[M+1]^+$	175.1 mg, 91% cream solid
	IQ-034	AnalpH2_MeOH_QC: Rt 4.94 min; m/z 293 $[M+1]^+$	133 mg, 58% pale yellow solid
	IQ-147	AnalpH2_MeOH_QC(1): Rt 8.32 min; m/z 448 $[M+1]^+$	36 mg, 8%, white solid

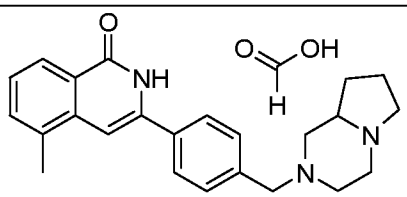
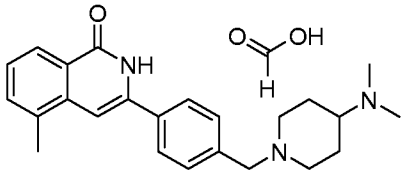
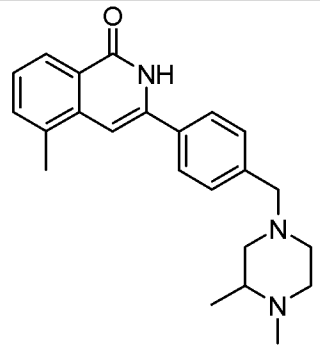
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-089	AnalpH2_MeOH_QC(1): Rt 6.02 min; m/z 460 $[M+1]^+$	11.8 mg, 31%, off-white foam
	IQ-069	AnalpH2_MeOH_QC(1): Rt 6.51 min; m/z 438 $[M+1]^+$	111 mg, 51%, pink solid
	IQ-066	AnalpH2_MeOH_QC(1): Rt 6.45 min; m/z 448 $[M+1]^+$	131 mg, 43%, cream solid
	IQ-064	AnalpH2_MeOH_QC(1): Rt 7.05 min; m/z 496 $[M+1]^+$	28 mg, 7.3%, white solid

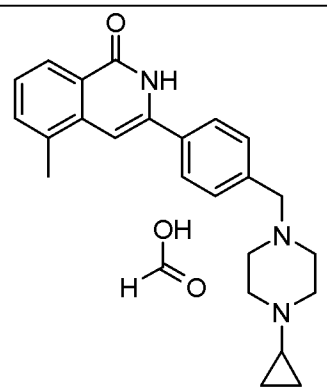
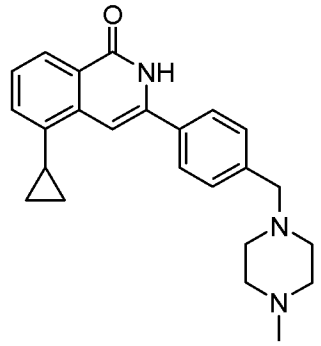
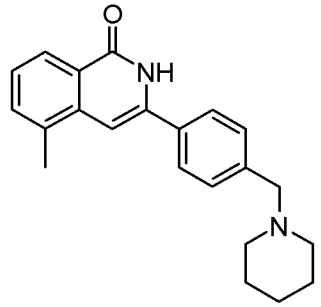
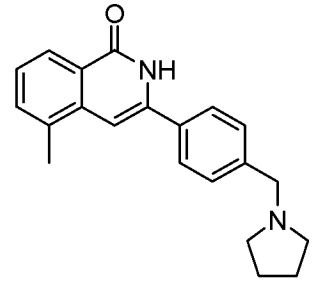
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-061	AnalpH2_MeOH_QC(1): Rt 8.89 min; m/z 462 $[M+1]^+$	180 mg, 46%, cream solid
	IQ-060	AnalpH2_MeOH_QC(1): Rt 6.03 min; m/z 448 $[M+1]^+$	160 mg, 38%, off-white solid
	IQ-085	AnalpH2_MeOH_QC: Rt 6.01 min; m/z 446 $[M+1]^+$	37 mg, 18%, white solid
	IQ-143	AnalpH2_MeOH_QC: Rt 7.21 min; m/z 448 $[M+1]^+$	98 mg, 30%, white solid
	IQ-142	AnalpH2_MeOH_QC: Rt 6.42 min; m/z 448 $[M+1]^+$	164 mg, 50%, white solid

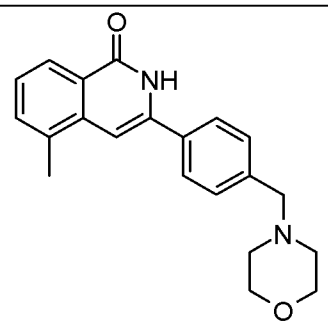
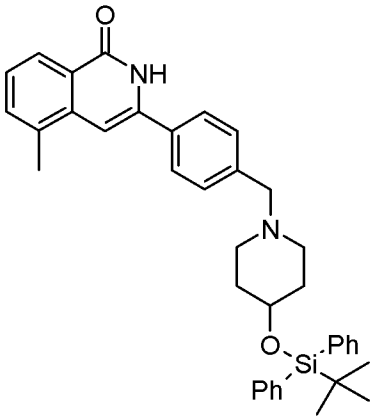
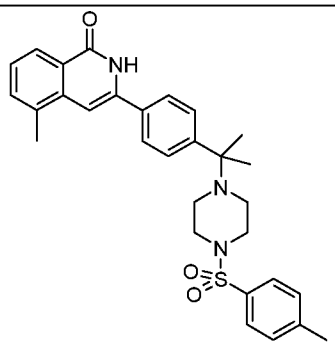
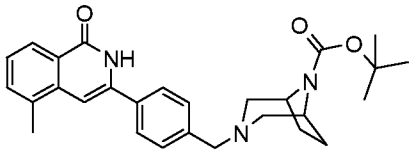
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-047	AnalpH2_MeOH_QC: Rt 6.82 min; m/z 460 $[M+1]^+$	38 mg, 16%, white solid
	IQ-044	AnalpH2_MeOH_QC: Rt 6.91 min; m/z 454 $[M+1]^+$	138 mg, 46%, white solid
	IQ-040	AnalpH2_MeOH_QC: Rt 6.41 min; m/z 434 $[M+1]^+$	395 mg, 46%, white solid
	IQ-058	AnalpH2_MeOH_QC(1): Rt 7.21 min; m/z 452 $[M+1]^+$	120 mg, 39%, pale yellow solid

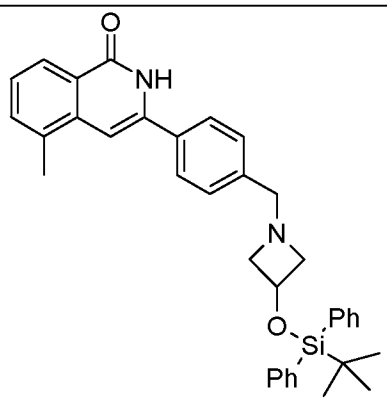
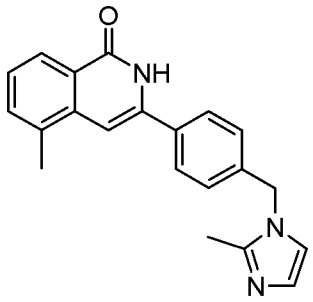
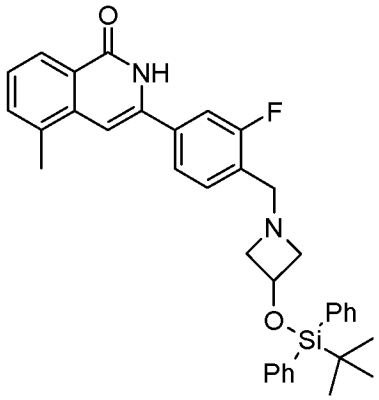
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-039	AnalpH2_MeOH_QC: Rt 5.23 min; m/z 337 $[M+1]^+$	29 mg, 11%, pale yellow solid
	IQ-038	AnalpH2_MeOH_QC: Rt 5.47 min; m/z 348 $[M+1]^+$	615 mg, 59%, white solid ^{1}H NMR (400 MHz, DMSO-d_6): δ11.56 (br s, 1H), 8.07 (d, J = 8.1 Hz, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 6.8 Hz, 1H), 7.41 (d, J = 8.3 Hz, 2H), 7.37 (t, J = 7.6 Hz, 1H), 6.85 (s, 1H), 3.51 (s, 2H), 2.56 (s, 3H), 2.33 (br s, 8H), 2.16 (s, 3H).
	IQ-048	AnalpH2_MeOH_QC: Rt 5.77 min; m/z 362 $[M+1]^+$	44 mg, 15%, cream solid

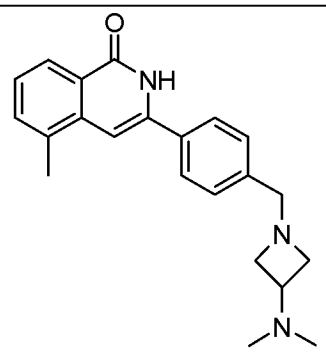
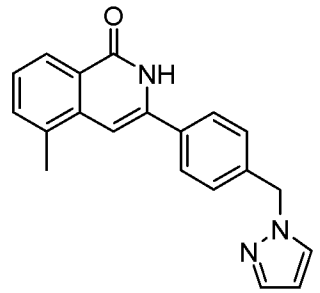
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-056	AnalpH9_MeOH_QC(Sunfire 1): Rt 7.22 min; m/z 382 $[M+1]^+$	16 mg, 4%, light beige solid
	IQ-065	AnalpH2_MeOH_QC(1): Rt 4.49 min; m/z 362 $[M+1]^+$	14 mg, 5%, cream solid
	IQ-088	AnalpH2_MeOH_QC(Sunfire): Rt 2.93 min; m/z 388 $[M+1]^+$	12 mg, 13%, white solid
	IQ-043	AnalpH2_MeOH_QC: Rt 5.75 min; m/z 368 $[M+1]^+$	92 mg, 38%, white solid
	IQ-054	AnalpH2_MeOH_QC(Sunfire): Rt 6.13 min; m/z 362 $[M+1]^+$	19 mg, 6%, pale orange solid

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-087	AnalpH2_MeOH_QC: Rt 4.69 min; m/z 374 $[M+1]^+$	17 mg, 16%, orange solid
	IQ-053	AnalpH2_MeOH_QC: Rt 4.09 min; m/z 376 $[M+1]^+$	14 mg, 3%, white solid ^{1}H NMR (400 MHz, DMSO-d_6): δ11.53 (br s, 1H), 8.30 (s, formic acid CHO, 0.5H), 8.07 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 6.8 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.0 Hz, 1H), 6.85 (s, 1H), 3.50 (s, 2H), 2.86-2.83 (m, 2H), 2.56 (s, 3H), 2.18 (s, 6H), 2.12-2.04 (m, 1H), 1.98-1.92 (m, 2H), 1.74-1.71 (m, 2H), 1.44-1.34 (m, 2H).
	IQ-052	AnalpH2_MeOH_QC: Rt 5.70 min; m/z 362 $[M+1]^+$	37 mg, 21%, white solid

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-050	AnalpH2_MeOH_QC: Rt 5.60 min; m/z 374 $[M+1]^+$	9 mg, 8.5%, beige solid
	IQ-046	AnalpH2_MeOH_QC: Rt 5.81 min; m/z 374 $[M+1]^+$	154 mg, 32%, yellow yellow solid
	IQ-037	AnalpH2_MeOH_QC: Rt 5.27 min; m/z 665 $[2M+1]^+$	79 mg, 30%, beige solid
	IQ-036	AnalpH2_MeOH_QC: Rt 5.12 min; m/z 319 $[M+1]^+$	172 mg, 68%, yellow/orange solid

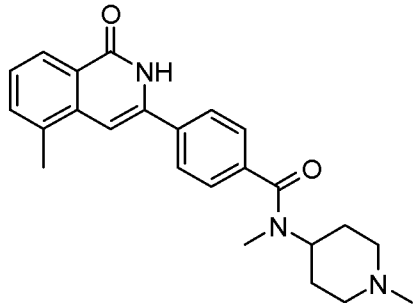
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-035	AnalpH2_MeOH_QC: Rt 5.11 min; m/z 335 $[M+1]^+$	51 mg, 19%, white solid
		AnalpH2_MeOH_4min(1): Rt 2.86 min m/z 587$[M+1]^+$.	213 mg, 46%, white solid
	IQ-148	AnalpH2_MeOH_QC(1): Rt 7.99 min m/z 516$[M+1]^+$.	34 mg (29%) White solid
	IQ-155	AnalpH2_MeOH_QC: Rt 7.77 min m/z 460$[M+1]^+$.	32 mg, 23%, white solid

Compound	Code	Analytical Data	Mass, %Yield, State
	Intermediate for IQ-167	AnalpH2_MeOH_4min(3): Rt 2.77 min; m/z 559 $[M+1]^+$	210 mg, 89%, off-white solid
	IQ-168	AnalpH2_MeOH_QC(2): Rt 4.74 min; m/z 330 $[M+1]^+$	8.2 mg, 52 %, pale yellow solid ^{1}H NMR (400 MHz, DMSO-d_6): δ11.59 (br s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 6.8 Hz, 1H), 7.48 (s, 1H), 7.40-7.36 (m, 3H), 7.24 (s, 1H), 6.87 (s, 1H), 5.35 (s, 2H), 2.56 (s, 3H), 2.45 (s, 3H).
	Intermediate for IQ-169	AnalpH2_MeOH_4min(3): Rt 2.89 min; m/z 577 $[M+1]^+$	35 mg, 54%, cream solid

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-174	AnalpH2_MeOH_QC(1): Rt 4.77 min; m/z 348 $[M+1]^+$	119.5 mg, 43 %, off-white solid
	IQ-182	AnalpH2_MeOH_QC(2): Rt 7.52 min; m/z 316 [M+1]+	61 mg, 10 % off-white solid ^{1}H NMR (400 MHz, DMSO-d_6): δ11.57 (br s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 7.2 Hz, 1H), 7.49 (d, J = 1.6 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 6.84 (s, 1H), 6.30 (t, J = 2.0 Hz, 1H), 5.41 (s, 2H), 2.55 (s, 3H).

Scheme A, Step B (Protocol 2): Synthesis of Boc-protected *2H*-isoquinolin-1-one Derivatives of formula **4** via Reverse Addition Protocol

N-Methyl-4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-*N*-(1-methyl-piperidin-4-yl)-benzamide (IQ-100)



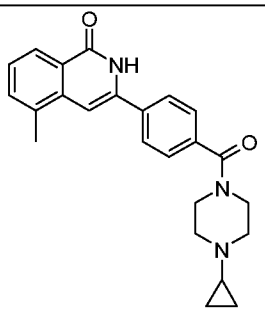
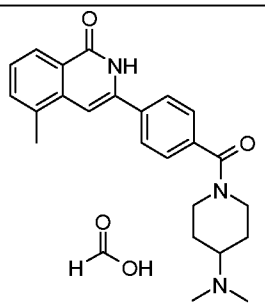
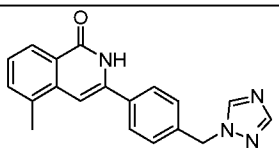
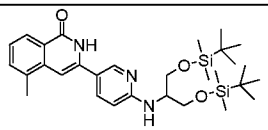
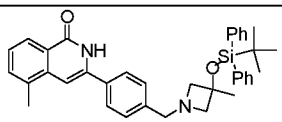
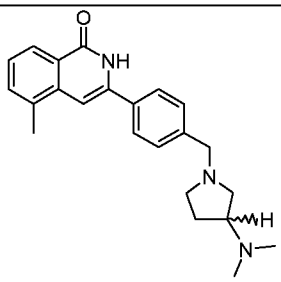
To a solution of *N,N*-diethyl-2,3-dimethyl-benzamide (578 mg, 2.82 mmol) in anhydrous THF (3 mL) under N_2 at -78 °C was added dropwise *n*-BuLi (2.5M in n-hexanes, 2.4 mL, 5.92 mmol) to give a deep red solution. The reaction mixture was stirred at -78 °C for 30 minutes. The reaction mixture was transferred dropwise, via syringe, to a reaction vessel containing 4-cyano-*N*-methyl-*N*-(1-methyl-piperidin-4-yl)-benzamide (725 mg, 2.82 mmol) in anhydrous THF (5 mL) at -78 °C and under N_2,. The reaction mixture was stirred at -78 °C for 3.5 h. Water (10 mL) was added and the reaction mixture was extracted with EtOAc (10 mL) and CH_2Cl_2 (10 mL). The combined organic layers concentrated *in vacuo* and the resultant solid was triturated with 2:1 isohexane/EtOAc, filtered and dried *in vacuo*. The crude material was purified by silica gel column chromatography, eluting with CH_2Cl_2 and increasing the polarity to 15% MeOH/CH_2Cl_2 to afford *N*-methyl-4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-*N*-(1-methyl-piperidin-4-yl)-benzamide as a white solid (487 mg, 44%).

^{1}H NMR (400 MHz, DMSO-d_6): δ11.80-11.41 (br s, 1H), 8.10 (d, J = 8 Hz, 1H), 7.89 (d, J = 8 Hz, 2H), 7.58 (d, J = 7 Hz, 1H), 7.48 (d, J = 8 Hz, 2H), 7.39 (t, J = 7 Hz, 1H), 6.93 (s, 1H), 3.31 (s, 3H), 2.96-2.70 (m, 5H), 2.58 (s, 3H), 2.23-1.96 (m, 3H), 1.93-1.71 (br s, 2H), 1.71-1.53 (br s, 2H).

AnalpH2_MeOH_QC(Sunfire): Rt 4.29 min; m/z 390 $[M+1]^+$.

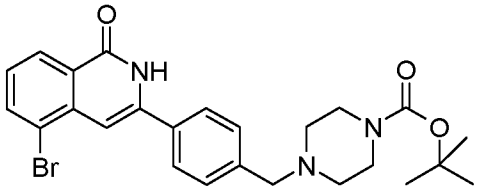
The following *2H*-isoquinolin-1-one derivatives are prepared using analogous procedures.

Table 11: *2H*-isoquinolin-1-one derivatives of Formula **4**

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-105	AnalpH2_MeOH_QC(1): Rt 4.97 min; m/z 388 $[M+1]^+$	2.7 mg, 3%, white solid
	IQ-106	AnalpH2_MeOH_QC(1): Rt 4.98 min; m/z 390 $[M+1]^+$	4 mg, 2%, white solid
	IQ-171	AnalpH2_MeOH_QC(1): Rt 7.41 min; m/z 317 $[M+1]^+$	8.5 mg, 4 %, white solid
	Intermediate for IQ-219	AnalpH2_MeOH_4min(3) : Rt 2.59 min; m/z 554 $[M+1]^+$	Used in next step as crude material
	Intermediate for IQ-172	AnalpH2_MeOH_4min(3) : Rt 2.86 min; m/z 573 $[M+1]^+$	63 mg, 27 %, white solid
	IQ-173	AnalpH2_MeOH_QC(1): Rt 4.46 min; m/z 363 $[M+1]^+$	41 mg, 23 %, white solid

Scheme A, Step B (Protocol 3): Synthesis of Boc-protected *2H*-isoquinolin-1-one Derivatives of formula **4** (LDA Protocol)

4-[4-(5-Bromo-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester (IQ-149)

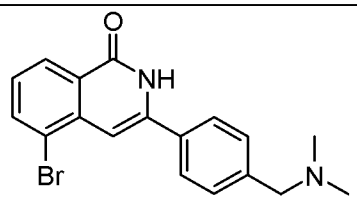
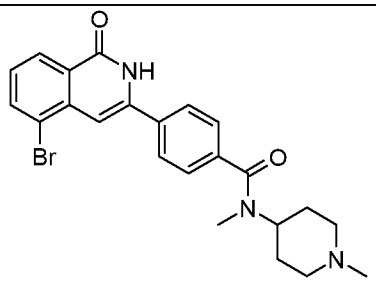


To a stirred solution of *N,N*-diisopropylamine (1.56 mL, 11.10 mmol) in THF (5 mL) under N_2 at -78 °C was added *n*-BuLi (2.5M in hexanes) (4.44 mL, 11.10 mmol) and the reaction stirred at -78 °C for 20 min, after which time a solution of 3-bromo-*N,N*-diethyl-2-methyl-benzamide (1 g, 3.70 mmol) in THF (5 mL) was added, and the reaction stirred at -78 °C for 30 minutes. A solution of 4-(4-cyano-benzyl)-piperazine-1-carboxylic acid *tert*-butyl ester (1.15g, 3.70 mmol) in THF (5 mL) was added and the reaction stirred at -78 °C for 2 h. The reaction was quenched with ice and water, EtOAc added and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography, eluting with isohexane and increasing the polarity to 100% EtOAc to afford 4-[4-(5-bromo-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzyl]-piperazine-1-carboxylic acid *tert*-butyl ester as a cream solid (1.22 g, 66%).

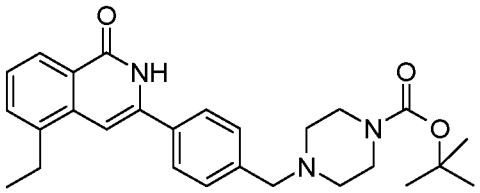
AnalpH2_MeOH_QC: Rt 6.94 min; m/z 498 $[M+1]^+$.

The following *2H*-isoquinolin-1-one derivatives are prepared using analogous procedures.

Table 12: *2H*-isoquinolin-1-one derivatives of Formula **4**

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-033	AnalpH2_MeOH_QC: Rt 5.40 min; m/z 357 $[M+1]^+$	56 mg, 15% cream solid
	IQ-156	AnalpH2_MeoH_4min: Rt 1.85 min; m/z 454 $[M+1]^+$.	122 mg, 71%, pale yellow solid

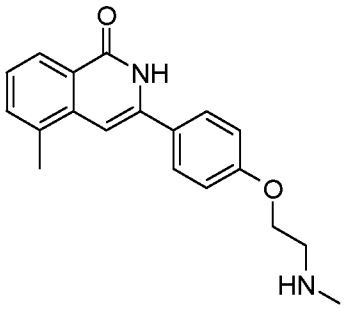
4-[4-(5-Ethyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzyl]-piperazine-1-carboxylic acid *tert*-butyl ester (IQ-151)



To a stirred solution of 4-[4-(5-Bromo-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzyl]-piperazine-1-carboxylic acid *tert*-butyl ester (200 mg, 0.4 mmol) in anhydrous THF (4 mL) under N_2 was added dichlorobis(tri-o-tolylphosphine)palladium(II) (14 mg, 0.02 mmol), $CeCl_3$ (99 mg, 0.4 mmol) and $AlEt_3$ (1M in hexanes, 1.5 mL, 1.2 mmol) and the reaction stirred at RT for 4 h. The reaction was quenched with ice, diluted with 0.5M aqueous Rochelle's salts (30 mL) and extracted with EtOAc (3 x 40 mL). The combined organics were washed with Rochelle's salts (2 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* and the crude residue purified by reverse phase preparative HPLC-MS to afford 4-[4-(5-ethyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzyl]-piperazine-1-carboxylic acid *tert*-butyl ester as an orange solid (83 mg, 61%).

AnalpH2_MeOH_QC(1):Rt 5.13min; m/z 446 $[M+1]^+$.

5-Methyl-3-[4-(2-methylamino-ethoxy)-phenyl]-*2H*-isoquinolin-1-one (IQ-127)

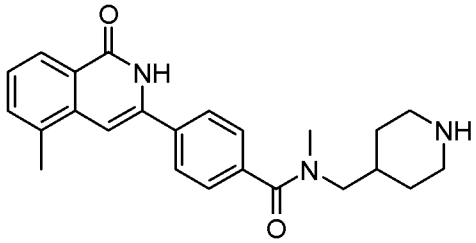


1-Chloro-ethyl chloroformate (97 mg, 0.68 mmol) in 1,2-dichloroethane (0.3 mL) was added to a solution of 3-[4-(2-dimethylamino-ethoxy)-phenyl]-5-methyl-*2H*-isoquinolin-1-one (35 mg, 0.109 mmol) in 1,2-dichloroethane (0.6 mL) at cooled to 0 °C, and stirred for 10 min. The reaction mixture was irradiated using a microwave (300W, 180 °C, 15 min) then concentrated *in vacuo* and EtOH (0.8 mL) added. The reaction mixture was heated at 80 °C for 15 h, allowed to cool and passed through a SCX-2 cartridge (1 g), eluting with 0.5M NH_3 in MeOH. The crude material was concentrated *in vacuo* and purified by reverse phase preparative HPLC-MS to afford 5-methyl-3-[4-(2-methylamino-ethoxy)-phenyl]-*2H*-isoquinolin-1-one as a white solid (4 mg, 12%).

AnalpH2_MeOH_QC: Rt 5.43 min; m/z 309 $[M+1]^+$.

Scheme A, Step C (Protocol 1): Synthesis of *2H*-isoquinolin-1-one Derivatives of formula **5** (via BOC deprotection)

N-Methyl-4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-*N*-piperidin-4-ylmethyl-benzamide (IQ-093)



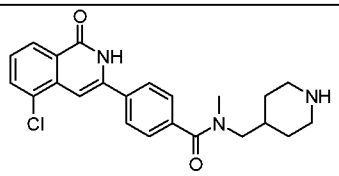
To 4-({methyl-[4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzoyl]-amino}-methyl)-piperidine-1-carboxylic acid *tert*-butyl ester (170 mg, 0.35 mmol) in CH_2Cl_2 (5 mL) was added 4M HCl/dioxane (2 mL) and the reaction mixture stirred at RT for 4 h. The solvent was removed *in vacuo* and the crude product purified by reverse phase preparative HPLC-MS to obtain *N*-methyl-4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-*N*-piperidin-4-ylmethyl-benzamide as a pale orange solid (44 mg, 33%).

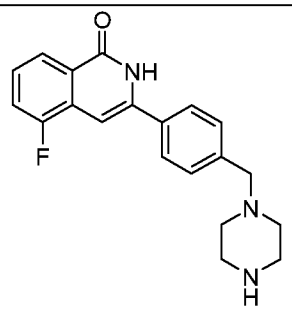
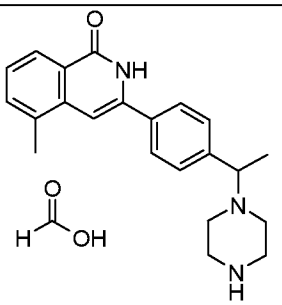
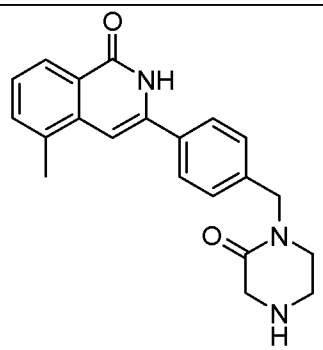
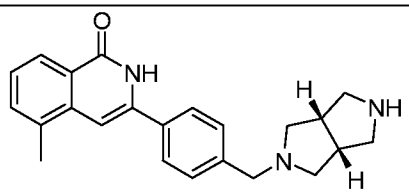
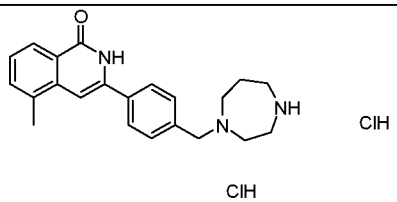
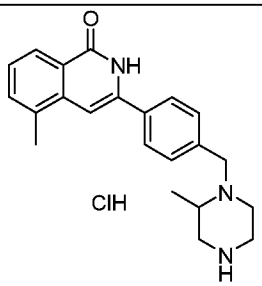
^{1}H NMR (400 MHz, DMSO-d_6): δ8.09 (d, *J* = 8 Hz, 1H), 7.89 (d, *J* = 8 Hz, 2H), 7.57 (d, *J* = 7 Hz, 1H), 7.50 (br d, *J* = 8 Hz, 1H), 7.45 (br d, *J* = 8 Hz, 1H), 6.92 (s, 1H), 3.35 (d, *J* = 7 Hz, 1H), 3.15 (d, *J* = 7 Hz, 1H), 2.97 (s, 2H), 2.92 (s, 3H), 2.84-2.82 (m, 1H), 2.51 (s, 3H), 2.46-2.36 (m, 1H), 1.84 (s, 0.5H), 1.77 (s, 0.5H), 1.61 (d, *J* = 10 Hz, 1H), 1.42 (d, *J* = 10 Hz, 1H), 1.11-1.08 (m, 1H), 0.70-0.68 (m, 1H).

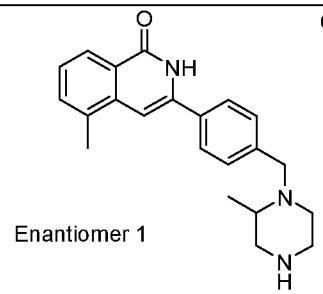
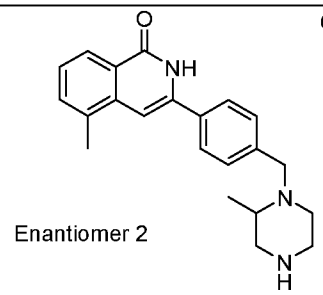
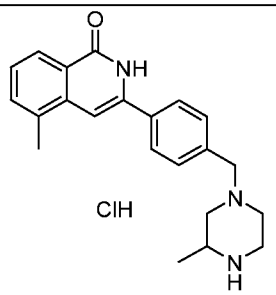
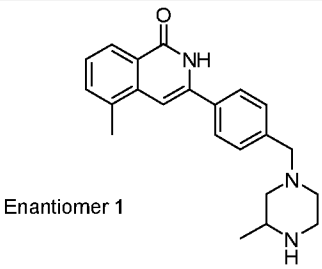
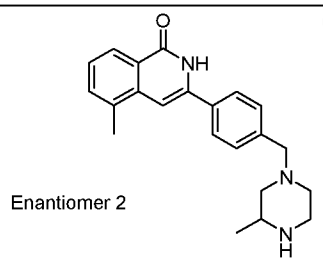
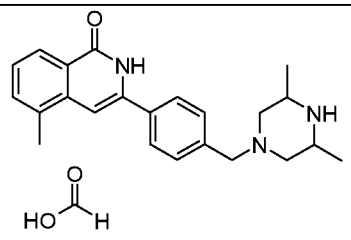
AnalpH2_MeOH_QC(Sunfire1): Rt 4.49 min; m/z 390 $[M+1]^+$.

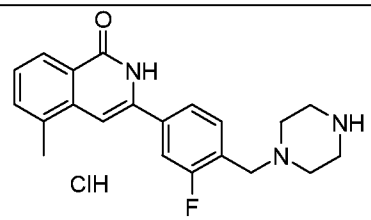
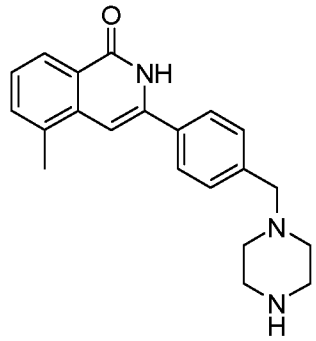
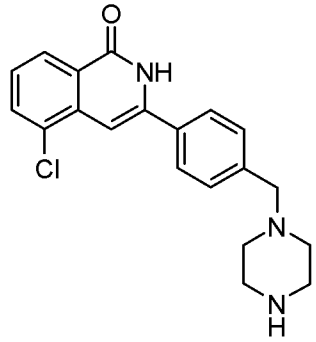
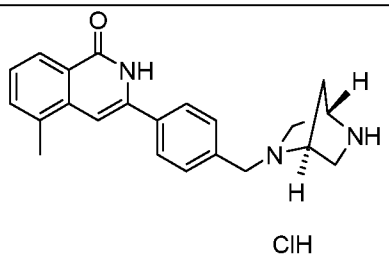
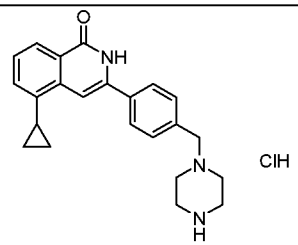
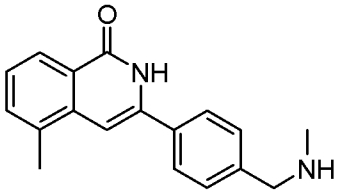
The following *2H*-isoquinolin-1-one derivatives are prepared using analogous procedures.

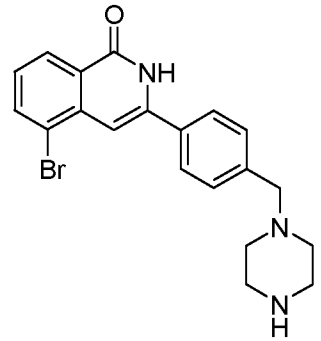
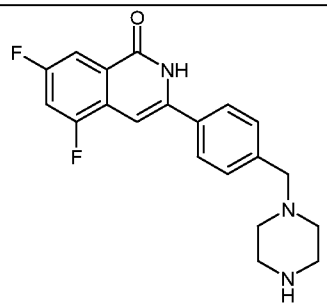
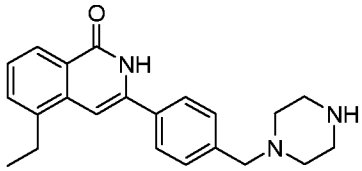
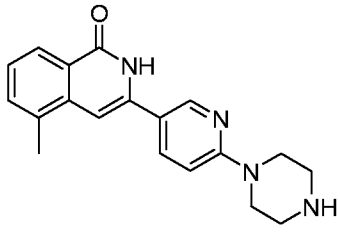
Table 13: *2H*-isoquinolin-1-one Formula **5**

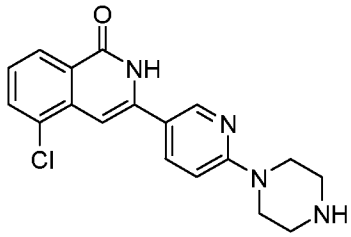
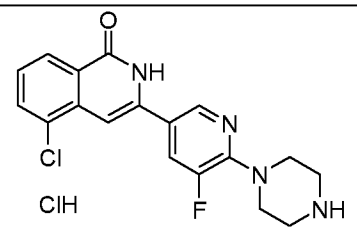
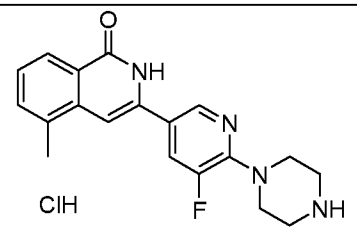
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-094	AnalpH2_MeOH_QC(Sunfire1): Rt 4.82 min; m/z 410 $[M+1]^+$	66 mg, 60%, white solid

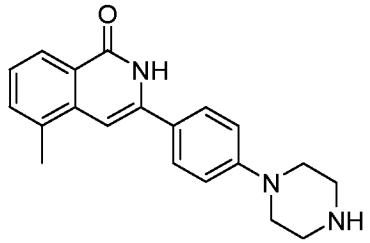
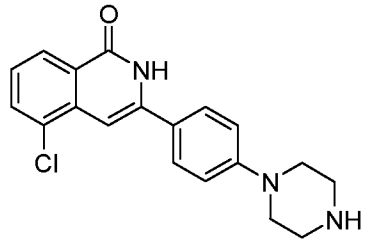
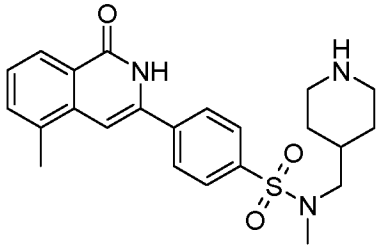
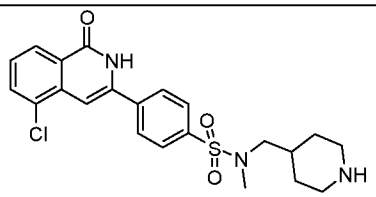
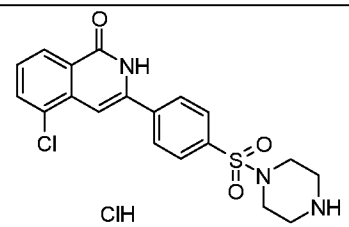
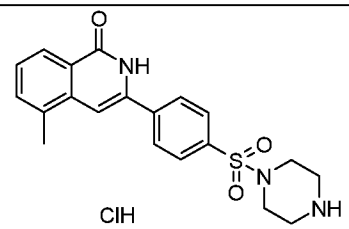
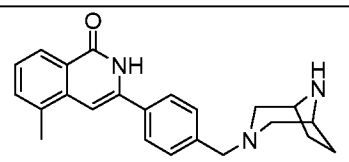
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-070	AnalpH2_MeOH_Q C(1): Rt 5.19 min; m/z 338 $[M+1]^+$	63 mg, 94%, pale pink solid
	IQ-067	AnalpH2_MeOH_Q C(1): Rt 5.57 min; m/z 348 $[M+1]^+$	14 mg, 12%, orange solid
	IQ-073	AnalpH2_MeOH_Q C(1): Rt 5.32 min; m/z 348 $[M+1]^+$	7 mg, 28%, white solid
	IQ-090	AnalpH2_MeOH_Q C(1): Rt 3.96 min; m/z 360 $[M+1]^+$	48 mg, 33%, pale yellow solid
	IQ-062	AnalpH2_MeOH_Q C(1): Rt 4.23 min; m/z 348 $[M+1]^+$	211 mg, 100%, pale orange solid
	IQ-051-1	AnalpH2_MeOH_Q C: Rt 5.65 min; m/z 348 $[M+1]^+$	108 mg, 77%, cream solid

Compound	Code	Analytical Data	Mass, %Yield, State
 Chiral Enantiomer 1	IQ-051-2	AnalpH2_MeOH_QC(1): Rt 5.47 min; m/z 348 $[M+1]^+$	10.2 mg, 35% recovery, off-white solid; obtained via Chiral_Method_2
 Chiral Enantiomer 2	IQ-051-3	AnalpH2_MeOH_QC(1): Rt 5.47 min; m/z 348 $[M+1]^+$	8.3 mg, 29% recovery, off-white solid; obtained via Chiral_Method_2
 ClH	IQ-084-3	AnalpH2_MeOH_QC: Rt 5.61 min; m/z 348 $[M+1]^+$	34 mg, 42%, cream solid
 Chiral Enantiomer 1	IQ-084-1	AnalpH2_MeOH_QC(Sunfire1): Rt 4.67 min; m/z 348 $[M+1]^+$	4.5 mg, 13% recovery, white solid; obtained via Chiral_Method_1
 Chiral Enantiomer 2	IQ-084-2	AnalpH2_MeOH_QC(Sunfire1): Rt 4.66 min; m/z 348 $[M+1]^+$	3.5 mg, 11% recovery, white solid; obtained via Chiral_Method_1
	IQ-063	AnalpH2_MeOH_QC(1): Rt 5.56 min; m/z 362 $[M+1]^+$	87 mg, 55%, cream solid

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-059	AnalpH2_MeOH_QC(1): Rt 5.51 min; m/z 352 $[M+1]^+$	112 mg, 100%, pale orange solid
	IQ-082	AnalpH2_MeOH_QC: Rt 5.36 min; m/z 334 $[M+1]^+$	107 mg, 38%, white solid
	IQ-083	AnalpH2_MeOH_QC: Rt 5.87 min; m/z 354 $[M+1]^+$	115 mg, 97%, yellow yellow solid
	IQ-086	AnalpH2_MeOH_QC: Rt 4.77 min; m/z 346 $[M+1]^+$	22 mg, 72%, white solid
	IQ-049	AnalpH2_MeOH_QC: Rt 5.91 min; m/z 360 $[M+1]^+$	25 mg, 96%, off-white solid
	IQ-029	AnalpH2_MeOH_QC: Rt 5.00 min; m/z 279 $[M+1]^+$	9 mg, 24%, off-white solid

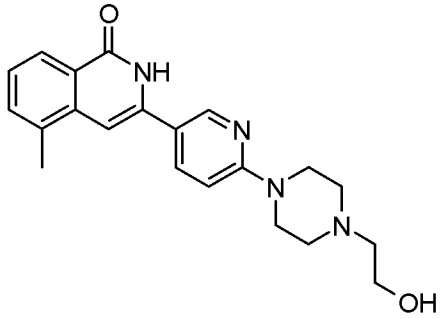
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-150	AnalpH2_MeOH_QC(1): Rt 5.83 min; m/z 400 $[M+1]^+$	367 mg, 56%, cream solid
	IQ-158	AnalpH2_MeOH_QC: Rt 5.62 min; m/z 356 $[M+1]^+$	22 mg, 65% white solid
	IQ-081	AnalpH2_MeOH_QC(1): Rt 5.71 min; m/z 348 $[M+1]^+$	29 mg, 48%, pale peach solid
	IQ-028-1	AnalpH2_MeOH_QC(Sunfire1): Rt 4.29 min; m/z 321 $[M+1]^+$	212 mg, 45%, orange solid ^{1}H NMR (400 MHz, DMSO-d_6): δ11.42 (br s, 1H), 8.58 (d, J = 2.3 Hz, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.97 (dd, J = 8.8, 1.0Hz, 1H), 7.53 (d, J = 6.8 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 6.9 (d, J = 8.8 Hz, 1H), 6.77 (s, 1H), 3.53 (t, J = 5.1 Hz, 4H), 2.81 (t, J = 5.1 Hz, 4H), 2.54 (s, 3H).

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-027	AnalpH2_MeOH_QC(Sunfire1): Rt 4.73 min; m/z 341 $[M+1]^+$	460 mg, 66%, pale yellow solid ^{1}H NMR (400 MHz, DMSO-d_6): δ8.54 (d, J = 2.2 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.93 (dd, J = 9.1, 2.5 Hz, 1H), 7.85 (dd, J = 7.6 Hz, 1.0 1H), 7.43 (t, J = 7.8 Hz, 1H), 6.90 (d, J = 9.1 Hz, 1H), 6.83 (s, 1H), 3.54-3.52 (m, 4H), 2.80-2.78 (m, 4H).
	IQ-024	AnalpH2_MeOH_QC: Rt 5.74 min; m/z 359 $[M+1]^+$	82 mg, 67%, pale orange solid
	IQ-023	AnalpH2_MeOH_QC: Rt 5.41 min; m/z 339 $[M+1]^+$	51 mg, 97%, yellow solid

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-016	AnalpH2_MeOH_QC: Rt 5.35 min; m/z 320 $[M+1]^+$	59 mg, 41%, beige solid
	IQ-014	AnalpH2_MeOH_QC: Rt 5.65 min; m/z 340 $[M+1]^+$	20 mg, 10%, yellow yellow solid
	IQ-115	AnalpH2_MeOH_QC(Sunfire1): RT 4.81 min; m/z 426 $[M+1]^+$.	60 mg, 32%, cream solid
	IQ-116	AnalpH2_MeOH_QC(Sunfire1): RT 5.13 min; m/z 446 $[M+1]^+$.	36 mg, 21%, pale orange solid
	IQ-124	AnalpH2_MeOH_QC: RT 5.79 min; m/z 404 $[M+1]^+$.	146 mg, 89%, yellow yellow solid
	IQ-123	AnalpH2_MeOH_QC: RT 5.50 min; m/z 384 $[M+1]^+$.	54 mg, 59%, yellow yellow solid
	IQ-159	AnalpH2_MeOH_QC: Rt 6.08 min; m/z 360 $[M+1]^+$	4.4 mg, 17% pale cream solid

Scheme A, Step C (Protocol 2): Synthesis of *2H*-isoquinolin-1-one Derivatives of formula **5** (via TBDMS Deprotection)

3-{6-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-pyridin-3-yl}-5-methyl-*2H*-isoquinolin-1-one (IQ-011)



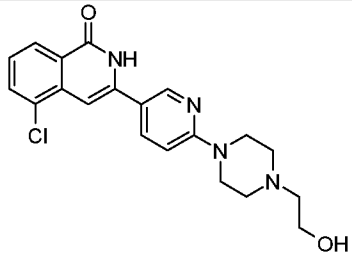
To a solution of 3-(6-{4-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-piperazin-1-yl}-pyridin-3-yl)-5-methyl-*2H*-isoquinolin-1-one (214 mg, 0.45 mmol) in THF (1.5 mL) at 5 °C was added 1M TBAF/THF (0.58 mL, 0.58 mmol) dropwise. The reaction mixture was allowed to warm to RT and stirred for 1 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with water and brine. The organic layer was concentrated *in vacuo* and purified by reverse phase preparative HPLC-MS to obtain 3-{6-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-pyridin-3-yl}-5-methyl-*2H*-isoquinolin-1-one as a yellow solid (27 mg, 16%).

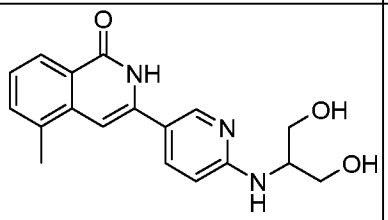
^{1}H NMR (400 MHz, DMSO-d_6): δ11.61-11.29 (br s, 1H), 8.59 (d, J = 2.5 Hz, 1H), 8.05 (d, J = 8 Hz, 1H), 7.98 (dd, J = 9, 2.5 Hz, 1H), 7.53 (d, J = 8 Hz, 1H), 7.32 (t, J = 8 Hz, 1H), 6.92 (d, J = 9 Hz, 1H), 6.77 (s, 1H), 4.43 (t, J = 5 Hz, 1H), 3.59-3.54 (m, 6H), 2.54 (s, 3H), 2.54-2.52 (m, 4H), 2.44 (t, J = 5 Hz, 2H).

AnalpH2_MeOH_QC: Rt 5.04 min; m/z 365 $[M+1]^+$.

The following *2H*-isoquinolin-1-one of formula **5** derivatives are prepared using analogous procedures.

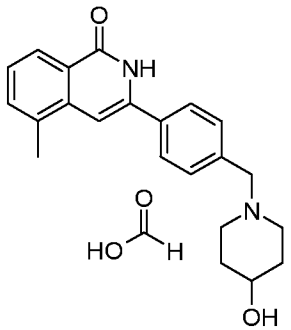
Table 14: *2H*-isoquinolin-1-one derivatives of Formula **5**

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-012	AnalpH2_MeOH_QC: Rt 5.40 min; m/z 385 $[M+1]^+$	21 mg, 12%, pale yellow solid

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-219	AnalpH2_MeOH_QC(1): Rt 5.08 min; m/z 326 $[M+1]^+$	65 mg, 13 %, white solid

Scheme A, Step C (Protocol 3): Synthesis of *2H*-isoquinolin-1-one Derivatives of formula **5** (via TBDPS Deprotection)

3-[4-(4-Hydroxy-piperidin-1-ylmethyl)-phenyl]-5-methyl-*2H*-isoquinolin-1-one (IQ-074)



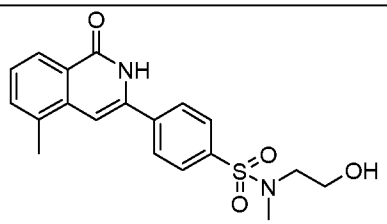
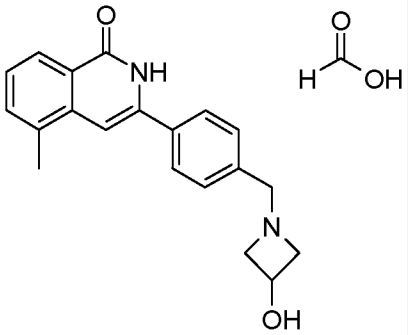
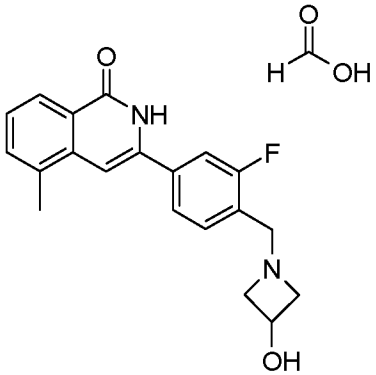
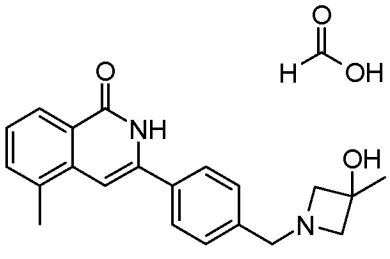
To a stirred solution of 3-{4-[4-(*tert*-butyl-diphenyl-silanyloxy)-piperidin-1-ylmethyl]-phenyl}-5-methyl-*2H*-isoquinolin-1-one (213 mg, 0.36 mmol) in CH_2Cl_2 (2 mL) was added 1.25M methanolic HCl (1 mL) and the reaction stirred at RT for 48 h. The reaction mixture was concentrated *in vacuo* and the crude residue purified by reverse phase preparative HPLC-MS to afford 3-[4-(4-hydroxy-piperidin-1-ylmethyl)-phenyl]-5-methyl-*2H*-isoquinolin-1-one as a pale yellow solid (80 mg, 64%).

AnalpH2_MeOH_QC(1): Rt 5.03 min; m/z 349 $[M+1]^+$.

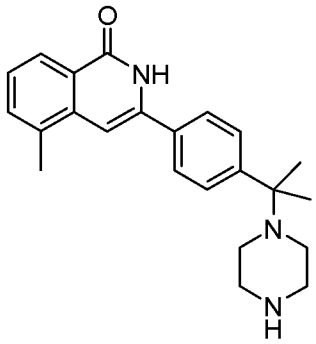
^{1}H NMR (400 MHz, DMSO-d_6): δ11.63-11.35 (br s, 1H), 8.15 (s, 0.8H) 8.07 (d, J = 7 Hz, 1H), 7.78 (d, J = 8 Hz, 2H), 7.56 (d with fine coupling, J = 7 Hz, 1H), 7.41 (d, J = 8 Hz, 2H), 7.37 (t, J = 8 Hz, 1H), 6.85 (s, 1H), 4.66-4.52 (br s,1H), 3.52 (s, 2H), 3.50-3.45 (m, 1H), 2.70-2.67 (m, 2H), 2.56 (s, 3H), 2.11-2.06 (m, 2H), 1.74-1.70 (m, 2H), 1.45-1.36 (m, 2H).

The following *2H*-isoquinolin-1-one derivatives are prepared using analogous procedures.

Table 15: *2H*-isoquinolin-1-one derivatives of Formula **5**

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-120	AnalpH2_MeOH_QC(1): Rt 7.31 min; m/z 373 $[M+1]^+$	39 mg, 60%, white solid
	IQ-167	AnalpH2_MeOH_QC(1): Rt 5.04 min; m/z 321 $[M+1]^+$	70 mg, 50 %, off-white solid
	IQ-169	AnalpH2_MeOH_QC(1): Rt 5.11 min; m/z 339 $[M+1]^+$	3.5 mg, 15 %, off-white solid
	IQ-172	AnalpH2_MeOH_QC(1): Rt 5.09 min; m/z 335 $[M+1]^+$	17 mg, 49 %, off-white solid

Scheme A, Step C (Protocol 4): Synthesis of *2H*-isoquinolin-1-one Derivatives of formula **5** (via Tosyl Deprotection) (IQ-075)

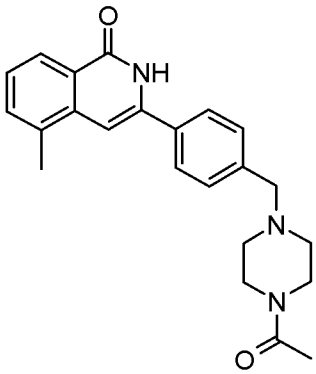


To a solution of 5-methyl-3-(4-{1-methyl-1-[4-(toluene-4-sulfonyl)-piperazin-1-yl]-ethyl}-phenyl)-*2H*-isoquinolin-1-one (33 mg, 0.064 mmol) in HBr (33% w/w in acetic acid) (0.25 mL) was added 4-hydroxybenzoic acid (27 mg, 0.194 mmol) and the reaction stirred for 16 h at RT afterwhich time the rection was concentrated *in vacuo* and the crude residue purified by preperative HPLC to afford 5-Methyl-3-[(4-(1-methyl-1-piperazin-1-yl]-ethyl)-phenyl]-*2H*-isoquinolin-1-one as a pale orange solid (1.06 mg, 4.5%).

AnalpH2_MeOH_QC(1): RT 6.01 min; m/z 362 $[M+1]^+$.

Scheme A, Step D (Protocol 1): Synthesis of *2H*-isoquinolin-1-one Derivatives of formula **6** (via acylation)

3-[4-(4-Acetyl-piperazin-1-ylmethyl)-phenyl]-5-methyl-*2H*-isoquinolin-1-one (IQ-055)



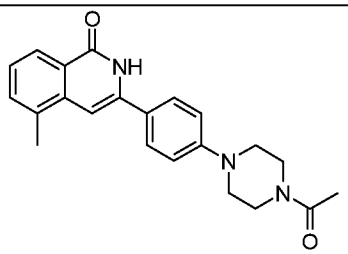
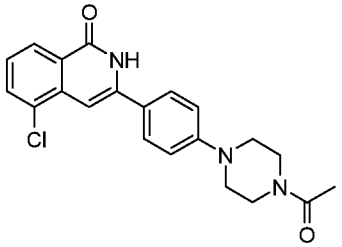
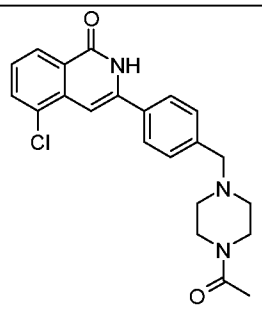
To a stirred solution of acetic acid (0.005 mL, 0.068 mmol) in CH_2Cl_2 (5 mL) was added TBTU (22 mg, 0.068 mmol) and *N,N*-diisopropylethylamine (0.036 mL, 0.20 mmol) and the reaction stirred for 10 min at RT. 5-Methyl-3-(4-piperazin-1-ylmethylphenyl)-*2H*-isoquinolin-1-one (23 mg, 0.068 mmol) was then added and the reaction stirred for 2 h at RT. The reaction mixture was concentrated *in vacuo* and purified by reverse phase preparative HPLC-MS to afford 3-[4-(4-acetyl-piperazine-1-ylmethyl)-phenyl]-5-methyl-*2H*-isoquinolin-1-one as a white solid (2 mg, 9%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.70-11.38 (br s, 1H), 8.08 (d, J = 8 Hz, 1H), 7.80 (d, J = 8 Hz, 2H), 7.56 (d, J = 8 Hz, 1H), 7.44 (d, J = 8 Hz, 2H), 7.37 (t, J = 8 Hz, 1H), 6.92 (s, 1H), 3.57 (s, 2H), 3.46-3.42, (m, 4H), 2.56 (s, 3H), 2.44-2.39 (m, 2H), 2.35-2.32 (m, 2H), 1.99 (3H, s).

AnalpH2_MeOH_QC(Sunfire): Rt 4.38 min; m/z 376 $[M+1]^+$.

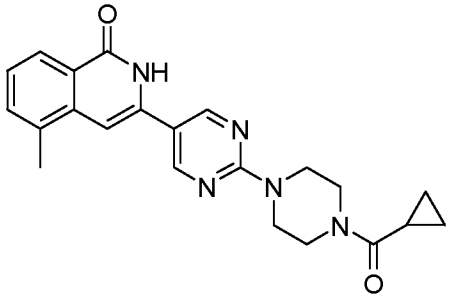
The following *2H*-isoquinolin-1-one derivatives are prepared using analogous procedures.

Table 16 *2H*-isoquinolin-1-one derivatives of Formula **6**

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-017	AnalpH2_MeOH_QC: Rt 7.76 min; m/z 362 $[M+1]^+$	18 mg, 36%, beige solid
	IQ-015	AnalpH2_MeOH_QC: Rt 8.16 min; m/z 382 $[M+1]^+$	11 mg, 43%, yellow solid
	IQ-045	AnalpH2_MeOH_QC Rt 5.62 min m/z 396 $[M+1]^+$.	17 mg, 42%, white solid

Scheme A, Step D (Protocol 2): Synthesis of *2H*-isoquinolin-1-one Derivatives of formula **6** (via acylation)

3-[2-(4-Cyclopropanecarbonyl-piperazin-1-yl)-pyrimidin-5-yl]-5-methyl-2*H*-isoquinolin-1-one (IQ-157)

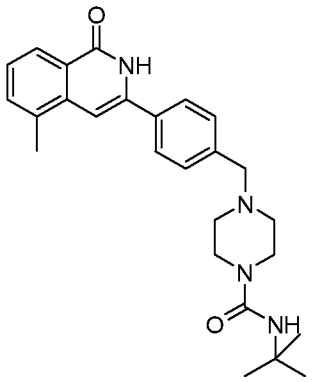


Cyclopropylcarbonyl chloride (9 µL, 2.28 mmol) was added to a stirred solution of 5-methyl-3-(2-piperazin-1-yl-pyrimidin-5-yl)-2*H*-isoquinolin-1-one (36 mg, 0.11 mmol) and *N,N*-diisopropylethylamine (23 µL, 0.132 mmol) in CH_2Cl_2 (2 mL) at -20 °C and allowed to stir for 10 min. The reaction mixture was concentrated *in vacuo*. The crude residue was purified by reverse phase preparative HPLC-MS to afford 3-[2-(4-cyclopropanecarbonyl-piperazin-1-yl)-pyrimidin-5-yl]-5-methyl-2*H*-isoquinolin-1-one as a white solid (19 mg, 45%).

^{1}H NMR (400 MHz, DMSO-d_6): δ11.82-11.11 (br s, 1H), 8.85 (s, 2H), 8.05 (d, J = 8 Hz, 1H), 7.55 (d, J = 8 Hz, 1H), 7.35 (t, J = 8 Hz, 1H), 6.84 (s, 1H), 3.96-3.76 (br m, 6H), 3.64-3.54 (br s, 2H), 2.54 (s, 3H), 2.08-2.00 (m, 1H), 0.82-0.70 (m, 4H).

AnalpH2_MeOH_QC(1): Rt 8.05 min; m/z 390 $[M+1]^+$.

Scheme A, Step D (Protocol 3): Synthesis of *2H*-isoquinolin-1-one Derivatives of formula **6** (urea formation) (IQ-068)



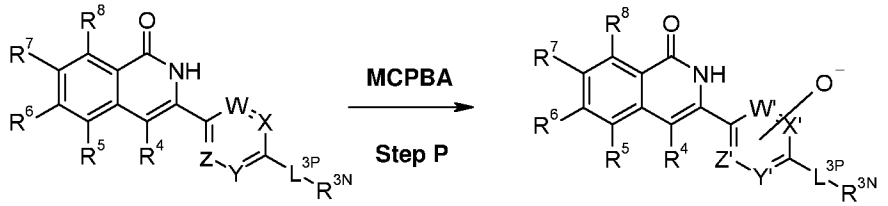
To a stirred solution of 5-methyl-3-(4-piperazin-1-ylmethyl-phenyl)-*2H*-isoquinolin-1-one (40 mg, 0.12 mmol) in CH_2Cl_2 (0.5 mL) was added *tert*-butyl isocyanate (0.014 mL, 0.12 mmol) and the reaction mixture stirred at RT for 1 h after which time the solvent was removed *in vacuo* and the crude residue purified by reverse phase preparative HPLC-MS to afford 4-[4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzyl]-piperazine-1-carboxylic acid *tert*-butylamide as a white solid (28 mg, 54%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.50-11.12 (br s, 1H), 7.83 (d, J = 8 Hz, 1H), 7.55 (d, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 1H), 7.19 (d, J = 8 Hz, 2H), 7.13 (t, J = 8 Hz, 1H), 6.62 (s, 1H), 5.49 (s, 1H), 3.30 (s, 2H), 3.03-3.01, (m, 4H) 2.32 (s, 3H), 2.10-2.08 (m, 4H), 1.01 (s, 9H).

AnalpH2_MeOH_QC(1): Rt 5.83 min; m/z 433 $[M+1]^+$.

Synthesis of 3-(1-Oxy-pyridin-3-yl]-*2H*-isoquinolin-1-one Derivatives **27**

Scheme H

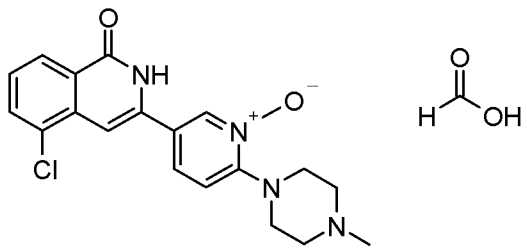


where at least one of W or X or Y or Z is N — **4**

where at least one of W' or X' or Y' or Z' is N^+ — **27**

Scheme H, Step P: *N*-Oxidation of 3-(pyridinyl]-*2H*-isoquinolin-1-one Derivatives **27**

5-Chloro-3-[6-(4-methyl-piperazin-1-yl)-1-oxy-pyridin-3-yl]-*2H*-isoquinolin-1-one (IQ-002-2)



MCPBA (41 mg, 0.184 mmol) was added to a solution of 5-chloro-3-[6-(4-methyl-piperazin-1-yl)-pyridin-3-yl]-*2H*-isoquinolin-1-one (58 mg, 0.164 mmol) in CH_2Cl_2 (7 mL) at -78 °C and allowed to warm to RT and stirred at this temperature for a further 40 minutes. The reaction mixture was quenched with saturated, aqueous $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 followed by EtOAc. The combined organic layer was concentrated *in vacuo* and passed through an SCX-2 cartridge (5 g), eluting with 10% NH_3/MeOH. The desired fractions were concentrated *in vacuo* and the crude material purified by reverse phase preparative HPLC-MS to obtain 5-chloro-3-[6-(4-methyl-piperazin-1-yl)-1-oxy-pyridin-3-yl]-*2H*-isoquinolin-1-one as a white solid (19 mg, 33%).

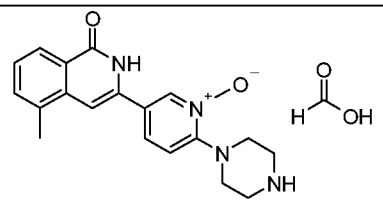
^{1}H NMR (400 MHz, DMSO-d_6): δ12.30-12.00 (br s, 1H), 8.59 (d, J = 8 Hz, 1H), 8.31 (s, 0.6H), 8.17 (d, J = 9 Hz, 1H), 8.01 (dd, J = 9, 3 Hz, 1H), 7.84 (d, J = 8 Hz, 1H), 7.43 (t, J =

8 Hz, 1H), 7.03 (d, *J* = 9 Hz, 1H), 6.84 (s, 1H), 4.29-4.27 (m, 2H), 3.59-3.49 (m, 4H), 3.35-3.31 (m, 2H), 3.25 (s, 3H).

AnalpH9_MeOH_QC: Rt 7.20 min; m/z 371 $[M+1]^+$.

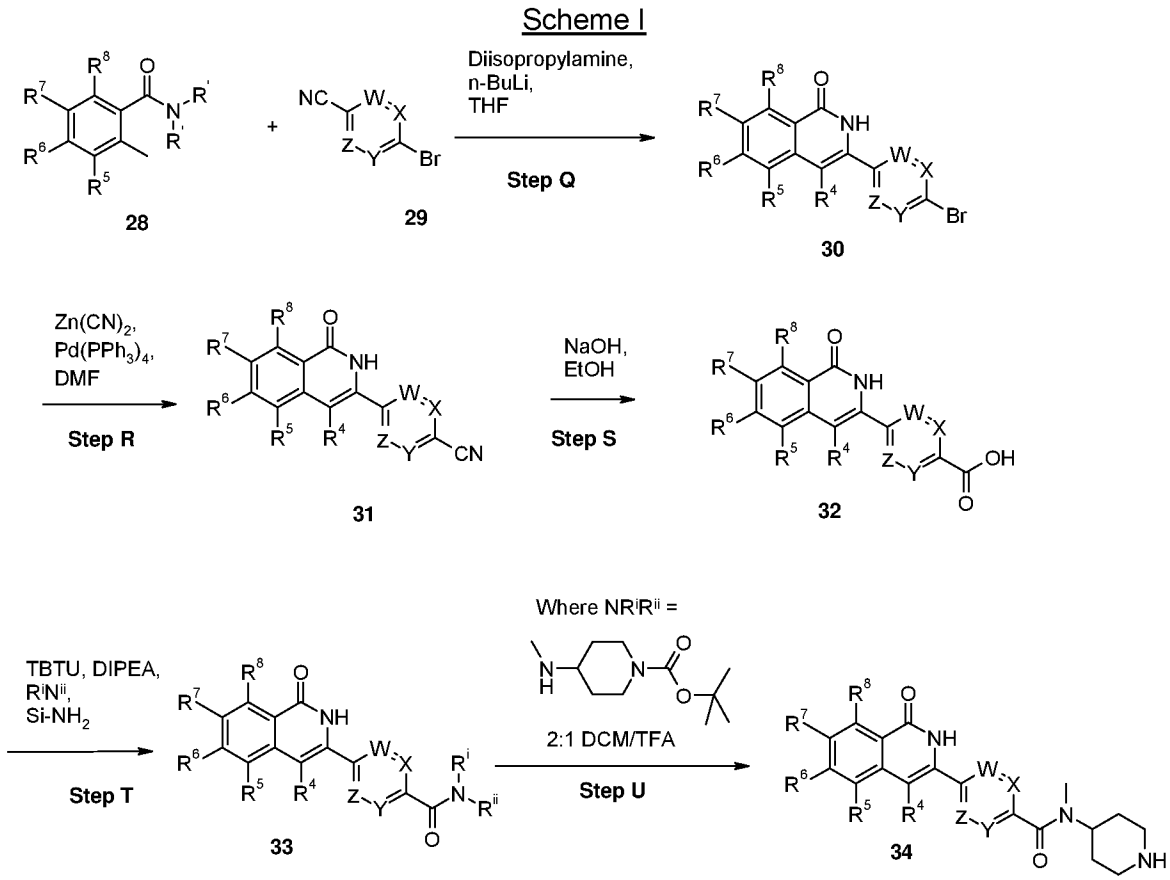
The following *2H*-isoquinolin-1-one derivatives are prepared using analogous procedures.

Table 17: *2H*-isoquinolin-1-one derivatives **27**

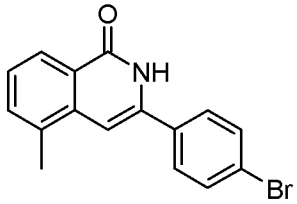
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-028-2	AnalpH9_MeOH_QC (Sunfire1): Rt 5.86 min; m/z 337 $[M+1]^+$	48 mg, 57%, brown solid

General Procedure for Synthesis of *2H*-isoquinolin-1-one derivatives of Formula **34**

Scheme I



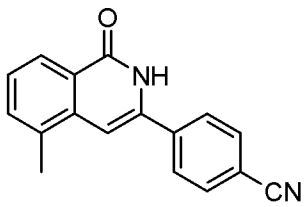
Scheme I, Step Q Synthesis of 3-(4-Bromo-phenyl)-5-methyl-*2H*-isoquinolin-1-one



To *N,N*-diisopropylamine (2.54 mL, 18 mmol) in anhydrous THF (15 mL), under N_2 at -78 °C was added *n*-BuLi dropwise (2.5M in n-hexanes, 7.2 mL, 18 mmol) and the reaction mixture maintained at this temperature for 30 minutes. A solution of *N,N*-diethyl-2,3-dimethyl-benzamide (1.23 g, 6 mmol) in anhydrous THF (15 mL) was added dropwise to give a deep red solution. After 20 minutes at -78 °C, 4-bromobenzonitrile (1.09 g, 6 mmol) in anhydrous THF (15 mL) was added dropwise and the reaction mixture allowed to stir at this temperature for 2.5 h. The reaction mixture was quenched by adding dropwise onto ice, upon which a pale yellow solid precipitated out. The solid was triturated with iso-hexane/EtOAc (2:1), filtered and dried *in vacuo* to afford 3-(4-bromo-phenyl)-5-methyl-*2H*-isoquinolin-1-one as a pale yellow solid (1.1 g, 58%).

AnalpH2_MeOH_4min(1): Rt 3.25 min; m/z 314 $[M+1]^+$.

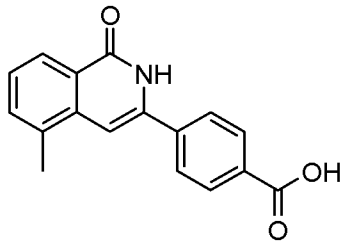
Scheme I, Step R: Synthesis of 4-(5-Methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzonitrile



3-(4-Bromo-phenyl)-5-methyl-*2H*-isoquinolin-1-one (200 mg, 0.64 mmol), zinc cyanide (90 mg, 0.76 mmol) and tetrakis(triphenylphosphine)palladium(0) (74 mg, 0.064 mmol) were stirred in DMF (2.1 mL) and degassed with N_2. The reaction mixtures were irradiated using a microwave (300W, 180 °C, 30 min). The reaction mixtures were combined and the resulting precipitate was filtered, washed with DMF and water and dried to give 4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzonitrile as a yellowish solid (718 mg, 79%) which was used in the next step without further purification.

AnalpH2_MeOH_4min(1): Rt 2.83 min; m/z 261 $[M+1]^+$.

Scheme I, Step S: Synthesis of 4-(5-Methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzoic acid

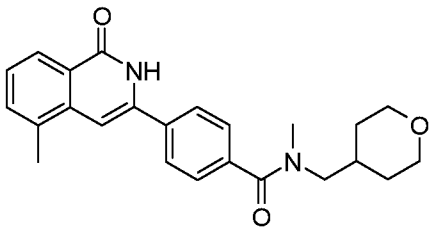


To 4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzonitrile (100 mg, 0.38 mmol) was added 2M NaOH (1.5 mL) and the reaction mixture irradiated using a microwave (300W, 130 °C, 20 min). The reaction mixtures was diluted with water and adjusted to pH2 with 2M HCl whereupon a pale yellow solid precipitated out of solution. The solid was filtered, washed with water and dried. The solid was dissolved in DMF and passed through a Si-thiol cartridge to remove any residual palladium, eluting with DMF. The eluent was removed *in vacuo* to give 4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzoic acid as a pale yellow solid (120 mg, 63%).

AnalpH9_MeOH_4min(1): Rt 2.24 min; m/z 280 $[M+1]^+$.

Scheme I, Step T: Synthesis of 3-Benzamide-5-Methyl-*2H*-Isoquinolin-1-one Derivatives of formula **33**

N-Methyl-4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-*N*-(tetrahydro-pyran-4-ylmethyl)-benzamide (IQ-097)



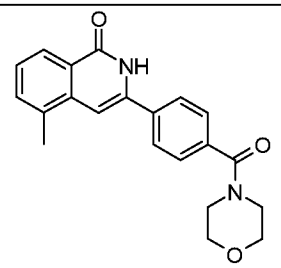
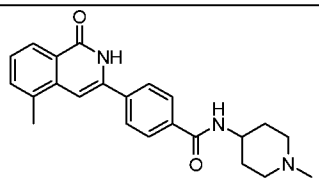
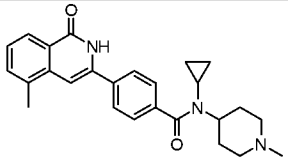
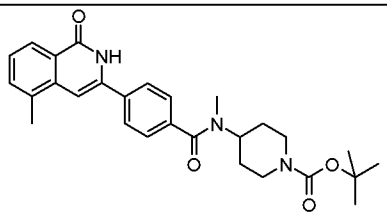
To 4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzoic acid (35 mg, 0.125 mmol), TBTU (40 mg, 0.125 mmol) was added 0.36M *N,N*-diisopropylethylamine/CH_2Cl_2 (0.35 mL, 0.125 mmol) and anhydrous DMF (0.9 mL). The reaction mixture was stirred at RT for 45 min after which time methyl-(tetrahydro-pyran-4-ylmethyl)-amine (19 mg, 0.15 mmol) in anhydrous DMF (0.45 mL) was added and the reaction mixture was stirred at RT overnight. The reaction mixture was passed through a Si-NH_2 cartridge (1 g), eluting with DMF (2 x column volumes), MeOH (2 x column volumes) and the solvent removed *in vacuo* and the crude product purified by reverse phase preparative HPLC-MS to obtain *N*-methyl-4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-*N*-(tetrahydro-pyran-4-ylmethyl)-benzamide as a yellow foam (24 mg, 48%).

^{1}H NMR (400 MHz, DMSO-d_6): δ11.69-11.54 (br s, 1H), 8.09 (d, J = 7 Hz, 1H), 7.89 (d, J = 8 Hz, 2H), 7.58 (d, J = 7 Hz, 1H), 7.52 (br d, J = 8 Hz, 1H), 7.46 (br d, J = 8 Hz, 1H), 7.40 (t, J = 7 Hz, 1H), 6.92 (s, 1H), 3.90 (br d, J = 11 Hz, 1H), 3.75 (br d, J = 11 Hz, 1H), 3.40-3.17 (m, 4H), 2.99 (br s, 1H), 2.94 (br s, 2H), 2.58 (s, 3H), 2.08-1.82 (br m, 1H), 1.63 (br d, J = 12 Hz, 1H), 1.44 (br d, J = 12 Hz, 1H), 1.32-1.25 (m, 1H), 0.95-0.80 (m, 1H).

AnalpH2_MeOH_QC(1): Rt 7.69 min; m/z 391 $[M+1]^+$.

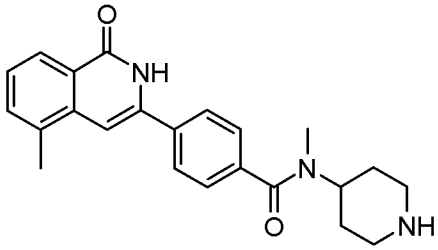
The following *2H*-isoquinolin-1-one derivatives are prepared using analogous procedures

Table 18: *2H*-isoquinolin-1-one derivatives of Formula **33**

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-107	AnalpH2_MeOH_QC(1): Rt 7.44 min; m/z 349 $[M+1]^+$	12 mg, 51%, white solid
	IQ-146	AnalpH2_MeOH_QC(1): Rt 5.27 min; m/z 376 $[M+1]^+$	16 mg, 35%, off-white solid
	IQ-098	AnalpH2_MeOH_QC(1): Rt 5.51 min; m/z 416 $[M+1]^+$	15 mg, 29%, off-white solid
	IQ-153	AnalpH2_MeOH_4min: Rt 3.15 min; m/z 476 $[M+1]^+$	21 mg, 100%, beige solid

Scheme I, Step U: Synthesis of 3-Benzamide-5-Methyl-*2H*-Isoquinolin-1-one Derivatives of formula **34**

N-Methyl-4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-*N*-piperidin-4-yl-benzamide (IQ-096)

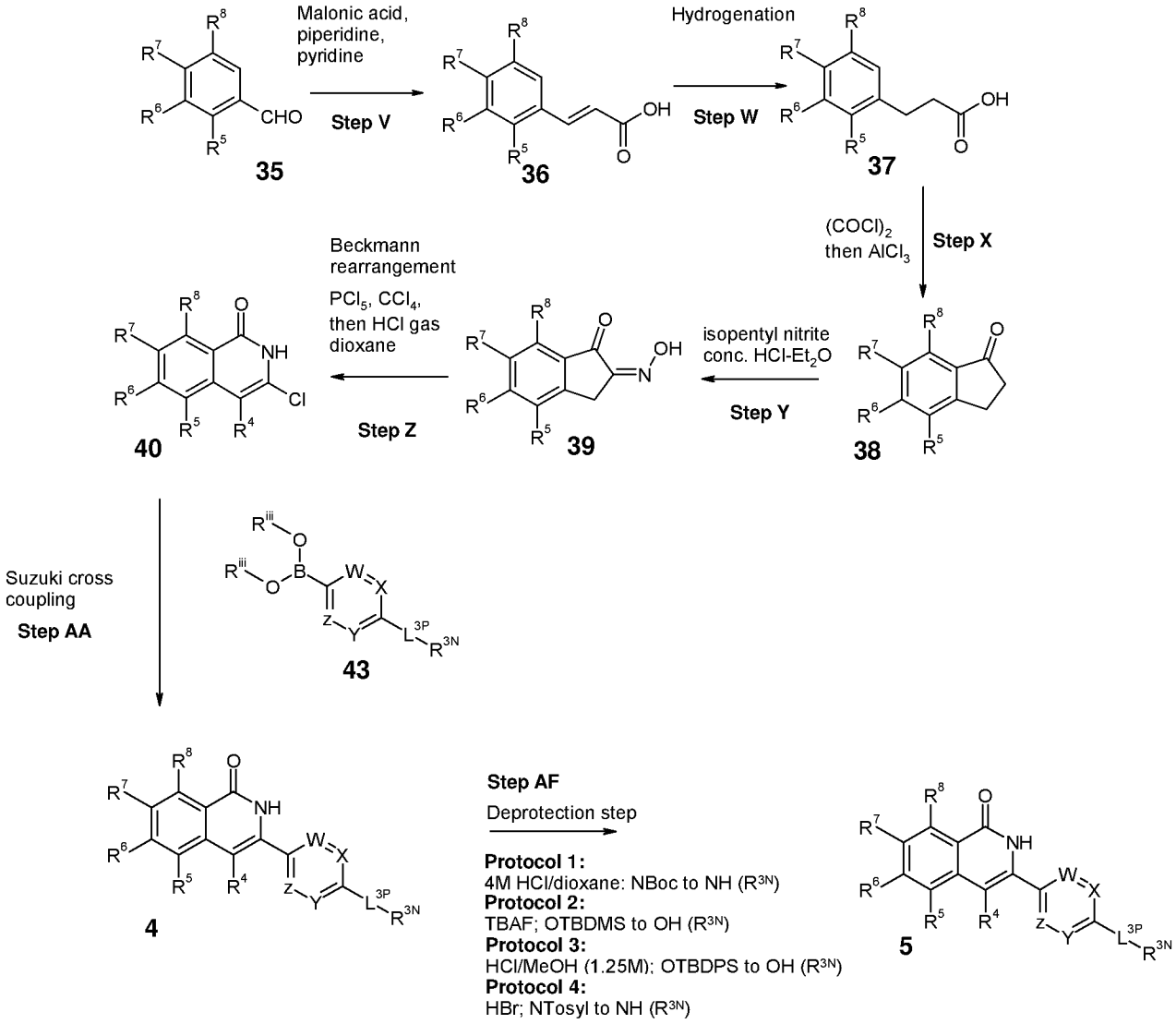


To 4-{methyl-[4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzoyl]-amino}-piperidine-1-carboxylic acid *tert*-butyl ester (21 mg, 0.044 mmol) was added 2:1 CH_2Cl_2/TFA (1 mL) and the reaction mixture stirred at RT for 1 h. The solvent was removed *in vacuo*, re-dissolved in MeOH and passed through an SCX-2 cartridge (1 g). The column was washed with MeOH (4 x column volumes), the desired product eluted from the cartridge with 0.5M NH_3/MeOH (4 x column volumes) and concentrated *in vacuo*. The crude product was purified by reverse phase preparative HPLC-MS to obtain *N*-methyl-4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-*N*-piperidin-4-yl-benzamide as a white solid (2.4 mg, 14%).

AnalpH2_MeOH_QC(1): Rt 5.10 min; m/z 376 $[M+1]^+$.

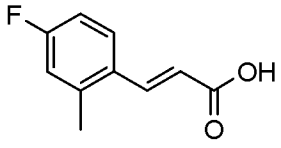
Synthesis of *2H*-isoquinolin-1-one derivatives of Formula **4 & 5**
(via Route 2)

Scheme J



Scheme J, Step V: Synthesis of phenyl acrylic acid derivatives of formula **36**

(E)-3-(4-Fluoro-2-methylphenyl)acrylic acid



A stirred solution of 4-fluoro-2-methyl-benzaldehyde (20 g, 144.9 mmol) and malonic acid (30.1 g, 289.8 mmol) in pyridine (100 mL) was heated to 50 °C. Piperidine (10 mL) was added and the reaction mixture was heated at 70 °C for 18 h. The reaction mixture was cooled RT and poured into chilled aqueous 1N HCl solution (1500 mL), the resulting

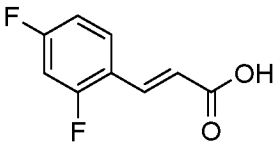
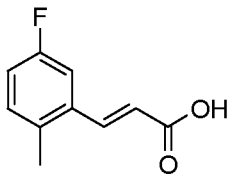
precipitate was filtered and washed with petroleum ether 60-80 and dried *in vacuo* to obtain *(E)*-3-(4-fluoro-2-methylphenyl)acrylic acid (18 g, 69%) as an off white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ8.00 (d, *J* = 16 Hz, 1H), 7.60-7.55 (m, 1H), 6.96-6.90 (m, 2H), 6.32 (d, *J* = 16 Hz, 1H), 2.44 (s, 3H).

AnalpH2_MeCN_FA_7min(XTERRA1.m): Rt 3.34 min; m/z 181 $[M+1]^+$.

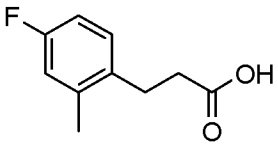
The following phenyl acrylic acid derivatives of formula **36** are prepared using analogous procedures.

Table 19: Phenyl acrylic acid Derivatives **36**

Compound	Reference	Analytical Data	Mass, %Yield, State
	Reported as commercially available	AnalpH2_MeCN_FA_7min(XTERRA1.m): Rt 3.16 min; m/z 185 $[M+1]^+$.	25 g, 64%, off-white solid
	Reported as commercially available	AnalpH2_MeOH_4min(3): Rt 2.63 min; m/z not observed	6.3 g, 97%, white solid

Scheme J, Step W: Synthesis of Phenyl Propanoic Derivatives **37**

3-(4-Fluoro-2-methylphenyl)propanoic acid



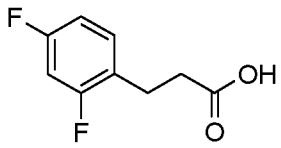
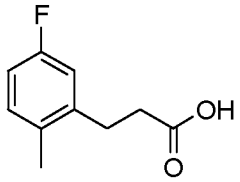
To a solution of *(E)*-3-(4-fluoro-2-methylphenyl)acrylic acid (13 g, 72.22 mmol) in EtOH (250 mL) was added PtO_2 (250 mg) and then hydrogenated at 30 psi for 3 h. The reaction mixture was filtered on a Celite® pad, washed with MeOH (100 mL), and the filtrate was concentrated, washed with diethyl ether (20 mL), *n*-pentane (50 mL) and dried *in vacuo* to give 3-(4-fluoro-2-methylphenyl)propanoic acid as an off-white solid (10 g, 77%).

^{1}H NMR (400MHz, $CDCl_3$): δ 7.13-7.05 (m, 1H), 6.90-6.79 (m, 2H), 2.95-2.85 (2H, m), 2.65-2.55 (2H, m), 2.31 (s, 3H)

AnalpH2_MeCN_FA_7min(XTERRA1.m): Rt 3.33 min; m/z 181 $[M-1]^-$.

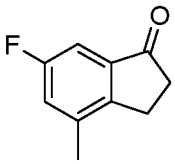
The following phenyl propanoic derivatives **37** are prepared using analogous procedures.

Table 20: Phenyl Propanoic Derivatives **37**

Compound	Reference	Analytical Data	Mass, %Yield, State
	Reported as commercially available	AnalpH2_MeCN_FA_7min(XTERRA1.m): Rt 3.19 min; m/z 185 $[M-1]^-$.	8g, 73%, off-white solid
	Reported as commercially available	AnalpH2_MeOH_4min(3): Rt 2.58 min; m/z not observed	6.37 g, 100%, white solid

Scheme J, Step X: Indanone Synthesis

6-Fluoro-4-methyl-2,3-dihydro-1H-inden-1-one



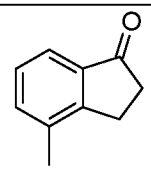
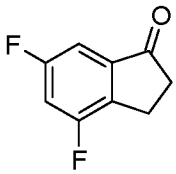
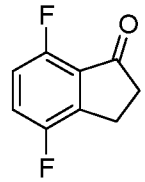
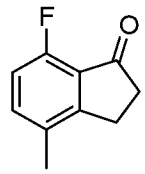
To a solution of 3-(4-fluoro-2-methylphenyl)propanoic acid (12 g, 65.93 mmol) in CH_2Cl_2 (200 mL) was added oxalyl chloride (11.3 mL, 131.7 mmol) and stirred at RT for 16h. The reaction mixture was concentrated *in vacuo* and re-dissolved in CH_2Cl_2 (150 mL) and added to a suspension of $AlCl_3$ (11.4 g, 85.7 mmol) in CH_2Cl_2 (150 mL) at 0 °C. The reaction mixture was heated at 50 °C for 3 h and allowed to stir at RT for 16h. The reaction mixture poured into ice water (150 mL), extracted with CH_2Cl_2 (2 x 100 mL), the organic extract was washed with 1N NaOH solution (2 x 50 mL), brine solution (50 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The crude material was purified by silica gel column chromatography, eluting with 10% EtOAc/petroleum ether 60-80 to afford 6-fluoro-4-methyl-2,3-dihydro-1H-inden-1-one as an off white solid (7 g, 70%).

^{1}H NMR (400MHz, $CDCl_3$): δ 7.28-7.25 (m, 1H), 7.18-7.12 (m, 1H), 3.03-2.96 (m, 2H), 2.78-2.73 (m, 2H), 2.35 (s, 3H).

AnalpH2_MeCN_TFA_4min(1): Rt 1.89 min; m/z 165 $[M+1]^+$.

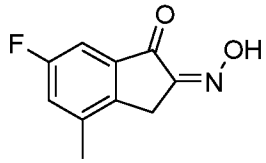
The following indanone derivatives **38** are prepared using analogous procedures.

Table 21: Indanone Derivatives **38**

Compound	Reference	Analytical Data	Mass, %Yield, State
	Commercially available	N/A	N/A
	Reported as commercially available	AnalpH2_MeCN_TFA_4min(1): Rt 1.80 min; m/z 169 $[M+1]^+$.	5.2 g, 57%, off-white solid
	Commercially available	N/A	N/A
	Reported as commercially available	AnalpH2_MeOH_4min(3): Rt 2.23 min; m/z 165 $[M+1]^+$	5.62 g, 98%, off-white solid

Scheme J, Step Y: Synthesis 2-(hydroxyimino -2,3-dihydro-1H-inden-1-one Derivatives **39**

6-Fluoro-2-(hydroxyimino)-4-methyl-2,3-dihydro-1H-inden-1-one



To a stirred solution of 6-fluoro-4-methyl-2,3-dihydro-1H-inden-1-one (1 g, 6.09 mmol) in a mixture of diethyl ether (10 mL) and concentrated HCl (10 mL) was added isopentyl nitrite (0.73 mL, 5.47 mmol) and stirred at RT for 3 h. The precipitated solid was collected

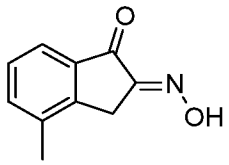
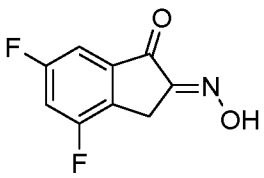
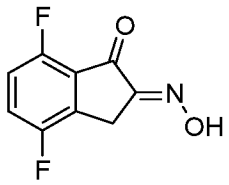
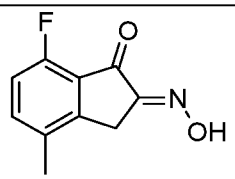
by filtration and washed with MeOH to obtain 6-fluoro-2-(hydroxyimino)-4-methyl-2,3-dihydro-1H-inden-1-one as a brown solid (800 mg, 68%).

^{1}H NMR (400MHz, DMSO-d_6): δ12.73 (s, 1H), 7.52–7.45 (m, 1H), 7.32-7.29 (m, 1H), 3.67 (s, 2H), 2.35 (s, 3H).

AnalpH2_MeCN_FA_7min(XTERRA1.m): Rt 3.04 min; m/z 194 $[M+1]^+$.

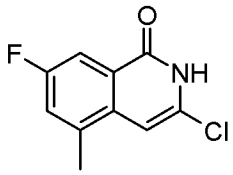
The following 2-(hydroxyimino -2,3-dihydro-1H-inden-1-one derivatives **39** are prepared using analogous procedures.

Table 22: 2-(hydroxyimino -2,3-dihydro-1H-inden-1-one Derivatives of formula **39**

Compound	Reference	Analytical Data	Mass, %Yield, State
		AnalpH9_MeCN_AB_10min(Develosil): Rt 2.85 min; m/z 176 $[M+1]^+$	5 g, 43%, pale yellow solid.
		AnalpH2_MeCN_FA_7min(XTERRA1.m): Rt 2.93 min; m/z 198 $[M+1]^+$.	1 g, 57%, brown solid
		AnalpH2_MeOH_4min(1): Rt 2.08 min; m/z 198 $[M+1]^+$	4.27 g, 72%, beige solid
		AnalpH2_MeOH_4min(3): Rt 2.17 min; m/z 194 $[M+1]^+$	3.84 g, 58%, pale brown solid

Scheme J, Step Z: Synthesis of 3-chloro-isoquinolin-1(2*H*)-one derivatives of formula **40**

3-Chloro-7-fluoro-5-methylisoquinolin-1(2*H*)-one



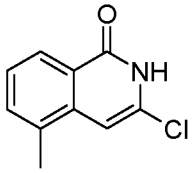
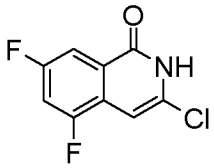
To a solution of 6-fluoro-2-(hydroxyimino)-4-methyl-2,3-dihydro-1H-inden-1-one (800 mg, 4.12 mmol) in anhydrous CCl_4 (100 mL) was added PCl_5 (1.28g, 6.18 mmol) and stirred at RT for 16 h. The reaction mixture was concentrated *in vacuo* and the residue dissolved in anhydrous 1,4-dioxane (100 mL), cooled 0 °C, the solution was saturated with HCl gas and allowed to stir RT for 16 h. The reaction mixture was heated at 60 °C for 2 h, cooled to RT and diluted with EtOAc (50 mL), washed with water (25 mL), saturated $NaHCO_3$ solution (25 mL), brine solution (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude material was washed with diethyl ether (10 mL), *n*-pentane (10 mL) and was dried *in vacuo* to obtain 3-chloro-7-fluoro-5-methylisoquinolin-1(2*H*)-one as a pale yellow solid (550 mg, 68%).

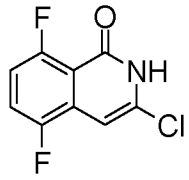
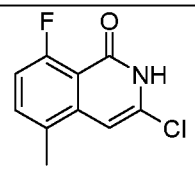
^{1}H NMR (400MHz, DMSO-d_6): δ12.55-12.40 (br s, 1H), 7.70-7.63 (m, 1H), 7.55-7.49 (m, 1H), 6.84-6.70 (br s, 1H), 2.48 (s, 3H).

AnalpH2_MeOH_4min(1): Rt 2.74 min; m/z 212 $[M+1]^+$.

The following 3-chloro-isoquinolin-1(2*H*)-one derivatives **40** are prepared using analogous procedures.

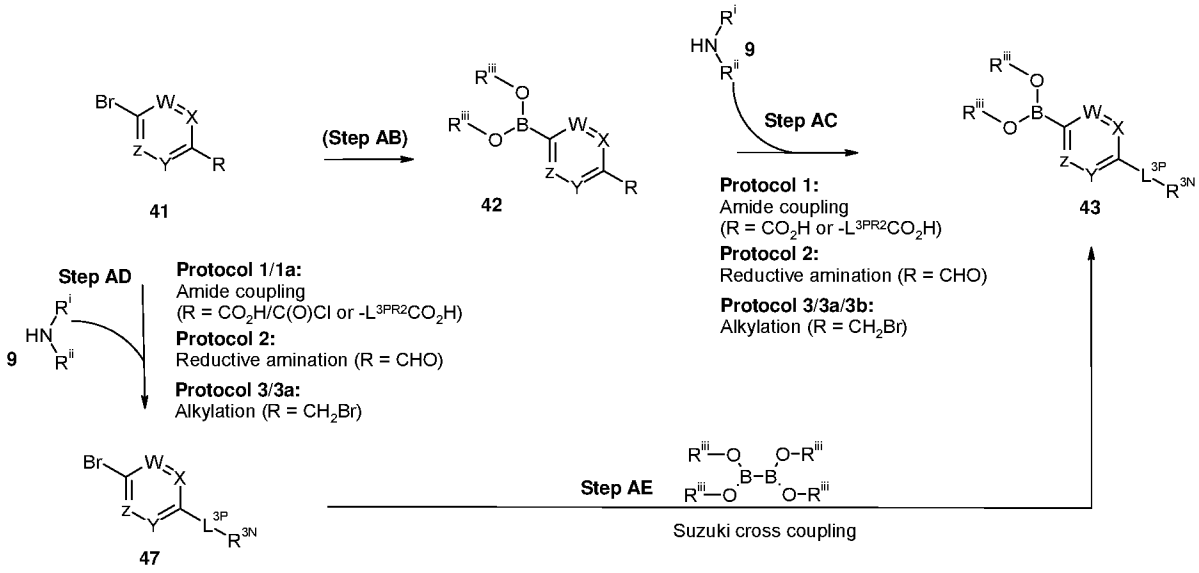
Table 23: 3-Chloro-isoquinolin-1(2*H*)-one Derivatives of formula **40**

Compound	Reference	Analytical Data	Mass, %Yield, State
	Compound reported by Krämer *et al.*, 1969	AnalpH2_MeOH_4min: Rt 2.67 min(1); m/z 193 $[M+1]^+$	1.1 g, 20%, white solid
	Novel	AnalpH2_MeOH_4min(1): Rt 2.78 min; m/z 216 $[M+1]^+$	650 mg, 62%, off white solid

Compound	Reference	Analytical Data	Mass, %Yield, State
	Novel	AnalpH2_MeOH_4min(1): Rt 2.51 min; m/z 215 $[M+1]^+$	150 mg, 28%, off-white solid
		AnalpH2_MeOH_4min(3): Rt 2.46 min; m/z 212 $[M+1]^+$	2.43 g, 58%, pale yellow solid

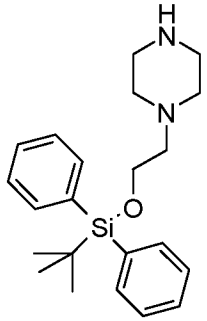
Synthesis of Boronic Acid/Ester Intermediates 43 (required for Step AA, Scheme J)

Scheme JJ



Scheme JJ: Synthesis of an example of amine of formula **9**

1-[2-(*tert*-Butyl-diphenyl-silanyloxy)-ethyl]-piperazine

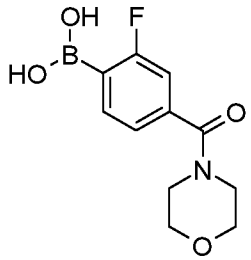


To 2-piperazin-1-yl-ethanol (2g, 15.36 mmol) in CH_2Cl_2 (70 mL) and pyridine (1.85 mL, 23.04 mmol) was added DMAP (188 mg, 1.53 mmol) and TBDPS chloride (3.37 mL, 18.44 mmol) and the reaction mixture stirred at RT for 18 h. The reaction mixture was concentrated *in vacuo* and the crude material was purified by silica gel column chromatography, eluting with CH_2Cl_2 and increasing the polarity to 10% MeOH/CH_2Cl_2 to obtain 1-[2-(*tert*-butyl-diphenyl-silanyloxy)-ethyl]-piperazine as a colourless oil (1.1 g, 21%).

AnalpH2_MeOH_4min(3): Rt 2.48 min; m/z 369 $[M+1]^+$.

Scheme JJ, Step AC (Protocol 1): Synthesis of aryl boronic acid or boronic ester derivatives of formula **43** (via amide coupling)

2-Fluoro-4-(morpholine-4-carbonyl)-boronic acid

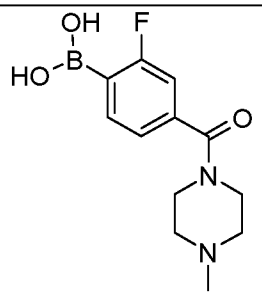
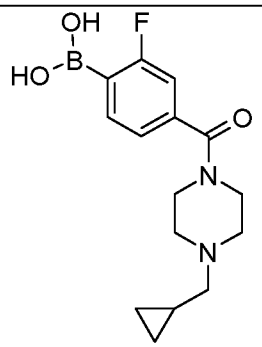
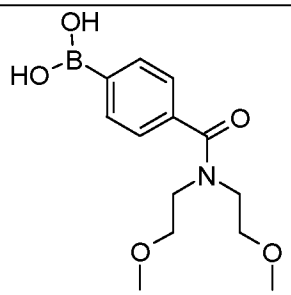
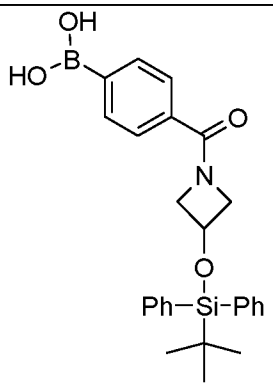


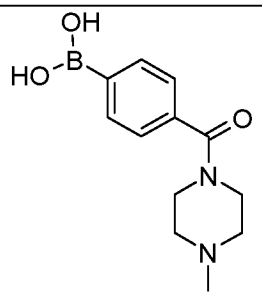
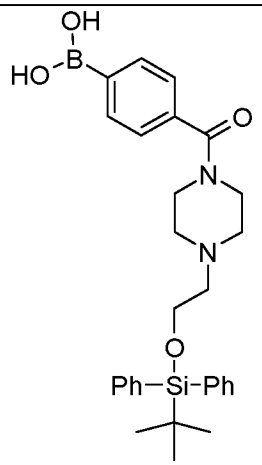
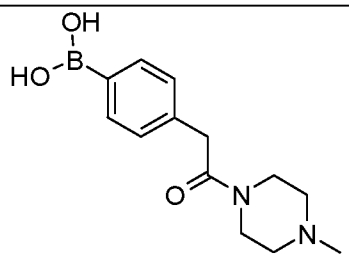
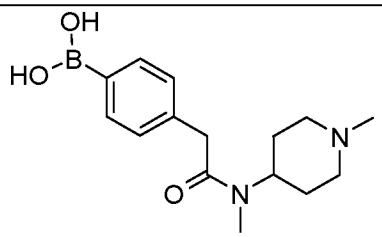
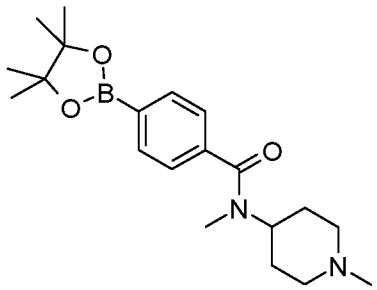
To 4-carboxy-2-fluoro-benzene boronic acid (150 mg, 0.82 mmol), TBTU (262 mg, 0.82 mmol) in anhydrous DMF (8 mL), was added 0.36M *N,N*-diisopropylethylamine in anhydrous CH_2Cl_2 (2.3 mL, 0.82 mmol) and the reaction mixture stirred at RT for 45 min. Morpholine (85 mg, 0.99 mmol) in anhydrous DMF (1 mL) was added and the reaction mixture stirred for 18 hr at RT. The reaction mixture was concentrated *in vacuo* and the crude material was purified by reverse phase preparative HPLC-MS to afford 2-fluoro-4-(morpholine-4-carbonyl)-boronic acid as a white solid (98 mg, 47%).

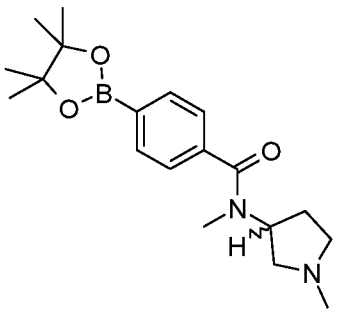
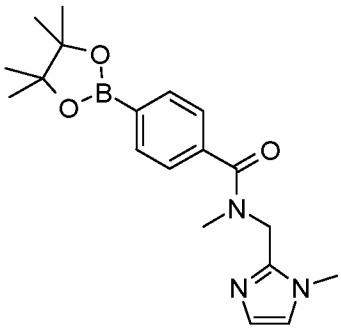
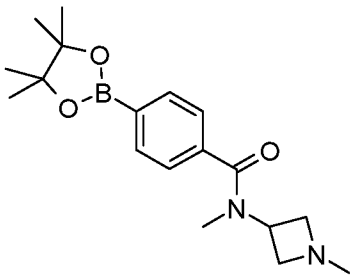
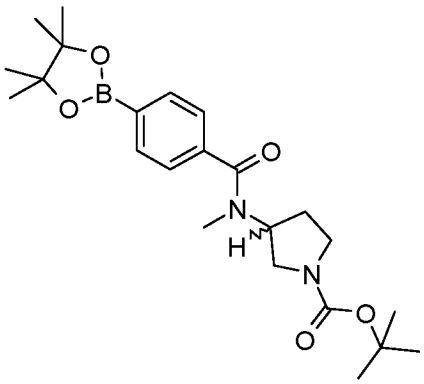
AnalpH2_MeOH_4min: Rt 1.47 min; m/z 254 $[M+1]^+$.

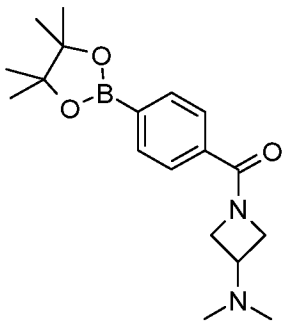
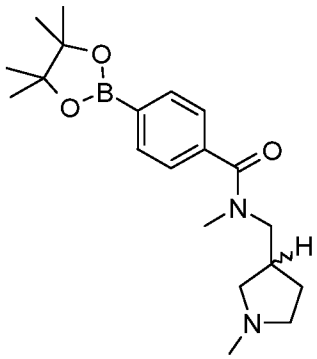
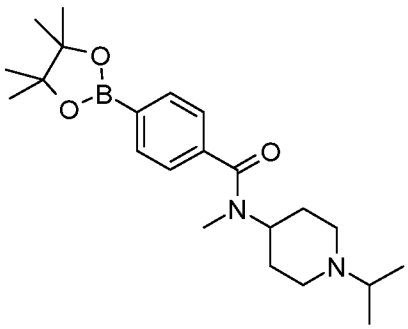
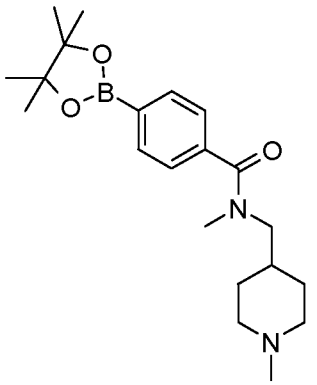
The following aryl boronic acid or boronic ester derivatives **43** are prepared using analogous procedures.

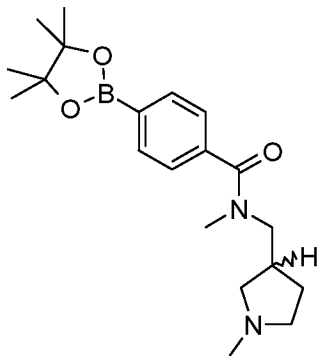
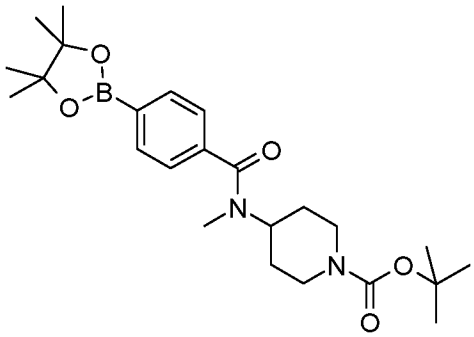
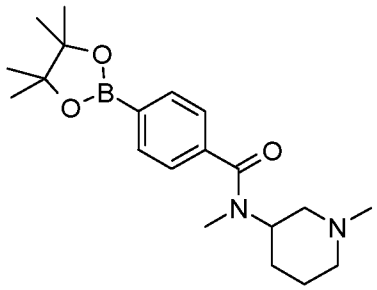
Table 24: Aryl boronic acid or boronic ester derivatives of Formula **43**

Compound	Analytical Data	Mass, %Yield, State
	AnalpH2_MeOH_4 min: Rt 0.32, 0.43 min; m/z 267 $[M+1]^+$	240 mg, 55%, white solid
	AnalpH2_MeOH_4 min: Rt 0.33, 0.61 min; m/z 307 $[M+1]^+$	245 mg, 49%, white solid
	AnalpH2_MeOH_4 min(3): Rt 1.83 min; m/z 282 $[M+1]^+$	554 mg, 65%, off-white solid
	AnalpH2_MeOH_4 min(3): Rt 3.45 min; m/z 460 $[M+1]^+$	1.56 g, 96%, cream solid

Compound	Analytical Data	Mass, %Yield, State
	AnalpH2_MeOH_4 min(3): Rt 0.31 min; m/z 249 $[M+1]^+$	1.54 g, 54%, colourless oil
	AnalpH2_MeOH_4 min(3): Rt 2.76 min; m/z 516 $[M+1]^+$	978 mg, 64%, white solid
	AnalpH9_MeOH_4 min(2): Rt 1.62 min; m/z 263 $[M+1]^+$	242 mg, 83%, dark orange oil
	AnalpH2_MeOH_4 min(3): Rt 0.77 min; m/z 291 $[M+1]^+$	127 mg, 65%, white solid
	AnalpH2_MeOH_4 min(3): Rt 1.71 min; m/z 359.5 $[M+1]^+$	992 mg, 46%, pale yellow solid

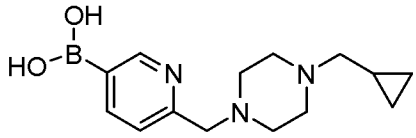
Compound	Analytical Data	Mass, %Yield, State
	AnalpH2_MeOH_4 min(3): Rt 1.70 min; m/z 345 $[M+1]^+$	294 mg, 24%, off-white solid
	AnalpH2_MeOH_4 min(3): Rt 1.72 min; m/z 356 $[M+1]^+$	532 mg, 74%, yellow oil
	AnalpH2_MeOH_4 min(3): Rt 1.66 min; m/z 331 $[M+1]^+$	118 mg, 25%, white solid
	AnalpH2_MeOH_4 min(3): Rt 3.21 min; m/z 431 $[M+1]^+$	899 mg, 67%, cream solid

Compound	Analytical Data	Mass, %Yield, State
	AnalpH2_MeOH_4 min(3): Rt 1.68 min; m/z 331 $[M+1]^+$	233 mg, 49%, yellow solid
	AnalpH2_MeOH_4 min(3): Rt 1.73 min; m/z 359 $[M+1]^+$	149 mg, 19%, yellow oil
	AnalpH2_MeOH_4 min(3): Rt 1.74 min; m/z 387 $[M+1]^+$	995 mg, 91%, yellow solid
	AnalpH2_MeOH_4 min(3): Rt 1.77 min; m/z 373 $[M+1]^+$	589 mg, 81%, yellow solid

Compound	Analytical Data	Mass, %Yield, State
	AnalpH2_MeOH_4 min(3): Rt 1.80 min; m/z 373 $[M+1]^+$	593 mg, 82%, dark yellow solid
	AnalpH2_MeOH_4 min(3): Rt 3.25 min; m/z 445 $[M+1]^+$	889 mg, quant., white solid
	AnalpH2_MeOH_4 min(3): Rt 1.75 min; m/z 359 $[M+1]^+$	784 mg, 73%, yellow/orange foam

Scheme JJ, Step AC (Protocol 2): Synthesis of aryl boronic acid derivatives of Formula **43** (via reductive amination)

Pyridin-2-ylmethyl-[1-(4-cyclopropylmethyl-piperazine)]-5-boronic acid

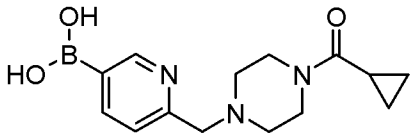
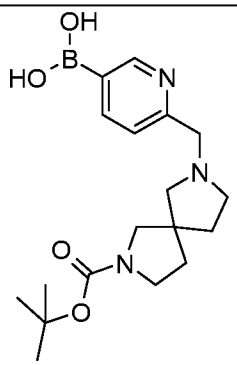
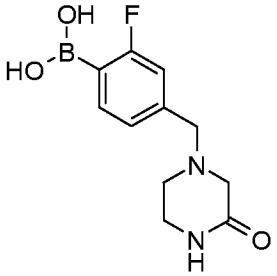


To a stirred solution of 2-formylpyridine-5-boronic acid pinacolate (200 mg, 1.33 mmol) in DCE (10 mL) was added 1-(cyclopropylmethyl) piperazine (0.217 mL, 1.46 mmol) and stirred at RT for 30 min. Sodium triacetoxyborohydride (424 mg, 2.00 mmol) was added and the reaction mixture stirred for 18 h at RT. The reaction mixture *concentrated in*

vacuo and the residue was diluted with water (20 mL) and the aqueous layer washed with EtOAc. The combined aqueous layer was concentrated *in vacuo* and the crude material was purified by reverse phase preparative HPLC-MS to obtain pyridin-2-ylmethyl-[1-(4-cyclopropylmethyl-piperazine)]-5-boronic acid as a pale yellow oil (140 mg, 38%). AnalpH2_MeOH_4min: Rt 0.33 min; m/z 275 $[M+1]^+$.

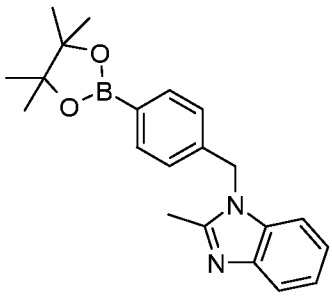
The following aryl boronic acid derivatives **43** are prepared using analogous procedures.

Table 25: Aryl boronic acid derivatives of Formula **43**

Compound	Analytical Data	Mass, %Yield, State
	AnalpH9_MeOH_4 min: Rt 1.85 min; m/z 290 $[M+1]^+$	122 mg, 32%, brown oil
	AnalpH2_MeOH_4 min: Rt 1.72 min; m/z 362 $[M+1]^+$	68 mg, 47%, pale yellow solid
	AnalpH2_MeOH_4 min: Rt 0.73 min; m/z 253 $[M+1]^+$	164 mg, 55%, off-white solid

Scheme JJ, Step AC (Protocol 3): Synthesis of aryl boronic ester derivatives of Formula **43** (via alkylation)

2-Methyl-1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-1*H*-benzoimidazole

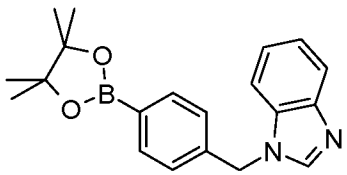
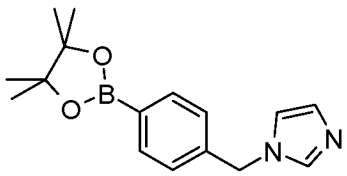


To a solution of 4-bromomethylphenylboronic acid pinacol ester (564 mg, 1.90 mmol) in acetone (19 mL) was added 2-methylbenzimidazole (377 mg, 2.85 mmol), potassium iodide (16 mg, 0.095 mmol) and K_2CO_3 (394 mg, 2.85 mmol) and the reaction mixture heated at 60 ºC for 3.25 h. The reaction mixture was diluted with H_2O and extracted with EtOAc (x2). The organic layers were combined, dried (phase separation cartridge) and concentrated *in vacuo*. The crude material was purified by reverse phase preparative HPLC-MS to afford 2-Methyl-1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl] 1*H*-benzoimidazole as an off-white solid (234 mg, 35%).

AnalpH2_MeOH_4min(3): Rt 2.26 min; m/z 349 $[M+1]^+$.

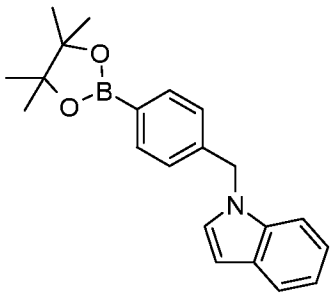
The following aryl boronic ester derivatives **43** are prepared using analogous procedures.

Table 26: Aryl boronic ester derivatives of Formula **43**

Compound	Analytical Data	Mass, %Yield, State
	AnalpH2_MeOH_4 min(3): Rt 2.49 min; m/z 335 $[M+1]^+$.	385 mg, 53%, white solid
	Commercially available	N/A

Scheme JJ, Step AC (Protocol 3a): Synthesis of aryl boronic ester derivatives of Formula **43** (via alkylation)

1-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-1*H*-indole

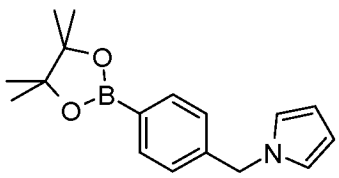


To NaH (78 mg, 1.94 mmol) in anhydrous DMF (4 mL) under N_2, at 0 ºC was added indole (227 mg, 1.94 mmol) in anhydrous DMF (5 mL). The reaxtion mixture was maintained at this temperature for 10 min. 4-bromomethylphenylboronic acid pinacol ester (523 mg, 1.76 mmol) in anhydrous DMF (8 mL) was added and the reaction stirred at RT for 18 h. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 (x2). The organic phases were combined, washed with brine, dried (phase separation cartridge) and the solvent removed *in vacuo*. The crude material was purified by silica gel column chromatography eluting with isohexane and increasing the polarity to 5% EtOAc/isohexane. The compound was further purified by reverse phase preparative HPLC-MS to afford 1-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-1*H*-indole as an off-white solid (120 mg, 10%).

AnalpH2_MeOH_4min(3): Rt 3.50 min; m/z 334 $[M+1]^+$.

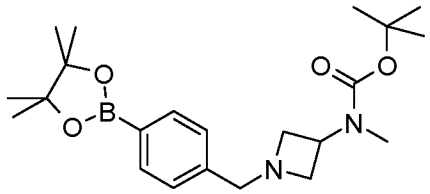
The following aryl boronic ester derivatives **43** are prepared using analogous procedures.

Table 27: Aryl boronic ester derivatives of Formula **43**

Compound	Analytical Data	Mass, %Yield, State
	AnalpH2_MeOH_4 min(3): Rt 3.34 min; m/z 284 $[M+1]^+$	130 mg, 23%, white solid

Scheme JJ, Step AC (Protocol 3b): Synthesis of aryl boronic ester derivatives of Formula **43** (via alkylation)

Methyl-{1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-azetidin-3-yl}-carbamic acid *tert*-butyl ester

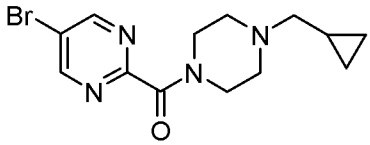


To 4-bromomethylboronic acid pinacol ester (500 mg, 168 mmol) and azetidin-3-yl-methyl-carbamic acid *tert*-butyl ester hydrochloride (561 mg, 2.52 mmol) in anhydrous THF (12 mL) was added NEt_3 (704 µl, 5.05 mmol). The reaction mixture was stirred at RT, under N_2 balloon, for 18 h. The reaction mixture was concentrated in vacuo, suspended in CH_2Cl_2 and washed with H_2O. The aqueous layer was separated and washed with CH_2Cl_2. The organic layers were combined, dried (phase separation cartridge) and cthe solvent removed in vacuo. The crude material was purified by silica gel column chromatography eluting with CH_2Cl_2 and increasing the polarity to 20% MeOH/CH_2Cl_2 to afford methyl-{1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzyl]-azetidin-3-yl}-carbamic acid *tert*-butyl ester as a colourless oil (441 mg, 65%).

AnalpH2_MeOH_4min(3): Rt 2.21 min; m/z 403 $[M+1]^+$.

Scheme JJ, Step AD (Protocol 1): Synthesis of aryl bromide derivatives of formula **47** (via amide coupling)

(5-Bromo-pyrimidin-2-yl)-(4-cyclopropylmethyl-piperazin-1-yl)-methanone

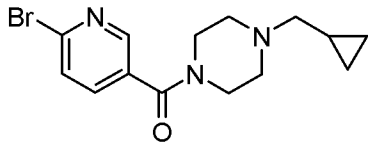
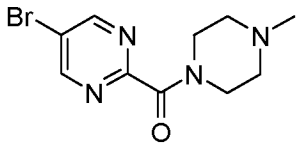
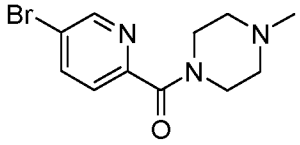
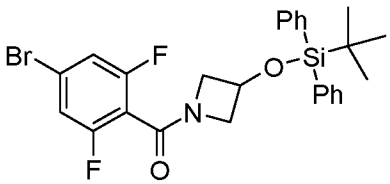
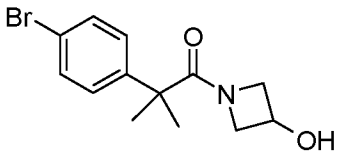
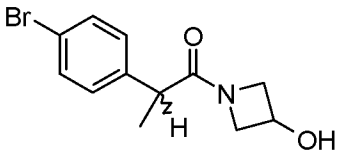


To 5-bromopyrimidine-2-carboxylic acid (100 mg, 0.49 mmol) and TBTU (158 mg, 0.49 mmol) in anhydrous DMF 94.4. mL) was added DIPEA (0.36M in CH_2Cl_2, 1.4 mL, 0.49 mmol) and the reaction mixture stirred at RT for 40 min. *N*-cyclopropylmethylpiperazine (83 mg, 0.59 mmol) in anhydrous DMF (1 mL) was added and the reaction stirred at RT for 18 h. The reaction mixture was passed through a Si-NH_2 cartridge (5g), eluting with DMF and MeOH. The eluents were combined, concentrated *in vacuo* and purified by reverse phase preparative HPLC-MS to obtain (5-bromo-pyrimidin-2-yl)-(4-cyclopropylmethyl-piperazin-1-yl)-methanone as a pale yellow solid (46 mg, 29%).

AnalpH2_MeOH_4min(3): Rt 0.35, 0.81 min; m/z 325 $[M+1]^+$.

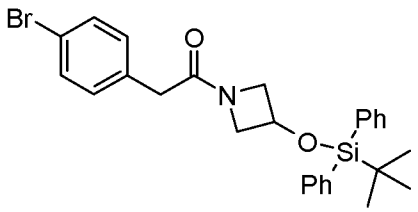
The following bromo aryl derivatives **47** are prepared using analogous procedures.

Table 28: Aryl bromide derivatives of Formula **47**

Compound	Analytical Data	Mass, %Yield, State
	AnalpH2_MeOH_4 min(3): Rt 0.84 min; m/z 325 $[M+1]^+$	390 mg, 53%, colorless oil, solidifies on standing
	AnalpH9_MeOH_4 min(2): Rt 1.64 min; m/z 285 $[M+1]^+$	314 mg, 50%, tan solid
	AnalpH9_MeOH_4 min(2): Rt 2.06 min; m/z 284 $[M+1]^+$	1.17 g, 83%, dark orange oil
	AnalpH2_MeOH_4 min(3): Rt 3.65 min; m/z 530 $[M+1]^+$	971 mg, 82%, orange oil
	AnalpH2_MeOH_4 min(3): Rt 2.64 min; m/z 298 $[M+1]^+$	500 mg, 81%, white solid
	AnalpH2_MeOH_4 min(3): Rt 2.47 min; m/z 284 $[M+1]^+$	457 mg, 67%, pale yellow solid

Scheme JJ, Step AD (Protocol 1a): Synthesis of aryl bromide derivatives of formula **47** (via amide coupling-via acid chloride)

2-(4-Bromo-phenyl)-1-[3-(*tert*-butyl-diphenyl-silanyloxy)-azetidin-1-yl]-ethanone

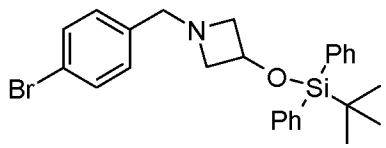


To 4-bromophenyl acetylchloride (300 mg, 1.28 mmol) in CH_2Cl_2 (5 mL) was added 3-(*tert*-Butyl-diphenyl-silanyloxy)-azetidine (399 mg, 1.28 mmol), DIPEA (670 µL, 3.85 mmol) and the reaction stirred at RT for 2 h. The crude material was purified by silica gel column chromatography, eluting with isohexane and increasing the polarity to 80% EtOAc/isohexane to obtain 2-(4-bromo-phenyl)-1-[3-(*tert*-butyl-diphenyl-silanyloxy)-azetidin-1-yl]-ethanone as a colourless glass (632 mg, 97%).

AnalpH2_MeOH_4min(3): Rt 3.71 min; m/z 510 $[M+1]^+$.

Scheme JJ, Step AD (Protocol 3): Synthesis of aryl bromide derivatives of formula **47** (via alkylation)

1-(4-Bromo-benzyl)-3-(*tert*-butyl-diphenyl-silanyloxy)-azetidine

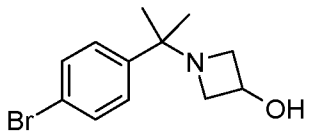


To 4-bromomethylbenzyl bromide (300 mg, 1.2 mmol) in THF (5 mL) was added NEt_3 (418 µl, 3 mmol) and the reaction mixture stirred at RT for 10 min. 3-(*tert*-Butyl-diphenyl-silanyloxy)-azetidine hydrochloride (628 mg, 1.8 mmol) was added and the reaction stirred at RT for 18 h. The reaction mixture was concentrated *in vacuo* and the residue partitioned between CH_2Cl_2 and 5% $NaHCO_3$ (aq). The organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography, eluting with isohexane and increasing the polarity to 50% EtOAc/isohexane to obtain 1-(4-Bromo-benzyl)-3-(*tert*-butyl-diphenyl-silanyloxy)-azetidine as a colourless oil (328 mg, 57%).

AnalpH2_MeOH_4min(3): Rt 2.77 min; m/z 480 $[M+1]^+$.

Scheme JJ, Step AD (Protocol 3a): Synthesis of aryl bromide derivatives of formula **47** (via alkylation)

1-[1-(4-Bromo-phenyl)-1-methyl-ethyl]-azetidin-3-ol

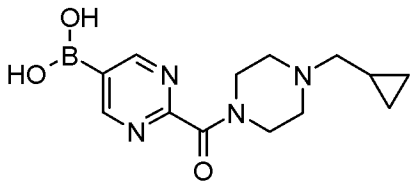


1-(4-Bromophenyl)-1-methyl-ethylamine (1g, 4.67 mmol) and epichlorohydrin (439 µl, 5.6 mmol) in EtOH (15 mL) were heated at 70 ºC for 18 h. The reaction mixture was concentrated *in vacuo* and purified by reverse phase preparative HPLC-MS to obtain 1-[1-(4-bromo-phenyl)-1-methyl-ethyl]-azetidin-3-ol as a white solid (489 mg, 38%).

AnalpH2_MeOH_4min(3): Rt 2.77 min; m/z 480 $[M+1]^+$.

Scheme JJ, Step AE: Synthesis of aryl boronic acid or boronic ester derivatives of Formula **43**

2-(4-Cyclopropylmethyl-piperazine-1-carbonyl)-pyrimidine-5-boronic acid

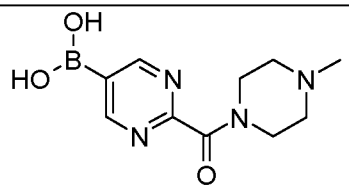
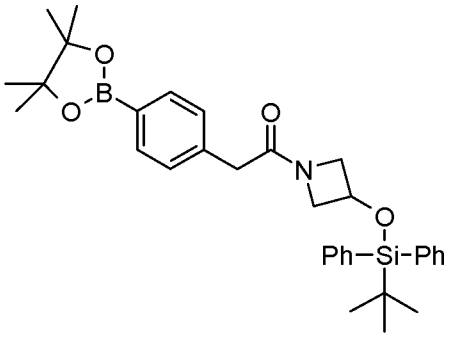


(5-Bromo-pyrimidin-2-yl)-(4-cyclopropylmethyl-piperazin-1-yl)-methanone (46 mg, 0.14 mmol), *bis*(pinacolato)diboron (43 mg, 0.17 mmol), $Pd(dppf)Cl_2$ (12 mg, 0.014 mmol) and potassium acetate (42 mg, 0.42 mmol) in 1,4-dioxane (0.7 mL) were added to a microwave vial and the reaction mixture purged with N_2 for 10 min. The reaction mixture was irradiated using a microwave reactor (300W, 120 °C, 20 min). The reaction mixture was passed through a Si-thiol cartridge (2 g) and the column washed with MeOH (4 x column volumes). The solvent was removed in vacuo and purified by reverse phase preparative HPLC-MS. The sample was passed through a SCX-2 cartridge (500 mg) and the column washed with MeOH (4 x column volumes). The compound was eluted from the column with 0.5M NH_3/MeOH to afford 2-(4-cyclopropylmethyl-piperazine-1-carbonyl)-pyrimidine-5-boronic acid as a white solid (29 mg, 70%).

AnalpH9_MeOH_4min(2): Rt 1.15 min; m/z 291 $[M+1]^+$.

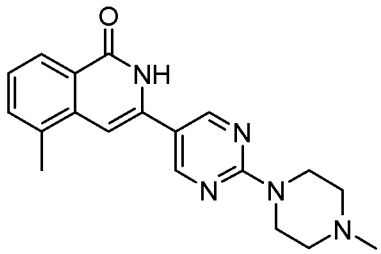
The following aryl boronic acid or boronic ester derivatives **43** are prepared using analogous procedures.

Table 29: Aryl boronic acid or boronic ester derivatives of Formula **43**

Compound	Analytical Data	Mass, %Yield, State
	AnalpH2_MeOH_4 min(3): Rt 0.3 min; m/z 251 $[M+1]^+$	163 mg, 68%, white solid
	AnalpH2_MeOH_4 min(3): Rt 3.72 min; m/z 556 $[M+1]^+$	141 mg, 47%, brown oil

Scheme J, Step AA: Synthesis of *2H*-isoquinolin-1-one derivatives of formula **4** (via Suzuki cross-coupling)

5-Methyl-3-[2-(4-methyl-piperazin-1-yl)-pyrimidin-5-yl]-*2H*-isoquinolin-1-one (IQ-025)

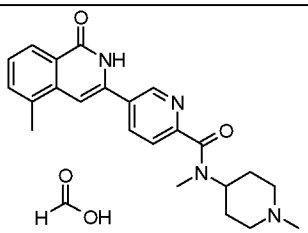
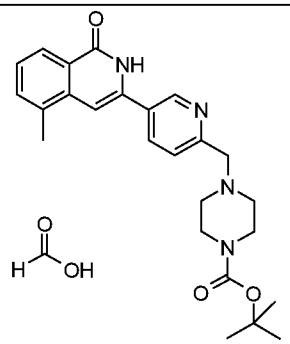
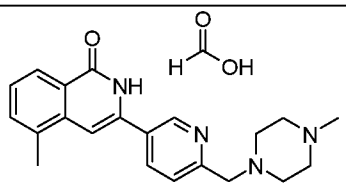
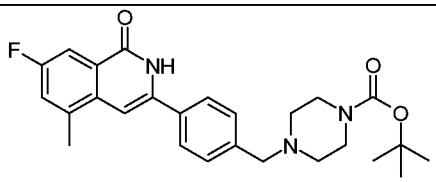
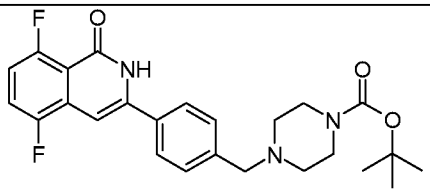
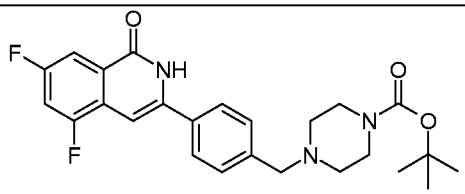


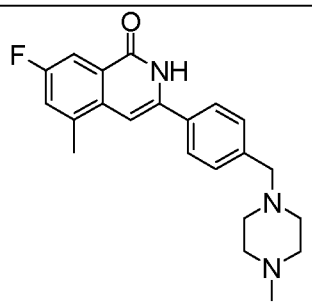
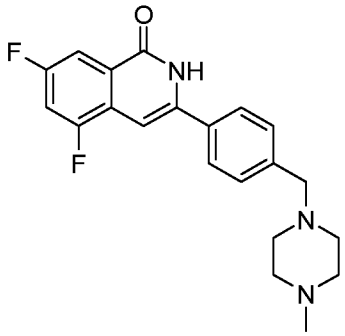
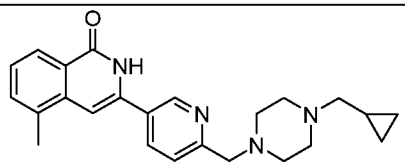
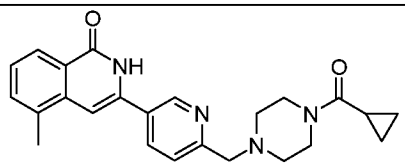
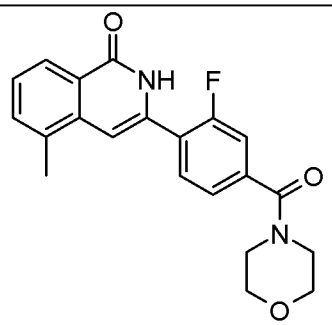
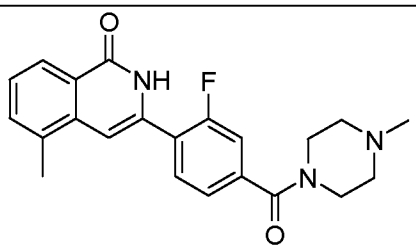
3-Chloro-5-methyl-*2H*-isoquinolin-1-one (50 mg, 0.26 mmol), 2-(4-methylpiperazin-1-yl)pyrimidine-5-boronic acid pinacol ester (118 mg, 0.39 mmol), K_2CO_3 (73 mg, 0.52 mmol) and $Pd(dppf)Cl_2$ (10 mg, 0.013 mmol) in DME/EtOH/H_2O 4:0.5:1 (2.75 mL) were added to a microwave vial and the reaction mixture purged with N_2 for 10 min. The reaction mixture was irradiated using a microwave reactor (300W, 100 °C, 60 min). The reaction mixture was filtered through celite and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography, eluting with CH_2Cl_2 and increasing the polarity to 50% MeOH/CH_2Cl_2. The crude material was trituared with MeOH and washed with isohexane to afford 5-methyl-3-[2-(4-methyl-piperazin-1-yl)-pyrimidin-5-yl]-*2H*-isoquinolin-1-one as an off-white solid (28 mg, 32%).

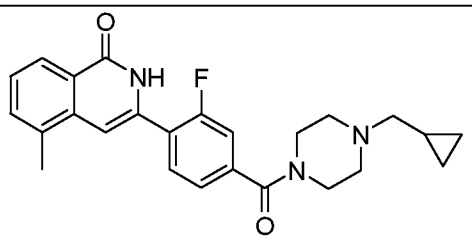
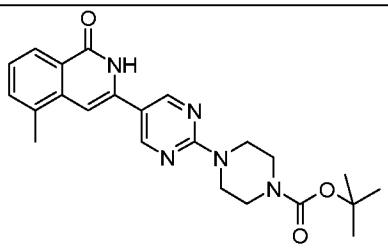
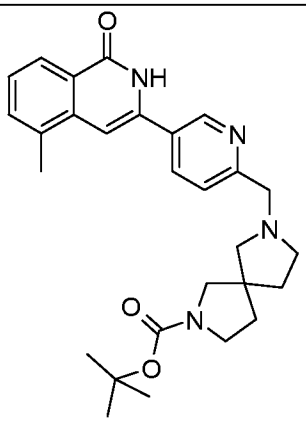
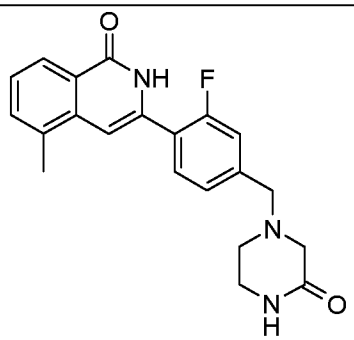
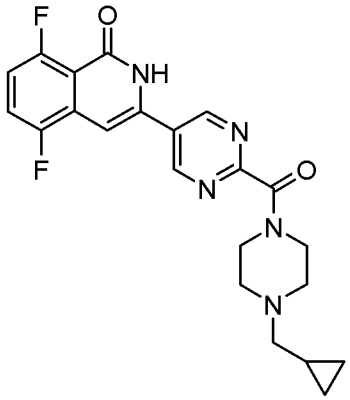
AnalpH2_MeOH_QC(1): Rt 4.97 min; m/z 336 $[M+1]^+$.

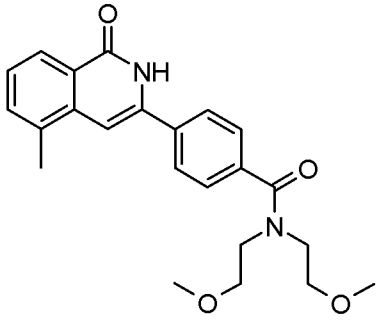
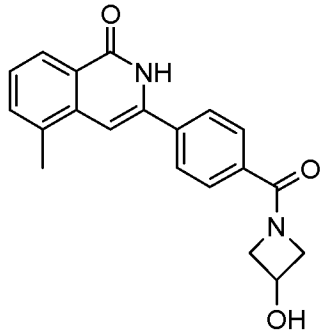
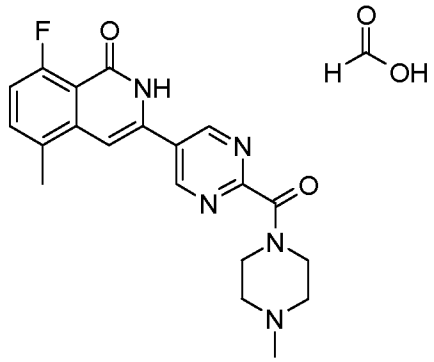
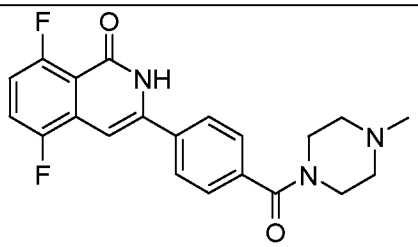
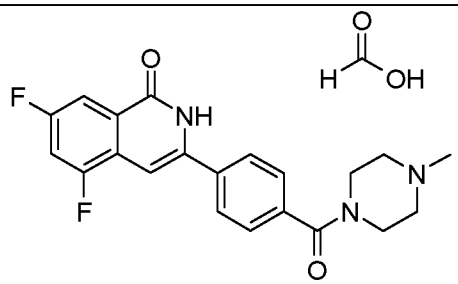
The following *2H*-isoquinolin-1-one derivatives are prepared using analogous procedures.

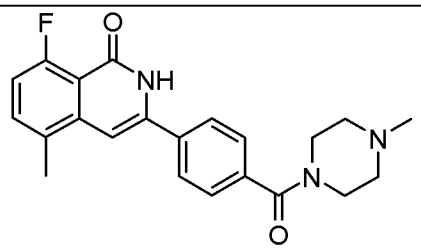
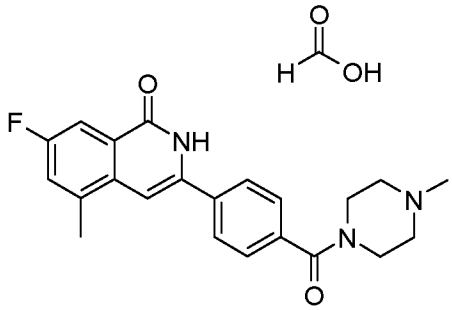
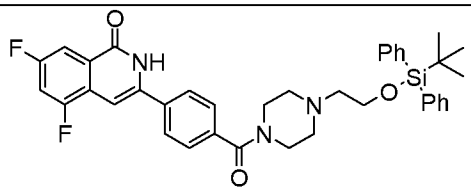
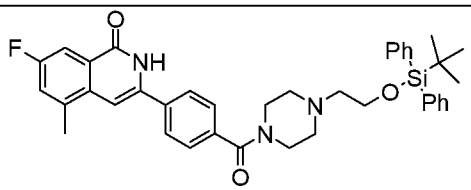
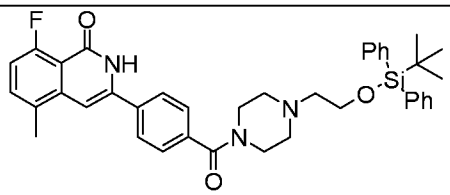
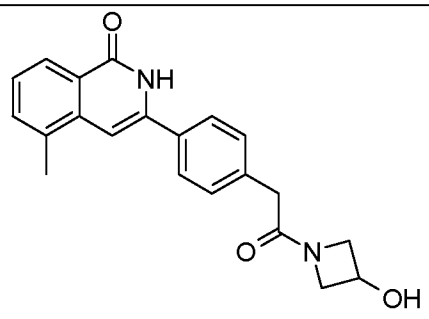
Table 30: *2H*-isoquinolin-1-one derivatives of Formula **4**

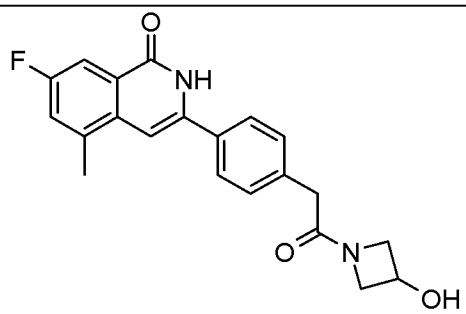
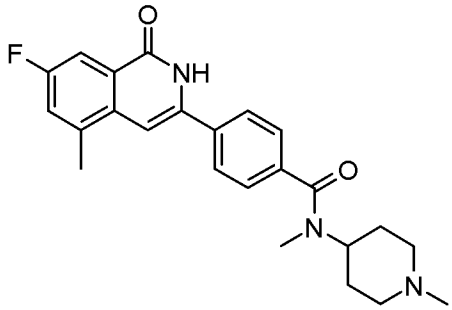
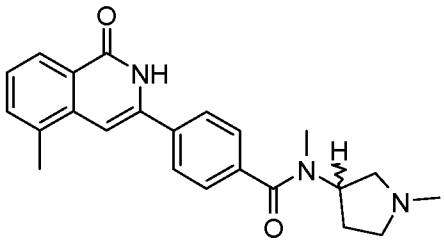
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-099	AnalpH2_MeOH _QC(1): Rt 4.74 min; m/z 391 $[M+1]^+$	13 mg, 10%, cream solid
	IQ-071	AnalpH2_MeOH _QC(1): Rt 6.35 min; m/z 435 $[M+1]^+$	31 mg, 27%, cream solid
	IQ-057	AnalpH2_MeOH _QC(1): Rt 4.84 min; m/z 349 $[M+1]^+$	17 mg, 20%, pale orange solid
	IQ-076	AnalpH2_MeOH _QC(1): Rt 6.56 min; m/z 452 $[M+1]^+$	72 mg, 66%, pale orange solid
	IQ-077	AnalpH2_MeOH _QC(1): Rt 6.69 min; m/z 456 $[M+1]^+$	46 mg, 29%, pale brown solid
	IQ-154	AnalpH2_MeOH _QC(1):: Rt 6.69 min; m/z 456 $[M+1]^+$	46 mg, 29%, pale brown solid

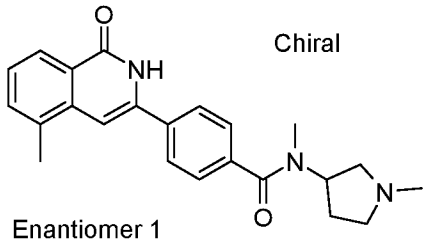
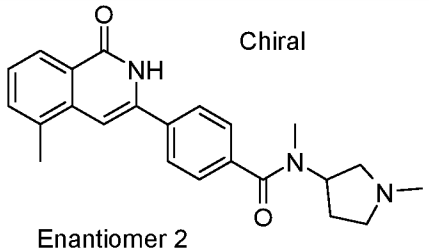
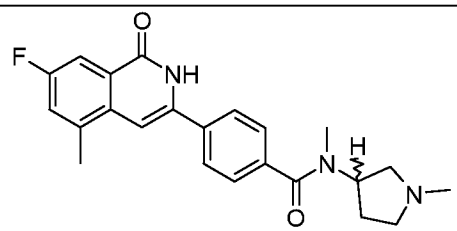
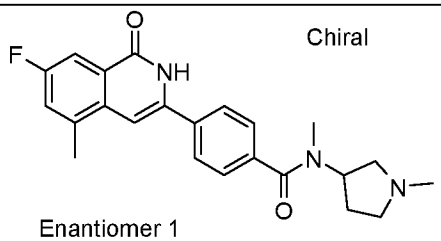
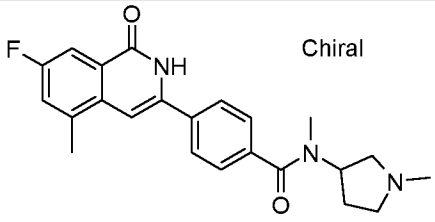
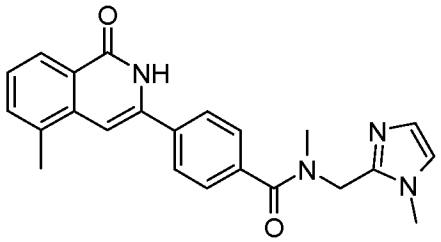
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-080	AnalpH2_MeOH _QC(1): Rt 5.57 min; m/z 366 $[M+1]^+$	39 mg, 45%, brown solid
	IQ-138	AnalpH2_MeOH _QC(1): Rt 5.63 min; m/z 370 $[M+1]^+$	25 mg, 29%, white solid
	IQ-161	AnalpH2_MeOH _QC: Rt 5.19 min; m/z 389 $[M+1]^+$	44 mg, 40%, pale brown solid
	IQ-162	AnalpH2_MeOH _QC: Rt 5.41 min; m/z 404 $[M+1]^+$	48 mg, 43%, pale brown solid
	IQ-163	AnalpH2_MeOH _QC: Rt 7.44 min; m/z 367 $[M+1]^+$	19 mg, 11%, off-white solid
	IQ-164	AnalpH2_MeOH _QC: Rt 5.19 min; m/z 380 $[M+1]^+$	40 mg, 23%, beige solid

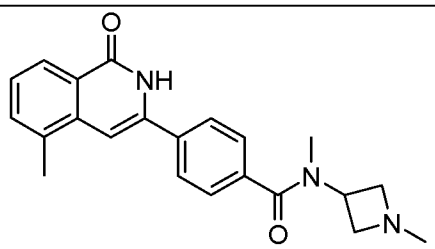
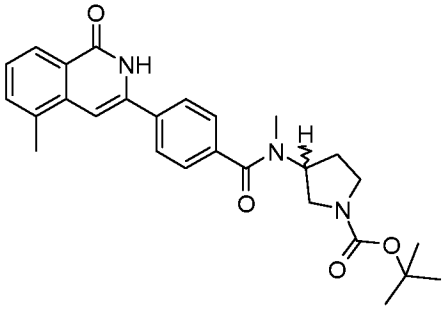
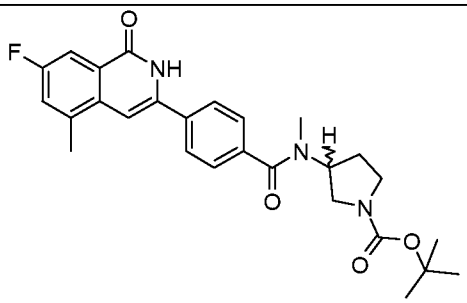
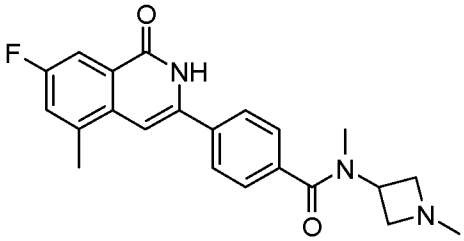
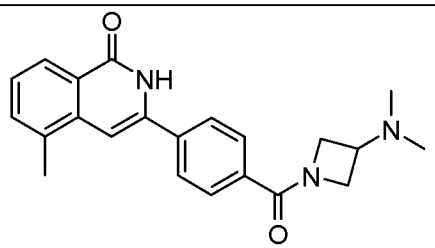
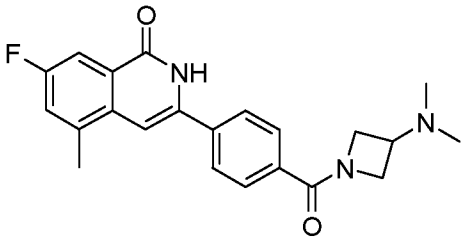
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-165	AnalpH2_MeOH _QC: Rt 5.38 min; m/z 420 $[M+1]^+$	50 mg, 26%, light brown solid
		AnalpH2_MeOH _4min(1): Rt 3.31 min; m/z 422 $[M+1]^+$	Used in next step as crude material
		AnalpH2_MeOH _4min: Rt 2.31 min; m/z 476 $[M+1]^+$	Used in next step as crude material
	IQ-166	AnalpH2_MeOH _QC: Rt 7.23 min; m/z 366 $[M+1]^+$	23 mg, 20%, white solid
	IQ-229	AnalpH2_MeOH _QC(1): Rt 4.36 min; m/z 426 $[M+1]^+$	4.8 mg, 15%, off-white solid

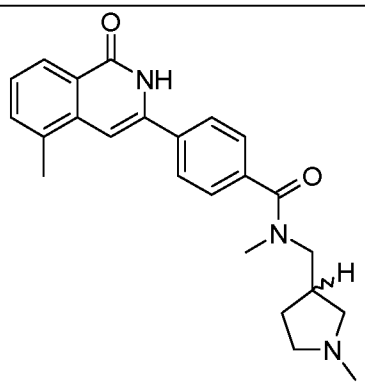
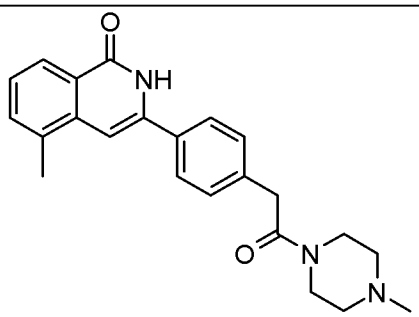
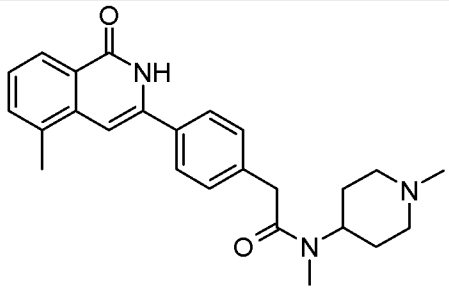
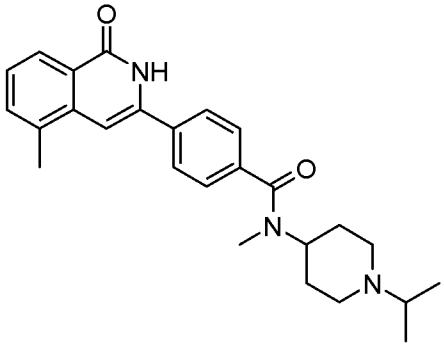
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-187	AnalpH2_MeOH _QC(1): Rt 8.05 min; m/z 395 $[M+1]^+$	79 mg, 42%, off-white solid
	IQ-188	AnalpH2_MeOH _QC(1): Rt 7.10 min; m/z 335 $[M+1]^+$	92 mg, 27%, white solid
	IQ-225	AnalpH2_MeOH _QC(1): Rt 4.27 min; m/z 382 $[M+1]^+$	7 mg, 8%, pale yellow solid
	IQ-226	AnalpH2_MeOH _QC(1): Rt 4.74 min; m/z 384 $[M+1]^+$	3.6 mg, 4%, beige solid
	IQ-227	AnalpH2_MeOH _QC(1): Rt 5.19 min; m/z 384 $[M+1]^+$	3.4 mg, 3%, white solid

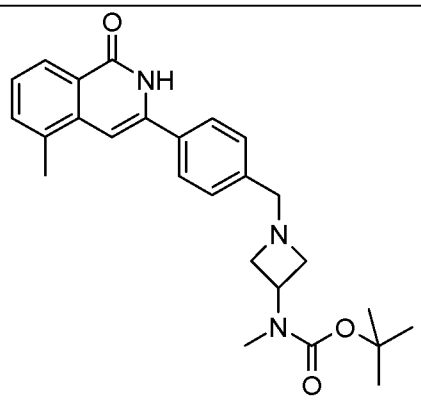
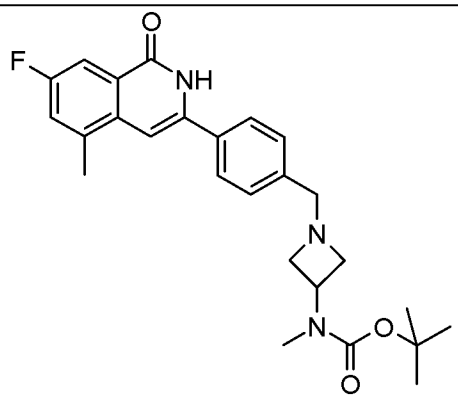
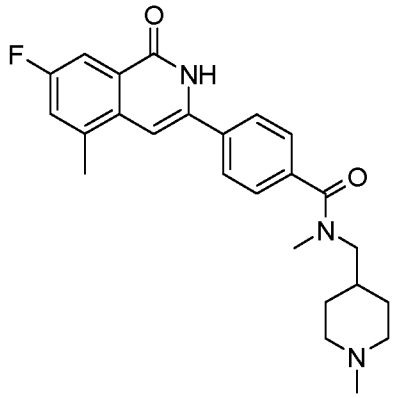
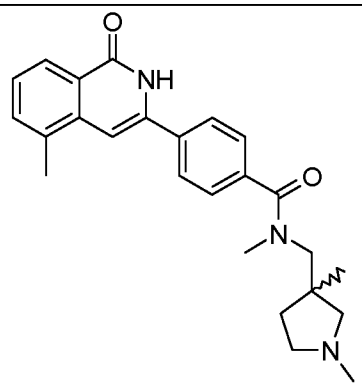
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-189	AnalpH2_MeOH _QC(1): Rt 4.89 min; m/z 380 $[M+1]^+$	4.7 mg, 5%, white solid
	IQ-190	AnalpH2_MeOH _QC(1): Rt 5.25 min; m/z 380 $[M+1]^+$	5 mg, 5%, white solid
	Intermediate for IQ-228	AnalpH2_MeOH _4min(3): Rt 3.22 min; m/z 652 $[M+1]^+$	83 mg, 54%, beige solid
	Intermediate for IQ-192	AnalpH2_MeOH _4min(3): Rt 3.19 min; m/z 649 $[M+1]^+$	63 mg, 36%, beige solid
	Intermediate for IQ-193	AnalpH2_MeOH _4min(3): Rt 3.10 min; m/z 649 $[M+1]^+$	79 mg, 44%, beige solid
	IQ-214	AnalpH2_MeOH _QC(1): Rt 7.24 min; m/z 349 $[M+1]^+$	20 mg, 17 %, off-white solid

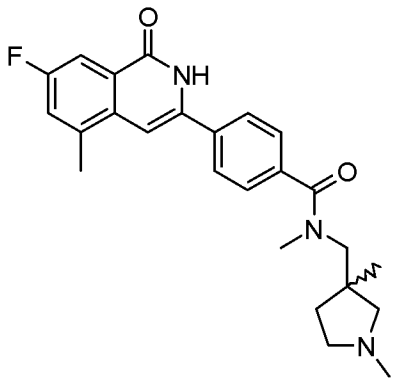
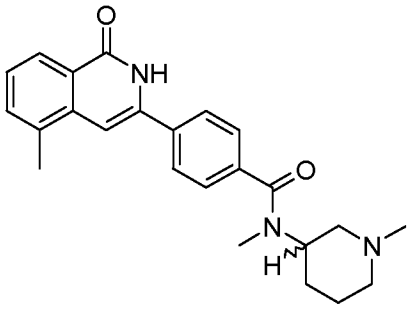
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-215	AnalpH2_MeOH_QC(1): Rt 7.45 min; m/z 367 $[M+1]^+$	44 mg, 37 %, off-white solid
	IQ-195	AnalpH2_MeOH_QC(1): Rt 5.35 min; m/z 408 $[M+1]^+$	72 mg, 38 %, white solid ^{1}H NMR (400 MHz, DMSO-d_6): δ11.77 (br s, 1H), 7.89 (d, J = 8.8 Hz, 2H), 7.74 (dd, J = 9.6, 2.8 Hz, 1H), 7.52 (dd, J = 9.6, 2.8 Hz, 1H), 7.48 (d, J = 7.6 Hz, 2H), 6.94 (s, 1H), 4.33-4.24 (br s, 0.5H), 2.92-2.73 (m, 5H), 2.61 (s, 3H), 2.22-1.93 (m, 4H), 1.92-1.55 (m, 5.5H).
	IQ-196	AnalpH2_MeOH_QC(1): Rt 5.17 min; m/z 377 $[M+1]^+$	99 mg, 81 %, brown solid

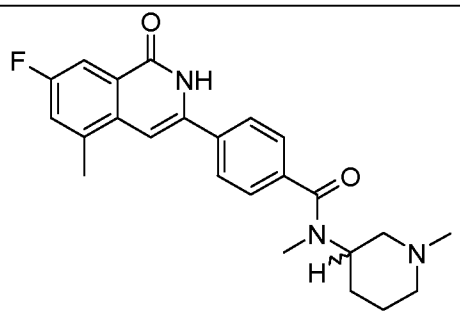
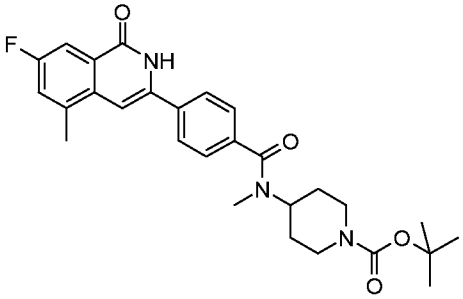
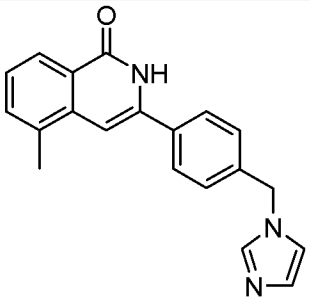
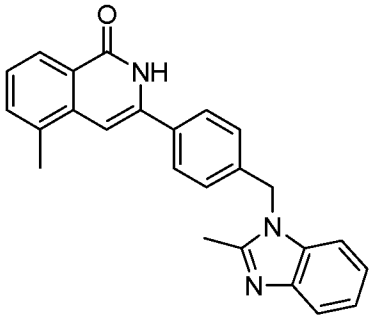
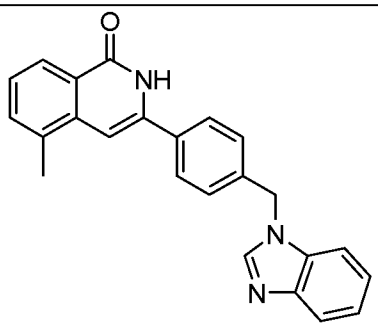
Compound	Code	Analytical Data	Mass, %Yield, State
 Chiral Enantiomer 1	IQ-205-1	AnalpH2_MeOH_QC(2): Rt 4.69 min; m/z 376.5 $[M+1]^+$	13.4 mg, 37.5 %, off-white solid; obtained via Chiral_Method_3
 Chiral Enantiomer 2	IQ-205-2	AnalpH2_MeOH_QC(2): Rt 4.67 min; m/z 376.5 $[M+1]^+$	12.4 mg, 34.7 %, off-white solid; obtained via Chiral_Method_3
	IQ-197	AnalpH2_MeOH_QC(1): Rt 5.35 min; m/z 394 $[M+1]^+$	60 mg, 48 %, off-white solid
 Chiral Enantiomer 1	IQ-207-1	AnalpH2_MeOH_QC(2): Rt 4.84 min; m/z 394 $[M+1]^+$	5.5 mg, 37 %, white solid; obtained via Chiral_Method_3
 Chiral Enantiomer 2	IQ-207-2	AnalpH2_MeOH_QC(2): Rt 4.83 min; m/z 394.5 $[M+1]^+$	4.9 mg, 33 %, white solid; obtained via Chiral_Method_3
	IQ-198	AnalpH2_MeOH_QC(1): Rt 5.22 min; m/z 388 $[M+1]^+$	80 mg, 40 %, off-white solid

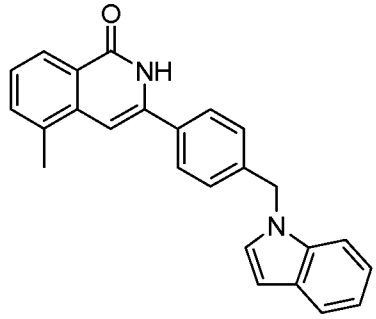
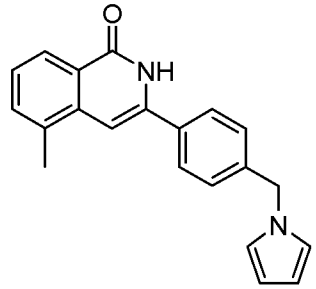
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-199	AnalpH2_MeOH _QC(1): Rt 5.11 min; m/z 362 $[M+1]^+$	70 mg, 72 %, off-white solid
	Intermediate for IQ-200	AnalpH2_MeOH _4min(3): Rt 3.08 min; m/z 462.5 $[M+1]^+$	Used in next step as crude material
	Intermediate for IQ-186	AnalpH2_MeOH _4min(3): Rt 3.12 min; m/z 480.5 $[M+1]^+$	Used in next step as crude material
	IQ-201	AnalpH2_MeOH _QC(1): Rt 5.31 min; m/z 380.4 $[M+1]^+$	37 mg, 34 %, off-white solid
	IQ-202	AnalpH2_MeOH _QC(1): Rt 5.11 min; m/z 362 $[M+1]^+$	16 mg, 16 %, white solid
	IQ-203	AnalpH2_MeOH _QC(1): Rt 5.35 min; m/z 381 $[M+1]^+$	16 mg, 15 %, white solid

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-204	AnalpH2_MeOH _QC(1): Rt 5.29 min; m/z 390.5 $[M+1]^+$	57mg, 42 %, off-white solid
	IQ-175	AnalpH2_MeOH _QC(1): Rt 5.30 min; m/z 376.5 $[M+1]^+$	131mg, 49 %, off-white solid
	IQ-176	AnalpH2_MeOH _QC(1): Rt 5.48 min; m/z 404.5 $[M+1]^+$	43 mg, 31 %, off-white solid
	IQ-20	AnalpH2_MeOH _QC(2): Rt 4.91 min; m/z 418.5 $[M+1]^+$	28 mg, 13 %, white solid

Compound	Code	Analytical Data	Mass, %Yield, State
	Intermediate for IQ-177	AnalpH2_MeOH _4min(3): Rt 2.16 min; m/z 434.5 $[M+1]^+$	154 mg, 83 %, brown, sticky solid
	Intermediate for IQ-178	AnalpH2_MeOH _4min(3): Rt 2.21 min; m/z 452.5 $[M+1]^+$	159 mg, 83 %, brown, sticky solid
	IQ-208	AnalpH2_MeOH _QC(2): Rt 4.96 min; AnalpH2_MeOH _4min(2):m/z 422 $[M+1]^+$	42 mg, 19 %, white solid
	IQ-209	AnalpH2_MeOH _QC(2): Rt 4.89 min; AnalpH2_MeOH _4min(2): m/z 404 $[M+1]^+$	86 mg, 38 %, beige solid

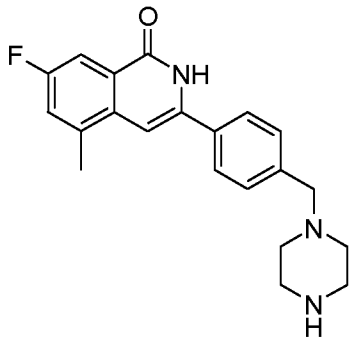
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-210	AnalpH2_MeOH_QC(2): Rt 5.02 min; AnalpH2_MeOH_4min(2):m/z 422.5 $[M+1]^+$	92 mg, 29 %, off-white solid ^{1}H NMR (400 MHz, DMSO-d_6): δ11.72 (br s, 1H), 7.88 (d, J = 8.3 Hz, 2H), 7.74 (br dd, J = 9.3, 2.7 Hz, 1H), 7.55-7.44 (m, 3H), 6.93 (s, 1H), 3.63 (br d, J = 13.2 Hz, 1H), 3.44 (br d, J = 13.2 Hz, 1H), 3.00 (br s, 3H), 2.60 (s, 3H), 2.48-2.44 (m, 1H), 2.29 (d, J = 9.1 Hz, 1H), 2.24 (s, 3H), 2.13 (br s, 1H), 1.86-1.79 (m, 1H), 1.56-1.50 (m, 1H), 1.13 (s, 3H), 0.89 (br s, 1H).
	IQ-211	AnalpH2_MeOH_QC(2): Rt 4.76 min; m/z 390.5 $[M+1]^+$	22 mg, 10 %, off-white solid

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-212	AnalpH2_MeOH_QC(2): Rt 4.89 min; AnalpH2_MeOH_4min(2):m/z 408 $[M+1]^+$	84 mg, 37 %, off-white solid
	Intermediate for IQ-213	AnalpH2_MeOH_4min(3): Rt 3.16 min; m/z 494 $[M+1]^+$	Used in next step as crude material
	IQ-180	AnalpH2_MeOH_QC(2): Rt 4.75 min; m/z 316 $[M+1]^+$	140 mg, 79%, beige solid
	IQ-179	AnalpH2_MeOH_QC(2): Rt 5.81 min; m/z 380.5 $[M+1]^+$	66 mg, 31%, beige solid
	IQ-181	AnalpH2_MeOH_QC(2): Rt 6.56 min; m/z 366.5 $[M+1]^+$	101 mg, 49%, beige solid

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-183	AnalpH2_MeOH _QC(2): Rt 8.54 min; m/z 365.5 $[M+1]^+$	17 mg, 16%, beige solid
	IQ-184	AnalpH2_MeOH _QC(2): Rt 8.16 min; m/z 315 $[M+1]^+$	10.6 mg, 5%, brown solid

Scheme J, Step AF (Protocol 1): Synthesis of *2H*-isoquinolin-1-one Derivatives of formula **5** (via BOC deprotection)

7-Fluoro-5-methyl-3-(4-piperazin-1-ylmethyl-phenyl)-*2H*-isoquinolin-1-one (IQ-078)



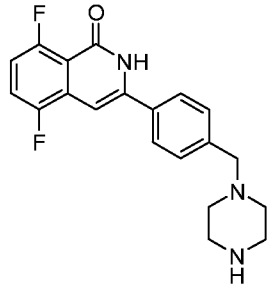
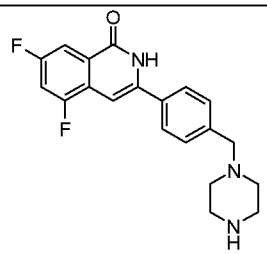
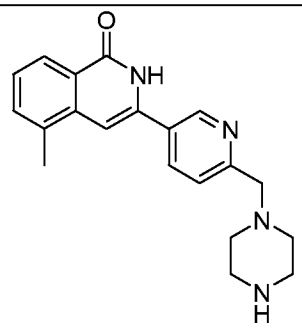
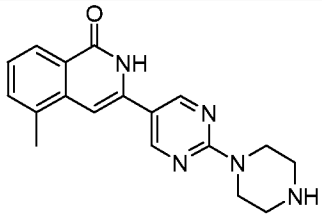
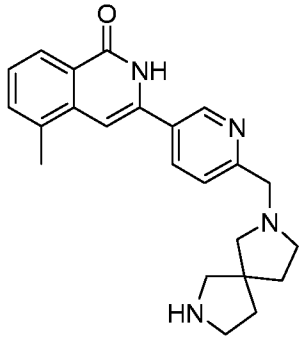
The synthesis is analogous to the Boc deprotection procedure used in Scheme A, Step C (Protocol 1) above to give 7-Fluoro-5-methyl-3-(4-piperazin-1-ylmethyl-phenyl)-*2H*-isoquinolin-1-one as an off-white solid (18.4 mg, 37%).

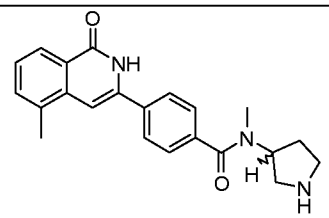
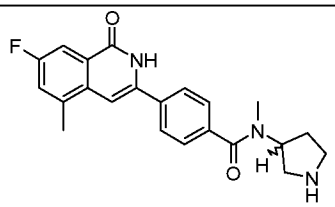
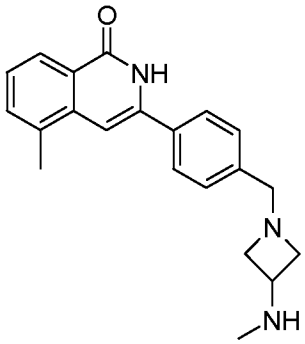
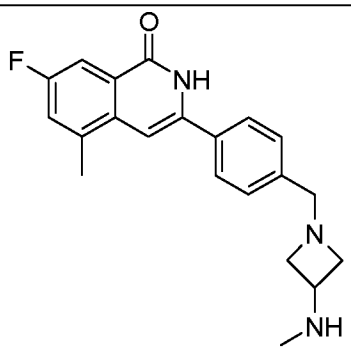
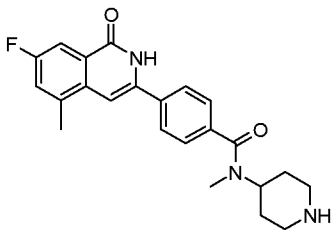
^{1}H NMR (400 MHz, DMSO-d_6): δ7.86 (d, J = 8 Hz, 2H), 7.81 (dd, J = 9, 3 Hz, 1H), 7.60 (dd, J = 9, 3 Hz, 1H), 7.50 (d, J = 8 Hz, 2H), 6.94 (s, 1H), 3.57 (s, 2H), 2.79-2.77 (m, 4H), 2.68 (s, 3H), 2.39 (br s, 4H).

AnalpH2_MeOH_QC(1): Rt 5.49 min; m/z 352 $[M+1]^+$

The following *2H*-isoquinolin-1-one derivatives are prepared using analogous procedures.

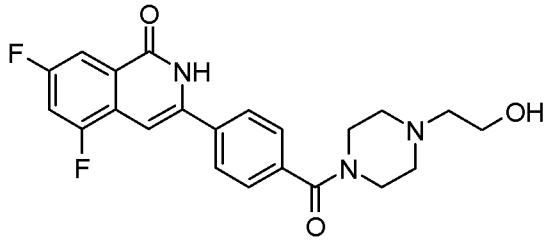
Table 31: *2H*-isoquinolin-1-one Formula **5**

Compound	Reference	Analytical Data	Mass, %Yield, State
	IQ-079	AnalpH2_MeOH_QC(1): Rt 5.05 min; m/z 356 $[M+1]^+$	8 mg, 14%, off-white solid
	IQ-158	AnalpH2_MeOH_QC: Rt 5.62 min; m/z 356 $[M+1]^+$	22 mg, 65% white solid
	IQ-072	AnalpH2_MeOH_QC(1): Rt 4.87 min; m/z 335 $[M+1]^+$	11 mg, 50%, white solid
	IQ-026	AnalpH2_MeOH_QC(1): Rt 5.05 min; m/z 322 $[M+1]^+$	28 mg, 17%, white solid
	IQ-160	AnalpH2_MeOH_QC: Rt 4.31 mins; m/z 375 $[M+1]^+$	16 mg, 29% light brown solid

Compound	Reference	Analytical Data	Mass, %Yield, State
	IQ-200	AnalpH2_MeOH_QC(1): Rt 5.21 min; m/z 362.5 $[M+1]^+$	210 mg, 76 %, off-white solid
	IQ-186	AnalpH2_MeOH_QC(1): Rt 5.39 min; m/z 380.5 $[M+1]^+$	135 mg, 61 %, off-white solid
	IQ-177	AnalpH2_MeOH_QC(2): Rt 3.68 min; m/z 334.5 $[M+1]^+$	35 mg, 29 %, white solid
	IQ-178	AnalpH2_MeOH_QC(2): Rt 3.84 min; m/z 352.5 $[M+1]^+$	42 mg, 34 %, white solid
	IQ-213	AnalpH2_MeOH_QC(2): Rt 4.81 min; AnalpH2_MeOH_4min(2): m/z 394 $[M+1]^+$	80 mg, 36 %, off-white solid

Scheme J, Step AF (Protocol 3): Synthesis of *2H*-isoquinolin-1-one Derivatives of formula **5** (via TBDPS deprotection)

5,7-Difluoro-3-{4-[4-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-phenyl}-*2H*-isoquinolin-1-one (IQ-228)



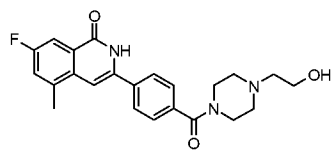
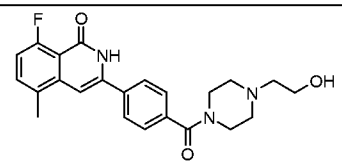
The synthesis is analogous to the TBDPS deprotection procedure used in Scheme A, Step C (Protocol 3) above to give 5,7-difluoro-3-{4-[4-(2-hydroxy-ethyl)-piperazine-1-carbonyl]-phenyl}-*2H*-isoquinolin-1-one as a white solid (20 mg, 48%).

^{1}H NMR (400 MHz, DMSO-d_6): δ11.96 (br s, 1H), 7.87 (d, J = 8 Hz, 2H), 7.80-7.75 (m, 2H), 7.50 (d, J = 8 Hz, 2H), 6.91 (s, 1H), 4.46-4.44 (m, 1H), 3.63 (br s, 2H), 3.50 (q, J = 7 Hz, 2H), 3.35 (br s, 6H), 2.42 (t, J = 6 Hz, 2H).

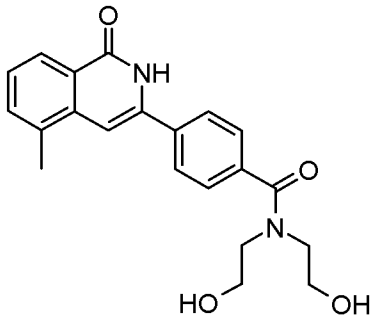
AnalpH2_MeOH_QC(1): Rt 5.19 min; m/z 414 $[M+1]^+$.

The following *2H*-isoquinolin-1-one derivatives are prepared using analogous procedures.

Table 32: *2H*-isoquinolin-1-one Formula **5**

Compound	Reference	Analytical Data	Mass, %Yield, State
	IQ-192	AnalpH2_MeOH_QC(3): Rt 9.23 min; m/z 410 $[M+1]^+$	26 mg, 64 %, white solid
	IQ-193	AnalpH2_MeOH_QC(1): Rt 4.90 min; m/z 410 $[M+1]^+$	37 mg, 75 %, white solid

N,N-Bis-(2-hydroxy-ethyl)-4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzamide (IQ-191)



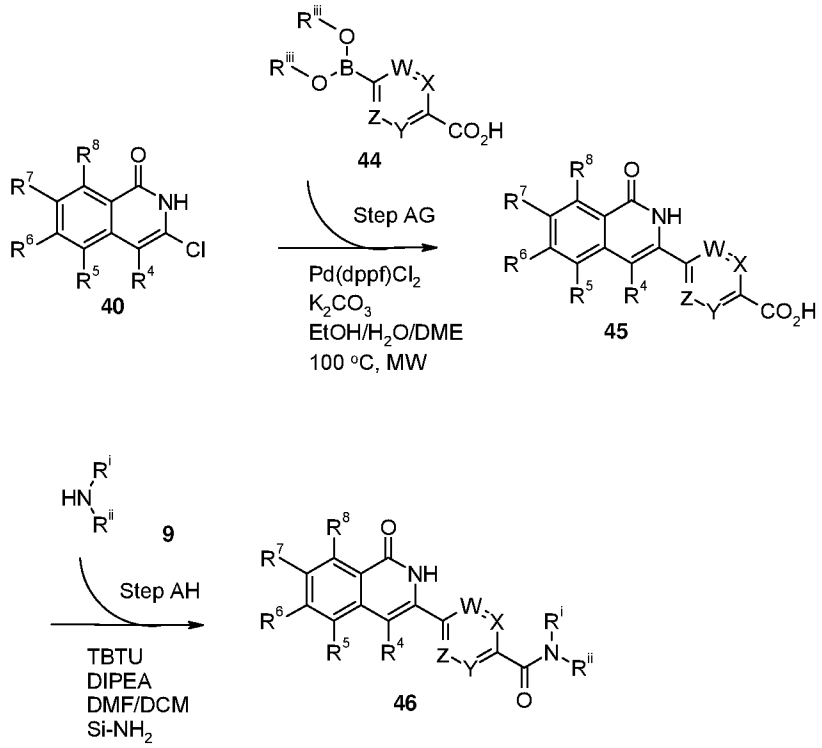
To a stirred solution of *N,N*-Bis-(2-methoxy-ethyl)-4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzamide (40 mg, 0.10 mmol) in CH_2Cl_2 (2.5 mL) under N_2 at -78 ºC was added boron tribromide (1M in CH_2Cl_2, 2.54 mL, 2.54 mmol). The reaction was allowed to warm to RT and stirred for 16 h. The reaction mixture was quenched with H_2O and extracted with EtOAc (5 mL) upon which a pale yellow solid precipitated and was filtered off. The aqueous phase was further extracted with CH_2Cl_2 (5 mL). The combined organics were evaporated to dryness. Product was found to be also present in the aqueous phase and was passed through an Isolute-103 cartridge (500 mg), washing with H_2O (4 x column volumes). The product was eluted from the column with MeOH (4 x column volumes) and evaporated to dryness. The combined crude product was purified by reverse phase preparative HPLC-MS to obtain *N,N*-bis-(2-hydroxy-ethyl)-4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzamide as a white solid (23 mg, 63%).

^{1}H NMR (400 MHz, DMSO-d_6): δ11.64 (br s, 1H), 8.09 (d, J = 8 Hz, 1H), 7.88 (d, J = 8 Hz, 2H), 7.58 (d, J = 7 Hz, 1H), 7.52 (d, J = 8.6 Hz, 2H), 7.39 (t, J = 7.6 Hz, 1H), 6.92 (s, 1H), 4.88-4.82 (m, 2H), 3.66-3.62 (m, 2H), 3.56-3.53 (m, 2H), 3.49-3.48 (m, 2H), 2.58 (s, 3H).

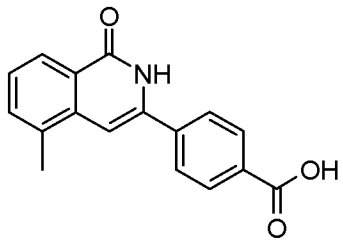
AnalpH2_MeOH_QC(1): Rt 6.76 min; m/z 367 $[M+1]^+$.

General Procedure for Synthesis of *2H*-isoquinolin-1-ones amide derivatives of Formula **4**

Scheme K



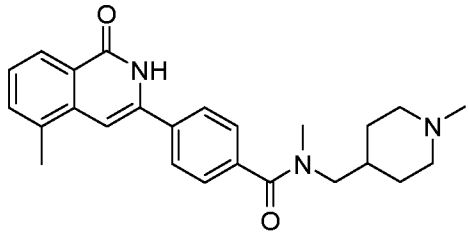
Scheme K, Step AG: Synthesis of 4-(5-Methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzoic acid



3-Chloro-5-methyl-*2H*-isoquinolin-1-one (50 mg, 0.26 mmol), 4-carboxybenezeneboronic acid (64 mg, 0.39 mmol), K_2CO_3 (73 mg, 0.52 mmol) and $Pd(dppf)Cl_2$ (11 mg, 0.013 mmol) in DME/EtOH/H2O 4:0.5:1 (2.75 mL) were added to a microwave vial and the reaction mixture purged with N_2 for 10 min. The reaction mixture was irradiated using a microwave (300W, 120 °C, 2 h). The reaction mixture was concentrated *in vacuo*, water added and the mixture acidified to pH2 with 0.2M HCl aq. A brown solid precipiated from the solution which was filtered and dried *in vacuo*, dissolved in DMF and passed through a Si-thiol cartridge, eluting with DMF (4 x column volumes) and the solvent removed *in vacuo*. The resulting solid was triturated with MeOH, filtered and dried to give 4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-benzoic acid as a beige solid (29 mg, 40%).

AnalpH2_MeOH_QC(1): Rt 7.93 min; m/z 280 $[M+1]^+$.

Scheme K, Step AE: Synthesis of *N*-Methyl-4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-*N*-(1-methyl-piperidin-4-ylmethyl)-benzamide (IQ-095)



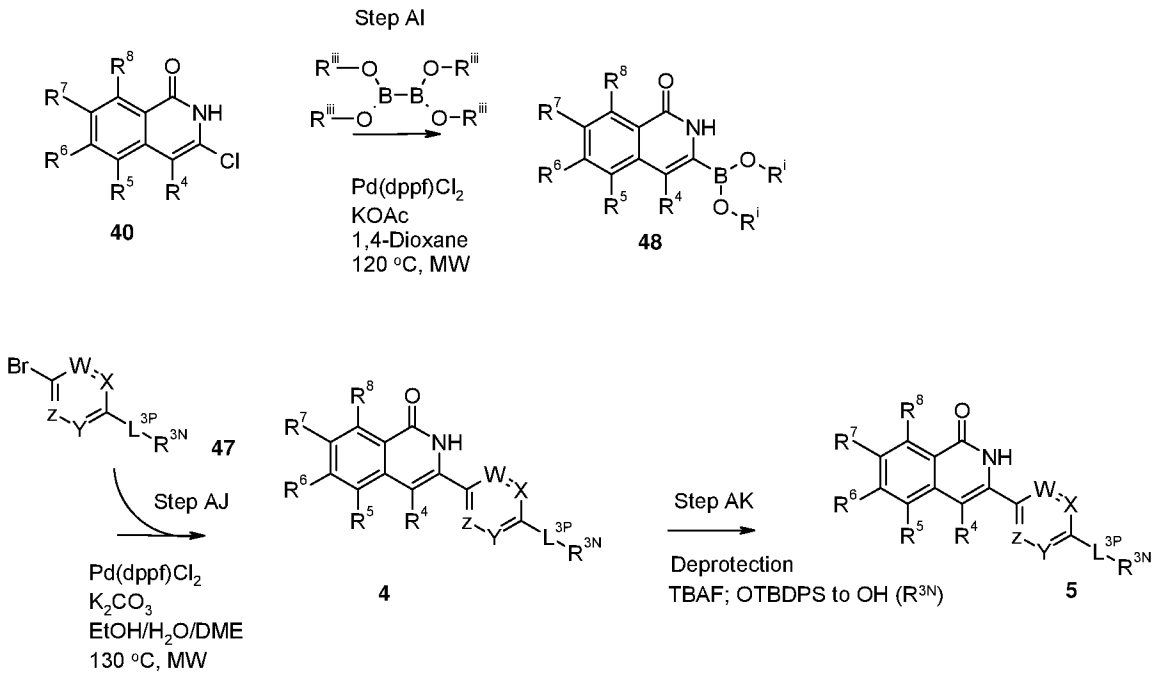
The synthesis is analogous to the acid coupling procedure used in Step E above to give *N*-methyl-4-(5-methyl-1-oxo-1,2-dihydro-isoquinolin-3-yl)-*N*-(1-methyl-piperidin-4-ylmethyl)-benzamide as a pale yellow foam (27 mg, 93%).

^{1}H NMR (400 MHz, DMSO-d_6): δ11.65-11.59 (br s, 1H), 8.09 (d, J = 8 Hz, 1H), 7.89 (d, J = 8 Hz, 2H), 7.57 (d, J = 7 Hz, 1H) 7.51 (br d, J = 7 Hz, 1H), 7.45 (br d, J = 7 Hz, 1H) 7.39 (t, J = 7 Hz, 1H), 6.92 (s, 1H), 3.39-3.37 (m, 1H), 3.18-3.14 (m, 1H), 2.98 (s, 1H), 2.93 (s, 2H), 2.78 (d, J = 10 Hz, 1H), 2.66 (d, J = 10 Hz, 1H), 2.58 (s, 3H), 2.16 (s, 2H), 2.08 (s, 1H), 1.88-1.63 (m, 4H), 1.48-1.44 (d, J = 10 Hz, 1H), 1.28-1.21 (m, 1H), 0.89-0.80 (m, 1H).

AnalpH2_MeOH_QC(1): Rt 5.18 min; m/z 404 $[M+1]^+$.

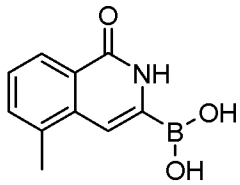
General Procedure for Synthesis of *2H*-isoquinolin-1-ones amide derivatives of Formula **4** **& 5** (Via Route 2a)

Scheme L



Scheme L, Step AI: Synthesis of aryl boronic acid derivatives of Formula **48**

5-Methyl-1-oxo-1,2-dihydro-isoquinoline-3-boronic acid

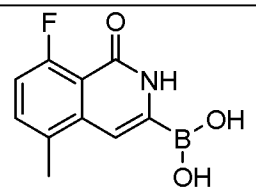
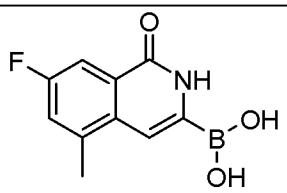


3-Chloro-5-methyl-2*H*-isoquinolin-1-one (100 mg, 0.52 mmol), *bis*(pinacolato)diboron (157 mg, 0.62 mmol), Pd(dppf)Cl_2 (42 mg, 0.054 mmol) and KOAc (153 mg, 1.56 mmol) in 1,4-dioxane (2 mL) were added to a microwave vial and the reaction mixture purged with N_2 for 10 min. The reaction mixture was irradiated using a microwave reactor (300W, 120 °C, 20 min). The reaction mixture was passed through a Si-thiol cartridge and concentrated in vacuo. The crude product was purified by reverse phase preparative HPLC-MS to afford 5-methyl-1-oxo-1,2-dihydro-isoquinoline-3-boronic acid as a white solid (51 mg, 49%).

AnalpH2_MeOH_4min(3): Rt 2.18 min; m/z 204 $[M+1]^+$.

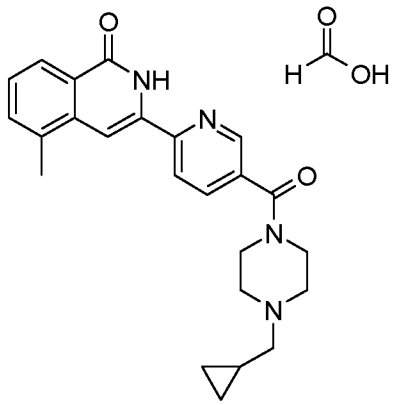
The following boronic acid derivatives **48** are prepared using analogous procedures.

Table 33: Boronic acid derivatives of Formula **48**

Compound	Analytical Data	Mass, %Yield, State
	AnalpH2_MeOH_4 min(3): Rt 2.18 min; m/z 222 $[M+1]^+$	59 mg, 38%, pale yellow solid
	AnalpH2_MeOH_4 min(3): Rt 2.41 min; m/z 222 $[M+1]^+$	84 mg, 40%, off-white solid

Scheme L, Step AJ: Synthesis of *2H*-isoquinolin-1-one derivatives of formula **4** (via Suzuki cross-coupling)

3-[5-(4-Cyclopropylmethyl-piperazine-1-carbonyl)-pyridin-2-yl]-5-methyl-2*H*-isoquinolin-1-one (IQ-223)

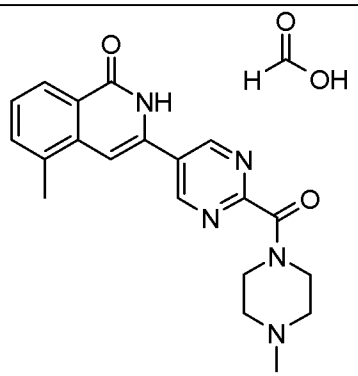
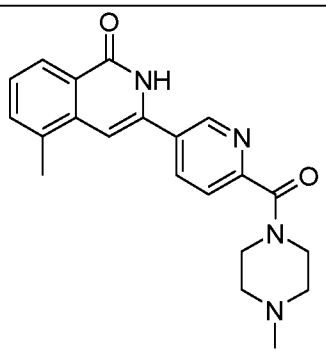
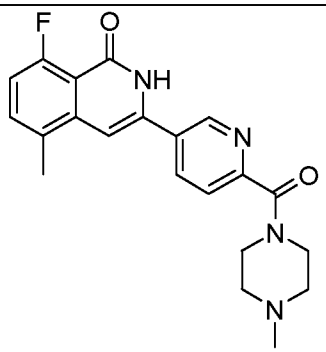
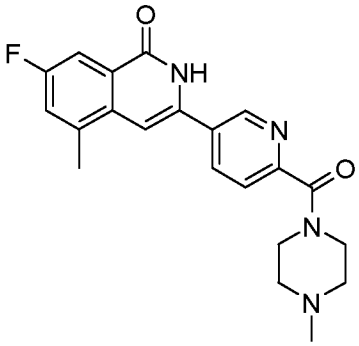


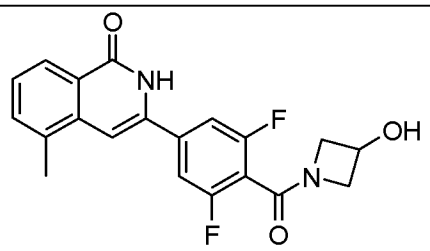
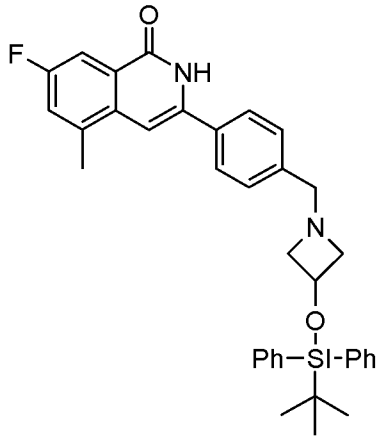
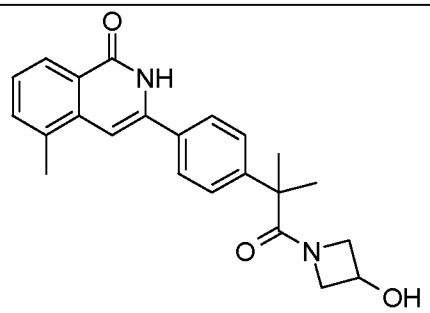
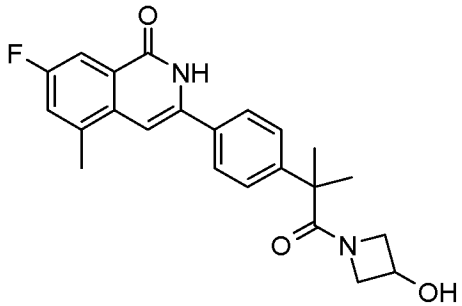
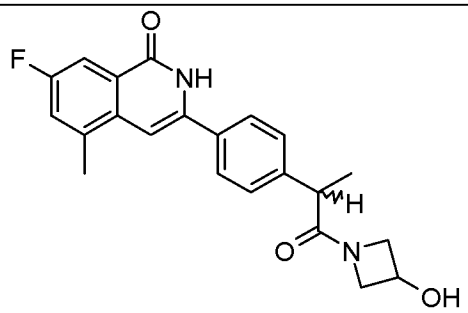
5-Methyl-1-oxo-1,2-dihydro-isoquinoline-3-boronic acid (40 mg, 0.20 mmol), (6-bromo-pyridin-3-yl)-(4-cyclopropylmethyl-piperazin-1-yl)-methanone (95 mg, 0.30 mmol), K_2CO_3 (56 mg, 0.4 mmol) and $Pd(dppf)Cl_2$ (16 mg, 0.02 mmol) in DME/EtOH/H_2O 4:0.5:1 (3.5 mL) were added to a microwave vial and the reaction mixture purged with N_2 for 10 min. The reaction mixture was irradiated using a microwave reactor (300W, 130 °C, 60 min). The reaction mixture was filtered through a Si-thiol and concentrated *in vacuo*. The crude material was purified by reverse phase preparative HPLC-MS to obtain 3-[5-(4-cyclopropylmethyl-piperazine-1-carbonyl)-pyridin-2-yl]-5-methyl-2*H*-isoquinolin-1-one as a brown solid (18 mg, 22%).

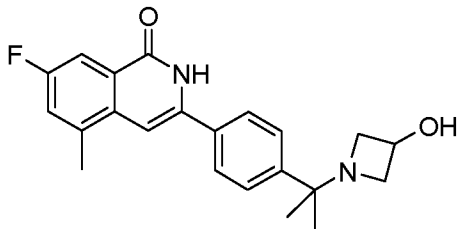
AnalpH2_MeOH_QC(1): Rt 4.97 min; m/z 403 $[M+1]^+$.

The following *2H*-isoquinolin-1-one derivatives are prepared using analogous procedures.

Table 34: *2H*-isoquinolin-1-one derivatives of Formula **4**

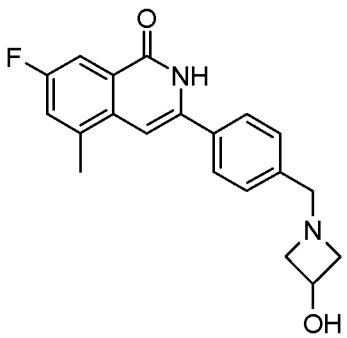
Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-224	AnalpH2_MeOH_QC(1): Rt 4.41 min; m/z 364 $[M+1]^+$	3.2 mg, 16 %, off-white solid
	IQ-220	AnalpH2_MeOH_QC(3): Rt 8.03 min; m/z 363 [M+1]+	34 mg, 34 %, white solid
	IQ-221	AnalpH2_MeOH_QC(3): Rt 7.66 min; m/z 381 [M+1]+	78 mg, 76 %, beige solid
	IQ-222	AnalpH2_MeOH_QC(1): Rt 4.96 min; m/z 381 $[M+1]^+$	35 mg, 24 %, beige solid

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-194	AnalpH2_MeOH_QC(1): Rt 7.15 min; m/z 371 $[M+1]^+$	32 mg, 16 %, white solid
	Intermediate for IQ-170	AnalpH2_MeOH_4min(3): Rt 2.80 min; m/z 577 $[M+1]^+$	300 mg, quant., black oil
	IQ-217	AnalpH2_MeOH_QC(1): Rt 7.87 min; m/z 378 $[M+1]^+$	41 mg, 32 %, pale brown solid
	IQ-218	AnalpH2_MeOH_QC(1): Rt 8.00 min; m/z 396 $[M+1]^+$	37 mg, 27 %, off-white solid
	IQ-216	AnalpH2_MeOH_QC(1): Rt 7.74 min; m/z 381 $[M+1]^+$	140 mg, 69 %, off-white solid

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-185	AnalpH2_MeOH_QC(1): Rt 5.54 min; m/z 367 $[M+1]^+$	14.4 mg, 5.5 %, white solid ^{1}H NMR (400 MHz, DMSO-d_6): δ11.68 (br s, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.58 (dd, J = 9.2, 2.8 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.51 (dd, J = 9.6, 2.8 Hz, 1H), 6.85 (s, 1H), 5.22 (d, J = 6.4 Hz, 1H), 4.22-4.15 (m, 1H), 3.25 (dd, J = 7.2, 6.0 Hz, 2H), 2.87 (dd, J = 7.2, 6.0 Hz, 2H), 2.59 (s, 3H), 1.28 (s, 6H).

Scheme L, Step AK: Synthesis of *2H*-isoquinolin-1-one derivatives of formula **5** (via TBDPS deprotection)

7-Fluoro-3-[4-(3-hydroxy-azetidin-1-ylmethyl)-phenyl]-5-methyl-2*H*-isoquinolin-1-one (IQ-170)

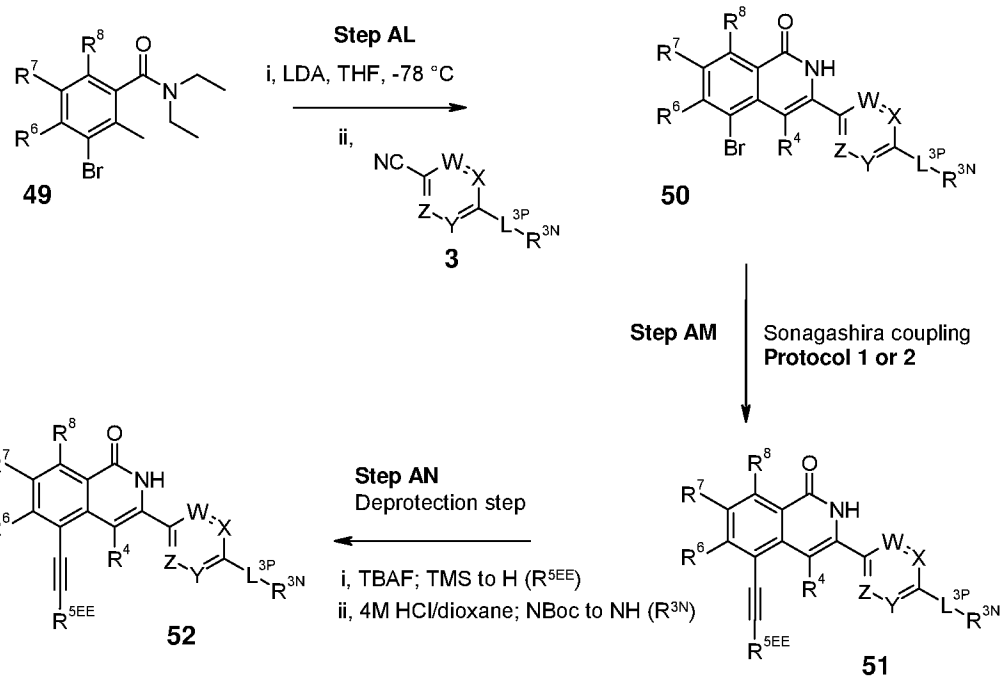


The synthesis is analogous to the TBDPS deprotection procedure used in Scheme A, Step C (Protocol 3) above to give 7-Fluoro-3-[4-(3-hydroxy-azetidin-1-ylmethyl)-phenyl]-5-methyl-2*H*-isoquinolin-1-one as a white solid (3 mg, 11 %).

AnalpH2_MeOH_QC(1): Rt 5.25 min; m/z 339 $[M+1]^+$.

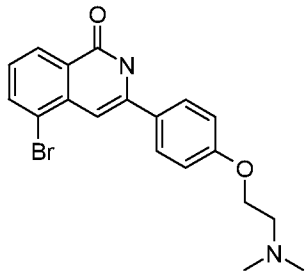
General Procedure for Synthesis of *2H*-isoquinolin-1-one acetylene derivatives of Formula **51 & 52**

Scheme M



Scheme M, Step AL: Synthesis of *2H*-isoquinolin-1-one derivatives of formula **50**

5-Bromo-3-[4-(2-dimethylaminoethoxy)phenyl]-*2H*-isoquinolin-1-one (IQ-237)



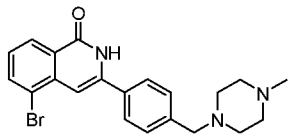
The synthesis is analogous to the cyclisation procedure used in Scheme A Step B (protocol 3) above to give 5-bromo-3-[4-(2-dimethylaminoethoxy)phenyl]-*2H*-isoquinolin-1-one as a yellow solid (1.23 g, 86%).

^{1}H NMR (400 MHz, DMSO-d_6): δ11.78 (br s, 1H), 8.21 (d, J = 8 Hz, 1H), 8.02 (d, J = 8 Hz, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.37 (t, J = 7.8 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 6.80 (s, 1H), 4.11 (t, J = 5.8 Hz, 2H), 2.64 (t, J = 5.8 Hz, 2H), 2.22 (s, 6H).

AnalpH2_MeOH_QC: Rt 5.69 min; m/z 387 $[M+1]^+$.

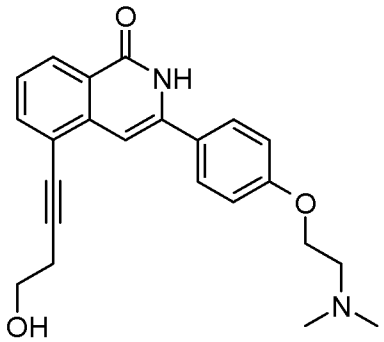
The following *2H*-isoquinolin-1-one derivatives are prepared using analogous procedures.

Table 35: *2H*-isoquinolin-1-one derivatives of Formula **4**

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-238	AnalpH2_MeOH_4min: Rt 1.97 min; m/z 412 $[M+1]^+$	845 mg, 79%, pale orange/pink solid

Scheme M, Step AM (Protocol 1): Synthesis of *2H*-isoquinolin-1-one derivatives of formula **51**

3-[4-(2-Dimethylaminoethoxy)phenyl]-5-(4-hydroxybut-1-ynyl)-2*H*-isoquinolin-1-one (IQ-236)



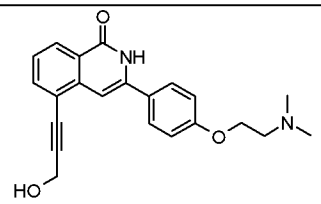
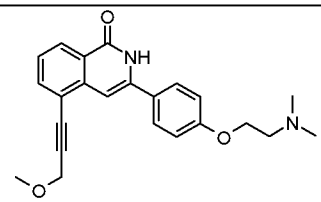
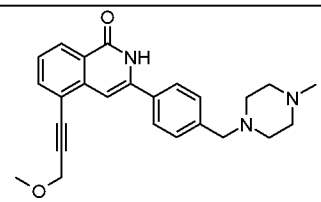
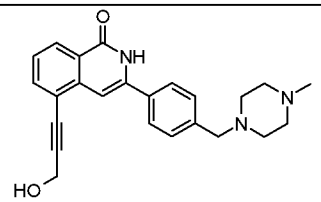
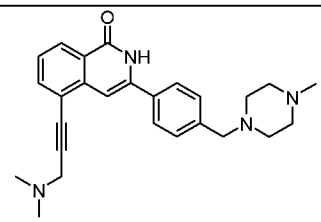
5-Bromo-3-[4-(2-dimethylaminoethoxy)phenyl]-2H-isoquinolin-1-one (50.0 mg, 0.130 mmol), triethylamine (1.1 mL, 8.36 mmol), dichlorobis(triphenylphosphine)palladium(II) (5.0 mg, 0.0065 mmol), copper (I) iodide (3.0 mg, 0.009 mmol), 3-butyn-1-ol (20 µL, 0.260 mmol) in DMF (1.1 mL) were added to a microwave vial and the reaction mixture purged with N_2 for 5 min. The reaction mixture was irradiated using a microwave reactor (300W, 100°C, 90 min). The reaction mixture was filtered through Celite® 545, diluted with DMSO and was purified by reverse phase preparative HPLC-MS to obtain 3-[4-(2-dimethylaminoethoxy)phenyl]-5-(4-hydroxybut-1-ynyl)-2*H*-isoquinolin-1-one as a brown solid (19.0 mg, 39%).

^{1}H NMR (400 MHz, $CDCl_3$): δ9.77 (br s, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 7.75 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.17 (s, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 4.29 (t, *J* = 5.2 Hz, 2H), 3.91 (t, *J* = 6.2 Hz, 2H), 3.12 (t, *J* = 4.4 Hz, 2H), 2.83 (t, *J* = 6.2 Hz, 2H), 2.60 (s, 6H).

AnalpH2_MeOH_QC: Rt 5.17 min; m/z 377 $[M+1]^+$.

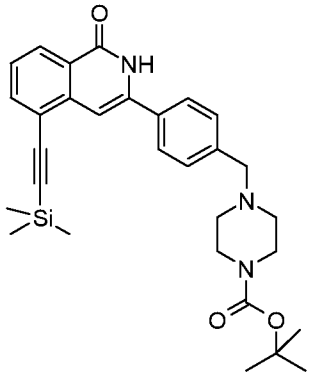
The following *2H*-isoquinolin-1-one derivatives are prepared using analogous procedures.

Table 36: *2H*-isoquinolin-1-one Formula **51**

Compound	Code	Analytical Data	Mass, %Yield, State
	IQ-232	AnalpH2_MeOH_QC: Rt 4.93 min; m/z 363 $[M+1]^+$	19 mg, 20%, brown oil
	IQ-234	AnalpH2_MeOH_QC: Rt 5.53 min; m/z 377 $[M+1]^+$	36 mg, 34%, beige solid
	IQ-233	AnalpH2_MeOH_QC(1): Rt 5.70 min; m/z 402 $[M+1]^+$	23 mg, 44%, beige solid
	IQ-231	AnalpH2_MeOH_QC(1): Rt 5.06 min; m/z 388 $[M+1]^+$	25 mg, 41%, beige solid
	IQ-235	AnalpH2_MeOH_4min: Rt 0.94 min m/z 415 $[M+1]^+$	36 mg, 54%, off-white solid

Scheme M, Step AM (Protocol 2): Synthesis of *2H*-isoquinolin-1-one derivatives of formula **51**

4-[4-(1-Oxo-5-trimethylsilanylethynyl-1,2-dihydroisoquinolin-3-yl)benzyl]piperazine-1-carboxylic acid *tert*-butyl ester

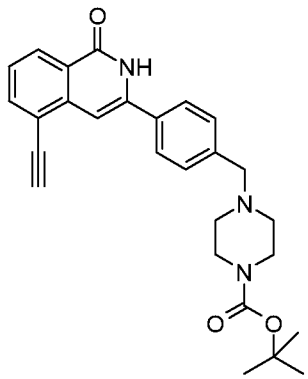


4-[4-(5-Bromo-1-oxo-1,2-dihydro-isoquinolin-3-yl)benzyl]piperazine-1-carboxylic acid (140.0 mg, 0.281 mmol), ethynyltrimethylsilane (119 µL, 0.843 mmol), triethylamine (391 µL, 2.81 mmol), dichlorobis(triphenylphosphine)palladium(II) (19.6 mg, 0.028 mmol), and triphenylphosphine (3.67 mg, 0.014 mmol) in anhydrous DMF (3 mL) were added to a microwave vial and the reaction mixture purged with N_2 for 5 min. Copper (I) iodide (5.33 mg, 0.028 mmol) was added and the mixture was degassed for a further minute. The reaction mixture was irradiated using a microwave reactor (300W, 110°C, 1 h). The reaction mixture was then concentrated *in vacuo*, diluted with water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography, eluting with *iso*-hexane and increasing the polarity to 100% EtOAc/*iso*-hexane to afford 4-[4-(1-oxo-5-trimethylsilanylethynyl-1,2-dihydroisoquinolin-3-yl)benzyl]piperazine-1-carboxylic acid *tert*-butyl ester as a yellow solid (70.3 mg, 49%).

AnalpH2_MeOH_4min (3): Rt 3.05 min; m/z 515.5 $[M+1]^+$.

Scheme M, Step AN (Step 1): Synthesis of *2H*-isoquinolin-1-one derivatives of formula **52**

4-[4-(5-Ethynyl-1-oxo-1,2-dihydroisoquinolin-3-yl)benzyl]piperazine-1-carboxylic acid *tert*-butyl ester

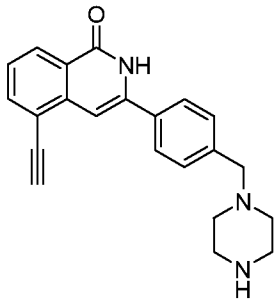


To a stirred solution of 4-[4-(1-oxo-5-trimethylsilanylethynyl-1,2-dihydroisoquinolin-3-yl)benzyl]piperazine-1-carboxylic acid tert-butyl ester compound (70.0 mg, 0.136 mmol) in THF (5 mL) was added TBAF (1M in THF, 272 µL, 0.272 mmol). The resulting reaction mixture was stirred at RT for 2 h and then quenched by the addition of water (20 mL). The mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to obtain 4-[4-(5-ethynyl-1-oxo-1,2-dihydroisoquinolin-3-yl)benzyl]piperazine-1-carboxylic acid *tert*-butyl ester (60.3 mg, 100%) as an orange solid. The crude compound was used for the next step without further purification.

AnalpH2_MeOH_4min (3): Rt 2.35 min; m/z 444.5 $[M+1]^+$.

Scheme M, Step AN (Step 2): Synthesis of *2H*-isoquinolin-1-one Derivatives of formula **52**

5-Ethynyl-3-(4-piperazin-1-ylmethylphenyl)-2H-isoquinolin-1-one (IQ-230)



4-[4-(5-Ethynyl-1-oxo-1,2-dihydroisoquinolin-3-yl)benzyl]piperazine-1-carboxylic acid *tert*-butyl ester (60.3 mg, 0.136 mmol) and 4M HCl/dioxane (3 mL) in CH_2Cl_2 (3 mL) were stirred at RT for 2 h. The reaction mixture was concentrated *in vacuo* and the crude material was purified by reverse phase preparative HPLC-MS to obtain 5-ethynyl-3-(4-piperazin-1-ylmethylphenyl)-2*H*-isoquinolin-1-one as an off-white solid (16.0 mg, 34%).

^{1}H NMR (400 MHz, DMSO-d_6): δ8.23 (d, J = 8 Hz, 1H), 7.89 (dd, J = 7.6 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 6.97 (s, 1H), 4.67 (s, 1H), 3.48 (s, 2H), 2.69-2.67 (m, 4H), 2.30 (br s, 4H).

AnalpH2_MeOH_QC (1): Rt 5.46 min; m/z 344.5 $[M+1]^+$.

Biological Methods

Biochemical Assay 1:
TNKS1/PARP Biochemical assay

Tankyrase activity was assayed using a 96-well format HT Universal Chemiluminescent PARP Assay Kit (Trevigen, Inc, cat. no. 4676-096-K) according to the manufacturer's instructions. In short, tankyrase/PARP activity is quantified by the incorporation of biotinylated nicotinamide adenine dinucleotide (biotin-NAD^+) onto the immobilised pseudo substrate, Histone. The extent of poly(Biotin-ADP)ribosylation (PARylation) in the presence of increasing dose of inhibitor is then quantified by binding of streptavidin conjugated horse radish peroxidase (strep-HRP) followed by chemiluminescent detection.

Prior to assay initiation, inhibitor stocks were prepared in aqueous DMSO (10 % (v/v)) from 5 millimolar (mM) stock in 100% DMSO (Sigma Aldrich, cat. no. 265855) as 10x concentrations. For the primary assay (i.e., single dose at 1 micromolar (μM) final concentration) this corresponded to 10 μM in 10% DMSO. For IC_{50} determination, this corresponded to 100 μM, 30 μM, 10 μM, 3.0 μM, 1.0 μM, 0.30 μM, 0.10 μM and 0 μM in 10% DMSO for final concentrations of 10 μM, 3.0 μM, 1.0 μM, 0.30 μM, 0.10 μM, 0.030 μM, 0.010 μM and 0 μM with 1% (v/v) final DMSO. The assay was initiated by the addition of 10x inhibitor (5 microlitres (μL)) or 10% aqueous DMSO (5 μL) to triplicate wells. Twenty microlitres of diluted TNKS1 protein (200 nanomolar (nM) final conc.) in PARP buffer (Trevigen, Inc, cat. no. 4671-096-02) was added to each histone coated well, which was previously hydrated with PARP buffer. Triplicate wells with 1% DMSO/buffer alone (no enzyme) were also added as a measure of assay 'noise'. Positive control for PARP inhibition included the addition of 4-amino-1,8-naphthalimide (Sigma Aldrich, cat. no A0966) in corresponding doses.

The mixture was incubated for 10 minutes at room temperature and the PARylation reaction initiated by the addition of PARP cocktail (25 μL, Trevigen, Inc) containing biotin-NAD^+ (Trevigen, Inc, cat. no. 4670-500-01), activated DNA (Trevigen, Inc, cat. no. 4671-096-06) and PARP buffer. The reaction was incubated for 1.5 hours (for TNKS1) or 1 hour (for PARP1) at room temperature. The reaction mixture was then removed by aspiration and the wells washed (3 x 200 μL) with phosphate buffered saline containing Triton X-100 (0.1% (v/v), Sigma Aldrich cat. no. T8787). The wells were then washed (3 x 200 μL) with phosphate buffered saline and then incubated with strep-HRP (50 μL, Trevigen, Inc, cat. no. 4800-30-06) in strep-diluent (1:500 dilution, Trevigen Inc, cat. no. 4671-096-04) for 1 hour at room temperature. The Strep-HRP mixture was then aspirated and the wells washed (3 x 200 μL) with phosphate buffered saline containing Triton X-100 (0.1% (v/v)) followed by phosphate buffered saline (3 x 200 μL) and then

incubated with PeroxyGlow™ reagent (100 µL, Trevigen, Inc, cat. nos. 4675-096-01, 4675-096-02, room temperature, mixed 1:1).

The amount of light emitted as a result of the peroxidase-chemiluminescent reagent reaction was in proportion to the extent of poly(Biotin-ADP)ribosylation and was immediately measured with a Victor^2 plate reader (Perkin Elmer, luminescence detection assay, luminescent units described as 'Counts Per Second' (CPS)). The data were normalised to the DMSO control after subtraction of 'noise' and was expressed as % PARP activity as a function of inhibitor dose. Inhibition was expressed as 100% - (% PARP activity). Dose response curves used to determine IC_{50} values were Log transformed and analysed by non-linear regression analysis (variable slope) using Prism (GraphPad Software, Inc) and were presented as IC_{50} with 95% confidence interval to determine relative potency.

Preparation of recombinant proteins:

Tankyrase1 (pNIC-Bsa4-TNKS1^{PARP}) expression construct was obtained from the Structural Genomics Consortium (SGC) and expresses the active PARP domain of TNKS1 as a polyhistidine tagged protein. The expression and purification of TNKS1 protein was carried out according to the SGC protocol provided at http:// www.thesgc.org/ structures/ materials_methods/ 2RF5/, which is summarised in the following table.

Structure	TNKS1
PDB Code	2RF5
Entry clone accession	BC098394
Entry clone source	Mammalian Gene Collection
Tag	N-terminal hexahistidine tag with integrated TEV protease cleavage site: mhhhhhhssgvdlgtenlyfq*s(m)
Construct sequence	mhhhhhhssgvdlgtenlyfq*sMQGTNPYLTFHCVNQGTILLDLAPEDKEYQS VEEEMQSTIREHRDGGNAGGIFNRYNVIRIQKVVNKKLRERFCHRQKE VSEENHNHHNERMLFHGSPFINAIIHKGFDERHAYIGGMFGAGIYFAEN SSKSNQYVYGIGGGTGCPTHKDRSCYICHRQMLFCRVTLGKSFLQFSTI KMAHAPPGHHSVIGRPSVNGLAYAEYVIYRGEQAYPEYLITYQIMKPEA PSQTATAAEQ
Vector	pNIC-Bsa4
Expression host	*E.coli* Rosetta2(DE3) (Novagen)

Growth method	Cells from a glycerol stock were streaked onto LB-agar plates. 5-10 colonies were used to inoculate 20 mL TB supplemented with 8 g/l glycerol, 100 µg/mL kanamycin and 34 µg/mL chloramphenicol. The cells were grown at 30ºC overnight. The overnight culture (20 mL) was used to inoculate 1.5 l TB supplemented with 8 g/l glycerol, 50 µg/mL kanamycin and approximately 200 µl PPG P2,000 81380 anti-foam solution (Fluka). The culture was grown in a LEX bioreactor system (Harbinger Biotechnology) at 37ºC until OD_{600} reached ~2. The culture was down-tempered to 18ºC over a period of 1 hour before target expression was induced by addition of 0.5 mM IPTG. Expression was allowed to continue overnight and cells were harvested the following morning by centrifugation (5,500 x *g*, 10 min, 4 ºC). The resulting cell pellet (38.2 g wet cell weight) was resuspended in lysis buffer (2 mL/g cell pellet), supplemented with one tablet of Complete EDTA-free protease inhibitor (Roche Applied Science). The cell suspension was stored at -80ºC.
Extraction buffers	Lysis buffer: 50 mM HEPES, 300 mM NaCl, 10% glycerol, 10 mM imidazole, 0.5 mM TCEP, pH 7.8
Extraction procedure	The cell suspension was quickly thawed in water and 2500 U Benzonase (Merck) was added. Cells were disrupted by sonication (Vibra-Cell, Sonics) at 80% amplitude for 3 min effective time (pulsed 4s on, 4s off) and cell debris was removed by centrifugation (49,100 x *g*, 20 min, 4 ºC). The supernatant was decanted and filtered through a 0.45 µm flask filter.
Purification buffers	IMAC wash1 buffer: 30 mM HEPES, 500 mM NaCl, 10% glycerol, 10 mM imidazole, 0.5 mM TCEP, pH 7.5. IMAC wash2 buffer: 30 mM HEPES, 500 mM NaCl, 10% glycerol, 25 mM imidazole, 0.5 mM TCEP, pH 7.5. IMAC elution buffer: 30 mM HEPES, 500 mM NaCl, 10% glycerol, 500 mM imidazole, 0.5 mM TCEP, pH 7.5. Gel filtration (GF) buffer: 30 mM HEPES, 300 mM NaCl, 10% glycerol, 0.5 mM TCEP, pH 7.5

Purification procedure	Columns: IMAC: Ni-charged 1 mL HiTrap Chelating HP (GE Healthcare). Gel filtration column: HiLoad 16/60 Superdex 75 Prep Grade (GE Healthcare). Procedure: Purification of the protein was performed as a two step process on an ÄKTAxpress system (GE Healthcare). Prior to purification, columns were equilibrated with IMAC wash1 buffer and gel filtration buffer, respectively. The filtered lysate was loaded onto the Ni-charged HiTrap Chelating column and washed with IMAC wash1 buffer followed by IMAC wash2 buffer. Bound protein was eluted from the IMAC column with IMAC elution buffer and automatically loaded onto the gel filtration column. Fractions containing the target protein were pooled and fresh TCEP was added to a final concentration of 2 mM. The protein was subsequently concentrated using a Amicon Ultra-15 centrifugal filter device, 10,000 NMWL (Millipore) to 22.8 mg/mL in a volume of 0.28 mL. The identity of the protein was confirmed by mass spectrometry.

Tankyrase2 (pNIC-Bsa4-TNKS2^{PARP}) expression construct was also obtained from the Structural Genomics Consortium (SGC) and prepared in an analogous method to TNKS1.

PARP1 protein was commercially available and was obtained from Trevigen, Inc (PARP-HSA 'High Specific Activity', cat. no. 4668-50-010).

Cell-Based Assay 1:
Wnt-Luciferase Reporter Assay

Generation of reporter cell lines:

A Wnt dependent cell line (i.e., DLD1 colorectal adenocarcinoma cell line) was transduced with replication incompetent VSV-g pseudotyped lentiviral particles expressing the firefly luciferase gene under the control of minimal cytomegalovirus (mCMV) promoter and tandem repeats of the TCF/LEF transcriptional response element. Post-transduction selection using puromycin (Sigma Aldrich, cat. no. P8833, 1.5 micrograms per millilitre (ug/mL)) for one week resulted in an enriched polyclonal cell population (DLD1-Wnt-Luc cells) that was expanded and collected for minimal passage and stored in liquid nitrogen.

Wnt-reporter assay:

DLD1-Wnt-Luc cells were seeded (5000 cells/well) in a 96-well plate (Greiner Bio-One, cat. no. 655098) in Dubelco's Modified Eagle Medium (DMEM, GIBCO/Invitrogen, cat no. 41965-039) supplemented with Fetal Bovine Serum (FBS, 10%, GIBCO/Invitrogen, cat no. 10108-165). After overnight incubation, the media was replaced with OptiMEM (GIBCO/Invitrogen, cat no. 11058-021) supplemented with FBS (0.5%) and non-essential amino acids (1%, GIBCO/Invitrogen, cat no. 11140-035) and the appropriate putative TNKS inhibitor at a final concentration of 10 μM, 3 μM, 1 μM, 0.30 μM, 0.10 μM, 0.030 μM, 0.010 μM and 0 μM with 1% (v/v) final DMSO in double-triplicate wells. Positive control includes the use of XAV-939 (Maybridge, FisherScientific, 3,5,7,8-tetrahydro-2-[4-(trifluoromethyl)phenyl]-4*H*-thiopyrano[4,3-*d*]pyrimidin-4-one, cat. no. RF03920, see: Huang *et al.*, Nature, 2009, Vol. 461, pp. 614-620). Cells were incubated for 20-22 hours before assaying for luciferase (first set of triplicates: Wnt activation) and viability (second set of triplicates: cell survival for data normalisation vs Wnt-activation) using ONE-Glo (Promega, cat. no. E6110) and CellTiter-Glo (Promega, cat. no. G7570) reagents consecutively. The assay was measured using a Victor^2 plate reader. The data were normalised to the DMSO control and were expressed as % Wnt activity as a function of inhibitor dose. Dose response curves used to determine IC_{50} values were Log transformed and analysed by non-linear regression analysis (variable slope) using Prism (GraphPad Software, Inc).

Cell-Based Assay 2:
Western Blotting for Direct and Downstream Targets of TNKS Inhibitors: Axin 1

DLD1 cells were assayed for the effect of putative Tankyrase1/2 inhibitors on TNKS1/2, Axin1/2 and β-catenin protein levels. Effective TNKS inhibitors will (1) increase TNKS protein levels by inhibition of auto-PARylation and subsequent proteasomal degradation, (2) increase Axin1/2 protein levels by inhibition of TNKS induced PARylation and subsequent proteasomal degradation and, consequently, stabilisation of the Axin/APC/GSK/CK destruction complex leading to (3) decrease of β-catenin protein levels. Reduction of nuclear accumulation of β-catenin and ultimately, reduction of β-catenin/TCF/LEF transcriptional activation of Wnt target genes should correlate with loss of Wnt-luc reporter signal in the Wnt reporter assay.

DLD1 cells were seeded in a 6-well dish at 10000 cells/well in DMEM supplemented with 10% FBS. After overnight incubation, cells were dosed with an appropriate amount of putative Tankyrase1/2 inhibitor (2 uM, 0.75 uM, 0.25 uM, 0 uM) in DMEM (0.5% FBS, 1% DMSO). After 20-22 hours incubation, the cells were washed in cold PBS and lysed in lysis buffer (50 mM Tris pH 8.0, 500 mM NaCl, 0.5% NP-40, complete protease inhibitor cocktail (Roche, cat. no. 11836153001)), centrifuged at 15000 rpm for 10 minutes and the

protein concentration of the supernatant quantified using Bradford reagent (BioRad protein assay reagent, cat. no. 500-0006). Protein samples (25-50 ug) in protein sample loading buffer ('Laemmli buffer', Laemmli, U.K., *Nature*, 1970, 227, 680-685) were denatured by boiling and loaded onto a sodium dodecyl sulfate - polyacrylamide gel (SDS-PAGE with 10% acrylamide) and separated by electrophroresis followed by electroblotting onto nitrocellulose membrane. The membrane was blocked in skimmed milk (5% in Tris-base saline with 0.01% Tween^{20} (TBS-T)) and subsequently probed overnight with the required antibody: Tankyrase1/2 (1:1000, Santa Cruz, cat. no. sc-8337); Axin1 (1:1000, Cell Signalling Technology, cat. no. 2087); Axin2 (1:1000, Cell Signalling Technology, cat. no. 2151); β-catenin (1:1000, Cell Signalling Technology, cat. no. 9581). After washing in TBS-T, the membrane was probed with a species specific secondary antibody conjugated to HRP (1:5000, Pierce/ThermoFisher), washed again in TBS-T and reacted with chemiluminescent detection reagents (ECL, GE Healthcare, cat. no. RPN2109) followed by exposure to X-ray film (FujiFilm XR).

Cell-Based Assay 3:
Western Blotting for Direct and Downstream Targets of TNKS Inhibitors Unrelated to the Wnt Pathway: TNKS

Appropriate cell lines (HeLa, HT1080, HTC75) were also assayed for the effect of TNKS inhibition on TNKS stabilisation (see, e.g., Smith *et al.*, Science, 1998, Vol. 282, pp. 1484-1487). Cells were seeded, dosed and whole cell lysates were isolated and western blotted as described above. Primary antibodies included TNKS (1:1000, Santa Cruz Biotech, cat. no. SC8377).

Cell-Based Assay 4:
Clonogenic Inhibition in DLD1 or HT55 Cells

In order to determine the efficacy of chronic dosing of putative TNKS inhibitors, long term clonogenic or 'colony formation' assays were carried out. This included the sparse seeding of cells in a 6-well dish followed by continuous dosing of cells over 12-14 days (depending on relative cell growth). Appropriate cell lines (DLD1 or HT55) were seeded at 500 cells/well in a 6-well dish in DMEM supplemented with FBS. After overnight incubation, cells were treated with the appropriate putative TNKS inhibitor at 10 μM, 3 μM, 1 μM, 0.30 μM, 0.1 μM and 0 μM at 0.2-1% final DMSO concentration (cell line dependent) in DMEM supplemented with 10% FBS (DLD1 cells were dosed in DMEM supplemented with 0.5% FBS). Dosages were carried out in triplicate. Cell media containing compound or DMSO only was replenished every 48 hours. Termination of the assay included the fixation of cells with trichlororacetic acid (1 mL, 10% (v/v), Sigma Aldrich, cat. no. T6399) and incubation for 16 hours at 4 °C. Fixed cells were then washed with water, allowed to dry and stained with sulforhodamine B solution

(sulforhodamine B 0.05% (w/v), Sigma Aldrich cat. no. S1402, acetic acid 1% (v/v), Fisher Scientific, cat. no. A/0400/PB17)) for 12 hours at room temperature. The stain was then removed and the cells washed copiously with aqueous acetic acid (1% v/v) and allowed to dry.

Quantification of colony formation was then carried out by dissolution of incorporated sulforhodamine B in Tris-base (1 mL, 10 mM, pH 10) and measurement of absorbance at 560 nM. The data was normalised to the DMSO control and was expressed as surviving fraction as a function of inhibitor dose. Dose response curves used to determine GI_{50} values were Log transformed and analysed by non-linear regression analysis (variable slope) using Prism (GraphPad Software, Inc).

Biological Data

The following compounds were tested in the TNKS1/PARP Biochemical Assay described above:

IQ-001, IQ-002-1, IQ-002-2, IQ-003, IQ-004, IQ-005, IQ-006, IQ-007, IQ-008, IQ-009, IQ-010, IQ-011, IQ-012, IQ-013, IQ-014, IQ-015, IQ-016, IQ-017, IQ-018, IQ-019, IQ-020, IQ-021, IQ-023, IQ-024, IQ-025, IQ-026, IQ-027, IQ-028-1, IQ-028-2, IQ-029, IQ-030, IQ-031, IQ-032, IQ-033, IQ-034, IQ-035, IQ-036, IQ-037, IQ-038, IQ-039, IQ-040, IQ-041, IQ-042, IQ-043, IQ-044, IQ-045, IQ-046, IQ-047, IQ-048, IQ-049, IQ-050, IQ-051-1, IQ-051-2, IQ-051-3, IQ-052, IQ-053, IQ-054, IQ-055, IQ-056, IQ-057, IQ-059, IQ-060, IQ-062, IQ-063, IQ-065, IQ-067, IQ-068, IQ-070, IQ-071, IQ-072, IQ-073, IQ-074, IQ-075, IQ-076, IQ-077, IQ-078, IQ-079, IQ-080, IQ-081, IQ-082, IQ-083, IQ-084-1, IQ-084-2, IQ-084-3, IQ-085, IQ-086, IQ-087, IQ-088, IQ-089, IQ-090, IQ-091, IQ-092, IQ-093, IQ-094, IQ-095, IQ-096, IQ-097, IQ-098, IQ-099, IQ-100, IQ-101, IQ-102, IQ-103, IQ-104, IQ-105, IQ-106, IQ-107, IQ-108, IQ-109, IQ-110, IQ-111, IQ-112, IQ-113, IQ-114, IQ-115, IQ-116, IQ-117, IQ-118, IQ-119, IQ-120, IQ-121, IQ-122, IQ-123, IQ-124, IQ-125, IQ-126, IQ-127, IQ-128, IQ-129, IQ-130, IQ-131, IQ-132, IQ-133, IQ-134, IQ-135, IQ-136, IQ-138, IQ-139, IQ-140, IQ-141, IQ-142, IQ-143, IQ-144, IQ-145, IQ-148, IQ-149, IQ-150, IQ-151, IQ-154, IQ-157, IQ-158, IQ-160, IQ-161, IQ-162, IQ-163, IQ-164, IQ-165, IQ-166, IQ-167, IQ-168, IQ-169, IQ-170, IQ-171, IQ-172, IQ-173, IQ-174, IQ-175, IQ-176, IQ-177, IQ-178, IQ-179, IQ-180, IQ-181, IQ-182, IQ-183, IQ-184, IQ-185, IQ-186, IQ-187, IQ-188, IQ-189, IQ-190, IQ-191, IQ-192, IQ-193, IQ-194, IQ-195, IQ-196, IQ-197, IQ-198, IQ-199, IQ-200, IQ-201, IQ-202, IQ-203, IQ-204, IQ-205-1, IQ-205-2, IQ-206, IQ-207-1, IQ-207-2, IQ-208, IQ-209, IQ-210, IQ-211, IQ-212, IQ-213, IQ-214, IQ-215, IQ-216, IQ-217, IQ-218, IQ-219, IQ-220, IQ-221, IQ-222, IQ-223, IQ-224, IQ-225, IQ-226, IQ-227, IQ-228, IQ-229, IQ-230, IQ-231, IQ-232, IQ-233, IQ-234, IQ-236.

All of the compounds have a TNKS1 IC_{50} of less than 5 μM.

The following compounds have a TNKS1 IC_{50} of less than 0.5 μM:

IQ-001, IQ-002-1, IQ-002-2, IQ-003, IQ-004, IQ-005, IQ-006, IQ-007, IQ-008, IQ-009, IQ-010, IQ-011, IQ-012, IQ-013, IQ-014, IQ-015, IQ-016, IQ-017, IQ-018, IQ-019, IQ-020, IQ-021, IQ-023, IQ-024, IQ-025, IQ-026, IQ-027, IQ-028-1, IQ-028-2, IQ-029, IQ-031, IQ-032, IQ-033, IQ-034, IQ-035, IQ-036, IQ-037, IQ-038, IQ-039, IQ-040, IQ-041, IQ-042, IQ-043, IQ-044, IQ-045, IQ-046, IQ-047, IQ-048, IQ-049, IQ-050, IQ-051-1, IQ-051-2, IQ-051-3, IQ-052, IQ-053, IQ-054, IQ-055, IQ-056, IQ-057, IQ-059, IQ-060, IQ-062, IQ-063, IQ-065, IQ-067, IQ-068, IQ-070, IQ-071, IQ-072, IQ-073, IQ-074, IQ-075, IQ-076, IQ-077, IQ-078, IQ-079, IQ-080, IQ-081, IQ-082, IQ-083, IQ-084-1, IQ-084-2, IQ-084-3, IQ-085, IQ-086, IQ-087, IQ-088, IQ-089, IQ-090, IQ-091, IQ-092, IQ-093, IQ-094, IQ-095,

IQ-096, IQ-097, IQ-098, IQ-099, IQ-100, IQ-101, IQ-102, IQ-103, IQ-104, IQ-105, IQ-106, IQ-107, IQ-108, IQ-109, IQ-110, IQ-111, IQ-112, IQ-113, IQ-114, IQ-115, IQ-116, IQ-117, IQ-118, IQ-119, IQ-120, IQ-121, IQ-122, IQ-123, IQ-124, IQ-125, IQ-126, IQ-127, IQ-128, IQ-129, IQ-130, IQ-132, IQ-133, IQ-134, IQ-135, IQ-136, IQ-138, IQ-140, IQ-142, IQ-143, IQ-145, IQ-148, IQ-149, IQ-150, IQ-154, IQ-157, IQ-158, IQ-160, IQ-161, IQ-162, IQ-163, IQ-164, IQ-165, IQ-166, IQ-167, IQ-168, IQ-169, IQ-170, IQ-171, IQ-172, IQ-173, IQ-174, IQ-175, IQ-176, IQ-177, IQ-178, IQ-179, IQ-180, IQ-181, IQ-182, IQ-184, IQ-185, IQ-186, IQ-187, IQ-188, IQ-189, IQ-190, IQ-191, IQ-192, IQ-193, IQ-194, IQ-195, IQ-196, IQ-197, IQ-198, IQ-199, IQ-200, IQ-201, IQ-202, IQ-203, IQ-204, IQ-205-1, IQ-205-2, IQ-206, IQ-207-1, IQ-207-2, IQ-208, IQ-209, IQ-210, IQ-211, IQ-212, IQ-213, IQ-214, IQ-215, IQ-216, IQ-217, IQ-218, IQ-219, IQ-220, IQ-221, IQ-222, IQ-223, IQ-224, IQ-225, IQ-226, IQ-227, IQ-228, IQ-229, IQ-230, IQ-231, IQ-232, IQ-234, IQ-236.

The following compounds have a TNKS1 IC_{50} of less than 0.05 μM:

IQ-001, IQ-002-1, IQ-003, IQ-004, IQ-005, IQ-006, IQ-007, IQ-008, IQ-011, IQ-012, IQ-013, IQ-014, IQ-015, IQ-016, IQ-017, IQ-018, IQ-019, IQ-021, IQ-023, IQ-025, IQ-026, IQ-027, IQ-028-1, IQ-028-2, IQ-029, IQ-032, IQ-033, IQ-034, IQ-035, IQ-036, IQ-037, IQ-038, IQ-042, IQ-045, IQ-048, IQ-050, IQ-051-1, IQ-051-2, IQ-051-3, IQ-052, IQ-053, IQ-054, IQ-055, IQ-056, IQ-057, IQ-059, IQ-062, IQ-065, IQ-067, IQ-068, IQ-070, IQ-073, IQ-074, IQ-078, IQ-080, IQ-081, IQ-082, IQ-083, IQ-084-1, IQ-084-2, IQ-084-3, IQ-085, IQ-086, IQ-087, IQ-088, IQ-090, IQ-093, IQ-094, IQ-095, IQ-096, IQ-097, IQ-098, IQ-099, IQ-100, IQ-101, IQ-102, IQ-104, IQ-105, IQ-106, IQ-107, IQ-108, IQ-109, IQ-111, IQ-112, IQ-115, IQ-116, IQ-117, IQ-118, IQ-120, IQ-121, IQ-123, IQ-124, IQ-125, IQ-127, IQ-129, IQ-130, IQ-134, IQ-138, IQ-149, IQ-158, IQ-160, IQ-162, IQ-167, IQ-168, IQ-169, IQ-170, IQ-171, IQ-172, IQ-173, IQ-174, IQ-175, IQ-176, IQ-177, IQ-178, IQ-180, IQ-182, IQ-185, IQ-187, IQ-188, IQ-189, IQ-190, IQ-191, IQ-192, IQ-193, IQ-194, IQ-195, IQ-196, IQ-197, IQ-198, IQ-199, IQ-200, IQ-201, IQ-203, IQ-204, IQ-205-1, IQ-205-2, IQ-206, IQ-207-1, IQ-207-2, IQ-208, IQ-209, IQ-210, IQ-211, IQ-212, IQ-213, IQ-214, IQ-215, IQ-216, IQ-217, IQ-218, IQ-219, IQ-220, IQ-222, IQ-224, IQ-226, IQ-227, IQ-228, IQ-231.

The following compounds have a TNKS1 IC_{50} of less than 0.02 μM:

IQ-001, IQ-004, IQ-005, IQ-006, IQ-008, IQ-011, IQ-014, IQ-016, IQ-017, IQ-018, IQ-025, IQ-028-1, IQ-029, IQ-032, IQ-034, IQ-038, IQ-048, IQ-051-1, IQ-054, IQ-055, IQ-062, IQ-082, IQ-086, IQ-088, IQ-093, IQ-097, IQ-099, IQ-100, IQ-102, IQ-104, IQ-107, IQ-109, IQ-115, IQ-117, IQ-118, IQ-120, IQ-123, IQ-125, IQ-130, IQ-162, IQ-167, IQ-168, IQ-170, IQ-172, IQ-175, IQ-176, IQ-177, IQ-178, IQ-180, IQ-182, IQ-188, IQ-189, IQ-190, IQ-191, IQ-192, IQ-193, IQ-194, IQ-195, IQ-196, IQ-197, IQ-198, IQ-199, IQ-200, IQ-204, IQ-205-2, IQ-208, IQ-209, IQ-210, IQ-211, IQ-213, IQ-214, IQ-215, IQ-219, IQ-222, IQ-227.

For example, IQ-016 has a TNKS1 IC_{50} of 0.012 μM.

The following compounds were tested in the Wnt-Luciferase Reporter Assay described above:

IQ-001, IQ-002-1, IQ-003, IQ-004, IQ-005, IQ-006, IQ-007, IQ-008, IQ-009, IQ-010, IQ-011, IQ-012, IQ-013, IQ-014, IQ-015, IQ-016, IQ-017, IQ-018, IQ-019, IQ-020, IQ-021, IQ-023, IQ-024, IQ-025, IQ-026, IQ-027, IQ-028-1, IQ-029, IQ-031, IQ-032, IQ-033, IQ-034, IQ-035, IQ-036, IQ-037, IQ-038, IQ-040, IQ-041, IQ-042, IQ-043, IQ-045, IQ-046, IQ-048, IQ-050, IQ-051-1, IQ-051-2, IQ-051-3, IQ-052, IQ-053, IQ-054, IQ-055, IQ-056, IQ-057, IQ-059, IQ-060, IQ-062, IQ-063, IQ-065, IQ-067, IQ-068, IQ-070, IQ-071, IQ-072, IQ-073, IQ-074, IQ-075, IQ-076, IQ-077, IQ-078, IQ-079, IQ-080, IQ-081, IQ-082, IQ-083, IQ-084-1, IQ-084-2, IQ-084-3, IQ-085, IQ-086, IQ-087, IQ-088, IQ-089, IQ-090, IQ-091, IQ-093, IQ-094, IQ-095, IQ-096, IQ-097, IQ-098, IQ-099, IQ-100, IQ-101, IQ-102, IQ-103, IQ-104, IQ-105, IQ-106, IQ-107, IQ-108, IQ-109, IQ-110, IQ-111, IQ-112, IQ-115, IQ-116, IQ-117, IQ-118, IQ-119, IQ-120, IQ-121, IQ-122, IQ-123, IQ-124, IQ-125, IQ-127, IQ-128, IQ-129, IQ-130, IQ-132, IQ-133, IQ-134, IQ-135, IQ-138, IQ-142, IQ-143, IQ-148, IQ-149, IQ-150, IQ-151, IQ-154, IQ-157, IQ-158, IQ-160, IQ-161, IQ-162, IQ-163, IQ-164, IQ-165, IQ-166, IQ-167, IQ-168, IQ-169, IQ-170, IQ-171, IQ-172, IQ-173, IQ-174, IQ-175, IQ-176, IQ-177, IQ-178, IQ-179, IQ-180, IQ-181, IQ-182, IQ-183, IQ-184, IQ-185, IQ-186, IQ-187, IQ-188, IQ-189, IQ-190, IQ-191, IQ-192, IQ-193, IQ-194, IQ-195, IQ-196, IQ-197, IQ-198, IQ-199, IQ-200, IQ-201, IQ-202, IQ-203, IQ-204, IQ-205-1, IQ-205-2, IQ-206, IQ-207-1, IQ-207-2, IQ-208, IQ-209, IQ-210, IQ-211, IQ-212, IQ-213, IQ-214, IQ-215, IQ-216, IQ-217, IQ-218, IQ-219, IQ-220, IQ-221, IQ-222, IQ-223, IQ-224, IQ-225, IQ-226, IQ-227, IQ-228, IQ-229, IQ-230, IQ-231, IQ-232, IQ-234, IQ-236.

All of the compounds have a Wnt IC_{50} of less than 10 μM.

The following compounds have a Wnt IC_{50} of less than 5 μM:

IQ-001, IQ-002-1, IQ-003, IQ-004, IQ-005, IQ-006, IQ-007, IQ-008, IQ-009, IQ-010, IQ-011, IQ-012, IQ-013, IQ-014, IQ-015, IQ-016, IQ-017, IQ-018, IQ-019, IQ-020, IQ-021, IQ-023, IQ-024, IQ-025, IQ-026, IQ-027, IQ-028-1, IQ-029, IQ-031, IQ-032, IQ-033, IQ-034, IQ-035, IQ-036, IQ-037, IQ-038, IQ-040, IQ-041, IQ-042, IQ-043, IQ-045, IQ-046, IQ-048, IQ-050, IQ-051-1, IQ-051-2, IQ-051-3, IQ-052, IQ-053, IQ-054, IQ-055, IQ-056, IQ-057, IQ-059, IQ-060, IQ-062, IQ-063, IQ-065, IQ-067, IQ-068, IQ-070, IQ-071, IQ-072, IQ-073, IQ-074, IQ-075, IQ-076, IQ-077, IQ-078, IQ-079, IQ-080, IQ-081, IQ-082, IQ-083, IQ-084-1, IQ-084-2, IQ-084-3, IQ-085, IQ-086, IQ-087, IQ-088, IQ-089, IQ-090, IQ-091, IQ-093, IQ-094, IQ-095, IQ-096, IQ-097, IQ-098, IQ-099, IQ-100, IQ-101, IQ-102, IQ-103, IQ-104, IQ-105, IQ-106, IQ-107, IQ-108, IQ-109, IQ-110, IQ-111, IQ-112, IQ-115, IQ-116,

IQ-117, IQ-118, IQ-119, IQ-120, IQ-121, IQ-122, IQ-123, IQ-124, IQ-125, IQ-127, IQ-128, IQ-129, IQ-130, IQ-132, IQ-133, IQ-134, IQ-135, IQ-138, IQ-142, IQ-143, IQ-148, IQ-149, IQ-150, IQ-151, IQ-154, IQ-157, IQ-158, IQ-160, IQ-161, IQ-162, IQ-163, IQ-164, IQ-165, IQ-166, IQ-167, IQ-168, IQ-169, IQ-170, IQ-171, IQ-172, IQ-173, IQ-174, IQ-175, IQ-176, IQ-177, IQ-178, IQ-179, IQ-180, IQ-181, IQ-182, IQ-183, IQ-184, IQ-185, IQ-186, IQ-187, IQ-188, IQ-189, IQ-190, IQ-191, IQ-192, IQ-193, IQ-194, IQ-195, IQ-196, IQ-197, IQ-198, IQ-199, IQ-200, IQ-201, IQ-202, IQ-203, IQ-204, IQ-205-1, IQ-205-2, IQ-206, IQ-207-1, IQ-207-2, IQ-208, IQ-209, IQ-210, IQ-211, IQ-212, IQ-213, IQ-214, IQ-215, IQ-216, IQ-217, IQ-218, IQ-219, IQ-220, IQ-221, IQ-222, IQ-223, IQ-224, IQ-225, IQ-226, IQ-227, IQ-228, IQ-230, IQ-231, IQ-232, IQ-234.

The following compounds have a Wnt IC_{50} of less than 0.5 μM:

IQ-001, IQ-002-1, IQ-003, IQ-004, IQ-005, IQ-006, IQ-007, IQ-008, IQ-009, IQ-010, IQ-011, IQ-012, IQ-013, IQ-014, IQ-015, IQ-016, IQ-017, IQ-018, IQ-019, IQ-020, IQ-021, IQ-023, IQ-025, IQ-026, IQ-027, IQ-028-1, IQ-029, IQ-031, IQ-034, IQ-035, IQ-036, IQ-037, IQ-038, IQ-040, IQ-041, IQ-042, IQ-043, IQ-045, IQ-048, IQ-050, IQ-051-1, IQ-051-2, IQ-051-3, IQ-052, IQ-053, IQ-054, IQ-055, IQ-056, IQ-057, IQ-059, IQ-060, IQ-062, IQ-063, IQ-065, IQ-067, IQ-068, IQ-071, IQ-072, IQ-073, IQ-074, IQ-075, IQ-076, IQ-077, IQ-078, IQ-079, IQ-080, IQ-082, IQ-083, IQ-084-1, IQ-084-2, IQ-084-3, IQ-085, IQ-086, IQ-087, IQ-088, IQ-089, IQ-090, IQ-091, IQ-095, IQ-096, IQ-097, IQ-098, IQ-099, IQ-100, IQ-101, IQ-102, IQ-104, IQ-105, IQ-106, IQ-107, IQ-108, IQ-109, IQ-110, IQ-111, IQ-112, IQ-115, IQ-116, IQ-117, IQ-118, IQ-119, IQ-120, IQ-121, IQ-122, IQ-123, IQ-125, IQ-127, IQ-130, IQ-133, IQ-134, IQ-138, IQ-142, IQ-143, IQ-148, IQ-154, IQ-157, IQ-158, IQ-161, IQ-162, IQ-166, IQ-167, IQ-168, IQ-169, IQ-170, IQ-171, IQ-172, IQ-173, IQ-174, IQ-175, IQ-176, IQ-177, IQ-178, IQ-179, IQ-180, IQ-181, IQ-182, IQ-183, IQ-184, IQ-185, IQ-186, IQ-187, IQ-188, IQ-189, IQ-190, IQ-192, IQ-193, IQ-194, IQ-195, IQ-196, IQ-197, IQ-198, IQ-199, IQ-200, IQ-201, IQ-202, IQ-203, IQ-204, IQ-205-1, IQ-205-2, IQ-206, IQ-207-1, IQ-207-2, IQ-208, IQ-209, IQ-210, IQ-211, IQ-212, IQ-213, IQ-214, IQ-215, IQ-218, IQ-219, IQ-220, IQ-222, IQ-226, IQ-227, IQ-228, IQ-231, IQ-234.

The following compounds have a Wnt IC_{50} of less than 0.05 μM:

IQ-001, IQ-003, IQ-004, IQ-005, IQ-006, IQ-008, IQ-011, IQ-015, IQ-016, IQ-017, IQ-018, IQ-028-1, IQ-035, IQ-038, IQ-040, IQ-042, IQ-048, IQ-051-2, IQ-051-3, IQ-054, IQ-055, IQ-062, IQ-065, IQ-067, IQ-068, IQ-073, IQ-078, IQ-080, IQ-097, IQ-098, IQ-100, IQ-102, IQ-104, IQ-105, IQ-106, IQ-107, IQ-108, IQ-109, IQ-111, IQ-117, IQ-118, IQ-120, IQ-121, IQ-123, IQ-125, IQ-133, IQ-148, IQ-157, IQ-167, IQ-168, IQ-170, IQ-171, IQ-173, IQ-174, IQ-175, IQ-176, IQ-177, IQ-178, IQ-179, IQ-180, IQ-181, IQ-182, IQ-184, IQ-185, IQ-190, IQ-192, IQ-195, IQ-198, IQ-201, IQ-206, IQ-209, IQ-210, IQ-211, IQ-212, IQ-215, IQ-234.

For example, IQ-016 has a Wnt IC_{50} of 0.014 μM.

The following compounds were studied using the Western Blotting Assays described above, and were found to stabilize Axin1 and to stabilize TNKS: IQ-002-1, IQ-003, IQ-027, IQ-034, IQ-036, IQ-037, IQ-038, IQ-053, IQ-100, IQ-102, IQ-127, IQ-130, IQ-133.

The following compounds were tested in the Long-Term Clonogenic Assay described above (DLD1 cells):

IQ-001, IQ-002-1, IQ-003, IQ-004, IQ-005, IQ-006, IQ-007, IQ-008, IQ-009, IQ-011, IQ-016, IQ-017, IQ-018, IQ-019, IQ-021, IQ-023, IQ-026, IQ-027, IQ-028-1, IQ-032, IQ-034, IQ-038, IQ-040, IQ-042, IQ-043, IQ-048, IQ-051-2, IQ-051-3, IQ-053, IQ-054, IQ-057, IQ-065, IQ-067, IQ-068, IQ-072, IQ-073, IQ-074, IQ-075, IQ-081, IQ-082, IQ-083, IQ-084-1, IQ-084-2, IQ-086, IQ-088, IQ-090, IQ-091, IQ-095, IQ-096, IQ-097, IQ-099, IQ-100, IQ-101, IQ-102, IQ-103, IQ-104, IQ-105, IQ-106, IQ-107, IQ-108, IQ-109, IQ-111, IQ-118, IQ-121, IQ-123, IQ-125, IQ-127, IQ-128, IQ-129, IQ-130, IQ-149, IQ-161, IQ-162, IQ-166, IQ-167, IQ-168, IQ-169, IQ-188, IQ-189, IQ-190, IQ-231, IQ-234.

All of the compounds have a Clonogenic SF_{50} (DLD1) of less than 10 μM.

The following compounds have a Clonogenic SF_{50} (DLD1) of less than 2 μM:

IQ-001, IQ-002-1, IQ-003, IQ-005, IQ-006, IQ-007, IQ-008, IQ-009, IQ-011, IQ-016, IQ-017, IQ-018, IQ-019, IQ-021, IQ-023, IQ-027, IQ-028-1, IQ-034, IQ-038, IQ-040, IQ-042, IQ-043, IQ-048, IQ-051-2, IQ-051-3, IQ-053, IQ-054, IQ-057, IQ-065, IQ-067, IQ-068, IQ-073, IQ-074, IQ-075, IQ-081, IQ-082, IQ-083, IQ-084-1, IQ-084-2, IQ-086, IQ-088, IQ-090, IQ-091, IQ-102, IQ-104, IQ-105, IQ-106, IQ-107, IQ-108, IQ-109, IQ-111, IQ-118, IQ-121, IQ-123, IQ-125, IQ-127, IQ-129, IQ-149, IQ-161, IQ-162, IQ-166, IQ-168, IQ-190.

The following compounds have a Clonogenic SF_{50} (DLD1) of less than 0.5 μM:

IQ-006, IQ-007, IQ-008, IQ-011, IQ-016, IQ-018, IQ-027, IQ-028-1, IQ-040, IQ-042, IQ-051-2, IQ-053, IQ-065, IQ-067, IQ-073, IQ-075, IQ-081, IQ-082, IQ-083, IQ-088, IQ-090, IQ-091, IQ-104, IQ-105, IQ-107, IQ-108, IQ-109, IQ-111, IQ-118, IQ-123, IQ-125, IQ-161, IQ-162, IQ-166, IQ-168.

For example, IQ-016 has a Clonogenic SF_{50} (DLD1) of 0.291 μM.

The following compounds were tested in the Long-Term Clonogenic Assay described above (HT55 cells):

IQ-168, IQ-185, IQ-007, IQ-018, IQ-027, IQ-053, IQ-173, IQ-006, IQ-195, IQ-075, IQ-080, IQ-170, IQ-016, IQ-011, IQ-182, IQ-174, IQ-177, IQ-178, IQ-197, IQ-201, IQ-158, IQ-204, IQ-048, IQ-196, IQ-117, IQ-210, IQ-199, IQ-176, IQ-059, IQ-179, IQ-198, IQ-054, IQ-209, IQ-005, IQ-042, IQ-213, IQ-218, IQ-100, IQ-127, IQ-171, IQ-208, IQ-206, IQ-205-1, IQ-205-2, IQ-207-1, IQ-207-2, IQ-028-1.

All of the compounds have a Clonogenic SF_{50} (HT55) of less than 10 μM.

The following compounds have a Clonogenic SF_{50} (HT55) of less than 3 μM:

IQ-006, IQ-007, IQ-011, IQ-016, IQ-018, IQ-027, IQ-028-1, IQ-048, IQ-053, IQ-059, IQ-075, IQ-080, IQ-117, IQ-158, IQ-168, IQ-170, IQ-173, IQ-174, IQ-176, IQ-177, IQ-178, IQ-179, IQ-182, IQ-185, IQ-195, IQ-196, IQ-197, IQ-199, IQ-201, IQ-204, IQ-205-1, IQ-205-2, IQ-207-1, IQ-207-2, IQ-210.

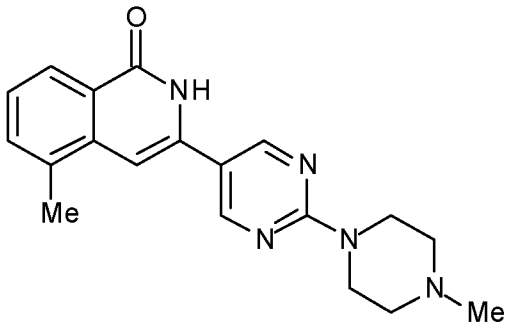
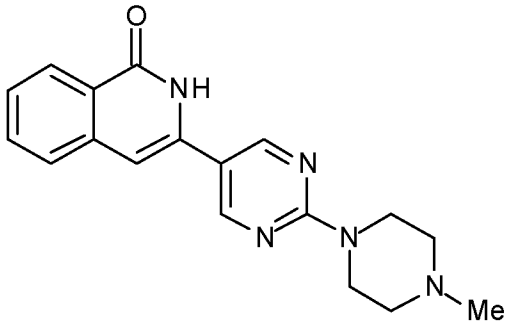
The following compounds have a Clonogenic SF_{50} (HT55) of less than 1.5 μM:

IQ-006, IQ-007, IQ-011, IQ-016, IQ-018, IQ-027, IQ-028-1, IQ-053, IQ-075, IQ-080, IQ-168, IQ-170, IQ-173, IQ-185, IQ-195, IQ-205-1, IQ-207-1.

For example, IQ-016 has a Clonogenic SF_{50} (HT55) of 1.235 μM.

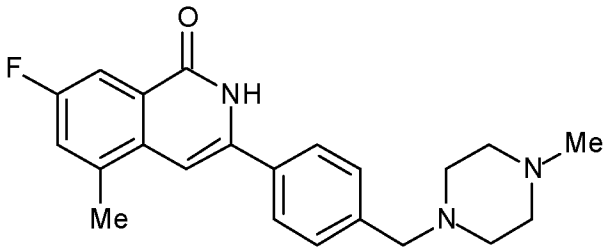
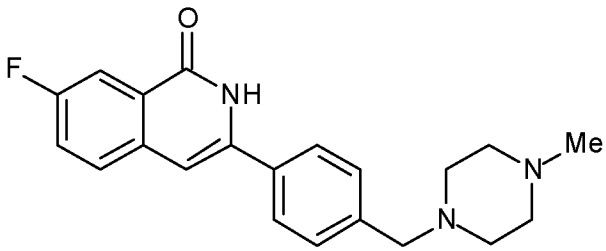
-R^5 Comparison No. 1:

As demonstrated by this comparison, the presence of R^5 as -Me (as compared to -H) *decreased* Wnt IC_{50} by a factor of about 13.

Code	Structure	TNKS1 IC_{50} (μM)	Wnt IC_{50} (μM)
IQ-025		0.017	0.062
REF-1		0.033	0.825

-R^5 Comparison No. 2:

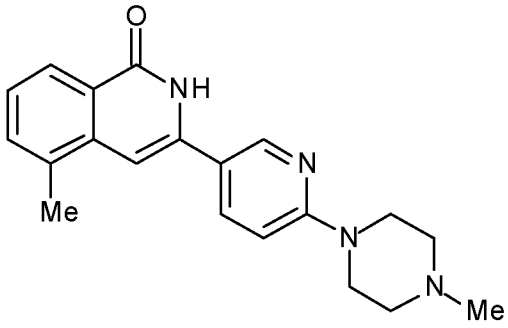
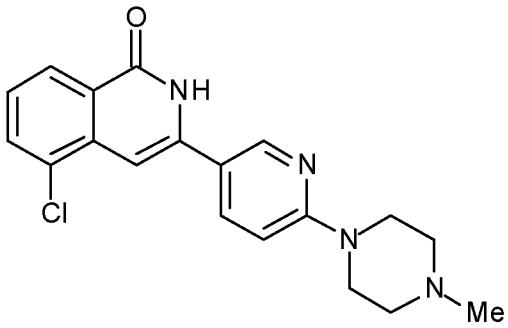
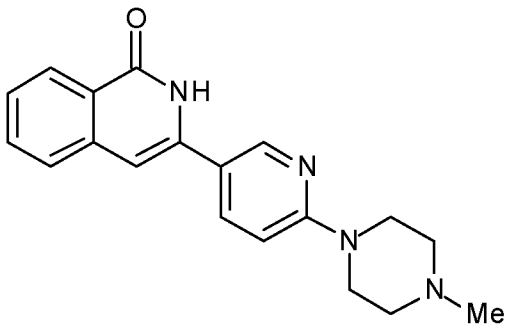
As demonstrated by this comparison, the presence of R^5 as -Me (as compared to -H) *decreased* Wnt IC_{50} (by a factor of about 24).

Code	Structure	TNKS1 IC_{50} (μM)	Wnt IC_{50} (μM)
IQ-080		0.029	0.042
REF-2		0.048	1.003

-R^5 Comparison No. 3:

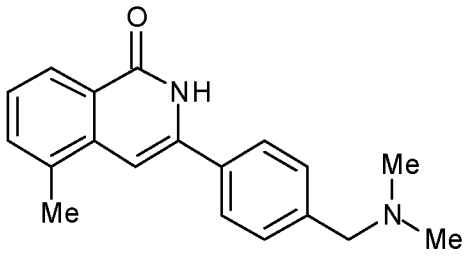
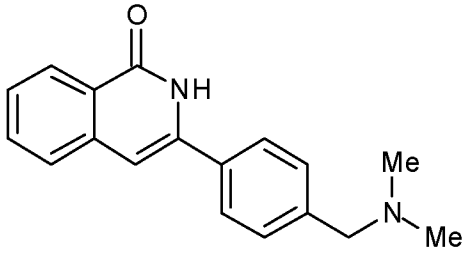
As demonstrated by this comparison, the presence of R^5 as -Me (as compared to -H) *decreased* Wnt IC_{50} (by a factor of about 62).

Also as demonstrated by this comparison, the presence of R^5 as -Cl (as compared to -H) *decreased* Wnt IC_{50} (by a factor of about 4).

Code	Structure	TNKS1 IC_{50} (μM)	Wnt IC_{50} (μM)
IQ-003		0.021	0.012
IQ-002		0.039	0.179
REF-3		0.024	0.742

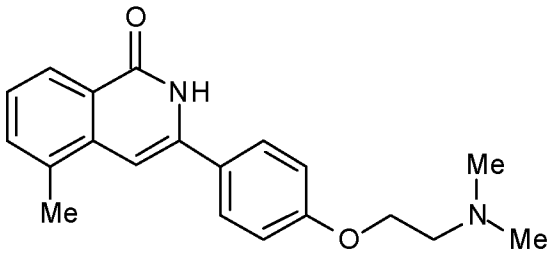
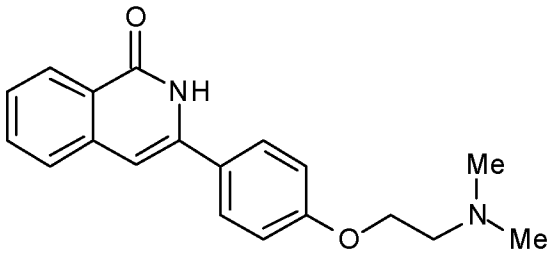
-R^5 Comparison No. 4:

As demonstrated by this comparison, the presence of R^5 as -Me (as compared to -H) *decreased* Wnt IC_{50} (by a factor of at least 9).

Code	Structure	TNKS1 IC_{50} (μM)	Wnt IC_{50} (μM)
IQ-034		0.012	1.07
REF-4		0.018	>10

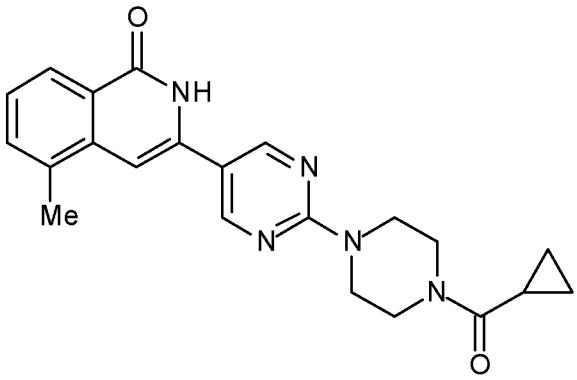
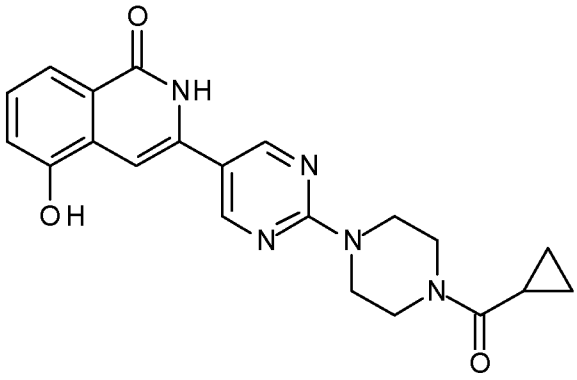
-R^5 Comparison No. 5:

As demonstrated by this comparison, the presence of R^5 as -Me (as compared to -H) *decreased* Wnt IC_{50} (by a factor of at least 60).

Code	Structure	TNKS1 IC_{50} (μM)	Wnt IC_{50} (μM)
IQ-130		0.016	0.165
REF-5		0.017	>10

-R^5 Comparison No. 6:

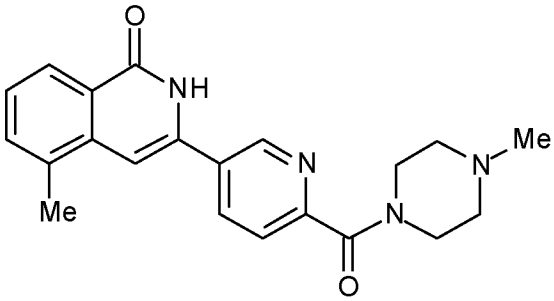
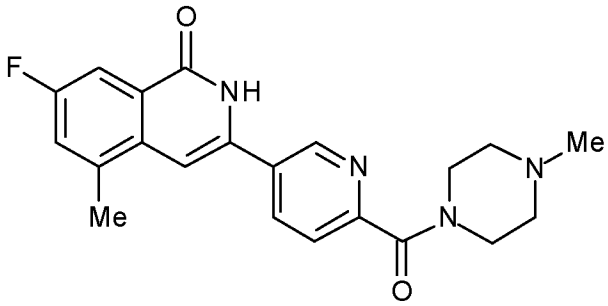
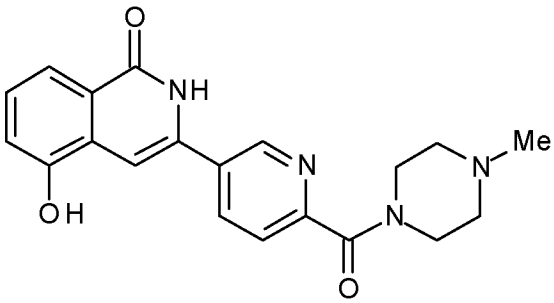
As demonstrated by this comparison, the presence of R^5 as -Me (as compared to -OH) decreased Wnt IC_{50} (by a factor of at least 14).

Code	Structure	TNKS1 IC_{50} (μM)	Wnt IC_{50} (μM)
IQ-157		0.051	0.041
REF-6		0.024	0.611

-R^5 Comparison No. 7:

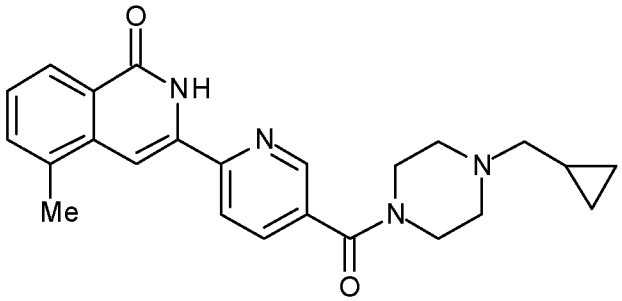
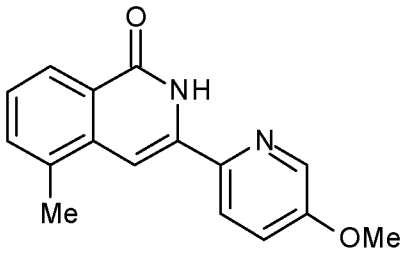
As demonstrated by this comparison, the presence of R^5 as -Me (as compared to -OH) *decreased* Wnt IC_{50} (by a factor of at least 36).

Also as demonstrated by this comparison, the additional change of R^7 as -F (as compared to -H) *further decreased* Wnt IC_{50} (now by a factor of at least 60).

Code	Structure	TNKS1 IC_{50} (μM)	Wnt IC_{50} (μM)
IQ-220		0.026	0.274
IQ-222		0.016	0.174
REF-7		0.042	>10

-L^{3P}-R^{3N} Comparison No. 1:

As demonstrated by this comparison, the presence of -L^{3P}-R^{3N} as N-(cyclopropylmethyl)-piperazino-carbonyl (as compared to -OMe) *decreased* Wnt IC_{50} (by a factor of at least about 3).

Code	Structure	TNKS1 IC_{50} (μM)	Wnt IC_{50} (μM)
IQ-223		0.076	1.34
REF-8		0.039	4.32

The foregoing has described the principles, preferred embodiments, and modes of operation of the present invention. However, the invention should not be construed as limited to the particular embodiments discussed. Instead, the above-described embodiments should be regarded as illustrative rather than restrictive. It should be appreciated that variations may be made in those embodiments by workers skilled in the art without departing from the scope of the present invention.

REFERENCES

A number of publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below. Each of these references is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference.

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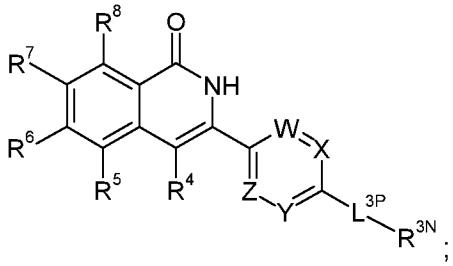
CLAIMS

1. A compound selected from compounds of the following formula, and pharmaceutically acceptable salts, N-oxides, hydrates, and solvates thereof:



;

wherein:

W is CR^W, X is CR^X, Y is CR^Y, and Z is CR^Z ("phenyl"); or
W is N, X is CR^X, Y is CR^Y, and Z is CR^Z ("pyrid-2-yl"); or
W is CR^W, X is N, Y is CR^Y, and Z is CR^Z ("pyrid-3-yl"); or
W is N, X is CR^X, Y is CR^Y, and Z is N ("pyrimidin-2-yl"); or
W is CR^W, X is N, Y is N, and Z is CR^Z ("pyrimidin-5-yl"); or
W is N, X is CR^X, Y is N, and Z is CR^Z ("pyrazin-2-yl"); or
W is N, X is N, Y is CR^Y, and Z is CR^Z ("pyridazin-3-yl");

wherein:

$-R^W$ is independently -H or $-R^{WW}$;
$-R^X$ is independently -H or $-R^{XX}$;
$-R^Y$ is independently -H or $-R^{YY}$; and
$-R^Z$ is independently -H or $-R^{ZZ}$;

wherein:

$-R^{WW}$ is independently $-X^1$, $-R^1$, -OH, $-OR^1$, $-CF_3$, or $-OCF_3$;
$-R^{XX}$ is independently $-X^1$, $-R^1$, -OH, $-OR^1$, $-CF_3$, or $-OCF_3$;
$-R^{YY}$ is independently $-X^1$, $-R^1$, -OH, $-OR^1$, $-CF_3$, or $-OCF_3$; and
$-R^{ZZ}$ is independently $-X^1$, $-R^1$, -OH, $-OR^1$, $-CF_3$, or $-OCF_3$;

wherein:

each $-X^1$ is independently -F, -Cl, -Br, or -I; and
each $-R^1$ is independently linear or branched saturated C_{1-4}alkyl;

and wherein:

$-L^{3P}-$ is independently a single covalent bond or $-L^{3PL}-$;

wherein:

$-L^{3PL}-$ is independently $-L^{3PR1}-$, $-C(=O)-$, $-L^{3PR2}-C(=O)-$, $-S(=O)_2-$, $-L^{3PR3}-S(=O)_2-$, or $-O-L^{3PR4}-$;

wherein:

each $-L^{3PR1}-$ is linear or branched saturated C_{1-4}alkylene;

each $-L^{3PR2}-$ is linear or branched saturated C_{1-4}alkylene;

each $-L^{3PR3}-$ is linear or branched saturated C_{1-4}alkylene;

each $-L^{3PR4}-$ is linear or branched saturated C_{1-4}alkylene;

and wherein:

$-R^{3N}$ is independently $-NH_2$, $-NHR^A$, $-NR^AR^B$, or $-NR^CR^D$;

wherein:

each $-R^A$ is independently:

$-R^{A1}$, $-R^{A2}$, $-R^{A3}$, $-R^{A4}$, $-R^{A5}$, $-L^A-R^{A2}$, $-L^A-R^{A3}$, $-L^A-R^{A4}$, or $-L^A-R^{A5}$;

each $-R^{A1}$ is linear or branched saturated C_{1-6}alkyl,

and is optionally substituted with one or more groups $-R^{S1}$;

each $-R^{A2}$ is saturated C_{3-6}cycloalkyl,

and is optionally substituted with one or more groups $-R^{S2C}$;

each $-R^{A3}$ is non-aromatic C_{3-7}heterocyclyl,

and is optionally substituted *on carbon* with one or more groups $-R^{S2C}$,

and is optionally substituted *on secondary nitrogen, if present,* with a group $-R^{SN}$;

each $-R^{A4}$ is independently phenyl or naphthyl,

and is optionally substituted with one or more groups $-R^{S3C}$;

each $-R^{A5}$ is C_{5-10}heteroaryl,

and is optionally substituted *on carbon* with one or more groups $-R^{S3C}$,

and is optionally substituted *on secondary nitrogen, if present,* with a group $-R^{SN}$;

each $-L^A-$ is linear or branched saturated C_{1-4}alkylene;

and wherein:

each $-R^{S1}$ is independently:

$-F$, $-Cl$, $-Br$, $-I$,

$-OH$, $-OR^{TT}$,

$-OCF_3$,

$-NH_2$, $-NHR^{TT}$, $-NR^{TT}_2$, $-R^{TM}$,

$-C(=O)OH$, $-C(=O)OR^{TT}$, $-OC(=O)R^{TT}$,

-C(=O)NH_2, -C(=O)NHR^{TT}, -C(=O)NR^{TT}_2, -C(=O)R^{TM},
-$NHC(=O)R^{TT}$, -$NR^{TN}C(=O)R^{TT}$,
-$NHC(=O)NH_2$, -$NHC(=O)NHR^{TT}$, -$NHC(=O)NR^{TT}_2$, -$NHC(=O)R^{TM}$,
-$NR^{TN}C(=O)NH_2$, -$NR^{TN}C(=O)NHR^{TT}$, -$NR^{TN}C(=O)NR^{TT}_2$, -$NR^{TN}C(=O)R^{TM}$,
-$NHC(=O)OR^{TT}$, -$NR^{TN}C(=O)OR^{TT}$,
-$OC(=O)NH_2$, -$OC(=O)NHR^{TT}$, -$OC(=O)NR^{TT}_2$, -$OC(=O)R^{TM}$,
-$C(=O)R^{TT}$,
-$S(=O)_2NH_2$, -$S(=O)_2NHR^{TT}$, -$S(=O)_2NR^{TT}_2$, -$S(=O)_2R^{TM}$,
-$NHS(=O)_2R^{TT}$, -$NR^{TN}S(=O)_2R^{TT}$,
-$S(=O)_2R^{TT}$,
-CN, -NO_2, -SR^{TT}, or =O;

each -R^{S2C} is independently:

-R^{TT},
-F, -Cl, -Br, -I,
-OH, -OR^{TT},
-L^T-OH, -L^T-OR^{TT},
-CF_3, -OCF_3,
-NH_2, -NHR^{TT}, -NR^{TT}_2, -R^{TM},
-L^T-NH_2, -L^T-NHR^{TT}, -L^T-NR^{TT}_2, -L^T-R^{TM},
-C(=O)OH, -C(=O)OR^{TT}, -$OC(=O)R^{TT}$,
-$C(=O)NH_2$, -$C(=O)NHR^{TT}$, -$C(=O)NR^{TT}_2$, -C(=O)R^{TM},
-$NHC(=O)R^{TT}$, -$NR^{TN}C(=O)R^{TT}$,
-$NHC(=O)NH_2$, -$NHC(=O)NHR^{TT}$, -$NHC(=O)NR^{TT}_2$, -$NHC(=O)R^{TM}$,
-$NR^{TN}C(=O)NH_2$, -$NR^{TN}C(=O)NHR^{TT}$, -$NR^{TN}C(=O)NR^{TT}_2$, -$NR^{TN}C(=O)R^{TM}$,
-$NHC(=O)OR^{TT}$, -$NR^{TN}C(=O)OR^{TT}$,
-$OC(=O)NH_2$, -$OC(=O)NHR^{TT}$, -$OC(=O)NR^{TT}_2$, -$OC(=O)R^{TM}$,
-$C(=O)R^{TT}$,
-$S(=O)_2NH_2$, -$S(=O)_2NHR^{TT}$, -$S(=O)_2NR^{TT}_2$, -$S(=O)_2R^{TM}$,
-$NHS(=O)_2R^{TT}$, -$NR^{TN}S(=O)_2R^{TT}$,
-$S(=O)_2R^{TT}$,
-CN, -NO_2, -SR^{TT}, or =O;

each -R^{S3C} is independently:

-R^{TT},
-F, -Cl, -Br, -I,
-OH, -OR^{TT},
-L^T-OH, -L^T-OR^{TT},
-CF_3, -OCF_3,

$-NH_2$, $-NHR^{TT}$, $-NR^{TT}_2$, $-R^{TM}$,
$-L^T-NH_2$, $-L^T-NHR^{TT}$, $-L^T-NR^{TT}_2$, $-L^T-R^{TM}$,
$-C(=O)OH$, $-C(=O)OR^{TT}$, $-OC(=O)R^{TT}$,
$-C(=O)NH_2$, $-C(=O)NHR^{TT}$, $-C(=O)NR^{TT}_2$, $-C(=O)R^{TM}$,
$-NHC(=O)R^{TT}$, $-NR^{TN}C(=O)R^{TT}$,
$-NHC(=O)NH_2$, $-NHC(=O)NHR^{TT}$, $-NHC(=O)NR^{TT}_2$, $-NHC(=O)R^{TM}$,
$-NR^{TN}C(=O)NH_2$, $-NR^{TN}C(=O)NHR^{TT}$, $-NR^{TN}C(=O)NR^{TT}_2$, $-NR^{TN}C(=O)R^{TM}$,
$-NHC(=O)OR^{TT}$, $-NR^{TN}C(=O)OR^{TT}$,
$-OC(=O)NH_2$, $-OC(=O)NHR^{TT}$, $-OC(=O)NR^{TT}_2$, $-OC(=O)R^{TM}$,
$-C(=O)R^{TT}$,
$-S(=O)_2NH_2$, $-S(=O)_2NHR^{TT}$, $-S(=O)_2NR^{TT}_2$, $-S(=O)_2R^{TM}$,
$-NHS(=O)_2R^{TT}$, $-NR^{TN}S(=O)_2R^{TT}$,
$-S(=O)_2R^{TT}$,
$-CN$, $-NO_2$, or $-SR^{TT}$;

and additionally, two adjacent groups $-R^{S3C}$, if present, may together form: $-O-CH_2-O-$ or $-O-CH_2CH_2-O-$;

each $-R^{SN}$ is independently:

$-R^{TT}$,
$-L^T-OH$, $-L^T-OR^{TT}$,
$-L^T-NH_2$, $-L^T-NHR^{TT}$, $-L^T-NR^{TT}_2$, $-L^T-R^{TM}$,
$-C(=O)R^{TT}$,
$-C(=O)OR^{TT}$,
$-C(=O)NH_2$, $-C(=O)NHR^{TT}$, $-C(=O)NR^{TT}_2$, $-C(=O)R^{TM}$, or
$-S(=O)_2R^{TT}$;

wherein:

each $-L^T-$ is linear or branched saturated C_{1-4}alkylene;
each $-R^{TT}$ is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl; wherein said linear or branched saturated C_{1-4}alkyl is optionally substituted with -OH or $-OR^{TTT}$, wherein $-R^{TTT}$ is linear or branched saturated C_{1-4}alkyl;
each $-R^{TN}$ is linear or branched saturated C_{1-4}alkyl;
each $-R^{TM}$ is independently azetidino, pyrrolidino, piperidino, piperazino, morpholino, azepano, or diazepano, and is:
optionally substituted *on carbon* with one or more groups selected from: $-R^{TMM}$, $-C(=O)R^{TMM}$, $-S(=O)_2R^{TMM}$, -F, $-NH_2$, $-NHR^{TMM}$, $-NR^{TMM}_2$, -OH, and $-OR^{TMM}$; and

optionally substituted *on secondary nitrogen, if present,* with a group selected from: $-R^{TMM}$, $-C(=O)R^{TMM}$, $-C(=O)OR^{TMM}$, and $-S(=O)_2R^{TMM}$;

wherein each $-R^{TMM}$ is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl;

and wherein:

$-R^B$ is independently $-R^{B1}$, $-R^{B2}$, or $-L^B-R^{B2}$;

$-R^{B1}$ is linear or branched saturated C_{1-6}alkyl, and is optionally substituted with -OH or $-OR^{BB}$, wherein $-R^{BB}$ is linear or branched saturated C_{1-4}alkyl;

$-R^{B2}$ is saturated C_{3-6}cycloalkyl; and

$-L^B-$ is linear or branched saturated C_{1-4}alkylene;

and wherein:

$-NR^CR^D$ is independently $-NR^{C1}R^{D1}$, $-NR^{C2}R^{D2}$, $-NR^{C3}R^{D3}$, $-NR^{C4}R^{D4}$, or $-NR^{C5}R^{D5}$;

wherein:

$-NR^{C1}R^{D1}$ is a monocyclic non-aromatic heterocyclyl group having from 4 to 8 ring atoms, wherein exactly 1 of said ring atoms is a ring heteroatom, and is N, or exactly 2 of said ring atoms are ring heteroatoms, and are both N, or exactly 2 of said ring atoms are ring heteroatoms, and are N and O, or exactly 2 of said ring atoms are ring heteroatoms, and are N and S, wherein said S is optionally in the form of $S(=O)$ or $S(=O)_2$;

and wherein said monocyclic non-aromatic heterocyclyl group is:
optionally substituted *on carbon* with one or more groups $-R^{NC}$, and
optionally substituted *on secondary nitrogen, if present,* with a group $-R^{NN}$;

$-NR^{C2}R^{D2}$ is a fused bicyclic non-aromatic heterocyclyl group having from 7 to 12 ring atoms, wherein exactly 1 of said ring atoms is a ring heteroatom, and is N, or exactly 2 of said ring atoms are ring heteroatoms, and are both N, or exactly 2 of said ring atoms are ring heteroatoms, and are N and O, or exactly 2 of said ring atoms are ring heteroatoms, and are N and S, wherein said S is optionally in the form of $S(=O)$ or $S(=O)_2$, or exactly 3 of said ring atoms are ring heteroatoms, one of which is N, and each of the other two is independently N, O, or S, wherein said S is optionally in the form of $S(=O)$ or $S(=O)_2$;

and wherein said fused bicyclic non-aromatic heterocyclyl group is:
optionally substituted *on carbon* with one or more groups $-R^{NC}$, and

optionally substituted *on secondary nitrogen, if present,* with a group -R^{NN};

-$NR^{C3}R^{D3}$ is a bridged non-aromatic heterocyclyl group having from 7 to 11 ring atoms, wherein exactly 1 of said ring atoms is a ring heteroatom, and is N, or exactly 2 of said ring atoms are ring heteroatoms, and are both N, or exactly 2 of said ring atoms are ring heteroatoms, and are N and O, or exactly 2 of said ring atoms are ring heteroatoms, and are N and S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$, or exactly 3 of said ring atoms are ring heteroatoms, one of which is N, and each of the other two is independently N, O, or S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$;

and wherein said bridged non-aromatic heterocyclyl group is:
optionally substituted *on carbon* with one or more groups -R^{NC}, and
optionally substituted *on secondary nitrogen, if present,* with a group -R^{NN};

-$NR^{C4}R^{D4}$ is a spiro non-aromatic heterocyclyl group having from 6 to 12 ring atoms, wherein exactly 1 of said ring atoms is a ring heteroatom, and is N, or exactly 2 of said ring atoms are ring heteroatoms, and are both N, or exactly 2 of said ring atoms are ring heteroatoms, and are N and O, or exactly 2 of said ring atoms are ring heteroatoms, and are N and S, or exactly 3 of said ring atoms are ring heteroatoms, one of which is N, and each of the other two is independently N, O, or S, wherein said S is optionally in the form of S(=O) or $S(=O)_2$;

and wherein said spiro non-aromatic heterocyclyl group is:
optionally substituted *on carbon* with one or more groups -R^{NC}, and
optionally substituted *on secondary nitrogen, if present,* with a group -R^{NN};

wherein:

each -R^{NC} is independently:

-R^{QQ},
-F, -Cl, -Br, -I,
-OH, -OR^{QQ},
-L^{Q}-OH, -L^{Q}-OR^{QQ},
-CF_3, -OCF_3,
-NH_2, -NHR^{QQ}, -$NR^{QQ}{}_2$, -R^{QM},
-L^{Q}-NH_2, -L^{Q}-NHR^{QQ}, -L^{Q}-$NR^{QQ}{}_2$, -L^{Q}-R^{QM},
-C(=O)OH, -C(=O)OR^{QQ}, -OC(=O)R^{QQ},
-C(=O)NH_2, -C(=O)NHR^{QQ}, -C(=O)$NR^{QQ}{}_2$, -C(=O)R^{QM},
-NHC(=O)R^{QQ}, -NR^{QN}C(=O)R^{QQ},
-NHC(=O)NH_2, -NHC(=O)NHR^{QQ}, -NHC(=O)$NR^{QQ}{}_2$, -NHC(=O)R^{QM},
-NR^{QN}C(=O)NH_2, -NR^{QN}C(=O)NHR^{QQ},

$-NR^{QN}C(=O)NR^{QQ}{}_2$, $-NR^{QN}C(=O)R^{QM}$,
$-NHC(=O)OR^{QQ}$, $-NR^{QN}C(=O)OR^{QQ}$,
$-OC(=O)NH_2$, $-OC(=O)NHR^{QQ}$, $-OC(=O)NR^{QQ}{}_2$, $-OC(=O)R^{QM}$,
$-C(=O)R^{QQ}$,
$-S(=O)_2NH_2$, $-S(=O)_2NHR^{QQ}$, $-S(=O)_2NR^{QQ}{}_2$, $-S(=O)_2R^{QM}$,
$-NHS(=O)_2R^{QQ}$, $-NR^{QN}S(=O)_2R^{QQ}$,
$-S(=O)_2R^{QQ}$,
$-CN$, $-NO_2$, $-SR^{QQ}$, or $=O$;

each $-R^{NN}$ is independently:

$-R^{QQ}$,
$-L^{Q}$-OH, $-L^{Q}$-OR^{QQ},
$-L^{Q}$-NH_2, $-L^{Q}$-NHR^{QQ}, $-L^{Q}$-$NR^{QQ}{}_2$, $-L^{Q}$-R^{QM},
$-C(=O)R^{QQ}$,
$-C(=O)OR^{QQ}$,
$-C(=O)NH_2$, $-C(=O)NHR^{QQ}$, $-C(=O)NR^{QQ}{}_2$, $-C(=O)R^{QM}$, or
$-S(=O)_2R^{QQ}$;

wherein:

each $-L^{Q}-$ is linear or branched saturated C_{1-4}alkylene;
each $-R^{QQ}$ is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl or benzyl; wherein said linear or branched saturated C_{1-4}alkyl is optionally substituted with -OH or $-OR^{QQQ}$, and said phenyl and benzyl are optionally substituted with $-R^{QQQ}$, wherein each $-R^{QQQ}$ is linear or branched saturated C_{1-4}alkyl;
each $-R^{QN}$ is linear or branched saturated C_{1-4}alkyl;
each $-R^{QM}$ is independently azetidino, pyrrolidino, piperidino, piperazino, morpholino, azepano, or diazepano, and is:
optionally substituted *on carbon* with one or more groups selected from: $-R^{QMM}$, $-C(=O)R^{QMM}$, $-S(=O)_2R^{QMM}$, -F, $-NH_2$, $-NHR^{QMM}$, $-NR^{QMM}{}_2$, -OH, and $-OR^{QMM}$; and
optionally substituted *on secondary nitrogen, if present,* with a group selected from: $-R^{QMM}$, $-C(=O)R^{QMM}$, $-C(=O)OR^{QMM}$, and $-S(=O)_2R^{QMM}$;
wherein each $-R^{QMM}$ is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl;

and wherein:

$-NR^{C5}R^{D5}$ is independently: 1H-pyrrol-1-yl; 2H-isoindol-2-yl; 1H-indol-1-yl; 1H-pyrazol-1-yl; 1H-benzoimidazol-1-yl; 1H-imidazol-1-yl; 2H-indazol-2-yl; 1H-indazol-1-yl; 4H-[1,2,4]triazol-4-yl; 1H-[1,2,3]triazol-1-yl; 1H-[1,2,4]triazol-1-yl; 1H-benzotriazol-1-yl; or 1H-tetrazol-1-yl; and is optionally substituted with one or more groups $-R^{H}$;

wherein each $-R^{H}$ is independently:

$-R^{HH}$,
-F, -Cl, -Br, -I,
$-OH$, $-OR^{HH}$,
$-L^{H}-OH$, $-L^{H}-OR^{HH}$,
$-CF_3$, $-OCF_3$,
$-NH_2$, $-NHR^{HH}$, $-NR^{HH}{}_2$, $-R^{HM}$,
$-L^{H}-NH_2$, $-L^{H}-NHR^{HH}$, $-L^{H}-NR^{HH}{}_2$, $-L^{H}-R^{HM}$,
$-C(=O)OH$, $-C(=O)OR^{HH}$, $-OC(=O)R^{HH}$,
$-C(=O)NH_2$, $-C(=O)NHR^{HH}$, $-C(=O)NR^{HH}{}_2$, $-C(=O)R^{HM}$,
$-NHC(=O)R^{HH}$, $-NR^{HN}C(=O)R^{HH}$,
$-NHC(=O)NH_2$, $-NHC(=O)NHR^{HH}$, $-NHC(=O)NR^{HH}{}_2$, $-NHC(=O)R^{HM}$,
$-NR^{HN}C(=O)NH_2$, $-NR^{HN}C(=O)NHR^{HH}$, $-NR^{HN}C(=O)NR^{HH}{}_2$, $-NR^{HN}C(=O)R^{HM}$,
$-NHC(=O)OR^{HH}$, $-NR^{HN}C(=O)OR^{HH}$,
$-OC(=O)NH_2$, $-OC(=O)NHR^{HH}$, $-OC(=O)NR^{HH}{}_2$, $-OC(=O)R^{HM}$,
$-C(=O)R^{HH}$,
$-S(=O)_2NH_2$, $-S(=O)_2NHR^{HH}$, $-S(=O)_2NR^{HH}{}_2$, $-S(=O)_2R^{HM}$,
$-NHS(=O)_2R^{HH}$, $-NR^{HN}S(=O)_2R^{HH}$,
$-S(=O)_2R^{HH}$,
-CN, $-NO_2$, or $-SR^{HH}$;

wherein:

each $-L^{H}-$ is linear or branched saturated C_{1-4}alkylene;
each $-R^{HH}$ is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl; wherein said linear or branched saturated C_{1-4}alkyl is optionally substituted with -OH or $-OR^{HHH}$, wherein $-R^{HHH}$ is linear or branched saturated C_{1-4}alkyl;
each $-R^{HN}$ is linear or branched saturated C_{1-4}alkyl;
each $-R^{HM}$ is independently azetidino, pyrrolidino, piperidino, piperazino, morpholino, azepano, or diazepano, and is:
optionally substituted *on carbon* with one or more groups selected from: $-R^{HMM}$, $-C(=O)R^{HMM}$, $-S(=O)_2R^{HMM}$, -F, $-NH_2$, $-NHR^{HMM}$, $-NR^{HMM}{}_2$, -OH, and $-OR^{HMM}$; and

optionally substituted *on secondary nitrogen, if present,* with a group selected from: $-R^{HMM}$, $-C(=O)R^{HMM}$, $-C(=O)OR^{HMM}$, and $-S(=O)_2R^{HMM}$;

wherein each $-R^{HMM}$ is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, saturated C_{3-6}cycloalkyl-methyl, phenyl, or benzyl;

and wherein:

$-R^5$ is independently $-R^{5A}$, $-R^{5B}$, $-R^{5C}$, $-R^{5D}$, or $-R^{5E}$;
$-R^{5A}$ is linear or branched saturated C_{1-4}alkyl;
$-R^{5B}$ is saturated C_{3-6}cycloalkyl;
$-R^{5C}$ is independently -F, -Cl, -Br, or -I;
$-R^{5D}$ is $-CF_3$; and
$-R^{5E}$ is independently $-C\equiv CH$ or C_{3-6}alkynyl optionally substituted with one or more groups $-R^{EE}$; wherein each $-R^{EE}$ is independently selected from -OH, $-OR^{EEE}$, $-NH_2$, $-NHR^{EEE}$, and $-NR^{EEE}_2$; wherein each $-R^{EEE}$ is linear or branched saturated C_{1-4}alkyl;

and wherein:

$-R^4$ is -H;
$-R^6$ is independently -H or -F; and
$-R^7$ is independently -H or -F; and
$-R^8$ is independently -H or -F.

2. A compound according to claim 1, wherein:
W is CR^W, X is CR^X, Y is CR^Y, and Z is CR^Z ("phenyl").

3. A compound according to claim 1, wherein:
W is CR^W, X is N, Y is CR^Y, and Z is CR^Z ("pyrid-3-yl").

4. A compound according to claim 1, wherein:
W is CR^W, X is N, Y is N, and Z is CR^Z ("pyrimidin-5-yl").

5. A compound according to any one of claims 1 to 4, wherein $-R^W$, if present, is -H.

6. A compound according to any one of claims 1 to 4, wherein $-R^W$, if present, is $-R^{WW}$.

7. A compound according to any one of claims 1 to 6, wherein $-R^X$, if present, is -H.

8. A compound according to any one of claims 1 to 6, wherein $-R^X$, if present, is $-R^{XX}$.

9. A compound according to any one of claims 1 to 8, wherein $-R^Y$, if present, is -H.

10. A compound according to any one of claims 1 to 8, wherein $-R^Y$, if present, is $-R^{YY}$.

11. A compound according to any one of claims 1 to 10, wherein $-R^Z$, if present, is -H.

12. A compound according to any one of claims 1 to 10, wherein $-R^Z$, if present, is $-R^{ZZ}$.

13. A compound according to any one of claims 1 to 12, wherein $-R^{WW}$, if present, is independently $-X^1$.

14. A compound according to any one of claims 1 to 13, wherein $-R^{XX}$, if present, is independently $-X^1$.

15. A compound according to any one of claims 1 to 14, wherein $-R^{YY}$, if present, is independently $-X^1$.

16. A compound according to any one of claims 1 to 15, wherein $-R^{ZZ}$, if present, is independently $-X^1$.

17. A compound according to any one of claims 1 to 16, wherein each $-X^1$, if present, is independently -F, -Cl, or -Br.

18. A compound according to any one of claims 1 to 16, wherein each $-X^1$, if present, is -F.

19. A compound according to any one of claims 1 to 18, wherein $-L^{3P}-$ is a single covalent bond.

20. A compound according to any one of claims 1 to 18, wherein $-L^{3P}-$ is $-L^{3PL}-$.

21. A compound according to any one of claims 1 to 20, wherein $-L^{3PL}-$, if present, is $-L^{3PR1}-$.

22. A compound according to any one of claims 1 to 20, wherein $-L^{3PL}-$, if present, is -C(=O)-.

23. A compound according to any one of claims 1 to 20, wherein -L^{3PL}-, if present, is -L^{3PR2}-C(=O)-.

24. A compound according to any one of claims 1 to 20, wherein -L^{3PL}-, if present, is -$S(=O)_2$-.

25. A compound according to any one of claims 1 to 20, wherein -L^{3PL}-, if present, is -L^{3PR3}-$S(=O)_2$-.

26. A compound according to any one of claims 1 to 20, wherein -L^{3PL}-, if present, is -O-L^{3PR4}-.

27. A compound according to any one of claims 1 to 26, wherein each -L^{3PR1}-, if present, is independently -CH_2-, -CH(Me)-, or -$C(Me)_2$-.

28. A compound according to any one of claims 1 to 26, wherein each -L^{3PR1}-, if present, is -CH_2-.

29. A compound according to any one of claims 1 to 26, wherein each -L^{3PR1}-, if present, is -CH_2CH_2-.

30. A compound according to any one of claims 1 to 29, wherein each -L^{3PR2}-, if present, is independently -CH_2-, -CH(Me)-, or -$C(Me)_2$-.

31. A compound according to any one of claims 1 to 29, wherein each -L^{3PR2}-, if present, is -CH_2-.

32. A compound according to any one of claims 1 to 31, wherein each -L^{3PR4}-, if present, is -CH_2CH_2-.

33. A compound according to any one of claims 1 to 32, wherein -R^{3N} is -NH_2.

34. A compound according to any one of claims 1 to 32, wherein -R^{3N} is -NHR^A.

35. A compound according to any one of claims 1 to 32, wherein -R^{3N} is -NR^AR^B.

36. A compound according to any one of claims 1 to 32, wherein -R^{3N} is -NR^CR^D.

37. A compound according to any one of claims 1 to 36, wherein each -R^A, if present, is independently: -R^{A1}, -R^{A3}, or -L^A-R^{A3}.

38. A compound according to any one of claims 1 to 36, wherein each $-R^{A}$, if present, is $-L^{A}-R^{A5}$.

39. A compound according to any one of claims 1 to 38, wherein each $-R^{A1}$, if present, is independently linear or branched saturated C_{1-4}alkyl, and is optionally substituted with one or more groups $-R^{S1}$.

40. A compound according to any one of claims 1 to 38, wherein each $-R^{A1}$, if present, is independently linear or branched saturated C_{1-4}alkyl, and is optionally substituted with one or more groups selected from: -OH and $-OR^{TT}$.

41. A compound according to any one of claims 1 to 38, wherein each $-R^{A1}$, if present, is -Me.

42. A compound according to any one of claims 1 to 41, wherein each $-R^{A3}$, if present, is tetrahydropyranyl, and is optionally substituted *on carbon* with one or more groups $-R^{S2C}$.

43. A compound according to any one of claims 1 to 41, wherein each $-R^{A3}$, if present, is piperidinyl,
and is optionally substituted *on carbon* with one or more groups $-R^{S2C}$,
and is optionally substituted *on secondary nitrogen* with a group $-R^{SN}$.

44. A compound according to any one of claims 1 to 41, wherein each $-R^{A3}$, if present, is pyrrolidinyl,
and is optionally substituted *on carbon* with one or more groups $-R^{S2C}$,
and is optionally substituted *on secondary nitrogen* with a group $-R^{SN}$.

45. A compound according to any one of claims 1 to 41, wherein each $-R^{A3}$, if present, is azetidinyl,
and is optionally substituted *on carbon* with one or more groups $-R^{S2C}$,
and is optionally substituted *on secondary nitrogen* with a group $-R^{SN}$.

46. A compound according to any one of claims 1 to 45, wherein each $-R^{A5}$, if present, is imidazolyl,
and is optionally substituted *on carbon* with one or more groups $-R^{S3C}$,
and is optionally substituted *on secondary nitrogen* with a group $-R^{SN}$.

47. A compound according to any one of claims 1 to 46, wherein each $-L^{A}-$, if present, is $-CH_2-$.

48. A compound according to any one of claims 1 to 47, wherein each $-R^{S1}$, if present, is independently -OH or $-OR^{TT}$.

49. A compound according to any one of claims 1 to 48, wherein each $-R^{SN}$, if present, is independently:
$-R^{TT}$,
$-C(=O)R^{TT}$, or
$-C(=O)OR^{TT}$.

50. A compound according to any one of claims 1 to 49, wherein each $-R^{TT}$, if present, is linear or branched saturated C_{1-4}alkyl.

51. A compound according to any one of claims 1 to 49, wherein each $-R^{TT}$, if present, is -Me.

52. A compound according to any one of claims 1 to 51, wherein $-R^{B}$, if present, is $-R^{B1}$.

53. A compound according to any one of claims 1 to 51, wherein $-R^{B}$, if present, is $-R^{B2}$.

54. A compound according to any one of claims 1 to 53, wherein $-R^{B1}$, if present, is independently: -Me; or -Et that is optionally substituted with -OH or $-OR^{BB}$, wherein $-R^{BB}$ is linear or branched saturated C_{1-4}alkyl.

55. A compound according to any one of claims 1 to 53, wherein $-R^{B1}$, if present, is independently -Me, -Et, $-CH_2CH_2OH$, or $-CH_2CH_2OMe$.

56. A compound according to any one of claims 1 to 53, wherein $-R^{B1}$, if present, is -Me.

57. A compound according to any one of claims 1 to 56, wherein $-R^{B2}$, if present, is cyclopropyl.

58. A compound according to any one of claims 1 to 57, wherein $-NR^{C}R^{D}$, if present, is $-NR^{C1}R^{D1}$.

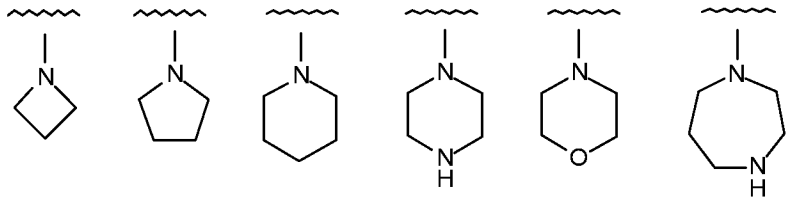
59. A compound according to any one of claims 1 to 57, wherein $-NR^{C}R^{D}$, if present, is $-NR^{C2}R^{D2}$.

60. A compound according to any one of claims 1 to 57, wherein $-NR^CR^D$, if present, is $-NR^{C3}R^{D3}$.

61. A compound according to any one of claims 1 to 57, wherein $-NR^CR^D$, if present, is $-NR^{C4}R^{D4}$.

62. A compound according to any one of claims 1 to 57, wherein $-NR^CR^D$, if present, is $-NR^{C5}R^{D5}$.

63. A compound according to any one of claims 1 to 62, wherein, $-NR^{C1}R^{D1}$, if present, is independently selected from the following groups, and is:
optionally substituted *on carbon* with one or more groups $-R^{NC}$, and
optionally substituted *on secondary nitrogen, if present,* with a group $-R^{NN}$:



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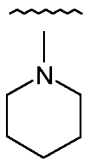
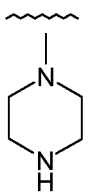
64. A compound according to any one of claims 1 to 62, wherein, $-NR^{C1}R^{D1}$, if present, is the following group, and is optionally substituted *on carbon* with one or more groups $-R^{NC}$:



.

65. A compound according to any one of claims 1 to 62, wherein, $-NR^{C1}R^{D1}$, if present, is the following group, and is:
optionally substituted *on carbon* with one or more groups $-R^{NC}$, and
optionally substituted *on secondary nitrogen* with a group $-R^{NN}$:



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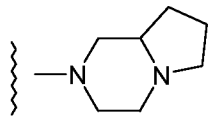
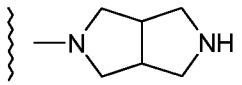
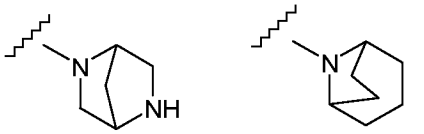
66. A compound according to any one of claims 1 to 65, wherein, -$NR^{C2}R^{D2}$, if present, is the following group, and is optionally substituted *on carbon* with one or more groups -R^{NC}:



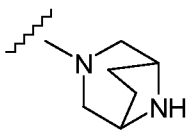
67. A compound according to any one of claims 1 to 65, wherein, -$NR^{C2}R^{D2}$, if present, is the following group, and is:
optionally substituted *on carbon* with one or more groups -R^{NC}, and
optionally substituted *on secondary nitrogen* with a group -R^{NN}:



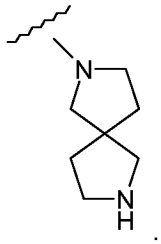
68. A compound according to any one of claims 1 to 67, wherein, -$NR^{C3}R^{D3}$, if present, is independently selected from the following groups, and is:
optionally substituted *on carbon* with one or more groups -R^{NC}, and
optionally substituted *on secondary nitrogen, if present,* with groups -R^{NN}:



69. A compound according to any one of claims 1 to 67, wherein, -$NR^{C3}R^{D3}$, if present, is the following group, and is:
optionally substituted *on carbon* with one or more groups -R^{NC}, and
optionally substituted *on secondary nitrogen* with groups -R^{NN}:



70. A compound according to any one of claims 1 to 69, wherein, $-NR^{C4}R^{D4}$, if present, is the following group, and is:
optionally substituted *on carbon* with one or more groups $-R^{NC}$, and
optionally substituted *on secondary nitrogen* with a group $-R^{NN}$:



71. A compound according to any one of claims 1 to 70, wherein each $-R^{NC}$, if present, is independently:
$-R^{QQ}$,
$-OH$, $-OR^{QQ}$,
$-NH_2$, $-NHR^{QQ}$, $-NR^{QQ}{}_2$, $-R^{QM}$, or
$=O$.

72. A compound according to any one of claims 1 to 71, wherein each $-R^{NN}$, if present, is independently:
$-R^{QQ}$,
$-L^{Q}$-OH, $-L^{Q}$-OR^{QQ},
$-L^{Q}$-NH_2, $-L^{Q}$-NHR^{QQ}, $-L^{Q}$-$NR^{QQ}{}_2$, $-L^{Q}$-R^{QM},
$-C(=O)R^{QQ}$, or
$-C(=O)OR^{QQ}$.

73. A compound according to any one of claims 1 to 71, wherein each $-R^{NN}$, if present, is independently: $-R^{QQ}$, $-L^{Q}$-OH, or $-L^{Q}$-OR^{QQ}.

74. A compound according to any one of claims 1 to 71, wherein each $-R^{NN}$, if present, is independently $-R^{QQ}$.

75. A compound according to any one of claims 1 to 71, wherein each $-R^{NN}$, if present, is independently $-L^{Q}$-OH.

76. A compound according to any one of claims 1 to 75, wherein each $-R^{QQ}$, if present, is independently linear or branched saturated C_{1-4}alkyl, saturated C_{3-6}cycloalkyl, or saturated C_{3-6}cycloalkyl-methyl.

77. A compound according to any one of claims 1 to 75, wherein each $-R^{QQ}$, if present, is -Me.

78. A compound according to any one of claims 1 to 75, wherein each $-R^{QQ}$, if present, is cyclopropyl.

79. A compound according to any one of claims 1 to 75, wherein each $-R^{QQ}$, if present, is cyclopropyl-methyl.

80. A compound according to any one of claims 1 to 79, wherein $-NR^{C5}R^{D5}$ is: 1H-pyrrol-1-yl; and is optionally substituted with one or more groups $-R^{H}$.

81. A compound according to any one of claims 1 to 79, wherein $-NR^{C5}R^{D5}$, if present, is: 1H-pyrazol-1-yl; and is optionally substituted with one or more groups $-R^{H}$.

82. A compound according to any one of claims 1 to 79, wherein $-NR^{C5}R^{D5}$, if present, is: 1H-imidazol-1-yl; and is optionally substituted with one or more groups $-R^{H}$.

83. A compound according to any one of claims 1 to 79, wherein $-NR^{C5}R^{D5}$, if present, is 1H-[1,2,4]triazol-1-yl; and is optionally substituted with one or more groups $-R^{H}$.

84. A compound according to any one of claims 1 to 79, wherein $-NR^{C5}R^{D5}$, if present, is 1H-benzoimidazol-1-yl; and is optionally substituted with one or more groups $-R^{H}$.

85. A compound according to any one of claims 1 to 79, wherein $-NR^{C5}R^{D5}$, if present, is 1H-indol-1-yl; and is optionally substituted with one or more groups $-R^{H}$.

86. A compound according to any one of claims 1 to 85, wherein each $-R^{H}$, if present, is independently $-R^{HH}$.

87. A compound according to any one of claims 1 to 86, wherein each $-R^{HH}$, if present, is -Me.

88. A compound according to any one of claims 1 to 87, wherein $-R^{5}$ is $-R^{5A}$.

89. A compound according to any one of claims 1 to 87, wherein $-R^{5}$ is $-R^{5B}$.

90. A compound according to any one of claims 1 to 87, wherein $-R^{5}$ is $-R^{5C}$.

91. A compound according to any one of claims 1 to 87, wherein $-R^{5}$ is $-R^{5D}$.

92. A compound according to any one of claims 1 to 87, wherein -R^5 is -R^{5E}.

93. A compound according to any one of claims 1 to 92, wherein -R^{5A}, if present, is -Me.

94. A compound according to any one of claims 1 to 92, wherein -R^{5A}, if present, is cyclopropyl.

95. A compound according to any one of claims 1 to 94, wherein -R^{5C}, if present, is -F.

96. A compound according to any one of claims 1 to 94, wherein -R^{5C}, if present, is -Cl.

97. A compound according to any one of claims 1 to 94, wherein -R^{5C}, if present, is -Br.

98. A compound according to any one of claims 1 to 97, wherein -R^{5E}, if present, is -C≡CH.

99. A compound according to any one of claims 1 to 97, wherein -R^{5E}, if present, is C_{3-4}alkynyl optionally substituted with one or more groups -R^{EE}; wherein each -R^{EE} is independently selected from -OH, -OR^{EEE}, -NH_2, -NHR^{EEE}, and -NR^{EEE}_2; wherein each -R^{EEE} is linear or branched saturated C_{1-4}alkyl.

100. A compound according to any one of claims 1 to 99, wherein each -R^{EEE}, if present, is -Me.

101. A compound according to any one of claims 1 to 100, wherein -R^6 is -H.

102. A compound according to any one of claims 1 to 100, wherein -R^6 is -F.

103. A compound according to any one of claims 1 to 102, wherein -R^7 is -H.

104. A compound according to any one of claims 1 to 102, wherein -R^7 is -F.

105. A compound according to any one of claims 1 to 104, wherein -R^8 is -H.

106. A compound according to any one of claims 1 to 104, wherein -R^8 is -F.

107. A compound according to claim 1, selected from compounds of the following formulae and pharmaceutically acceptable salts, N-oxides, hydrates, and solvates thereof: IQ-001 through IQ-238.

108. A pharmaceutical composition comprising a compound according to any one of claims 1 to 107, and a pharmaceutically acceptable carrier or diluent.

109. A method of preparing a pharmaceutical composition comprising the step of mixing a compound according to any one of claims 1 to 107, and a pharmaceutically acceptable carrier or diluent.

110. A method of inhibiting PARP function in a cell, *in vitro* or *in vivo,* comprising contacting the cell with an effective amount of a compound according to any one of claims 1 to 107.

111. A method of inhibiting TNKS1 and/or TNKS2 function in a cell, *in vitro* or *in vivo,* comprising contacting the cell with an effective amount of a compound according to any one of claims 1 to 107.

112. A method of inhibiting Wnt signalling in a cell, *in vitro* or *in vivo,* comprising contacting the cell with an effective amount of a compound according to any one of claims 1 to 107.

113. A compound according to any one of claims 1 to 107, for use in a method of treatment of the human or animal body by therapy.

114. A compound according to any one of claims 1 to 107, for use in a method of treatment of a disorder of the human or animal body that is ameliorated by the inhibition of PARP.

115. A compound according to any one of claims 1 to 107, for use in a method of treatment of a disorder of the human or animal body that is ameliorated by the inhibition of TNKS1 and/or TNKS2.

116. A compound according to any one of claims 1 to 107, for use in a method of treatment of a disorder of the human or animal body that is ameliorated by the inhibition of Wnt signalling.

117. A compound according to any one of claims 1 to 107, for use in a method of treatment of a proliferative condition.

118. A compound according to any one of claims 1 to 107, for use in a method of treatment of cancer.

119. A compound according to any one of claims 1 to 107, for use in a method of treatment of: head and neck cancer; nervous system cancer; lung/mediastinum cancer; breast cancer; oesophagus cancer; stomach cancer; liver cancer; biliary tract cancer; pancreatic cancer; small bowel cancer; large bowel cancer; gynaecological cancer; genito-urinary cancer; thyroid gland cancer; adrenal gland cancer; skin cancer; bone sarcoma; soft tissue sarcoma; paediatric malignancy; Hodgkin's disease; non-Hodgkin's lymphoma; myeloma; leukaemia; or metastasis from an unknown primary site.

120. A compound according to any one of claims 1 to 107, for use in a method of treatment of: a neurodegenerative disorder, such as multiple sclerosis (MS); a neurological disorder associated with demyelination; neonatal hypoxic ischemic encephalopathy (HIE); neonatal periventricular leukomalacia (PVL); a cardiac related pathology, such as myocardial infarction; cardiac damage (e.g., to repair cardiac damage); an infectious disease, such as a pathology related to Herpes Simplex Virus (HSV); a pathology related to Epstein-Barr Virus (EBV); a metabolic disease, such as a metabolic disease where glucose uptake is dysfunctional, such as diabetes, such as type 2 diabetes; or fibrosis (e.g., lung fibrosis).

121. A compound according to any one of claims 1 to 107, for use in a method of treatment of: Alzheimer's disease; late onset Alzheimer's disease; Dupuytren skin disease; tooth agenesis; vascular defects in the eye; Osteoperosis-pseudoglioma Syndrome (OPPG); exudative vitreoretinopathy; familial exudative vitreoretinopathy; retinal angiogenesis; schizophrenia; osteoporosis; dermal hypoplasia; XX sex reversal; Mullerian-duct regression and virilization; SERKAL syndrome; anonychia; hyponychia; sclerosteosis; van Buchem disease; Fuhrmann syndrome; odonto-onchyo-dermal hypoplasia; Type 2 diabetes; obesity; early onset obesity; a nephropathy, such as HIV-associated nephropathy; early coronary disease; bone density defects; tetra-amelia syndrome; split-hand/foot malformation; caudal duplication; Fuhrmann syndrome; odonto-onycho-dermal dysplasia; skeletal dysplasia; focal dermal hypoplasia; autosomal recessive anonychia; or neural tube defects.

122. Use of a compound according to any one of claims 1 to 107 in the manufacture of a medicament for the treatment of a disorder of the human or animal body that is ameliorated by the inhibition of PARP.

123. Use of a compound according to any one of claims 1 to 107 in the manufacture of a medicament for the treatment of a disorder of the human or animal body that is ameliorated by the inhibition of TNKS1 and/or TNKS2.

124. Use of a compound according to any one of claims 1 to 107 in the manufacture of a medicament for the treatment of a disorder of the human or animal body that is ameliorated by the inhibition of Wnt signalling.

125. Use of a compound according to any one of claims 1 to 107 in the manufacture of a medicament for the treatment of a proliferative condition.

126. Use of a compound according to any one of claims 1 to 107 in the manufacture of a medicament for the treatment of cancer.

127. Use of a compound according to any one of claims 1 to 107 in the manufacture of a medicament for the treatment of: head and neck cancer; nervous system cancer; lung/mediastinum cancer; breast cancer; oesophagus cancer; stomach cancer; liver cancer; biliary tract cancer; pancreatic cancer; small bowel cancer; large bowel cancer; gynaecological cancer; genito-urinary cancer; thyroid gland cancer; adrenal gland cancer; skin cancer; bone sarcoma; soft tissue sarcoma; paediatric malignancy; Hodgkin's disease; non-Hodgkin's lymphoma; myeloma; leukaemia; or metastasis from an unknown primary site.

128. Use of a compound according to any one of claims 1 to 107 in the manufacture of a medicament for the treatment of: a neurodegenerative disorder, such as multiple sclerosis (MS); a neurological disorder associated with demyelination; neonatal hypoxic ischemic encephalopathy (HIE); neonatal periventricular leukomalacia (PVL); a cardiac related pathology, such as myocardial infarction; cardiac damage (e.g., to repair cardiac damage); an infectious disease, such as a pathology related to Herpes Simplex Virus (HSV); a pathology related to Epstein-Barr Virus (EBV); a metabolic disease, such as a metabolic disease where glucose uptake is dysfunctional, such as diabetes, such as type 2 diabetes; or fibrosis (e.g., lung fibrosis).

129. Use of a compound according to any one of claims 1 to 107 in the manufacture of a medicament for the treatment of: Alzheimer's disease; late onset Alzheimer's disease; Dupuytren skin disease; tooth agenesis; vascular defects in the eye; Osteoperosis-pseudoglioma Syndrome (OPPG); exudative vitreoretinopathy; familial exudative vitreoretinopathy; retinal angiogenesis; schizophrenia; osteoporosis; dermal hypoplasia; XX sex reversal; Mullerian-duct regression and virilization; SERKAL syndrome; anonychia; hyponychia; sclerosteosis; van Buchem disease; Fuhrmann syndrome; odonto-onchyo-dermal hypoplasia; Type 2 diabetes; obesity; early onset obesity; a nephropathy, such as HIV-associated nephropathy; early coronary disease; bone density defects; tetra-amelia syndrome; split-hand/foot malformation; caudal duplication; Fuhrmann syndrome; odonto-onycho-dermal dysplasia; skeletal dysplasia; focal dermal hypoplasia; autosomal recessive anonychia; or neural tube defects.

130. A method of treatment of a disorder of the human or animal body that is ameliorated by the inhibition of PARP, comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 107.

131. A method of treatment of a disorder of the human or animal body that is ameliorated by the inhibition of TNKS1 and/or TNKS2, comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 107.

132. A method of treatment of a disorder of the human or animal body that is ameliorated by the inhibition of Wnt signalling, comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 107.

133. A method of treatment of a proliferative condition, comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 107.

134. A method of treatment of cancer, comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 107.

135. A method of treatment of: head and neck cancer; nervous system cancer; lung/mediastinum cancer; breast cancer; oesophagus cancer; stomach cancer; liver cancer; biliary tract cancer; pancreatic cancer; small bowel cancer; large bowel cancer; gynaecological cancer; genito-urinary cancer; thyroid gland cancer; adrenal gland cancer; skin cancer; bone sarcoma; soft tissue sarcoma; paediatric malignancy; Hodgkin's disease; non-Hodgkin's lymphoma; myeloma; leukaemia; or metastasis from an unknown primary site, comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 107.

136. A method of treatment of: a neurodegenerative disorder, such as multiple sclerosis (MS); a neurological disorder associated with demyelination; neonatal hypoxic ischemic encephalopathy (HIE); neonatal periventricular leukomalacia (PVL); a cardiac related pathology, such as myocardial infarction; cardiac damage (e.g., to repair cardiac damage); an infectious disease, such as a pathology related to Herpes Simplex Virus (HSV); a pathology related to Epstein-Barr Virus (EBV); a metabolic disease, such as a metabolic disease where glucose uptake is dysfunctional, such as diabetes, such as type 2 diabetes; or fibrosis (e.g., lung fibrosis); comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 107.

137. A method of treatment of: Alzheimer's disease; late onset Alzheimer's disease; Dupuytren skin disease; tooth agenesis; vascular defects in the eye; Osteoperosis-pseudoglioma Syndrome (OPPG); exudative vitreoretinopathy; familial exudative vitreoretinopathy; retinal angiogenesis; schizophrenia; osteoporosis; dermal hypoplasia; XX sex reversal; Mullerian-duct regression and virilization; SERKAL syndrome; anonychia; hyponychia; sclerosteosis; van Buchem disease; Fuhrmann syndrome; odonto-onchyo-dermal hypoplasia; Type 2 diabetes; obesity; early onset obesity; a nephropathy, such as HIV-associated nephropathy; early coronary disease; bone density defects; tetra-amelia syndrome; split-hand/foot malformation; caudal duplication; Fuhrmann syndrome; odonto-onycho-dermal dysplasia; skeletal dysplasia; focal dermal hypoplasia; autosomal recessive anonychia; or neural tube defects; comprising administering to a subject in need of treatment a therapeutically-effective amount of a compound according to any one of claims 1 to 107.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2013/050561

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P35/00 A61K31/472 C07D401/14 C07D217/14 C07D217/16
C07D401/04 C07D401/10 C07D401/12 C07D405/12 C07D487/04
C07D487/08 C07D487/10 A61K31/4725 A61K31/496 A61K31/506

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 557 414 A1 (MITSUBISHI PHARMA CORP [JP] MITSUBISHI TANABE PHARMA CORP [JP]) 27 July 2005 (2005-07-27) the whole document	1-137
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A	US 2007/049555 A1 (JAGTAP PRAKASH [US] ET AL) 1 March 2007 (2007-03-01) the whole document	1-137

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 May 2013	17/05/2013

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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