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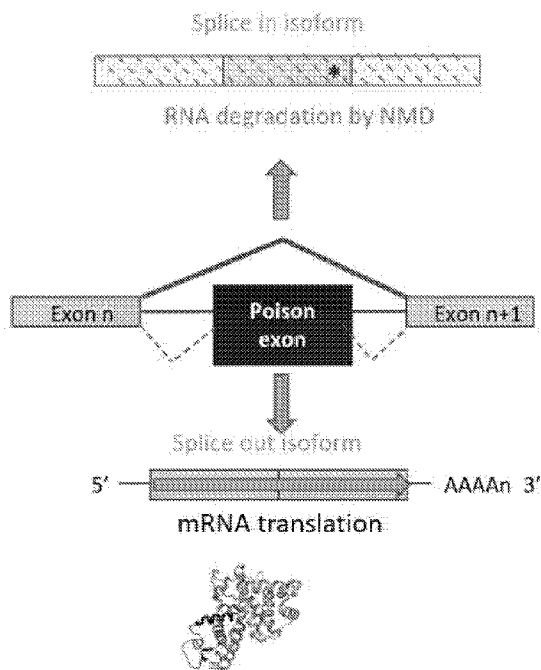


FIG. 4

(57) Abstract: Described herein are compositions, methods, and systems for modulating splicing of MSH3 pre-mRNA such that the resulting MSH3 mRNA transcript includes a poison exon. Further disclosed herein are compositions, methods, and systems for treating a disease or condition associated with a nucleotide repeat expansion in a gene.

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COMPOSITIONS, METHODS, AND SYSTEMS FOR MODULATING SPLICING OF MSH3**CROSS REFERENCE**

[0001] This application claims the benefit of U.S. Provisional Application No. 63/506,564, filed on June 6, 2023, and U.S. Provisional Application No. 63/580,945, filed on September 6, 2023, each of which is herein incorporated by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in XML file format and is hereby incorporated by reference in its entirety. The XML copy, created on June 4, 2024, is named 62236-703_601_SL.xml and is 27,601 bytes in size.

BACKGROUND

[0003] The accumulation of nucleotide repeats in a gene can lead to manifestation of a disease or condition. For example, a nucleotide repeat expansion of nucleotides CAG is the leading cause of Huntington's disease, where a subject having the CAG repeat expansion at low abundance does not exhibit any symptoms. However, as the subject ages, the CAG nucleotide repeat accumulates (or expands), leading to manifestation of symptoms of Huntington's disease. Because of the latency associated with the nucleotide repeat expansion and the manifestation of the disease or condition, treatment options for nucleotide repeat expansion diseases or conditions are limited and ineffective. Often times, there is no cure once the subject exhibits symptoms associated with the nucleotide repeat expansion disease or condition. Treatment options at this particular timepoint is now only limited to palliative care.

SUMMARY

[0004] There is an unmet need for compositions, methods, and systems for treating nucleotide repeat expansion diseases or conditions. There is also an unmet need for compositions, methods, and systems to prevent or decrease nucleotide repeat expansions in a subject. This disclosure addresses this unmet need.

[0005] In one aspect, a method for modulating splicing of MSH3 pre-mRNA is provided, the method comprising contacting a cell with an agent which modulates splicing of MSH3 pre-mRNA such that an MSH3 mRNA transcript comprising a poison exon is produced, thereby modulating splicing of MSH3 pre-mRNA. In another aspect, a method for treating a disease or condition in a subject is provided, the method comprising administering to the subject an agent which modulates splicing of MSH3 pre-mRNA such that an MSH3 mRNA transcript comprising a poison exon is produced in a cell of the subject, thereby treating the disease or condition.

[0006] In some cases, the method results in decreased expression of MSH3 protein in the cell. In some cases, the method results in decreased nucleotide repeat expansion of a target gene in the cell. In some cases, the nucleotide repeat expansion comprises a trinucleotide repeat expansion. In some cases, the nucleotide repeat expansion comprises expansion of a four-nucleotide repeat, a five-nucleotide repeat, a six-nucleotide repeat, a seven-nucleotide repeat, an eight-nucleotide repeat, a nine-nucleotide repeat, a

ten-nucleotide repeat, an eleven-nucleotide repeat, or a twelve-nucleotide repeat. In some cases, the nucleotide repeat expansion is in an exon of the target gene. In some cases, the nucleotide repeat expansion is in an intron of the target gene. In some cases, the nucleotide repeat expansion is in a UTR of the target gene. In some cases, the nucleotide repeat expansion is in a promoter of the target gene. In some cases, the gene is selected from the group consisting of: ATN1, HTT, AR, ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7, PPP2R2B, TBP, TCF4, JPH3, DMPK, ATXN8, ZNF713, FMR1, AFF/FMR2, FXN, ZFN9, ATXN10, NOP56, C9orf72, CSTB, and any combination thereof. In some cases, the nucleotide repeat expansion in the cell comprises at least 20 repeats, at least 30 repeats, at least 40 repeats, at least 50 repeats, at least 60 repeats, at least 70 repeats, at least 80 repeats, at least 90 repeats, at least 100 repeats, at least 200 repeats, at least 500 repeats, at least 1000 repeats, at least 2000 repeats, at least 5000 repeats, at least 10,000 repeats, or at least 20,000 repeats. In some cases, the nucleotide repeat expansion in the target gene is decreased by at least about 0.1 fold, at least about 0.2 fold, at least about 0.5 fold, at least about 1.0 fold, at least about 2.0 fold, at least about 5.0 fold, at least about 10.0 fold, or at least about 100.0 fold, as compared to a level of nucleotide repeat expansion in the target gene in the absence of the agent. In some cases, the poison exon comprises a nucleic acid sequence that has at least about 80% sequence identity to the nucleic acid sequence of SEQ ID NO: 1. In some cases, the poison exon is or comprises exon 21A, or a portion thereof, of MSH3. In some cases, the poison exon is located at or within position chr5:80832901-80832994 of Human Genome Assembly hg38 of December 2013. In some cases, the poison exon comprises a nucleic acid sequence that has at least about 80% sequence identity to the nucleic acid sequence of SEQ ID NO: 2 or SEQ ID NO: 3. In some cases, the poison exon is or comprises exon 14A_1, or a portion thereof, of MSH3. In some cases, the poison exon is or comprises exon 14A_2, or a portion thereof, of MSH3. In some cases, the poison exon is located at or within position chr5:80763222-80763369 or position chr5:80763222-80767932 of Human Genome Assembly hg38 of December 2013. In some cases, the poison exon is selected from the group consisting of any one of the poison exons listed in **Table 1** or **Table 2**. In some cases, the poison exon introduces a premature termination codon (PTC) into the MSH3 mRNA transcript. In some cases, the agent forms a complex with the MSH3 pre-mRNA and a spliceosomal RNA. In some cases, the agent increases binding of a spliceosomal RNA to the MSH3 pre-mRNA. In some cases, the spliceosomal RNA comprises a small nuclear RNA (snRNA). In some cases, the snRNA is selected from the group consisting of: U1 snRNA, U2 snRNA, U4 snRNA, U5 snRNA, U6 snRNA, and any combination thereof. In some cases, the snRNA comprises U1 snRNA. In some cases, the agent is selected from the group consisting of: a small molecule, a polypeptide, an oligosaccharide, a polysaccharide, an oligonucleotide, an aptamer, a ribonucleoprotein (RNP), an enzyme, a nuclease, and any combination thereof. In some cases, the agent is a small molecule. In some cases, the disease or condition is a nucleotide repeat disorder. In some cases, the disease or condition is selected from the group consisting of: dentatorubropallidoluysian atrophy (DRPLA), Huntington's disease (HD), spinal and bulbar muscular atrophy (SBMA), spinocerebellar ataxia (SCA) type 1, spinocerebellar ataxia (SCA) type 2, spinocerebellar ataxia (SCA) type 3, spinocerebellar ataxia (SCA) type 6, spinocerebellar ataxia (SCA)

type 7, spinocerebellar ataxia (SCA) type 8, spinocerebellar ataxia (SCA) type 10, spinocerebellar ataxia (SCA) type 12, spinocerebellar ataxia (SCA) type 17, spinocerebellar ataxia (SCA) type 31, spinocerebellar ataxia (SCA) type 36, spinocerebellar ataxia (SCA) type 37, spinocerebellar ataxia (SCA) type 50, Friedreich ataxia, fragile X syndrome (FRAXA), fragile X-associated tremor/ataxia syndrome (FXTAS), Baratela-Scott syndrome (BSS), myotonic dystrophy (DM) type 1, myotonic dystrophy (DM) type 2, amyotrophic lateral sclerosis (ALS), Kennedy's disease, fragile X E mild mental retardation (FRAXE), progressive myoclonus epilepsy (EPM1), oculopharyngodistal myopathy (OPDM) type 1, oculopharyngodistal myopathy (OPDM) type 2, oculopharyngeal myopathy with leukoencephalopathy (OPML), frontotemporal dementia (FTD), Neuronal intranuclear inclusion disease (NIID), essential tremor, global developmental delay, progressive ataxia, and elevated glutamine (GDPAG), familial myoclonic epilepsy (FAME) type 1, familial myoclonic epilepsy (FAME) type 2, familial myoclonic epilepsy (FAME) type 3, familial myoclonic epilepsy (FAME) type 4, familial myoclonic epilepsy (FAME) type 6, familial myoclonic epilepsy (FAME) type 7, premature ovarian failure (FXPOF), cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS), multiple system atrophy (MSA), refractory chronic cough, Fuchs endothelial corneal dystrophy (FECD), X-linked dystonia-parkinsonism (XDP), intellectual disability (FRA12A type), Jacobsen syndrome (CBL2), and any combination thereof. In some cases, the MSH3 mRNA comprising the poison exon undergoes nonsense mediated decay (NMD).

[0007] In another aspect, a system comprising: (a) an MSH3 pre-mRNA; (b) a spliceosomal RNA; and (c) an agent which modulates splicing of the MSH3 pre-mRNA such that an MSH3 mRNA transcript comprising the poison exon is produced. In some cases, the system further comprises the MSH3 mRNA transcript comprising the poison exon. In some cases, the agent, the MSH3 pre-mRNA, and the spliceosomal RNA are in a complex. In some cases, the agent is an agent that induces binding of the spliceosomal RNA to the MSH3 pre-mRNA. In some cases, the poison exon introduces a premature termination codon into the MSH3 mRNA. In some cases, the poison exon comprises a nucleic acid sequence that has at least 80% sequence identity to the nucleic acid sequence of SEQ ID NO: 1. In some cases, the poison exon is or comprises exon 21A, or a portion thereof, of MSH3. In some cases, the poison exon is located at or within position chr5:80832901-80832994 of Human Genome Assembly hg38 of December 2013. In some cases, the poison exon comprises a nucleic acid sequence that has at least 80% sequence identity to the nucleic acid sequence of SEQ ID NO: 2 or SEQ ID NO: 3. In some cases, the poison exon is or comprises exon 14A_1, or a portion thereof, of MSH3. In some cases, the poison exon is or comprises exon 14A_2, or a portion thereof, of MSH3. In some cases, the poison exon is located at or within position chr5:80763222-80763369 or position chr5:80763222-80767932 of Human Genome Assembly hg38 of December 2013. In some cases, the poison exon is selected from the group consisting of any one of the poison exons listed in **Table 1** or **Table 2**. In some cases, the MSH3 pre-mRNA and the spliceosomal RNA are partially complementary. In some cases, the spliceosomal RNA comprises a small nuclear RNA (snRNA). In some cases, the snRNA is selected from the group consisting of: U1 snRNA, U2 snRNA, U4 snRNA, U5 snRNA, U6 snRNA, and any combination thereof.

In some cases, the snRNA comprises U1 snRNA. In some cases, the agent is selected from the group consisting of: a small molecule, a polypeptide, a carbohydrate, a monosaccharide, a oligosaccharide, a polysaccharide, an oligonucleotide, an aptamer, a biologic, a ribonucleoprotein (RNP), and any combination thereof. In some cases, the agent comprises a small molecule.

[0008] In yet another aspect, a vessel containing the system of any one of the preceding is provided. In some cases, the vessel is selected from the group consisting of: a vial, a tube, a plate, and a dish.

[0009] In yet another aspect, a cell containing the system of any one of the preceding is provided.

[0010] In yet another aspect, an mRNA transcript comprising an MSH3 mRNA and at least one poison exon is provided. In some cases, the at least one poison exon comprises a nucleic acid sequence that has at least about 80% sequence identity to the nucleic acid sequence of SEQ ID NO: 1. In some cases, the at least one poison exon is or comprises exon 21A, or a portion thereof, of MSH3. In some cases, the at least one poison exon is located at or within position chr5:80832901-80832994 of Human Genome Assembly hg38 of December 2013. In some cases, the at least one poison exon comprises a nucleic acid sequence that has at least about 80% sequence identity to the nucleic acid sequence of SEQ ID NO: 2 or SEQ ID NO: 3. In some cases, the at least one poison exon is or comprises exon 14A_1, or a portion thereof, of MSH3. In some cases, the at least one poison exon is or comprises exon 14A_2, or a portion thereof, of MSH3. In some cases, the poison exon is located at or within position chr5:80763222-80763369 or position chr5:80763222-80767932 of Human Genome Assembly hg38 of December 2013. In some cases, the at least one poison exon is selected from the group consisting of any one of the poison exons listed in **Table 1** or **Table 2**. In some cases, the at least one poison exon introduces a premature termination codon (PTC) into the MSH3 mRNA.

[0011] In yet another aspect, a cell comprising the mRNA transcript of any one of the preceding is provided.

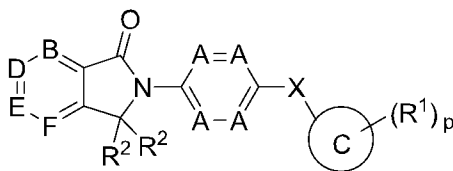
[0012] In yet another aspect, a method of screening for an agent that modulates splicing of an MSH3 pre-mRNA is provided, the method comprising: (a) contacting a cell with a candidate agent; (b) detecting presence or absence of a poison exon in an MSH3 mRNA transcript; and (c) identifying the candidate agent as an agent that modulates splicing of the MSH3 pre-mRNA when the poison exon is detected in the MSH3 mRNA transcript. In some cases, the detecting comprises sequencing the MSH3 mRNA transcript. In some cases, the detecting comprises detecting an amount of the MSH3 mRNA transcript comprising the poison exon. In some cases, the detecting comprises determining a level of MSH3 protein expression. In some cases, the identifying comprises identifying the candidate agent as an agent that modulates splicing of the MSH3 pre-mRNA when the level of MSH3 protein expression is decreased as compared to a level of MSH3 protein expression in the absence of the candidate agent. In some cases, the detecting comprises determining or measuring a level of MSH3 mRNA transcript. In some cases, the identifying comprises identifying the candidate agent as an agent that modulates splicing of the MSH3 pre-mRNA when the level of MSH3 mRNA transcript is decreased as compared to a level of MSH3 mRNA transcript in the absence of the candidate agent. In some cases, the detecting comprises detecting viability of the cell. In some cases, the identifying comprises identifying the candidate agent as an agent

that modulates splicing of the MSH3 pre-mRNA when viability is decreased as compared to in the absence of the candidate agent. In some cases, the method further comprises contacting the cell with an inhibitor of nonsense-mediated decay (NMD). In some cases, the inhibitor of NMD is cycloheximide. In some cases, the method further comprises determining that the poison exon leads to NMD of the MSH3 mRNA transcript when a level of the MSH3 mRNA transcript is decreased in the absence of the inhibitor of NMD, and a level of the MSH3 mRNA transcript is increased in the presence of the inhibitor of NMD. In some cases, the method further comprises contacting a plurality of cells with a library of candidate agents, wherein each cell of the plurality of cells is contacted with a different candidate agent.

[0013] In yet another aspect, an agent is provided that modulates splicing of MSH3 pre-mRNA such that an MSH3 mRNA transcript comprising a poison exon is produced, for use in a method of treatment of the human or animal body by therapy.

[0014] In yet another aspect, an agent is provided that modulates splicing of MSH3 pre-mRNA such that an MSH3 mRNA transcript comprising a poison exon is produced, for use in a method of treatment of an expansion repeat disorder. In some cases, the expansion repeat disorder is selected from the group consisting of: wherein the disease or condition is selected from the group consisting of: dentatorubropallidoluysian atrophy (DRPLA), Huntington's disease (HD), spinal and bulbar muscular atrophy (SBMA), spinocerebellar ataxia (SCA) type 1, spinocerebellar ataxia (SCA) type 2, spinocerebellar ataxia (SCA) type 3, spinocerebellar ataxia (SCA) type 6, spinocerebellar ataxia (SCA) type 7, spinocerebellar ataxia (SCA) type 8, spinocerebellar ataxia (SCA) type 10, spinocerebellar ataxia (SCA) type 12, spinocerebellar ataxia (SCA) type 17, spinocerebellar ataxia (SCA) type 31, spinocerebellar ataxia (SCA) type 36, spinocerebellar ataxia (SCA) type 37, spinocerebellar ataxia (SCA) type 50, Friedreich ataxia, fragile X syndrome (FRAXA), fragile X-associated tremor/ataxia syndrome (FXTAS), Baratela-Scott syndrome (BSS), myotonic dystrophy (DM) type 1, myotonic dystrophy (DM) type 2, amyotrophic lateral sclerosis (ALS), Kennedy's disease, fragile X E mild mental retardation (FRAXE), progressive myoclonus epilepsy (EPM1), oculopharyngodistal myopathy (OPDM) type 1, oculopharyngodistal myopathy (OPDM) type 2, oculopharyngeal myopathy with leukoencephalopathy (OPML), frontotemporal dementia (FTD), Neuronal intranuclear inclusion disease (NIID), essential tremor, global developmental delay, progressive ataxia, and elevated glutamine (GDPAG), familial myoclonic epilepsy (FAME) type 1, familial myoclonic epilepsy (FAME) type 2, familial myoclonic epilepsy (FAME) type 3, familial myoclonic epilepsy (FAME) type 4, familial myoclonic epilepsy (FAME) type 6, familial myoclonic epilepsy (FAME) type 7, premature ovarian failure (FXPOF), cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS), multiple system atrophy (MSA), refractory chronic cough, Fuchs endothelial corneal dystrophy (FECD), X-linked dystonia-parkinsonism (XDP), intellectual disability (FRA12A type), Jacobsen syndrome (CBL2), and any combination thereof.

[0015] In some cases, the agent of any of the preceding is a compound having the structure of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I''),

wherein,

ring C is 4 to 10-membered heterocycloalkyl or 4 to 10-membered heterocycloalkenylene;

each R¹ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c; or

two R¹ are taken together to form an oxo; or

two R¹ are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^c; or

two R¹ are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^c;

each R² is independently hydrogen, halogen, -OH, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; or

X is absent, -CH₂-, -O-, -OCH₂-, -S-, or -NR³-;

R³ is hydrogen, C₁-C₃alkyl, C₁-C₃hydroxyalkyl, C₁-C₃haloalkyl, or C₃-C₆cycloalkyl;

each A is independently N or CR⁴, wherein at least two of A are N;

each R⁴ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl;

or R³ and one of R⁴ are taken together to form a 5 or 6-membered heterocycloalkylene or 5 or 6-membered heteroarylene;

B is N or CR⁵;

D is N or CR⁶;

E is N or CR⁷;

F is N or CR⁸;

R⁵, R⁶, R⁷ or R⁸ are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -OCH₂R^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, 4 to 6 membered heterocycloalkyl, 5 to 10-membered heteroaryl, or -O-(C₁-C₆alkylene)-5 to 10-membered heteroaryl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

wherein at least one of R⁵, R⁶, R⁷ or R⁸ is C₂-C₆alkene, C₃-C₆cycloalkyl, 4 to 6 membered

heterocycloalkyl, 5 to 10-membered heteroaryl, or -O-(C₁-C₆alkylene)-5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R^c;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

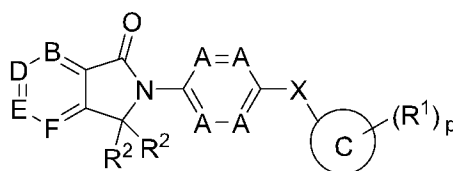
each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

p is an integer from 1-9.

[0016] In some cases, the agent is a compound having the structure of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I'),

wherein,

ring C is 4 to 10-membered heterocycloalkyl or 4 to 10-membered heterocycloalkenylene;

each R¹ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c; or

two R¹ are taken together to form an oxo; or

two R¹ are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^c; or

two R¹ are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^c;

each R² is independently hydrogen, halogen, -OH, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; or

X is absent, -CH₂-, -O-, -S-, or -NR³-;

R³ is hydrogen, C₁-C₃alkyl, C₁-C₃hydroxyalkyl, C₁-C₃haloalkyl, or C₃-C₆cycloalkyl;

each A is independently N or CR⁴, wherein at least two of A are N;

each R⁴ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl;

B is N or CR⁵;

D is N or CR⁶;

E is N or CR⁷;

F is N or CR⁸;

R⁵ and R⁸ are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c;

one of R⁶ or R⁷ is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R¹⁰; and the other of R⁶ or R⁷ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, and heterocycloalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c; wherein R⁷ is not pyridyl substituted with two methoxy groups;

each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^c; or

two R¹⁰ are taken together to form an oxo;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

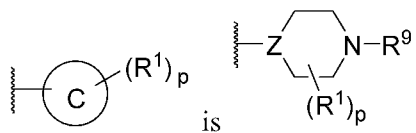
R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

p is an integer from 1-9.

[0017] In some cases, each R² is independently hydrogen. In some cases, D is CR⁶ or E is CR⁷. In some cases, R⁶ is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R¹⁰; and R⁷ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6 membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e. In some cases, R⁷ is hydrogen, halogen, -OH, -OR^a, C₁-C₆alkyl, or C₁-C₆haloalkyl. In some cases, R⁷ is hydrogen. In some cases, R⁶ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, and heterocycloalkyl, wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e; and R⁷ is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R¹⁰. In some cases, R⁶ is hydrogen, halogen, -OH, -OR^a, C₁-C₆alkyl, or C₁-C₆haloalkyl. In some cases, R⁶ is hydrogen. In some cases, ring C is a 6-membered heterocycloalkyl. In some cases, ring C is piperidine, piperazine, or morpholine. In some cases, ring C is piperazine. In some cases, ring C is piperidine.

[0018] In some cases,



wherein,

Z is N or CH;

each R^1 is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d,

C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R^1 are taken together to form an oxo; or

two R^1 are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R^1 are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^e;

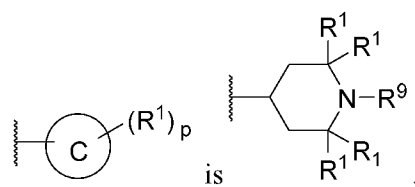
R⁹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R^e;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e; and

each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heteroaryl.

[0019] In some cases,



wherein,

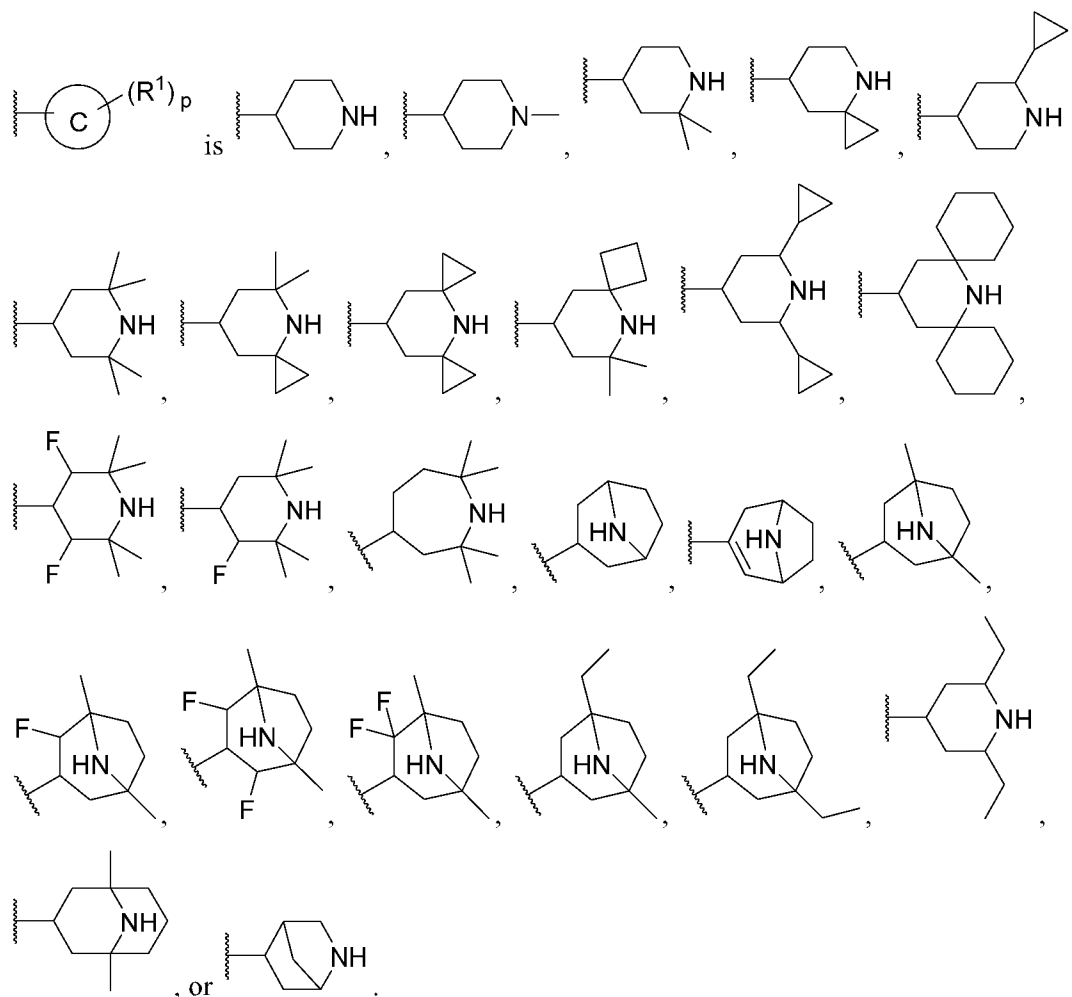
each R¹ is independently hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c; or

two R¹ are taken together to form a C₁-C₃alkylene or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^c; or

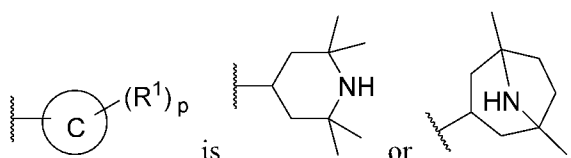
two R¹ are taken together to form a C₃-C₆cycloalkyl; and

R⁹ is hydrogen.

[0020] In some cases,

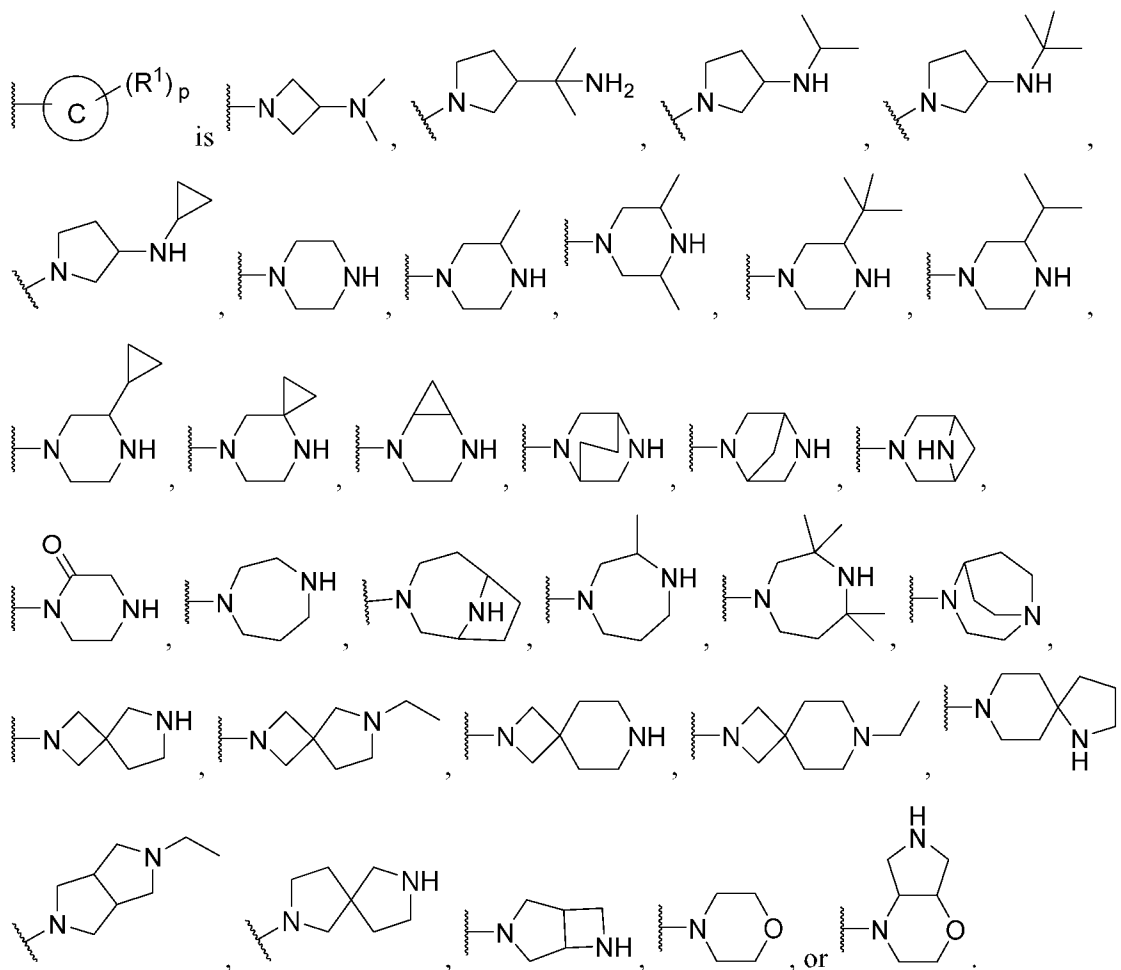


[0021] In some cases,

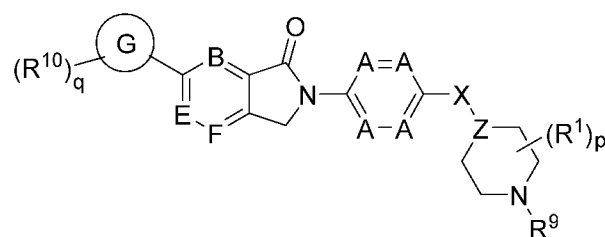


[0022] In some cases, X is -O- or -NR³-.

[0023] In some cases, X is absent; and



[0024] In some cases, the compound has the structure of Formula (II'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each R¹ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d,

C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the

alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4

substituents independently selected from R^e; or

two R¹ are taken together to form an oxo; or

two R¹ are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^c; or

two R¹ are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^c;

X is bond, -CH₂-, -O-, -S-, or -NR³-;

Z is CH or N, wherein when X is -O-, -S-, or -NR³-, then Z is CH;

R³ is hydrogen, C₁-C₃alkyl, C₁-C₃hydroxyalkyl, C₁-C₃haloalkyl, or C₃-C₆cycloalkyl;

each A is independently N or CR⁴, wherein at least two of A are N;

each R⁴ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl;

B is N or CR⁵;

E is N or CR⁷;

F is N or CR⁸;

R⁵, R⁷, and R⁸ are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d,

C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or

C₁-C₆aminoalkyl; wherein each of the alkyl, haloalkyl, alkene, alkyne, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c;

R⁹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R^c;

each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^c; or

two R¹⁰ are taken together to form an oxo;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

R^c and R^d are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c ;

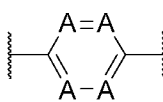
each R^c is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_3 - C_6 cycloalkyl, or 4 to 6-membered heteroaryl; and

p is 8;

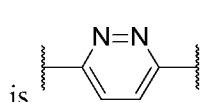
q is 0, 1, 2, or 3.

[0025] In some cases, X is -CH₂-, -O-, -S-, or -NR³-; and Z is CH. In some cases, X is bond and Z is N.

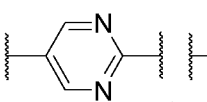
In some cases, each A is independently N or CH, wherein two of A are N. In some cases,



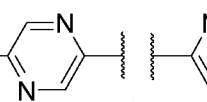
is



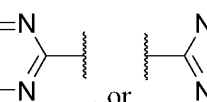
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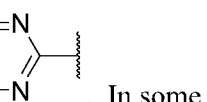
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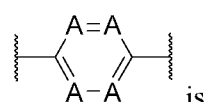
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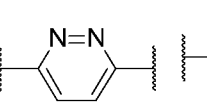
, or



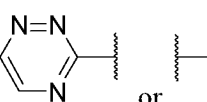
. In some cases,



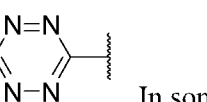
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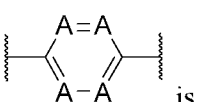
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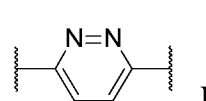
, or



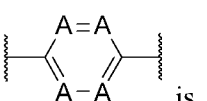
. In some cases,



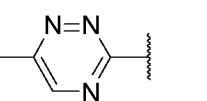
is



. In some cases,

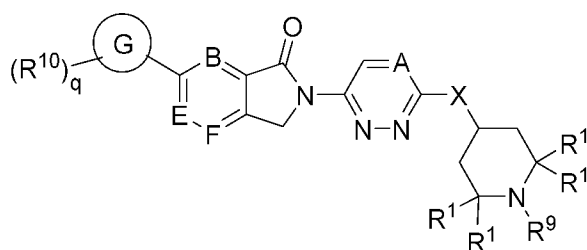


is



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[0026] In some cases, compound has the structure of Formula (III'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each R^1 is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d,

C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, or C_1 - C_6 aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c ; or

two R¹ are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^c; or

two R¹ are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^c;

X is -CH₂-, -O-, -S-, or -NR³-;

R³ is hydrogen, C₁-C₃alkyl, C₁-C₃hydroxyalkyl, C₁-C₃haloalkyl, or C₃-C₆cycloalkyl;

A is N or CH;

B is N or CR⁵;

E is N or CR⁷;

F is N or CR⁸;

R⁵, R⁷, and R⁸ are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d,

C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or

C₁-C₆aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c;

R⁹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R^c;

each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^c; or

two R¹⁰ are taken together to form an oxo;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl,

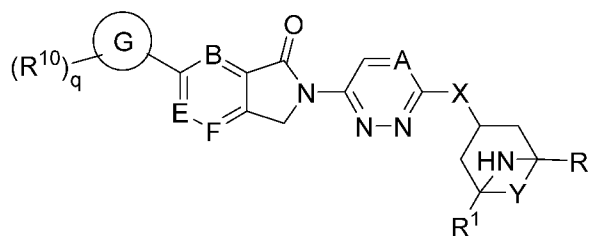
heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

q is 0, 1, 2, or 3.

[0027] In some cases, two R¹ are taken together to form a C₁-C₃alkylene or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e. In some cases, R¹ are taken together to form a C₁-C₃alkylene.

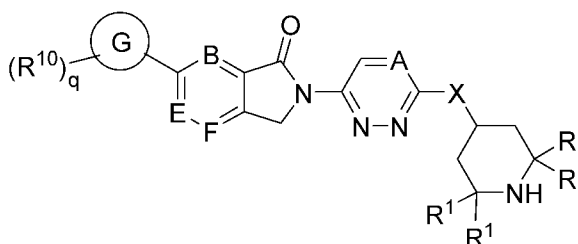
[0028] In some cases, the compound of Formula (III') has the structure of Formula (IIIa'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIa'),

wherein Y is C₁-C₃alkylene. In some cases, Y is -CH₂CH₂-.

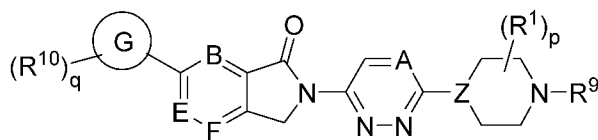
[0029] In some cases, the compound of Formula (III') has the structure of Formula (IIIb'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIb').

[0030] In some cases, two R¹ are taken together to form a C₃-C₆cycloalkyl. In some cases, two R¹ are taken together to form a cyclopropyl. In some cases, each R¹ is independently hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e. In some cases, each R¹ is independently hydrogen, halogen, or C₁-C₆alkyl. In some cases, each R¹ is independently hydrogen or methyl. In some cases, X is -O- or -NR³-. In some cases, X is -O-. In some cases, X is -NR³-. In some cases, R³ is hydrogen, C₁-C₃alkyl or C₃-C₆ cycloalkyl. In some cases, R³ is hydrogen, methyl, ethyl, or cyclopropyl. In some cases, R³ is hydrogen or methyl.

[0031] In some cases, compound has the structure of Formula (IV'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each R^1 is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d,

C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R^1 are taken together to form an oxo; or

two R^1 are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R^1 are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^e;

Z is CH or N;

A is N or CH;

B is N or CR⁵;

E is N or CR⁷;

F is N or CR⁸;

R⁵, R⁷, and R⁸ are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d,

C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or

C₁-C₆aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R⁹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered

heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R^e;

each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e; or

two R¹⁰ are taken together to form an oxo;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl,

cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

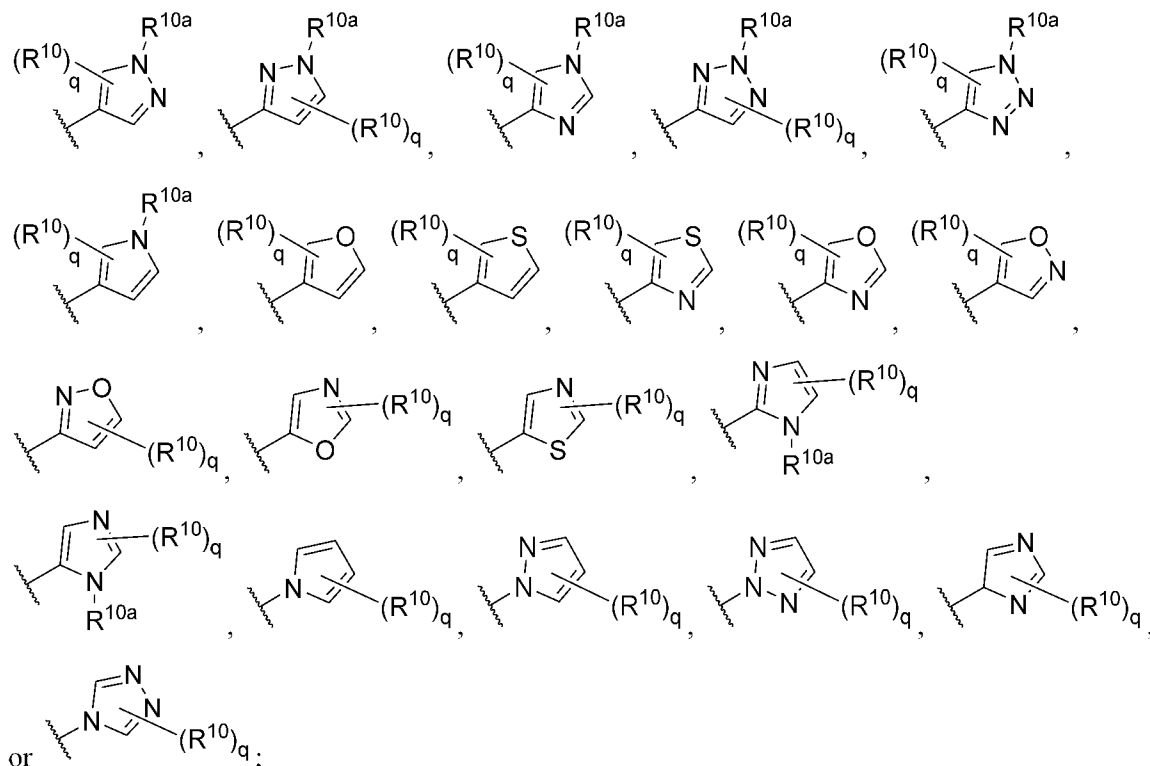
each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl;

p is 8; and

q is 0, 1, 2, or 3.

[0032] In some cases, Z is CH. In some cases, Z is N. In some cases, two R¹ are taken together to form a C₁-C₃alkylene or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e. In some cases, two R¹ are taken together to form a C₁-C₃alkylene. In some cases, two R¹ are taken together to form a C₃-C₆cycloalkyl. In some cases, each R¹ is independently hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl, wherein each of the alkyl, haloalkyl, or hydroxyalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e. In some cases, each R¹ is independently hydrogen, halogen, or C₁-C₆alkyl. In some cases, each R¹ is independently hydrogen or methyl. In some cases, A is N. In some cases, A is CH. In some cases, B is CR⁵. In some cases, B is N. In some cases, R⁵ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e. In some cases, R⁵ is hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl. In some cases, B is CH. In some cases, F is CR⁸. In some cases, F is N. In some cases, R⁸ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e. In some cases, R⁸ is hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl. In some cases, E is CR⁷. In some cases, E is N. In some cases, R⁷ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents

independently selected from R^c . In some cases, R^7 is hydrogen, halogen, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl. In some cases, E is CH. In some cases, ring G a 5 to 6-membered heteroaryl optional substituted with 1 or 4 substituents selected from R^c . In some cases, ring G is a 5-membered heteroaryl optional substituted with 1 or 2 substituents selected from R^c . In some cases, ring G is pyrrole, imidazole, triazole, tetrazole, thiophene, oxazole, thiazole, or thiadiazole. In some cases, ring G is:



wherein,

each R^{10} is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_3 - C_6 cycloalkyl, or 4 to 6-membered heterocycloalkyl wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^c ;

each R^{10a} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^c ; and

q is 0, 1, 2, or 3.

[0033] In some cases, each R^{10} is independently halogen, -CN, -NO₂, -OH, -OR^a, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, or 4 to 6-membered heterocycloalkyl;

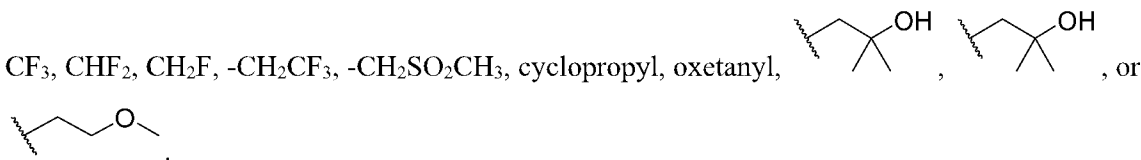
each R^{10a} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

q is 0, 1, or 2.

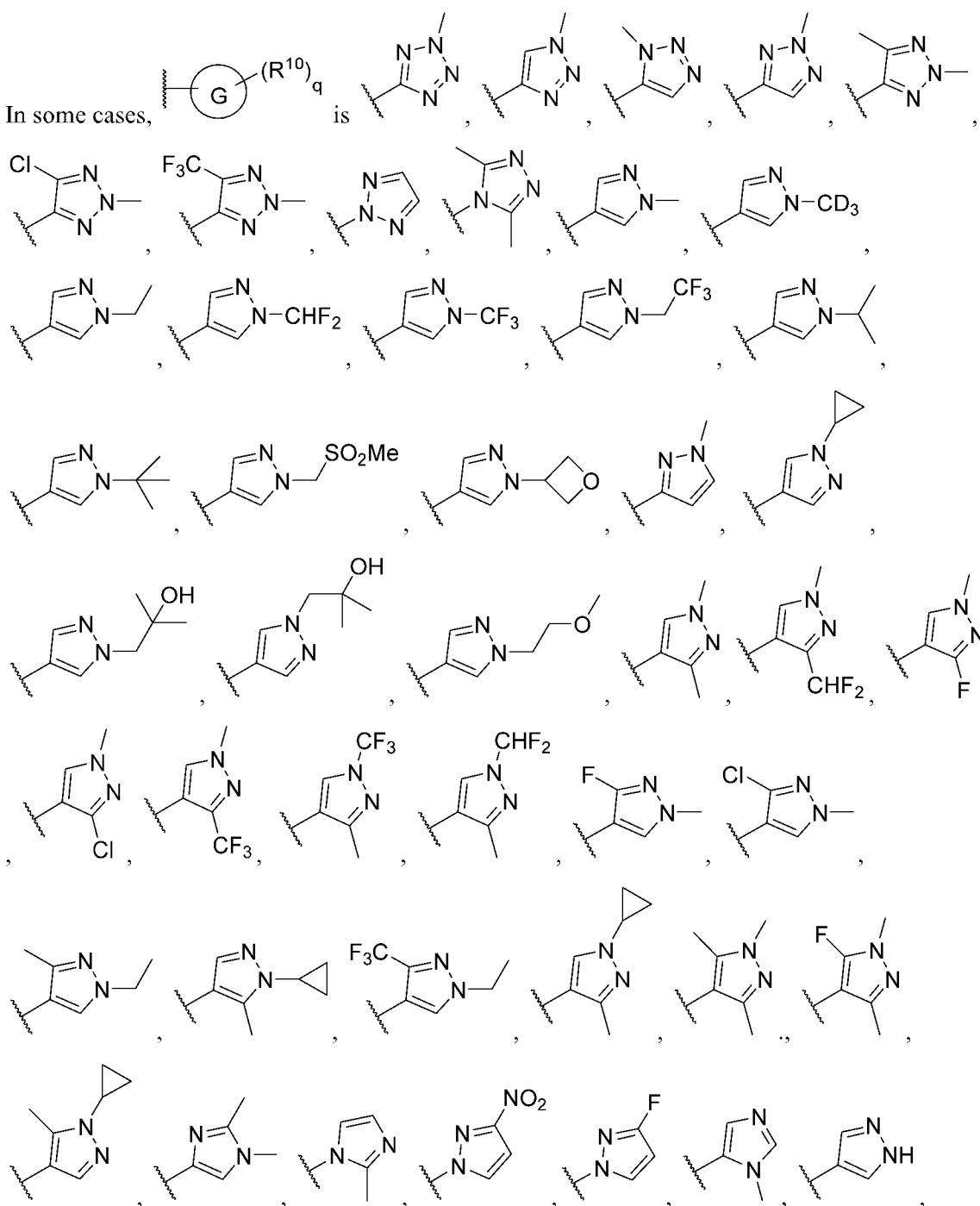
[0034] In some cases, each R^{10} is independently -F, -Cl, methyl, ethyl, -OCH₃, -CF₃, -CHF₂, or -CH₂F.

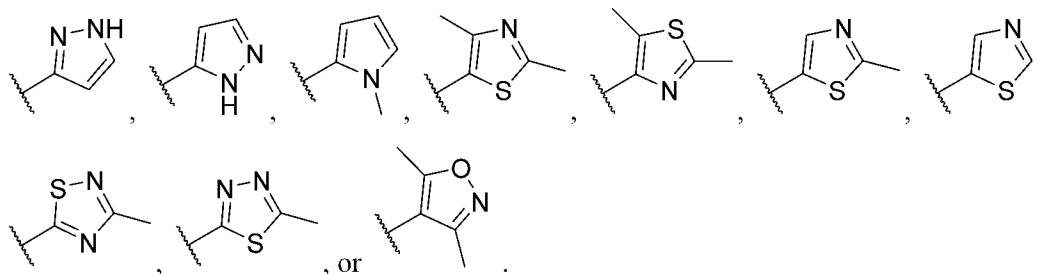
[0035] In some cases, each R^{10a} is independently C_1 - C_6 alkyl which is optionally substituted with 1 to 4-substituents independently selected from halogen, -OH, $-CH_2S(=O)_2CH_3$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, and C_1 - C_6 hydroxyalkyl.

[0036] In some cases, each R^{10a} is independently hydrogen, methyl, ethyl, isopropyl, tert-butyl, $-CD_3$, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CF_3$, $-CH_2SO_2CH_3$, cyclopropyl, oxetanyl,

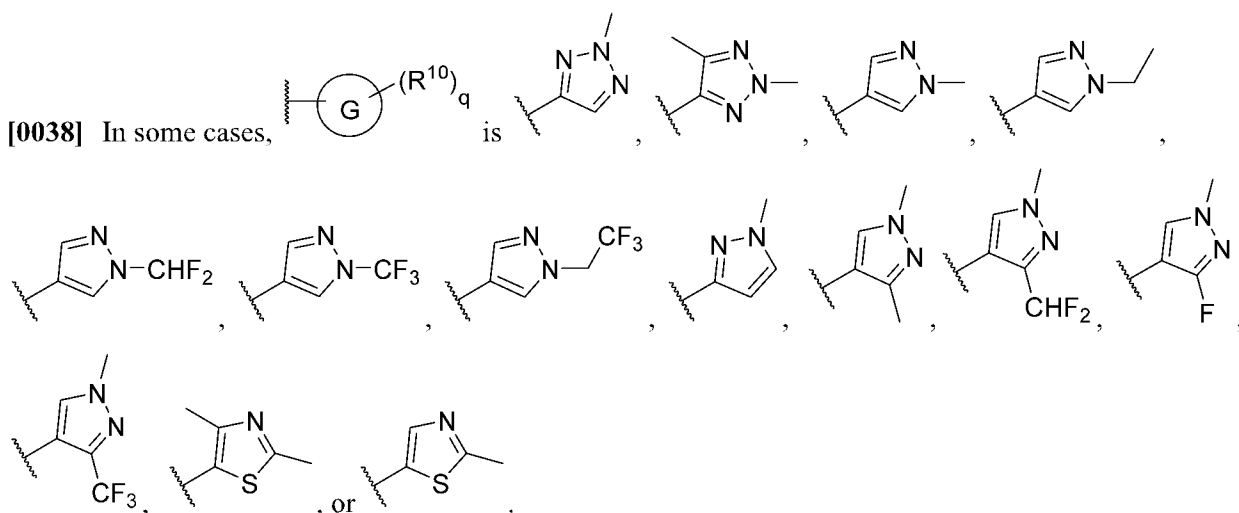


[0037] In some cases, $(R^{10})_q$ is

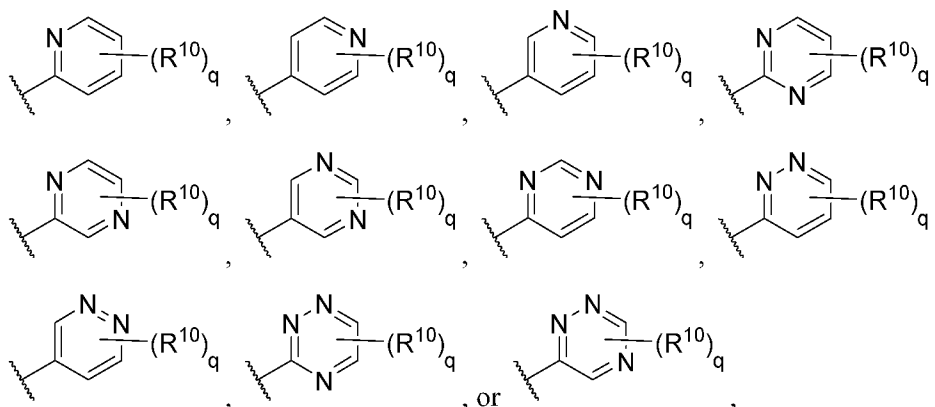




[0038] In some cases,



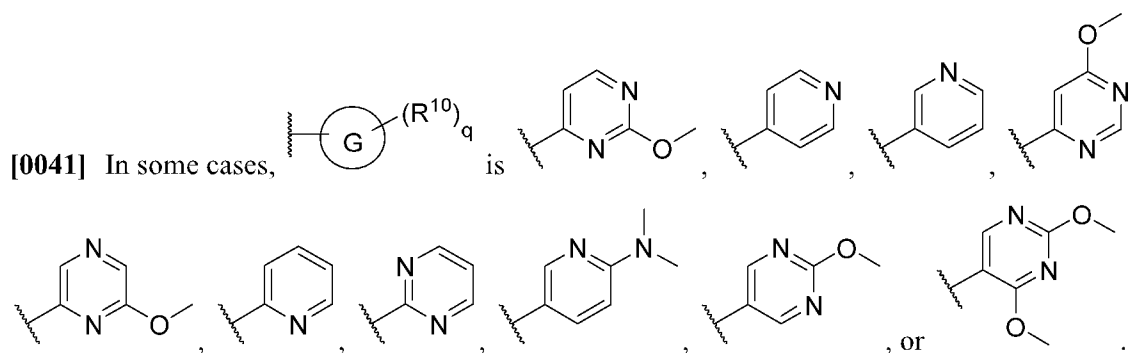
[0039] In some cases, ring G is a 6-membered heteroaryl optional substituted with 1 to 4 substituents selected from R^c . In some cases, ring G is pyridine, pyrimidine, or triazine. In some cases, ring G is:



wherein,

each R^{10} is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^c ; and
q is 0, 1, 2, or 3.

[0040] In some cases, each R^{10} is independently -OCH₃ or -N(CH₃)₂; and q is 0, 1, or 2.



[0042] In some cases, ring G is a 9 or 10-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S; and optional substituted with 1 to 4 substituents selected from R^c.

[0043] In some cases, ring G is a 9-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N; and optional substituted with 1 to 4 substituents selected from R^c.

[0044] In some cases, each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆hydroxyalkyl, wherein each of the alkyl, haloalkyl, and hydroxyalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆hydroxyalkyl, wherein each of the alkyl, haloalkyl, and hydroxyalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c; and

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, or C₁-C₆haloalkyl, wherein each of the alkyl, and haloalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c.

[0045] In some cases, each R^a is independently C₁-C₆alkyl;

each R^b is independently hydrogen or C₁-C₆alkyl; and

R^c and R^d are each independently hydrogen or C₁-C₆alkyl.

[0046] In some cases, each R^a is independently methyl, ethyl, isopropyl, or tert-butyl;

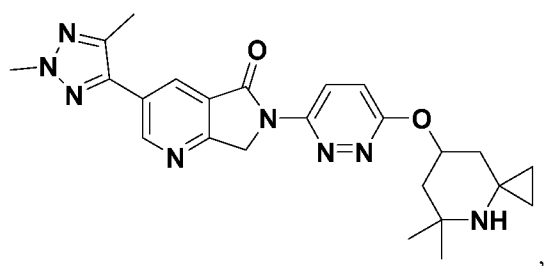
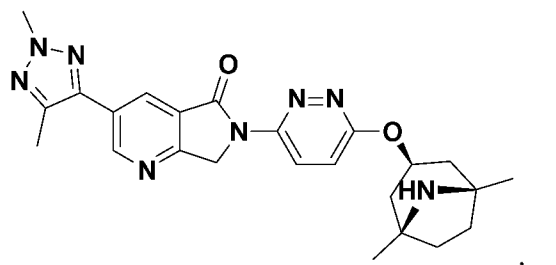
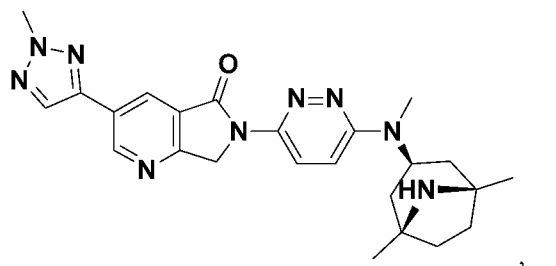
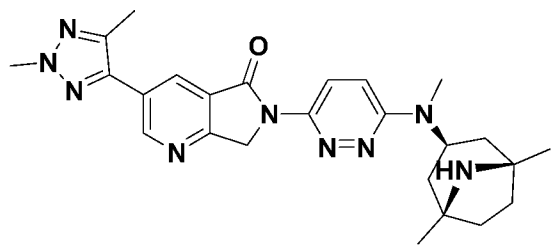
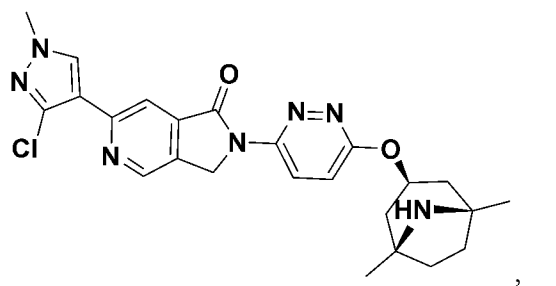
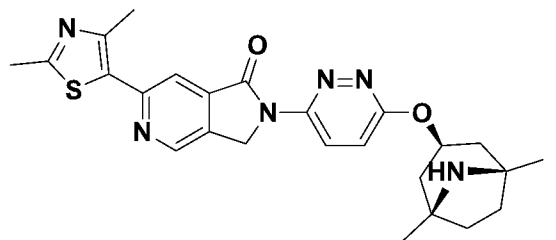
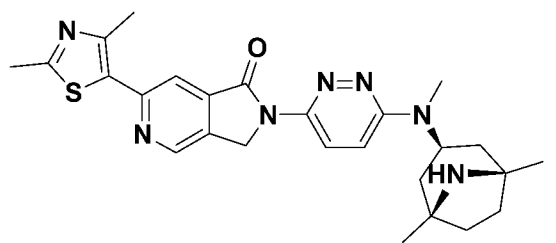
each R^b is independently hydrogen, methyl or ethyl; and

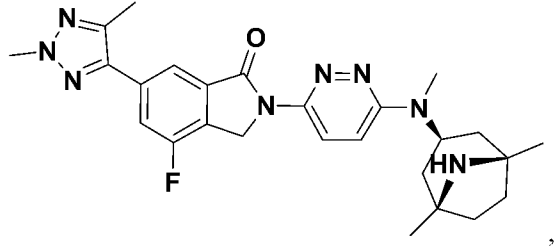
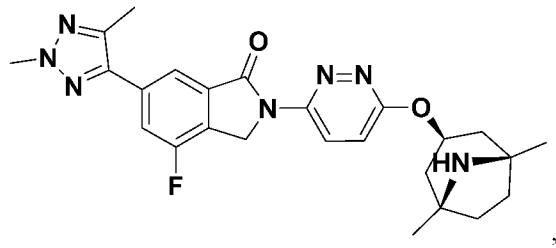
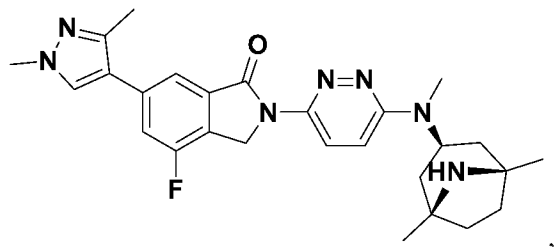
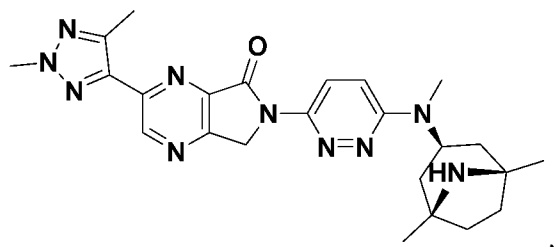
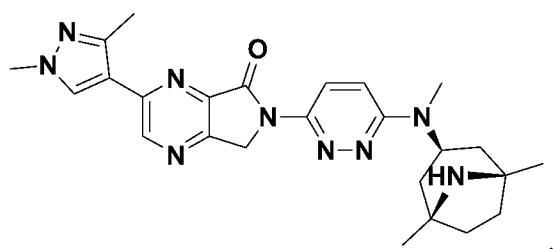
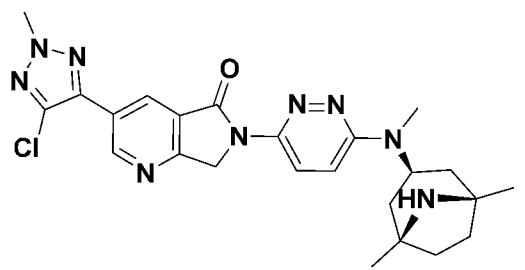
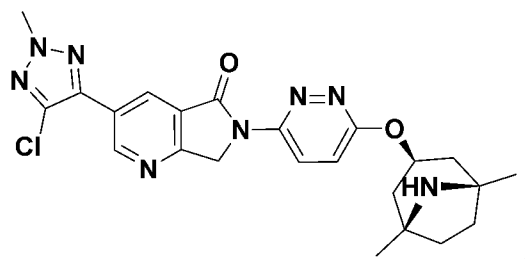
R^c and R^d are each independently hydrogen, methyl, or ethyl.

[0047] In some cases, each R^c is independently halogen, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl. In some cases, each R^c is independently -F, -Cl, -OH, -CH₂S(=O)₂CH₃, methyl, ethyl, isopropyl, tertbutyl, -OCH₃, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or azetidine, oxytane, piperidine, piperazine, or morpholine. In some cases, each R^c is independently -F, -OH, -CF₃, -CHF₂, -OCH₃, or methyl.

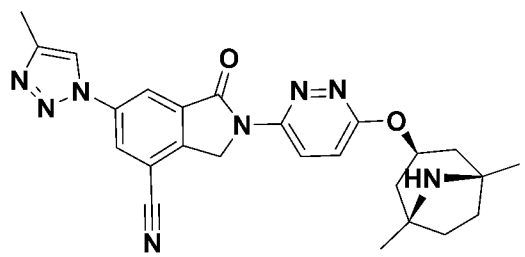
[0048] In some cases, the compound is selected from a compound of Table 3A, Table 3B, Table 3C, Table 4, or Table 5, or a pharmaceutically acceptable salt or solvate thereof.

[0049] In some cases, the compound is selected from the group consisting of:





, and



or a pharmaceutically acceptable salt or solvate thereof.

[0050] In some cases, the compound is provided in a pharmaceutical composition comprising a compound of any one of the preceding, or a pharmaceutically acceptable salt or solvate thereof; and a pharmaceutically acceptable excipient.

INCORPORATION BY REFERENCE

[0051] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

BRIEF DESCRIPTION OF THE DRAWINGS

[0052] The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the disclosure are utilized, and the accompanying drawings (also “Figure” and “FIG.” herein), of which:

[0053] **FIG. 1A** and **FIG. 1B** illustrate progression of nucleotide repeat expansion during a subject’s lifespan. **FIG. 1A** illustrates manifestation of a nucleotide repeat expansion disease or condition triggered by the accumulation of the nucleotide repeat expansion. **FIG. 1B** illustrates the nucleotide repeat expansion occurring at an allelic level.

[0054] **FIG. 2** illustrates a flowchart of nucleotide repeat expansion mechanism. Without wishing to be bound by theory, nucleotide repeat expansion forms a hairpin in the DNA (top), where the presence of the hairpin recruits MutS homolog (MSH) complexes for repairing the hairpin (middle). The repair of the hairpin creates a gap in the genome, where the gap is filled with additional nucleotide repeats, leading to nucleotide repeat expansion (bottom).

[0055] **FIG. 3** illustrates compounds capable of downregulating MSH3 mRNA expression, where the decreased expression of MSH3 can inhibit repair and the subsequent nucleotide repeat expansion of a target gene.

[0056] **FIG. 4** illustrates the presence of an exemplary poison exon in a gene. Without wishing to be bound by theory, under physiological conditions, Exon n and Exon n+1 are spliced together in an mRNA

transcript to encode a functional protein. The poison is typically spliced out of the mRNA transcript. When the poison exon is spliced in to the mRNA transcript, a Premature Termination Codon (PTC) is introduced into the mRNA transcript. The mRNA transcript comprising the poison exon, instead of being translated into a functional protein, is degraded by endogenous cellular mechanisms such as nonsense-mediated mRNA decay (NMD).

[0057] FIG. 5 illustrates a non-limiting illustration of an exemplary agent of the disclosure in a complex with the pre-mRNA and the U1 snRNA. Without wishing to be bound by theory, the agent may enhance binding and/or stabilization of the U1 snRNA to the pre-mRNA comprising the poison exon. **FIG. 5** discloses **SEQ ID NO: 12**.

[0058] FIG. 6 illustrates screening and identifying of poison exons in the MSH3 gene that can be modulated by agents of the disclosure.

[0059] FIG. 7 illustrates examples of agents of the disclosure that modulate the splicing of Exon 21A into the MSH3 mRNA transcript.

[0060] FIG. 8 illustrates splicing and mRNA expression changes for targets regulated by an agent of the disclosure. Compound 1 and CHX increased poison exon expression (Exon 21A) and decreased total RNA (e.g., due to NMD).

[0061] FIG. 9 illustrates splicing and mRNA expression changes for targets regulated by an agent of the disclosure. Compound 1 and CHX increased poison exon expression (Exon 14A_1 or Exon 14A_2) and decreased total RNA (e.g., due to NMD).

[0062] FIGS. 10A-10C illustrate an exemplary system for screening and validating an agent of the disclosure.

[0063] FIG. 11A illustrates MSH3 total expression (assay spanning exons 13/14) in cells treated with an exemplary compound of the disclosure. **FIG. 11B** illustrates MSH3 PE5 expression (assay spanning exons 13/14A) in cells treated with an exemplary compound of the disclosure.

[0064] FIG. 12A illustrates MSH3 total expression (assay spanning exons 20/21) in cells treated with an exemplary compound of the disclosure. **FIG. 12B** illustrates MSH3 PE4 expression (assay spanning exons 20/21A) in cells treated with an exemplary compound of the disclosure. **FIG. 12C** illustrates MSH3 protein expression in cells treated with an exemplary compound of the disclosure.

[0065] FIG. 13 illustrates modulation of splicing of MSH3 poison exon 14A in cynomolgus monkey and human cells treated with an exemplary compound of the disclosure, as determined by RT-PCR.

DETAILED DESCRIPTION

[0066] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference.

[0067] Unless the context requires otherwise, throughout the specification and claims which follow, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.” Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[0068] Reference throughout this specification to “some embodiments” or “an embodiment” means that a particular feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases “in one embodiment” or “in an embodiment” in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments. Also, as used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise.

[0069] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[0070] “oxo” refers to =O.

[0071] “Carboxyl” refers to -COOH.

[0072] “Cyano” refers to -CN.

[0073] “Alkyl” refers to a straight-chain, or branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, more preferably one to six carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl and the like. Whenever it appears herein, a numerical range such as “C₁-C₆ alkyl” or “C₁₋₆alkyl”, means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, the alkyl is a C₁₋₁₀alkyl. In some embodiments, the alkyl is a C₁₋₆alkyl. In some embodiments, the alkyl is a C₁₋₅alkyl. In some embodiments, the alkyl is a C₁₋₄alkyl. In some embodiments, the alkyl is a C₁₋₃alkyl. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkyl is optionally substituted with oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkyl is optionally substituted with halogen.

[0074] “Alkenyl” refers to a straight-chain, or branched-chain hydrocarbon monoradical having one or more carbon-carbon double-bonds and having from two to about ten carbon atoms, more preferably two to about six carbon atoms. The group may be in either the *cis* or *trans* conformation about the double bond(s), and should be understood to include both isomers. Examples include, but are not limited to ethenyl (-CH=CH₂), 1-propenyl (-CH₂CH=CH₂), isopropenyl [-C(CH₃)=CH₂], butenyl, 1,3-butadienyl and the like. Whenever it appears herein, a numerical range such as “C₂-C₆ alkenyl” or “C₂₋₆alkenyl”, means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon

atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkenyl” where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkenyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkenyl is optionally substituted with oxo, halogen, -CN, -COOH, -COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkenyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkenyl is optionally substituted with halogen.

[0075] “Alkynyl” refers to a straight-chain or branched-chain hydrocarbon monoradical having one or more carbon-carbon triple-bonds and having from two to about ten carbon atoms, more preferably from two to about six carbon atoms. Examples include, but are not limited to ethynyl, 2-propynyl, 2-butynyl, 1,3-butadiynyl and the like. Whenever it appears herein, a numerical range such as “C₂-C₆ alkynyl” or “C₂₋₆alkynyl”, means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term “alkynyl” where no numerical range is designated. Unless stated otherwise specifically in the specification, an alkynyl group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkynyl is optionally substituted with oxo, halogen, -CN, -COOH, COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkynyl is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkynyl is optionally substituted with halogen.

[0076] “Alkylene” refers to a straight or branched divalent hydrocarbon chain. Unless stated otherwise specifically in the specification, an alkylene group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkylene is optionally substituted with oxo, halogen, -CN, -COOH, COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkylene is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkylene is optionally substituted with halogen.

[0077] “Alkoxy” refers to a radical of the formula -OR_a where R_a is an alkyl radical as defined. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -COOH, COOMe, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the alkoxy is optionally substituted with halogen, -CN, -OH, or -OMe. In some embodiments, the alkoxy is optionally substituted with halogen.

[0078] “Aryl” refers to a radical derived from an aromatic monocyclic or aromatic polycyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or aromatic polycyclic hydrocarbon ring system can contain only hydrogen and carbon and from five to eighteen carbon atoms, where at least one of the rings in the ring system is aromatic, *i.e.*, it

contains a cyclic, delocalized $(4n+2)$ π -electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene. The aryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the aryl is bonded through an aromatic ring atom) or bridged ring systems. In some embodiments, the aryl is a 6- to 10-membered aryl. In some embodiments, the aryl is a 6-membered aryl (phenyl). Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of anthrylene, naphthylene, phenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, as-indacene, s-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, an aryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the aryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the aryl is optionally substituted with halogen.

[0079] “Carbocycle” refers to a saturated, unsaturated, or aromatic rings in which each atom of the ring is carbon. Carbocycle may include 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 6- to 12-membered bridged rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated, and aromatic rings. An aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated, and aromatic bicyclic rings, as valence permits, are included in the definition of carbocyclic. Exemplary carbocycles include cyclopentyl, cyclohexyl, cyclohexenyl, adamantyl, phenyl, indanyl, and naphthyl. Unless stated otherwise specifically in the specification, a carbocycle may be optionally substituted.

[0080] “Cycloalkyl” refers to a partially or fully saturated, monocyclic, or polycyclic carbocyclic ring, which may include fused (when fused with an aryl or a heteroaryl ring, the cycloalkyl is bonded through a non-aromatic ring atom), spiro, or bridged ring systems. In some embodiments, the cycloalkyl is fully saturated. Representative cycloalkyls include, but are not limited to, cycloalkyls having from three to fifteen carbon atoms (e.g., C₃-C₁₅ fully saturated cycloalkyl or C₃-C₁₅ cycloalkenyl), from three to ten carbon atoms (e.g., C₃-C₁₀ fully saturated cycloalkyl or C₃-C₁₀ cycloalkenyl), from three to eight carbon atoms (e.g., C₃-C₈ fully saturated cycloalkyl or C₃-C₈ cycloalkenyl), from three to six carbon atoms (e.g., C₃-C₆ fully saturated cycloalkyl or C₃-C₆ cycloalkenyl), from three to five carbon atoms (e.g., C₃-C₅ fully saturated cycloalkyl or C₃-C₅ cycloalkenyl), or three to four carbon atoms (e.g., C₃-C₄ fully saturated cycloalkyl or C₃-C₄ cycloalkenyl). In some embodiments, the cycloalkyl is a 3- to 10-membered fully saturated cycloalkyl or a 3- to 10-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 3- to 6-membered fully saturated cycloalkyl or a 3- to 6-membered cycloalkenyl. In some embodiments, the cycloalkyl is a 5- to 6-membered fully saturated cycloalkyl or a 5- to 6-membered cycloalkenyl.

Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl, decalyl, bicyclo[3.3.0]octane, bicyclo[4.3.0]nonane, cis-decalin, trans-decalin, bicyclo[2.1.1]hexane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, and bicyclo[3.3.2]decane, and 7,7-dimethyl-bicyclo[2.2.1]heptanyl. Partially saturated cycloalkyls include, for example cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless stated otherwise specifically in the specification, a cycloalkyl is optionally substituted, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a cycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the cycloalkyl is optionally substituted with halogen.

[0081] "Cycloalkenyl" refers to an unsaturated non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused or bridged ring systems, preferably having from three to twelve carbon atoms and comprising at least one double bond. In certain embodiments, a cycloalkenyl comprises three to ten carbon atoms. In other embodiments, a cycloalkenyl comprises five to seven carbon atoms. The cycloalkenyl may be attached to the rest of the molecule by a single bond. Examples of monocyclic cycloalkenyls includes, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl.

[0082] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo. In some embodiments, halogen is fluoro or chloro. In some embodiments, halogen is fluoro.

[0083] As used herein, the term "haloalkyl" or "haloalkane" refers to an alkyl radical, as defined above, that is substituted by one or more halogen radicals, for example, trifluoromethyl, dichloromethyl, bromomethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. In some embodiments, the alkyl part of the fluoroalkyl radical is optionally further substituted. Examples of halogen substituted alkanes ("haloalkanes") include halomethane (*e.g.*, chloromethane, bromomethane, fluoromethane, iodomethane), di- and trihalomethane (*e.g.*, trichloromethane, tribromomethane, trifluoromethane, triiodomethane), 1-haloethane, 2-haloethane, 1,2-dihaloethane, 1-halopropane, 2-halopropane, 3-halopropane, 1,2-dihalopropane, 1,3-dihalopropane, 2,3-dihalopropane, 1,2,3-trihalopropane, and any other suitable combinations of alkanes (or substituted alkanes) and halogens (*e.g.*, Cl, Br, F, I, etc.). When an alkyl group is substituted with more than one halogen radicals, each halogen may be independently selected *e.g.*, 1-chloro,2-fluoroethane.

[0084] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like.

[0085] "Hydroxyalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more hydroxyls. In some embodiments, the alkyl is substituted with one hydroxyl. In some embodiments, the alkyl is substituted with one, two, or three hydroxyls. Hydroxyalkyl include, for example,

hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, or hydroxypentyl. In some embodiments, the hydroxyalkyl is hydroxymethyl.

[0086] “Aminoalkyl” refers to an alkyl radical, as defined above, that is substituted by one or more amines. In some embodiments, the alkyl is substituted with one amine. In some embodiments, the alkyl is substituted with one, two, or three amines. Aminoalkyl include, for example, aminomethyl, aminoethyl, aminopropyl, aminobutyl, or aminopentyl. In some embodiments, the aminoalkyl is aminomethyl.

[0087] “Heteroalkyl” refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen (e.g., -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C₁-C₆ heteroalkyl wherein the heteroalkyl is comprised of 1 to 6 carbon atoms and one or more atoms other than carbon, e.g., oxygen, nitrogen (e.g., -NH-, -N(alkyl)-), sulfur, phosphorus, or combinations thereof wherein the heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. Examples of such heteroalkyl are, for example, -CH₂OCH₃, -CH₂CH₂OCH₃, -CH₂CH₂OCH₂CH₂OCH₃, -CH(CH₃)OCH₃, -CH₂NHCH₃, -CH₂N(CH₃)₂, -CH₂CH₂NHCH₃, or -CH₂CH₂N(CH₃)₂. Unless stated otherwise specifically in the specification, a heteroalkyl is optionally substituted for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, a heteroalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroalkyl is optionally substituted with halogen.

[0088] “Heterocycloalkyl” refers to a 3- to 24-membered partially or fully saturated ring radical comprising 2 to 23 carbon atoms and from one to 8 heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, silicon, and sulfur. In some embodiments, the heterocycloalkyl is fully saturated. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the heterocycloalkyl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heterocycloalkyl comprises one to three nitrogens. In some embodiments, the heterocycloalkyl comprises one or two nitrogens. In some embodiments, the heterocycloalkyl comprises one nitrogen. In some embodiments, the heterocycloalkyl comprises one nitrogen and one oxygen. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with an aryl or a heteroaryl ring, the heterocycloalkyl is bonded through a non-aromatic ring atom), spiro, or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heterocycloalkyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Representative heterocycloalkyls include, but are not limited to, heterocycloalkyls having from two to fifteen carbon atoms (e.g., C₂-C₁₅ fully saturated heterocycloalkyl or C₂-C₁₅ heterocycloalkenyl), from two to ten carbon atoms (e.g., C₂-C₁₀ fully saturated heterocycloalkyl or C₂-C₁₀ heterocycloalkenyl), from two to eight carbon atoms (e.g., C₂-

C₈ fully saturated heterocycloalkyl or C₂-C₈ heterocycloalkenyl), from two to seven carbon atoms (e.g., C₂-C₇ fully saturated heterocycloalkyl or C₂-C₇ heterocycloalkenyl), from two to six carbon atoms (e.g., C₂-C₆ fully saturated heterocycloalkyl or C₂-C₆ heterocycloalkenyl), from two to five carbon atoms (e.g., C₂-C₅ fully saturated heterocycloalkyl or C₂-C₅ heterocycloalkenyl), or two to four carbon atoms (e.g., C₂-C₄ fully saturated heterocycloalkyl or C₂-C₄ heterocycloalkenyl). Examples of such heterocycloalkyl radicals include, but are not limited to, aziridinyl, azetidiny, oxetanyl, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranly, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, 1,3-dihydroisobenzofuran-1-yl, 3-oxo-1,3-dihydroisobenzofuran-1-yl, methyl-2-oxo-1,3-dioxol-4-yl, and 2-oxo-1,3-dioxol-4-yl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides, and the oligosaccharides. In some embodiments, heterocycloalkyls have from 2 to 10 carbons in the ring. It is understood that when referring to the number of carbon atoms in a heterocycloalkyl, the number of carbon atoms in the heterocycloalkyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocycloalkyl (i.e. skeletal atoms of the heterocycloalkyl ring). In some embodiments, the heterocycloalkyl is a 3- to 8-membered fully saturated heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered fully saturated heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered fully saturated heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered fully saturated heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered fully saturated heterocycloalkyl. In some embodiments, the heterocycloalkyl is a 3- to 8-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 7-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 3- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 4- to 6-membered heterocycloalkenyl. In some embodiments, the heterocycloalkyl is a 5- to 6-membered heterocycloalkenyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl may be optionally substituted as described below, for example, with oxo, halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heterocycloalkyl is optionally substituted with oxo, halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the heterocycloalkyl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heterocycloalkyl is optionally substituted with halogen.

[0089] “Heteroaryl” refers to a 5- to 14-membered ring system radical comprising one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen, phosphorous, and sulfur, and at least one aromatic ring. In some embodiments, the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments,

the heteroaryl comprises one to three heteroatoms selected from the group consisting of nitrogen and oxygen. In some embodiments, the heteroaryl comprises one to three nitrogens. In some embodiments, the heteroaryl comprises one or two nitrogens. In some embodiments, the heteroaryl comprises one nitrogen. The heteroaryl radical may be a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include fused (when fused with a cycloalkyl or heterocycloalkyl ring, the heteroaryl is bonded through an aromatic ring atom) or bridged ring systems; and the nitrogen, carbon, or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. In some embodiments, the heteroaryl is a 5- to 10-membered heteroaryl. In some embodiments, the heteroaryl is a 5- to 6-membered heteroaryl. In some embodiments, the heteroaryl is a 6-membered heteroaryl. In some embodiments, the heteroaryl is a 5-membered heteroaryl. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[b][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothieryl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indoliziny, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinoxalinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e., thienyl). Unless stated otherwise specifically in the specification, a heteroaryl may be optionally substituted, for example, with halogen, amino, nitrile, nitro, hydroxyl, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, carboxyl, carboxylate, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, and the like. In some embodiments, the heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -COOH, COOMe, -CF₃, -OH, -OMe, -NH₂, or -NO₂. In some embodiments, the heteroaryl is optionally substituted with halogen, methyl, ethyl, -CN, -CF₃, -OH, or -OMe. In some embodiments, the heteroaryl is optionally substituted with halogen.

[0090] The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons or substitutable heteroatoms, e.g., NH, of the structure. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *i.e.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. In certain embodiments, substituted refers to moieties having substituents replacing two hydrogen atoms on the same carbon atom, such as substituting the two hydrogen atoms on a single carbon with an oxo, imino or thioxo group. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched, and unbranched, carbocyclic, and heterocyclic, aromatic, and non-aromatic substituents of organic compounds. The permissible

substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms.

[0091] The term “one or more” when referring to an optional substituent means that the subject group is optionally substituted with one, two, three, or four substituents. In some embodiments, the subject group is optionally substituted with one, two, or three substituents. In some embodiments, the subject group is optionally substituted with one or two substituents. In some embodiments, the subject group is optionally substituted with one substituent. In some embodiments, the subject group is optionally substituted with two substituents.

[0092] The term “salt” or “pharmaceutically acceptable salt” refers to salts derived from a variety of organic and inorganic counter ions well known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0093] The phrases “parenteral administration” and “administered parenterally” as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0094] The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0095] The phrase “pharmaceutically acceptable excipient” or “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or

solid filler, diluent, excipient, solvent, or encapsulating material. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[0096] An “effective amount” or “therapeutically effective amount” refers to an amount of a compound administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect.

[0097] The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating, or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition.

[0098] Diseases or conditions associated with nucleotide repeat expansion are prevalent. Nucleotide repeat expansion may be caused by a wild-type (WT) allele first having certain nucleotide repeats (e.g., CAG repeat for Huntington’s disease). The presence of nucleotide repeats at low abundance may not manifest into pathology. However, as the nucleotide repeat accumulates (or expands), symptoms of the disease or condition begin to manifest. **FIG. 1A** and **FIG. 1B** illustrate this concept. Without wishing to be bound by theory, as illustrated by **FIG. 2**, nucleotide repeats are thought to lead to formation of a hairpin loop in the genome, where the hairpin loop serves as a substrate for repair complexes such as MutS homolog (MSH) complexes for repairing the hairpin loop. Upon repair of the hairpin loop, aberrant gap filling at the site of the repair creates longer nucleotide repeats or nucleotide repeat expansion. **FIG. 2** depicts components of the MutS homolog (MSH) complex that may be targeted for modulating the repair of the nucleotide repeat. For example, by modulating and inhibiting expression of MSH3, the repair of the nucleotide repeat is inhibited or decreased, thus decreasing nucleotide repeat expansion.

[0099] Provided herein are compositions, methods, and systems for modulating splicing of MSH3 pre-mRNA such that the resulting MSH3 mRNA transcript includes at least one poison exon. The poison exon introduces a Premature Termination Codon (PTC) into the mRNA transcript, and leads to elimination of the MSH3 mRNA transcript containing the PTC(s) by, e.g., the nonsense-mediated mRNA decay (NMD) pathway. Elimination of the MSH3 mRNA transcript may lead to reduced expression of MSH3 protein. Reduction in the levels of MSH3 protein may lead to a reduction in the activity of the

DNA mismatch repair mechanism associated with nucleotide repeat expansion, which, in turn, may lead to reduction of nucleotide repeat expansion of a target gene (e.g., *HTT*). The compositions, methods, and systems provided herein generally involve the use of agents (e.g., small molecules) that modulate the splicing of MSH3 pre-mRNA such that the resulting MSH3 mRNA transcript includes the poison exon(s). Without wishing to be bound by theory, the agent may enhance and/or stabilize binding of small nuclear RNA (e.g., U1 snRNA) to the pre-mRNA transcript, thereby causing splicing in of the poison exon into the MSH3 mRNA. Without wishing to be bound by theory, the agent may form a complex with the snRNA (e.g., U1 snRNA) and the pre-mRNA transcript. Further provided herein are compositions, methods, and systems for treating a disease or condition (e.g., using the agents provided herein). In some cases, the disease or condition is an expansion repeat disease or condition.

[0100] In some aspects, provided herein is a method for modulating splicing of MSH3 pre-mRNA, the method comprising contacting a cell with an agent which modulates splicing of MSH3 pre-mRNA such that an MSH3 mRNA transcript comprising a poison exon is produced, thereby modulating splicing of MSH3 pre-mRNA.

[0101] In another aspect, provided herein is a method for treating a disease or condition in a subject, the method comprising administering to the subject an agent which modulates splicing of MSH3 pre-mRNA such that an MSH3 mRNA transcript comprising a poison exon is produced in a cell of the subject, thereby treating the disease or condition. In some embodiments, the disease or condition described herein is associated with a gene comprising a nucleotide repeat expansion as described herein. **Table 6** illustrates examples of diseases or conditions associated with a gene having a nucleotide repeat expansion that may be treated using the compositions, methods, and systems provided herein.

[0102] In another aspect, provided herein is a system comprising: (a) an MSH3 pre-mRNA; (b) a spliceosomal RNA; and (c) an agent which modulates splicing of the MSH3 pre-mRNA such that an MSH3 mRNA transcript comprising the poison exon is produced. In another aspect, provided herein are compositions comprising an agent for modulating splicing of MSH3 pre-mRNA such that an MSH3 mRNA transcript comprising a poison exon is produced.

[0103] In another aspect, a vessel is provided containing any system of the disclosure. The vessel may be selected from the group consisting of: a vial, a tube, a plate, and a dish. In another aspect, a cell is provided containing any system of the disclosure.

[0104] In another aspect, an mRNA transcript is provided comprising an MSH3 mRNA and at least one poison exon, as described herein. In some cases, the mRNA transcript is non-naturally occurring (e.g., does not exist in nature in the absence of the compositions, methods, and systems provided herein).

[0105] In some embodiments, the compositions, methods, and systems provided herein involve modulating splicing of MSH3 pre-mRNA such that the MSH3 mRNA transcript contains a poison exon. In some embodiments, the poison exon comprises a nucleic acid sequence that has at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% sequence identity to the nucleic acid sequence of **SEQ ID NO: 1**. In some embodiments, the poison exon consists of or comprises the nucleic acid sequence of **SEQ ID NO: 1**, or a portion thereof. In

some embodiments, the poison exon consists of or comprises Exon 21A, or a portion thereof, of MSH3. In some embodiments, the poison exon is located at or within position chr5:80832901-80832994 of Human Genome Assembly hg38 of December 2013.

[0106] In some embodiments, the poison exon comprises a nucleic acid sequence that has at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% sequence identity to **SEQ ID NO: 2** or **SEQ ID NO: 3**. In some embodiments, the poison exon consists of or comprises the nucleic acid sequence of **SEQ ID NO: 2** or **SEQ ID NO: 3**, or a portion thereof. In some embodiments, the poison exon consists of or comprises Exon 14A₁, or a portion thereof, of MSH3. In some embodiments, the poison exon consists of or comprises Exon 14A₂, or a portion thereof, of MSH3. In some embodiments, the poison exon is located at or within position chr5:80763222-80763369 or position chr5:80763222-80767932 of Human Genome Assembly hg38 of December 2013. In some embodiments, the poison exon is selected from the group consisting of any one of the poison exons listed in **Table 1**. In some embodiments, the poison exon introduces a premature termination codon (PTC) into the MSH3 mRNA transcript. In some embodiments, the poison exon may comprise a splice donor site according to any one of the splice donor sites described in **Table 2**. In some embodiments, the poison exon may be located at any of the chromosomal locations described in **Table 2**. In some embodiments, the poison exon may comprise a PTC beginning at a chromosomal location as described in **Table 2**.

Table 1. MSH3 poison exons

Poison Exon	Nucleic acid sequence (5' to 3')
Exon 21A	CATTTTCCTTGCAAAAGGCCAGAGATTGTGATTTGAAGGGACAGAAGCCCCTC CATTTGCCTGAGAGACATCTAGAATATTATCTCAAATA (SEQ ID NO: 1)
Exon 14A ₁	AGTTTTACTAGAATGATAAGTACTGCTTCTAAGAATACTTGAGGTGCCCAAGAGG ACTTACGTAAGTGTGTTTACATGCCTCAGCTAAATTTGAAAACAATGCACAAGCCAG AACTGGAAATACTGATCCTGGGGAGAAAGATATATGA (SEQ ID NO: 2)
Exon 14A ₂	AGTTTTACTAGAATGATAAGTACTGCTTCTAAGAATACTTGAGGTGCCCAAGAGG ACTTACGTAAGTGTGTTTACATGCCTCAGCTAAATTTGAAAACAATGCACAAGCCAG AACTGGAAATACTGATCCTGGGGAGAAAGATATATGAGTTGGTTATGGGGCCGGG GAGCCTATTGCATCATTATTGGGTACACCATGTTATTGTTTGTCTGGCAATAGCAG AAGCTGTGCTGATAGTCGCAAGTTTTATGGTAGACCTTTTGAAGTTGCAATGTGG GTGCCAAACCATTTGTTGTTTTATCCTTGGCTCAGAGCCTGAAAATTGATGCATA TTAACCTTCTTTAAACAACAGATCTCCAGGCACCTTGCCTTAACTACTTCAAAGGA TTCAGTACAGATGTCAGAGATTTGAAAACAGAAAGCTGAAAATCTTTTCAG TGGCTACTCAAATGCACAAAGTCAAAGTGTCCATGGCATCAAGATGGCAGCATCA GTTTCATGGGGCTGTGATTTCTATTCCACCTTCTGCCTTTTGTAACTTTACTTTG ATGTTTGTATTGCACAGGGTTTGTGTATTTATAAAAGTTTCAAACCTCTAGTAAAG TCAGAATCTAATTCATTTAAAAAGTGGCCGGTATGCAGTGCAAGAATGACTTATTT TGGAATTTCAAATATAGTTTACTAACGGAACCTTATACTCACTTGGAAAGCCATTC CTTGTTGCTGTTTGTGTTTGTGTTTACACAAGAATGTACCTAAAGATTAGTTTGAA GGGTGAAGAGTAGAAATGATCTGGTAACAAACCAACTCAGGAAAGCTGAATGCT TTAAACCAATGTTTATAGATTAGTTGGCTGGCTGTGTACACACCATCAAACAT ATGTCTGTTCTTATTATTAGATTACTCTAAATAAGCTTCTACTGTGTACACCACAT AGTGGGTGATGTCCTGGGTACAGATTGTGCCAATTATGTGAAATTCATAAAATGA GAAGGAACACTGGATGTTGTGGGAAGTGGTTAGCATAGGCTGTATGGTTTTGTGG

AACGTGCCCTGGAATATGTACCAATAGGTGTTTTATGGTGATAATGATAGAGGAT
CTCAAGTGAGCTGATTCTGGTATAAAATAGACATTTCTTCTTCTTTTTTTTTTTT
GAAACAAGATCTCACTGTGTCACCCATGCTGGAATGCAGTGGTGCGACCACAGCT
CACTACAGCTTCAGCCTCCAGCCTTCTGAGTAGTTGGGACAACAGGCACGTGCCA
CCATGCCCAGCTATTTTTTTTTTTTTTTTTTGCATTTTTTTGTAGAGACAAGGTGTTGC
CATGTTGCCCAGGCTGGTCTCCAGCTCCTGGGTCAAGAGATCCTCCCACCTTGGA
CTCCCAGTGTGTTGGGATTACGGGTGTGAGCCACTGTGCTTAGCCTAAAATAAACA
TTTCTTTTGATGGCAAAATGTTAAATTCAAATCCTGTAAATAGTGCTAGTCACAGG
AACCATAATAACTTTGCTCAAGAAGTGTGTTGTAAGAAATTCTTAAGTAACTGCC
GAGGTTGGTGAATACATTTAAAGGATAATCGCACTTAGCAAATGTTGAGGAGAGT
GTTTTCAGAATTTCCCTAGGTGAAAATCTTTTTTTAGCTAAGCAGGAATAAGCCAC
AGCTGCATGTTCAGTGTGGCACTTAAGCTGGGGTCTTCCCACCTGTGTCCAGTG
AGGCCCTGCCACCATACTTGTGGGTCTGTGCTCAAGCTCTCCAGTGAGACAGCTG
CTGCCAGAAGTAGGGCTGAACCTCGAGAGTGACTTCAGGAGCAGCCACTTACC
CATCCTCAGCTTTCTTGTAGCTTCTTTTTGAGTTCTTTTTGCTTAAGAACTTGAGAAC
AACCTGCTGCCTCTGGCTTTCAACATGATTGTAAAGCACTACTGGTTTTACCTTG
CTTCTGTTGCTGACTTAACCTTACATTGTGTCTCAGCTTGGAAAATTAATCATTTTTC
TTGGGATTACAATAATCATAAGAGGTTAATATTCAAAATTATATTGAAAATGTTTG
TGTTTGTTTCTTTACTTTTGTTAAAAGGTATCATTAAATTGACTAGTGGCCAAAAAGC
TTCCAGGTTTCACATTTATTTAAACAGTCCAGCTTCTGTATAGGGTGGGGAGGGG
GTCTTTCTGGAGAAAAGTTGCCTCATGATACACTTAGAATTCACATTTGCTCAGT
TGGACCTAACTTCTTATTTTTTTGCATAATTCACCCTTTGTGGTTAGTAATTACCT
TTTTGAATACGTTCTTAGCCTTAATCTATTTCATATATACTATCTATTATGTGCCTT
ATTACTTTACCCCTAAATTGTTTTCTCATCTCAAGACAGTTCTTTTCAGCCAACATT
TTGTCAGTTTTATTTTCCTGAGCTGTCTTCTAGAGCCTTCTAACTTGATCCAGTCTG
GACTGGTTGTCCCATATCTGTTGTATAGTACTATCTTAGATTCCCTTTACTTCCCT
TGAGTTGAATCTTTTATTTTCTATATTCCATGTCCTTCTCGTTTATTTCTTCATT
TTGGTGGAGTATATATCCTCTAGAACCTTCTGAGAAAGCACGTTGGAAGTAAATC
TTTTGAAACATTTCATGTCTGAAAGTGGTTTTTTTTGTTGTTGTTATTATTGTTACTAC
CTTCACATTTGATTGGTAGTTTGGATTGGTATAAAATTCTAGGTTTTAGATGACTTC
ATTATCTTTACTTCCCTCTTCTGTTGAATTTTTCTATTCTACTATTATGCTTTAATTC
CAAGAATTTTTGTTTTCTTGCTCCCAAATGTTTTTTCTTTTTAAAAGTAGCATCTT
GTTTCATGGTTGTAGTATCTTCTGTTTCATGGAAGATATTATTAATATTTTTAGAAG
TTCCCTAACAGGGCAGAATCCATATTGGTACACAAGTCTTTTTGGATTCTTGATGT
AAATTGTGTCTCCGTTTTCTTAAAGGACAGTTTAAATTCAGATACCTTGAGTCTTT
TAAGTCAATTACTGTTTATTTGTTTACTTTATAGCTTCTAACATATTATTGTGTGTG
TCTTCTTTTCTAGTGTGTTTTTTCTTTTTTTTTTTTTTTTTTTTTTTTTTTGAGACGGAA
TCTTGCTCTGTTGCCCAGGCAGGAGTGCAGTGGCACGATCTCGGCTCACTGCAGTC
TCCGCCTTCCAGGCTCAAGCGATTCTCCTGCCTCGCCACCTGAGTCACTGGGATCA
CAGGCGAGCGCCACCACACCCAGCTAATTTTTGTATTTTTAGTAGAGATGGGGTTT
CACCATGTTGGTAGGGCTGGTCTCGAACTCCTGACCTTGTGATCTGCCCCTCAG
CCTCCCAAAGTGCTGGGATTACAGGCGTGAGTCACTGCGTCTGGCTGGTTTTATGC
CGTTTTAAACAATCTCTTAAGTGTGTTTCAAGATGGAGAGAAATTAGATGCATGT
GTTTAACTCACTGTTTACCAGAAGCTATGATATAAAAATTATTCATGTTTCATGTTA
AAAAAAAACACTACAGTAGTATGCAGGGGTATGCAGTAAAGGGTAAAAAGTCTCC
CTCTGCCACCCTTCCATACCTACTACCCAGAGGTAACCAGAGTAAGTCACATGTGT
TACCTCCTAAAATTTTTATTGATATTTAGATTTTTTTATTTATATAGAATAATGTATA
TCATTTAAAGAATACAAAGAAAGTGTTACCATGTAAATACATAAAAATATATACA
TATATGGTATATGATATAAACATACTGTATATATTCAATGTATGTTGAAATTATGG
AGTTCTATACTGATGCAAACAGATCTTAATTTTCTTTTAGCTGTTTCGTAGTACTAC
ACTGCATGAGTTTTTCCCAATAAGATCCCAATTGATGGACATTTATTTCTTATTCAT
CTTTTTAAATTATAAGCAGCGCTACTATGAATATTCAGACACACATATTTTTCACT
ATTTGTTAGTCTATTTTTAGATAAATTATTTAAAGTGGTGCTTATTCAAAGGGTTAT
GTGCACTTTTTTATTACGAAGACATGCCAAGTTGTTTTTCAAAAAGGTTAGTCCTC
TGCTAAGAGTATATAAAAGTGTCTTTTTTTTTCTTTTACATCCTGTTACATGGTTATT
GTGAAGCTTTTAAATCTTTGGCGTCCGATAAGTGAAAAATGCTATCCTATATTTT
TAATTTGCTTGTCTTTAATTATATATGAAGATAATCGTATACATACTTGCTGTTCTC
TTTCTATGAGCTGCATATTCAGTTTGTGTTAGCCATTGTTCTTTGGATTATTCATCTTT
TTCTTGTCAATTTGTAAGAGCCTATTATGTTTGGGAGAATTTGCCTTGTGTCTGTT
ATGCCTTACAGATATTATCCTTCACATTTTTTAACTTGTTTAACTTATTTTGCTAT
ATGGTTTATGTTATTTTTAAAAATGAAAAATACTAAACAAGTATTGGCTTTGTTTT
CCTTGCCTAAAATTTTCTTTTATACCTTTAAAAATATTACATAGTATTTAACTCA
TTTAGAAAATATCAGTGATATTTTATTTCACTAACTAGTTAATAGAAAATTTAAA

	CTTTCCTCAATTCTGATTCTAACTTTTAAAAGTCACTAATTAACTTCATTTTCATG TATCTTATGCTATTTCATAAAAAATATTCTATTTTCAG (SEQ ID NO: 3)

Table 2. MSH3 poison exon splice donor sites

Poison exon region	Donor site	PTC
chr5:80848448-80848612	CAGGTAAAG	80848474
chr5:80719484-80719535	TATGTAAGT	80725463
chr5:80830637-80830740	TTCGTAAGT	80830684
chr5:80875163-80875265	CAGGTACTC	80875180
chr5:80762038-80762127	AAGGTGAGT	80762081
chr5:80752160-80752256	GAGGTAAGG	80752192
chr5:80697162-80697289	AAGGTGCCT	80697194
chr5:80832901-80832994	ATAGTAAGA	80832936
chr5:80792227-80792455	AAGGTAAAC	80792235
chr5:80790565-80790680	AAGGTATAA	80790573
chr5:80746749-80746917	ATGGTTTGG	80746811
chr5:80869483-80869661	AAGGTATTC	80869513
chr5:80739646-80739775	GAGGTAAAG	80739666
chr5:80763222-80763369	ATGAGTTGGT (SEQ ID NO: 4)	80763262
chr5:80763222-80763409	TTGGGTACAC (SEQ ID NO: 5)	80763262
chr5:80763222-80767315	AAAGGTTAGT (SEQ ID NO: 6)	80763262
chr5:80814725-80832994	AATAGTAAGA (SEQ ID NO: 7)	80814796
chr5:80814725-80836261	TTGAGTAAGT (SEQ ID NO: 8)	80814796
chr5:80814725-80848612	GCAGGTAAAG (SEQ ID NO: 9)	80814796
chr5:80814725-80851699	CTTGGTATGT (SEQ ID NO: 10)	80814796
chr5:80814725-80852834	AAAGGTACAT (SEQ ID NO: 11)	80814796

[0107] In some embodiments, the poison exon can decrease expression of the MSH3 mRNA transcript in a cell. In some embodiments, the poison exon is a cryptic exon that is not normally spliced into the MSH3 mRNA. In some embodiments, the poison exon is an exon that is not spliced into the MSH3 mRNA, in the absence of an agent that modulates splicing of the MSH3 pre-mRNA, as disclosed herein. In some embodiments, the MSH3 mRNA transcript comprising the poison exon that is produced by the compositions, methods, and systems provided herein, is a non-naturally occurring MSH3 mRNA transcript. In other words, the MSH3 mRNA comprising the poison exon that is produced by the compositions, methods, and systems provided herein does not ordinarily occur in nature, absent intervention with the agent provided herein. In some embodiments, the poison exon is spliced into the

MSH3 mRNA transcript when contacted with an agent described herein. In some embodiments, the poison exon, when spliced into the MSH3 mRNA transcript, decreases expression of the MSH3 mRNA transcript. In some embodiments, the poison exon introduces a PTC into the MSH3 mRNA transcript. In some embodiments, the PTC directs the MSH3 mRNA transcript for degradation, thereby decreasing expression of the MSH3 mRNA transcript. In some cases, the MSH3 mRNA transcript is degraded by nonsense-mediated mRNA decay (NMD). In some embodiments, MSH3 expression is decreased by at least 0.1 fold, at least 0.2 fold, at least 0.5 fold, at least 1.0 fold, at least 2.0 fold, at least 5.0 fold, at least 10.0 fold, or at least about 100.0 fold, compared to a level of MSH3 in absence of the agent.

[0108] In some embodiments, the compositions, methods, and systems provided herein involve the use of an agent that induces splicing of a poison exon into MSH3 mRNA transcript. Without wishing to be bound by theory, in some embodiments, the agent may form a complex with the MSH3 pre-mRNA (e.g., at the poison exon) and a small nuclear RNA (snRNA) (e.g., U1 snRNA). Without wishing to be bound by theory, in some embodiments, the agent may enhance and/or stabilize binding of the snRNA to the MSH3 pre-mRNA (e.g., at the poison exon), such that a poison exon is spliced into the MSH3 mRNA. In some embodiments, the snRNA is part of the spliceosome. In some embodiments, the snRNA is complexed with small nuclear ribonucleoproteins (snRNP). In some embodiments, the snRNA is a spliceosomal RNA. In some embodiments, the snRNA is a U1 spliceosomal RNA. In some embodiments, the presence of the poison exon in the MSH3 mRNA transcript leads to elimination or reduction of MSH3 mRNA transcript such that expression of the MSH3 protein is reduced. Generally, the poison exon introduces a premature termination codon (PTC) into the MSH3 mRNA transcript. In some embodiments, the poison exon induces degradation of the MSH3 mRNA transcript by an endogenous mechanism such as nonsense-mediated mRNA decay (NMD). In some cases, the MSH3 pre-mRNA comprising the poison exon, the agent, and the snRNA are in a complex. In some embodiments, the agent causes splicing of the poison exon into the MSH3 mRNA transcript (i.e., in the absence of the agent, the poison exon is spliced out of the MSH3 mRNA transcript). In some embodiments, the agent is a compound, such as a small molecule. In some embodiments, the agent is any compound disclosed herein. In some embodiments, the agent is for use in a method of treatment of the human or animal body by therapy. In some embodiments, the agent is for use in a method of treatment of a nucleotide expansion repeat disease or condition.

[0109] In some embodiments, the spliceosomal RNA comprises a small nuclear RNA (snRNA). In some embodiments, the snRNA is selected from the group consisting of: U1 snRNA, U2 snRNA, U4 snRNA, U5 snRNA, U6 snRNA, and any combination thereof. In some embodiments, the snRNA comprises U1 snRNA. In some embodiments, the snRNA comprises U2 snRNA. In some embodiments, the snRNA comprises U4 snRNA. In some embodiments, the snRNA comprises U5 snRNA. In some embodiments, the snRNA comprises U6 snRNA. In some embodiments, the MSH3 pre-mRNA and the spliceosomal RNA are partially complementary. In some embodiments, the MSH3 pre-mRNA and the U1 snRNA are partially complementary. In some embodiments, the MSH3 pre-mRNA and the U2 snRNA are partially complementary. In some embodiments, the MSH3 pre-mRNA and the U4 snRNA are partially

complementary. In some embodiments, the MSH3 pre-mRNA and the U5 snRNA are partially complementary. In some embodiments, the MSH3 pre-mRNA and the U6 snRNA are partially complementary.

[0110] In some embodiments, the MSH3 pre-mRNA and the spliceosomal RNA are partially complementary, where the complexing between the MSH3 pre-mRNA and the spliceosomal RNA is caused by an agent described herein. In some embodiments, the agent described herein induces the complexing between the MSH3 pre-mRNA and the spliceosomal RNA. In some embodiments, the agent, upon complexing with the MSH3 pre-mRNA and the spliceosomal RNA, induces splicing in of the poison exon into the MSH3 mRNA.

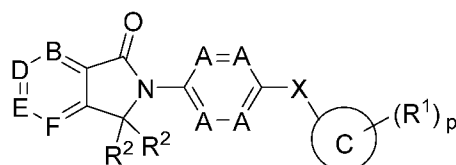
[0111] In some embodiments, the poison exon and the spliceosomal RNA are partially complementary. In some embodiments, the poison exon and the U1 snRNA are partially complementary. In some embodiments, the poison exon and the U2 snRNA are partially complementary. In some embodiments, the poison exon and the U4 snRNA are partially complementary. In some embodiments, the poison exon and the U5 snRNA are partially complementary. In some embodiments, the poison exon and the U6 snRNA are partially complementary.

[0112] In some embodiments, the poison exon and the spliceosomal RNA are partially complementary, where the complexing between the poison exon and the spliceosomal RNA is caused by an agent described herein. In some embodiments, the agent described herein induces the complexing between the poison exon and the spliceosomal RNA. In some embodiments, the agent, upon complexing with the poison exon and the spliceosomal RNA, induces splicing in of the poison exon into the MSH3 mRNA.

[0113] In some embodiments, the agent is selected from the group consisting of: a small molecule, a polypeptide, an oligosaccharide, a polysaccharide, an oligonucleotide, an aptamer, a ribonucleoprotein (RNP), an enzyme, a nuclease (e.g., a Cas nuclease), and any combination thereof. In some embodiments, the agent comprises a gene editing tool, (e.g., CRISPR/Cas, TALENs, zinc finger nucleases, homing endonucleases or meganucleases, etc.) for targeting and inclusion of a poison exon into MSH3.

[0114] In particular embodiments, the agent is a small molecule. In some embodiments, the agent is any molecule or compound described herein.

[0115] In some embodiments, the compound is represented by Formula (I''), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I''),

wherein,

ring C is 4 to 10-membered heterocycloalkyl or 4 to 10-membered heterocycloalkenylene;

each R^1 is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^eR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R^1 are taken together to form an oxo; or

two R^1 are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R^1 are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^2 is independently hydrogen, halogen, -OH, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; or

X is absent, -CH₂-, -O-, -OCH₂-, or -NR³-;

R^3 is hydrogen, C₁-C₃alkyl, C₁-C₃hydroxyalkyl, C₁-C₃haloalkyl, or C₃-C₆cycloalkyl;

each A is independently N or CR⁴, wherein at least two of A are N;

each R^4 is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^eR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl;

or R^3 and one of R^4 are taken together to form a 5 or 6-membered heterocycloalkylene or 5 or 6-membered heteroarylene;

B is N or CR⁵;

D is N or CR⁶;

E is N or CR⁷;

F is N or CR⁸;

R^5 , R^6 , R^7 or R^8 are independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^eR^d, -NR^eR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^eR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, 4 to 6 membered heterocycloalkyl, 5 to 10-membered heteroaryl, or O-(C₁-C₆alkylene)-5 to 10-membered heteroaryl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

wherein at least one of R^5 , R^6 , R^7 or R^8 is C₂-C₆alkene, C₃-C₆cycloalkyl, 4 to 6 membered heterocycloalkyl, 5 to 10-membered heteroaryl, or -O-(C₁-C₆alkylene)-5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R^e;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

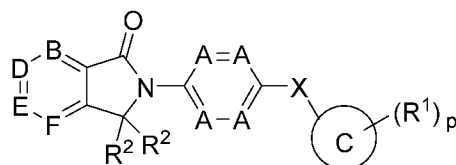
each R^b is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c ;

R^c and R^d are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e ;

each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -C(O)N(CH₃)₂, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_3 - C_6 cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

p is an integer from 1-9.

[0116] In some embodiments, the compound is represented by Formula (I'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I'),

wherein,

ring C is 4 to 10-membered heterocycloalkyl or 4 to 10-membered heterocycloalkenylene;

each R^1 is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, or C_1 - C_6 aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e ; or

two R^1 are taken together to form an oxo; or

two R^1 are taken together to form a bond, C_1 - C_3 alkylene or C_1 - C_3 heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e ; or

two R^1 are taken together to form a C_3 - C_6 cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^e ;

each R^2 is independently hydrogen, halogen, -OH, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, or C_1 - C_6 aminoalkyl; or

two R^2 are taken together to form an oxo;

X is absent, -CH₂-, -O-, -S-, or -NR³-; wherein

R³ is hydrogen, C₁-C₃alkyl, C₁-C₃hydroxyalkyl, C₁-C₃haloalkyl, or C₃-C₆cycloalkyl;

each A is independently N or CR⁴, wherein at least two of A are N;

each R⁴ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl;

B is N or CR⁵;

D is N or CR⁶;

E is N or CR⁷;

F is N or CR⁸;

R⁵ and R⁸ are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl,

C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e;

one of R⁶ or R⁷ is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R¹⁰; and the other of R⁶ or R⁷ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, and heterocycloalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; wherein R⁷ is not pyridyl substituted with two methoxy groups;

each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e; or two R¹⁰ are taken together to form an oxo;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or

heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

each R^c is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -C(O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

p is an integer from 1-9.

[0117] In some embodiments of Formula (I''), (I'), or (I), each R² is independently hydrogen, halogen, -OH, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl. In some embodiments of Formula (I''), (I'), or (I), each R² is independently halogen. In some embodiments of Formula (I''), (I'), or (I), each R² is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl. In some embodiments of Formula (I''), (I'), or (I), each R² is independently C₁-C₆alkyl. In some embodiments of Formula (I''), (I'), or (I), each R² is independently C₁-C₆haloalkyl. In some embodiments of Formula (I''), (I'), or (I), each R² is independently C₁-C₆hydroxyalkyl. In some embodiments of Formula (I''), (I'), or (I), each R² is independently C₁-C₆aminoalkyl. In some embodiments of Formula (I''), (I'), or (I), each R² is independently -OH. In some embodiments of Formula (I''), (I'), or (I), each R² is independently hydrogen.

[0118] In some embodiments of Formula (I''), (I'), or (I), two R² together with the atom to which they are attached form an oxo.

[0119] In some embodiments of Formula (I''), (I'), or (I), D is CR⁶. In some embodiments of Formula (I''), (I'), or (I), D is N.

[0120] In some embodiments of Formula (I'') or (I'), R⁶ is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents selected from R¹⁰; and R⁷ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, and heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e. In some embodiments of Formula (I''), (I'), or (I), R⁶ is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents selected from R¹⁰; and R⁷ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, and heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e. In some embodiments of Formula (I''), (I'), or (I), R⁶ is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R¹⁰; and R⁷ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a,

-SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6 membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), R⁶ is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R¹⁰; and R⁷ is hydrogen, halogen, -OH, -OR^a, C₁-C₆alkyl, or C₁-C₆haloalkyl. In some embodiments of Formula (I''), (I'), or (I), R⁶ is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R¹⁰; and R⁷ is hydrogen, halogen, or C₁-C₆alkyl. In some embodiments of Formula (I''), (I'), or (I), R⁶ is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R¹⁰; and R⁷ is hydrogen.

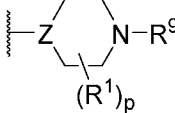
[0121] In some embodiments of Formula (I'') or (I'), R⁷ is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents selected from R¹⁰; wherein R⁷ is not pyridyl substituted with two methoxy groups; and R⁶ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, and heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c. In some embodiments of Formula (I''), (I'), or (I), R⁷ is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents selected from R¹⁰; wherein R⁷ is not pyridyl substituted with two methoxy groups; and R⁶ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, and heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c. In some embodiments of Formula (I''), (I'), or (I), R⁷ is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R¹⁰; and R⁶ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6 membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), R⁷ is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R¹⁰; and R⁶ is hydrogen, halogen, -OH, -OR^a, C₁-C₆alkyl, or C₁-C₆haloalkyl. In some embodiments of Formula (I''), (I'), or (I), R⁷ is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R¹⁰; and R⁶ is hydrogen, halogen, or C₁-C₆alkyl. In some embodiments of Formula (I''), (I'), or (I), R⁷ is a 5 to 8-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R¹⁰; and R⁶ is hydrogen.

[0122] In some embodiments of Formula (I''), (I'), or (I), ring C is a 4 to 10-membered heterocycloalkenylene. In some embodiments of Formula (I''), (I'), or (I), ring C is a 4 to 8-membered heterocycloalkenylene. In some embodiments of Formula (I''), (I'), or (I), ring C is a 4 to 6-membered

heterocycloalkenylene. In some embodiments of Formula (I''), (I'), or (I), ring C is a 6-membered heterocycloalkenylene. In some embodiments of Formula (I''), (I'), or (I), ring C is a 7-membered heterocycloalkenylene. In some embodiments of Formula (I''), (I'), or (I), ring C is a 8-membered heterocycloalkenylene.

[0123] In some embodiments of Formula (I''), (I'), or (I), ring C is a 4 to 10-membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), ring C is a 4 to 8-membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), ring C is a 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), ring C is a 4-membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), ring C is a 5-membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), ring C is a 6-membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), ring C is a 7-membered heterocycloalkyl. In some embodiments of Formula (I''), (I'), or (I), ring C is a 8-membered heterocycloalkyl.

[0124] In some embodiments of Formula (I''), (I'), or (I), ring C is piperidine, piperazine, or morpholine. In some embodiments of Formula (I''), (I'), or (I), ring C is piperidine. In some embodiments of Formula (I''), (I'), or (I), ring C is piperazine. In some embodiments of Formula (I''), (I'), or (I), ring C is morpholine.

[0125] In some embodiments of Formula (I''), (I'), or (I),  is , wherein,

Z is CH or N;

each R¹ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^eR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R¹ are taken together to form an oxo; or

two R¹ are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R¹ are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^e;

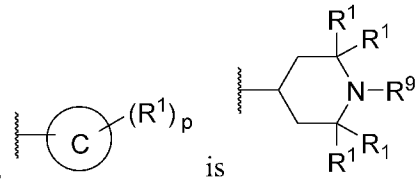
R⁹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R^e;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl,

heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c; and

each R^c is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl.

[0126] In some embodiments of Formula (I''), (I'), or (I),  is

wherein,

each R¹ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c; or

two R¹ are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^c; or two R¹ are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^c;

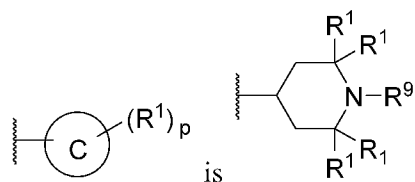
R⁹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R^c;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c; and

each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl.

[0127] In some embodiments of Formula (I''), (I'), or (I),

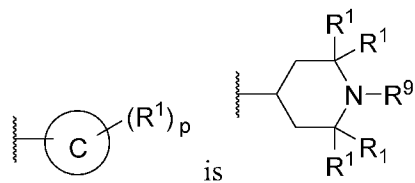


wherein,

each R¹ is independently hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R¹ are taken together to form a C₁-C₃alkylene or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e; or two R¹ are taken together to form a C₃-C₆cycloalkyl; and R⁹ is hydrogen.

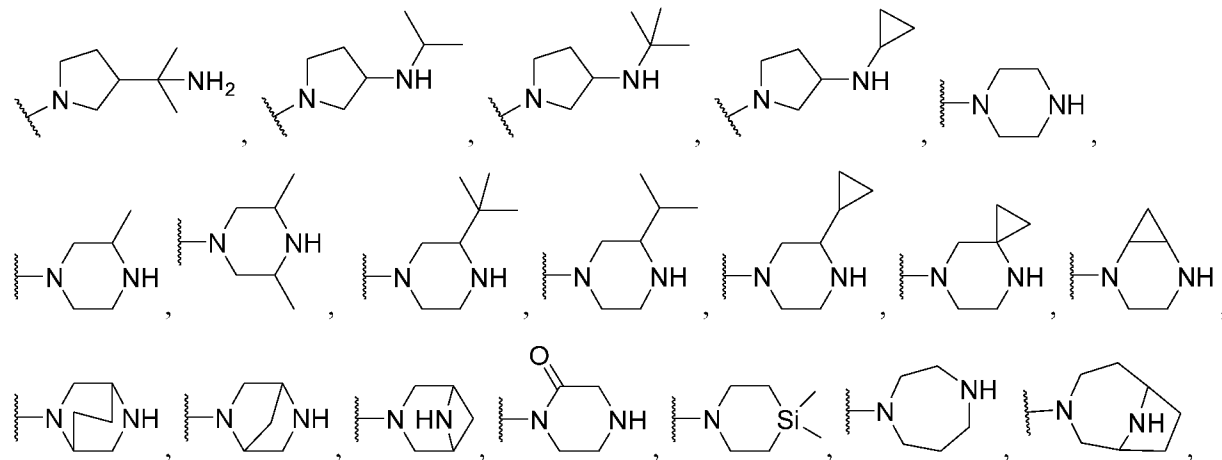
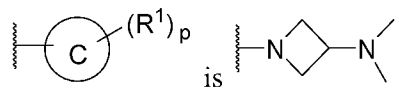
[0128] In some embodiments of Formula (I''), (I'), or (I),

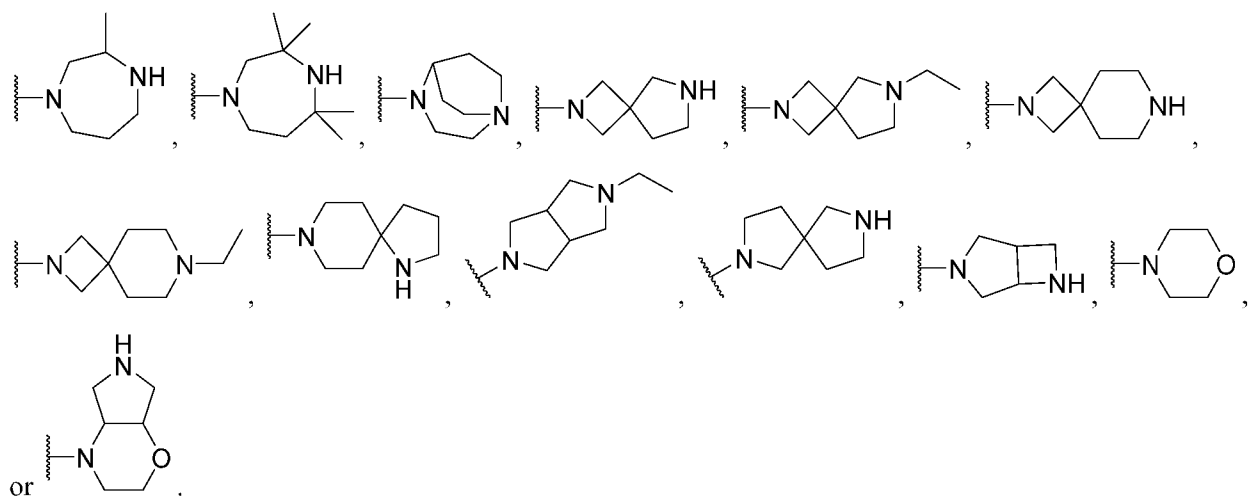


wherein,

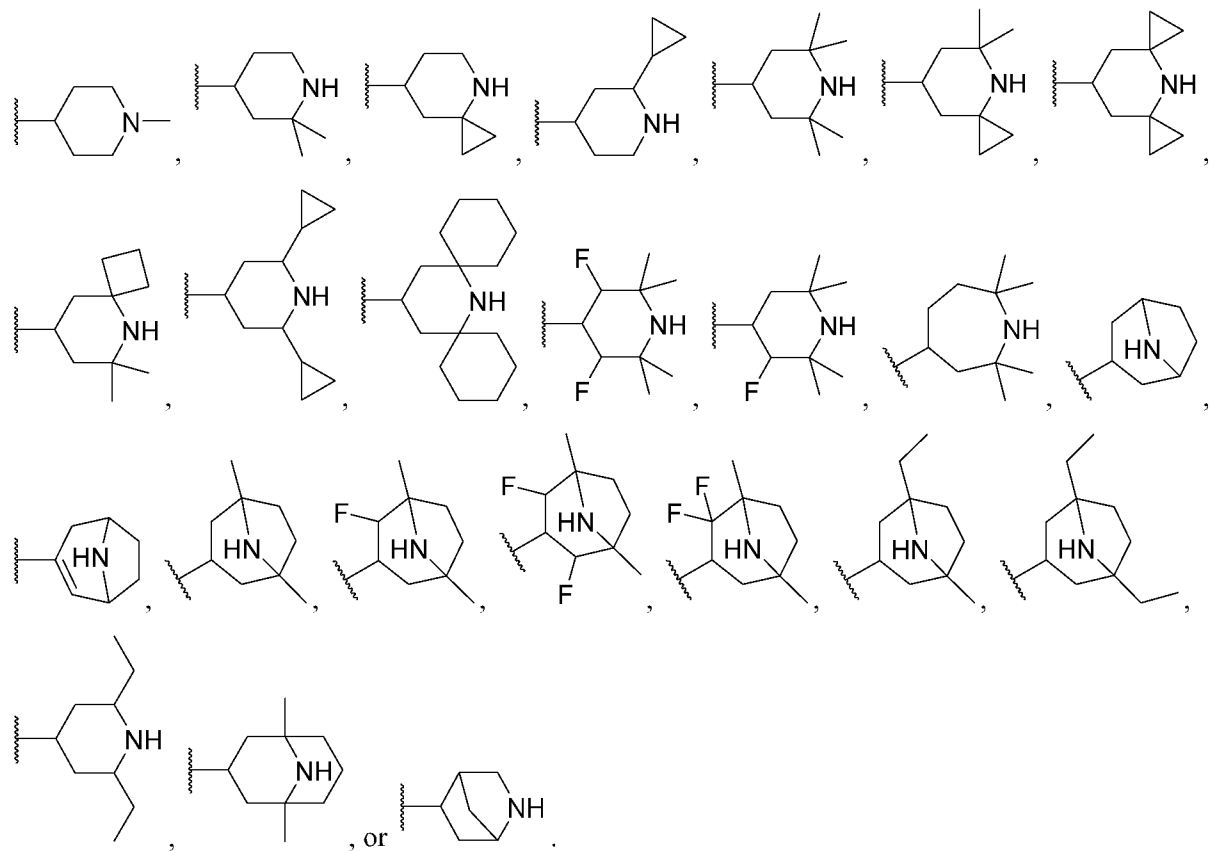
each R¹ is independently hydrogen or C₁-C₆alkyl; or
two R¹ are taken together to form a C₁-C₃alkylene; or
two R¹ are taken together to form a C₃-C₆cycloalkyl; and
R⁹ is hydrogen.

[0129] In some embodiments of Formula (I''), (I'), or (I),

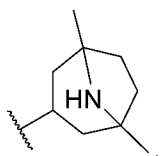




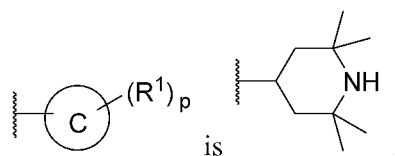
[0130] In some embodiments of Formula (I''), (I'), or (I),  is .



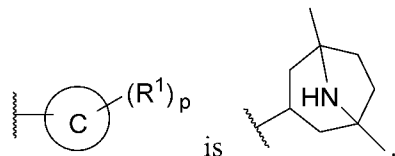
[0131] In some embodiments of Formula (I''), (I'), or (I),  is  or



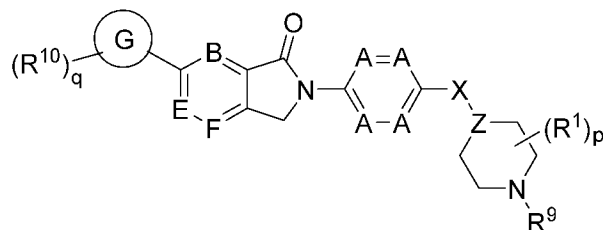
[0132] In some embodiments of Formula (I''), (I'), or (I),



[0133] In some embodiments of Formula (I''), (I'), or (I),



[0134] In some embodiments, the compound is represented by Formula (II'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each R^1 is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl,

C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R^1 are taken together to form an oxo; or

two R^1 are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R^1 are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^e;

X is bond, -CH₂-, -O-, -S-, or -NR³-, wherein

R³ is hydrogen, C₁-C₃alkyl, C₁-C₃hydroxyalkyl, C₁-C₃haloalkyl, or C₃-C₆cycloalkyl;

Z is CH or N, when X is -O-, -S-, or -NR³-, then Z is CH;

each A is independently N or CR⁴, wherein at least two of A are N;

each R⁴ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl;

B is N or CR⁵;

E is N or CR⁷;

F is N or CR⁸;

R⁵, R⁷, and R⁸ are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl,

alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R⁹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R^e;

each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆heteroalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e; or two R¹⁰ are taken together to form an oxo;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

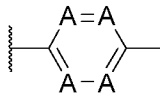
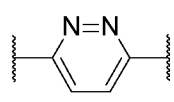
R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

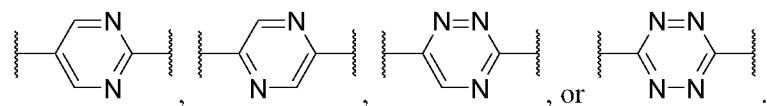
each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -C(O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl;

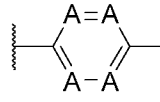
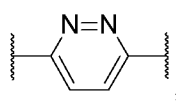
p is 8; and

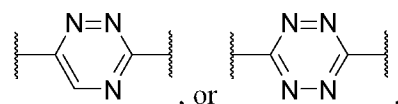
q is 0, 1, 2, or 3.

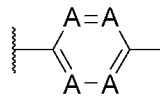
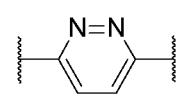
[0135] In some embodiments of Formula (I''), (I'), or (II'), two of A are N. In some embodiments of Formula (I''), (I'), or (II'), three of A are N. In some embodiments of Formula (I''), (I'), or (II'), each A is

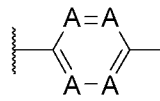
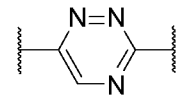
N. In some embodiments of Formula (I''), (I'), (I), (II), or (II'),  is .

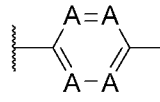
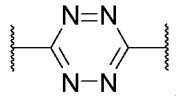


[0136] In some embodiments of Formula (I''), (I'), (I), (II), or (II'),  is .

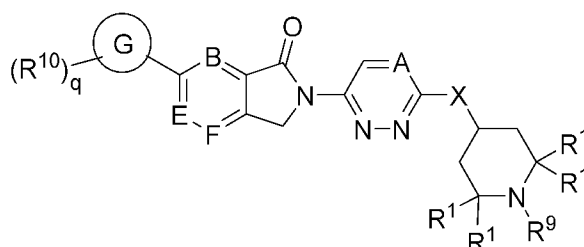


[0137] In some embodiments of Formula (I''), (I'), (I), (II), or (II'),  is .

[0138] In some embodiments of Formula (I''), (I'), (I), (II), or (II'),  is .

[0139] In some embodiments of Formula (I''), (I'), (I), (II), or (II'),  is .

[0140] In some embodiments, the compound is represented by Formula (III'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each R¹ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^eR^d, C₁-C₆alkyl,

C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R¹ are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e; or two R¹ are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^e;

X is -CH₂-, -O-, -S-, or -NR³-; wherein

R³ is hydrogen, C₁-C₃alkyl, C₁-C₃haloalkyl, C₁-C₃hydroxyalkyl, or C₃-C₆cycloalkyl;

A is N or CH;

B is N or CR⁵;

E is N or CR⁷;

F is N or CR⁸;

R⁵, R⁷, and R⁸ are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R⁹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R^e;

each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆heteroalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e; or two R¹⁰ are taken together to form an oxo;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

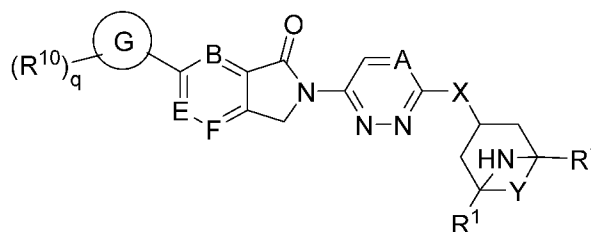
each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -C(O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

q is 0, 1, 2, or 3.

[0141] In some embodiments of Formula (II), (II'), (III), or (III'), R⁹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R^c. In some embodiments of Formula (II), (II'), (III), or (III'), R⁹ is hydrogen, C₁-C₆alkyl, or C₁-C₆haloalkyl. In some embodiments of Formula (II), (II'), (III), or (III'), R⁹ is hydrogen or C₁-C₆alkyl. In some embodiments of Formula (II), (II'), (III), or (III'), R⁹ is C₁-C₆haloalkyl. In some embodiments of Formula (II), (II'), (III), or (III'), R⁹ is C₁-C₆alkyl. In some embodiments of Formula (II), (II'), (III), or (III'), R⁹ is hydrogen.

[0142] In some embodiments of Formula (II), (II'), (III), or (III'), two R¹ are taken together to form a bond, C₁-C₃alkylene or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^c. In some embodiments of Formula (II), (II'), (III), or (III'), two R¹ are taken together to form a bond. In some embodiments of Formula (II), (II'), (III), or (III'), two R¹ are taken together to form a C₁-C₃alkylene. In some embodiments of Formula (II), (II'), (III), or (III'), two R¹ are taken together to form or a C₁-C₃heteroalkylene.

[0143] In some embodiments, the compound of Formula (III') has the structure of Formula (IIIa'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIa'),

wherein,

Y is C₁-C₃alkylene

ring G is a 5 to 10-membered heteroaryl;

each R¹ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl,

C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c; or

X is -CH₂-, -O-, or -NR³-, wherein

R³ is hydrogen, C₁-C₃alkyl, C₁-C₃hydroxyalkyl, C₁-C₃haloalkyl, or C₃-C₆cycloalkyl;

A is N or CH;

B is N or CR⁵;

E is N or CR⁷;

F is N or CR⁸;

R⁵, R⁷, and R⁸ are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl,

alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c;

each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆heteroalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^c; or two R¹⁰ are taken together to form an oxo;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

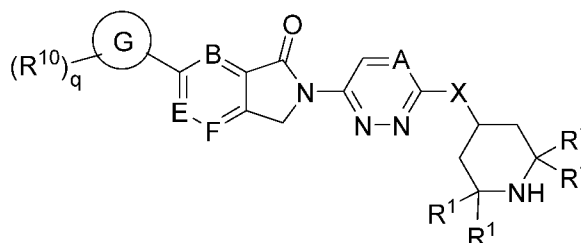
R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -C(O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

q is 0, 1, 2, or 3.

[0144] In some embodiments of Formula (IIIa'), Y is -CH₂CH₂CH₂-. In some embodiments of Formula (IIIa'), Y is -CH₂CH₂-. In some embodiments of Formula (IIIa'), Y is -CH₂-.

[0145] In some embodiments, the compound of Formula (III') has the structure of Formula (IIIb'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIb'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each R¹ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R¹ are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^e;

X is -CH₂-, -O-, -S-, or -NR³-, wherein

R³ is hydrogen, C₁-C₃alkyl, C₁-C₃hydroxyalkyl, C₁-C₃haloalkyl, or C₃-C₆ cycloalkyl;

A is N or CH;

B is N or CR⁵;

E is N or CR⁷;

F is N or CR⁸;

R⁵, R⁷, and R⁸ are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆heteroalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e; or

two R¹⁰ are taken together to form an oxo;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl,

alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

each R^c is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -C(O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

q is 0, 1, 2, or 3.

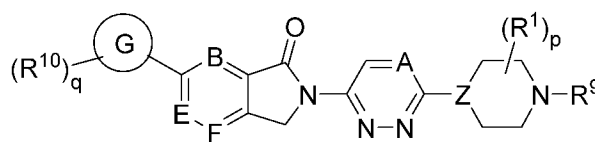
[0146] In some embodiments of Formula (II'), when X is -O-, -S-, or -NR³-, then Z is CH. In some embodiments of Formula (II) or (II'), when X is bond, then Z is CH or N. In some embodiments of Formula (II) or (II'), when X is bond, then Z is N. In some embodiments of Formula (II) or (II'), when X is -CH₂-, then Z is CH or N. In some embodiments of Formula (II) or (II'), when X is -CH₂-, then Z is CH. In some embodiments of Formula (II) or (II'), when X is -CH₂-, then Z is N.

[0147] In some embodiments of Formula (I''), (I'), or (II'), X is -O-, -S-, or -NR³-. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), X is -O- or -NR³-. In some embodiments of Formula (I''), (I'), or (II'), X is -S-. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), X is -O-. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), X is -NR³-. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), X is -NH-. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), X is -NCH₃-. In some embodiments of Formula (I'), (I), (II), (III), (IIIa), or (IIIb), X is -CH₂-. In some embodiments of Formula (I''), X is -OCH₂-.

[0148] In some embodiments of Formula (I''), (I'), (I), (II), or (II'), X is absent.

[0149] In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), R³ is hydrogen, C₁-C₃alkyl, or C₁-C₃hydroxyalkyl. In some embodiments of Formula (I''), (I'), (II'), (IIIa'), or (IIIb'), R³ is C₃-C₆cycloalkyl. In some embodiments of Formula (I''), (I'), (II'), (III'), (IIIa'), or (IIIb'), R³ is cyclopropyl or cyclobutyl. In some embodiments of Formula (I''), (I'), (II'), (III'), (IIIa'), or (IIIb'), R³ is cyclopropyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), R³ is hydrogen or C₁-C₃alkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), R³ is C₁-C₃hydroxyalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), R³ is C₁-C₃haloalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), R³ is C₁-C₃alkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), R³ is hydrogen or methyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), R³ is methyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), or (IIIb'), R³ is hydrogen.

[0150] In some embodiments, the compound is represented by Formula (IV'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each R^1 is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R^1 are taken together to form an oxo; or

two R^1 are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e; or two R^1 are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^e;

Z is CH or N;

A is N or CH;

B is N or CR⁵;

E is N or CR⁷;

F is N or CR⁸;

R⁵, R⁷, and R⁸ are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R⁹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R^e;

each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆heteroalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, heteroalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e; or

two R¹⁰ are taken together to form an oxo;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(O)NH₂, -C(O)NHCH₃, -C(O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl;

p is 8; and

q is 0, 1, 2, or 3.

[0151] In some embodiments of Formula (II), (II'), (IV), or (IV'), Z is N. In some embodiments of Formula (II), (II'), (IV), or (IV'), Z is CH.

[0152] In some embodiments of Formula (I''), (I'), (I), (II), or (II'), at least one of A is N.

[0153] In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each A is N. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each A is independently CR⁴.

[0154] In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each A is independently N or CH. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each A is CH.

[0155] In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV'), or (IV'), B is CR⁵. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), B is CH. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), B is N.

[0156] In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), E is CR⁷. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), E is CH. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), E is N.

[0157] In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), F is CR⁸. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), F is CH. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), F is N.

[0158] In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹ is independently hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹ is independently hydrogen, halogen, or C₁-C₆alkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹ is independently C₁-C₆alkyl, or C₁-C₆haloalkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹ is independently -CH₃, -CH₂CH₃, -CH(CH₃)₂, -CF₃, or -CHF₂. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹ is independently hydrogen, -CH₃, -CH₂CH₃, or -CH(CH₃)₂. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹ is independently halogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹ is independently Cl, Br, or F. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹ is independently F. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹ is independently hydrogen.

[0159] In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIb), (IIIb'), (IV), or (IV'), two R¹ are taken together to form a C₃-C₆cycloalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIb), (IIIb'), (IV), or (IV'), two R¹ are taken together to form a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIb), (IIIb'), (IV), or (IV'), two R¹ are taken together to form a cyclopropyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIb), (IIIb'), (IV), or (IV'), two R¹ are taken together to form a cyclobutyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIb), (IIIb'), (IV), or (IV'), two R¹ are taken together to form a cyclopentyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIb), (IIIb'), (IV), or (IV'), two R¹ are taken together to form a cyclohexyl.

[0160] In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIb), (IIIb'), (IV), or (IV'), two R¹ are taken together to form an oxo.

[0161] In some embodiments of Formula (I''), (I'), (I), (II), or (II'), each R⁴ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl. In some embodiments of Formula (I''), (I'), (I), (II), or (II'), each R⁴ is independently hydrogen, halogen, -CN, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl. In some embodiments of Formula (I''), (I'), (I), (II), or (II'), each R⁴ is independently hydrogen, halogen, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆hydroxyalkyl. In some embodiments

of Formula (I''), (I'), (I), (II), or (II'), each R^4 is independently hydrogen, halogen, or C_1 - C_6 alkyl. In some embodiments of Formula (I''), (I'), (I), (II), or (II'), each R^4 is independently halogen. In some embodiments of Formula (I''), (I'), (I), (II), or (II'), each R^4 is independently C_1 - C_6 alkyl. In some embodiments of Formula (I''), (I'), (I), (II), or (II'), each R^4 is independently hydrogen.

[0162] In some embodiments of Formula (I''), R^3 and one of R^4 are taken together to form a 5 or 6-membered heterocycloalkylene or 5 or 6-membered heteroaryl.

[0163] In some embodiments of Formula (I''), R^5 , R^6 , R^7 or R^8 are independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C_1 - C_6 alkyl, C_2 - C_6 alkene, C_2 - C_6 alkyne, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_3 - C_6 cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e; and wherein at least one of R^5 , R^6 , R^7 or R^8 is C_2 - C_6 alkene, C_3 - C_6 cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 8 membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R^e. In some embodiments of Formula (I''), R^5 , R^6 , R^7 or R^8 are independently hydrogen, halogen, -CN, -NO₂, C_1 - C_6 alkyl, C_2 - C_6 alkene, C_2 - C_6 alkyne, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl. In some embodiments of Formula (I''), R^5 , R^6 , R^7 or R^8 are independently hydrogen, halogen, -CN, C_3 - C_6 cycloalkyl, or 5 to 10-membered heteroaryl.

[0164] In some embodiments of Formula (I''), R^5 is 5 to 10-membered heteroaryl; and R^6 , R^7 and R^8 are independently hydrogen, halogen, -CN, -NO₂, C_1 - C_6 alkyl, C_2 - C_6 alkene, C_2 - C_6 alkyne, or C_1 - C_6 haloalkyl. In some embodiments of Formula (I''), R^6 is 5 to 10-membered heteroaryl; and R^5 , R^7 and R^8 are independently hydrogen, halogen, -CN, -NO₂, C_1 - C_6 alkyl, C_2 - C_6 alkene, C_2 - C_6 alkyne, or C_1 - C_6 haloalkyl. In some embodiments of Formula (I''), R^7 is 5 to 10-membered heteroaryl; and R^5 , R^6 and R^8 are independently hydrogen, halogen, -CN, -NO₂, C_1 - C_6 alkyl, C_2 - C_6 alkene, C_2 - C_6 alkyne, or C_1 - C_6 haloalkyl. In some embodiments of Formula (I''), R^8 is 5 to 10-membered heteroaryl; and R^5 , R^6 and R^7 are independently hydrogen, halogen, -CN, -NO₂, C_1 - C_6 alkyl, C_2 - C_6 alkene, C_2 - C_6 alkyne, or C_1 - C_6 haloalkyl.

[0165] In some embodiments of Formula (I''), B is CR⁵, wherein R^5 is C_2 - C_6 alkene, C_3 - C_6 cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R^e; and F is N.

[0166] In some embodiments of Formula (I''), (I'), (II'), (III'), (IIIa'), (IIIb'), or (IV'), D is CR⁶, wherein R^6 is C_2 - C_6 alkene, C_3 - C_6 cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R^e; and E is N. In some embodiments of Formula (I''), (I'), (II'), (III'), (IIIa'), (IIIb'), or (IV'), D is CR⁶, wherein R^6 is C_2 - C_6 alkene, C_3 - C_6 cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R^e; and F is N. In some

embodiments of Formula (I''), (I'), (II'), (III'), (IIIa'), (IIIb'), or (IV'), D is CR⁶, wherein R⁶ is C₂-C₆alkene, C₃-C₆cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R^c; B is N; and F is N. In some embodiments of Formula (I''), (I'), (II') (III'), (IIIa'), (IIIb'), or (IV'), D is CR⁶, wherein R⁶ is C₂-C₆alkene, C₃-C₆cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R^c; E is N; and F is N.

[0167] In some embodiments of Formula (I''), F is CR⁸, wherein R⁸ is C₂-C₆alkene, C₃-C₆cycloalkyl, 4 to 6-membered heterocycloalkyl, or 5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R^c; and E is N.

[0168] In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁵ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁵ is hydrogen, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁵ is C₁-C₆alkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁵ is C₁-C₆haloalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁵ is C₁-C₆hydroxyalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁵ is halogen or hydrogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁵ is halogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁵ is hydrogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁵ is fluorine. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁵ is chlorine.

[0169] In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁶ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁶ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a,

C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁶ is hydrogen, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁶ is C₁-C₆alkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁶ is C₁-C₆haloalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁶ is C₁-C₆hydroxyalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁶ is halogen or hydrogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁶ is halogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁶ is hydrogen.

[0170] In some embodiments of Formula (I'') (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁷ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁷ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁷ is hydrogen, halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁷ is C₁-C₆alkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁷ is C₁-C₆haloalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁷ is C₁-C₆hydroxyalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁷ is halogen or hydrogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁷ is halogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁷ is hydrogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁷ is fluorine. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁷ is chlorine. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁷ is hydroxyl. In some embodiments of Formula (I'), (I), (II), (III), (IIIa), (IIIb), or (IV), R⁷ is methoxy.

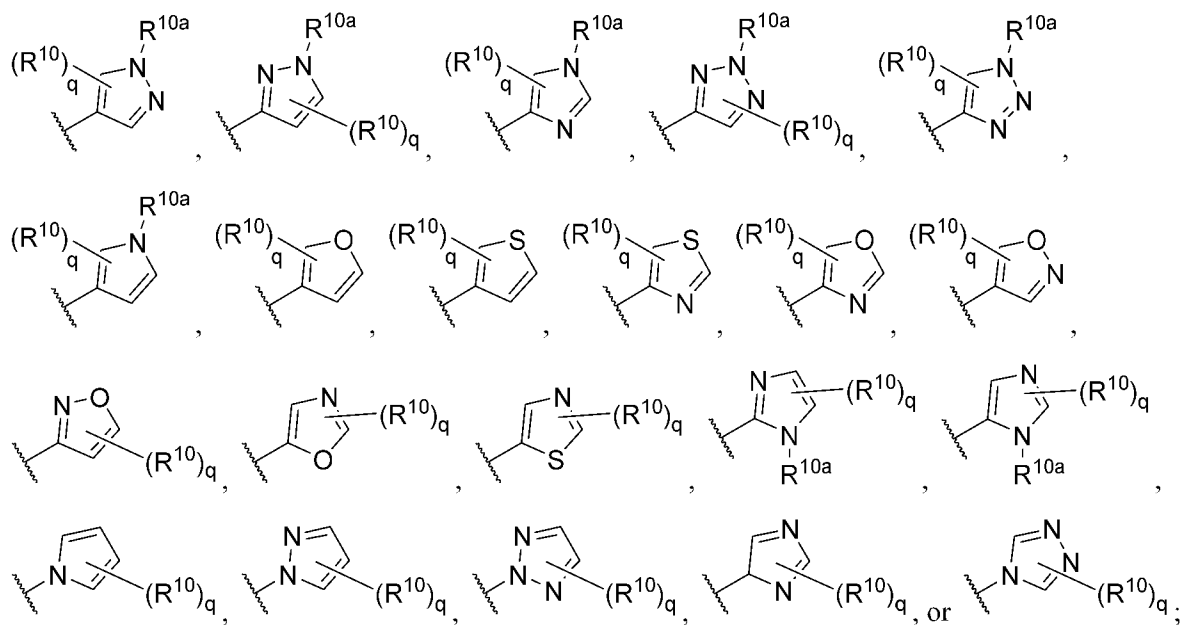
[0171] In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R⁸ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -

$S(=O)_2NR^cR^d$, $-NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, C_1-C_6 alkyl, C_2-C_6 alkene, C_2-C_6 alkyne, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, or C_1-C_6 aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents is hydrogen, halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, $-SH$, $-SR^a$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, or C_1-C_6 aminoalkyl; wherein each of the alkyl, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e . In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R^8 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, or C_1-C_6 aminoalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R^8 is C_1-C_6 alkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R^8 is C_1-C_6 haloalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R^8 is C_1-C_6 hydroxyalkyl. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R^8 is halogen or hydrogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R^8 is halogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R^8 is hydrogen. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R^8 is fluorine. In some embodiments of Formula (I''), (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), R^8 is chlorine.

[0172] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is a 5 to 6-membered heteroaryl optional substituted with 1 or 4 substituents selected from R^{10} .

[0173] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is a 5-membered heteroaryl optional substituted with 1 or 2 substituents selected from R^{10} . In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is pyrrole, imidazole, triazole, tetrazole, thiophene, oxazole, thiazole, or thiadiazole. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is pyrrole, imidazole, oxazole, triazole, thiazole, or thiadiazole. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is pyrrole, imidazole, oxazole, or thiadiazole. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is pyrrole. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is imidazole. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is thiadiazole. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is oxazole.

[0174] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is:



wherein,

each R^{10} is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl,

C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl,

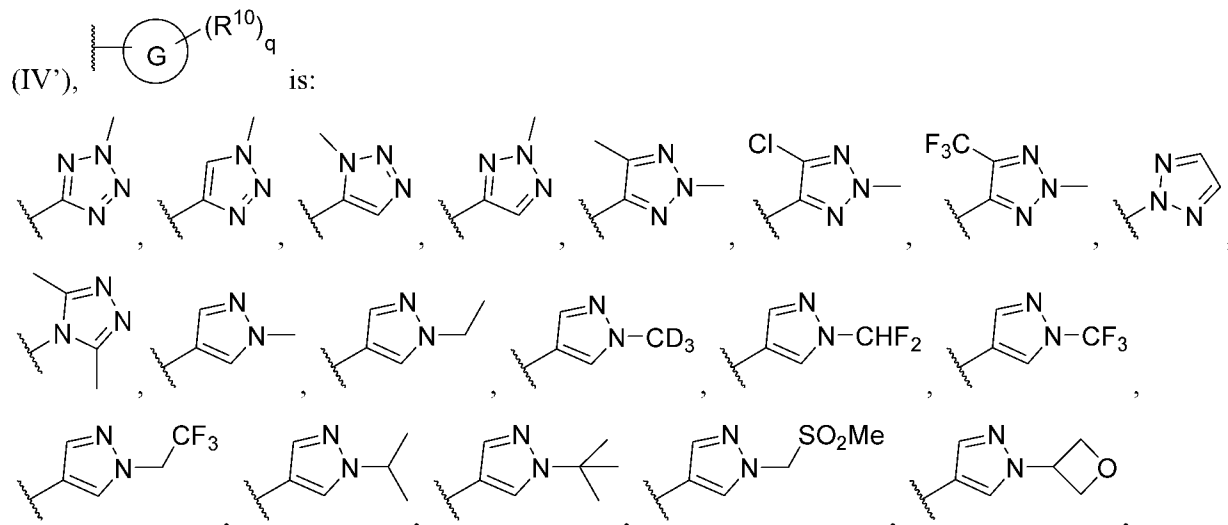
wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^c;

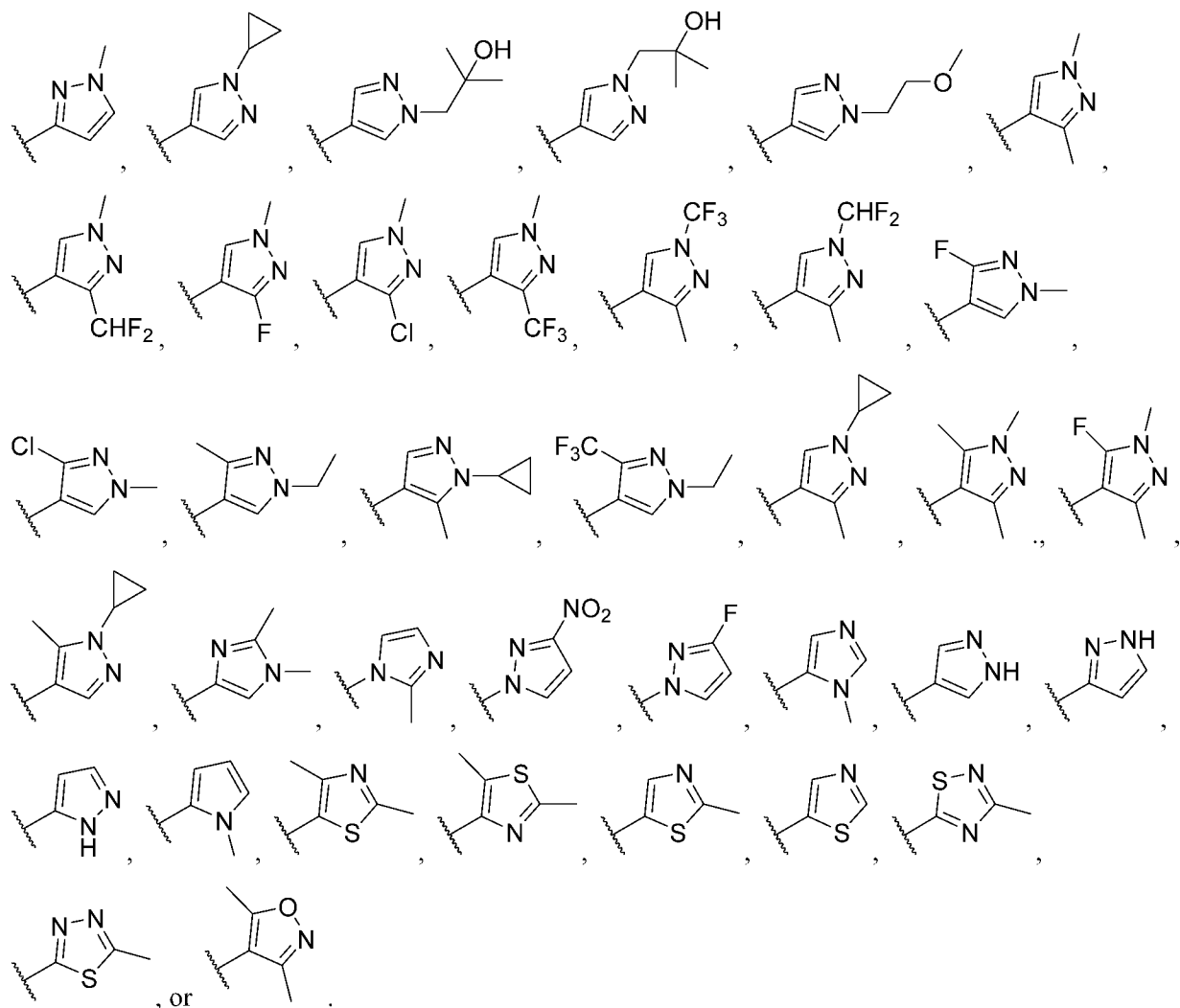
each R^{10a} is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^c; and

q is 0, 1, 2, or 3.

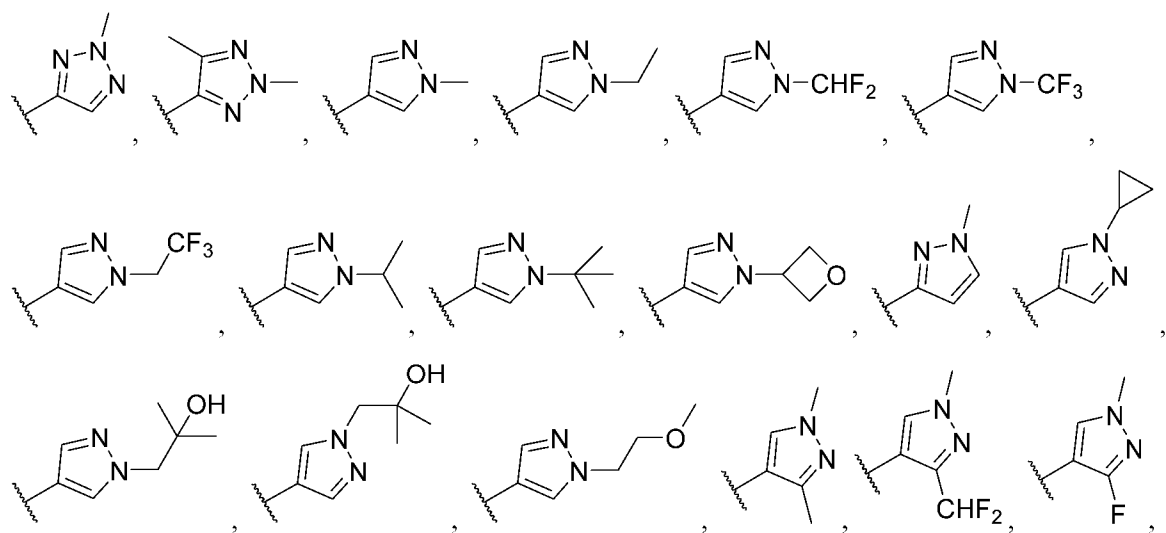
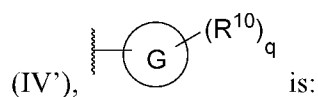
[0175] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'): each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl; each R^{10a} is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl; and p is 0, 1, or 2.

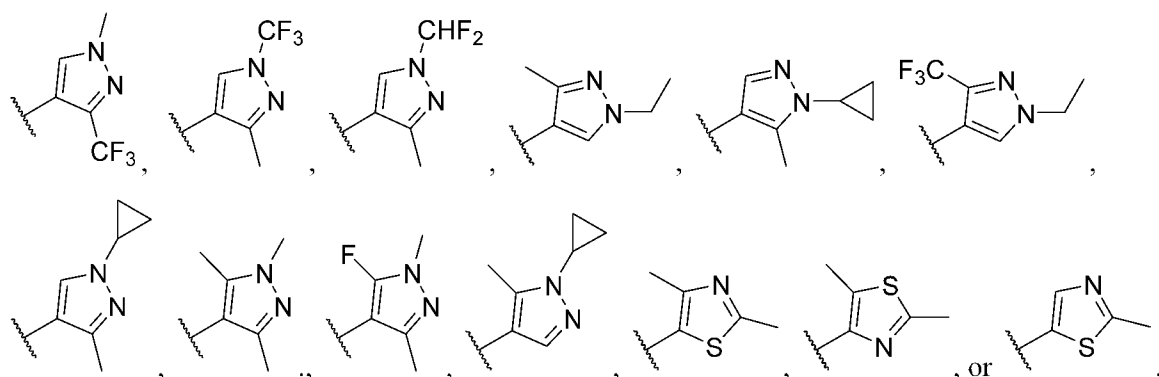
[0176] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or



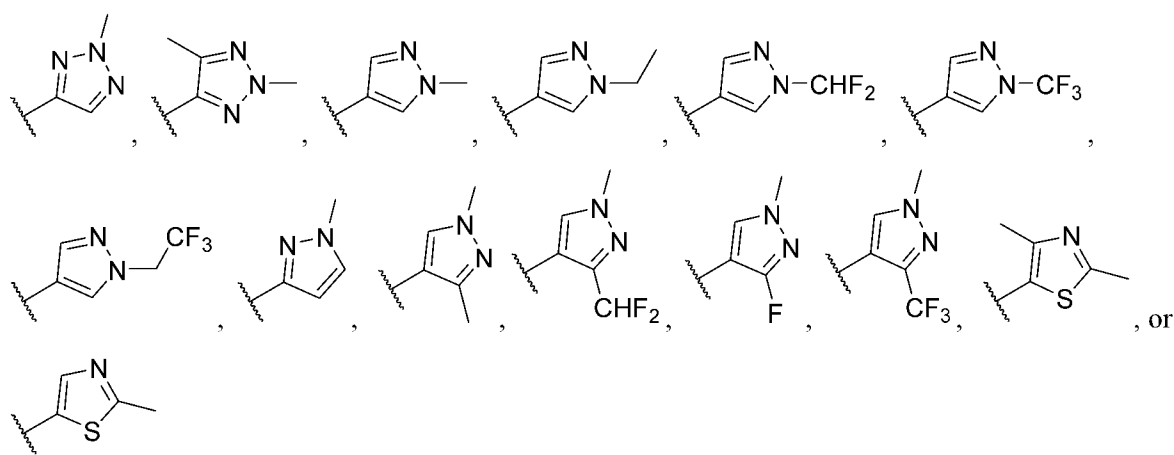
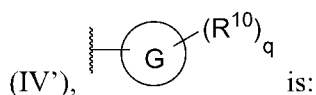


[0177] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or

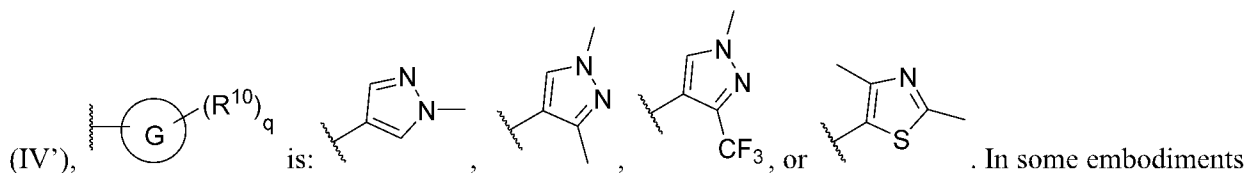




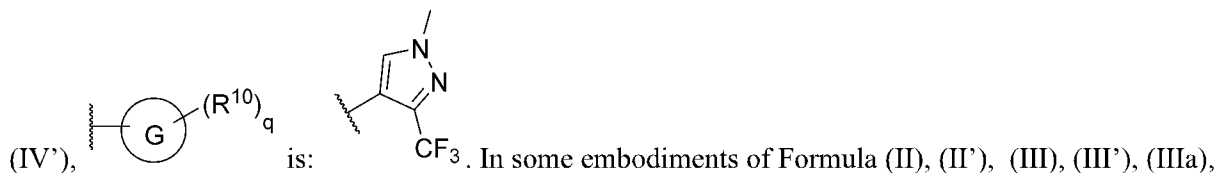
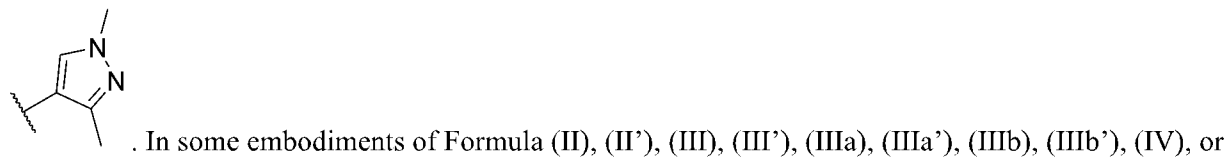
[0178] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or



[0179] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or



of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), is:



(IIIa'), (IIIb), (IIIb'), (IV), or (IV'),  is: . In some embodiments of Formula

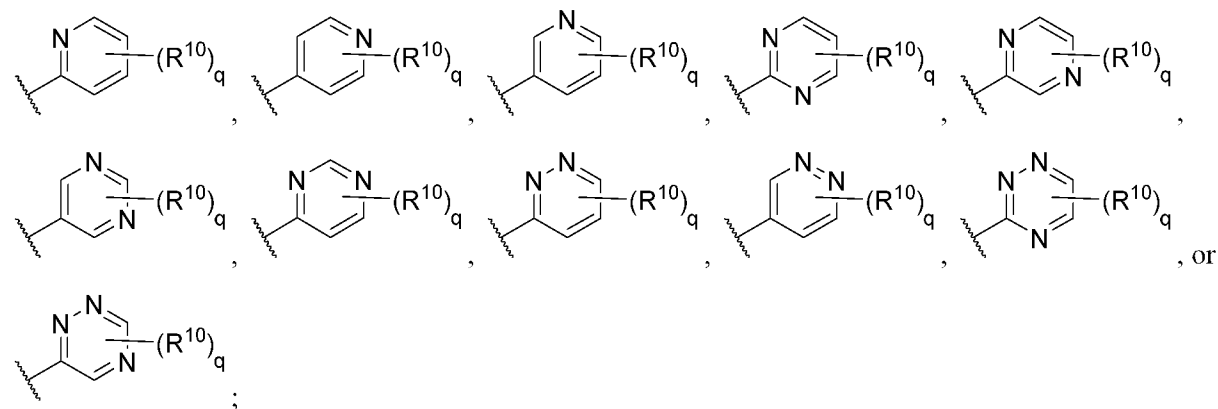
(II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'),


is:


[0180] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is a 6-membered heteroaryl optional substituted with 1 to 4 substituents selected from R¹⁰.

[0181] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is pyridine, pyrimidine, or triazine. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is pyridine. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is pyrimidine. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is triazine.

[0182] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is:



wherein,

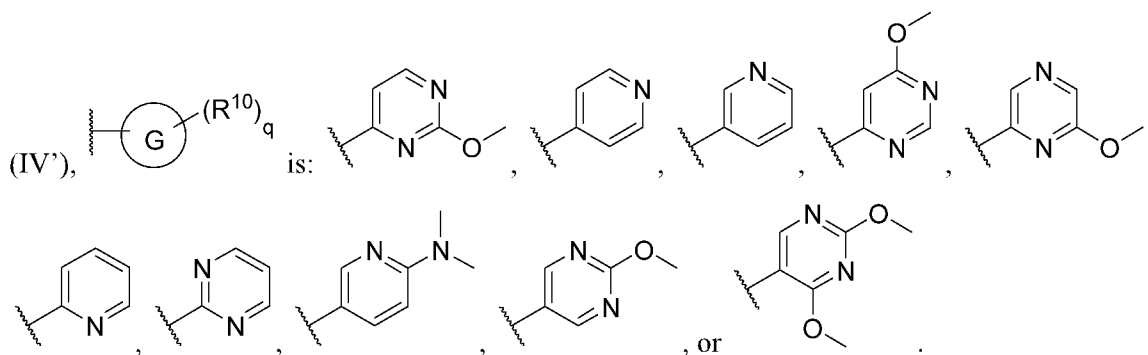
each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl,

C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl,

wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^c; and

q is 0, 1, 2, or 3.

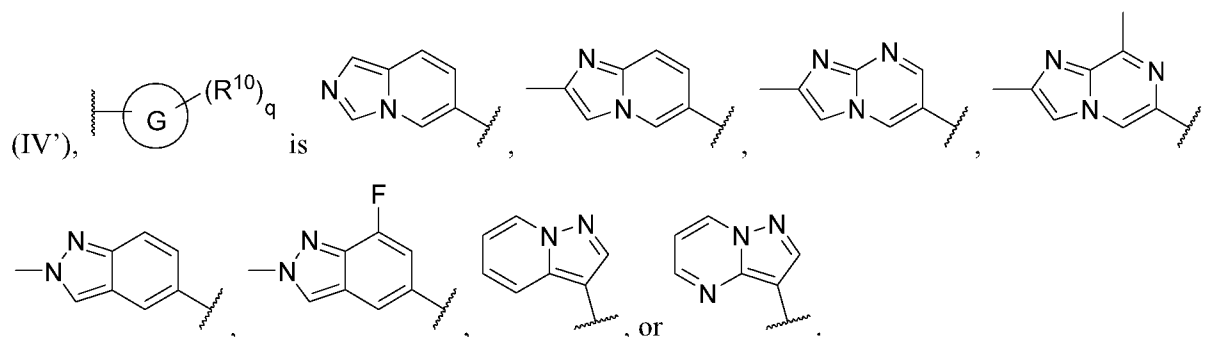
[0183] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or



[0184] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is an 8 to 10-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S; and optional substituted with 1 to 4 substituents selected from R^{10} . In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is a 10-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S; and optional substituted with 1 to 4 substituents selected from R^{10} . In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is an 8-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S; and optional substituted with 1 to 4 substituents selected from R^{10} . In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is an 8-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N; and optional substituted with 1 to 4 substituents selected from R^{10} .

[0185] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), ring G is imidazo[1,2-a]pyrazine, imidazo[1,2-a]pyrimidine, pyrazolo[1,5-a]pyridine, pyrazolo[1,5-a]pyrimidine, or 2-methyl-2H-indazole.

[0186] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or



[0187] In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10} is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e . In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10} is independently -CN, -NO₂, -OH, -OR^a, or -NR^cR^d. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10} is independently -OH or -OR^a. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10} is independently -OH or -OMe. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10} is independently halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, or C₃-C₆cycloalkyl. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10} is independently halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10} is independently halogen, C₁-C₆alkyl, C₁-C₆haloalkyl. In some embodiments of Formula (I'), (I), (II), (II'),

(III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹⁰ is independently C₁-C₆haloalkyl. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹⁰ is independently -CF₃, -CHF₂, -CH₂CF₃, or -CH₂CHF₂. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹⁰ is independently -CF₃ or -CHF₂. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹⁰ is independently C₁-C₆alkyl. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹⁰ is independently methyl, ethyl, isopropyl, or tert-butyl. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹⁰ is independently methyl. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹⁰ is independently halogen. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹⁰ is independently fluorine or chlorine. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹⁰ is independently fluorine. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹⁰ is independently chlorine.

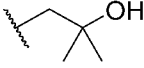
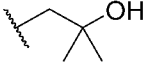
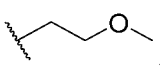
[0188] In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹⁰ is independently -F, -Cl, -CN, methyl, ethyl, -OCH₃, -CF₃, -CHF₂, or -CH₂F. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R¹⁰ is independently -F, -Cl, methyl, -CF₃, or -CHF₂.

[0189] In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), two R¹⁰ are taken together to form an oxo.

[0190] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently C₃-C₆cycloalkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently cyclopropyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently cyclopropyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently 4 to 6-membered heterocycloalkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently 4-membered heterocycloalkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently 5-membered heterocycloalkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently 6-membered heterocycloalkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently oxatanyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently C₁-C₆haloalkyl. In some

embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently $-CF_3$, $-CHF_2$, $-CH_2CF_3$, or $-CH_2CHF_2$. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently C_1 - C_6 alkyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently methyl, ethyl, isopropyl, or tert-butyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently methyl. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently hydrogen.

[0191] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), each R^{10a} is independently hydrogen, methyl, ethyl, isopropyl, tert-butyl, $-CD_3$, $-CF_3$, CHF_2 , CH_2F ,

$-CH_2CF_3$, $-CH_2SO_2CH_3$, cyclopropyl, oxetanyl, , , or .

[0192] In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is an integer from 1-9. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is an integer from 1-8. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is an integer from 1-6. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is an integer from 1-4. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1, 2, 3, 4, 5, 6, 7, or 8. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1, 2, 3, 4, 5, or 6. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1, 2, 3, or 4. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1, 2, 3, 4, 5, or 6. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1, 2, 3, or 4. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1, 2, 3, 4, 5, or 6. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1 or 2. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1, 2, 3, 4, 5, or 6. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 2. In some embodiments of Formula (I'), (I), (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), p is 1.

[0193] In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), q is 1, 2, or 3. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), q is 3. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), q is 1 or 2. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), q is 2. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), q is 1. In some embodiments of Formula (II), (II'), (III), (III'), (IIIa), (IIIa'), (IIIb), (IIIb'), (IV), or (IV'), q is 0.

[0194] In some embodiments of the compound disclosed herein each R^a is independently C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c . In some embodiments of a compound disclosed herein, each R^a is independently C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or cycloalkyl, heterocycloalkyl. In some embodiments of a compound disclosed herein, each R^a is independently C_1 - C_6 alkyl or C_1 - C_6 haloalkyl. In some embodiments of a compound disclosed herein, each R^a is independently C_1 - C_6 alkyl. In some embodiments of a compound disclosed herein, each R^a is independently methyl, ethyl, isopropyl, tert-butyl, $-OCH_3$, $-CF_3$, or $-CHF_2$. In some embodiments of a compound disclosed herein, each R^a is independently methyl, ethyl, isopropyl or tertbutyl.

[0195] In some embodiments of the compound disclosed herein, each R^b is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c . In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or cycloalkyl, heterocycloalkyl. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen or C_1 - C_6 alkyl. In some embodiments of a compound disclosed herein, each R^b is hydrogen. In some embodiments of a compound disclosed herein, each R^b is independently C_1 - C_6 alkyl. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, methyl, ethyl, isopropyl, tert-butyl, $-OCH_3$, $-CF_3$, or $-CHF_2$. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen, methyl, ethyl, isopropyl, or tert-butyl. In some embodiments of a compound disclosed herein, each R^b is independently hydrogen or methyl.

[0196] In some embodiments of the compound disclosed herein, R^c and R^d are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 aminoalkyl, C_1 - C_6 heteroalkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e . In some embodiments of a compound disclosed herein, each R^c and R^d are independently hydrogen, C_1 - C_6 alkyl or C_1 - C_6 haloalkyl. In some embodiments of a compound disclosed herein, each R^c and R^d are independently hydrogen or C_1 - C_6 alkyl. In some embodiments of a compound disclosed herein, each R^c and R^d are hydrogen. In some embodiments of a compound disclosed herein, each R^c and R^d are independently C_1 - C_6 alkyl. In some embodiments of a compound disclosed herein, each R^c and R^d are independently hydrogen methyl, ethyl, isopropyl, tert-butyl, $-OCH_3$, $-CF_3$, or $-CHF_2$. In some embodiments of a compound disclosed herein, each R^c and R^d are independently hydrogen, methyl, ethyl, isopropyl, or tert-

butyl. In some embodiments of a compound disclosed herein, each R^c and R^d are independently hydrogen or methyl. In some embodiments of a compound disclosed herein, each R^c and R^d are methyl.

[0197] In some embodiments of a compound disclosed herein, each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -CH₂S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl. In some embodiments of a compound disclosed herein, each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, or C₃-C₆cycloalkyl. In some embodiments of a compound disclosed herein, each R^e is independently halogen, oxo, -CN, -OH, -S(=O)C₁-C₆alkyl, -S(=O)₂C₁-C₆alkyl, -S(=O)₂NH₂, -S(=O)₂NHC₁-C₆alkyl, -S(=O)₂N(C₁-C₆alkyl)₂, -NH₂, -NHC₁-C₆alkyl, -N(C₁-C₆alkyl)₂, -C(=O)C₁-C₆alkyl, -C(=O)OH, -C(=O)OC₁-C₆alkyl, -NHC(=O)C₁-C₆alkyl, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, or C₃-C₆cycloalkyl. In some embodiments, R^e is -NHC(=O)C₁₋₃alkyl such as -NHC(=O)CH₃. In some embodiments of a compound disclosed herein, each R^e is independently halogen, -CN, -OH, or C₁-C₆alkyl. In some embodiments of a compound disclosed herein, each R^e is independently halogen, -OH, or C₁-C₆alkyl. In some embodiments of a compound disclosed herein, each R^e is independently halogen or C₁-C₆alkyl. In some embodiments of a compound disclosed herein, each R^e is independently halogen. In some embodiments of a compound disclosed herein, each R^e is independently -Cl or -F. In some embodiments of a compound disclosed herein, each R^e is independently halogen, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl. In some embodiments, each R^e is independently -F, -Cl, -OH, -CH₂S(=O)₂CH₃, methyl, ethyl, isopropyl, tertbutyl, -OCH₃, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or azetidine, oxytane, piperidine, piperazine, or morpholine. In some embodiments, each R^e is independently -F, -OH, -CF₃, -CHF₂, -OCH₃, or methyl. In some embodiments, each R^e is independently -F, -CF₃, -CHF₂, or methyl. In some embodiments, each R^e is methyl.

[0198] In some embodiments of a compound disclosed herein, one or more of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R^{10a}, R^a, R^b, R^c, R^d, and R^e groups comprise deuterium at a percentage higher than the natural abundance of deuterium.

[0199] In some embodiments of a compound disclosed herein, one or more ¹H are replaced with one or more deuteriums in one or more of the following groups R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R^{10a}, R^a, R^b, R^c, R^d, and R^e.

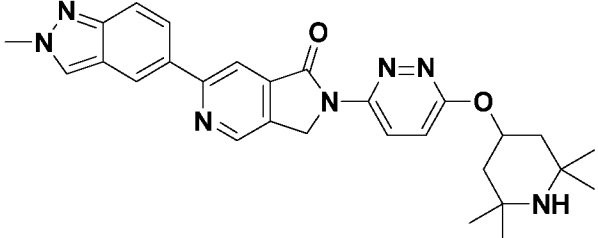
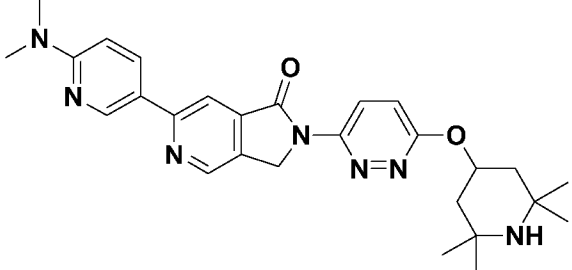
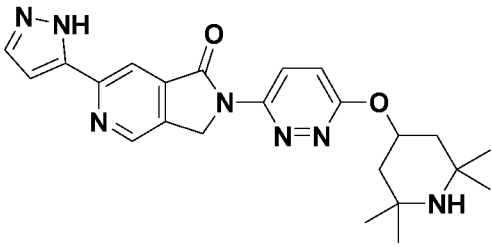
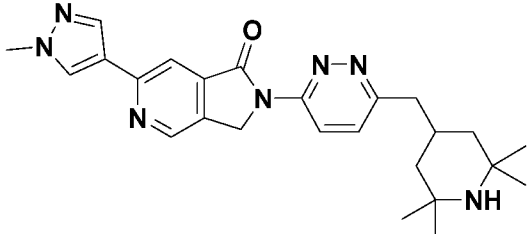
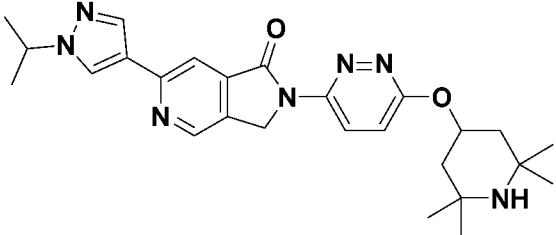
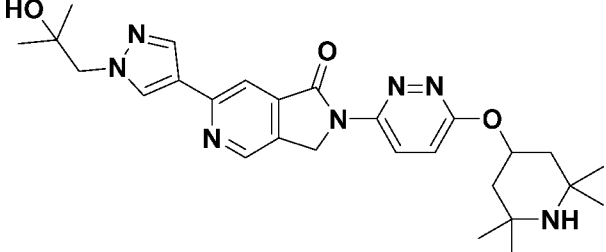
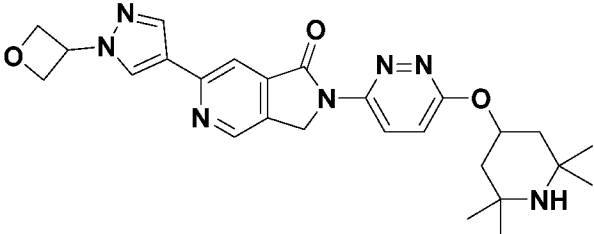
[0200] In some embodiments of a compound disclosed herein, the abundance of deuterium in each of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R^{10a}, R^a, R^b, R^c, R^d, and R^e is independently at least 1%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% by molar.

[0201] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[0202] In some embodiments the compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, is one of the compounds in **Table 3A**, **Table 3B**, or **Table 3C**.

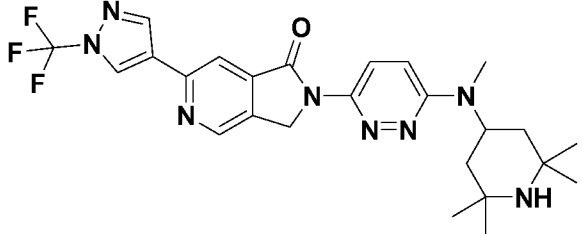
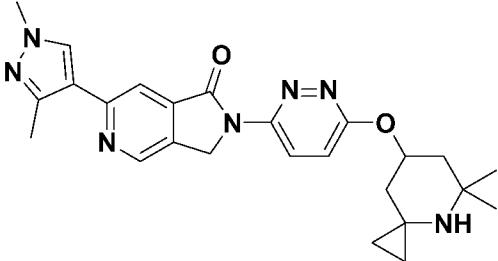
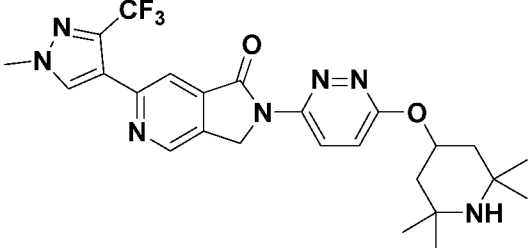
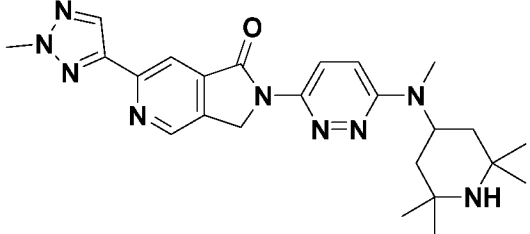
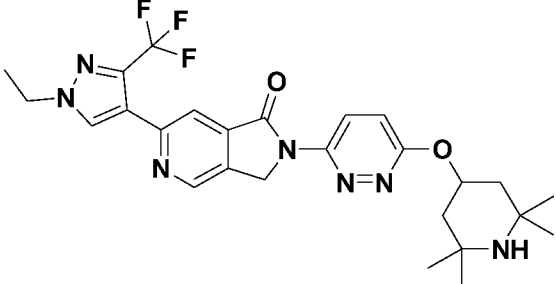
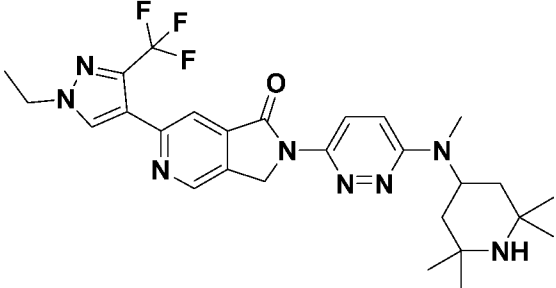
Table 3A.

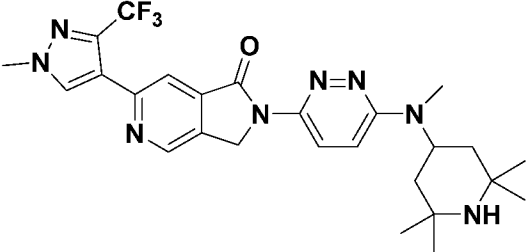
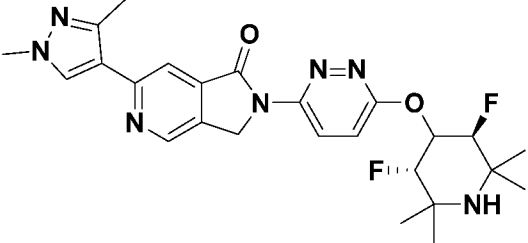
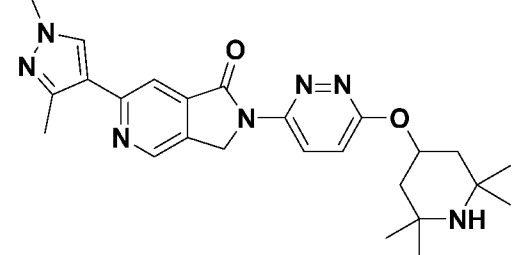
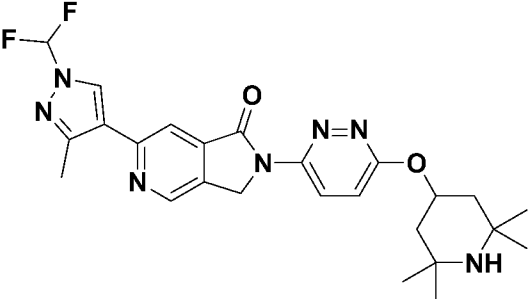
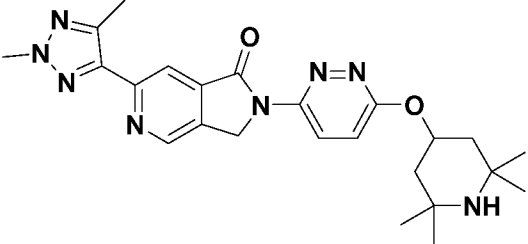
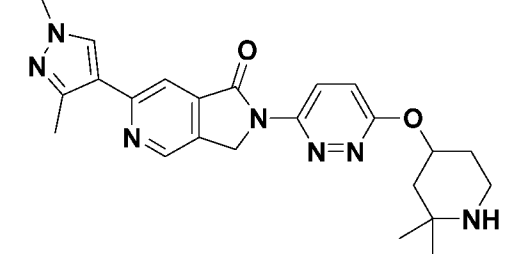
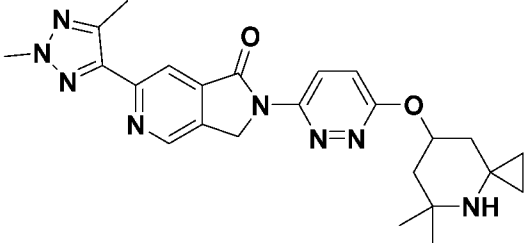
No.	Chemical Structure	Name
1		2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
2		6-(1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
3		2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
6		6-(1-methyl-1H-pyrazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
7		6-(1,5-dimethyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
8		6-(2,4-dimethoxypyrimidin-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

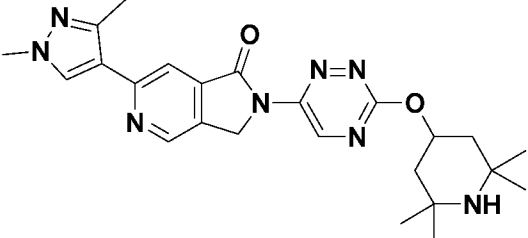
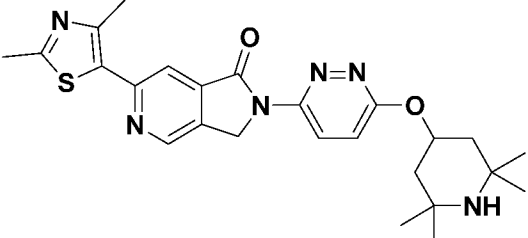
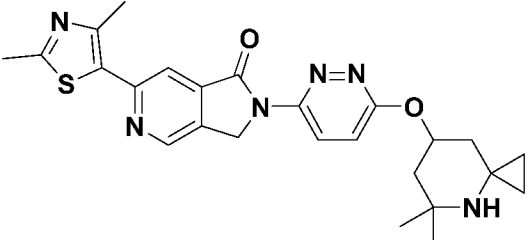
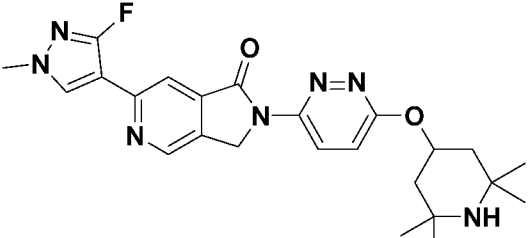
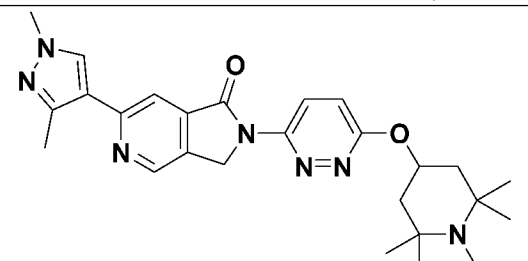
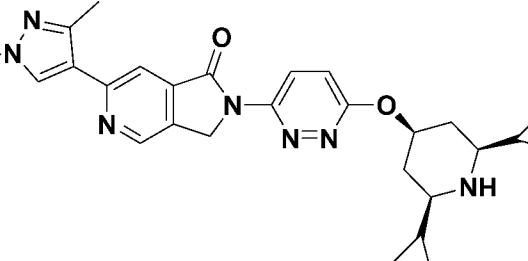
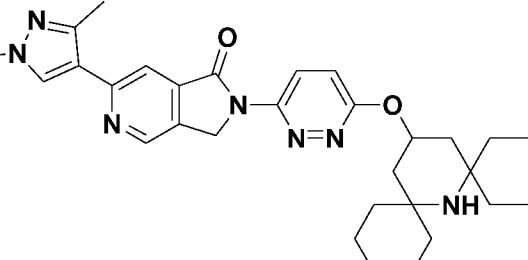
No.	Chemical Structure	Name
9		6-(2-methyl-2H-indazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
10		6-(6-(dimethylamino)pyridin-3-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
15		6-(1H-pyrazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
17		6-(1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)methyl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
18		6-(1-isopropyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
21		6-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
23		6-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

No.	Chemical Structure	Name
24		6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
26		6-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
28		6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
29		6-(imidazo[1,5-a]pyridin-6-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
30		2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
31		6-(1-(tert-butyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
35		6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

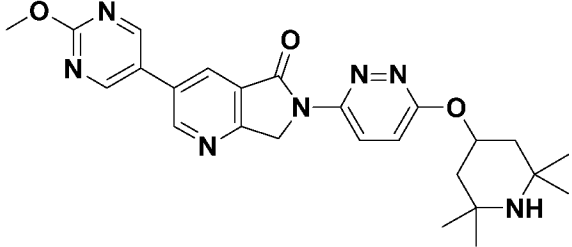
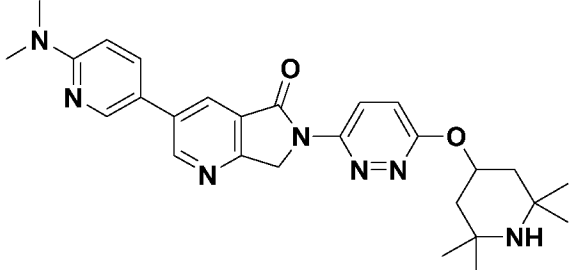
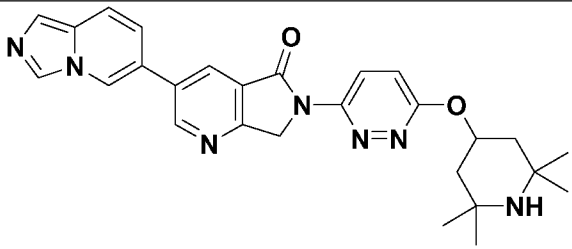
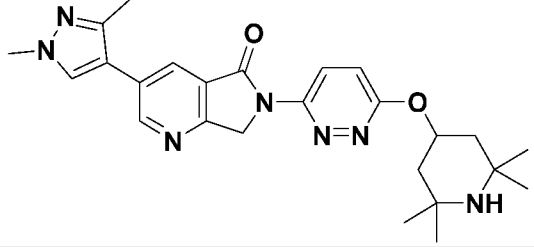
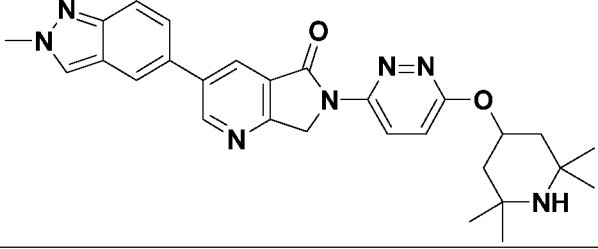
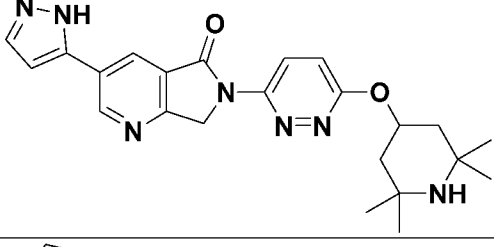
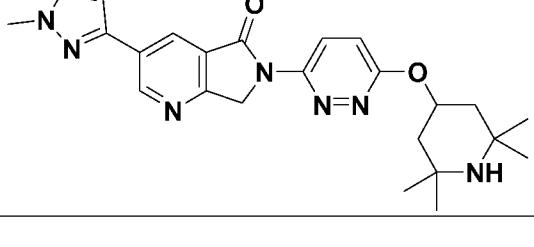
No.	Chemical Structure	Name
43		3-methyl-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
47		6-(1-ethyl-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
49		2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-(methyl-d3)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
51		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
54		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
56		2-(6-((4-azadispiro[2.1.2^5.3^3]decan-9-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
57		6-(2,4-dimethylthiazol-5-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

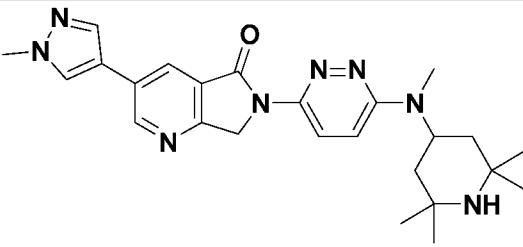
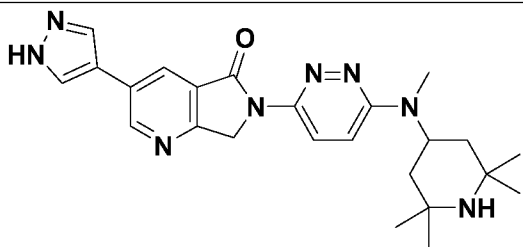
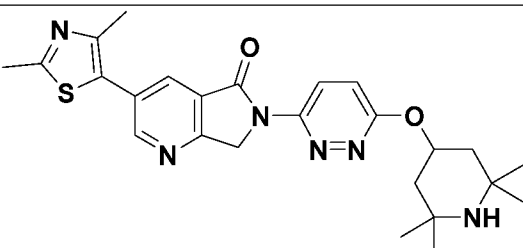
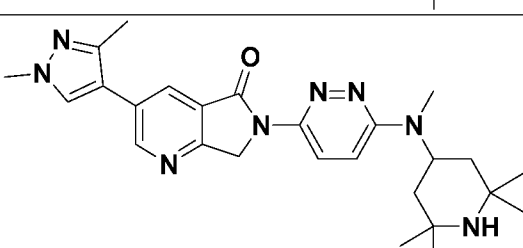
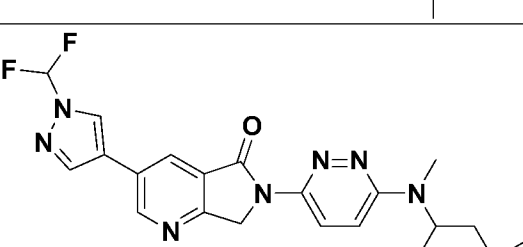
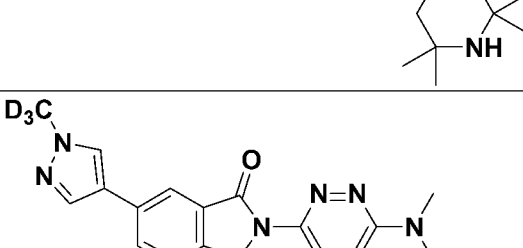
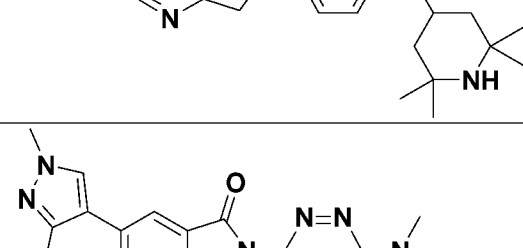
No.	Chemical Structure	Name
58		2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-(trifluoromethyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
59		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
63		6-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
64		2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
65		6-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
66		6-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

No.	Chemical Structure	Name
71		2-(6-((methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
75		2-(6-(((3S,5S)-3,5-difluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
76		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
78		6-(1-(difluoromethyl)-3-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
80		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
81		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((2,2-dimethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
83		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

No.	Chemical Structure	Name
84		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(3-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-1,2,4-triazin-6-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
86		6-(2,4-dimethylthiazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
88		2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
91		6-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
92		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((1,2,2,6,6-pentamethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
101		2-(6-(((2R,4s,6S)-2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
103		2-(6-(((7-azadispiro[5.1.5^8.3^6]hexadecan-15-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

No.	Chemical Structure	Name
104		2-(6-(((2S,6S)-2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
109		2-(6-(((2S,6S)-2,6-diisopropylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
113		2-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
115		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
119		2-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
134		3-(pyridin-3-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
135		3-(1,5-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
138		3-(2-methoxypyrimidin-5-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
139		3-(6-(dimethylamino)pyridin-3-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
140		3-(imidazo[1,5-a]pyridin-6-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
141		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
142		3-(2-methyl-2H-indazol-5-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
143		3-(1H-pyrazol-5-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
144		3-(1-methyl-1H-pyrazol-3-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
148		6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
149		6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
150		3-(2,4-dimethylthiazol-5-yl)-6-(6-(2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
156		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
160		3-(1-(difluoromethyl)-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
161		6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(1-(methyl-d3)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
162		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
163		3-(1-cyclopropyl-3-methyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
167		3-(2,4-dimethylthiazol-5-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
168		3-(1-cyclopropyl-5-methyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
172		3-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
173		3-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
176		3-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
177		6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
179		3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
180		3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
182		6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(1-(trifluoromethyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
184		3-(3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
187		3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
189		6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
190		3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
191		3-(2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
193		3-(2,5-dimethylthiazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
195		3-(2,4-dimethylthiazol-5-yl)-6-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
198		3-(3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
203		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(4-methoxy-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
205		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
207		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

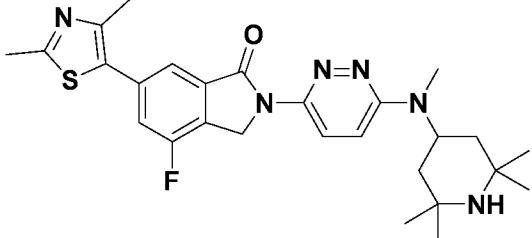
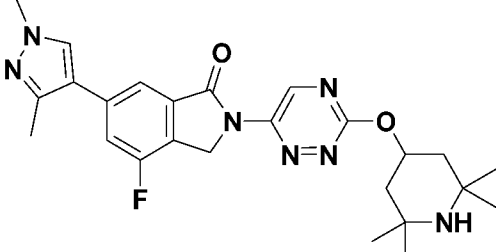
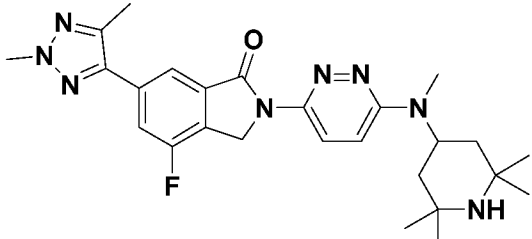
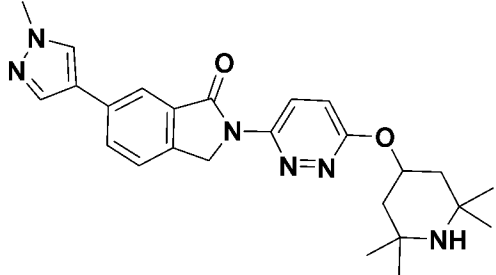
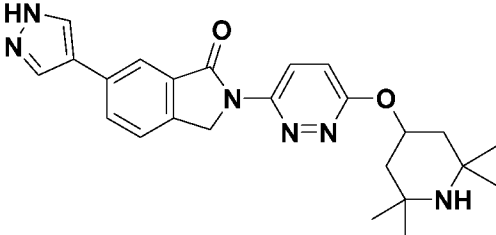
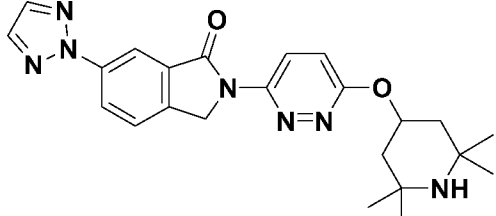
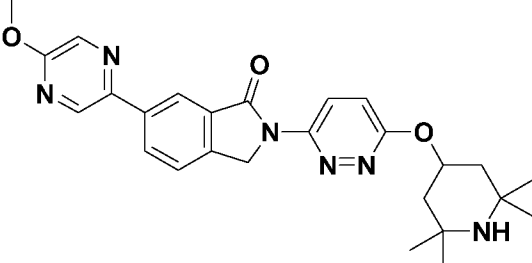
No.	Chemical Structure	Name
208		2-chloro-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
210		6-(6-(((3S,5S)-3,5-difluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
211		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((3S,4R)-3-fluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
212		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((3R,4R)-3-fluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
216		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(5-methoxy-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
218		6-(6-(((3S,5S)-3,5-difluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
221		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

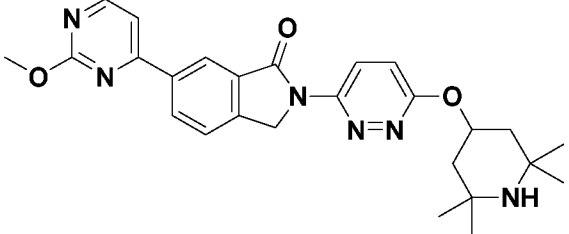
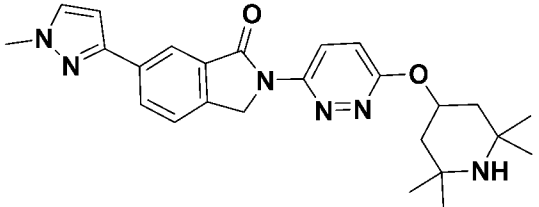
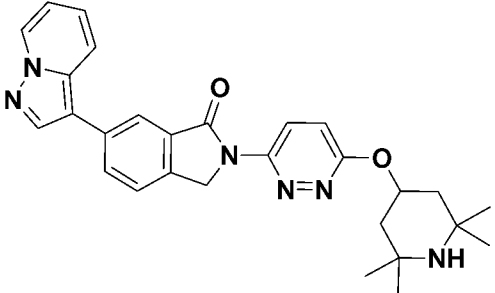
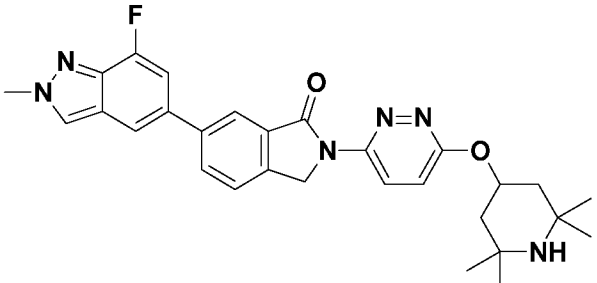
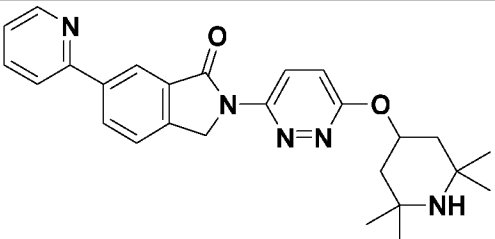
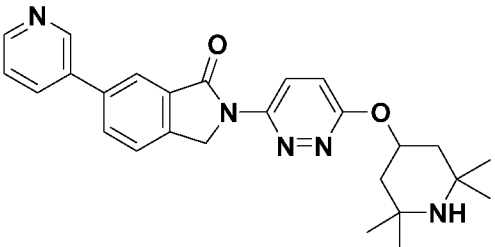
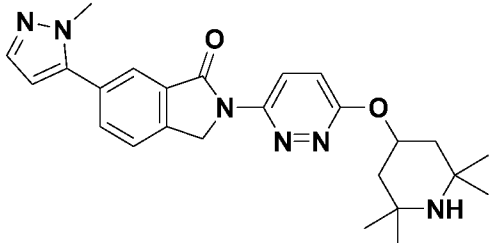
No.	Chemical Structure	Name
222		3-(1-methyl-1H-imidazol-5-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
223		3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
224		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(3-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
225		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2-hydroxyethyl)(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
226		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2-dimethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
228		3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
230		3-(1,2-dimethyl-1H-imidazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

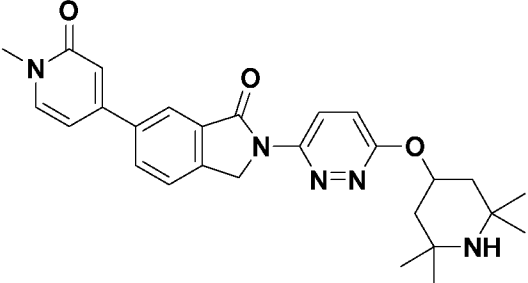
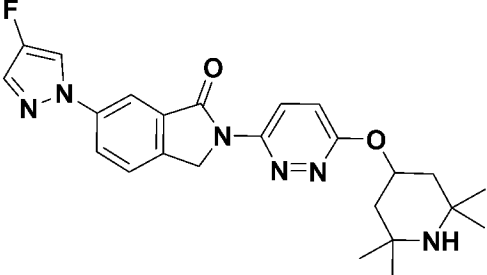
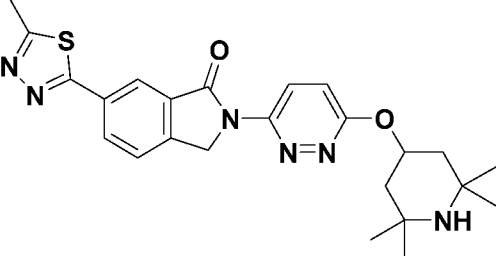
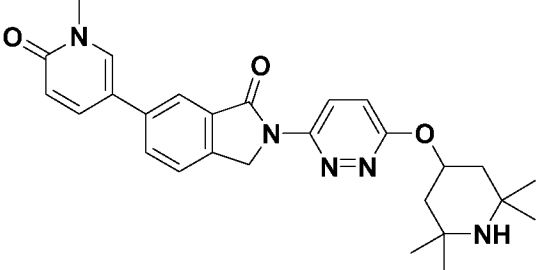
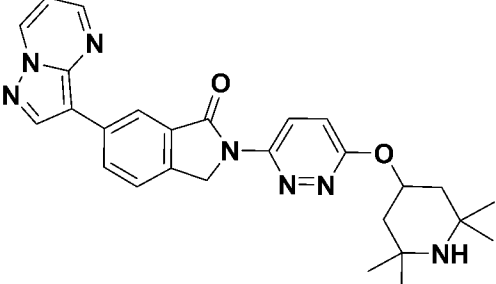
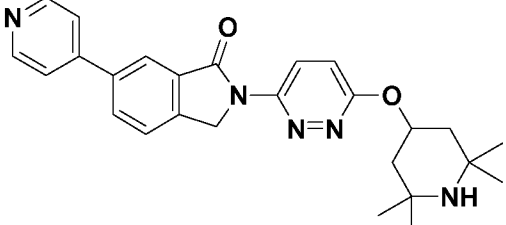
No.	Chemical Structure	Name
231		6-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
232		6-(6-((4-azadispiro[2.1.2 ⁵ .3 ³]decan-9-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
234		3-(2-methyl-1H-imidazol-1-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
235		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((1,2,2,6,6-pentamethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
237		3-(3,5-dimethyl-4H-1,2,4-triazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
241		6-(6-(((2R,4s,6S)-2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
243		6-(6-((7-azadispiro[5.1.5 ⁸ .3 ⁶]hexadecan-15-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
245		6-(6-(((2S,6S)-2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
247		6-(6-(((2S,6S)-2,6-diisopropylpiperidin-4-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
249		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
253		6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
275		6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one
276		6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
277		6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)isoindolin-1-one

No.	Chemical Structure	Name
279		4-fluoro-6-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-2-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)isoindolin-1-one
280		6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-(((3R,4S)-3-fluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
282		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
284		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-4-fluoroisoindolin-1-one
285		2-(6-(((3R,5R)-3,5-difluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisoindolin-1-one
287		6-(2,4-dimethylthiazol-5-yl)-4-fluoro-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
288		6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-(((3S,4S)-3-fluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one

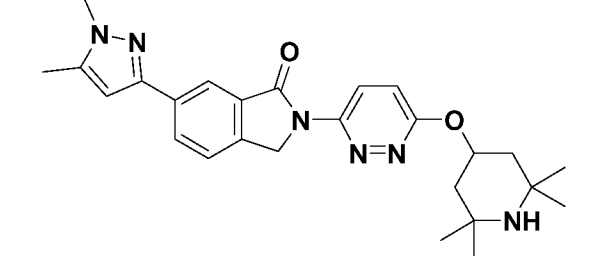
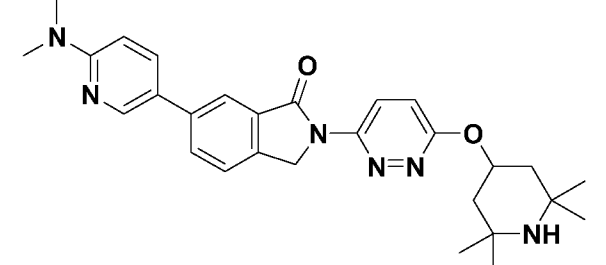
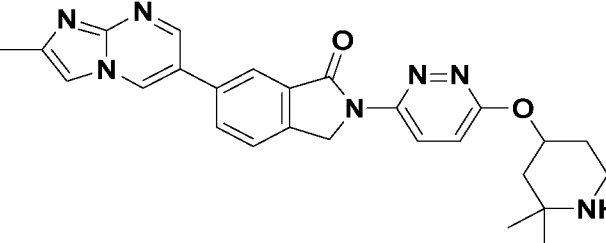
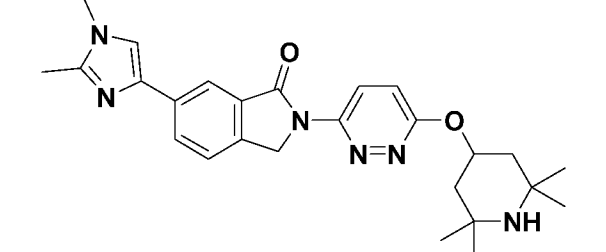
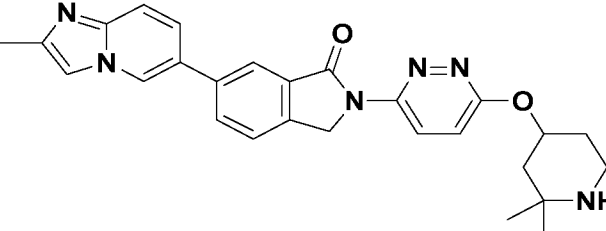
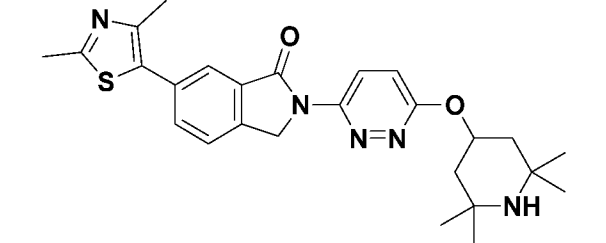
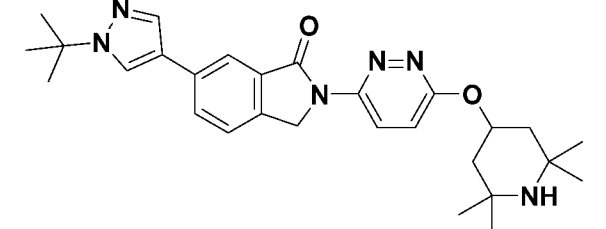
No.	Chemical Structure	Name
290		6-(2,4-dimethylthiazol-5-yl)-4-fluoro-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one
292		6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(3-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)-1,2,4-triazin-6-yl)isoindolin-1-one
293		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one
308		6-(1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
309		6-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
310		2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(2H-1,2,3-triazol-2-yl)isoindolin-1-one
311		6-(5-methoxypyrazin-2-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one

No.	Chemical Structure	Name
312		6-(2-methoxypyrimidin-4-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-ylisoindolin-1-one
313		6-(1-methyl-1H-pyrazol-3-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-ylisoindolin-1-one
314		6-(pyrazolo[1,5-a]pyridin-3-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-ylisoindolin-1-one
315		6-(7-fluoro-2-methyl-2H-indazol-5-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-ylisoindolin-1-one
316		6-(pyridin-2-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-ylisoindolin-1-one
317		6-(pyridin-3-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-ylisoindolin-1-one
318		6-(1-methyl-1H-pyrazol-5-yl)-2-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-ylisoindolin-1-one

No.	Chemical Structure	Name
319		6-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
320		6-(4-fluoro-1H-pyrazol-1-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
321		6-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
322		6-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
323		6-(pyrazolo[1,5-a]pyrimidin-3-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
324		6-(pyridin-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one

No.	Chemical Structure	Name
325		6-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
326		6-(2,8-dimethylimidazo[1,2-a]pyrazin-6-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
327		6-(pyrimidin-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
328		6-(2,7-dimethylimidazo[1,2-b]pyridazin-6-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
329		6-(2,4-dimethoxypyrimidin-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
330		6-(pyrimidin-2-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
331		2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(thiazol-2-yl)isoindolin-1-one

No.	Chemical Structure	Name
332		2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(thiazol-5-yl)isoindolin-1-one
333		6-(3,5-dimethylisoxazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
334		2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)isoindolin-1-one
335		6-(2-methyl-2H-indazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
336		6-(imidazo[1,5-a]pyridin-6-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
337		6-(1H-pyrazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
338		6-(1-methyl-1H-imidazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one

No.	Chemical Structure	Name
339		6-(1,5-dimethyl-1H-pyrazol-3-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
340		6-(6-(dimethylamino)pyridin-3-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
341		6-(2-methylimidazo[1,2-a]pyrimidin-6-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
342		6-(1,2-dimethyl-1H-imidazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
343		6-(2-methylimidazo[1,2-a]pyridin-6-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
346		6-(2,4-dimethylthiazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
347		6-(1-(tert-butyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one

No.	Chemical Structure	Name
348		6-(1-(tert-butyl)-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one
349		2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
350		6-(1-(difluoromethyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
351		6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one
352		6-(1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)methyl)pyridazin-3-yl)isoindolin-1-one
353		6-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)methyl)pyridazin-3-yl)isoindolin-1-one
354		2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1H-pyrazol-4-yl)isoindolin-1-one

No.	Chemical Structure	Name
355		6-(1-isopropyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
356		6-(1-methyl-1H-1,2,3-triazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
357		6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
358		6-(2-methyl-2H-tetrazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
359		2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)isoindolin-1-one
360		6-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
362		6-(2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one

No.	Chemical Structure	Name
363		2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)isoindolin-1-one
364		6-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one
365		6-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
368		2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-(oxetan-3-yl)-1H-pyrazol-4-yl)isoindolin-1-one
369		6-(1-methyl-1H-1,2,3-triazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
370		2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one
371		6-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one

No.	Chemical Structure	Name
372		2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-1,2,3-triazol-5-yl)isoindolin-1-one
373		2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(2-methyl-2H-tetrazol-5-yl)isoindolin-1-one
375		6-(1-isopropyl-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one
378		2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4,5-tetrazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
381		5-fluoro-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
382		5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
383		2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-(methyl-d3)-1H-pyrazol-4-yl)isoindolin-1-one

No.	Chemical Structure	Name
385		6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4,5-tetrazin-3-yl)isoindolin-1-one
392		6-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one
403		5-methoxy-6-(1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
406		6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)isoindolin-1-one
410		5-methoxy-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
411		5-hydroxy-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
417		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)isoindolin-1-one

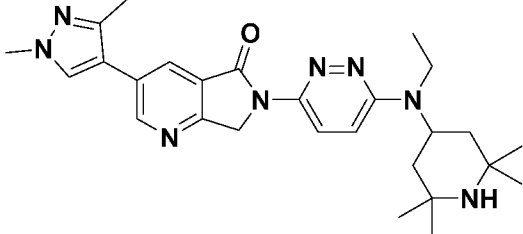
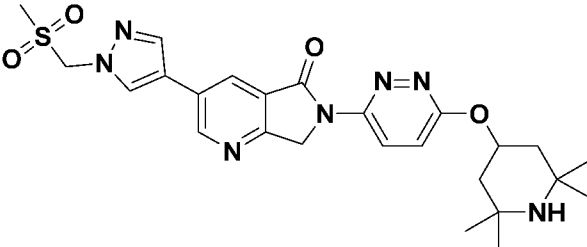
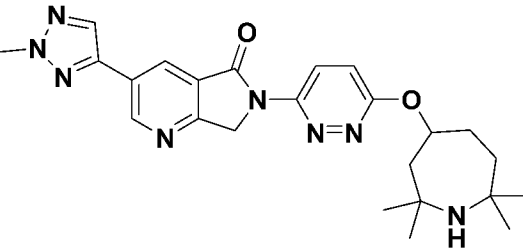
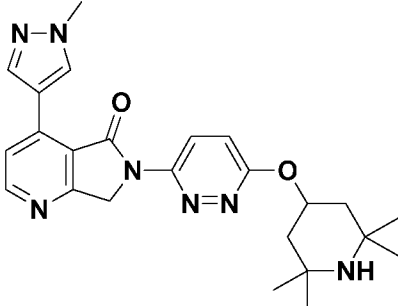
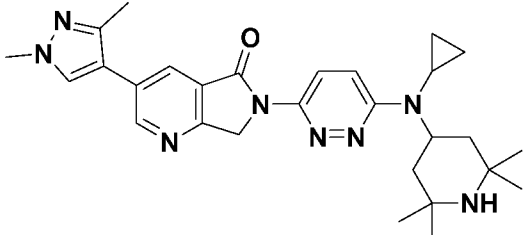
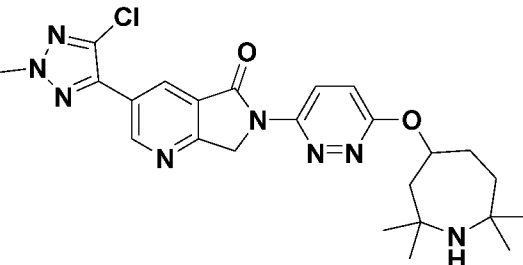
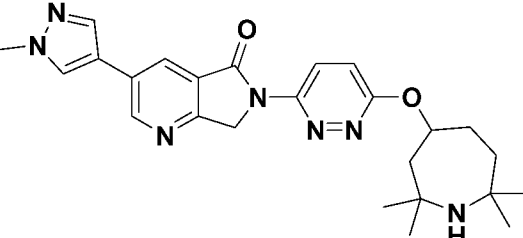
No.	Chemical Structure	Name
420		2-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one
421		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
424		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one
430		6-(2,4-dimethylthiazol-5-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one
431		6-(2,4-dimethylthiazol-5-yl)-2-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)isoindolin-1-one
433		6-(1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoro-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
435		6-(2,4-dimethylthiazol-5-yl)-2-(4-methoxy-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one

No.	Chemical Structure	Name
438		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)isoindolin-1-one
441		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(4-methoxy-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
442		6-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
443		2-(6-(((3S,5S)-3,5-difluoro-2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)isoindolin-1-one
444		2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)isoindolin-1-one
448		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)isoindolin-1-one
449		2-(6-((4-azadispiro[2.1.2^5.3^3]decan-9-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)isoindolin-1-one

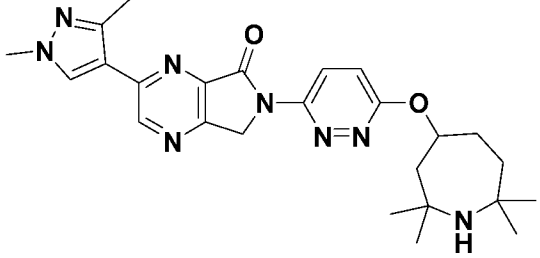
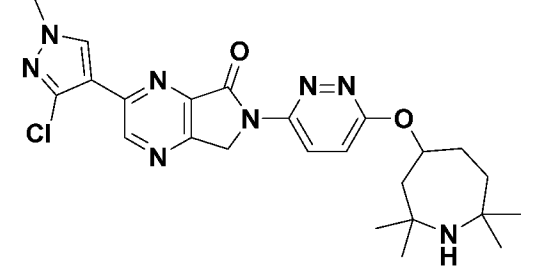
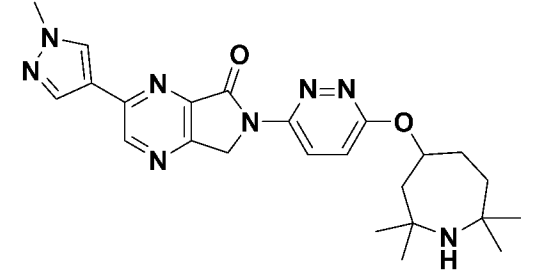
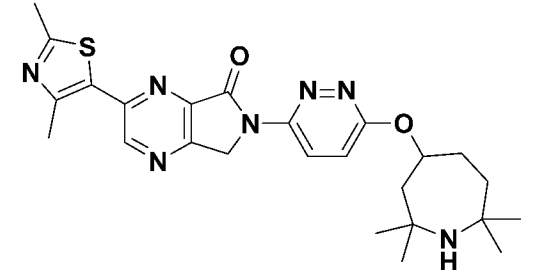
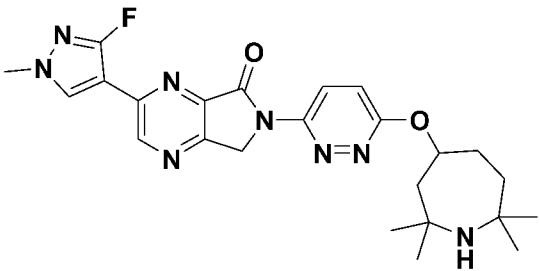
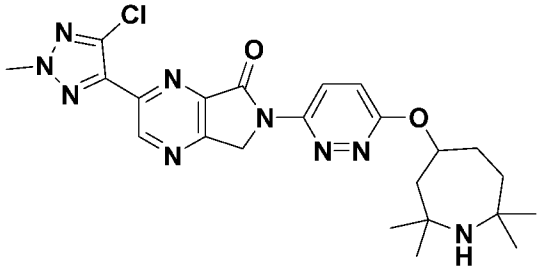
No.	Chemical Structure	Name
451		5-(3-methyl-1,2,4-thiadiazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
455		6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-c]pyridazin-5-one
457		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
459		2-(6-(((2S,4r,6R)-2,6-diethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
461		6-(2,4-dimethylthiazol-5-yl)-2-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
462		4-(1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
463		4-(1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

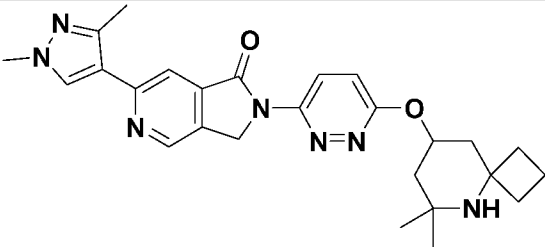
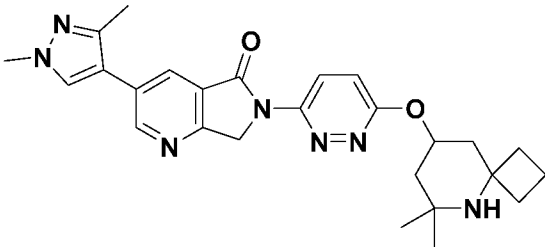
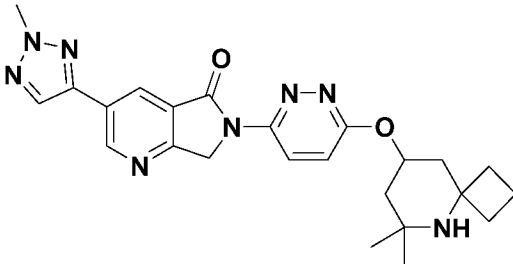
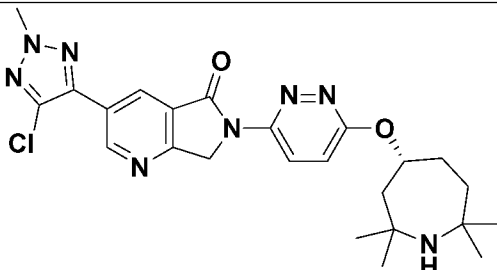
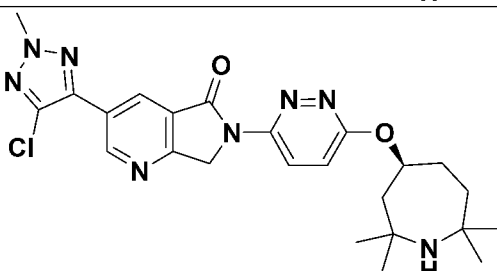
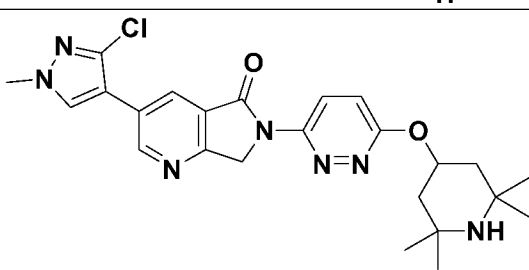
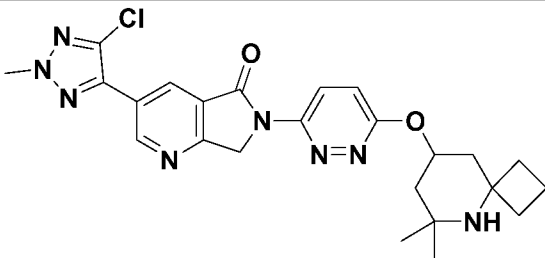
No.	Chemical Structure	Name
464		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(ethyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
465		6-(2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
466		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(7-(2,2,6,6-tetramethylpiperidin-4-yl)-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
468		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(8-(2,2,6,6-tetramethylpiperidin-4-yl)-7,8-dihydro-6H-pyridazino[4,3-b][1,4]oxazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
469		6-(1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
471		6-(3-chloro-1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
472		6-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-2-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

No.	Chemical Structure	Name
473		(S)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
474		(R)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
475		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(8-(2,2,6,6-tetramethylpiperidin-4-yl)-7,8-dihydropyrido[2,3-c]pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
476		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(7-(2,2,6,6-tetramethylpiperidin-4-yl)-7H-pyrrolo[2,3-c]pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
479		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
481		6-(6-(((2S,4R,6R)-2,6-diethylpiperidin-4-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
482		3-(2,4-dimethylthiazol-5-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
483		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(ethyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
484		3-(1-((methylsulfonyl)methyl)-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
485		3-(2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
486		4-(1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
487		6-(6-(cyclopropyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
488		3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
489		3-(1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
491		3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
492		3-(3-chloro-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
493		3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
494		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(7-(2,2,6,6-tetramethylpiperidin-4-yl)-6,7-dihydro-5H-pyrrolo[2,3-c]pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
497		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
499		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
500		3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one

No.	Chemical Structure	Name
504		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
505		3-(3-chloro-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
506		3-(1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
507		3-(2,4-dimethylthiazol-5-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
508		3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
509		3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one

No.	Chemical Structure	Name
593		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
597		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
601		6-(6-(((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
605		(R)-3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
607		(S)-3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(((2,2,7,7-tetramethylazepan-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
608		3-(3-chloro-1-methyl-1H-pyrazol-4-yl)-6-(6-(((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
619		3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

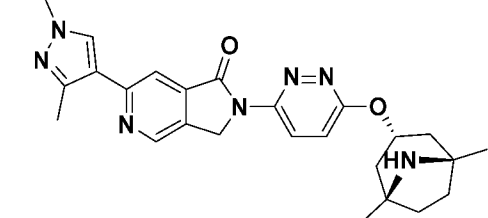
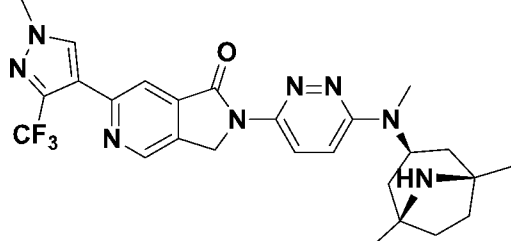
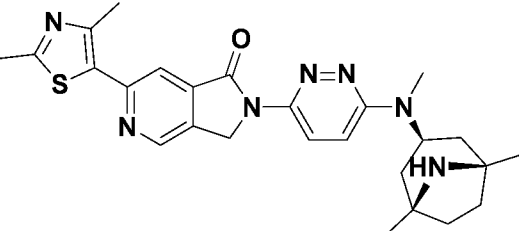
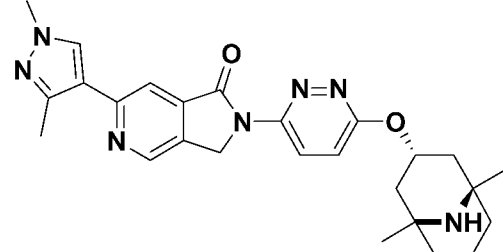
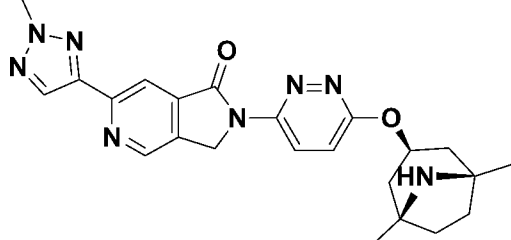
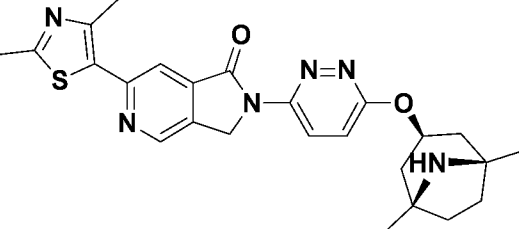
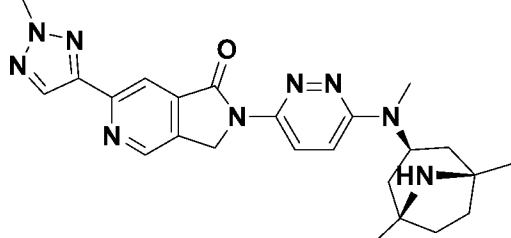
No.	Chemical Structure	Name
621		3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)(methylamino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
624		3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
626		3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)(methylamino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
628		3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
633		4-fluoro-6-(2-(2-hydroxy-2-methylpropyl)-2H-1,2,3-triazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one
635		4-fluoro-6-(2-(2-hydroxy-2-methylpropyl)-2H-1,2,3-triazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one

No.	Chemical Structure	Name
649		6-(3-chloro-1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-4-fluoro-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
664		4-chloro-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
677		4-chloro-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
678		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-1-oxoisindoline-4-carbonitrile
680		6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-1-oxo-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindoline-4-carbonitrile
682		6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-1-oxoisindoline-4-carbonitrile
683		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-methoxy-2-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)isoindolin-1-one

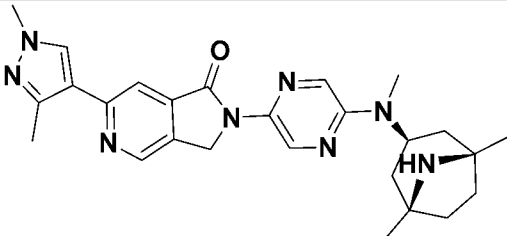
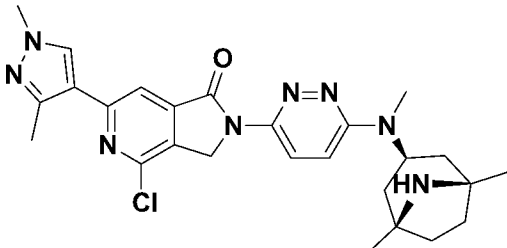
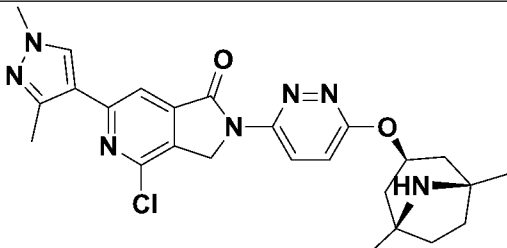
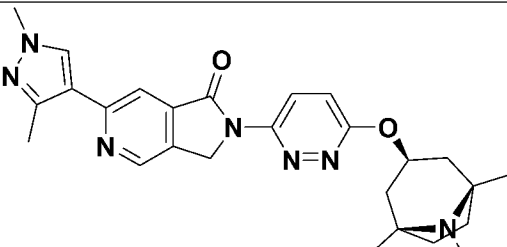
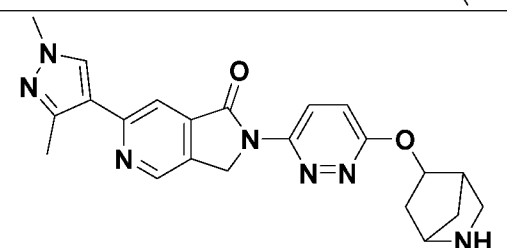
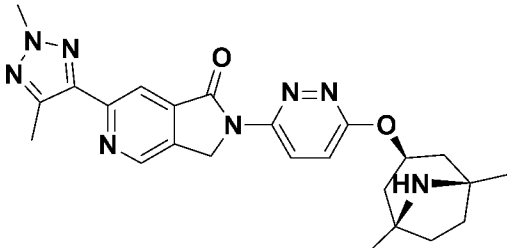
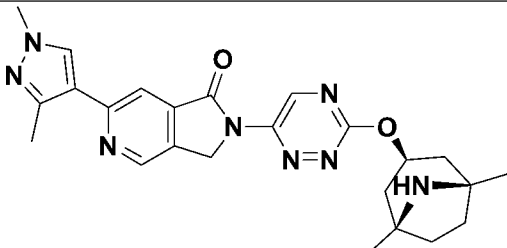
No.	Chemical Structure	Name
688		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-methoxy-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one
696		4-fluoro-5-((5-fluoropyridin-2-yl)methoxy)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one

Table 3B.

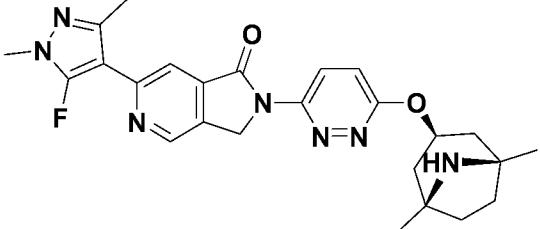
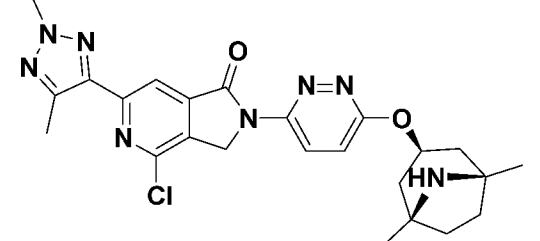
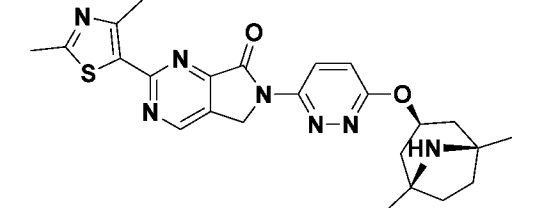
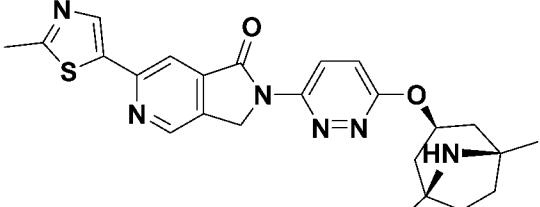
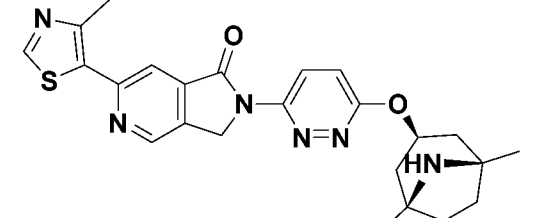
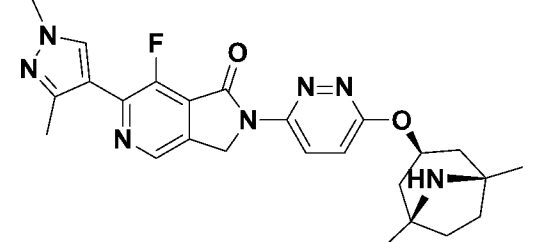
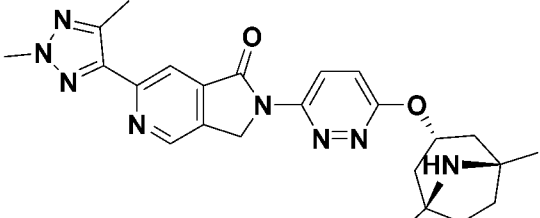
No.	Chemical Structure	Name
19		2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
20		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
27		2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(pyrimidin-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
42		2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-(methyl-d3)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
55		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

No.	Chemical Structure	Name
60		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
61		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
62		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
67		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3r,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
68		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
69		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
70		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

No.	Chemical Structure	Name
72		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
73		2-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
74		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
77		6-(1-(difluoromethyl)-3-methyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
79		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1S,2S,3R,5R)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
82		2-(6-(((1R,2S,3R,4S,5S)-2,4-difluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
85		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

No.	Chemical Structure	Name
89		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(5-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyrazin-2-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
90		4-chloro-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
93		4-chloro-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
94		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5,8-trimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
95		2-(6-((2-azabicyclo[2.2.1]heptan-5-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
96		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
97		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-1,2,4-triazin-6-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

No.	Chemical Structure	Name
98		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1S,3R,5R)-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
99		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
100		2-(6-(((1R,3s,5S)-1,5-diethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
102		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1,3,5-trimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
105		4-chloro-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
106		4-chloro-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
107		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

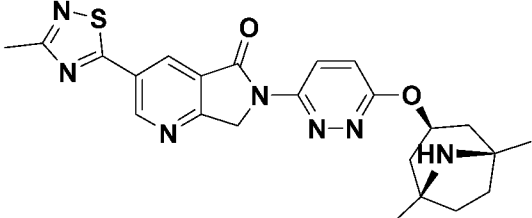
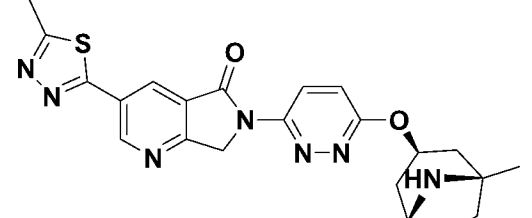
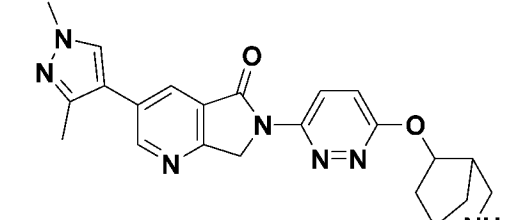
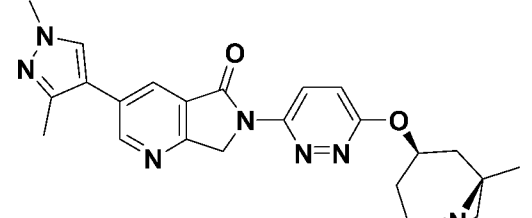
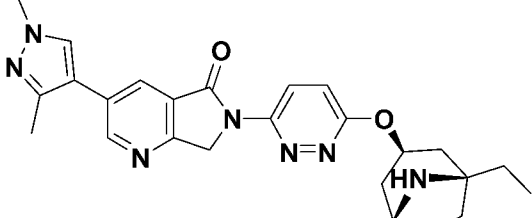
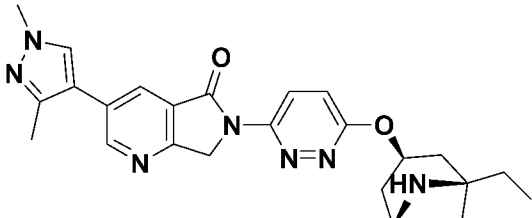
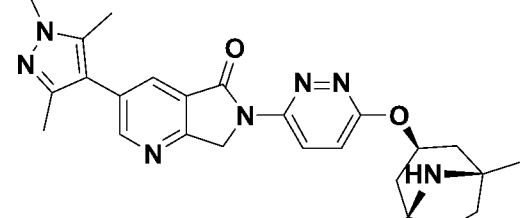
No.	Chemical Structure	Name
108		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(5-fluoro-1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
110		4-chloro-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
111		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2-(2,4-dimethylthiazol-5-yl)-5,6-dihydro-7H-pyrrolo[3,4-d]pyrimidin-7-one
112		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2-methylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
114		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(4-methylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
116		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-7-fluoro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
117		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

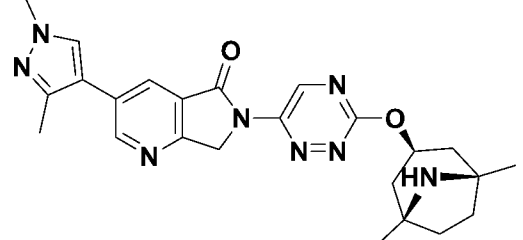
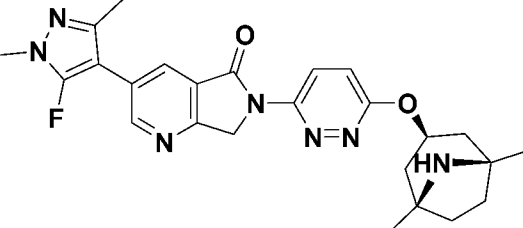
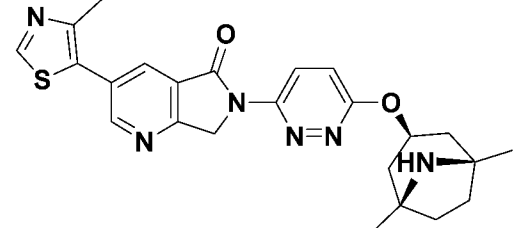
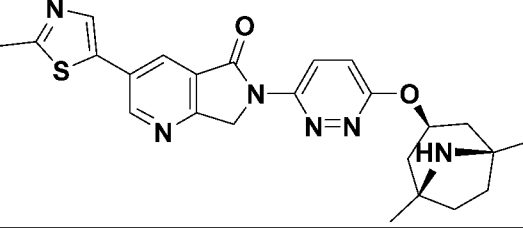
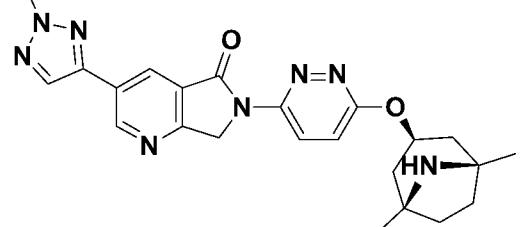
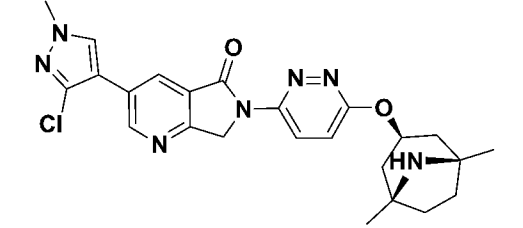
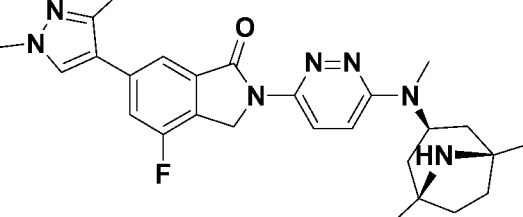
No.	Chemical Structure	Name
118		2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
164		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
166		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
169		3-(1-(difluoromethyl)-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
171		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
174		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
175		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

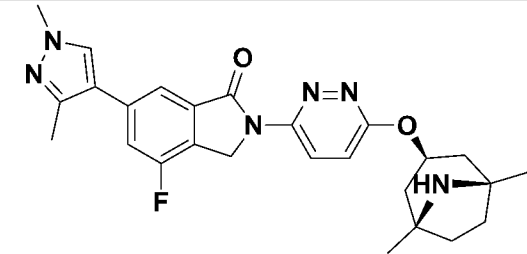
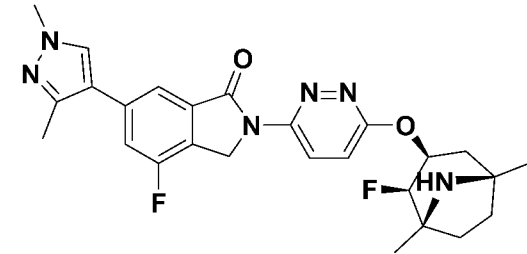
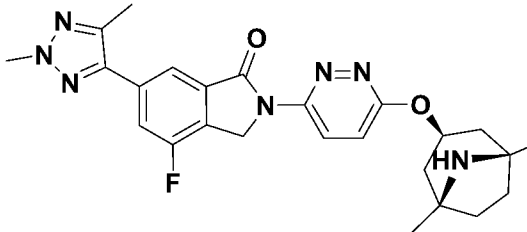
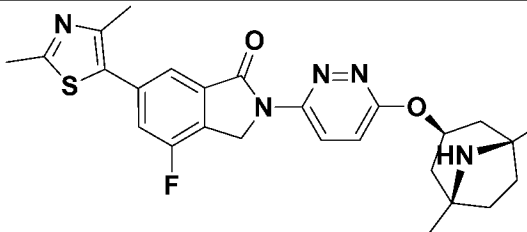
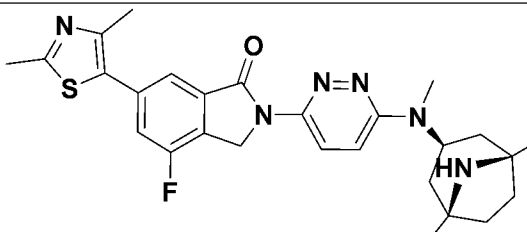
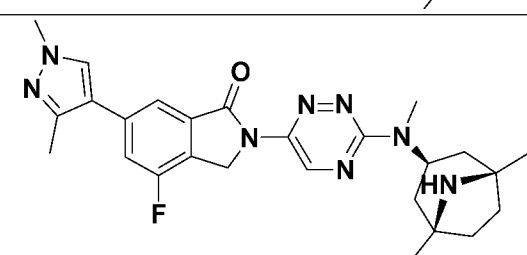
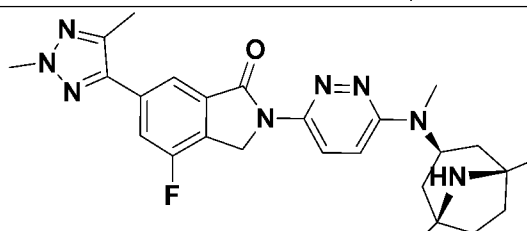
No.	Chemical Structure	Name
178		3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
181		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1S,2R,3S,5R)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
183		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
185		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3r,5S)-1,5-dimethyl-9-azabicyclo[3.3.1]nonan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
186		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
188		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
194		6-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
196		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)pyridazin-3-yl)-3-(2,5-dimethylthiazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
197		6-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2,5-dimethylthiazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
199		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
200		6-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methylamino)-1,2,4-triazin-6-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
201		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
202		6-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
206		3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
209		2-chloro-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
213		3-(1-(difluoromethyl)-3-methyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
214		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1S,2S,3R,5R)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
215		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1S,2R,3R,5R)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
217		6-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
219		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(3,5-dimethylisoxazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
220		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(pyridin-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

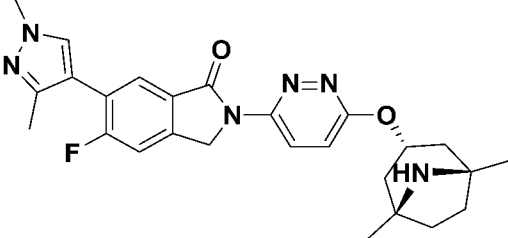
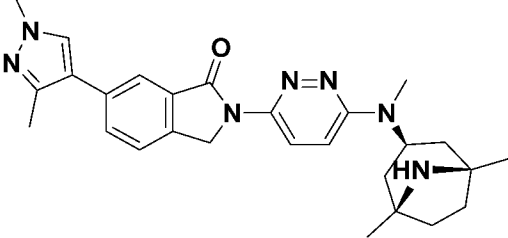
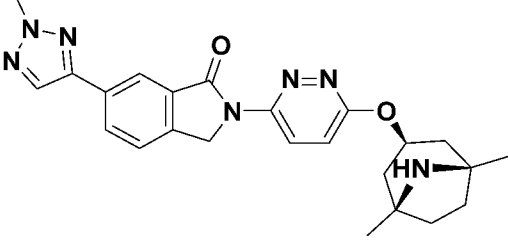
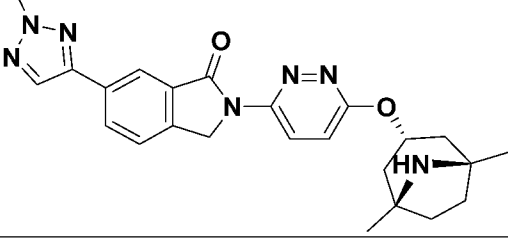
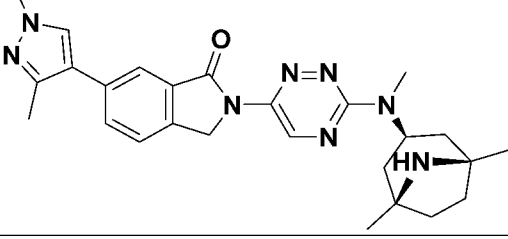
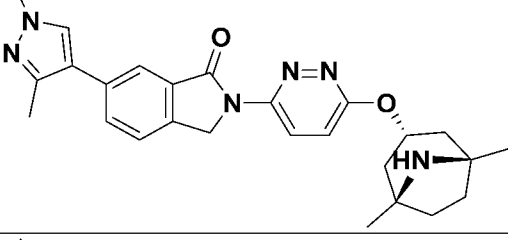
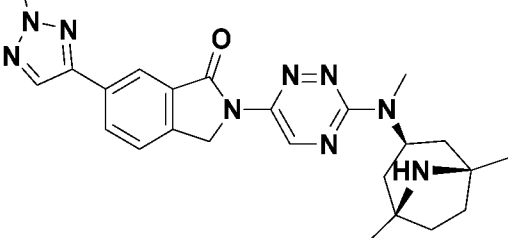
No.	Chemical Structure	Name
227		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(3-methyl-1,2,4-thiadiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
233		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(5-methyl-1,3,4-thiadiazol-2-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
236		6-(6-((2-azabicyclo[2.2.1]heptan-5-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
238		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5,8-trimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
239		6-(6-(((1R,3s,5S)-1,5-diethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
240		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1S,3R,5R)-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
242		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(1,3,5-trimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
244		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
246		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(5-fluoro-1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
248		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(4-methylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
250		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2-methylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
251		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
261		3-(3-chloro-1-methyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
274		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-fluoroisindolin-1-one

No.	Chemical Structure	Name
278		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-fluoroisindolin-1-one
281		6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-(((1R,2R,3S,5S)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isindolin-1-one
283		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-fluoroisindolin-1-one
286		2-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-4-fluoroisindolin-1-one
289		2-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-4-fluoroisindolin-1-one
291		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(3-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-4-fluoroisindolin-1-one
294		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoroisindolin-1-one

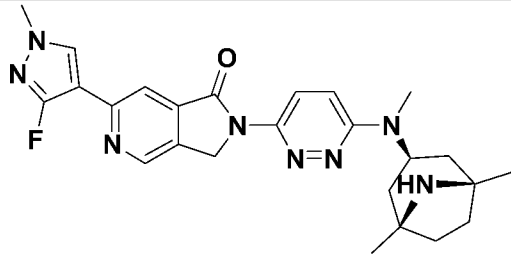
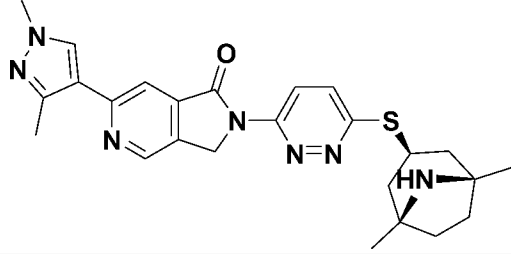
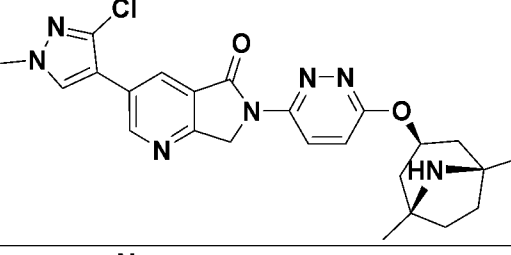
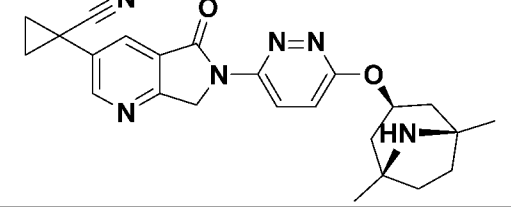
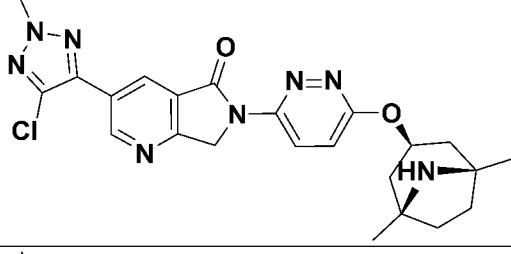
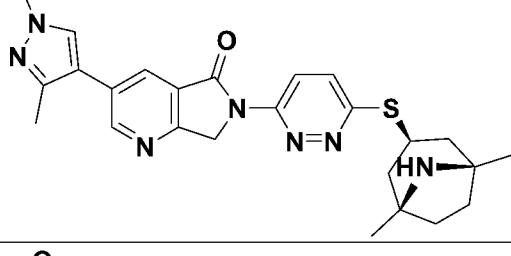
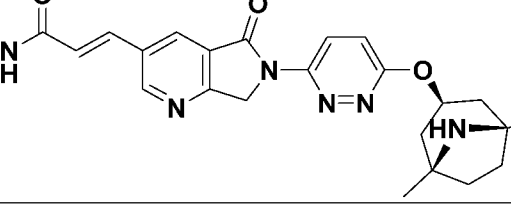
No.	Chemical Structure	Name
303		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-fluoro-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one
366		2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
367		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
376		2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)isoindolin-1-one
377		2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(pyrimidin-5-yl)isoindolin-1-one
386		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
387		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-(methyl-d3)-1H-pyrazol-4-yl)isoindolin-1-one

No.	Chemical Structure	Name
396		2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
397		2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-5-fluoro-6-(1-isopropyl-1H-pyrazol-4-yl)isoindolin-1-one
398		2-(6-(((1R,3s,5S)-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(1-cyclopropyl-1H-pyrazol-4-yl)-5-fluoroisoindolin-1-one
413		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-fluoroisoindolin-1-one
415		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)isoindolin-1-one
416		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoindolin-1-one
418		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
419		2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one

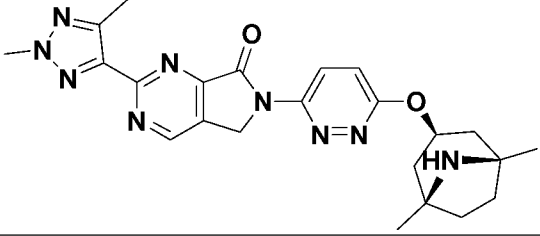
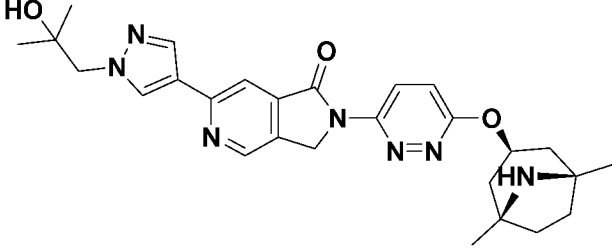
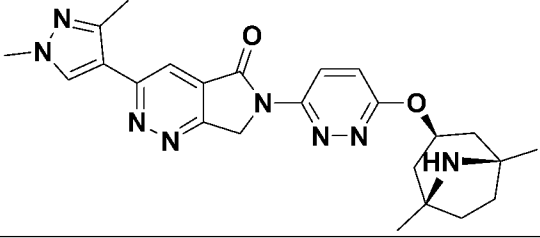
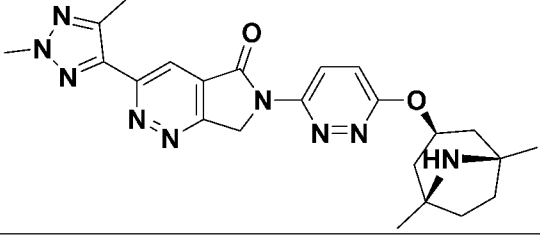
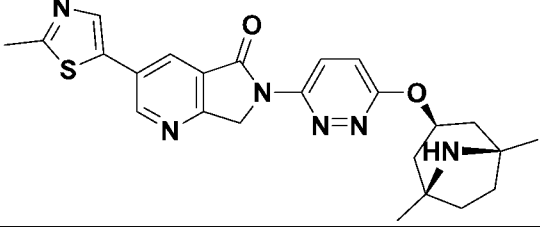
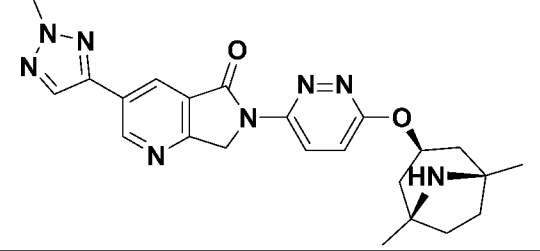
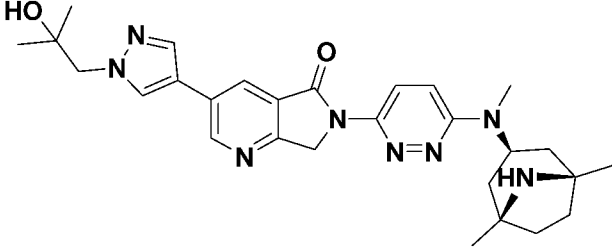
No.	Chemical Structure	Name
422		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-fluoroisoindolin-1-one
423		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)isoindolin-1-one
425		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one
426		2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one
427		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)isoindolin-1-one
428		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoindolin-1-one
429		2-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one

No.	Chemical Structure	Name
432		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)isoindolin-1-one
434		2-(6-(((1R,3r,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)isoindolin-1-one
436		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-methoxyisoindolin-1-one
437		2-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-6-(2,4-dimethylthiazol-5-yl)isoindolin-1-one
439		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoindolin-1-one
445		4-chloro-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)isoindolin-1-one
446		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-1-oxoisoindoline-4-carbonitrile

No.	Chemical Structure	Name
447		4-chloro-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoindolin-1-one
452		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
453		3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
454		1-(2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-1-oxo-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)cyclopropane-1-carbonitrile
456		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(3-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
458		6-(3-chloro-1-methyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
460		6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

No.	Chemical Structure	Name
467		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
470		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)thio)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
477		3-(3-chloro-1-methyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
478		1-(6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-3-yl)cyclopropane-1-carbonitrile
480		3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
490		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)thio)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
495		(E)-3-(6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-3-yl)-N-methylacrylamide

No.	Chemical Structure	Name
496		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
498		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
502		3-(3-chloro-1-methyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
503		3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
589		3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
590		3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
591		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(4-methyl-1H-1,2,3-triazol-1-yl)-1-oxoisindoline-4-carbonitrile

No.	Chemical Structure	Name
592		2-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-5,6-dihydro-7H-pyrrolo[3,4-d]pyrimidin-7-one
594		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
595		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-c]pyridazin-5-one
596		3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-c]pyridazin-5-one
598		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2-methylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
599		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
604		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
606		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)thio)pyridazin-3-yl)-3-(2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
609		3-(3-chloro-1-methyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
610		3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)thio)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
611		3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)thio)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
612		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-(2-methyl-2H-tetrazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
622		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
623		3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one

No.	Chemical Structure	Name
625		6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-3-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
627		3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
631		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-fluoro-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one
632		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoro-6-(1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl)isoindolin-1-one
634		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoro-6-(2-(2-hydroxy-2-methylpropyl)-2H-1,2,3-triazol-4-yl)isoindolin-1-one
660		4-chloro-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)isoindolin-1-one
661		4-chloro-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoindolin-1-one

No.	Chemical Structure	Name
673		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoro-6-(2H-1,2,3-triazol-2-yl)isoindolin-1-one
676		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-1-oxoisoindoline-4-carbonitrile
679		4-chloro-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)isoindolin-1-one
681		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-1-oxoisoindoline-4-carbonitrile
684		6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-methoxyisoindolin-1-one
685		6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-1-oxoisoindoline-4-carbonitrile
686		6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-methoxyisoindolin-1-one

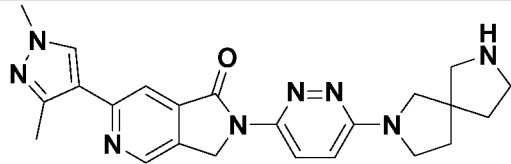
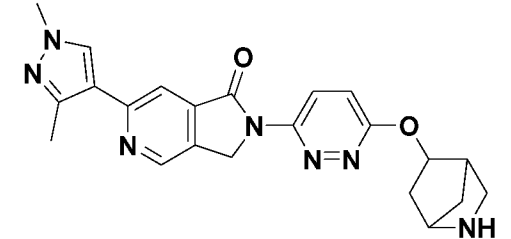
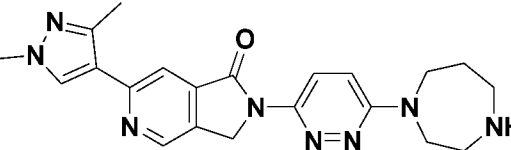
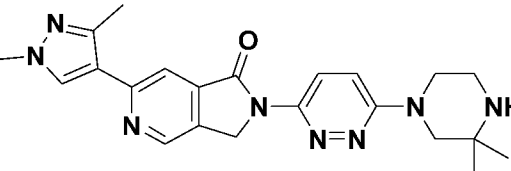
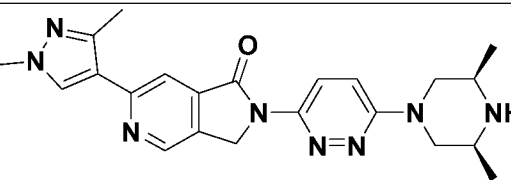
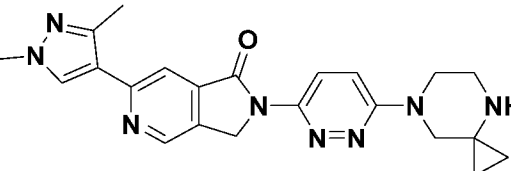
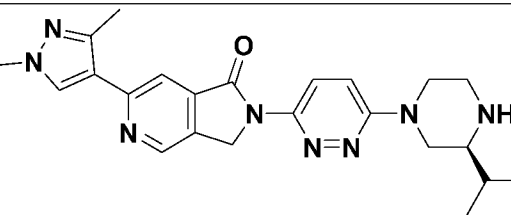
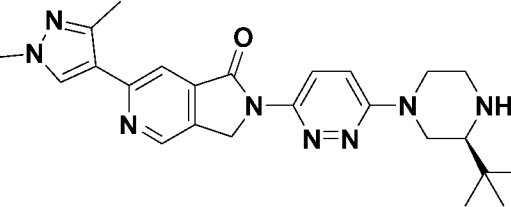
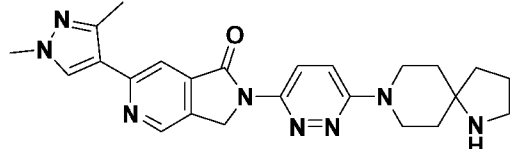
No.	Chemical Structure	Name
687		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-methoxyisoindolin-1-one
689		6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-hydroxyisoindolin-1-one
693		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(2-methyl-2H-tetrazol-5-yl)-1-oxoisindoline-4-carbonitrile
694		3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
695		2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6-(4-methyl-1H-1,2,3-triazol-1-yl)-1-oxoisindoline-4-carbonitrile

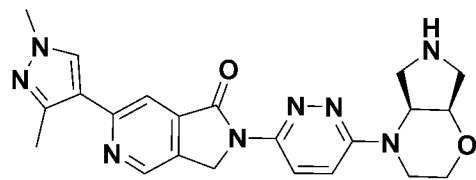
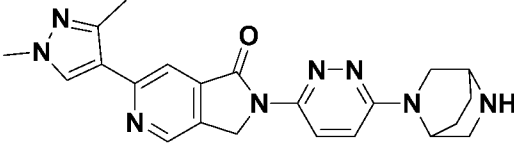
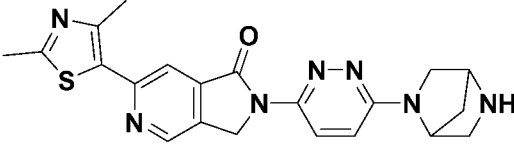
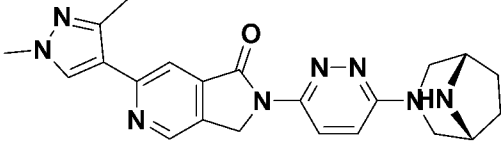
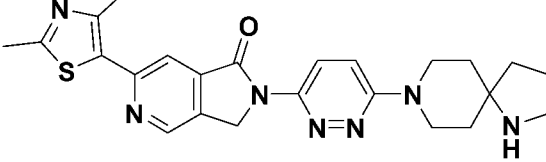
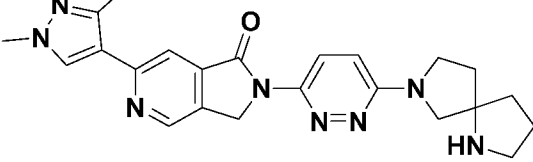
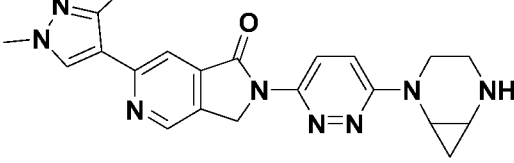
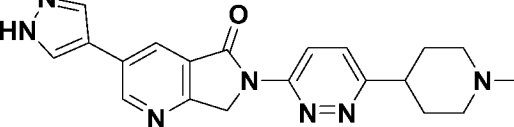
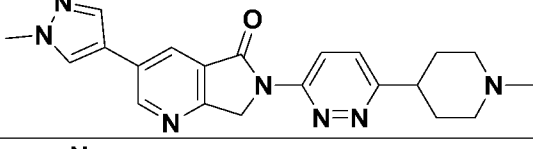
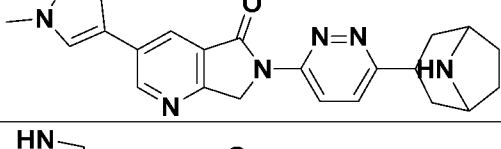
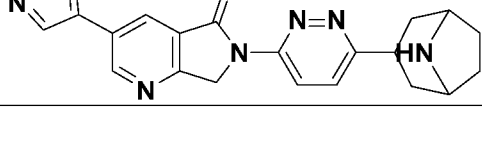
Table 3C

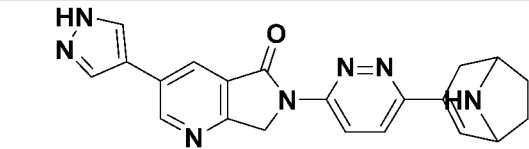
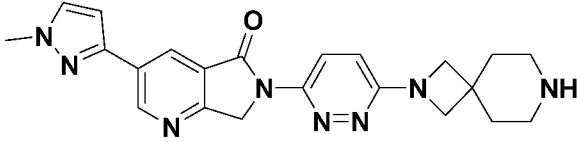
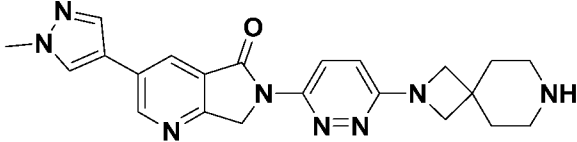
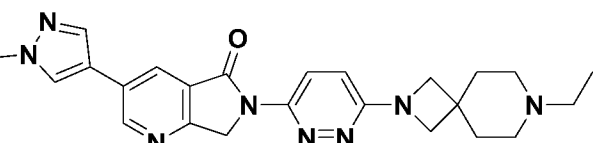
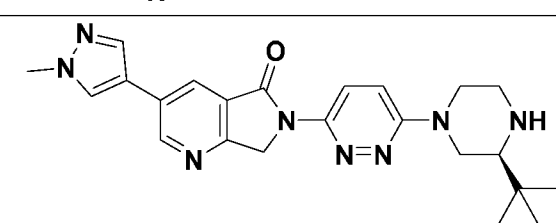
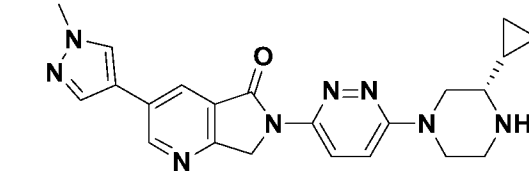
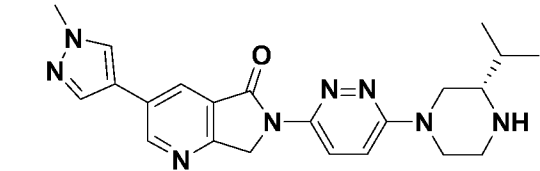
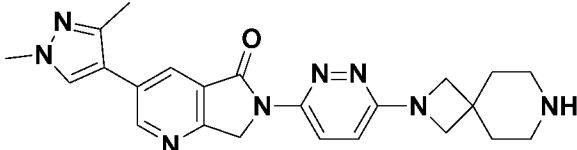
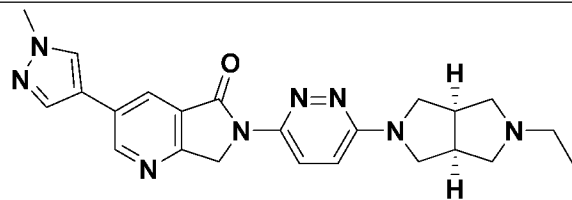
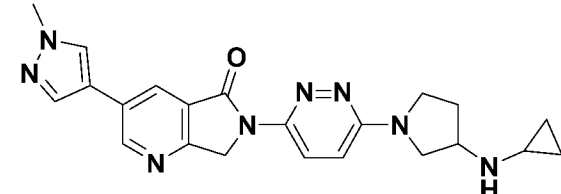
No.	Chemical Structure	Name
4		2-(6-(8-azabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
5		6-(1-methyl-1H-pyrazol-4-yl)-2-(6-(1-methylpiperidin-4-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
11		2-(6-(8-azabicyclo[3.2.1]oct-2-en-3-yl)pyridazin-3-yl)-6-(1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

No.	Chemical Structure	Name
12		2-(6-(1-methylpiperidin-4-yl)pyridazin-3-yl)-6-(1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
13		6-(2-methoxypyrimidin-4-yl)-2-(6-(1-methylpiperidin-4-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
14		2-(6-(8-azabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
16		2-(6-(8-azabicyclo[3.2.1]oct-2-en-3-yl)pyridazin-3-yl)-6-(2-methoxypyrimidin-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
22		2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
25		2-(6-(8-azabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(2-methoxypyrimidin-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
32		2-(6-(7-ethyl-2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
33		2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(pyrimidin-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
34		(S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
36		2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
37		2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(2-methyl-2H-indazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

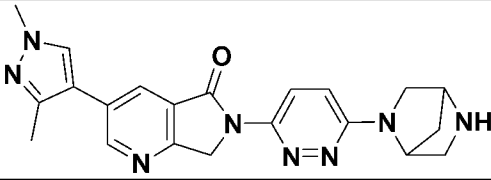
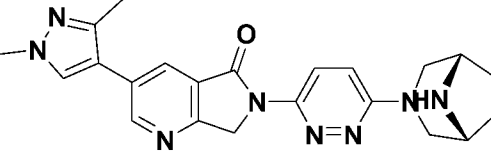
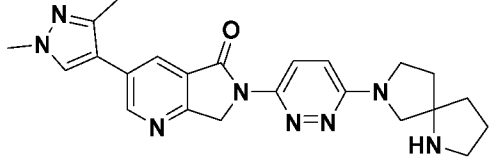
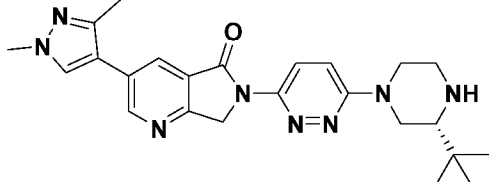
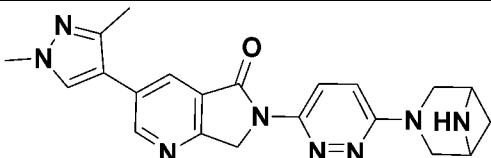
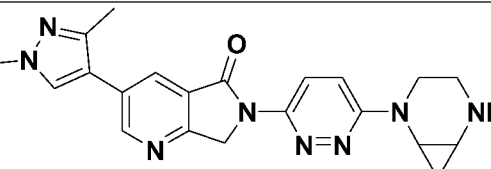
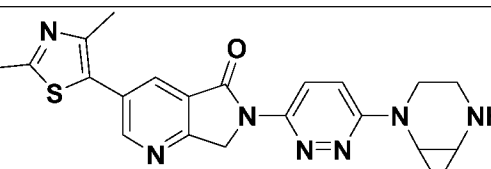
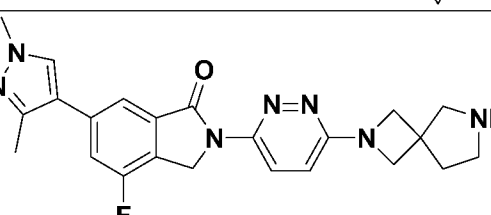
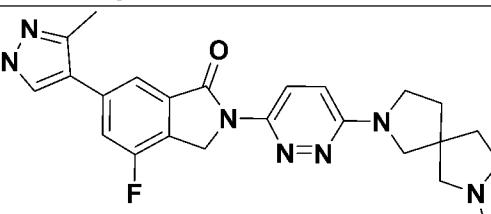
No.	Chemical Structure	Name
38		2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
39		(S)-2-(6-(3-cyclopropylpiperazin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
40		2-(6-((3aR,6aS)-5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
41		(S)-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
44		2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
45		(S)-2-(6-(3-isopropylpiperidin-1-yl)pyridazin-3-yl)-6-(1-(methyl-d3)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
46		2-(6-(3-(isopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
48		2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
50		2-(6-(7-ethyl-2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-(methyl-d3)-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
52		2-(6-(3-(cyclopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

No.	Chemical Structure	Name
53		2-(6-(2,7-diazaspiro[4.4]nonan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
95		2-(6-((2-azabicyclo[2.2.1]heptan-5-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
120		2-(6-(1,4-diazepan-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
121		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(3,3-dimethylpiperazin-1-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
122		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((3R,5S)-3,5-dimethylpiperazin-1-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
123		2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
124		(S)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
125		(S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
126		2-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

No.	Chemical Structure	Name
127		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-((4aS,7aR)-hexahydropyrrolo[3,4-b][1,4]oxazin-4(4aH)-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
128		2-(6-(2,5-diazabicyclo[2.2.2]octan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
129		2-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
130		2-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
131		2-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
132		2-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
133		2-(6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
136		6-(6-(1-methylpiperidin-4-yl)pyridazin-3-yl)-3-(1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
137		3-(1-methyl-1H-pyrazol-4-yl)-6-(6-(1-methylpiperidin-4-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
145		6-(6-(8-azabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
146		6-(6-(8-azabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-3-(1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
147		6-(6-(8-azabicyclo[3.2.1]oct-2-en-3-yl)pyridazin-3-yl)-3-(1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
151		6-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
152		6-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
153		6-(6-(7-ethyl-2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
154		(S)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
155		(S)-6-(6-(3-cyclopropylpiperazin-1-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
157		(S)-6-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
158		6-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
159		6-(6-((3aR,6aS)-5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
165		6-(6-(3-(cyclopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
170		6-(6-(2,7-diazaspiro[4.4]nonan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
252		(S)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
254		(S)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
255		3-(2,4-dimethylthiazol-5-yl)-6-(6-(2-oxopiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
256		(S)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
257		6-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
258		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((4aS,7aR)-hexahydropyrrolo[3,4-b][1,4]oxazin-4(4aH)-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
259		6-(6-(2,5-diazabicyclo[2.2.2]octan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
260		6-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
263		6-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

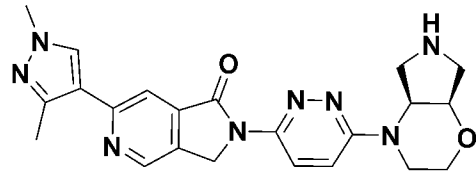
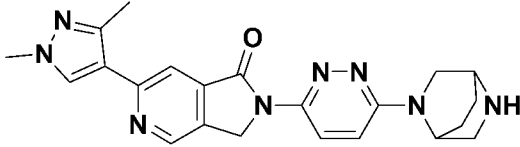
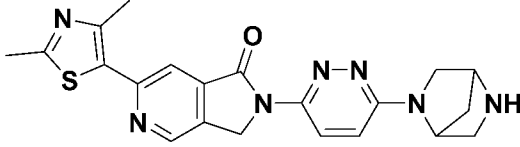
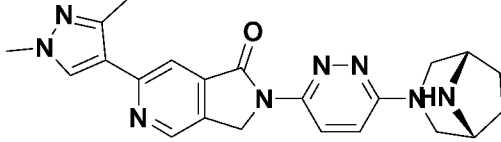
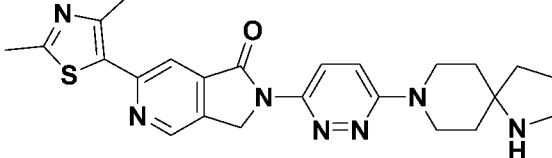
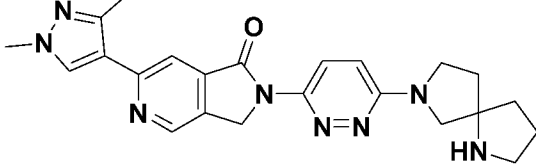
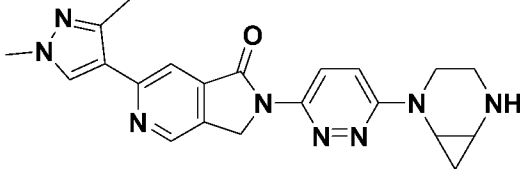
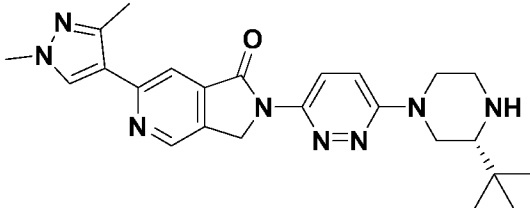
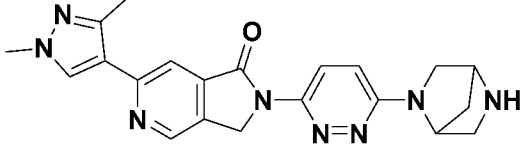
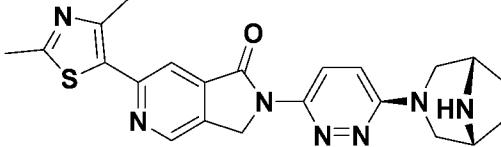
No.	Chemical Structure	Name
264		6-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
265		6-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
266		6-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
267		(R)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
268		6-(6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
270		6-(6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
271		6-(6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
272		2-(6-(2,6-diazaspiro[3.4]octan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one
273		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(7-ethyl-2,7-diazaspiro[4.4]nonan-2-yl)pyridazin-3-yl)-4-fluoroisindolin-1-one

No.	Chemical Structure	Name
295		(S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisoindolin-1-one
296		(S)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)isoindolin-1-one
297		2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisoindolin-1-one
298		(S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one
299		(S)-6-(2,4-dimethylthiazol-5-yl)-4-fluoro-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)isoindolin-1-one
300		2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-4-fluoroisoindolin-1-one
301		(S)-4-fluoro-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one
302		(S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-4-fluoro-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one
304		6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-(2-oxopiperazin-1-yl)pyridazin-3-yl)isoindolin-1-one

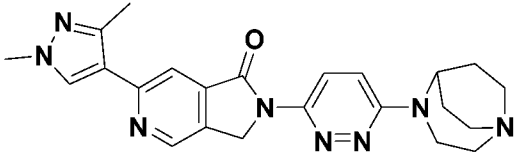
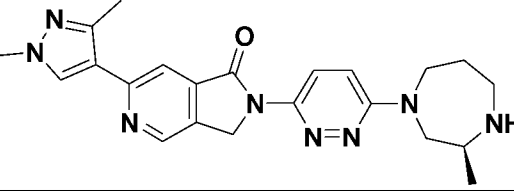
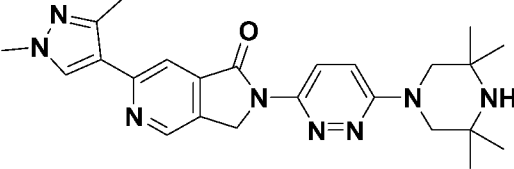
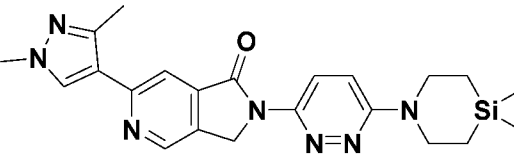
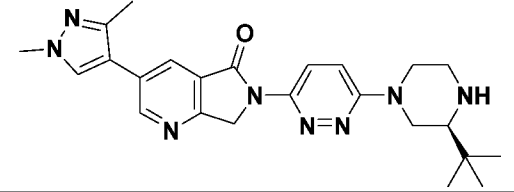
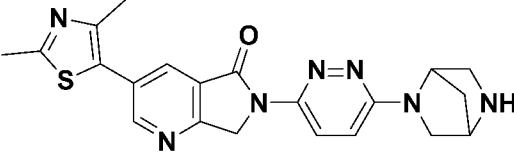
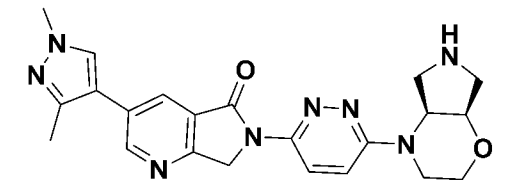
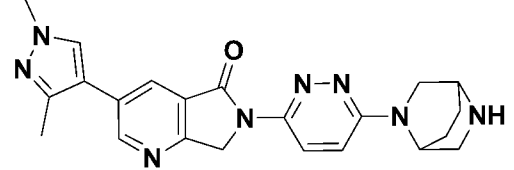
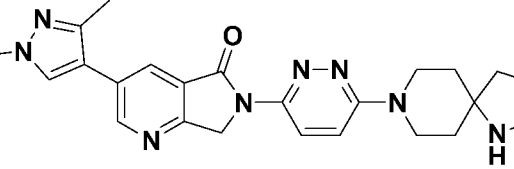
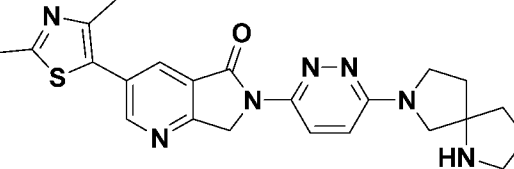
No.	Chemical Structure	Name
305		6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-((4aS,7aR)-hexahydropyrrolo[3,4-b][1,4]oxazin-4(4aH)-yl)pyridazin-3-yl)isoindolin-1-one
306		2-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisoindolin-1-one
344		6-(2-methoxypyrimidin-4-yl)-2-(6-(1-methylpiperidin-4-yl)pyridazin-3-yl)isoindolin-1-one
345		2-(6-(8-azabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(2-methoxypyrimidin-4-yl)isoindolin-1-one
361		2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
374		2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-3-yl)isoindolin-1-one
379		(S)-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
380		2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
384		2-(6-(1-methylpiperidin-4-yl)pyridazin-3-yl)-6-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)isoindolin-1-one
388		2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(pyrimidin-5-yl)isoindolin-1-one

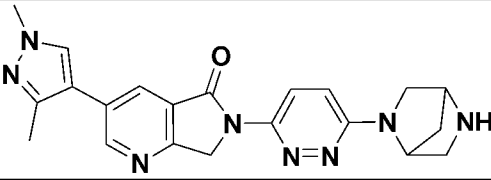
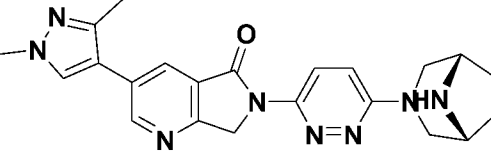
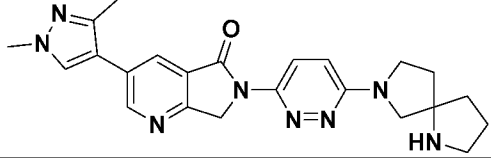
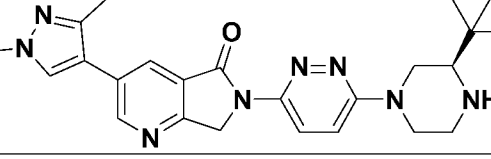
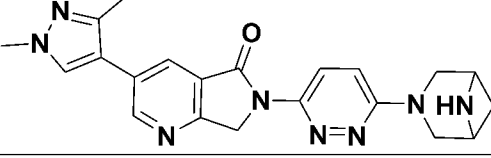
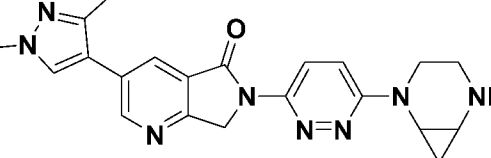
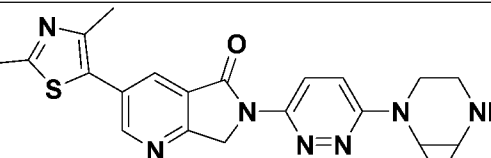
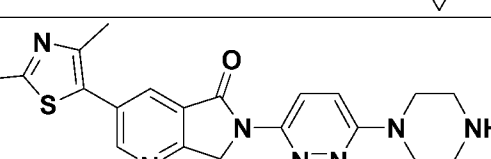
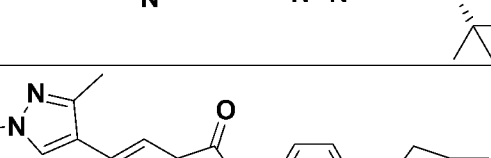
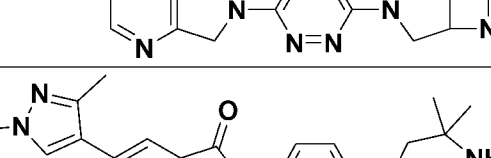
No.	Chemical Structure	Name
389		2-(6-(7-ethyl-2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-isopropyl-1H-pyrazol-4-yl)isoindolin-1-one
390		6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(6-(7-ethyl-2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)isoindolin-1-one
391		2-(6-((3aR,6aS)-5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
394		2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-5-fluoro-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
395		2-(6-(3-(isopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
399		(S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
400		2-(6-(7-ethyl-2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
401		6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(6-((3aR,6aS)-5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)isoindolin-1-one
402		2-(6-((3aR,6aS)-5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-6-(1-isopropyl-1H-pyrazol-4-yl)isoindolin-1-one
404		2-(6-(3-(tert-butylamino)pyrrolidin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one

No.	Chemical Structure	Name
405		6-(1-cyclopropyl-1H-pyrazol-4-yl)-2-(6-(3-(isopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)isoindolin-1-one
407		(S)-2-(6-(3-cyclopropylpiperazin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
408		2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoroisoindolin-1-one
409		6-(1-isopropyl-1H-pyrazol-4-yl)-2-(6-(3-(isopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)isoindolin-1-one
412		2-(6-(3-(cyclopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)-6-(1-methyl-1H-pyrazol-4-yl)isoindolin-1-one
414		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(7-ethyl-2,7-diazaspiro[4.4]nonan-2-yl)pyridazin-3-yl)-5-fluoroisoindolin-1-one
501		6-(6-(azetidin-3-ylmethoxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
510		(S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
511		2-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

No.	Chemical Structure	Name
512		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((4aS,7aR)-hexahydropyrrolo[3,4-b][1,4]oxazin-4(4aH)-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
513		2-(6-(2,5-diazabicyclo[2.2.2]octan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
514		2-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
515		2-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
516		2-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
517		2-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
518		2-(6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridine-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1-one
519		(R)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
520		2-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
521		2-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

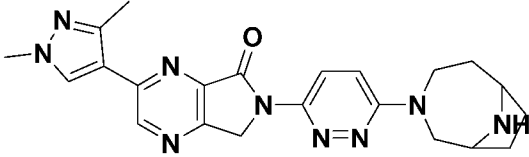
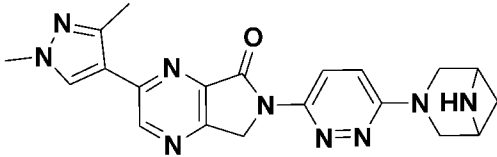
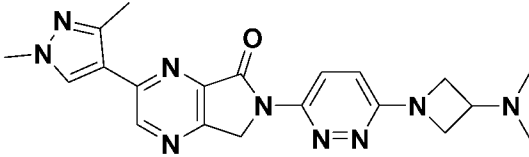
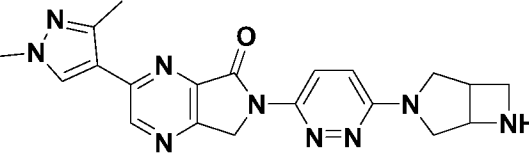
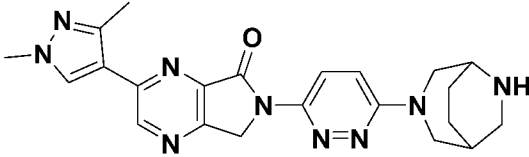
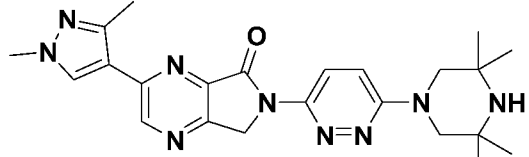
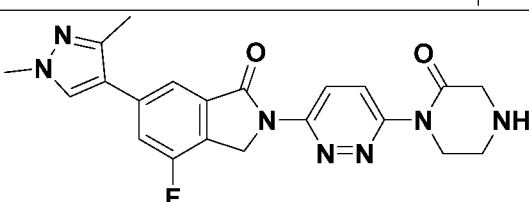
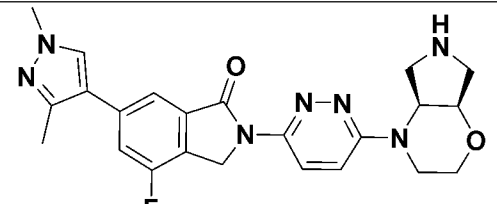
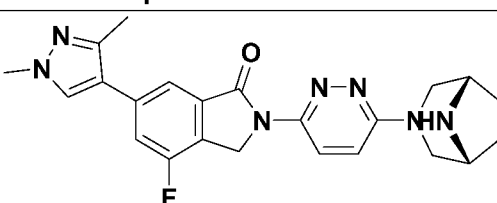
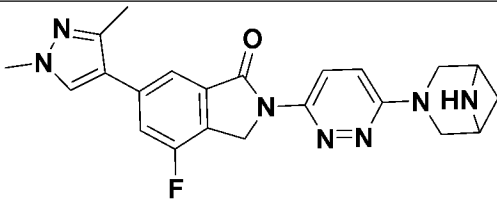
No.	Chemical Structure	Name
522		2-(6-(3,6-diazabicyclo[3.2.2]nonan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
523		2-(6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
524		2-(6-(3,6-diazabicyclo[3.2.0]heptan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
525		2-(6-(3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one Chemical Formula: C ₂₃ H ₂₆ N ₈ O Molecular Weight: 430.5160
526		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(3,3,5,5-tetramethyl-1,4-diazepan-1-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
527		2-(6-(4-amino-4-methylpiperidin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
528		2-(6-(3-(2-aminopropan-2-yl)pyrrolidin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
529		2-(6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
530		2-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
531		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(3-(dimethylamino)azetidin-1-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one

No.	Chemical Structure	Name
532		2-(6-(1,4-diazabicyclo[3.2.2]nonan-4-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
533		(S)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(3-methyl-1,4-diazepan-1-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
534		6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(3,3,5,5-tetramethylpiperazin-1-yl)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
535		2-(6-(4,4-dimethyl-1,4-azasilinan-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one
536		(S)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
537		6-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
538		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((4aS,7aR)-hexahydropyrrolo[3,4-b][1,4]oxazin-4(4aH)-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
539		6-(6-(2,5-diazabicyclo[2.2.2]octan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
540		6-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
541		6-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
542		6-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
543		6-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
544		6-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
545		(R)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
546		6-(6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
547		6-(6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
548		6-(6-(2,5-diazabicyclo[4.1.0]heptan-2-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
549		(R)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
550		6-(6-(3,6-diazabicyclo[3.2.0]heptan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
551		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3,3,5,5-tetramethyl-1,4-diazepan-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
552		3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(3-(dimethylamino)azetidin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
553		6-(6-(3,6-diazabicyclo[3.2.2]nonan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
554		6-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
555		6-(6-(3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
556		6-(6-(3-(2-aminopropan-2-yl)pyrrolidin-1-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
557		6-(6-(4-amino-4-methylpiperidin-1-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
558		6-(6-(1,4-diazabicyclo[3.2.2]nonan-4-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
559		6-(6-(3,6-diazabicyclo[3.2.0]heptan-3-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
560		6-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
561		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3-(dimethylamino)azetidin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
562		6-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-3-(2,4-dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
563		6-(6-(2,5-diazabicyclo[2.2.2]octan-2-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
564		3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-((4aR,7aS)-hexahydropyrrolo[3,4-b][1,4]oxazin-4(4aH)-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
565		6-(6-(3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one Chemical Formula: C ₂₂ H ₂₅ N ₉ O Molecular Weight: 431.5040
566		6-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
567		(S)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3-methyl-1,4-diazepan-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
568		6-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
569		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3,3,5,5-tetramethylpiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
570		6-(6-(4,4-dimethyl-1,4-azasilinan-1-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
571		6-(6-(3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
572		6-(6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
573		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3-(dimethylamino)azetidin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
574		6-(6-(3,6-diazabicyclo[3.2.0]heptan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
575		6-(6-(3,6-diazabicyclo[3.2.2]nonan-3-yl)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
576		3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3,3,5,5-tetramethylpiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one
577		6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-(2-oxopiperazin-1-yl)pyridazin-3-yl)isoindolin-1-one
578		6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-((4aS,7aR)-hexahydropyrrolo[3,4-b][1,4]oxazin-4(4aH)-yl)pyridazin-3-yl)isoindolin-1-one
579		2-(6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisoindolin-1-one
580		2-(6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisoindolin-1-one

No.	Chemical Structure	Name
581		2-(6-(3-(2-aminopropan-2-yl)pyrrolidin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one
582		2-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one
583		2-(6-(2,5-diazabicyclo[2.2.1]heptan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one
584		2-(6-(3,6-diazabicyclo[3.2.0]heptan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one
585		2-(6-(1,7-diazaspiro[4.4]nonan-7-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one
586		2-(6-(3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one
587		2-(6-(2,5-diazabicyclo[2.2.2]octan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one
588		(S)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoro-2-(6-(3-methyl-1,4-diazepan-1-yl)pyridazin-3-yl)isindolin-1-one
600		(S)-6-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
602		(S)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
603		6-(6-(1,8-diazaspiro[4.5]decan-8-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
613		3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-((2S,5R)-2,5-dimethylpiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
614		3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-((2S,5R)-2,5-dimethylpiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
615		(S)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
616		(R)-6-(6-(3-(tert-butylamino)piperidin-1-yl)pyridazin-3-yl)-3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
617		(R)-6-(6-(3-(tert-butylamino)piperidin-1-yl)pyridazin-3-yl)-3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
618		3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(4-(dimethylamino)piperidin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one
620		(S)-3-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-6-(6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one

No.	Chemical Structure	Name
629		(S)-4-fluoro-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one
630		(S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-4-fluoro-6-(2-methyl-2H-1,2,3-triazol-4-yl)isoindolin-1-one
636		6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-((3S,5R)-3,5-dimethylpiperazin-1-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one
637		(S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one
638		(R)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)isoindolin-1-one
639		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(5-methyl-1,4-diazepan-1-yl)pyridazin-3-yl)isoindolin-1-one
640		(R)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)isoindolin-1-one
641		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-((3S,5R)-3,5-dimethylpiperazin-1-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one
642		6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(3,3-dimethylpiperazin-1-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one

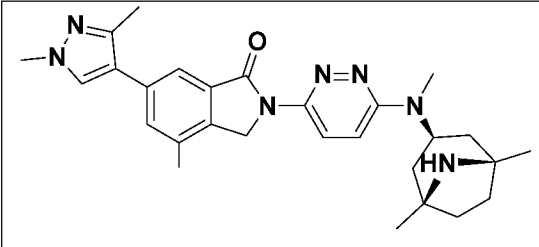
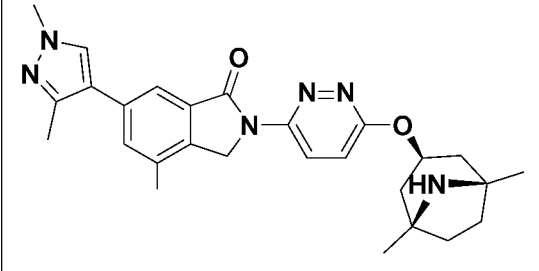
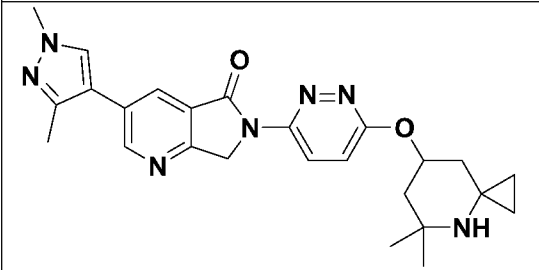
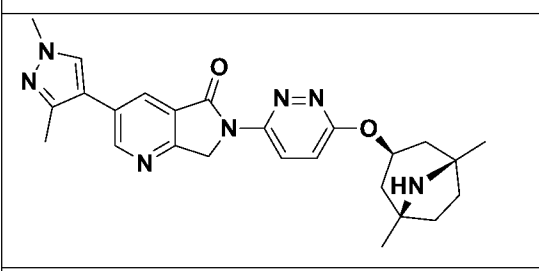
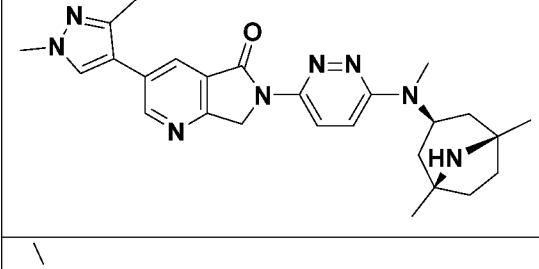
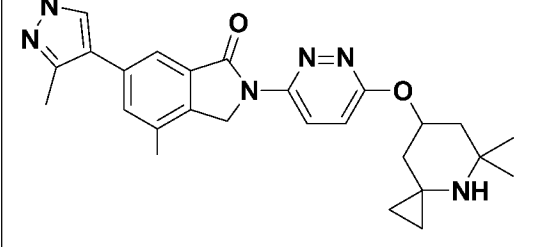
No.	Chemical Structure	Name
643		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(3,3-dimethylpiperazin-1-yl)pyridazin-3-yl)-4-fluoroisindolin-1-one
644		2-(6-(2,6-diazaspiro[3.4]octan-2-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisindolin-1-one
645		2-(6-(2,5-diazabicyclo[2.2.2]octan-2-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisindolin-1-one
646		2-(6-(2,7-diazaspiro[4.4]nonan-2-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisindolin-1-one
647		6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(3-(dimethylamino)azetidin-1-yl)pyridazin-3-yl)-4-fluoroisindolin-1-one
648		(R)-2-(6-(3-(tert-butylamino)pyrrolidin-1-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisindolin-1-one
650		2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisindolin-1-one
651		2-(6-(3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisindolin-1-one
652		6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(3-(cyclopropylamino)pyrrolidin-1-yl)pyridazin-3-yl)-4-fluoroisindolin-1-one

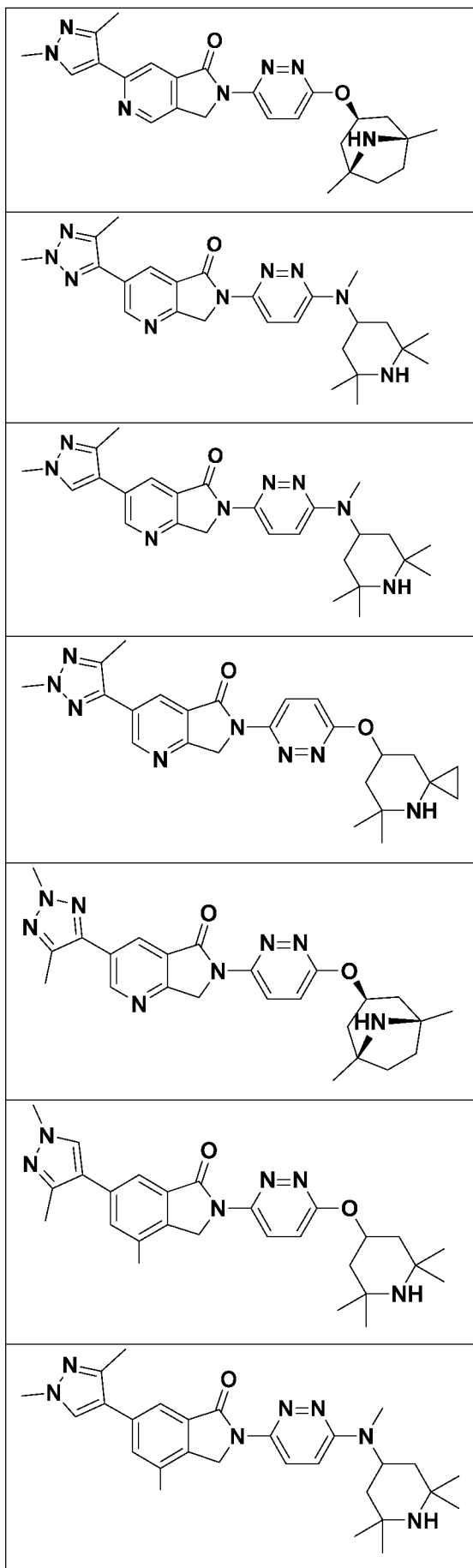
No.	Chemical Structure	Name
653		2-(6-(3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one
654		6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one
655		2-(6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one
656		(R)-2-(6-(3-(tert-butylamino)pyrrolidin-1-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one
657		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(3,3,5,5-tetramethyl-1,4-diazepan-1-yl)pyridazin-3-yl)isoindolin-1-one
658		2-(6-(3,8-diazabicyclo[3.2.1]octan-3-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one
659		2-(6-(3,9-diazabicyclo[4.2.1]nonan-3-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one
662		2-(6-(3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one
663		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(5-ethylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one

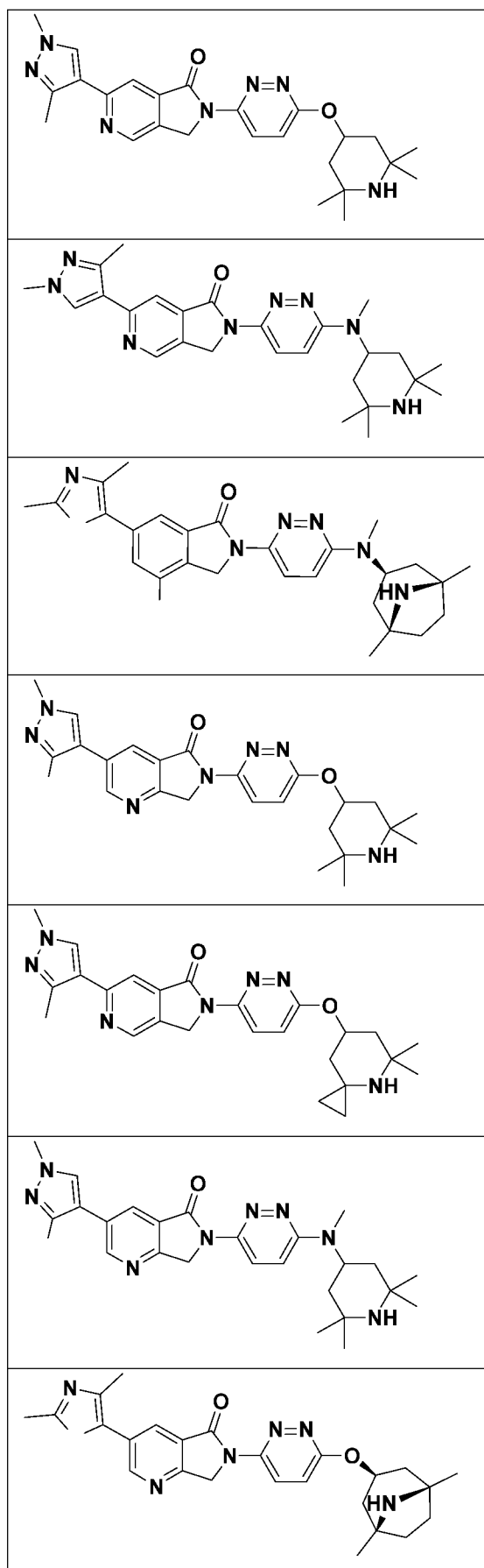
No.	Chemical Structure	Name
665		(S)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyridazin-3-yl)isoindolin-1-one
666		2-(6-(2,6-diazaspiro[3.3]heptan-2-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one
667		6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-2-(6-(4-(dimethylamino)piperidin-1-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one
668		6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(5-methyl-1,4-diazepan-1-yl)pyridazin-3-yl)isoindolin-1-one
669		2-(6-(1,4-diazepan-1-yl)pyridazin-3-yl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one
670		2-(6-(2,6-diazaspiro[3.3]heptan-2-yl)pyridazin-3-yl)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one
671		(S)-6-(5-chloro-2-methyl-2H-1,2,3-triazol-4-yl)-4-fluoro-2-(6-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)pyridazin-3-yl)isoindolin-1-one
672		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(4-(dimethylamino)piperidin-1-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one
674		6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-((2S,5R)-2,5-dimethylpiperazin-1-yl)pyridazin-3-yl)-4-fluoroisoindolin-1-one

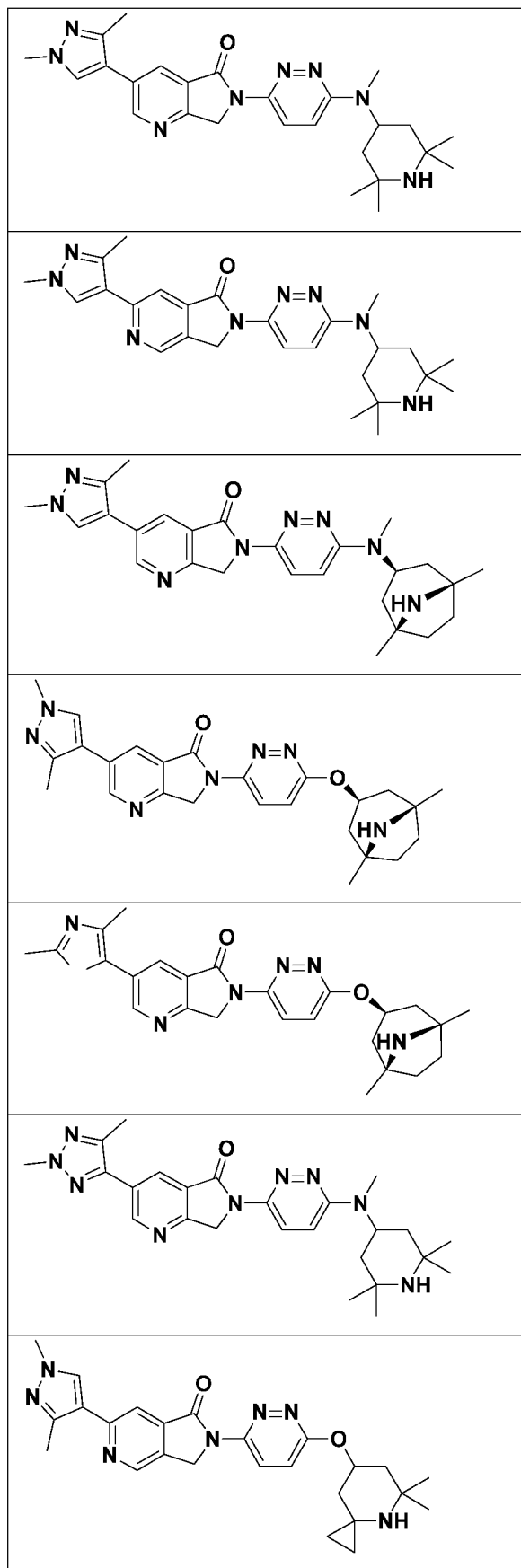
[0203] In some embodiments the compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, is one of the compounds **Table 4**. In some embodiments the compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, is one of the compounds in **Table 5**.

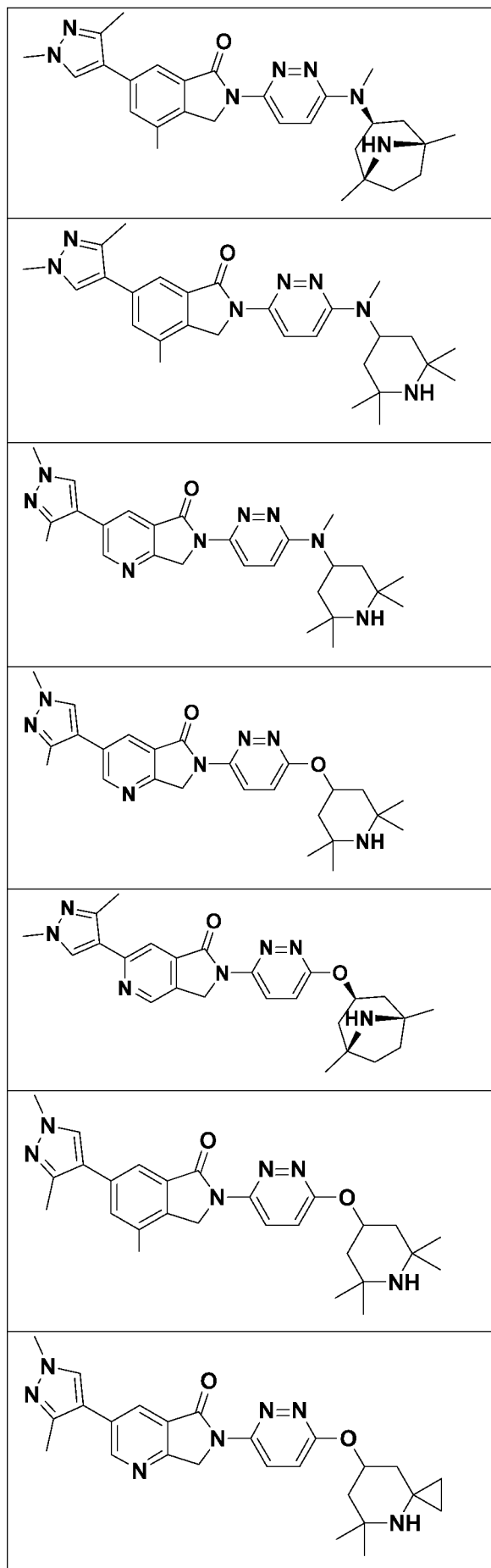
Table 4. Exemplary agents that modulate splicing of MSH3 mRNA

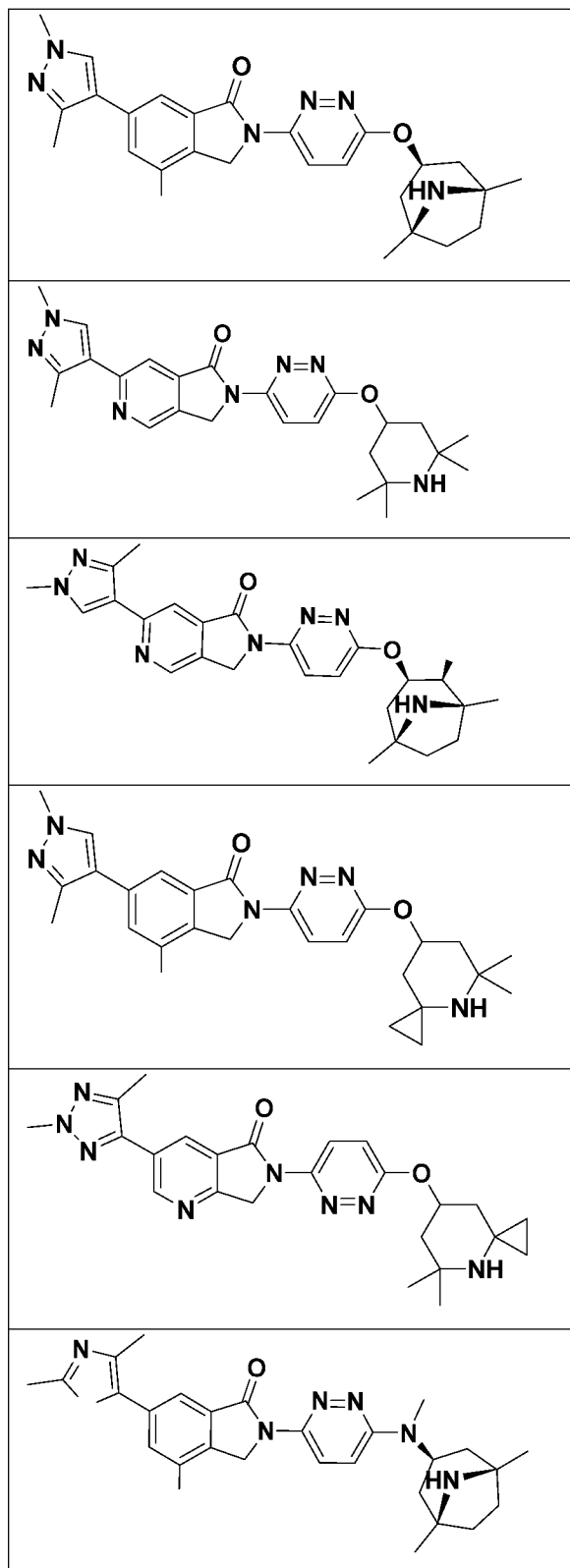









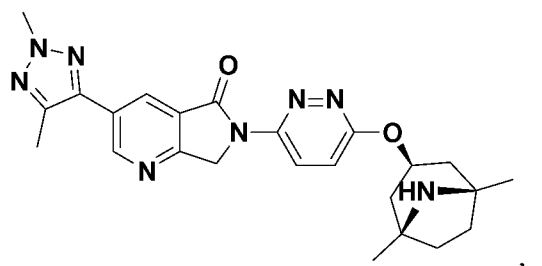
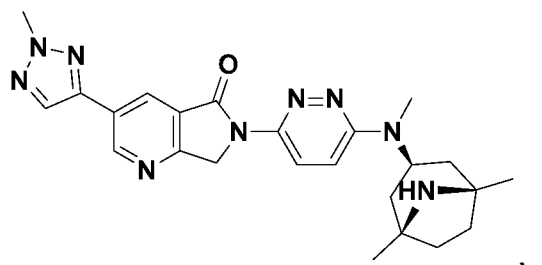
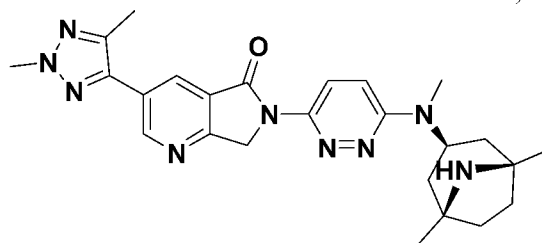
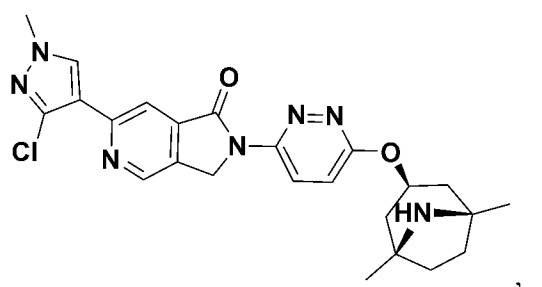
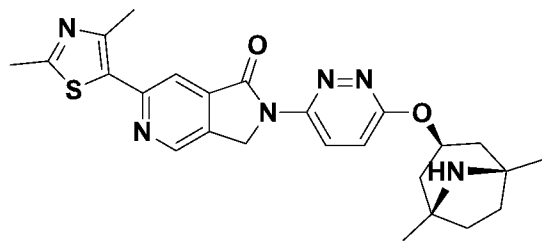
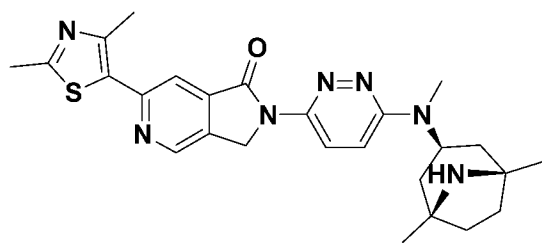
**Table 5. Exemplary agents that modulate splicing of MSH3 and HTT mRNA**

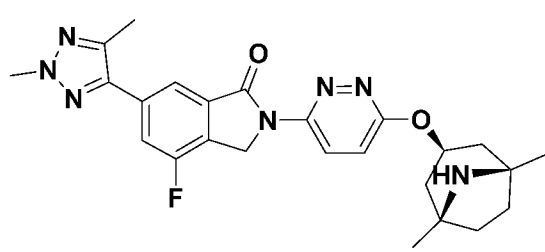
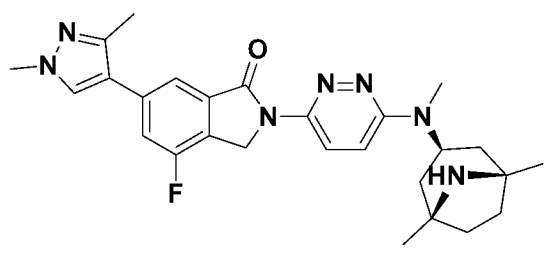
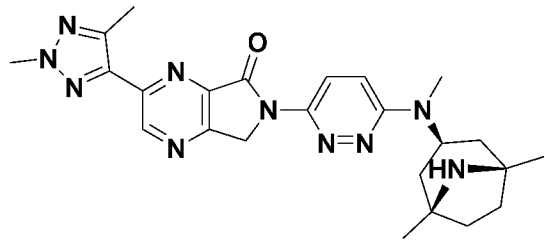
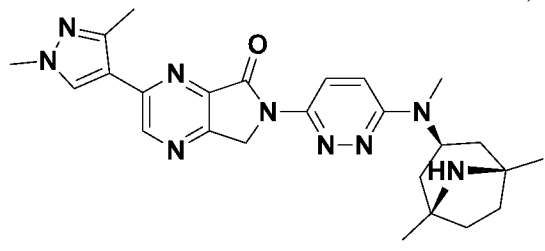
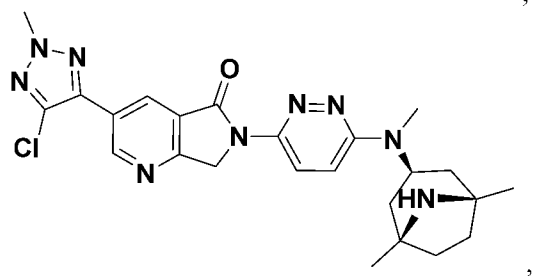
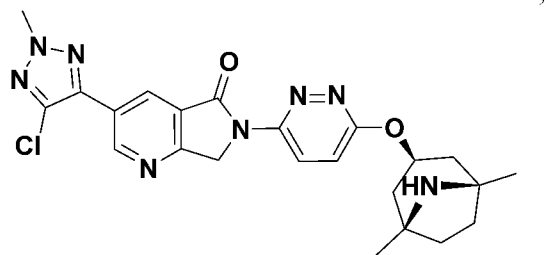
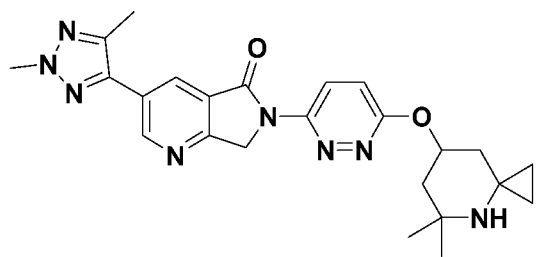


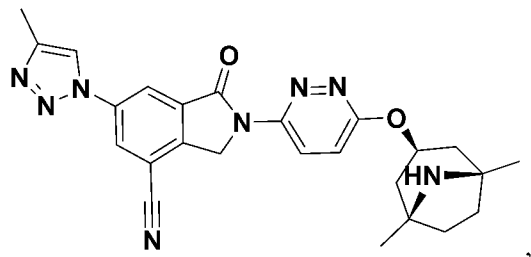
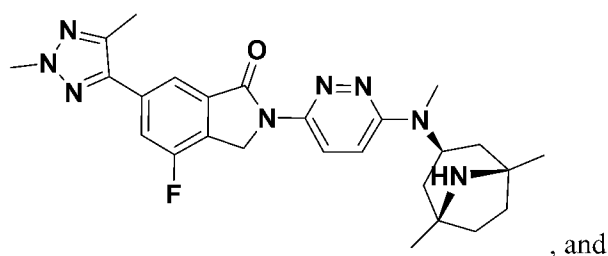




[0204] In some embodiments, the agent is a compound selected from the group consisting of:







or a pharmaceutically acceptable salt or solvate thereof.

[0205] In some embodiments, the agent is a compound that modulates splicing of the MSH3 pre-mRNA such that a poison exon is spliced into the MSH3 mRNA transcript. In some cases, the agent that modulates splicing of the MSH3 pre-mRNA such that a poison exon is spliced into the MSH3 mRNA transcript is selected from any compound from **Table 3A**, **Table 3B**, or **Table 3C**. In some cases, the agent that modulates splicing of the MSH3 pre-mRNA such that a poison exon is spliced into the MSH3 mRNA transcript is selected from any compound from **Table 4**. In some cases, the agent that modulates splicing of the MSH3 pre-mRNA such that a poison exon is spliced into the MSH3 mRNA transcript is selected from any compound from **Table 5**.

[0206] In some cases, the agent is an agent that modulates splicing of the MSH3 pre-mRNA as described herein and does not modulate splicing of other genes. In some cases, the agent that modulates splicing of the MSH3 pre-mRNA as described herein and does not modulate splicing of other genes is selected from **Table 4**.

[0207] In some cases, the agent modulates splicing of the MSH3 pre-mRNA as described herein, and also modulates splicing of at least one other gene. Advantageously, in such scenarios, a single agent species can be used to modulate splicing of more than one gene. In an exemplary instance, the agent can modulate splicing of MSH3 pre-mRNA as described herein, and can modulate splicing of HTT pre-mRNA. In some cases, the agent that modulates splicing of both MSH3 pre-mRNA and HTT pre-mRNA is selected from **Table 5**.

[0208] In some embodiments, reducing expression of MSH3 (such as by the compositions, methods, and systems provided herein), results in decreased nucleotide repeat expansion of a target gene in a cell. In some embodiments, the nucleotide repeat expansion comprises a trinucleotide repeat expansion. In some embodiments, the nucleotide repeat expansion comprises expansion of a four-nucleotide repeat, a five-nucleotide repeat, a six-nucleotide repeat, a seven-nucleotide repeat, an eight-nucleotide repeat, a nine-nucleotide repeat, a ten-nucleotide repeat, an eleven-nucleotide repeat, or a twelve-nucleotide repeat. In

some embodiments, the nucleotide repeat expansion is in an exon of the target gene. In some embodiments, the nucleotide repeat expansion is in an intron of the target gene. In some embodiments, the nucleotide repeat expansion is in a UTR of the target gene. In some embodiments, the nucleotide repeat expansion is in a promoter of the target gene. In some embodiments, the nucleotide repeat expansion in the cell comprises at least 20 repeats, at least 30 repeats, at least 40 repeats, at least 50 repeats, at least 60 repeats, at least 70 repeats, at least 80 repeats, at least 90 repeats, at least 100 repeats, at least 200 repeats, at least 500 repeats, at least 1000 repeats, at least 2000 repeats, at least 5000 repeats, at least 10,000 repeats, or at least 20,000 repeats. In some embodiments, the method decreases nucleotide repeat expansion in the target gene by at least about 0.1 fold, at least about 0.2 fold, at least about 0.5 fold, at least about 1.0 fold, at least about 2.0 fold, at least about 5.0 fold, at least about 10.0 fold, or at least about 100.0 fold, as compared to a level of nucleotide repeat expansion in the target gene in the absence of the agent.

[0209] In some cases, the target gene is selected from the group consisting of: ATN1, HTT, AR, ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7, PPP2R2B, TBP, TCF4, JPH3, DMPK, ATXN8, ZNF713, FMR1, AFF/FMR2, FXN, ZFN9, ATXN10, NOP56, C9orf72, CSTB, and any combination thereof. In some embodiments, the target gene is associated with a nucleotide repeat expansion disease or condition. In some embodiments, the nucleotide repeat expansion disease or condition is selected from the group consisting of: dentatorubropallidoluysian atrophy (DRPLA), Huntington's disease (HD), spinal and bulbar muscular atrophy (SBMA), spinocerebellar ataxia (SCA) type 1, spinocerebellar ataxia (SCA) type 2, spinocerebellar ataxia (SCA) type 3, spinocerebellar ataxia (SCA) type 6, spinocerebellar ataxia (SCA) type 7, spinocerebellar ataxia (SCA) type 8, spinocerebellar ataxia (SCA) type 10, spinocerebellar ataxia (SCA) type 12, spinocerebellar ataxia (SCA) type 17, spinocerebellar ataxia (SCA) type 31, spinocerebellar ataxia (SCA) type 36, spinocerebellar ataxia (SCA) type 37, spinocerebellar ataxia (SCA) type 50, Friedreich ataxia, fragile X syndrome (FRAXA), fragile X-associated tremor/ataxia syndrome (FXTAS), Baratela-Scott syndrome (BSS), myotonic dystrophy (DM) type 1, myotonic dystrophy (DM) type 2, amyotrophic lateral sclerosis (ALS), Kennedy's disease, fragile X E mild mental retardation (FRAXE), progressive myoclonus epilepsy (EPM1), oculopharyngodistal myopathy (OPDM) type 1, oculopharyngodistal myopathy (OPDM) type 2, oculopharyngeal myopathy with leukoencephalopathy (OPML), frontotemporal dementia (FTD), Neuronal intranuclear inclusion disease (NIID), essential tremor, global developmental delay, progressive ataxia, and elevated glutamine (GDPAG), familial myoclonic epilepsy (FAME) type 1, familial myoclonic epilepsy (FAME) type 2, familial myoclonic epilepsy (FAME) type 3, familial myoclonic epilepsy (FAME) type 4, familial myoclonic epilepsy (FAME) type 6, familial myoclonic epilepsy (FAME) type 7, premature ovarian failure (FXPOF), cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS), multiple system atrophy (MSA), refractory chronic cough, Fuchs endothelial corneal dystrophy (FECD), X-linked dystonia-parkinsonism (XDP), intellectual disability (FRA12A type), Jacobsen syndrome (CBL2), and any combination thereof. Accordingly, the compositions, methods, and systems may be used to treat any one of the nucleotide repeat expansion diseases or conditions provided herein. **Table 6** illustrates non-

limiting examples of diseases or conditions associated with a gene having a nucleotide repeat expansion (e.g., that can be treated by the compositions, methods, and systems provided herein).

Table 6. Nucleotide repeat expansions diseases or conditions

Nucleotide repeat expansion disease or condition	Gene	Nucleotide repeat
Fragile X E mild mental retardation (FRAXE)	AFF2	CCG
Dentatorubral pallidoluysian atrophy (DRPLA)	ATN1	CAG
Huntington's Disease (HD)	HTT	CAG
Huntington's Disease (HD)	HDL2	CTG
Progressive myoclonus epilepsy (EPM1)	CSTB	CCCCGCCCG CG (SEQ ID NO: 13)
Myotonic dystrophy (DM) type 1	DMPK	CTG
Myotonic dystrophy (DM) type 2	CNBP	CCTG
Oculopharyngodistal myopathy (OPDM) type 1	LR[12	CGG
Oculopharyngodistal myopathy (OPDM) type 2	GIPC1	CGG
Oculopharyngeal myopathy with leukoencephalopathy (OPML)	NUTM2B-AS1	CGG
Frontotemporal dementia (FTD)	C9orf72	GGGGCC
Amyotrophic lateral sclerosis (ALS)	C9orf72	GGGGCC
Neuronal intranuclear inclusion disease (NIID) and essential tremor	NOTCH2NL C	CGG
Global developmental delay, progressive ataxia, and elevated glutamine (GDPAG)	GLS	CGA
Spinocerebellar ataxia (SCA) type 1	ATXN1	CAG
Spinocerebellar ataxia (SCA) type 2	ATXN2	CAG
Spinocerebellar ataxia (SCA) type 3	ATXN3	CAG
Spinocerebellar ataxia (SCA) type 6	CACNA1A	CAG
Spinocerebellar ataxia (SCA) type 7	ATXN7	CAG
Spinocerebellar ataxia (SCA) type 12	PPP2R2B	CAG
Spinocerebellar ataxia (SCA) type 17	TBP	CAG
Familial myoclonic epilepsy (FAME) type 1	SAMD12	ATTTC
Familial myoclonic epilepsy (FAME) type 2	STARD7	ATTTC
Familial myoclonic epilepsy (FAME) type 3	MARCHF6	ATTTC
Familial myoclonic epilepsy (FAME) type 4	YEATS2	ATTTC
Familial myoclonic epilepsy (FAME) type 6	TNRC6A	ATTTC
Familial myoclonic epilepsy (FAME) type 7	RAPGEF2	ATTTC
Fragile X syndrome (FRAXA)	FMR1	CGG
Fragile X-associated tremor ataxia syndrome (FXTAS)	FMR1	CGG
Premature ovarian failure (FXPOF)	FMR1	CGG
Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS)	RFC1	AAGGG
Multiple system atrophy (MSA)	RFC2	AAGGG
Refractory chronic cough	RFC3	AAGGG

Nucleotide repeat expansion disease or condition	Gene	Nucleotide repeat
Spinocerebellar ataxia (SCA) type 8	ATXN8OS	CTG
Spinocerebellar ataxia (SCA) type 10	ATXN10	ATTCT
Spinocerebellar ataxia (SCA) type 31	TK2/BEAN1	TGGAA
Spinocerebellar ataxia (SCA) type 36	NOP56	GGCCTG
Spinocerebellar ataxia (SCA) type 37	DAB1	ATTTC
Spinocerebellar ataxia (SCA) type 50	FGF14	GAA
Fuchs endothelial corneal dystrophy (FECD)	TCF4	CTG
X-linked dystonia-parkinsonism (XDP)	TAF1	CCCTCT
Spinal and bulbar muscular atrophy (SBMA, or Kennedy's disease)	AR	CAG
Baratela-Scott syndrome (BSS)	XYLT1	GGC
Intellectual disability, FRA12A type	DIP2B	CGG
Jacobsen syndrome (CBL2)	CBL2	CGG
Friedreich ataxia (FA)	FXN	GAA

[0210] Further provided herein, in some aspects, is a method for screening for an agent that modulates splicing of an MSH3 pre-mRNA. In some embodiments, the method comprises: contacting a cell with a candidate agent; detecting presence or absence of a poison exon in an MSH3 mRNA transcript; and identifying the candidate agent as an agent that modulates splicing of the MSH3 pre-mRNA when the poison exon is detected in the MSH3 mRNA transcript. In some embodiments, the detecting comprises sequencing the MSH3 mRNA transcript. In some embodiments, the detecting comprises detecting an amount of the MSH3 mRNA transcript comprising the poison exon. In some embodiments, the detecting comprises determining a level of MSH3 protein expression. In some cases, the identifying comprises identifying the candidate agent as an agent that modulates splicing of the MSH3 pre-mRNA when the level of MSH3 protein expression is decreased as compared to a level of MSH3 protein expression in the absence of the candidate agent. In some embodiments, the detecting comprises determining or measuring a level of MSH3 mRNA transcript. In some embodiments, the method comprises identifying the candidate agent as an agent that modulates splicing of the MSH3 pre-mRNA when the level of MSH3 mRNA transcript is decreased as compared to a level of MSH3 mRNA transcript in the absence of the candidate agent. In some embodiments, the method comprises identifying the candidate agent as an agent that modulates splicing of the MSH3 pre-mRNA and the pre-mRNA of at least one additional gene. In some embodiments, the detecting comprises detecting viability of the cell. In some embodiments, the identifying comprises identifying the candidate agent as an agent that modulates splicing of the MSH3 pre-mRNA when viability of the cell is decreased as compared to in the absence of the candidate agent. In some embodiments, the method further comprises contacting the cell with an inhibitor of nonsense-mediated decay (NMD). In some cases, the inhibitor of NMD is cycloheximide. In some embodiments, the method further comprises determining that the poison exon leads to NMD of the MSH3 protein when a level of MSH3 protein expression is decreased in the absence of the inhibitor of NMD, and a level of MSH3 protein expression is increased in the presence of the inhibitor of NMD. In some embodiments,

the method further comprises contacting a plurality of cells with a library of candidate agents, wherein each cell of the plurality of cells is contacted with a different candidate agent.

[0211] In some embodiments, the method comprises screening for candidate agents by contacting the candidate agents with a poison exon comprising nucleic acid mutation for enhancing an output associated with the contacting of the candidate agents and the poison axon comprising the nucleic acid mutation. As shown in **FIG. 10A**, an engineered minigene donor (e.g., by mutating endogenous trinucleotides to CAG as shown in **FIG. 8** and **FIG. 9**) can drive expression of a luciferase reporter gene. **FIG. 10B** illustrates minigene PCR showing the presence of the poison exon comprising the CAG mutation. The wild-type (WT) mRNA did not have the poison exon as confirmed by the decreased nucleotide length. **FIG. 10C** illustrates increased luciferase signal generated by the presence of the minigene comprising the poison exon comprising the CAG mutation. In such case, the output can be the luciferase signal. In some embodiments, the output comprises RNASeq readout. In some embodiments, the output comprises detecting cell viability of a cell comprising the MSH3 pre-mRNA comprising the poison exon and the spliceosomal RNA. In some embodiments, output comprises a reporter signal, said reporter signal is encoded by the MSH3 pre-mRNA comprising the poison exon.

Further Forms of Compounds Disclosed Herein

Isomers/Stereoisomers

[0212] In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (R), and zusammen (Z) isomers as well as the corresponding mixtures thereof. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration, or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred. In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography.

Labeled compounds

[0213] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by

administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds disclosed herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chloride, such as ^2H (D), ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds described herein, and the pharmaceutically acceptable salts, solvates, or stereoisomers thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability.

[0214] In some embodiments, the abundance of deuterium in each of the substituents disclosed herein is independently at least 1%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% by molar. In some embodiments, one or more of the substituents disclosed herein comprise deuterium at a percentage higher than the natural abundance of deuterium. In some embodiments, one or more ^1H are replaced with one or more deuteriums in one or more of the substituents disclosed herein.

[0215] In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts

[0216] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[0217] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein, or a solvate, or stereoisomer thereof, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[0218] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid or inorganic base, such salts including, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate,

butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ -hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylateundeconate and xylenesulfonate.

[0219] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid and muconic acid. In some embodiments, other acids, such as oxalic, while not in themselves pharmaceutically acceptable, are employed in the preparation of salts useful as intermediates in obtaining the compounds disclosed herein, solvate, or stereoisomer thereof and their pharmaceutically acceptable acid addition salts.

[0220] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, sulfate, of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4} \text{ alkyl})_4$, and the like.

[0221] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Solvates

[0222] In some embodiments, the compounds described herein exist as solvates. In some embodiments, the disclosure provides for methods of treating diseases by administering the compounds in the form of such solvates. In some embodiments, the disclosure provides for methods of treating diseases by administering a composition comprising the compounds in the form of such solvates. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents.

Tautomers

[0223] In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

Dosing

[0224] In certain embodiments, the compositions containing the compound(s) described herein are administered for therapeutic treatments. In certain therapeutic applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician.

Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[0225] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[0226] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage, or the frequency of administration, or both, is reduced, as a function of the symptoms.

[0227] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[0228] In some embodiments, doses employed for adult human treatment are typically in the range of 0.01 mg-5000 mg per day. In some embodiments, the daily dosages appropriate for the compound

described herein, or a pharmaceutically acceptable salt thereof, are from about 0.01 to about 50 mg/kg per body weight. In various embodiments, the daily and unit dosages are altered depending on a number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

Routes of Administration

[0229] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[0230] In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation.

Pharmaceutical Compositions/Formulations

[0231] The compounds described herein are administered to a subject in need thereof, either alone or in combination with pharmaceutically acceptable carriers, excipients, or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. In some embodiments, the compounds described herein are administered to animals.

[0232] In another aspect, provided herein are pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable excipients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, (N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure.

[0233] In some embodiments, the pharmaceutically acceptable excipient is selected from carriers, binders, filling agents, suspending agents, flavoring agents, sweetening agents, disintegrating agents, dispersing agents, surfactants, lubricants, colorants, diluents, solubilizers, moistening agents, plasticizers, stabilizers, penetration enhancers, wetting agents, anti-foaming agents, antioxidants, preservatives, and any combinations thereof.

EXAMPLES

[0234] The following examples are offered to illustrate, but not to limit the claimed invention. The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

[0235] The following synthetic schemes are provided for purposes of illustration, not limitation. The following examples illustrate the various methods of making compounds described herein. It is understood that one skilled in the art may be able to make these compounds by similar methods or by combining other methods known to one skilled in the art. It is also understood that one skilled in the art would be able to make, in a similar manner as described below by using the appropriate starting materials and modifying the synthetic route as needed. In general, starting materials and reagents can be obtained from commercial vendors or synthesized according to sources known to those skilled in the art or prepared as described herein.

[0236] The compounds and salts of Formulas (I), (II), (III), (IIIa), (IIIb), and (IV) can be synthesized according to one or more illustrative schemes herein and/or techniques known in the art. Materials used herein are either commercially available or prepared by synthetic methods generally known in the art. These schemes are not limited to the compounds listed in the examples or by any particular substituents, which are employed for illustrative purposes. Although various steps are described and depicted in the synthesis schemes below, the steps in some cases may be performed in a different order than the order shown below. Numberings or R groups in each scheme do not necessarily correspond to that of the claims or other schemes or tables herein.

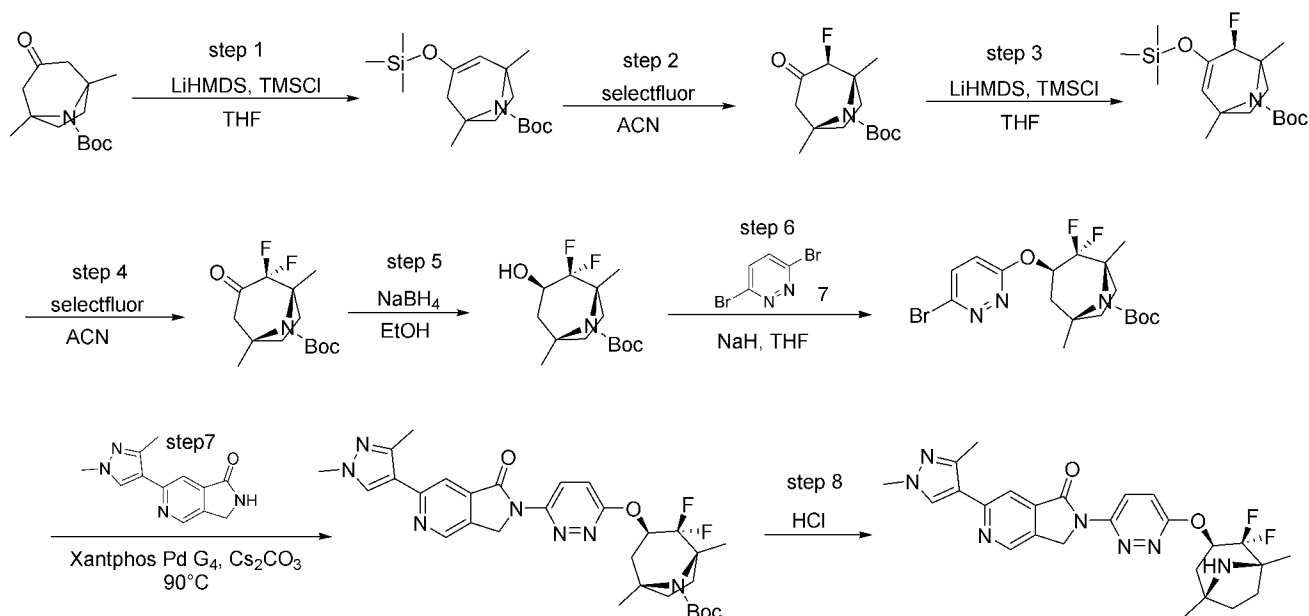
Abbreviations

AcOH:	Acetic acid
Boc ₂ O:	Di-tert-butyl dicarbonate
MeCN or ACN:	Acetonitrile
DavePhos:	2-Dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl
DCC:	N,N'-Dicyclohexylcarbodiimide
DCM:	Dichloromethane
DDQ:	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
Dioxane:	1,4-Dioxane
DIPEA:	N, N-Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide

EDCl:	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
eq	Equivalents
EtOAc	Ethyl acetate
Et ₃ N:	Triethylamine
g	Grams
h	Hour or hours
HATU:	Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium
HOBt:	1-Hydroxybenzotriazole
HOSu:	N-hydroxysuccinimide
LCMS:	Liquid chromatography–mass spectrometry
LAH:	Lithium aluminum hydride
MeOH:	Methanol
mg	Milligrams
min	Minute or minutes
mL	Milliliters
mmol	Millimoles
MS	Mass spectrometry
MTBE:	Methyl tertiary-butyl ether
NCS:	N-Chlorosuccinimide
NMR:	Nuclear Magnetic Resonance
PCC:	Pyridinium chlorochromate
Pd:	Palladium
Pd ₂ (dba) ₃ :	Tris(dibenzylideneacetone)dipalladium
Pd(dppf)Cl ₂ :	[1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride
RP-HPLC:	Reversed-Phase High-Performance Liquid Chromatography
rt or RT:	Room temperature, ambient, about 25 °C
THF:	Tetrahydrofuran
TLC:	Thin-layer chromatography

[0237] Example 1. Synthesis of 2-(6-(((1S,3R,5R)-2,2-difluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (Compound No. 82)

[0238] Scheme 1.



[0239] Step 1: To a solution of 2-methylpropan-2-yl 1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (2.50 g, 9.87 mmol) in THF (30 mL) was added LiHMDS (15.8 mL, 15.8 mmol) at -65°C . The reaction was stirred for 1.5 h and then TMSCl (1.6 mL, 12.83 mmol) was added and the reaction mixture stirring at -78°C for another 2 h. After the reactants were consumed, the reaction was diluted with EA and H_2O . The organic layer was separated, washed with further saturated NaCl solution, and concentrated in vacuo to afford 2-methylpropan-2-yl 1,5-dimethyl-3-[(trimethylsilyl)oxy]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (3.0 g, 93.4%) as a colorless oil which was used directly in the next step without further purification. MS (ESI, pos. ion) m/z 326.5 $[\text{M}+\text{H}]^+$.

[0240] Step 2: To a solution of 2-methylpropan-2-yl 1,5-dimethyl-3-[(trimethylsilyl)oxy]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (3.0 g, 9.22 mmol) in acetonitrile (15 mL) was added Selectfluor (5.24 g, 14.8 mmol) and the reaction mixture was stirred at room temperature overnight. After the reactants were consumed, the reaction was quenched with water and then diluted with EA (100 mL). The organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH=20/1, to provided 2-methylpropan-2-yl (1R,4S,5S)-4-fluoro-1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (1.8 g, 71.98%) as a white solid. MS (ESI, pos. ion) m/z 272.3 $[\text{M}+\text{H}]^+$.

[0241] Step 3: 2-Methylpropan-2-yl (1R,4S,5S)-4-fluoro-1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (1.3 g, 4.79 mmol) was dissolved in THF (30 mL) and LiHMDS (7.67 mL, 7.67 mmol) was added at 80°C . The reaction was stirred at -65°C for 1.5 h, and then TMSCl (0.79 mL, 6.23 mmol) was added. The reaction mixture was stirred for another 2 h at -78°C . After the reactants were consumed, the reaction was diluted with EA and H_2O . The organic layer was separated, washed with further saturated NaCl solution, and concentrated in vacuo to afford 2-methylpropan-2-yl (1S,5R)-2-fluoro-1,5-dimethyl-3-[(trimethylsilyl)oxy]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (1.6 g, 97.22%) as a colorless oil which was directly used in the next step without further purification. MS (ESI, pos. ion) m/z 343.5 $[\text{M}+\text{H}]^+$.

[0242] Step 4: To a solution of 2-methylpropan-2-yl 1,5-dimethyl-3-[(trimethylsilyl)oxy]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (1.6 g, 4.66 mmol) in acetonitrile (15 mL) was Selectfluor (1.65 g, 4.66 mmol) was added and the reaction mixture was stirred at room temperature overnight. After the reactants were consumed, the reaction was quenched with water, and diluted with EA (100 mL). The organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH=20/1, to provided tert-butyl (1S,5R)-2,2-difluoro-1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (837 mg, 3.04 mmol, 65.39%) as a white solid. MS (ESI, pos. ion) m/z 276.3 $[M+H]^+$.

[0243] Step 5: 2-Methylpropan-2-yl (1S,2S,4R,5R)-2,4-difluoro-5-methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (200 mg, 0.69 mmol) was dissolved in EtOH (1-5 mL) and $NaBH_4$ (32 mg, 0.83 mmol) was added at 80 °C. The reaction was refluxed for 3h. After the reactants were consumed, the mixture was cooled to room temperature, quenched with water and diluted with EA (50 mL). The mixture was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH to afford tert-butyl (1S,3R,5R)-2,2-difluoro-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.29 mmol, 39.71%) as a white solid. MS (ESI, pos. ion) m/z 291.1 $[M+H]^+$.

[0244] Step 6: To a solution of 2-methylpropan-2-yl (1S,2S,4R,5R)-2,4-difluoro-3-hydroxy-5-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (80 mg, 0.29 mmol) in THF (6 mL), NaH (16.5 mg, 0.41 mmol) was added and the reaction mixture was stirred for 20 min. Next 3,6-dibromo-1,2-diazine (85 mg, 0.35 mmol) was added and the reaction mixture was stirred at room temperature overnight. After the reactants were consumed, the mixture was cooled to room temperature, quenched with water and diluted with EA (50 mL). The mixture was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH to afford tert-butyl (1S,3R,5R)-3-((6-bromopyridazin-3-yl)oxy)-2,2-difluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (55 mg, 40.62%) as a white solid. MS (ESI, pos. ion) m/z 449.3 $[M+H]^+$.

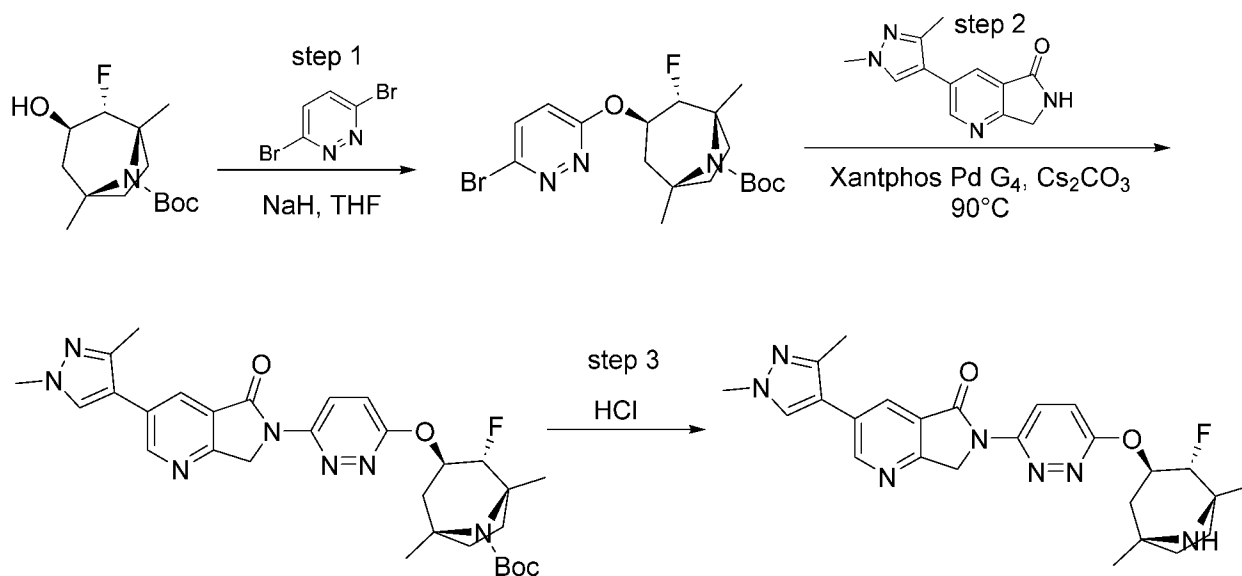
[0245] Step 7: To a solution of 6-(1,3-dimethylpyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (28 mg, 0.12) in dioxane (6 mL) was added 2-methylpropan-2-yl (1R,2R,3s,4S,5S)-3-[(6-bromo-1,2-diazin-3-yl)oxy]-2,4-difluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (55 mg, 0.12 mmol), XantPhos Pd G4 (11.81 mg, 0.01 m-mol) and Cs_2CO_3 (119.91 mg, 0.37 mmol) and the reaction mixture was stirred at 90 °C overnight. After the reactants were consumed, the reaction was diluted with EA and H_2O . The organic layer was separated, washed with further saturated NaCl solution, and concentrated in vacuo and then purified using silica gel column chromatography eluting with DCM/MeOH to afford tert-butyl (1S,3R,5R)-3-((6-(6-(1,3-dimethyl-1H-pyrazol-4-yl)-1-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)pyridazin-3-yl)oxy)-2,2-difluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (15 mg, 0.03 mmol, 20.53%). MS (ESI, pos. ion) m/z 596.6 $[M+H]^+$.

[0246] Step 8: 2-Methylpropan-2-yl 3-({6-[6-(1,3-dimethylpyrazol-4-yl)-1-oxo-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-2-yl]-1,2-diazin-3-yl}oxy)-2,4-difluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (15 mg, 20.53%) was dissolved in HCl (5 mL, in dioxane). The reaction mixture was stirred at room temperature for 3 h. After the reactants were consumed, the reaction was concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH to afford 2-(6-(((1S,3R,5R)-2,2-difluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (8.9 mg, 71.2 %) as a white solid.

[0247] ^1H NMR (DMSO- d_6) δ = 8.99 (s, 1H), 8.76 (br d, J = 9.6 Hz, 1H), 8.39 (s, 1H), 7.90 (s, 1H), 7.49 (br d, J = 9.8 Hz, 1H), 5.72-5.84 (m, 1H), 5.25 (s, 2H), 3.82 (s, 3H), 2.48 (s, 3H), 2.27-2.40 (m, 2H), 1.81-2.03 (m, 2H), 1.60-1.66 (m, 2H), 1.22 (s, 6H). LC/MS (ESI): 496.5 $[\text{M}+\text{H}]^+$.

[0248] Example 2. Synthesis of 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1S,2R,3R,5R)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 215)

[0249] Scheme 2.



[0250] Step 1: To a solution of 2-methylpropan-2-yl (1S,3S,4S,5R)-4-fluoro-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (120 mg, 0.44 mmol) in THF (6 mL) was added NaH (15.80 mg, 0.66 mmol). The reaction mixture was stirred for 20 min and then 3,6-dibromo-1,2-diazine (156.64 mg, 0.66 mmol) was added. The reaction mixture was further stirred at room temperature overnight. After the reactants were consumed, the mixture was cooled to room temperature, quenched with water and diluted with EA (50 mL). The mixture was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH to afford 2-methylpropan-2-yl (1S,3S,4S,5R)-3-[(6-bromo-1,2-diazin-3-yl)oxy]-4-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (50 mg, 26.47%) as a white solid.

[0251] MS (ESI, pos. ion) m/z 431.3 $[M+H]^+$. ^1H NMR (CHLOROFORM- d) δ = 7.43 (d, 1H, J = 9.2 Hz), 6.81 (d, 1H, J = 9.2 Hz), 5.48-5.61 (m, 1H), 4.62 (dd, 1H, J = 51.0, 8.4 Hz), 2.37-2.44 (m, 1H), 1.97-2.09 (m, 1H), 1.67-1.89 (m, 3H), 1.54-1.59 (m, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.42 (s, 9H).

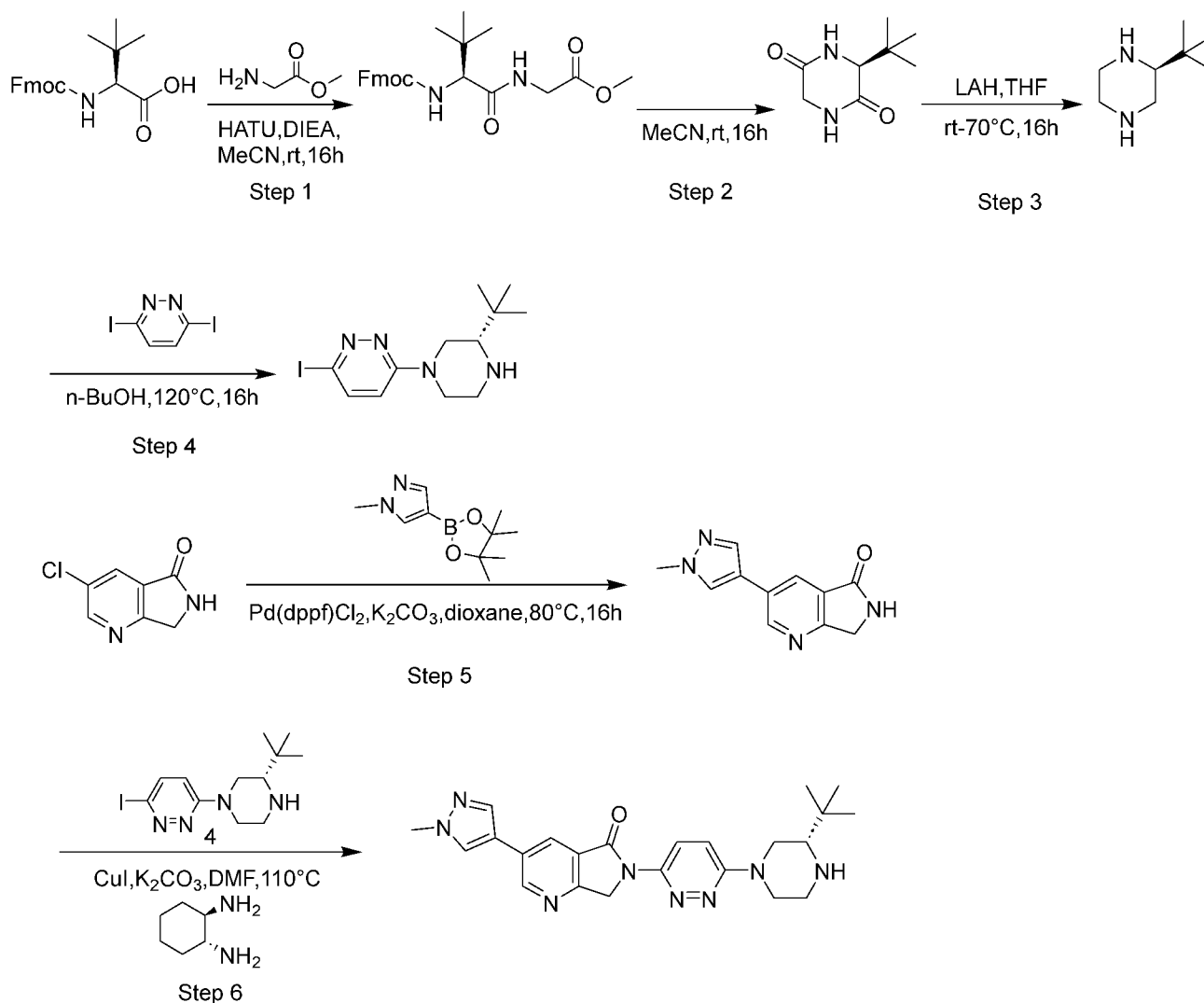
[0252] **Step 2:** To a solution of 3-(1,3-dimethylpyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[4,3-*b*]pyridin-5-one (23 mg, 0.10 mmol) in dioxane (6 mL) were added 2-methylpropan-2-yl (1*S*,3*S*,4*S*,5*R*)-3-[(6-bromo-1,2-diazin-3-yl)oxy]-4-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (43.36 mg, 0.10 mmol), XantPhos Pd G4 (9.70 mg, 0.01 mmol) and Cs_2CO_3 (98.33 mg, 0.30 mmol). The reaction mixture was stirred at 90 °C overnight. After the reactants were consumed, the reaction was diluted with EA and H_2O . The organic layer was separated, washed with saturated NaCl solution, and concentrated in vacuo and then purified using silica gel column chromatography eluting with DCM/MeOH to afford 2-methylpropan-2-yl (1*R*,2*S*,5*S*)-3-({6-[3-(1,3-dimethylpyrazol-4-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[4,3-*b*]pyridin-6-yl]-1,2-diazin-3-yl}oxy)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (13 mg, 22.33%). MS (ESI, pos. ion) m/z 578.7 $[M+H]^+$.

[0253] **Step 3:** 2-Methylpropan-2-yl (1*R*,2*R*,5*S*)-3-({6-[3-(1,3-dimethylpyrazol-4-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[4,3-*b*]pyridin-6-yl]-1,2-diazin-3-yl}oxy)-2-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (13 mg, 0.02 mmol) was dissolved in HCl (5 mL, in dioxane) and the reaction mixture was stirred at room temperature for 3 h. After the reactants were consumed, the mixture was concentrated in vacuo. The crude mixture was then purified by silica gel column chromatography with DCM/MeOH to afford 3-(1,3-dimethylpyrazol-4-yl)-6-(6-{[(1*S*,4*S*,5*R*)-4-fluoro-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl]oxy}-1,2-diazin-3-yl)-6,7-dihydro-5H-pyrrolo[4,3-*b*]pyridin-5-one (8 mg, 0.02 mmol, 74.44%) as a white solid.

[0254] ^1H NMR (DMSO- d_6) δ = 8.95-9.02 (m, 1H), 8.75 (d, J = 9.6 Hz, 1H), 8.13-8.26 (m, 3H), 7.43 (d, J = 9.6 Hz, 1H), 5.43-5.57 (m, 1H), 5.19 (s, 2H), 4.34-4.77 (m, 1H), 3.83 (s, 3H), 2.37 (s, 3H), 1.95-2.23 (m, 2H), 1.67-1.95 (m, 2H), 1.50-1.64 (m, 2H), 1.22 (s, 6H). LC/MS (ESI): 478.2 $[M+H]^+$.

[0255] **Example 3. Synthesis of 2-(6-(2,7-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoroisoindolin-1-one (Compound No. 154)**

[0256] **Scheme 3.**



[0257] Step 1: To a solution of (2*S*)-2-({[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}amino)-3,3-dimethylbutanoic acid (10 g, 28.29 mmol, 1.0 eq) and methyl aminoacetate (3.0 g, 33.95 mmol, 1.2 eq) in acetonitrile (50 mL) was added DIEA (9.1 g, 70.74 mmol, 2.5 eq) and HATU (11.8 g, 31.12 mmol, 1.1 eq), and then the reaction mixture was stirred at room temperature for 16 h. After the reactants were consumed, the reaction mixture was filtered to afford 9*H*-fluoren-9-ylmethyl {[[(7*S*)-8,8-dimethyl-3,6-dioxo-5-aza-2-oxanon-7-yl]amino}methanoate (9.5 g, 22.38 mmol, 79.09%) as slightly a yellow solid. MS *m/z* 425.5 [M+H]⁺.

[0258] Step 2: A solution of 9*H*-fluoren-9-ylmethyl {[[(7*S*)-8,8-dimethyl-3,6-dioxo-5-aza-2-oxanon-7-yl]amino}methanoate (5.0 g, 11.78 mmol, 1.0 eq) in acetonitrile (100 mL) was stirred room temperature for 16 h. After the reactants were consumed, the solution was concentrated in vacuo to afford 9*H*-fluoren-9-ylmethyl {[[(7*S*)-8,8-dimethyl-3,6-dioxo-5-aza-2-oxanon-7-yl]amino}methanoate (4.85 g, 11.43 mmol, 97.00%) as a yellow solid. MS *m/z* 171.2 [M+H]⁺.

[0259] Step 3: LiAlH₄ (2.14 g, 56.40 mmol, 6.0 eq) was added to a vigorous stirred solution of (3*S*)-3-(2-methylprop-2-yl)piperazine-2,5-dione (1.6 g, 9.40 mmol, 1.0 eq) in THF (20 mL) in an ice bath, and the mixture was further stirred at 70 °C for 16 h. After the reactants were consumed, the mixture was poured into KOH (6*N*) in an ice bath. The resulting mixture was further stirred for 1 h, filtered, and the filtrate was collected. The filtrate was extracted with EA, washed with brine, dried over Na₂SO₄, and

concentrated in vacuo to provided (2*S*)-2-(2-methylprop-2-yl)piperazine (1.2 g, 8.44 mmol, 89.74%) as a yellow oil. MS *m/z* 143.2 [M+H]⁺.

[0260] Step 4: DIEA (1.13 g, 8.79 mmol, 1.46 mL, 2.5 eq) was added to a vigorous stirred solution of (2*S*)-2-(2-methylprop-2-yl)piperazine (0.5 g, 3.51 mmol, 1.0 eq) and 3,6-diiodo-1,2-diazine (1.17 g, 3.51 mmol, 1.0 eq) in *n*-BuOH (7 mL) at room temperature, and the mixture was stirred at 120 °C for 16 h. After the reactants were consumed, the mixture was concentrated in vacuo to give a residue, which was diluted with EA, washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo to provided 6-iodo-3-[(3*S*)-3-(2-methylprop-2-yl)piperazin-1-yl]-1,2-diazine (450 mg, 1.30 mmol, 36.98%) as a yellow solid. MS *m/z* 347.2 [M+H]⁺.

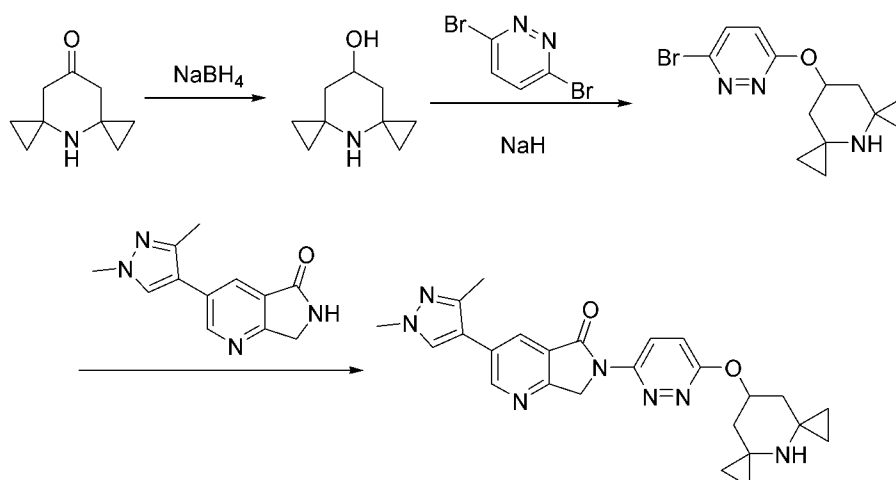
[0261] Step 5: Pd(dppf)Cl₂ (49 mg, 0.06 mmol, 0.05 eq) was added to a vigorous stirred solution of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (250 mg, 1.20 mmol, 1.0 eq), 3-bromo-6,7-dihydro-5*H*-pyrrolo[4,3-*b*]pyridin-5-one (256 mg, 1.20 mmol, 1.0 eq) and K₂CO₃ (332 mg, 2.40 mmol, 2.0 eq) in dioxane (5 mL) and water (1 mL). The mixture was stirred at 80 °C for 16 h. Then the reaction mixture was filtered and the filtrate was concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH 10/1, *v/v* to provide 3-(1-methylpyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[4,3-*b*]pyridin-5-one (135 mg, 0.63 mmol, 52.51%) as a slightly yellow solid. MS *m/z* 215.2 [M+H]⁺.

[0262] Step 6: 6-(1-Methylpyrazol-4-yl)-2,3-dihydro-1*H*-pyrrolo[4,3-*c*]pyridin-1-one (50 mg, 0.23 mmol, 1.0 eq) and 6-iodo-3-[(3*S*)-3-(2-methylprop-2-yl)piperazin-1-yl]-1,2-diazine (80 mg, 0.23 mmol, 1.0 eq) was dissolved in DMF (2 mL) and CuI (4 mg, 0.02 mmol, 0.10 eq), K₂CO₃ (97 mg, 0.70 mmol, 3.0 eq) and (1*R*,2*R*)-cyclohexane-1,2-diamine (2.7 mg, 0.02 mmol, 0.10 eq) was added and the reaction mixture was stirred at 100 °C for 16 h. After the reactants were consumed, the mixture was filtered and the filtrate was concentrated to give a crude product which was purified by pre-HPLC to provided 2-{6-[(3*S*)-3-(2-methylprop-2-yl)piperazin-1-yl]-1,2-diazin-3-yl}-6-(1-methylpyrazol-4-yl)-2,3-dihydro-1*H*-pyrrolo[4,3-*c*]pyridin-1-one (24.19 mg, 21.55%) as a white solid.

[0263] ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.12 (d, *J* = 2.0 Hz, 1H), 8.48 (d, *J* = 9.9 Hz, 1H), 8.44 (s, 1H), 8.36 (d, *J* = 2.1 Hz, 1H), 8.18 (s, 1H), 8.14 (s, 1H), 7.46 (d, *J* = 10.0 Hz, 1H), 5.13 (s, 2H), 4.39 - 4.31 (m, 1H), 4.10 (br d, *J* = 12.0 Hz, 1H), 3.89 (s, 3H), 3.08 - 3.03 (m, 1H), 2.86 - 2.55 (m, 3H), 2.35 - 2.31 (m, 1H), 0.96 (s, 9H). LC/MS (ESI): 433.5 [M+H]⁺.

[0264] Example 4. Synthesis of 6-(6-((4-azadispiro[2.1.25.33]decan-9-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1*H*-pyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one (Compound No. 232)

[0265] Scheme 4.



[0266] Step 1: To a 100 mL round-bottomed flask was added spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane]-7-one (500 mg, 3.31 mmol) in MeOH (5 mL). This was followed with the addition of NaBH₄ (0.18 mL, 4.96 mmol) at 0 °C over 5 min to give an off-white suspension. The resulting mixture was stirred for 1 h at room temperature. LCMS showed the desired MS (M+H: 154.1). The resulting mixture was cooled to 0 °C and quenched with HCl (2 M, 0.5 mL) and then concentrated in vacuo. The resulting mixture was added to a silica column and was eluted with DCM:MeOH (20:1) (0.1%TEA). Spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane]-7-ol (475 mg, 2.98 mmol, 90.00%) was obtained as a yellow solid. MS (ESI, pos. ion) m/z 154.1 [M+H]⁺.

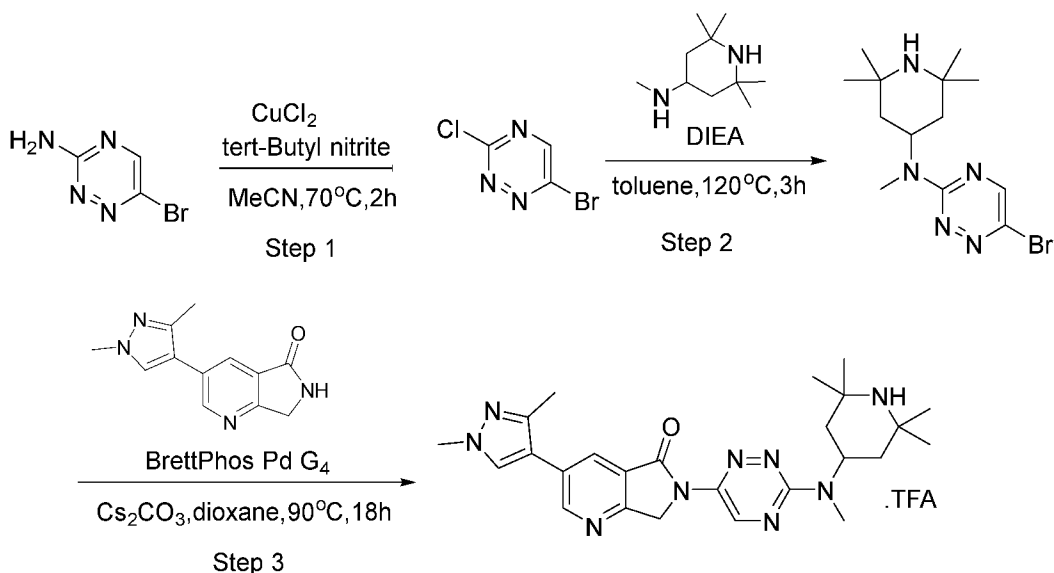
[0267] Step 2: To a solution of spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane]-7-ol (460 mg, 3.00 mmol) in THF (10 mL) was added NaH (270.20 mg, 4.50 mmol) at 0 °C and the resulting mixture was stirred for 30 min at room temperature. Next 3,6-dibromo-1,2-diazine (928.42 mg, 3.90 mmol) was added at 0 °C and the resulting mixture was stirred for 12 h at 60 °C. The reaction mixture was quenched with saturated NH₄Cl solution (50 mL) and the aqueous layer was extracted with EA (50 mL*3). The organic layer was concentrated under vacuum and residue was purified by column chromatography (SiO₂, PE:EA=0~50%, 30 min) to afford 7-[(6-bromo-1,2-diazin-3-yl)oxy]spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane] (360 mg, 1.11 mmol, 37.11%). MS (ESI, pos. ion) m/z 310.05 [M+H]⁺.

[0268] Step 3: To a flask containing 3-(1,3-dimethylpyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (40.47 mg, 0.18 mmol) in dioxane (2 mL) was added 7-[(6-bromo-1,2-diazin-3-yl)oxy]spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane] (50 mg, 0.16 mmol), Cs₂CO₃ (157.56 mg, 0.48 mmol) and 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (26.11 mg, 0.02 mmol) under nitrogen. The mixture was stirred at 90 °C for 18 h. The reaction mixture was concentrated under vacuum. The residue was dissolved in DCM (3 mL) and ACN (2 mL) was added drop wise to get white slurry. The off-white solid was filtered to obtain 3-(1,3-dimethylpyrazol-4-yl)-6-[6-(spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane]-7-yloxy)-1,2-diazin-3-yl]-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (4 mg, 0.01 mmol, 5.05%) as an off-white solid.

[0269] MS (ESI, pos. ion) m/z 458.3 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ = 8.89 - 8.79 (m, 2H), 8.14 (d, *J* = 1.9 Hz, 1H), 7.56 (s, 1H), 7.05 (d, *J* = 9.6 Hz, 1H), 5.75 - 5.65 (m, 1H), 5.28 (s, 2H), 3.92 (s, 3H), 2.44 (s, 3H), 2.02 - 1.89 (m, 2H), 1.86 - 1.77 (m, 2H), 0.75 - 0.52 (m, 6H), 0.46 - 0.39 (m, 2H).

[0270] Example 5. Synthesis of 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(3-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 162)

[0271] Scheme 5.



[0272] **Step 1:** To a solution of 6-bromo-1,2,4-triazin-3-amine (2.0 g, 11.43 mmol) and CuCl_2 (1.47 g, 14.86 mmol) in MeCN (25 mL) was added isoamyl nitrite (2.18 mL, 18.29 mmol) and the reaction mixture was stirred at 70 °C for 2 h. Next the reaction mixture was concentrated and the residue was purified by column chromatography (SiO_2 , PE:EA=10:1) to give 6-bromo-3-chloro-1,2,4-triazine (220 mg, 1.13 mmol, 9.90%) as a yellow solid.

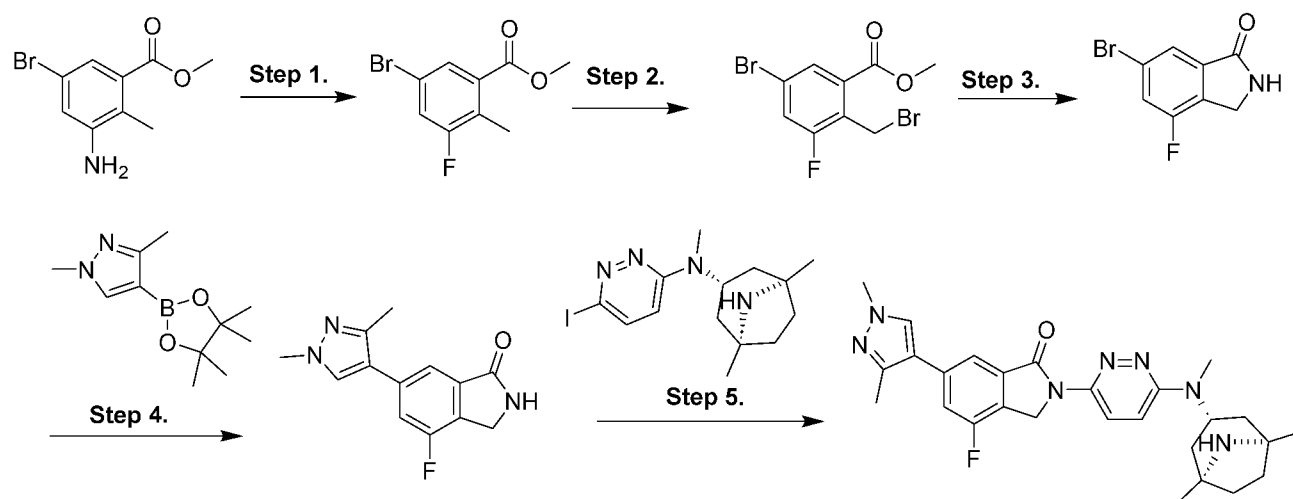
[0273] **Step 2:** To a solution of 6-bromo-3-chloro-1,2,4-triazine (200 mg, 1.03 mmol) and 2,2,6,6-tetramethyl-4-(methylamino)hexahydropyridine (192.71 mg, 1.13 mmol) in toluene (10 mL) was added DIEA (0.34 mL, 2.06 mmol) and the reaction mixture was stirred at 120 °C for 3 h. LCMS showed the reaction was completed. Next the reaction mixture was concentrated and the residue was purified by column chromatography (SiO_2 , DCM : MeOH=10:1) to give 6-bromo-3-[methyl(2,2,6,6-tetramethylhexahydropyridin-4-yl)amino]-1,2,4-triazine (0.23 g, 67.65%) as a yellow solid.

[0274] **Step 3:** To a solution of 3-(1,3-dimethylpyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (35 mg, 0.15 mmol) and 6-bromo-3-[methyl(2,2,6,6-tetramethylhexahydropyridin-4-yl)amino]-1,2,4-triazine (52 mg, 0.16 mmol) in dioxane (10 mL) was added BrettPhos Pd G4 (13.61 mg, 0.01 mmol) and Cs_2CO_3 (146.62 mg, 0.45 mmol). The reaction mixture was stirred at 90 °C for 16 h under N_2 . LCMS showed the reaction was completed. Next the reaction mixture was filtered and concentrated. The residue was purified by prep-HPLC (TFA) to give 3-(1,3-dimethylpyrazol-4-yl)-6-{3-[methyl(2,2,6,6-tetramethylhexahydropyridin-4-yl)amino]-1,2,4-triazin-6-yl}-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (8 mg, 10.97%) as a yellow solid.

[0275] MS (ESI, pos. ion) m/z : 476.3[M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.41 (s, 1H), 8.95 (d, J = 2.0 Hz, 1H), 8.22 - 8.14 (m, 2H), 5.14 (m, 3H), 3.83 (s, 3H), 3.09 (s, 3H), 2.35 (s, 3H), 1.99 - 1.82 (m, 4H), 1.51 (s, 6H), 1.43 (s, 6H), 1H not observed (NH).

[0276] Example 6. Synthesis of 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-4-fluoroisoindolin-1-one (Compound No. 274)

[0277] Scheme 6.



[0278] **Step 1:** To a solution of methyl 3-amino-5-bromo-2-methylbenzoate (1.0 g, 4.10 mmol) in DCM (10 mL) was added nitrosonium tetrafluoroborate (480 mg, 4.10 mmol) portion wise at 0 °C under N₂ to obtain a yellow solution which was stirred at 0 °C for 1 h. Then oxylene (30 mL) was added the reaction mixture was refluxed at 130 °C for 3 h. Next the reaction mixture was cooled to room temperature and poured into H₂O. The aqueous layer was extracted EA. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The crude mixture was purified by silica gel column chromatography with PE/EA 10/1, v/v to obtain methyl 5-bromo-3-fluoro-2-methylbenzoate (860 mg, 85%).

[0279] **Step 2:** To the solution of 5-bromo-3-fluoro-2-methylbenzoate (860 mg, 3.5 mmol) and NBS (623 mg, 3.5 mmol) in (trifluoromethyl)benzene (10 mL), was added AIBN (57 mg, 0.35 mmol). The reaction mixture was stirred under N₂ at 100 °C for 16 h. Next, the reaction mixture was cooled to room temperature and poured into H₂O. The aqueous layer was extracted EA. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The crude mixture was purified by silica gel column chromatography with PE/EA 10/1, v/v to obtain methyl 5-bromo-2-(bromomethyl)-3-fluorobenzoate (800 mg, 70%).

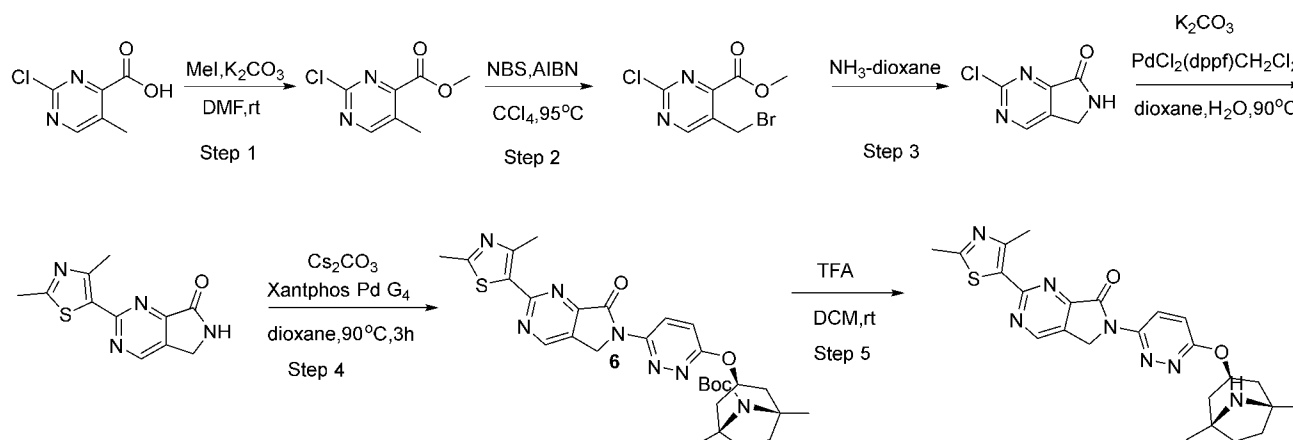
[0280] **Step 3:** Methyl 5-bromo-2-(bromomethyl)-3-fluorobenzoate (800 mg, 2.5 mmol) was dissolved in THF (7 mL) and NH₄OH (7 mL) was added. The reaction was stirred at room temperature for 4 h and was then filtered and concentrated under vacuum. The crude product was used directly in the next step without further purification.

[0281] Step 4: To the solution of 6-bromo-4-fluoroisindolin-1-one (100 mg, 0.43 mmol) and 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (96 mg, 0.43 mmol) in dioxane:H₂O (5:1) (2 mL : 0.4 mL), potassium carbonate (118 mg, 0.86 mmol) and PdCl₂(dppf) (31 mg, 0.043 mmol) were added. The reaction mixture was stirred under N₂ at 100 °C for 16 h. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was washed with EA. The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 6-(1,3-dimethyl-1*H*-pyrazol-4-yl)-4-fluoroisindolin-1-one (85 mg, 81%) as a yellow solid.

[0282] MS *m/z* 231.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.51 - 8.33 (m, 2H), 8.04 (s, 1H), 7.64 - 7.60 (m, 1H), 7.55 (d, *J* = 10.3 Hz, 1H), 7.31 (d, *J* = 10.0 Hz, 1H), 5.13 (s, 2H), 5.11 - 5.03 (m, 1H), 3.81 (s, 3H), 2.90 (s, 3H), 2.36 (s, 3H), 2.16 (br d, *J* = 8.1 Hz, 2H), 2.03 - 1.87 (m, 4H), 1.80 (br dd, *J* = 5.4, 13.6 Hz, 2H), 1.45 (s, 6H).

[0283] Example 7. Synthesis of 6-(6-(((1*R*,3*s*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2-(2,4-dimethylthiazol-5-yl)-5,6-dihydro-7*H*-pyrrolo[3,4-*d*]pyrimidin-7-one (Compound No. 111)

[0284] Scheme 7.



[0285] Step 1: To a mixture of 2-chloro-5-methylpyrimidine-4-carboxylic acid (5.0 g, 28.97 mmol) and K₂CO₃ (8.01 g, 57.95 mmol) in DMF (10 mL) was added MeI (5.41 mL, 86.92 mmol) at room temperature, and the mixture was stirred for 16 h. After the reaction was completed, the mixture was filtrated, quenched with H₂O, and extracted with EA. The combined organic layers were washed with aq. NaCl, dried over Na₂SO₄, and concentrated. The resulting residue was purified with chromatography on silica gel PE:EA=5:1 to give 2-chloro-5-methylpyrimidine-4-carboxylate (5.0 g, 92.49%) as a white solid.

[0286] Step 2: To a mixture of methyl 2-chloro-5-methylpyrimidine-4-carboxylate (5.0 g, 26.80 mmol) in CCl₄ (100 mL) was added NBS (6.20 g, 34.84 mmol) and AIBN (0.44 g, 2.68 mmol) at room temperature under N₂, and the resulting mixture was stirred at 95 °C for 2 h. Next NBS (2.38 g, 13.40 mmol) was added and the mixture was stirred at 95 °C for 1 h. Then NBS (1.43 g, 8.04 mmol) was added and the mixture was stirred at 95 °C for 1 h. After the reaction was completed, the mixture was

cooled to room temperature and was quenched with H₂O and extracted with DCM. The combined organic layers were washed with aq. NaCl, dried over Na₂SO₄, and concentrated. The residue was purified by chromatography on silica gel PE:EA=5:1 to give 5-(bromomethyl)-2-chloropyrimidine-4-carboxylate (4.0 g, 56.26%) as an oil.

[0287] Step 3: A mixture of methyl 5-(bromomethyl)-2-chloropyrimidine-4-carboxylate (4.0 g, 15.07 mmol) in NH₃-dioxane (30 mL) was stirred at room temperature for 1 h. LCMS analysis showed the reaction was completed. The mixture was filtered and concentrated to afford 2-chloro-6,7-dihydro-5H-pyrrolo[4,3-d]pyrimidin-7-one (1.3 g, 50.98%) as a red solid.

[0288] Step 4: To a mixture of 2-chloro-6,7-dihydro-5H-pyrrolo[4,3-d]pyrimidin-7-one (110 mg, 0.65 mmol) and 2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-thiazole (201.67 mg, 0.84 mmol) in dioxane: H₂O=5:1 (6 mL) was added PdCl₂(dppf) CH₂Cl₂ (52.98 mg, 0.06 mmol) and K₂CO₃ (268.95 mg, 1.95 mmol) at room temperature under N₂, and the mixture was stirred at 95 °C for 3 h. LCMS analysis showed the reaction was completed. Next the mixture was concentrated and the residue was purified by chromatography on silica gel DCM: MeOH=10:1 to give 2-(2,4-dimethyl-1,3-thiazol-5-yl)-6,7-dihydro-5H-pyrrolo[4,3-d]pyrimidin-7-one (0.1 g, 62.50%) as a yellow solid.

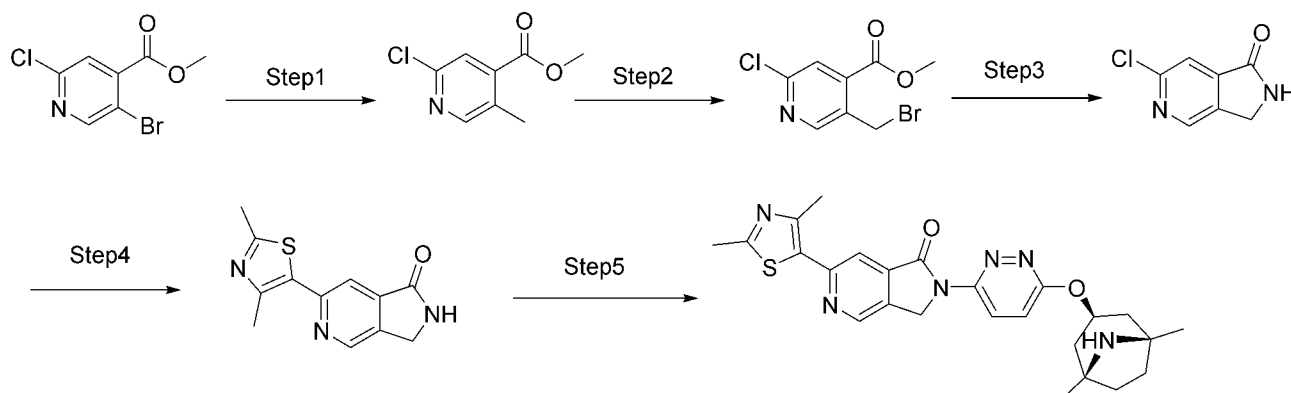
[0289] Step 5: To a mixture of 2-(2,4-dimethyl-1,3-thiazol-5-yl)-6,7-dihydro-5H-pyrrolo[4,3-d]pyrimidin-7-one (65 mg, 0.26 mmol), 2-methylpropan-2-yl (1R,3s,5S)-3-[(6-bromo-1,2-diazin-3-yl)oxy]-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (119.70 mg, 0.29 mmol) in dioxane (20 mL) was added XantPhos Pd G4 (42.76 mg, 0.03 mmol) and Cs₂CO₃ (257.97 mg, 0.79 mmol) at room temperature under N₂, and the mixture was stirred at 95 °C for 16 h. LCMS analysis showed the reaction was completed. Next the mixture was filtered and concentrated to afford 2-methylpropan-2-yl (1S,3s,5R)-3-({6-[2-(2,4-dimethyl-1,3-thiazol-5-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[4,3-d]pyrimidin-6-yl]-1,2-diazin-3-yl}oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (150 mg, 98.39%) as a yellow solid which was used in the next step without further purification.

[0290] Step 6: To a mixture of 2-methylpropan-2-yl (1S,3s,5R)-3-({6-[2-(2,4-dimethyl-1,3-thiazol-5-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[4,3-d]pyrimidin-6-yl]-1,2-diazin-3-yl}oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (100 mg, 0.17 mmol) in DCM (10 mL) was added TFA (1 mL) at room temperature and the mixture was stirred at room temperature for 0.5 h. LCMS analysis showed the reaction was completed. Next the mixture was concentrated and the residue was purified with pre-HPLC(TFA) to give 2-(2,4-dimethyl-1,3-thiazol-5-yl)-6-(6-[(1S,3s,5R)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl]oxy)-1,2-diazin-3-yl)-6,7-dihydro-5H-pyrrolo[4,3-d]pyrimidin-7-one (72 mg, 87.09%) as a white solid.

[0291] MS (ESI, pos. ion) m/z: 478.3[M+H]⁺. ¹H NMR (DMSO-*d*₆) δ = 9.32 (s, 1H), 8.94 (br s, 1H), 8.86 (br s, 1H), 8.74 (dd, *J* = 9.6, 0.9 Hz, 1H), 7.43 (d, *J* = 9.5 Hz, 1H), 5.49-5.60 (m, 1H), 5.21 (s, 2H), 2.84 (s, 3H), 2.67 (s, 3H), 2.42-2.48 (m, 2H), 2.17 (br d, *J* = 8.1 Hz, 2H), 1.89 (br d, *J* = 8.3 Hz, 2H), 1.76-1.85 (m, 2H), 1.46 (s, 6H).

[0292] Example 8. Synthesis of (2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (Compound No. 69)

[0293] Scheme 8.



[0294] Step 1: To a solution of methyl 5-bromo-2-chloroisonicotinate (5 g, 20 mmol, 1.0 eq), methylboronic acid (1.79 g, 29.8 mmol, 1.5 eq), K_3PO_4 (14.8 g, 69.9 mmol, 3.5 eq), $P(Cy)_3$ (1.11 g, 3.97 mmol, 0.2 eq) and $Pd(OAc)_2$ (448 mg, 2.00 mmol, 0.1 eq) in toluene (95 mL) and H_2O (4.5 mL) was degassed and purged with N_2 three times. Then the mixture was stirred at 100 °C for 2 hours under N_2 atmosphere. When full conversion was achieved, the reaction mixture was quenched with water (40 mL) and extracted with ethyl acetate (3 x 20 mL). The extracts were dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to get the crude residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=20/1 to 15/1) to give methyl 2-chloro-5-methylisonicotinate (2 g, 54% yield) as a yellow solid.

[0295] Step 2: 2-Chloro-5-methylisonicotinate (15.0 g, 81.7 mmol, 1.0 eq), *N*-bromosuccinimide (20.3 g, 113.9 mmol, 1.4 eq) and benzoyl peroxide (448.0 mg, 1.85 mmol, 0.03 eq) were combined with carbon tetrachloride (250 mL). The reaction mixture was heated to 80 °C and stirred for 3 h. The reaction mixture was cooled to rt and concentrated in vacuum. The obtained residue was purified by silica gel column chromatography with PE/EA to obtain methyl 5-(bromomethyl)-2-chloroisonicotinate (17.0 g, 79%) as a brown solid. LC/MS (ESI): 263.9, 265.9 $[M+H]^+$.

[0296] Step 3: Methyl 5-(bromomethyl)-2-chloroisonicotinate (17.0 g, 64.6 mmol, 1.0 eq) was suspended in 28 % aqueous ammonium hydroxide and the mixture was kept stirring at rt for 8 hrs. Then the mixture was filtered, and the residue was washed with water and methanol. The solid was collected, dried under vacuum and used in the next step without further purification. LC/MS (ESI): 169.0, 171.0 $[M+H]^+$.

[0297] Step 4: 6-Chloro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (336.0 mg, 2.0 mmol, 1.0 eq), 2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (526.1 mg, 2.20 mmol, 1.1 eq), aqueous potassium carbonate (2 M, 8.0 mL) and $PdCl_2(dppf) \cdot CH_2Cl_2$ adduct (146.3 mg, 0.2 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask. The flask was evacuated and backfilled three times with nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, washing the filter cake with

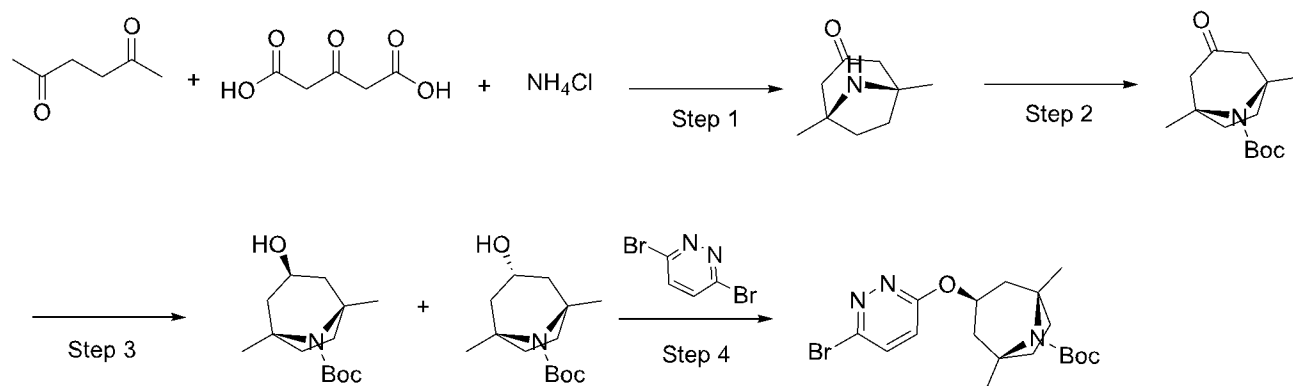
EtOAc (100 mL). The filtrate was washed with washed with brine, then the organic layer was collected and dried over sodium sulfate, then concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (245 mg, 52%) as brown solid. LC/MS (ESI): 246.0 [M+H]⁺.

[0298] Step 5: To a round bottom flask charged with 6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (36.7 mg, 0.15 mmol, 1.0 eq), *tert*-butyl (1*R*,3*s*,5*S*)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (61.8 mg, 0.15 mmol, 1.1 eq), Cs₂CO₃ (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min then heated at 90 °C for 8 hrs. The reaction mixture was cooled to RT and diluted with EtOAc. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude mixture was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain *tert*-butyl (1*R*,3*s*,5*S*)-3-((6-(6-(2,4-dimethylthiazol-5-yl)-1-oxo-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)pyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (42.2 mg), which was dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h, and then concentrated. The residue obtained was purified by RP HPLC using MeCN and H₂O as eluent to provide 2-(6-(((1*R*,3*s*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (12.2 mg, 17.3 %) as a white solid.

[0299] ¹H NMR (DMSO-d₆, 400 MHz) δ = 9.06 (s, 1H), 8.69 (d, *J* = 9.6 Hz, 1H), 8.24 (s, 1H), 7.92 (s, 1H), 7.35 (d, *J* = 9.6 Hz, 1H), 5.49 (s, 1H), 5.28 (s, 2H), 2.65 (s, 6H), 2.22 (br dd, *J* = 5.9, 12.3 Hz, 2H), 1.88 (br d, *J* = 7.4 Hz, 2H), 1.60 (br d, *J* = 6.9 Hz, 2H), 1.49 (br t, *J* = 11.4 Hz, 2H), 1.25 (s, 6H); LC/MS (ESI): 477.2 [M+H]⁺.

[0300] Example 9. Synthesis of 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1*R*,3*s*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (Compound No. 72)

[0301] Scheme 9.



[0302] Step 1: Potassium hydroxide (74.8 g, 1.33 mol, 4.5 eq) in water (60 mL) was added to a vigorous stirred solution of 3-oxopentanedioic acid (82.8 g, 0.566 mol, 4.5 eq) and hexane-2,5-dione (34.0 g, 35.0 mL, 0.298 mol, 1.0 eq) in water (120 mL) at 0 °C. After the addition, ammonium chloride (47.8 g, 0.896

mol, 3.0 eq) and sodium acetate (49.0 g, 0.596 mol, 2.0 eq) in water (200 mL) were added keeping the temperature at 5 °C. The pH value was adjusted to ~9 by using solid KOH. The mixture was stirred at room temperature for 4 days during which time the pH value was adjusted to ~9 by using additional solid KOH. The solution was diluted with 100 mL of water, cooled to 5 °C with vigorous stirring and acidified with pure sulfuric acid until pH = 2 (-60 mL). Gas evolution was observed during the acidification. Water layer was divided in two batches. Each batch was washed with EtOAc (2 x 100 mL) and basified with solid KOH with cooling until pH = 10. The water layer was extracted with 15% MeOH in DCM (4 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to afford 1,5-dimethyl-8- azabicyclo[3.2.1]octan-3-one (17.3 g, 37.5 %) as a dark brown oil. LC/MS (ESI): 154.1 [M+H]⁺.

[0303] Step 2: To an ice-cold solution of 1,5-dimethyl-8- azabicyclo[3.2.1]octan-3-one (3 g, 19.6 mmol, 1.0 eq) of DCM (60 mL) was added pyridine (4.0 mL, 49.0 mmol, 2.5 eq). Triphosgene (2.33g, 7.84 mmol, 0.4 eq) was dissolved in DCM (20mL) and added to the above solution dropwise. After 30 minutes, *t*-BuOH (3.78 mL, 39.2 mmol, 2.0 eq) was added and the mixture was gradually warmed to RT and stirred for 8 hrs. The reaction was quenched with water and diluted with DCM (300 mL). The mixture was washed with 1N HCl (1 x 50 mL), saturated sodium bicarbonate (1 x 50 mL), and brine (1 x 50 mL). The organic layer was collected and dried over sodium sulfate, and then concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with PE/EA 20/1, v/v to provide *tert*-butyl (1*R*,5*S*)-1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (2.3 g, 9.1 mmol, 46.3%) as a slightly yellow oil. LC/MS (ESI): 254.2 [M+H]⁺.

[0304] Step 3: (1*R*,5*S*)-1,5-Dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (2.3 g, 9.1 mmol) was dissolved in EtOH (50 mL) and the solution was heated to reflux. Sodium borohydride (336 mg, 1.0 eq) and was added the mixture was stirred for 15 min. The mixture was cooled to RT and quenched with aqueous ammonium chloride. The organic solvent was removed under vacuum and the residue was redissolved in EtOAc (100 mL). The mixture was washed with brine, and the organic layer was collected and dried over sodium sulfate, and then concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with PE/EtOAc to provided *tert*-butyl (1*R*,3*r*,5*S*)-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (1.2g, 52%, PE/EtOAc 3/1, v/v) and *tert*-butyl (1*R*,3*s*,5*S*)-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (1.1g, 48%, PE/EtOAc 2/1, v/v) as white solid. LC/MS (ESI): 256.2 [M+H]⁺.

[0305] Step 4: To a solution of (1*R*,3*s*,5*S*)-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (1.10g g, 4.34 mmol, 1.0 eq) in anhydrous THF (20 mL) was added NaH (60 wt %, 208 mg, 5.21 mmol, 1.2 eq). The solution was stirred at room temperature for 30 min, then 3,6-dibromopyridazine (1.24 g, 5.21 mmol, 1.2 eq) was added and the mixture was stirred at RT for 8 hrs. The reaction mixture was quenched with saturated ammonium chloride and diluted with EtOAc (100 mL). The mixture was washed with brine, dried over sodium sulfate, and then concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with PE/EA 20/1, v/v to provide *tert*-

butyl (1*R*,3*S*,5*S*)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (1.28g, 72%) as white solid. LC/MS (ESI): 412.2, 414.2 [M+H]⁺.

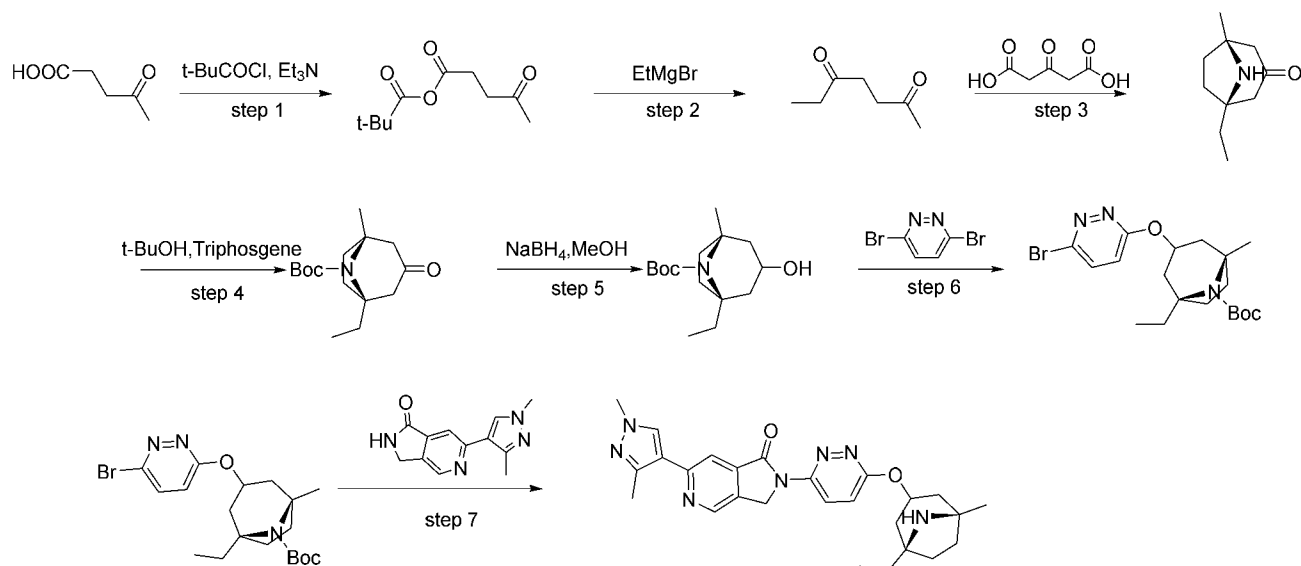
[0306] Step 5: A mixture of 6-(1,3-dimethylpyrazol-4-yl)-2,3-dihydro-1*H*-pyrrolo[4,3-*c*]pyridin-1-one (210 mg, 0.92 mmol), 2-methylpropan-2-yl (1*R*,3*S*,5*S*)-3-[(6-bromo-1,2-diazin-3-yl)oxy]-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (379.36 mg, 0.92 mmol) in dioxane (30 mL) was added Xantphos Pd G4 (149.05 mg, 0.09 mmol), Cs₂CO₃ (897.04 mg, 2.76 mmol) at RT under N₂ and the mixture was stirred at 95 °C for 16 h. The reaction mixture was concentrated and the residue was purification by chromatography on silica gel and eluted with DCM:MeOH=10:1 to give 2-methylpropan-2-yl (1*R*,3*S*,5*S*)-3-({6-[6-(1,3-dimethylpyrazol-4-yl)-1-oxo-2,3-dihydro-1*H*-pyrrolo[4,3-*c*]pyridin-2-yl]-1,2-diazin-3-yl}oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (400 mg, 77.68%) as a yellow solid.

[0307] Step 6: A mixture of 2-methylpropan-2-yl (1*R*,3*S*,5*S*)-3-({6-[6-(1,3-dimethylpyrazol-4-yl)-1-oxo-2,3-dihydro-1*H*-pyrrolo[4,3-*c*]pyridin-2-yl]-1,2-diazin-3-yl}oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (360 mg, 0.64 mmol) in DCM (10 mL) was added HCl-dioxane (20 mL) at RT and the mixture was stirred for 1 h. The reaction mixture was concentrated and the residue was purification by pre-HPLC(HCl) to give 6-(1,3-dimethylpyrazol-4-yl)-2-(6-[(1*R*,3*S*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl]oxy)-1,2-diazin-3-yl)-2,3-dihydro-1*H*-pyrrolo[4,3-*c*]pyridin-1-one (248 mg, 83.90%) as a yellow solid.

[0308] ¹H NMR (DMSO-*d*₆, 400 MHz) δ = 8.98 (s, 1H), 8.71 (d, *J* = 9.6 Hz, 1H), 8.37 (s, 1H), 8.23 (s, 1H), 7.88 (s, 1H), 7.37 (d, *J* = 9.6 Hz, 1H), 5.51 (br t, *J* = 5.7 Hz, 1H), 5.23 (s, 2H), 3.81 (s, 3H), 2.47-2.48 (s, 3H), 2.36 (br dd, *J* = 13.0, 5.9 Hz, 2H), 2.06 (br d, *J* = 7.8 Hz, 2H), 1.79 (br d, *J* = 8.0 Hz, 2H), 1.69 (br t, *J* = 11.9 Hz, 2H), 1.38 (s, 6H); LC/MS (ESI): 460.2 [M+H]⁺.

[0309] Example 10. Synthesis of 6-(1,3-dimethyl-1*H*-pyrazol-4-yl)-2-(6-(((1*S*,3*R*,5*R*)-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-1-one (Compound No. 98)

[0310] Scheme 10.



[0311] Step 1: A solution of pivaloyl chloride (41.96 mL, 341.03 mmol) in dry THF (50 mL) was added dropwise to a stirred and ice-cooled solution of 4-oxopentanoic acid (31.86 mL, 310.02 mmol) and triethylamine (128.92 mL, 930.07 mmol) in dry THF (300 mL) at 5 °C. The solution was stirred for 1.5 h at 5 °C, and the precipitated Et₃N·HCl was filtered off. The solid salt was washed with THF. The combined filtrate and washings were dried (MgSO₄), and concentrated in vacuo to give 2,2-dimethylpropanoic 4-oxopentanoic anhydride (57 g, 284.67 mmol, 91.82%) as a colorless oil which was used immediately in the next step. LC/MS (ESI): 201.1 [M+H]⁺.

[0312] Step 2: A solution of EtMgBr in THF (1 M, 323.14 mL, 313.14 mmol) was added dropwise over 30 min to a stirred and cooled solution of 2,2-dimethylpropanoic 4-oxopentanoic anhydride (57 g, 284.67 mmol) in dry THF (300 mL) at -60 °C under N₂. After the addition, the mixture was stirred for 30 min at -60 °C. Subsequently the cooling bath was removed and the mixture was stirred for an additional 1 h. The reaction was quenched with the addition of ice and NH₄Cl solution, and was then extracted with EA. The EA solution was washed successively with water and brine, dried over MgSO₄, and concentrated in vacuo. The residues obtained from two runs were combined and distilled in vacuo to give heptane-2,5-dione (25 g, 195.05 mmol, 68.52%) as a colorless oil. LC/MS (ESI): 129.1 [M+H]⁺.

[0313] Step 3: KOH (49.25 g, 877.74 mmol) in water (50 mL) was added to a vigorous stirred solution of heptane-2,5-dione (25 g, 195.05 mmol) and 3-oxopentanedioic acid (42.30 mL, 370.60 mmol) in water (250 mL) at 0 °C. NH₄Cl (20.59 mL, 585.16 mmol) and KOAc (38.29 g, 390.11 mmol) in water (200 mL) were added at 5 °C. The pH value was adjusted to ~9 by using solid KOH. The mixture was stirred at room temperature for 4 days during which time the pH value was adjusted to ~9 by using additional solid KOH. The solution was diluted with 300 mL of water and transferred to a 2 L beaker and cooled to 5 °C and acidified with pure sulfuric acid until pH = 2. Gas evolution was observed during the acidification. The aqueous layer divided in two batches. Each batch was washed with EA (2 x 1000 mL) and basified with solid KOH until pH = 10. The aqueous layer was extracted with 15% MeOH in DCM (4 x 1000 mL). The combined organic layers were washed with brine (1000 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to afford (1S,5R)-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octan-3-one (9 g, 53.81 mmol, 27.59%) as a dark brown oil. LC/MS (ESI): 169.1 [M+H]⁺.

[0314] Step 4: To an ice-cold solution of (1S,5R)-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octan-3-one (9 g, 53.81 mmol) in DCM (80 mL) was added pyridine (10.86 mL, 134.53 mmol). Trichloromethyl [(trichloromethyl)oxy]methanoate (3.59 mL, 21.52 mmol) was dissolved in DCM (20 mL) and added dropwise to the reaction mixture. After 30 minutes, 2-methylpropan-2-ol (10.23 mL, 107.62 mmol) was added and the mixture was gradually warmed to RT and stirred for 8 h. The reaction was quenched with water and diluted with DCM (300 mL). The mixture was washed with 1N HCl (1 x 50 mL), saturated sodium bicarbonate (1 x 100 mL) and brine (1 x 100 mL). The organic layer was collected and dried over sodium sulfate and then concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with PE/EA 20/1, v/v to provided 2-methylpropan-2-yl (1R)-5-ethyl-1-methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (7.5 g, 28.05 mmol, 52.13%) as a slightly yellow oil. LC/MS (ESI): 268.2 [M+H]⁺.

[0315] Step 5: 2-Methylpropan-2-yl (1R)-5-ethyl-1-methyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (7.5 g, 28.05 mmol) was dissolved in EtOH (60 mL) and the solution was heated to reflux. NaBH₄ (0.31 mL, 8.42 mmol) was added and the mixture was stirred for 15 min. The mixture was cooled to RT and quenched with aqueous ammonium chloride. The organic solvent was removed under vacuum and the residue was redissolved in EA (200 mL). The mixture was washed with brine, then the organic layer was collected and dried over sodium sulfate and then concentrated in vacuo. The residue was purified by silica gel column chromatography with PE/EtOAc to provided 2-methylpropan-2-yl (1R)-5-ethyl-3-hydroxy-1-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (3.7 g, 13.74 mmol, 48.97%). LC/MS (ESI): 270.2 [M+H]⁺.

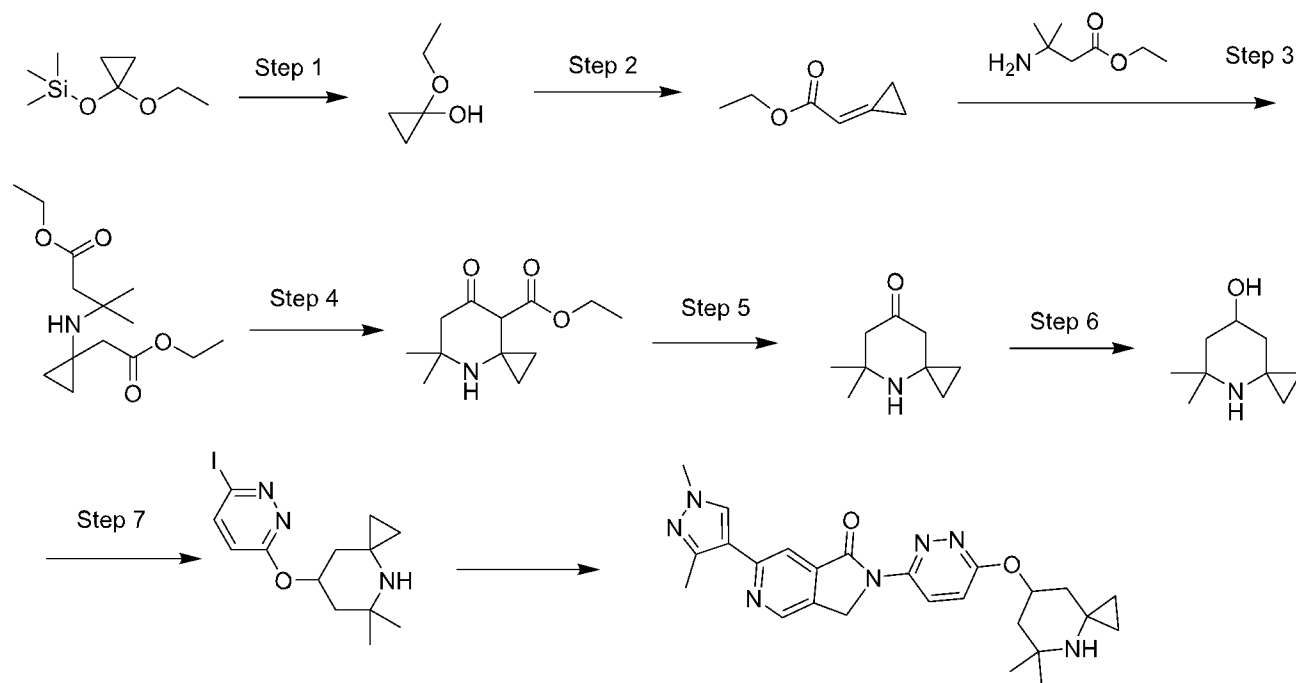
[0316] Step 6: To a solution of 2-methylpropan-2-yl (1R)-5-ethyl-3-hydroxy-1-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (3.7 g, 13.74 mmol) in anhydrous THF (35 mL) was added NaH (0.33 g, 13.74 mmol). The solution was stirred at room temperature for 30 min, then 3,6-dibromo-1,2-diazine (3.27 g, 13.74 mmol) was added and the mixture was stirred at RT for 8 h. The reaction mixture was quenched with saturated ammonium chloride and diluted with EA (200 mL). The mixture was washed with brine, the organic layer was collected and dried over sodium sulfate and then concentrated in vacuo. The crude was purified by silica gel column chromatography with PE/EA 20/1, v/v to provided 2-methylpropan-2-yl (1R)-3-[(6-bromo-1,2-diazin-3-yl)oxy]-5-ethyl-1-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (2 g, 4.69 mmol, 34.15%) as a white solid. LC/MS (ESI): 426.1 [M+H]⁺.

[0317] Step 7: To a round bottom flask charged with 2-methylpropan-2-yl (1S)-3-[(6-bromo-1,2-diazin-3-yl)oxy]-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (150 mg, 0.35 mmol), 6-(1,3-dimethylpyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (88.33 mg, 0.39 mmol), Cs₂CO₃ (102.23 mg, 0.31 mmol, and XantPhos Pd G4 (16.94 mg, 0.01 mmol) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and then heated at 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to afford 2-methylpropan-2-yl (1S,5R)-3-({6-[6-(1,3-dimethylpyrazol-4-yl)-1-oxo-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-2-yl]-1,2-diazin-3-yl}oxy)-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octane-8-carboxylate (60 mg), which was dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h and then concentrated. The residue was purified by RP HPLC using MeCN and H₂O to provide 6-(1,3-dimethylpyrazol-4-yl)-2-(6-{[(1S,5R)-1-ethyl-5-methyl-8-azabicyclo[3.2.1]octan-3-yl]oxy}-1,2-diazin-3-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (20 mg, 0.04 mmol, 12.00%) as a white solid.

[0318] ¹H NMR (DMSO-*d*₆, 400 MHz) δ = 8.98 (s, 1H), 8.70 (d, J = 9.6 Hz, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 7.88 (s, 1H), 7.34 (d, J = 9.6 Hz, 1H), 5.51 (s, 1H), 5.24 (s, 2H), 3.81 (s, 3H), 2.48 (s, 3H), 2.26 (br dd, J = 5.6, 12.4 Hz, 2H), 1.90 (br t, J = 7.1 Hz, 2H), 1.71 - 1.48 (m, 6H), 1.30 (s, 3H), 0.91 (t, J = 7.4 Hz, 3H); LC/MS (ESI): 474.2 [M+H]⁺.

[0319] **Example 11. Synthesis of 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (Compound No. 59)**

[0320] **Scheme 11.**



[0321] **Step 1:** A solution of 1-ethoxy-1-[(trimethylsilyl)oxy]cyclopropane (11.5 mL, 57.37 mmol, 1.0 eq) in MeOH (100 mL) was stirred at RT overnight. The reaction mixture was concentrated under vacuum and use directly in the next step without purification.

[0322] **Step 2:** A solution of 1-ethoxycyclopropan-1-ol (5.9 g, 57.38 mmol, 1.0 eq) and benzoic acid (1.4 g, 11.48 mmol, 0.2 eq) in toluene (6 mL) was stirred at 110 °C for 15 min. Then ethyl (triphenyl-λ5-phosphanylidene)acetate (20.0 g, 57.38 mmol, 1.0 eq) was added and the mixture was stirred at 110 °C for 48 hours. The reaction mixture was concentrated under vacuum. The crude product was purified by silica gel chromatography eluted with PE to give ethyl cyclopropylideneacetate (3.1 g, 42.4%).

[0323] **Step 3:** A solution of ethyl cyclopropylideneacetate (1.7 g, 13.47 mmol, 1.0 eq), ethyl 3-amino-3-methylbutanoate (2.3 g, 16.17 mmol, 1.2 eq) in DIEA (2.99 mL, 18.06 mmol, 1.34 eq) was stirred at 60 °C for 3 h. The reaction was monitored by TLC and LC/MS. The crude product was purified by silica gel chromatography eluted with PE:EA (5:1) to obtain ethyl 3-((1-(2-ethoxy-2-oxoethyl)cyclopropyl)amino)-3-methylbutanoate (1.2 g, 32.2%). LC/MS (ESI): 272.1 [M+H]⁺.

[0324] **Step 4:** To a solution of ethyl 3-((1-(2-ethoxy-2-oxoethyl)cyclopropyl)amino)-3-methylbutanoate (980 mg, 3.64 mmol, 1.0 eq) in THF (10 mL) was added t-BuOK (5.46 mL, 5.46 mmol) at 0 °C under N₂ atmosphere. The reaction mixture was stirred at 0 °C for 1 h. LC/MS showed the desired mass. The reaction mixture was poured into saturated aqueous NH₄Cl (10 mL). The resulting mixture was extracted with EA (2 x 20 mL). The organic layer was dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel chromatography eluted with PE/EA (3:1) to obtain ethyl 5,5-dimethyl-7-oxo-4-azaspiro[2.5]octane-8-carboxylate (618 mg, 76.1%). LC/MS (ESI): 226.1 [M+H]⁺.

[0325] Step 5: A solution of ethyl 7-oxospiro[4-azaspiro[2.5]octane-5,1'-cyclopropane]-8-carboxylate (618.0 mg, 2.77 mmol, 1.0 eq) in a mixture of H₂O (5 mL) and H₂SO₄ (5 mL) was stirred at 120 °C for 1 h. LC/MS showed desired mass. The reaction mixture was poured into ice water. The aqueous layer was adjusted to pH over 9 and extracted with EA (3 x 20 mL). The crude was concentrated under reduced pressure to yield 5,5-dimethyl-4-azaspiro[2.5]octan-7-one (326.0 mg, 77.9%). LC/MS (ESI): 154.1 [M+H]⁺.

[0326] Step 6: To a solution of spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane]-7-one (86.0 mg, 0.57 mmol, 1.0 eq) in MeOH (5 mL) was added NaBH₄ (64.5 mg, 1.71 mmol, 3.0 eq) at 0 °C. The mixture was stirred at RT for 1 h. LC/MS showed desired mass. The reaction mixture was diluted with H₂O and the pH was adjusted to 7. The aqueous layer was extracted with EA (2 x 10 mL) and (DCM/propan-2-ol:IPA, 10:1). The organic layer was dried over Na₂SO₄ and evaporated to dryness. The crude product was use directly in the next step without further purification. LC/MS (ESI): 156.1 [M+H]⁺.

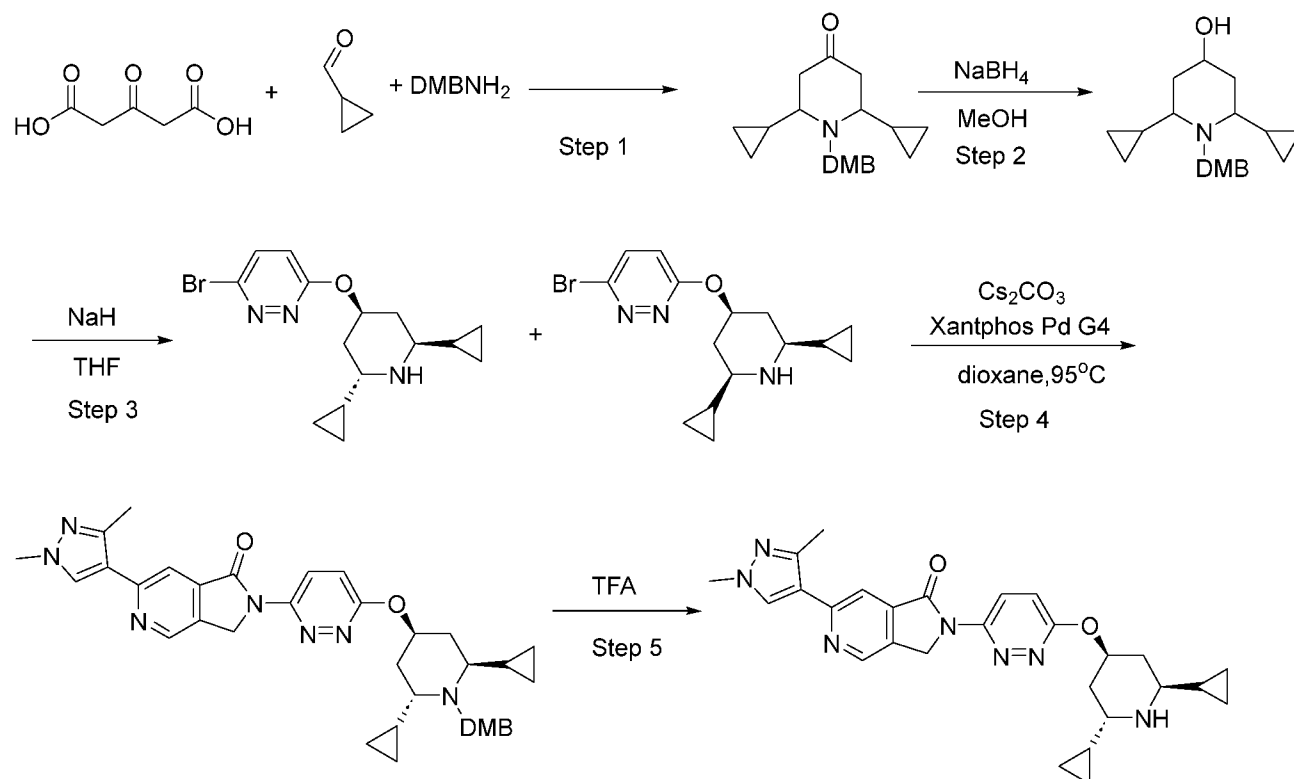
[0327] Step 7: To a solution of 5,5-dimethyl-4-azaspiro[2.5]octan-7-ol (106.0 mg, 0.69 mmol, 1.0 eq) in THF (5 mL) was added NaH (39.0 mg, 0.98 mmol, 1.4 eq) at 0 °C under N₂ atmosphere. The reaction mixture was stirred at 0 °C under N₂ atmosphere for 20 min. Then, 3,6-diiodo-1,2-diazine (252.5 mg, 0.76 mmol, 1.1 eq) was added the mixture was stirred at 60 °C overnight. The reaction was cooled to RT and diluted with DMF (5 mL) and then the reaction was stirred for another 3 h at 100 °C. LC/MS showed desired mass. The reaction was cooled to RT and then pouring into water. The aqueous layer was extracted with EA (3 x 10 mL). The organic layer was washed with brine, dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel chromatography eluted with PE: EA (1:1) to obtain 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-((5,5-dimethyl-4-azaspiro[2.5]octan-7-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (146.0 mg, 59.1%). LC/MS (ESI): 360.0 [M+H]⁺.

[0328] Step 8: A solution of 7-((6-iodopyridazin-3-yl)oxy)-5,5-dimethyl-4-azaspiro[2.5]octane (48.0 mg, 0.13 mmol, 1.0 eq), 3-(1,3-dimethylpyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (32.2 mg, 0.14 mmol, 1.05 eq), (1*R*,2*R*)-cyclohexane-1,2-diamine (1.5 mg, 0.01 mmol, 0.1 eq), CuI (2.7 mg, 0.01 mmol, 0.1 eq), K₂CO₃ (55.7 mg, 0.40 mmol, 3.0 eq) in DMF (3 mL) was stirred at 120 °C overnight under N₂ atmosphere. LC/MS showed desired mass and reactant consumed. The reaction mixture was evaporated to dryness. The crude product was purified by silica gel chromatography eluted with DCM/MeOH (10:1) then prep-HPLC(FA) to obtain 3-(1,3-dimethylpyrazol-4-yl)-6-[6-(spiro[4-azaspiro[2.5]octane-5,1'-cyclopropane]-7-yloxy)-1,2-diazin-3-yl]-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (12.92 mg, 19.1%).

[0329] ¹H NMR (DMSO-*d*₆, 400MHz) δ = 8.98 (s, 1H), 8.69 (d, J = 9.6 Hz, 1H), 8.37 (s, 1H), 8.19 (br s, 1H), 7.88 (s, 1H), 7.32 (d, J = 9.6 Hz, 1H), 5.63 - 5.53 (m, 1H), 5.24 (s, 2H), 3.81 (s, 3H), 2.48 (s, 3H), 2.11 (br dd, J = 3.6, 12.3 Hz, 1H), 1.88 - 1.80 (m, 1H), 1.63 (br dd, J = 4.3, 11.8 Hz, 1H), 1.37 (t, J = 11.6 Hz, 1H), 1.21 (s, 3H), 1.10 (s, 3H), 0.59 - 0.52 (m, 2H), 0.51 - 0.44 (m, 1H), 0.40 - 0.33 (m, 1H); LC/MS (ESI): 460.1 [M+H]⁺.

[0330] **Example 12. Synthesis of 2-(6-(((2S,6S)-2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (Compound No. 104)**

[0331] **Scheme 13.**



[0332] **Step 1:** To a solution of acetone dicarboxylic acid (3.0g, 0.5mmol) in water (20mL) was added cyclopropanecarbaldehyde (2.876 g, 41 mmol) and then (2,4-dimethoxyphenyl)methanamine (2.8 g, 20.5 mmol) was added portionwise over 10 min. The resulting reaction was stirred at room temperature for 3 days. The reaction mixture was extracted with DCM (3 x 60 mL) and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4 , and dried under vacuum to give a brown residue. The isomeric piperidones were separated by silica gel chromatography with hexane/ethyl acetate (7/1, v/v). The desired compound (3.4 g, 54 %) was obtained as a pale yellow oil.

[0333] **Step 2:** To a mixture of 2,6-dicyclopropyl-1-(3,4-dimethylbenzyl)piperidin-4-one (5.0 g, 15.18 mmol) in MeOH (50 mL) was added NaBH_4 (0.57 g, 15.18 mmol) at RT under N_2 and the mixture was stirred at for 2 h. The mixture was concentrated and the residue was purification by chromatography on silica gel DCM : MeOH=10:1 to give 2,6-dicyclopropyl-1-(3,4-dimethylbenzyl)piperidin-4-ol (2.0 g, 39.76%) as an oil.

[0334] **Step 3:** To a mixture of 2,6-dicyclopropyl-1-(3,4-dimethylbenzyl)piperidin-4-ol (2.0 g, 6.03 mmol) in THF (30 mL) was added NaH (0.48 g, 12.07 mmol) at RT under N_2 and the mixture was stirred for 1 h. Then 3,6-dibromo-1,2-diazine (1.87 g, 7.84 mmol) was added and the mixture was stirred at 50 °C for 16 h. The mixture was quenched with MeOH and concentrated under vacuum. The resulting residue was purification by chromatography on silica gel PE:EA=10:1-5:1 to give 3-bromo-6-(((2S,6S)-

2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazine (440, 14.93%) and 3-bromo-6-(((2R,4s,6S)-2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazine (800 mg, 1.64 mmol, 27.16%) as a white solid.

[0335] Step 4: To a mixture of 6-(1,3-dimethylpyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-3-one (70 mg, 0.31 mmol) and 3-bromo-6-(((2S,6S)-2,6-dicyclopropylpiperidin-4-yl)oxy)pyridazine (149.79 mg, 0.31 mmol) in dioxane (10 mL) was added XantPhos Pd G4 (49.68 mg, 0.03 mmol) and Cs_2CO_3 (299.77 mg, 0.92 mmol) at RT under N_2 and the mixture was stirred at 95 °C for 3h. The mixture was concentrated under reduced pressure and the residue was purification by chromatography on silica gel DCM : MeOH=10 to give 2-(6-(((2S,6S)-2,6-dicyclopropyl-1-(3,4-dimethylbenzyl)piperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (170 mg, 86.36%) as a yellow solid.

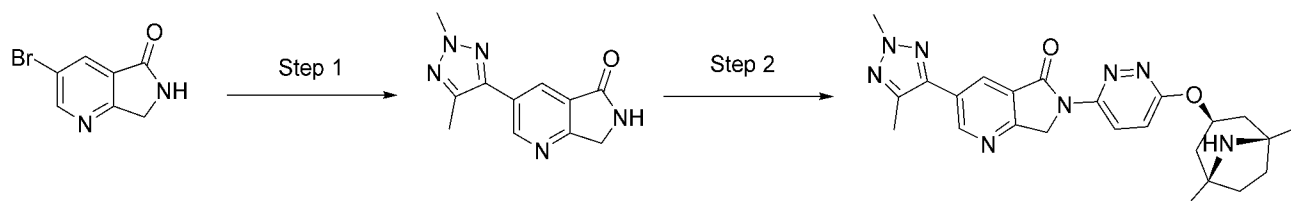
[0336] Step 5: A mixture of 2-(6-(((2S,6S)-2,6-dicyclopropyl-1-(3,4-dimethylbenzyl)piperidin-4-yl)oxy)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2,3-dihydro-1H-pyrrolo

[0337] [3,4-c]pyridin-1-one (170 mg, 0.27 mmol) in TFA (20 mL) was stirred at 110 °C for 48 h. After the reaction was completed, the mixture was concentrated under reduced pressure and the residue was purified by pre-HPLC(TFA) to give 6-(1,3-dimethylpyrazol-4-yl)-2-(6-(((2S,6S)-2,6-dicyclopropylhexahydropyridin-4-yl)oxy)-1,2-diazin-3-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (78.73 mg, 60.56%) as a yellow solid.

[0338] ^1H NMR ($\text{DMSO}-d_6$) δ = 8.98 (s, 1H), 8.73 (d, J = 9.6 Hz, 1H), 8.34 (s, 1H), 7.88 (s, 1H), 7.38 (d, J = 9.6 Hz, 1H), 5.64 (dt, J = 9.0, 4.7 Hz, 1H), 5.25 (s, 2H), 3.82 (s, 3H), 2.90-3.00 (m, 2H), 2.46-2.49 (m, 3H), 2.40-2.46 (m, 1H), 2.29-2.38 (m, 1H), 1.85-2.06 (m, 2H), 1.24-1.34 (m, 1H), 1.18 (td, J = 8.5, 4.0 Hz, 1H), 0.53-0.70 (m, 5H), 0.35-0.51 (m, 3H), 1H not observed (NH); LC/MS (ESI): 486.2 $[\text{M}+\text{H}]^+$.

[0339] Example 13. Synthesis of 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 206)

[0340] Scheme 13.



[0341] Step 1: 4-Bromo-2,5-dimethyl-2H-1,2,3-triazole (262.0 mg, 1.5 mmol, 1.5 eq); 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (762 mg, 3.0 mmol, 3.0 eq), potassium acetate (300 mg, 3.0 mmol, 3.0 eq) and $\text{PdCl}_2(\text{dppf})$ were added to the CH_2Cl_2 adduct (109.3 mg, 0.15 mmol, 0.1 eq) and the solids were degassed under N_2 . Anhydrous dioxane (9 mL) was added and the mixture was heated to 90 °C. After the reaction was completed, the reaction mixture was cooled to room temperature. Next 3-bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (211.9 mg, 1.0 mmol, 1.0 eq), aqueous potassium carbonate (2 M, 2mL) and $\text{PdCl}_2(\text{dppf})$ were added and the mixture was heated to 90 °C. After the reaction was completed, the mixture was cooled, filtered through Celite, and washed with EA (100 mL).

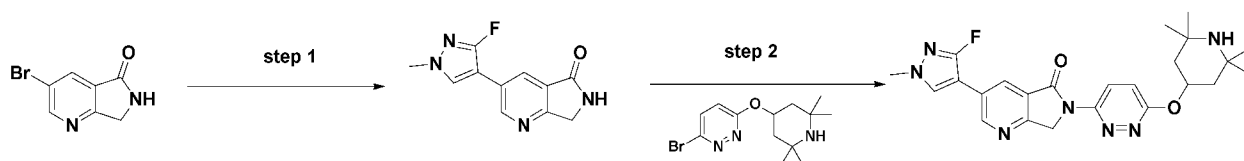
The filtrate was washed with brine and then the organic layer was collected, dried over sodium sulfate, and then concentrated under vacuo. The crude mixture was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (116 mg, 51%) as a brown solid. LC/MS (ESI): 230.1 [M+H]⁺.

[0342] Step 2: To a round bottom flask charged with 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (37.4 mg, 0.15 mmol, 1.0 eq), *tert*-butyl (1*R*,3*s*,5*S*)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (61.8 mg, 0.15 mmol, 1.1 eq), Cs₂CO₃ (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) 1,4-dioxane (4 mL) was added and the reaction mixture was degassed with argon for 5 min and then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v and was then dissolved HCl in dioxane (2 mL, 4.0 mol/L) and stirred for 1 h at RT. The product was concentrated under reduced pressure and the resulting residue was purified by RP HPLC using MeCN and H₂O as eluent to provide 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1*R*,3*s*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (37.8 mg, 54.7 %) as a white solid.

[0343] ¹H NMR (DMSO-*d*₆, 400MHz) δ = 9.18 (d, *J* = 2.0 Hz, 1H), 8.87 (br d, *J* = 10.6 Hz, 1H), 8.79 (br s, 1H), 8.75 (d, *J* = 9.6 Hz, 1H), 8.39 (d, *J* = 2.0 Hz, 1H), 7.41 (d, *J* = 9.5 Hz, 1H), 5.55 (tt, *J* = 10.9, 5.6 Hz, 1H), 5.24 (s, 2H), 4.19 (s, 3H), 2.46 (br d, *J* = 6.1 Hz, 2H), 2.18 (br d, *J* = 8.0 Hz, 2H), 1.90 (br d, *J* = 8.3 Hz, 2H), 1.80 (br t, *J* = 12.1 Hz, 2H), 1.46 (s, 6H), 3H not observed (triazole methyl overlapped with DMSO-*d*₆ residue); LC/MS (ESI): 461.2 [M+H]⁺.

[0344] Example 14. Synthesis of 3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 190)

[0345] Scheme 14.



[0346] Step 1: 4-Bromo-2,5-dimethyl-2H-1,2,3-triazole (262.0 mg, 1.5 mmol, 1.5 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (762 mg, 3.0 mmol, 3.0 eq), potassium acetate (300 mg, 3.0 mmol, 3.0 eq) and PdCl₂(dppf).CH₂Cl₂ adduct (109.3 mg, 0.15 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 90 °C. When full conversion was achieved, the reaction mixture was cooled to room temperature. 4-Bromo-3-fluoro-1-methyl-1H-pyrazole (177.9 mg, 1.0 mmol, 1.0 eq), aqueous potassium carbonate (2 M, 2 mL) and PdCl₂(dppf).CH₂Cl₂ adduct (109.3 mg, 0.15 mmol, 0.1 eq) were added and the mixture was heated to 90 °C. When full conversion was achieved, the mixture was cooled, filtered through a pad of Celite, and the filter cake was washed with EA (100 mL). The filtrate was washed with

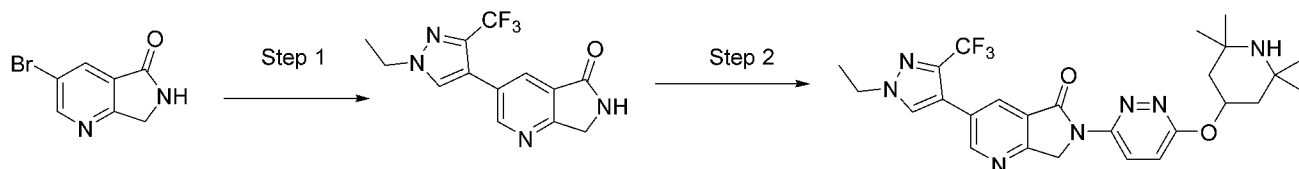
brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (116mg, 51%) as a brown solid. LC/MS (ESI): 233.1 [M+H]⁺.

[0347] Step 2: 3-[1-(Trifluoromethyl)pyrazol-4-yl]-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (106 mg, 0.46 mmol), 3-bromo-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazine (149.39 mg, 0.46 mmol), XantPhos Pd G4 (73.95 mg, 0.05 mmol) and Cs₂CO₃ (446.18 mg, 1.37 mmol) was dissolved in dioxane (8 mL) and the reaction mixture was stirred at 90 °C overnight. After the reactants was consumed, the mixture was cooled to room temperature, quenched with water and diluted with EA (100 mL). The mixture was washed with brine, and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH to provided 3-(3-fluoro-1-methyl-1H-pyrazol-4-yl)-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (24.1 mg, 0.05 mmol, 10.91%) as a white solid.

[0348] ¹H NMR (DMSO-*d*₆, 400MHz) δ = 8.99-9.09 (m, 1H), 8.68 (d, J = 9.6 Hz, 1H), 8.37-8.47 (m, 1H), 8.22-8.31 (m, 1H), 7.24-7.36 (m, 1H), 5.57-5.68 (m, 1H), 5.19 (s, 2H), 3.80 (s, 3H), 2.05-2.07 (m, 2H), 1.24-1.29 (m, 2H), 1.23 (s, 6H), 1.08-1.13 (m, 6H), 1H not observed (NH); LC/MS (ESI): 466.2 [M+H]⁺.

[0349] Example 15. Synthesis of 3-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 172)

[0350] Scheme 15.



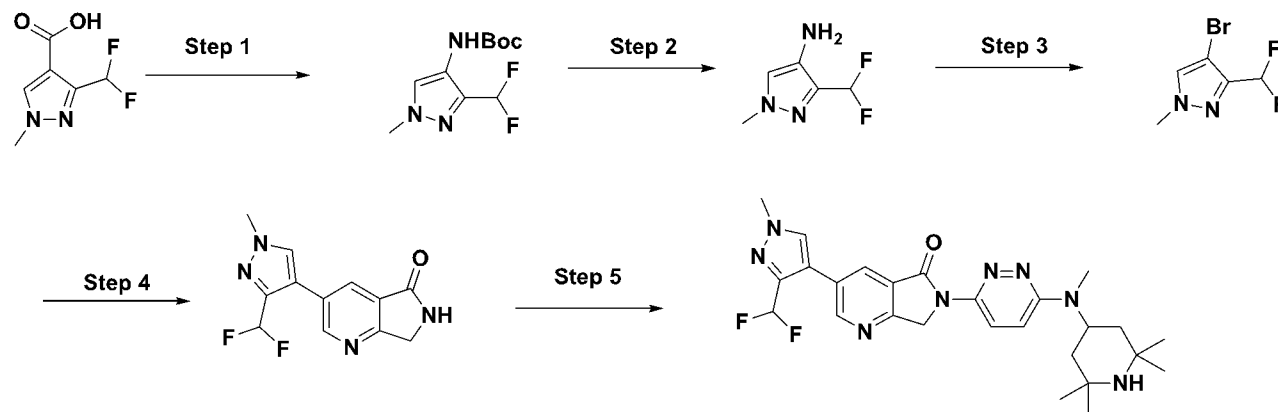
[0351] Step 1: 3-Bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (213.0 mg, 1.0 mmol, 1.0 eq), (1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)boronic acid (312. mg, 1.5 mmol, 1.5 eq), aqueous potassium carbonate (2 M, 2 mL) and PdCl₂(dppf).CH₂Cl₂ adduct (73.2 mg, 0.1 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 3-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (183.2 mg, 62%) as a brown solid. LC/MS (ESI): 297.1 [M+H]⁺.

[0352] Step 2: To a round bottom flask charged with 3-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (44.4 mg, 0.15 mmol, 1.0 eq), *tert*-butyl (1*R*,3*S*,5*S*)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (61.8 mg, 0.15 mmol, 1.1 eq), Cs₂CO₃ (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, *v/v*. The residue was purified by RP HPLC using MeCN and H₂O as eluent to provide 3-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (42.35 mg, 53.3 %) as a white solid.

[0353] ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.92 (d, 1H, *J* = 2.0 Hz), 8.71 (d, 1H, *J* = 9.6 Hz), 8.50 (s, 1H), 8.32 (s, 1H), 8.19 (d, 1H, *J* = 2.0 Hz), 7.35 (d, 1H, *J* = 9.6 Hz), 5.64 (s, 1H), 5.24 (s, 2H), 4.30 (q, 2H, *J* = 7.3 Hz), 2.17 (dd, 2H, *J* = 3.9, 12.4 Hz), 1.5-1.5 (m, 3H), 1.4-1.5 (m, 2H), 1.34 (s, 6H), 1.24 (s, 6H); LC/MS (ESI): 530.2 [M+H]⁺.

[0354] Example 16. Synthesis of 3-(3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 198)

[0355] Scheme 16.



[0356] Step 1: To a solution of 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid (6.58 mL, 56.78 mmol) in 2-methylpropan-2-ol (200 mL) was added ethyl[di(prop-2-yl)]amine (18.82 mL, 113.56 mmol) and diphenyl azidophosphonate (15.99 mL, 73.81 mmol) and the reaction mixture was stirred at 90 °C for 4 h under N₂. The mixture was diluted with EA (10 mL*3) and H₂O (30 mL) and the organic layer was washed with brine (5 mL*3), dried over sodium sulfate, and then concentrated in vacuo. The crude product was purified by silica gel column chromatography with PE/EA 10/1, *v/v* to provided *tert*-butyl (3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)carbamate (13.2 g, 53.39 mmol, 94.03%). LC/MS (ESI): 248.1 [M+H]⁺.

[0357] Step 2: To a solution of *tert*-butyl (3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)carbamate (13.2 g, 53.39 mmol) in MeOH (30 mL) was added 4M HCl-MeOH (60 mL) and the reaction mixture

was stirred at 25 °C overnight. Then the reaction mixture was concentrated to obtain the cured product 3-(difluoromethyl)-1-methyl-1H-pyrazol-4-amine (10.2 g) which was used in the next step without further purification. LC/MS (ESI): 148.1[M+H]⁺.

[0358] Step 3: To a solution of 3-(difluoromethyl)-1-methyl-1H-pyrazol-4-amine (3 g, 20.39 mmol) in acetonitrile (30 mL) was added 2-methyl-2-(nitrosooxidanyl)propane (3.67 mL, 30.59 mmol) and copper bromide (I) (1.24 mL, 40.78 mmol) and the reaction mixture was stirred at 70 °C for 1 h. The mixture was diluted with EA (50 mL*3) and H₂O (50 mL) and then the organic layer was washed with brine (30 mL*3), dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with PE/EA (50/1-20/1-10/1, v/v) to provide 4-bromo-3-(difluoromethyl)-1-methyl-1H-pyrazole (2.3 g, 10.90 mmol, 53.46%). LC/MS (ESI): 210.9, 212.9 [M+H]⁺.

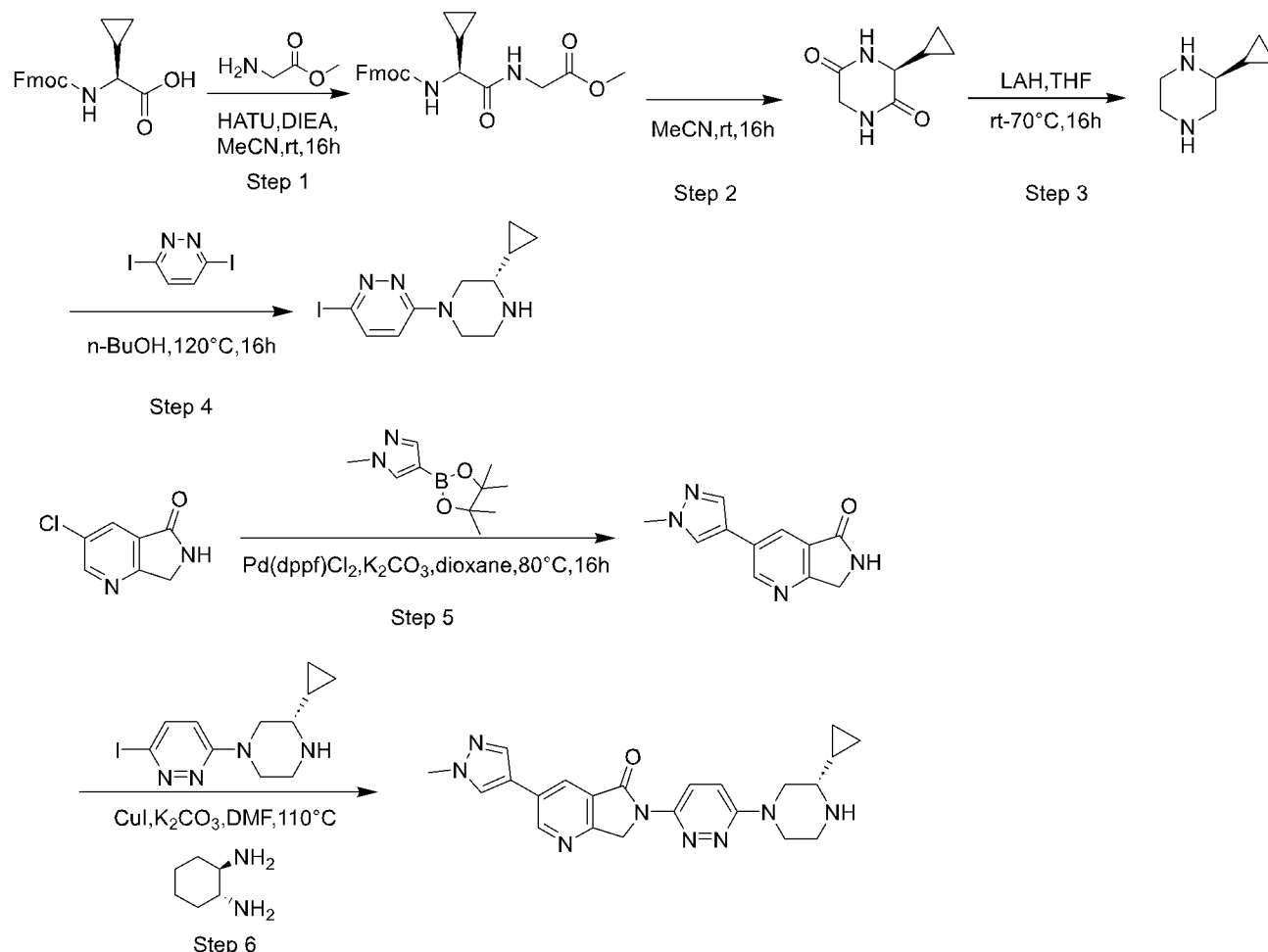
[0359] Step 4: 4-Bromo-3-(difluoromethyl)-1-methyl-1H-pyrazole (316.5 mg, 1.5 mmol, 1.5 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (762 mg, 3.0 mmol, 3.0 eq), potassium acetate (300 mg, 3.0 mmol, 3.0 eq) and PdCl₂(dppf).CH₂Cl₂ adduct (109.3 mg, 0.15 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 90 °C. When full conversion was achieved, the reaction mixture was cooled to room temperature. Next 3-bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (211.9 mg, 1.0 mmol, 1.0 eq), aqueous potassium carbonate (2 M, 2 mL) and PdCl₂(dppf).CH₂Cl₂ adduct (109.3 mg, 0.15 mmol, 0.1 eq) were added and the mixture was heated to 90 °C. When full conversion was achieved, the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 3-(3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (164.7 mg, 62%) as a brown solid. LC/MS (ESI): 265.1 [M+H]⁺.

[0360] Step 5: To a round bottom flask charged with 3-(3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (39.4 mg, 0.15 mmol, 1.0 eq), 6-bromo-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)pyridazin-3-amine (61.8 mg, 0.15 mmol, 1.1 eq), Cs₂CO₃ (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and then heated at 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, and then the residue was further purified by RP HPLC using MeCN and H₂O as eluent to provide 3-(3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)-6-(6-(methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (3.83 mg, 5.0 %) as a white solid.

[0361] ¹H NMR (400 MHz, Methanol-*d*₄) δ : 8.97 (d, *J* = 2.0 Hz, 1H), 8.63 (d, *J* = 9.9 Hz, 1H), 8.34 (d, *J* = 2.1 Hz, 1H), 8.12 (s, 1H), 7.29 (d, *J* = 10.0 Hz, 1H), 7.03 - 6.74 (m, 1H), 5.22 (s, 2H), 4.00 (s, 3H), 2.99 (s, 3H), 1.83 - 1.69 (m, 4H), 1.50 (s, 6H), 1.35 (s, 6H); LC/MS (ESI): 511.2 [M+H]⁺.

[0362] **Example 17. Synthesis of (S)-6-(6-(3-cyclopropylpiperazin-1-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 155)**

[0363] **Scheme 17.**



[0364] **Step 1:** To a solution of (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-cyclopropylacetic acid (10 g, 28.29 mmol, 1.0 eq) and methyl aminoacetate (3.0 g, 33.95 mmol, 1.2 eq) in acetonitrile (50 mL) was added DIEA (9.1 g, 70.74 mmol, 2.5 eq) and HATU (11.8 g, 31.12 mmol, 1.1 eq), and the reaction mixture was stirred at RT for 16 h. Next the reaction mixture was filtered to provided methyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-cyclopropylacetyl)glycinate (9.5 g, 22.38 mmol, 79.09%) as a slightly yellow solid. LC/MS (ESI): 409.2 [M+H]⁺.

[0365] **Step 2:** A solution of methyl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-cyclopropylacetyl)glycinate (5.0 g, 11.78 mmol, 1.0 eq) in acetonitrile (100 mL) was stirred RT for 16 h. After the reaction was completed, the solution was concentrated in vacuo to provided (S)-3-cyclopropylpiperazine-2,5-dione (4.85 g, 11.43 mmol, 97.00%) as a slightly yellow solid. LC/MS (ESI): 155.1 [M+H]⁺.

[0366] **Step 3:** LiAlH₄ (2.14 g, 56.40 mmol, 6.0 eq) was added to a vigorous stirred solution of (S)-3-cyclopropylpiperazine-2,5-dione (1.6 g, 9.40 mmol, 1.0 eq) in THF (20 mL) in an ice bath, and then the reaction mixture was stirred at 70 °C for 16 h. After the reaction was completed, the mixture was poured into KOH (6N) and stirred in an ice bath for 1 h. Next the mixture was filtered and the filtrate was

extracted with EA, washed with brine, dried over Na₂SO₄, and concentrated in vacuo to provided (S)-2-cyclopropylpiperazine (1.2 g, 8.44 mmol, 89.74%) as a yellow oil. LC/MS (ESI): 127.1 [M+H]⁺.

[0367] Step 4: DIEA (1.13 g, 8.79 mmol, 1.46 mL, 2.5 eq) was added to a vigorous stirred solution of (2S)-2-(2-methylprop-2-yl)piperazine (0.5 g, 3.51 mmol, 1.0 eq) and 3,6-diiodo-1,2-diazine (1.17 g, 3.51 mmol, 1.0 eq) in n-BuOH (7 mL), and the reaction mixture was stirred at 120 °C for 16 h. After the reaction was completed, the mixture was concentrated in vacuo and the residue was diluted with EA, washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo to provided (S)-3-(3-cyclopropylpiperazin-1-yl)-6-iodopyridazine (450 mg, 1.30 mmol, 36.98%) as a yellow solid. LC/MS (ESI): 331.1 [M+H]⁺.

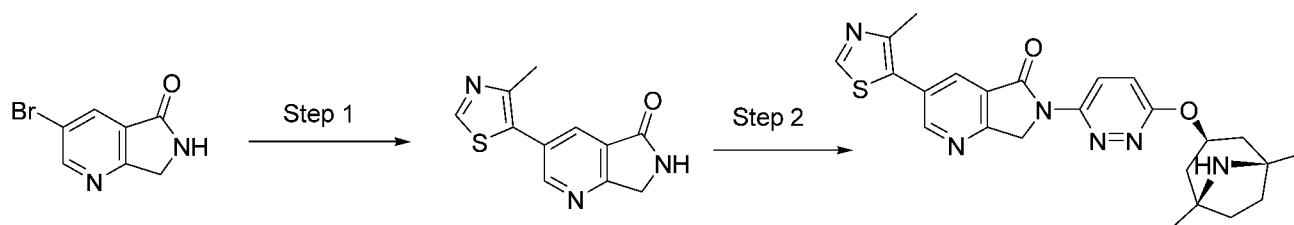
[0368] Step 5: Pd(dppf)Cl₂ (49 mg, 0.06 mmol, 0.05 eq) was added to a vigorous stirred solution of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (250 mg, 1.20 mmol, 1.0 eq), 3-bromo-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (256 mg, 1.20 mmol, 1.0 eq) and K₂CO₃ (332 mg, 2.40 mmol, 2.0 eq) in dioxane (5 mL) and water (1 mL). The reaction mixture was stirred at 80 °C for 16 h. Next the reaction mixture was filtered and the filtrate was concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 10/1, v/v to give 3-(1-methylpyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (135 mg, 0.63 mmol, 52.51%) as a slightly yellow solid. LC/MS (ESI): 215.2 [M+H]⁺.

[0369] Step 6: 6-(1-Methylpyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (50 mg, 0.23 mmol, 1.0 eq) and (S)-3-(3-cyclopropylpiperazin-1-yl)-6-iodopyridazine (80 mg, 0.23 mmol, 1.0 eq) were dissolved in DMF (2 mL), and CuI (4 mg, 0.02 mmol, 0.10 eq), K₂CO₃ (97 mg, 0.70 mmol, 3.0 eq) and (1R,2R)-cyclohexane-1,2-diamine (2.7 mg, 0.02 mmol, 0.10 eq) were added and the reaction mixture was stirred at 100 °C for 16 h. Next the reaction was filtered and the filtrate was concentrated. The crude product was purified by pre-HPLC to provide (S)-6-(6-(3-cyclopropylpiperazin-1-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (24.19 mg, 21.55%) as a white solid.

[0370] ¹H NMR (DMSO-*d*₆, 400 MHz) δ = 9.12 (d, J = 1.6 Hz, 1H), 8.49 (d, J = 9.8 Hz, 1H), 8.44 (s, 1H), 8.36 (d, J = 1.8 Hz, 1H), 8.14 (s, 1H), 7.51 (d, J = 10.0 Hz, 1H), 5.13 (s, 2H), 4.27 (br d, J = 11.1 Hz, 1H), 4.15 (br d, J = 10.8 Hz, 1H), 3.89 (s, 3H), 3.14 - 3.03 (m, 2H), 2.95 (br t, J = 11.5 Hz, 1H), 2.84 - 2.74 (m, 2H), 0.84 (br d, J = 7.1 Hz, 1H), 0.48 (br s, 2H), 0.33 (br s, 2H), 1H not observed (NH); LC/MS (ESI): 417.2 [M+H]⁺.

[0371] Example 18. Synthesis of 6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(4-methylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 248)

[0372] Scheme 18.



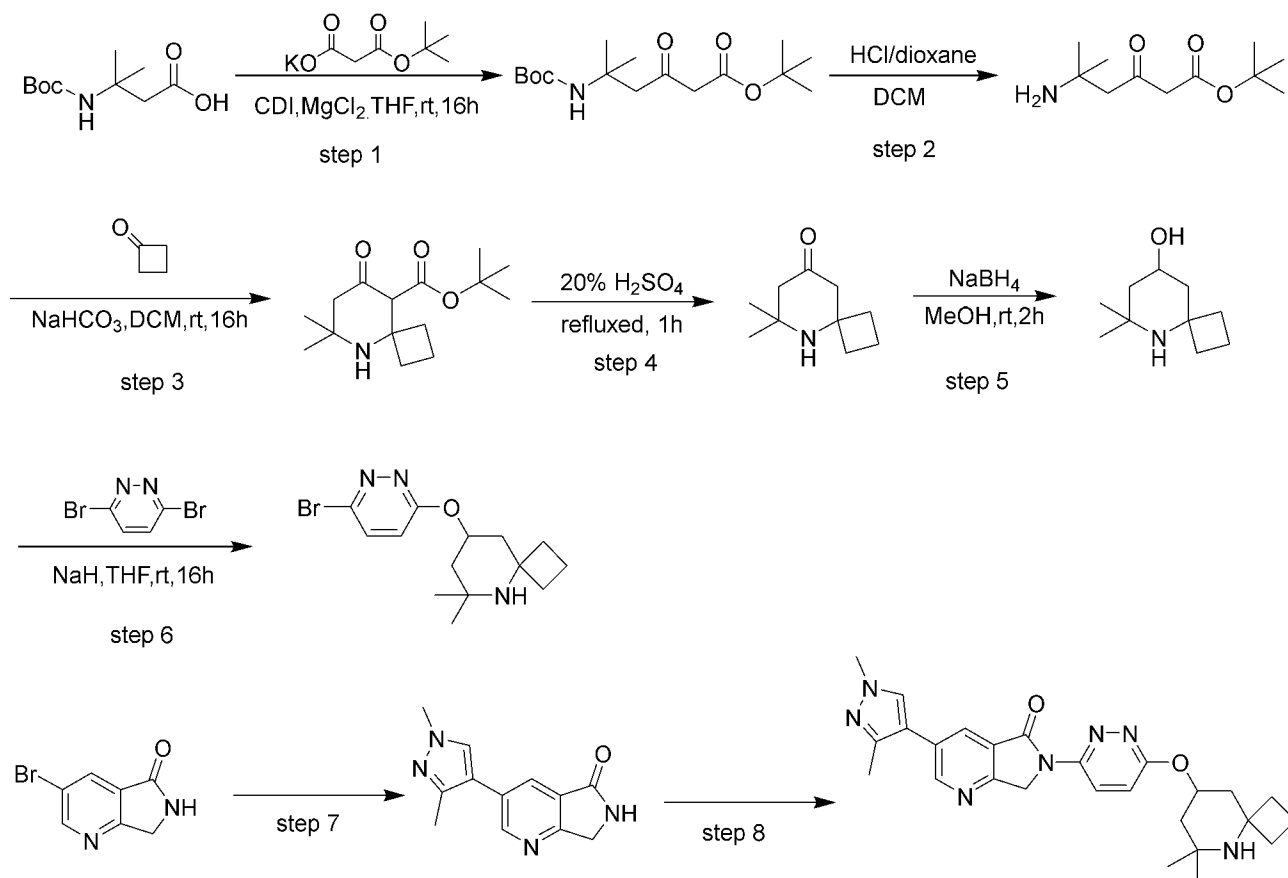
[0373] Step 1: 3-Bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (213.0 mg, 1.0 mmol, 1.0 eq), 4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (375 mg, 1.5 mmol, 1.5 eq), aqueous potassium carbonate (2 M, 2 mL) and PdCl₂(dppf).CH₂Cl₂ adduct (73.2 mg, 0.1 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 3-(4-methylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (143.2 mg, 62%) as brown solid. LC/MS (ESI): 232.1 [M+H]⁺.

[0374] Step 2: To a round bottom flask charged with 3-(4-methylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (44.4 mg, 0.15 mmol, 1.0 eq), *tert*-butyl (1*R*,3*S*,5*S*)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (61.8 mg, 0.15 mmol, 1.1 eq), Cs₂CO₃ (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v, and was then dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction mixture was stirred at RT for 1 h, and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H₂O as eluent to provide 6-(6-(((1*R*,3*S*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-3-(4-methylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (20.37 mg, 29.4 %) as a white solid.

[0375] ¹HNMR (400 MHz, DMSO-*d*₆) δ = 9.15 (s, 1H), 9.00 (s, 1H), 8.72 (br d, J = 9.5 Hz, 1H), 8.29 (br d, J = 12.3 Hz, 3H), 7.38 (br d, J = 9.5 Hz, 1H), 5.56 - 5.48 (m, 1H), 5.24 (s, 2H), 2.53 - 2.51 (m, 3H), 2.35 (br dd, J = 5.3, 12.4 Hz, 2H), 2.06 (br d, J = 7.5 Hz, 2H), 1.88 - 1.73 (m, 4H), 1.41 (br s, 6H); LC/MS (ESI): 463.2 [M+H]⁺.

[0376] Example 19. Synthesis of 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 249)

[0377] Scheme 19.



[0378] Step 1: To a solution of 3-((*tert*-butoxycarbonyl)amino)-3-methylbutanoic acid (12.0 g, 55.23 mmol, 1.0 eq) in THF (100 mL) was added CDI (10.75 g, 66.28 mmol, 1.20 eq) and the reaction mixture was stirred at RT for 1 h. Then added $MgCl_2$ (2.62 g, 43.08 mmol, 0.78 eq) and potassium 3-(*tert*-butoxy)-3-oxopropanoate (16.43 g, 82.85 mmol, 1.5 eq) were added and the reaction mixture was stirred at 50 °C overnight. Next the reaction mixture was concentrated and then diluted with H_2O (40 mL). The aqueous layer was extracted with EA (3 x 50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluted with PE: EA (10:1) to give *tert*-butyl 5-((*tert*-butoxycarbonyl)amino)-5-methyl-3-oxohexanoate (10.5 g, 20.27%). LC/MS (ESI): 260.2 $[M+H]^+$.

[0379] Step 2: To a solution of *tert*-butyl 5-((*tert*-butoxycarbonyl)amino)-5-methyl-3-oxohexanoate (5.0 g, 15.85 mmol, 1.0 eq) in DCM (10 mL) was added HCl/dioxane (5 mL) and the reaction mixture was stirred at RT for 1 h. After the reaction was completed, the reaction mixture was concentrated to give *tert*-butyl 5-amino-5-methyl-3-oxohexanoate (3.4 g, 99.9%). LC/MS (ESI): 216.2 $[M+H]^+$.

[0380] Step 3: To a solution of *tert*-butyl 5-amino-5-methyl-3-oxohexanoate (3.1 g, 16.84 mmol, 1.0 eq) in DCM (18 mL) was added K_2CO_3 (4.98 g, 36.0 mmol, 2.5 eq) and cyclobutanone (5.43 mL, 70.09 mmol, 5.0 eq) and the reaction mixture was stirred at RT for 72 h. LC/MS showed desired mass. The reaction mixture was filtered and the filtrate was washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product purified by silica gel chromatography eluted with PE: EA (3:1) to give *tert*-butyl 6,6-dimethyl-8-oxo-5-azaspiro[3.5]nonane-9-carboxylate (1.2 g, 31.1%). LC/MS (ESI): 268.2 $[M+H]^+$.

[0381] Step 4: To a solution of tert-butyl 6,6-dimethyl-8-oxo-5-azaspiro[3.5]nonane-9-carboxylate (1200 mg, 4.49 mmol, 1.0 eq) in a mixture of H₂O (18 mL) and H₂SO₄ (2 mL) was added and the reaction mixture was stirred at 120 °C for 1 h. LC/MS showed desired mass. The reaction mixture was poured into ice water and the pH was adjusted to over 9. The aqueous layer was extracted with EA (3 x 20 mL). The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluted with DCM: MeOH (10:1) to give 6,6-dimethyl-5-azaspiro[3.5]nonan-8-one (620 mg, 81.27%). LC/MS (ESI): 168.2 [M+H]⁺.

[0382] Step 5: To a solution of 6,6-dimethyl-5-azaspiro[3.5]nonan-8-one (620 mg, 3.71 mmol, 1.0 eq) in MeOH (10 mL) was added NaBH₄ (140 mg, 3.71 mmol, 1.0 eq) at 0 °C. The reaction mixture was stirred at RT for 1 h. LC/MS showed the desired mass. The reaction mixture was diluted with H₂O and the pH was adjusted to around 7. The aqueous layer was extracted with EA (2 x 10 mL) and (DCM/propan-2-ol:IPA, 10:1). The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluted with DCM: MeOH (10:1, 0.5% TEA) to give 6,6-dimethyl-5-azaspiro[3.5]nonan-8-ol (540 mg, 86.01%). LC/MS (ESI): 170.2 [M+H]⁺.

[0383] Step 6: To a solution of 6,6-dimethyl-5-azaspiro[3.5]nonan-8-ol (540.0 mg, 3.19 mmol, 1.0 eq) in THF (10 mL) was added NaH (153.13 mg, 3.83 mmol, 1.2 eq, 60%) at 0 °C under N₂ atmosphere and the reaction mixture was stirred for 20 min. Then, 3,6-dibromo-1,2-diazine (758.88 mg, 3.19 mmol, 1.0 eq) was added and the resulting mixture was stirred at 60 °C overnight. Next the reaction mixture was cooled to RT and the mixture was poured into water. The aqueous layer was extracted with EA (3 x 10 mL). The organic layer was washed with brine, dried over Na₂SO₄ and evaporated to dryness. The crude product was purified by silica gel chromatography eluted with DCM: MeOH (10:1, 0.5% TEA) to give 8-(((6-bromopyridazin-3-yl)oxy)-6,6-dimethyl-5-azaspiro[3.5]nonane (860 mg, 82.60%). LC/MS (ESI): 326.2 [M+H]⁺.

[0384] Step 7: 3-Bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (211.0 mg, 1.0 mmol, 1.0 eq), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (244.1 mg, 1.10 mmol, 1.1 eq), aqueous potassium carbonate (2 M, 8 mL) and PdCl₂(dppf).CH₂Cl₂ adduct (73.3 mg, 0.1 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was washed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (150.1 mg, 68%) as a brown solid. LC/MS (ESI): 229.1 [M+H]⁺.

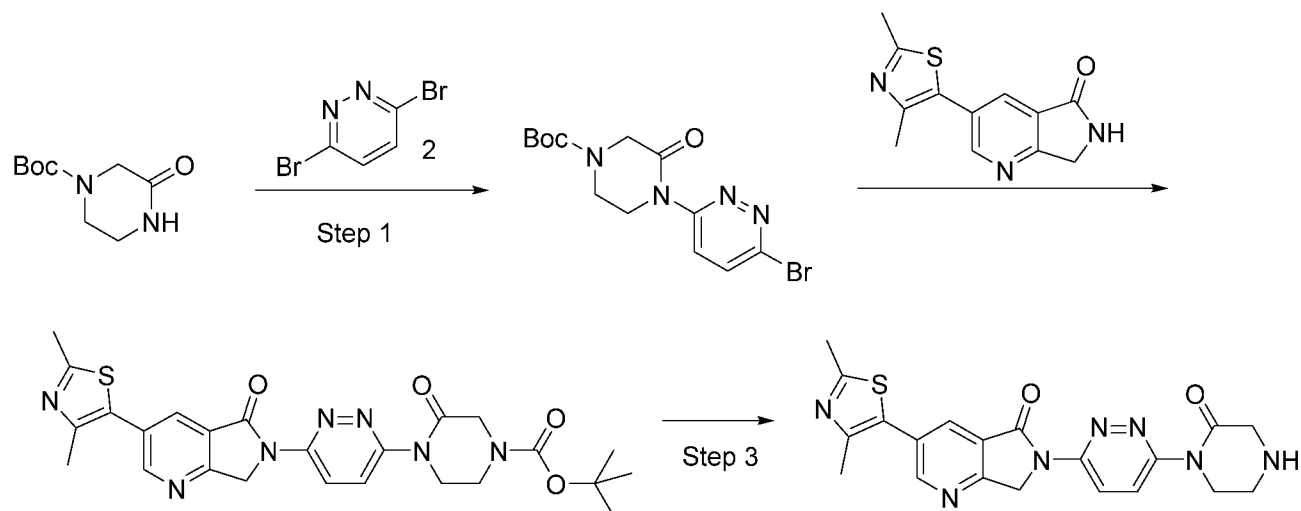
[0385] Step 8: To a round bottom flask charged with 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (34.2 mg, 0.15 mmol, 1.0 eq), 8-(((6-bromopyridazin-3-yl)oxy)-6,6-dimethyl-5-azaspiro[3.5]nonane (48.9 mg, 0.15 mmol, 1.1 eq), Cs₂CO₃ (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was

degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with A. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 5-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)isoindolin-1-one (42.2 mg), which was dissolved in HCl-dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h, and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H₂O as eluent to provide 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-((6,6-dimethyl-5-azaspiro[3.5]nonan-8-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (4.94 mg, 6.9 %) as a white solid.

[0386] ¹H NMR (DMSO-*d*₆, 400 MHz) δ = 8.95 (d, J = 2.0 Hz, 1H), 8.71 (d, J = 9.6 Hz, 1H), 8.22 (s, 1H), 8.19 - 8.15 (m, 2H), 7.35 (d, J = 9.6 Hz, 1H), 5.57 - 5.46 (m, 1H), 5.20 (s, 2H), 3.82 (s, 3H), 2.57 - 2.52 (m, 1H), 2.36 (s, 3H), 2.21 - 2.07 (m, 4H), 1.94 - 1.85 (m, 1H), 1.83 - 1.65 (m, 2H), 1.55 - 1.40 (m, 2H), 1.21 (s, 3H), 1.16 (s, 3H); LC/MS (ESI): 474.2 [M+H]⁺.

[0387] Example 20. Synthesis of 3-(2,4-dimethylthiazol-5-yl)-6-(6-(2-oxopiperazin-1-yl)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 255)

[0388] Scheme 20.



[0389] Step 1: A solution of 2-methylpropan-2-yl 3-oxopiperazine-1-carboxylate (2.00 g, 9.99 mmol, 1.00 eq), 3,6-dibromo-1,2-diazine (11.89 g, 99.90 mmol, 5.00 eq), Cs₂CO₃ (9.76 g, 29.97 mmol, 3.00 eq), Pd(dba)Cl₂ (1.00 g, 1.00 mmol, 0.10 eq) and Xanphos (1.00 g, 2.00 mmol, 0.20 eq) in 1,4-dioxane (150 mL) was stirred at 100 °C for 16 h. After completion, the reaction mixture was concentrated under vacuum. The crude product was purified by silica gel column chromatography with PE/EA 20/1~5/1, v/v to provided 2-methylpropan-2-yl 4-(6-bromo-1,2-diazin-3-yl)-3-oxopiperazine-1-carboxylate (655 mg, 1.83 mmol, 18.36%) as a yellow solid. LC/MS (ESI): 357.2 [M+H]⁺.

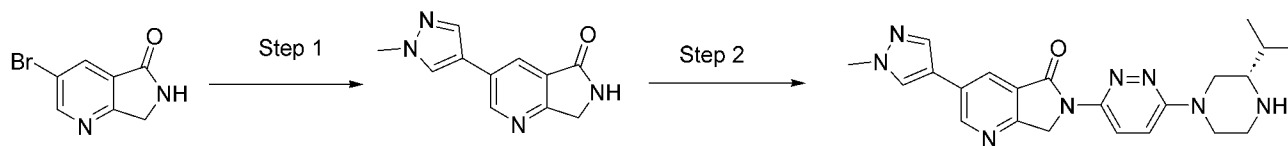
[0390] Step 2: A mixture of 3-(2,4-dimethyl-1,3-thiazol-5-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (100 mg, 0.41 mmol, 1.0 eq), 2-methylpropan-2-yl 4-(6-bromo-1,2-diazin-3-yl)-3-oxopiperazine-1-carboxylate (174.75 mg, 0.49 mmol, 1.2 eq), Cs₂CO₃ (398.48 mg, 1.22 mmol, 3.0 eq) and XantPhos Pd G4 (66.04 mg, 0.04 mmol, 0.1 eq) in dioxane (1 mL) was stirred under N₂ at 100 °C for 3 h. The reaction mixture was cooled to RT and concentrated under vacuum. The crude product was purified by silica gel

column chromatography with DCM/MeOH 20/1, v/v to provided 2-methylpropan-2-yl 4-{6-[3-(2,4-dimethyl-1,3-thiazol-5-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-6-yl]-1,2-diazin-3-yl}-3-oxopiperazine-1-carboxylate (100 mg, 47.03%) as a brown solid. LC/MS (ESI): 522.18 [M+H]⁺.

[0391] Step 3: A solution of 2-methylpropan-2-yl 4-{6-[3-(2,4-dimethyl-1,3-thiazol-5-yl)-5-oxo-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-6-yl]-1,2-diazin-3-yl}-3-oxopiperazine-1-carboxylate (100 mg, 0.19 mmol) in HCl (g) in 1,4-dioxane (4 M, 4 mL) was stirred at RT for 1 h. The reaction mixture was concentrated under vacuum. The crude product was purified by column chromatography (SiO₂, DCM:MeOH=50:1-25:1-10:1). The product was triturated with MeOH and filtered to provided 3-(2,4-dimethyl-1,3-thiazol-5-yl)-6-[6-(2-oxopiperazin-1-yl)-1,2-diazin-3-yl]-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (20.28 mg, 25.09%) as a white solid. LC/MS (ESI): 422.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ= 9.77 (br s, 2H), 8.98 (d, *J* = 2.1 Hz, 1H), 8.84 (d, *J* = 9.6 Hz, 1H), 8.27 (d, *J* = 2.0 Hz, 1H), 8.20 (d, *J* = 9.8 Hz, 1H), 5.29 (s, 2H), 4.31 - 4.22 (m, 2H), 4.02 (s, 2H), 3.65 - 3.58 (m, 2H), 2.68 (s, 3H), 2.43 (s, 3H); LC/MS (ESI): 422.95 [M+H]⁺.

[0392] Example 21. Synthesis of (S)-6-(6-(3-isopropylpiperazin-1-yl)pyridazin-3-yl)-3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 157)

[0393] Scheme 21.



[0394] Step 1: 3-Bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (213.0 mg, 1.0 mmol, 1.0 eq), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (312. mg, 1.5 mmol, 1.5 eq), aqueous potassium carbonate (2 M, 2 mL) and PdCl₂(dppf).CH₂Cl₂ adduct (73.2 mg, 0.1 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake with rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (183.2 mg, 85.2%) as a brown solid. LC/MS (ESI): 215.1 [M+H]⁺.

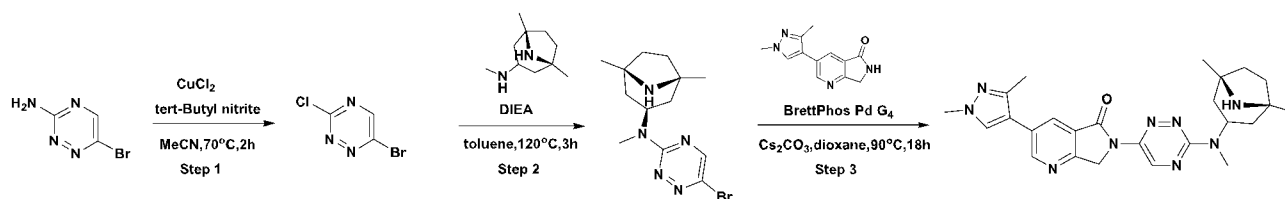
[0395] Step 2: To a round bottom flask charged with 3-(1-methyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (32.2 mg, 0.15 mmol, 1.0 eq), tert-butyl (S)-4-(6-bromopyridazin-3-yl)-2-isopropylpiperazine-1-carboxylate (57.6 mg, 0.15 mmol, 1.1 eq), Cs₂CO₃ (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated at 90 °C for 8 h. The reaction mixture was cooled to RT and was diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and was concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v, and was then dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was

stirred at RT for 1 h, and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H₂O as eluent to provide 3-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)-6-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (9.51 mg, 15.2 %) as a white solid.

[0396] ¹H NMR (DMSO-*d*₆, 400 MHz) δ 9.12 (d, 1H, J = 2.0 Hz), 8.48 (d, 1H, J = 10.0 Hz), 8.44 (s, 1H), 8.37 (d, 1H, J = 2.1 Hz), 8.18 (s, 1H), 8.14 (s, 1H), 7.48 (d, 1H, J = 9.9 Hz), 5.14 (s, 2H), 4.27-4.34 (m, 1H), 4.11-4.19 (m, 1H), 3.90 (s, 3H), 3.02-3.15 (m, 1H), 2.82-2.92 (m, 1H), 2.79-2.86 (m, 1H), 2.62-2.72 (m, 2H), 1.66-1.72 (m, 1H), 0.97 (d, 6H, J = 6.8 Hz); LC/MS (ESI): 419.2 [M+H]⁺.

[0397] Example 22. Synthesis of 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 175)

[0398] Scheme 22.



[0399] Step 1: To a solution of 6-bromo-1,2,4-triazin-3-amine (2.0 g, 11.43 mmol) and CuCl₂ (1.47 g, 14.86 mmol) in MeCN (25 mL) was added isoamyl nitrite (2.18 mL, 18.29 mmol) and the reaction mixture was stirred at 70 °C for 2 h. The reaction mixture was then concentrated and the resulting residue was purified by column chromatography (SiO₂, PE:EA=10:1) to give 6-bromo-3-chloro-1,2,4-triazine (220 mg, 1.13 mmol, 9.90%) as a yellow solid.

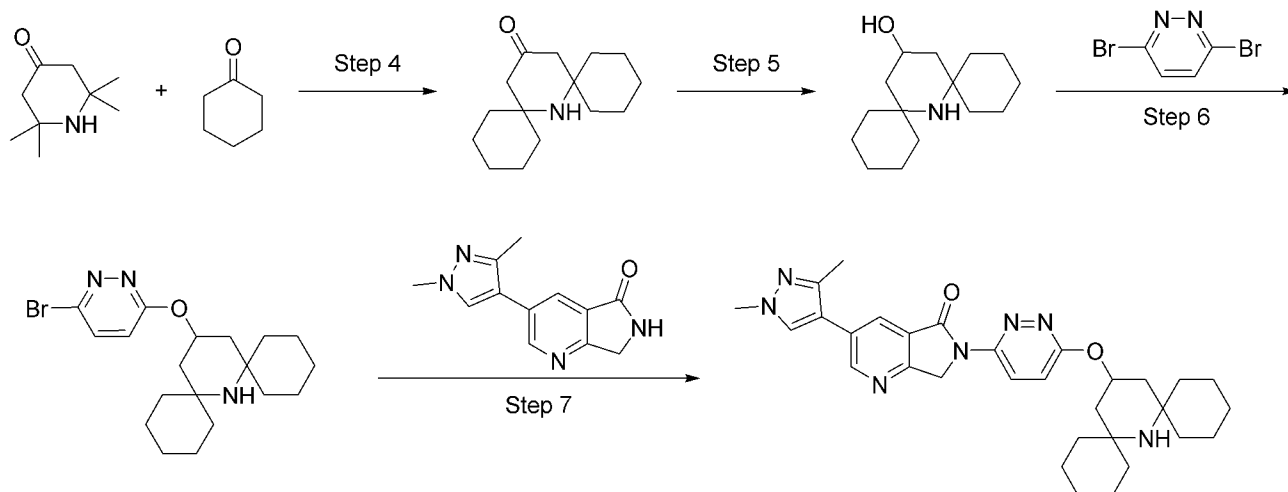
[0400] Step 2: To a solution of 6-bromo-3-chloro-1,2,4-triazine (200 mg, 1.03 mmol) and (1R,5S)-N,1,5-trimethyl-8-azabicyclo[3.2.1]octan-3-amine (192.71 mg, 1.13 mmol) in toluene (10 mL) was added DIEA (0.34 mL, 2.06 mmol) and the reaction mixture was stirred at 120 °C for 3 h. LC/MS showed the reaction was completed. The reaction mixture was concentrated and the resulting residue was purified by column chromatography (SiO₂, DCM : MeOH=10:1) to give (1R,3s,5S)-N-(6-bromo-1,2,4-triazin-3-yl)-N,1,5-trimethyl-8-azabicyclo[3.2.1]octan-3-amine (0.23 g, 67.65%) as a yellow solid.

[0401] Step 3: To a solution of 3-(1,3-dimethylpyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (35 mg, 0.15 mmol) and (1R,3s,5S)-N-(6-bromo-1,2,4-triazin-3-yl)-N,1,5-trimethyl-8-azabicyclo[3.2.1]octan-3-amine (52 mg, 0.16 mmol) in dioxane (10 mL) was added BrettPhos Pd G4 (13.61 mg, 0.01 mmol) and Cs₂CO₃ (146.62 mg, 0.45 mmol); and the reaction mixture was stirred at 90 °C for 16 h under N₂. LC/MS showed the reaction was completed. The reaction mixture was filtered and concentrated. The resulting residue was purified by pre-HPLC (TFA) to give 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(3-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)-1,2,4-triazin-6-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (30.25 mg, 39.86%) as a yellow solid.

[0402] ^1H NMR ($\text{DMSO-}d_6$, 400MHz) δ = 9.34 (s, 1H), 8.94 (d, J = 1.6 Hz, 1H), 8.18 (s, 2H), 5.13 (s, 2H), 5.01-5.10 (m, 1H), 3.82 (s, 3H), 3.02 (s, 3H), 2.36 (s, 3H), 1.78 (br d, J = 7.4 Hz, 2H), 1.51-1.65 (m, 6H), 1.20 (s, 6H), 1H not observed (NH); LC/MS (ESI): 474.3 $[\text{M}+\text{H}]^+$.

[0403] **Example 23. Synthesis of 6-((7-azadispiro[5.1.58.36]hexadecan-15-yl)oxy)pyridazin-3-yl)-3-(1,3-dimethyl-1H-pyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (Compound No. 243)**

[0404] **Scheme 23.**



[0405] **Step 1:** A solution of ethyl 5-bromo-2-methylnicotinate (3.00 g, 12.35 mmol, 1.00 eq), benzoyl peroxide (5.98 g, 24.70 mmol, 2.00 eq) and N-bromosuccinimide (4.37 g, 24.70 mmol, 2.00 eq) in carbon tetrachloride (30 mL) was stirred at 80 °C for 16 h. After consumption of the starting material, the reaction mixture was concentrated under vacuum. The crude product was purified by silica gel column chromatography with PE/EA 20/1~5/1, v/v to provided ethyl 5-bromo-2-(bromomethyl)nicotinate (2.37 g, 7.41 mmol, 61.03%) as a white solid. LC/MS (ESI): 324.0 $[\text{M}+\text{H}]^+$.

[0406] **Step 2:** A solution of ethyl 5-bromo-2-(bromomethyl)nicotinate (2.00 g, 6.23 mmol, 1.00 eq) and ammonia (1.06, 62.30 mmol, 10.0 eq) in isopropanol (10 mL) was stirred at 25 °C for 6 h. After consumption of the starting material, the reaction mixture was concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 50/1~10/1, v/v to provided 3-bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (1.06 g, 5.04 mmol, 81.32%) as a white solid. LC/MS (ESI): 214.0 $[\text{M}+\text{H}]^+$.

[0407] **Step 3:** 3-Bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (1.00 g, 5.0 mmol, 1.00 eq), 2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (1.31 g, 5.50 mmol, 1.10 eq), aqueous potassium carbonate (2 M, 8 mL) and $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ adduct (365.7 mg, 0.50 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 3-(2,4-

dimethylthiazol-5-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (335 mg, 68%) as a brown solid. LC/MS (ESI): 246.0 [M+H]⁺.

[0408] Step 4: A solution of 2,2,6,6-tetramethylhexahydropyridin-4-one (10.0 g, 64.42 mmol, 1.00 eq), cyclohexanone (18.97 g, 193.25 mmol, 3.00 eq) and NH₄Cl (20.67 g, 386.50 mmol, 6.00 eq) in DMSO (30 mL) was stirred at 80 °C for 48 h. After consumption of the starting material, the mixture was cooled to room temperature and diluted with 100 mL of water. The aqueous layer was extracted with EA (3 x 100 mL). The organic layer was washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel column chromatography with PE/EA 20/1~1/1, v/v to provided spiro[1-azaspiro[5.5]undecane-2,1'-cyclohexane]-4-one (15 g, 57.99 mmol, 90.03%) as a white solid. LC/MS (ESI): 237.2 [M+H]⁺.

[0409] Step 5: To a solution of spiro[1-azaspiro[5.5]undecane-2,1'-cyclohexane]-4-one (6.40 g, 27.19 mmol, 1.00 eq) in MeOH (65 mL), NaBH₄ (0.51 g, 13.60 mmol, 0.50 eq) was added at 0 °C; and the reaction mixture was stirred at room temperature for 3 h. After consumption of the starting material, the reaction mixture was concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 50/1~20/1, v/v to provided spiro[1-azaspiro[5.5]undecane-2,1'-cyclohexane]-4-ol (3.40 g, 14.32 mmol, 52.67%) as a yellow oil. LC/MS (ESI): 239.2 [M+H]⁺.

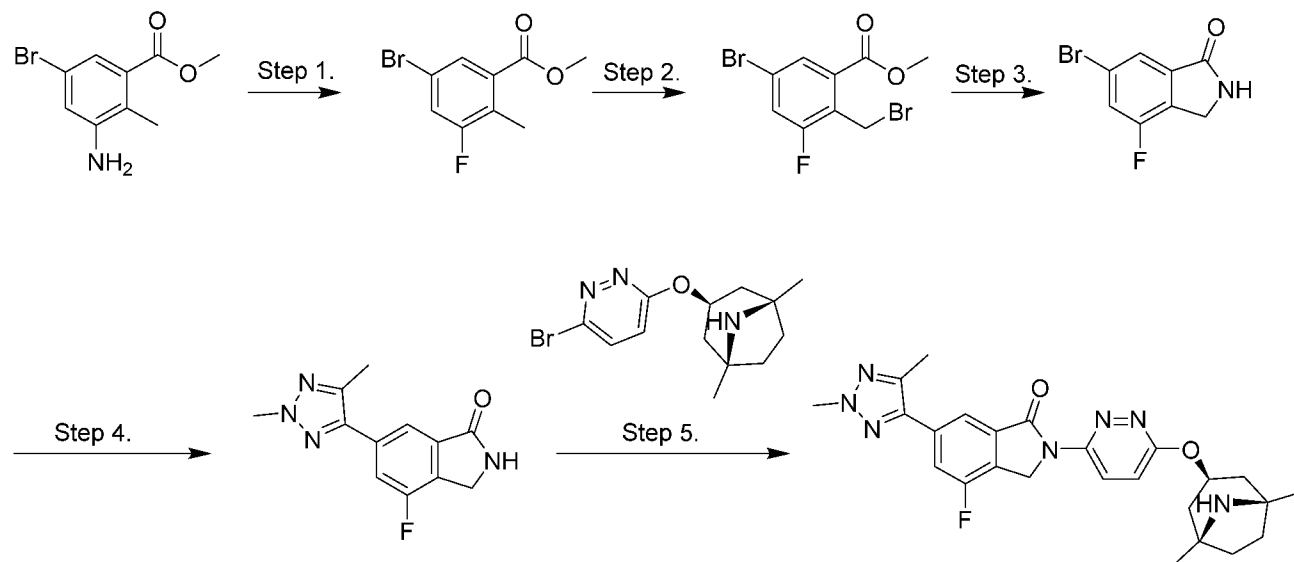
[0410] Step 6: To a solution of spiro[1-azaspiro[5.5]undecane-2,1'-cyclohexane]-4-ol (3.00 g, 12.64 mmol, 1.00 eq) in THF (30 mL), NaH (0.76 g, 31.59 mmol, 2.50 eq) was added dropwise over 30 min at 0 °C. Next the resulting mixture was stirred under N₂ at 25 °C for 0.5 h. Then 3,6-dibromo-1,2-diazine (3.61 g, 15.16 mmol, 1.20 eq) was added and the reaction mixture was stirred under N₂ at 25 °C for 24 h. After consumption of the starting material, the reaction mixture was quenched with saturated ammonium chloride and the reaction was concentrated under vacuum. The residue was extracted with EA (3 x 30 mL) and the organic layer was washed with brine, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with PE/EtOAc 20/1~1/1 to provided 4-[(6-bromo-1,2-diazin-3-yl)oxy]spiro[1-azaspiro[5.5]undecane-2,1'-cyclohexane] (1.80 g, 4.43 mmol, 35.03%) as a yellow solid. LC/MS (ESI): 395.3 [M+H]⁺.

[0411] Step 7: To a solution of 4-[(6-bromo-1,2-diazin-3-yl)oxy]spiro[1-azaspiro[5.5]undecane-2,1'-cyclohexane] (0.9 g, 2.28 mmol, 1.00 eq), 3-(1,3-dimethylpyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (0.63 g, 2.74 mmol, 1.20 eq) and Cs₂CO₃ (2.23 g, 6.85 mmol, 3.00 eq) in 1,4-dioxane (15 mL) was added XPhos Pd G4 (0.20 g, 0.23 mmol, 0.10 eq) at 25 °C; and the reaction mixture was stirred under N₂ at 90 °C for 4 h. After consumption of the starting material, the reaction mixture was concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 50/1~10/1, v/v to provided 3-(1,3-dimethylpyrazol-4-yl)-6-[6-(spiro[1-azaspiro[5.5]undecane-2,1'-cyclohexane]-4-yloxy)-1,2-diazin-3-yl]-6,7-dihydro-5H-pyrrolo[4,3-b]pyridin-5-one (0.43 g, 0.79 mmol, 34.82%) as a white solid.

[0412] ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.95 (d, J = 2.0 Hz, 1H), 8.70 (d, J = 9.6 Hz, 1H), 8.21 - 8.16 (m, 3H), 7.32 (d, J = 9.6 Hz, 1H), 5.61 - 5.51 (m, 1H), 5.20 (s, 2H), 3.82 (s, 3H), 2.36 (s, 3H), 1.79 - 1.49 (m, 10H), 1.49 - 1.30 (m, 14H); LC/MS (ESI): 542.4 [M+H]⁺.

[0413] Example 24. Synthesis of 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-fluoroisindolin-1-one (Compound No. 283)

[0414] Scheme 24.



[0415] **Step 1:** To the solution of methyl 3-amino-5-bromo-2-methylbenzoate (1.0 g, 4.10 mmol) in DCM (10 mL), nitrosonium tetrafluoroborate, (480 mg, 4.10 mmol) was added portionwise at 0 °C under N₂; and the reaction mixture was stirred at 0 °C for 1 h. Then oxylene (30 mL) was added and the reaction mixture was refluxed at 130 °C for 3 h. The reaction mixture was cooled to room temperature and poured into H₂O and the aqueous layer was extracted EA. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. The crude product was purified by silica gel column chromatography with PE/EA 10/1, v/v to afford methyl 5-bromo-3-fluoro-2-methylbenzoate (860 mg, 85%).

[0416] **Step 2:** To the solution of 5-bromo-3-fluoro-2-methylbenzoate (860 mg, 3.5 mmol) and NBS (623 mg, 3.5 mmol) in (trifluoromethyl)benzene (10 mL), was added AIBN (57 mg, 0.35 mmol); and the reaction mixture was stirred under N₂ at 100 °C for 16 h. Then the reaction mixture was cooled to room temperature and was poured into H₂O. The aqueous layer was extracted EA. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. The crude product was purified by silica gel column chromatography with PE/EA 10/1, v/v to afford methyl 5-bromo-2-(bromomethyl)-3-fluorobenzoate (800 mg, 70%).

[0417] **Step 3:** To a solution of methyl 5-bromo-2-(bromomethyl)-3-fluorobenzoate (800 mg, 2.5 mmol) in THF (7 mL), NH₄OH (7 mL) was added and the reaction mixture was stirred at RT for 4 h. The reaction mixture was filtered and concentrated under vacuum. The crude product was used for directly in the next step.

[0418] **Step 4:** 6-Bromo-4-fluoroisindolin-1-one (343.0 mg, 1.5 mmol, 1.5 eq), 4,4,4',4',5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (762 mg, 3.0 mmol, 3.0 eq), potassium acetate (300 mg, 3.0 mmol, 3.0 eq) and PdCl₂(dppf).CH₂Cl₂ adduct (109.3 mg, 0.15 mmol, 0.1 eq) were charged to a three-

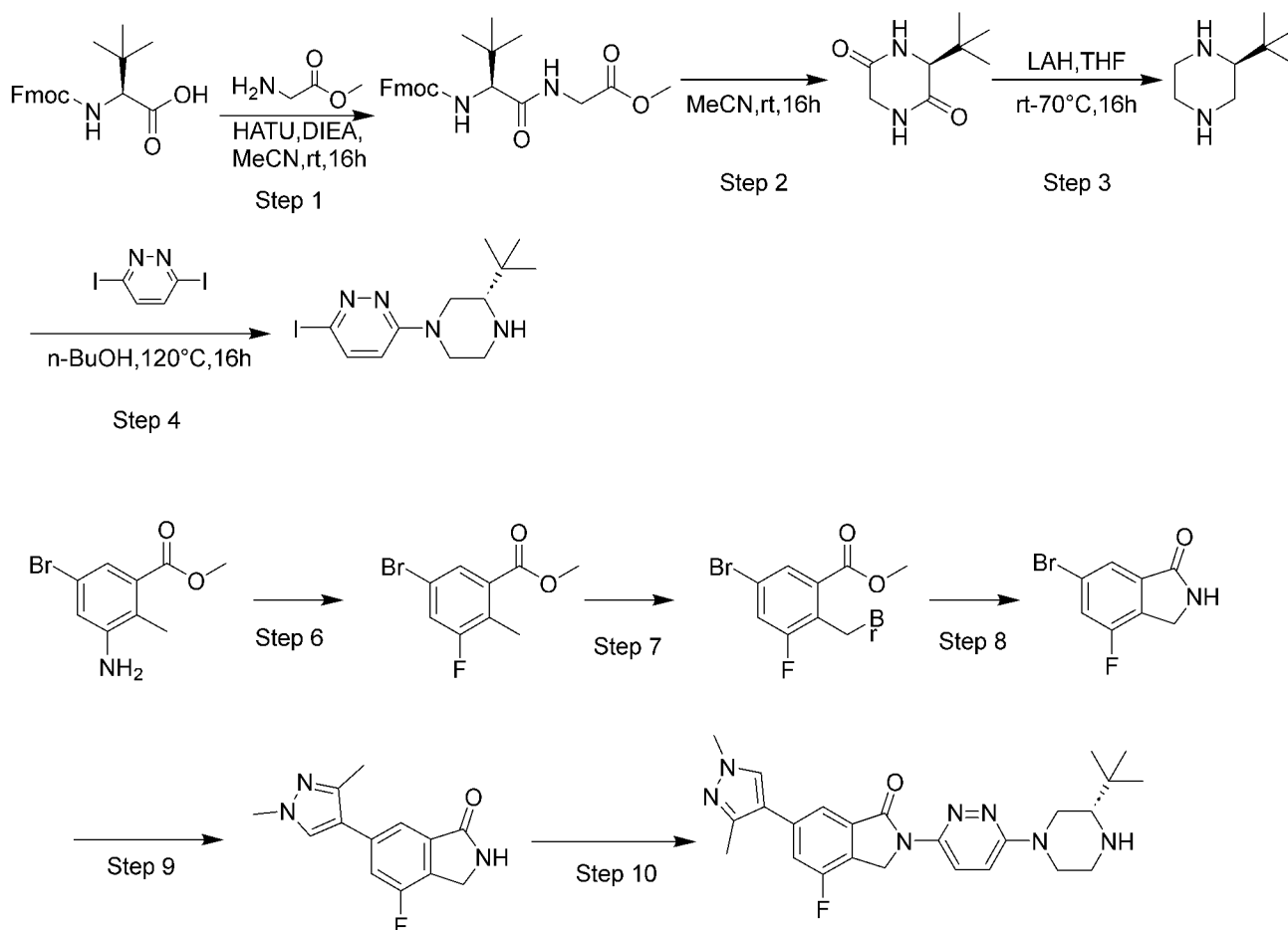
neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the mixture was heated to 90 °C. When full conversion was achieved, the reaction mixture was cooled to room temperature. Then 3-bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (211.9 mg, 1.0 mmol, 1.0 eq), aqueous potassium carbonate (2 M, 2 mL) and PdCl₂(dppf).CH₂Cl₂ adduct (109.3 mg, 0.15 mmol, 0.1 eq) were added and the mixture was heated to 90 °C. When full conversion was achieved, the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one (81.5 mg, 33%) as a brown solid. LC/MS (ESI): 247.1 [M+H]⁺.

[0419] Step 5: To a round bottom flask charged with 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-4-fluoroisoindolin-1-one (36.9 mg, 0.15 mmol, 1.0 eq), *tert*-butyl (1*R*,3*S*,5*S*)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (61.8 mg, 0.15 mmol, 1.1 eq), Cs₂CO₃ (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated at 90 °C for 8 h. The reaction mixture was cooled to RT and was then diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v, and was then dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h, and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H₂O as eluent to provide 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1*R*,3*S*,5*S*)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-4-fluoroisoindolin-1-one (28.8 mg, 40.3 %) as a white solid.

[0420] ¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.42 (br d, J = 7.4 Hz, 1H), 9.31 - 9.17 (m, 1H), 8.72 (d, J = 9.6 Hz, 1H), 7.89 (s, 1H), 7.83 (dd, J = 0.8, 9.9 Hz, 1H), 7.39 (d, J = 9.6 Hz, 1H), 5.52 (td, J = 5.3, 10.8 Hz, 1H), 5.27 (s, 2H), 4.16 (s, 3H), 2.48 (s, 3H), 2.41 (br dd, J = 5.8, 13.3 Hz, 2H), 2.13 (br d, J = 8.0 Hz, 2H), 1.95 - 1.81 (m, 4H), 1.48 (s, 6H); LC/MS (ESI): 478.2 [M+H]⁺.

[0421] Example 25. Synthesis of (S)-2-(6-(3-(*tert*-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisoindolin-1-one (Compound No. 295)

[0422] Scheme 25.



[0423] Step 1: To a solution of (2*S*)-2-({[(9*H*-fluoren-9-ylmethyl)oxy]carbonyl}amino)-3,3-dimethylbutanoic acid (10 g, 28.29 mmol, 1.0 eq) and methyl aminoacetate (3.0 g, 33.95 mmol, 1.2 eq) in acetonitrile (50 mL) was added DIEA (9.1 g, 70.74 mmol, 2.5 eq) and HATU (11.8 g, 31.12 mmol, 1.1 eq), and the reaction mixture was stirred at RT for 16 h. Next the reaction mixture was filtered to provided 9*H*-fluoren-9-ylmethyl {[[(7*S*)-8,8-dimethyl-3,6-dioxo-5-aza-2-oxanon-7-yl]amino}methanoate (9.5 g, 22.38 mmol, 79.09%) as a slightly yellow solid. LC/MS (ESI): 425.5 [M+H]⁺.

[0424] Step 2: A solution of 9*H*-fluoren-9-ylmethyl {[[(7*S*)-8,8-dimethyl-3,6-dioxo-5-aza-2-oxanon-7-yl]amino}methanoate (5.0 g, 11.78 mmol, 1.0 eq) in acetonitrile (100 mL) was stirred RT for 16 h. After the reaction was completed, the reaction mixture was concentrated in vacuo to provided 9*H*-fluoren-9-ylmethyl {[[(7*S*)-8,8-dimethyl-3,6-dioxo-5-aza-2-oxanon-7-yl]amino}methanoate (4.85 g, 11.43 mmol, 97.00%) as a slightly yellow solid. LC/MS (ESI): 171.2 [M+H]⁺.

[0425] Step 3: LiAlH₄ (2.14 g, 56.40 mmol, 6.0 eq) was added to a vigorous stirred solution of (3*S*)-3-(2-methylprop-2-yl)piperazine-2,5-dione (1.6 g, 9.40 mmol, 1.0 eq) in THF (20 mL) in an ice bath, and the resulting reaction mixture was stirred at 70 °C for 16 h. Next the mixture was poured into KOH (6*N*), and the mixture was stirred in an ice bath for 1 h and was then filtered. The filtrate was extracted with EA, washed with brine, dried over Na₂SO₄, and concentrated in vacuo to provided (2*S*)-2-(2-methylprop-2-yl)piperazine (1.2 g, 8.44 mmol, 89.74%) as a yellow oil. LC/MS (ESI): 143.2 [M+H]⁺.

[0426] Step 4: DIEA (1.13 g, 8.79 mmol, 1.46 mL, 2.5 eq) was added to a vigorous stirred solution of (2*S*)-2-(2-methylprop-2-yl)piperazine (0.5 g, 3.51 mmol, 1.0 eq) and 3,6-diiodo-1,2-diazine (1.17 g, 3.51

mmol, 1.0 eq) in n-BuOH (7 mL) at RT, and the reaction mixture was stirred at 120 °C for 16 h. Next the mixture was concentrated in vacuo and the resulting residue was diluted with EA, washed with water and brine, dried over Na₂SO₄, and concentrated in vacuo to provided 6-iodo-3-[(3*S*)-3-(2-methylprop-2-yl)piperazin-1-yl]-1,2-diazine (450 mg, 1.30 mmol, 36.98%) as a yellow solid. LC/MS (ESI): 347.2 [M+H]⁺.

[0427] Step 5: Pd(dppf)Cl₂ (49 mg, 0.06 mmol, 0.05 eq) was added to a vigorous stirred solution of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole (250 mg, 1.20 mmol, 1.0 eq), 3-bromo-6,7-dihydro-5*H*-pyrrolo[4,3-*b*]pyridin-5-one (256 mg, 1.20 mmol, 1.0 eq) and K₂CO₃ (332 mg, 2.40 mmol, 2.0 eq) in dioxane (5 mL) and water (1 mL) and the resulting reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 10/1, v/v to afford 3-(1-methylpyrazol-4-yl)-6,7-dihydro-5*H*-pyrrolo[4,3-*b*]pyridin-5-one (135 mg, 0.63 mmol, 52.51%) as a slightly yellow solid. LC/MS (ESI): 215.2 [M+H]⁺.

[0428] Step 6: To the solution of methyl 3-amino-5-bromo-2-methylbenzoate (1.0 g, 4.10 mmol) in DCM (10 mL), was nitrosonium tetrafluoroborate, (480 mg, 4.10 mmol) was added portionwise at 0 °C under N₂ and the resulting reaction mixture was stirred at 0 °C for 1 h. Then oxylene (30 mL) was added and the reaction mixture was refluxed at 130 °C for 3 h. The reaction mixture was cooled to room temperature and poured into H₂O. The aqueous layer was extracted EA. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. The crude product was purified by silica gel column chromatography with PE/EA 10/1, v/v to obtain methyl 5-bromo-3-fluoro-2-methylbenzoate (860 mg, 85%).

[0429] Step 7: To the solution of 5-bromo-3-fluoro-2-methylbenzoate (860 mg, 3.5 mmol) and NBS (623 mg, 3.5 mmol) in (trifluoromethyl)benzene (10 mL), was AIBN (57 mg, 0.35 mmol) was added; and the reaction mixture was stirred under N₂ at 100 °C for 16 h. The reaction mixture was then cooled to room temperature and poured into H₂O. The aqueous layer was extracted EA. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. The crude product was purified by silica gel column chromatography with PE/EA 10/1, v/v to obtain methyl 5-bromo-2-(bromomethyl)-3-fluorobenzoate (800 mg, 70%).

[0430] Step 8: To a solution of methyl 5-bromo-2-(bromomethyl)-3-fluorobenzoate (800 mg, 2.5 mmol) dissolved in THF (7 mL), NH₄OH (7 mL) was added and the reaction was stirred at RT for 4 . The reaction mixture was filtered and concentrated under vacuum. The crude product was used directly in the next step.

[0431] Step 9: 6-Bromo-4-fluoroisindolin-1-one (228 mg, 1.0 mmol, 1.0 eq), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (244.1 mg, 1.10 mmol, 1.1 eq), aqueous potassium carbonate (2 M, 8 mL) and PdCl₂(dppf).CH₂Cl₂ adduct (73.3 mg, 0.1 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the reaction mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the

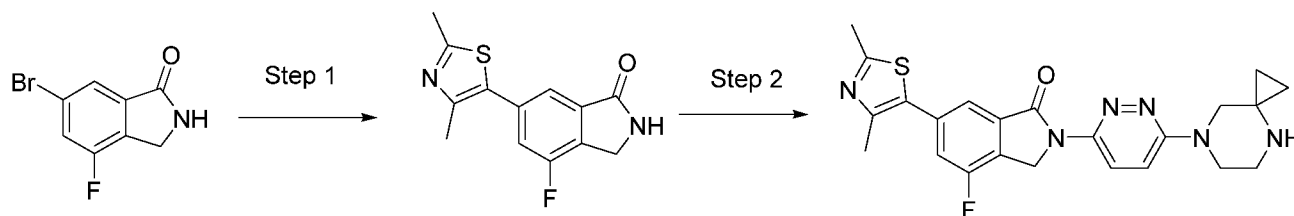
organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one (134.7 mg, 55%) as a brown solid. LC/MS (ESI): 246.1 [M+H]⁺.

[0432] Step 10: 6-(1,3-Dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one (50 mg, 0.23 mmol, 1.0 eq) and 6-iodo-3-[(3*S*)-3-(2-methylprop-2-yl)piperazin-1-yl]-1,2-diazine (80 mg, 0.23 mmol, 1.0 eq) were dissolved in DMF (2 mL), and CuI (4 mg, 0.02 mmol, 0.10 eq), K₂CO₃ (97 mg, 0.70 mmol, 3.0 eq) and (1*R*,2*R*)-cyclohexane-1,2-diamine (2.7 mg, 0.02 mmol, 0.10 eq) were added and the resulting reaction mixture was stirred at 100 °C for 16 h. Next the reaction mixture was filtered and the filtrate was concentrated. The crude product was purified by pre-HPLC to provided (S)-2-(6-(3-(tert-butyl)piperazin-1-yl)pyridazin-3-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-4-fluoroisindolin-1-one (24.19 mg, 21.55%) as a white solid.

[0433] ¹H NMR (DMSO-*d*₆, 400MHz) δ = 8.46 (d, *J* = 9.9 Hz, 1H), 8.13 (s, 1H), 7.64 (s, 1H), 7.61 - 7.56 (m, 1H), 7.47 (d, *J* = 10.0 Hz, 1H), 5.18 (s, 2H), 4.36 (br d, *J* = 12.1 Hz, 1H), 4.12 (br d, *J* = 11.9 Hz, 1H), 3.80 (s, 3H), 3.08 (br d, *J* = 11.4 Hz, 1H), 2.89 - 2.71 (m, 2H), 2.65 - 2.57 (m, 1H), 2.39 (dd, *J* = 2.4, 10.8 Hz, 1H), 2.35 (s, 3H), 0.96 (s, 9H), 1H not observed (NH); LC/MS (ESI): 464.2 [M+H]⁺.

[0434] Example 26. Synthesis of 2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-4-fluoroisindolin-1-one (Compound No. 300)

[0435] Scheme 26.



[0436] Step 1: 6-Bromo-4-fluoroisindolin-1-one (457.9 mg, 2.0 mmol, 1.0 eq), 2,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (526.1 mg, 2.20 mmol, 1.1 eq), aqueous potassium carbonate (2 M, 8 mL) and PdCl₂(dppf).CH₂Cl₂ adduct (146.3 mg, 0.2 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the reaction mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to afford 6-(2,4-dimethylthiazol-5-yl)-4-fluoroisindolin-1-one (273.6 mg, 57%) as a brown solid. LC/MS (ESI): 263.1 [M+H]⁺.

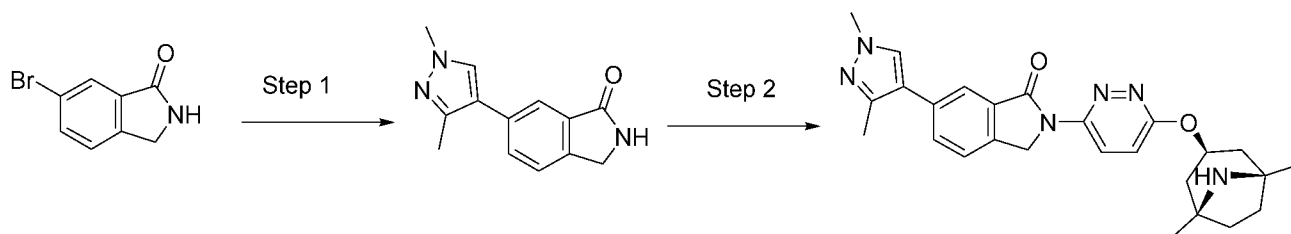
[0437] Step 2: To a round bottom flask charged with 6-(2,4-dimethylthiazol-5-yl)-4-fluoroisindolin-1-one (37.4 mg, 0.15 mmol, 1.0 eq), *tert*-butyl 7-(6-bromopyridazin-3-yl)-4,7-diazaspiro[2.5]octane-4-carboxylate (55.2 mg, 0.15 mmol, 1.1 eq), Cs₂CO₃ (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and was

then diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 5-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)isoindolin-1-one (42.2 mg), which was dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H₂O as eluent to provide 2-(6-(4,7-diazaspiro[2.5]octan-7-yl)pyridazin-3-yl)-6-(2,4-dimethylthiazol-5-yl)-4-fluoroisoindolin-1-one (13.59 mg, 20.1 %) as a white solid.

[0438] ¹HNMR (400 MHz, DMSO-*d*₆) δ = 8.44 (d, *J* = 9.9 Hz, 1H), 8.15 (d, *J* = 1.0 Hz, 1H), 7.70 - 7.65 (m, 1H), 7.63 (s, 1H), 7.44 (d, *J* = 10.0 Hz, 1H), 5.24 (s, 2H), 3.58 - 3.53 (m, 2H), 3.44 (s, 2H), 2.89 (br d, *J* = 4.5 Hz, 2H), 2.66 (s, 3H), 2.43 (s, 3H), 0.51 (br d, *J* = 9.8 Hz, 4H); LC/MS (ESI): 451.1 [M+H]⁺.

[0439] Example 27. Synthesis of 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoindolin-1-one (Compound No. 416)

[0440] Scheme 27.



[0441] Step 1: 6-Bromoisoindolin-1-one (426.0 mg, 2.0 mmol, 1.0 eq), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (488 mg, 2.20 mmol, 1.1 eq), aqueous potassium carbonate (2 M, 8 mL) and PdCl₂(dppf).CH₂Cl₂ adduct (146.3 mg, 0.2 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (9 mL) was added and the reaction mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to afford 6-(1,3-dimethyl-1H-pyrazol-4-yl)isoindolin-1-one (335 mg, 68%) as a brown solid. LC/MS (ESI): 228.1 [M+H]⁺.

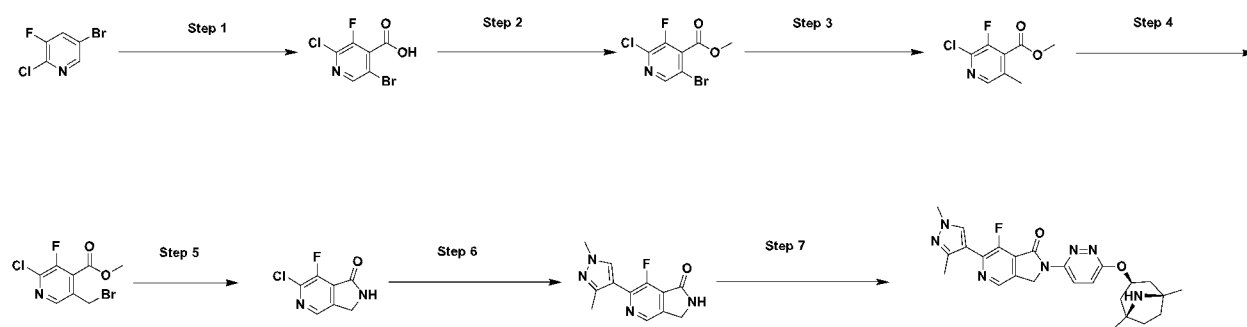
[0442] Step 2: To a round bottom flask charged with 6-(1,3-dimethyl-1H-pyrazol-4-yl)isoindolin-1-one (34.2 mg, 0.15 mmol, 1.0 eq), *tert*-butyl (1R,3s,5S)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (61.8 mg, 0.15 mmol, 1.1 eq), Cs₂CO₃ (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled down to RT and was then diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v, and was then dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H₂O as eluent to provide 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoindolin-1-one (Compound No. 416) as a white solid.

((((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)isoindolin-1-one (16.84 mg, 23.4%) as a white solid.

[0443] ¹H NMR (DMSO-*d*₆, 400 MHz) δ = 8.73 (d, *J* = 9.6 Hz, 1H), 8.20 (br d, *J* = 4.5 Hz, 1H), 8.06 (s, 1H), 7.81 - 7.77 (m, 2H), 7.76 - 7.73 (m, 1H), 7.33 (d, *J* = 9.5 Hz, 1H), 5.49 (s, 1H), 5.16 (s, 2H), 3.81 (s, 3H), 2.34 (s, 3H), 2.33 - 2.29 (m, 2H), 2.03 - 1.93 (m, 2H), 1.72 (br d, *J* = 2.5 Hz, 2H), 1.66 - 1.56 (m, 2H), 1.34 (br s, 6H); LC/MS (ESI): 459.3 [M+H]⁺.

[0444] Example 28. Synthesis of 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-7-fluoro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (Compound No. 116)

[0445] Scheme 28.



[0446] Step 1: LDA (48 mL, 2.0 mol in THF) was added dropwise into a solution of 5-bromo-2-chloro-3-fluoropyridine (10 g, 47.52 mmol) in THF (200 mL) at -78 °C under N₂ and the reaction mixture was stirred at -78 °C for 2 h. The mixture was poured into the CO₂ (solid) in THF. The reaction mixture was then concentrated under vacuum. The pH value of the residue was adjusted to 3 with 2 M HCl. The resulting mixture was extracted with EA, washed with brine, dried over MgSO₄, and concentrated under vacuum to afford the desired product (12 g, crude) as a white solid.

[0447] Step 2: To a solution of 5-bromo-2-chloro-3-fluoroisonicotinic acid (12 g, 51.2 mmol) and K₂CO₃ (5.7 g, 41.7 mmol) in DMF (80 mL), MeI (3.4 mL, 54.7 mmol) was added portionwise; and the reaction mixture was stirred at RT for 16 h. The reaction mixture was poured into H₂O. The aqueous layer was extracted EA. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. The crude product was purified by silica gel column chromatography with PE/EA 10/1, v/v to obtain methyl 5-bromo-2-chloro-3-fluoroisonicotinate (10 g, 79%).

[0448] Step 3: To the solution of 5-bromo-2-chloro-3-fluoroisonicotinate (2500 mg, 9.4 mmol) and 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane in dioxane (25 mL), was added potassium carbonate (2600 mg, 18.8 mmol) and PdCl₂(dppf) (500 mg, 0.94 mmol); and the reaction mixture was stirred under N₂ at 110 °C for 1 h. Then the mixture was cooled, filtered through a pad of Celite and the filter cake was washed with EA. The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with PE/EA 10/1, v/v to afford methyl 2-chloro-3-fluoro-5-methylisonicotinate (673 mg, 35.3%).

[0449] Step 4: To a solution of methyl 2-chloro-3-fluoro-5-methylisonicotinate (320 mg, 1.6 mmol) and NBS (285 mg, 1.6 mmol) in CCl₄ (10 mL), was added BPO (40 mg, 0.16 mmol); and the reaction mixture was stirred under N₂ at 80 °C for 16 h. The mixture was cooled to room temperature and was then poured into H₂O. The aqueous layer was extracted EA. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. The crude product was purified by silica gel column chromatography with PE/EA 5/1, v/v to afford methyl 5-(bromomethyl)-2-chloro-3-fluoroisonicotinate (356 mg, 80%).

[0450] Step 5: Methyl 5-(bromomethyl)-2-chloro-3-fluoroisonicotinate (356 mg, 1.26 mmol) was dissolved in THF (5 mL) and NH₄OH (5 mL) was added; and the reaction was stirred at RT for 3 h. The reaction mixture was filtered and concentrated under vacuum. The crude product was used directly in the next step.

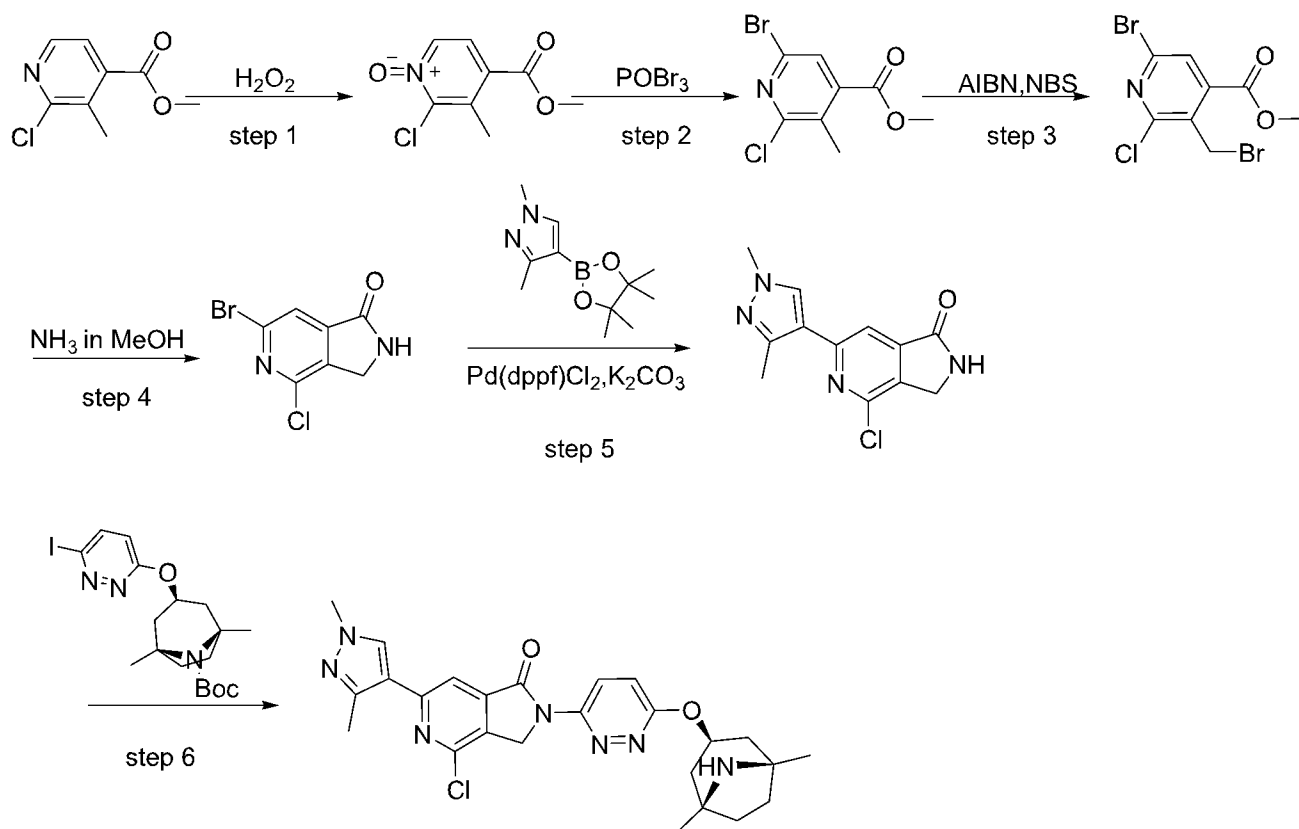
[0451] Step 6: 6-Chloro-7-fluoro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (186.0 mg, 1.0 mmol, 1.0 eq), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (312 mg, 1.5 mmol, 1.5 eq), aqueous potassium carbonate (2 M, 2 mL) and PdCl₂(dppf).CH₂Cl₂ adduct (73.2 mg, 0.1 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen and then anhydrous dioxane (9 mL) was added and the reaction mixture was heated to 85 °C overnight. The mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to afford 6-(1,3-dimethyl-1H-pyrazol-4-yl)-7-fluoro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (100.8 mg, 41.2%) as a brown solid. LC/MS (ESI): 247.1 [M+H]⁺.

[0452] Step 7: To a round bottom flask charged with 6-(1,3-dimethyl-1H-pyrazol-4-yl)-7-fluoro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (36.9 mg, 0.15 mmol, 1.0 eq), *tert*-butyl (S)-4-(6-bromopyridazin-3-yl)-2-isopropylpiperazine-1-carboxylate (57.6 mg, 0.15 mmol, 1.1 eq), Cs₂CO₃ (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and was diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v, and was then dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H₂O as eluent to provide 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-7-fluoro-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (3.93 mg, 5.6 %) as a white solid.

[0453] ¹HNMR (400 MHz, METHANOL-*d*₄) δ = 8.72 - 8.67 (m, 2H), 8.44 (s, 1H), 8.00 (d, *J* = 3.3 Hz, 1H), 7.15 (d, *J* = 9.6 Hz, 1H), 5.58 - 5.44 (m, 1H), 5.18 (s, 2H), 3.81 (s, 3H), 2.45 - 2.38 (m, 5H), 2.16 (br d, *J* = 8.3 Hz, 2H), 1.90 - 1.82 (m, 2H), 1.68 (br t, *J* = 12.0 Hz, 2H), 1.40 (s, 6H); LC/MS (ESI): 478.2 [M+H]⁺.

[0454] **Example 29. Synthesis of 4-chloro-6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-one (Compound No. 93)**

[0455] **Scheme 29.**



[0456] **Step 1:** To methyl 2-chloro-3-methylisonicotinate (5000 mg, 27.03 mmol) in TFA (50 mL), H_2O_2 (42.16 mL, 351.35 mmol) was added and the mixture was stirred for 4 h. The mixture was cooled to RT and quenched with aqueous Na_2SO_3 . The mixture was concentrated under vacuum and the residue was redissolved in EA (300 mL). The mixture was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with PE/EtOAc to provided 2-chloro-4-(methoxycarbonyl)-3-methylpyridine 1-oxide (3000 mg, 14.85 mmol, 54.95%). LC/MS (ESI): 202.0 $[\text{M}+\text{H}]^+$.

[0457] **Step 2:** POBr_3 (6398.79 mg, 22.32 mmol) was added to the solution of 2-chloro-4-(methoxycarbonyl)-3-methylpyridine 1-oxide (3000 mg, 14.88 mmol) in toluene (30 mL) at RT and the reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was cooled to RT and was quenched with aqueous Na_2CO_3 . This mixture was extracted with EA (3 x 100 mL) and the combined extracts were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography eluted with PE: EtOAc=2:1, to give methyl methyl 6-bromo-2-chloro-3-methylisonicotinate (1500 mg, 5.67 mmol, 38.11%) as a white solid. LC/MS (ESI): 263.9 $[\text{M}+\text{H}]^+$.

[0458] **Step 3:** Methyl 6-bromo-2-chloro-3-methylpyridine-4-carboxylate (1500 mg, 5.67 mmol), NBS (1513.80 mg, 8.50 mmol) and AIBN (0.17 mL, 1.13 mmol) were combined with carbon tetrachloride (40 mL); and the reaction mixture was heated to 80 °C for 3 h. The reaction mixture was cooled to RT and

concentrated under vacuum. The resulting residue was purified by silica gel column chromatography with PE/EA to afford ethyl methyl 6-bromo-3-(bromomethyl)-2-chloropyridine-4-carboxylate (1150 mg, 3.35 mmol, 59.05%) as a brown solid. LC/MS (ESI): 341.8 [M+H]⁺.

[0459] Step 4: Methyl 6-bromo-3-(bromomethyl)-2-chloropyridine-4-carboxylate (1150 mg, 3.35 mmol) was suspended in 28 % aqueous ammonium hydroxide and the mixture was stirred at RT for 8 h. Then the mixture was filtered, and the residue was washed with water and methanol. The solid was collected, dried under vacuum and used in the next step without further purification. LC/MS (ESI): 246.9 [M+H]⁺.

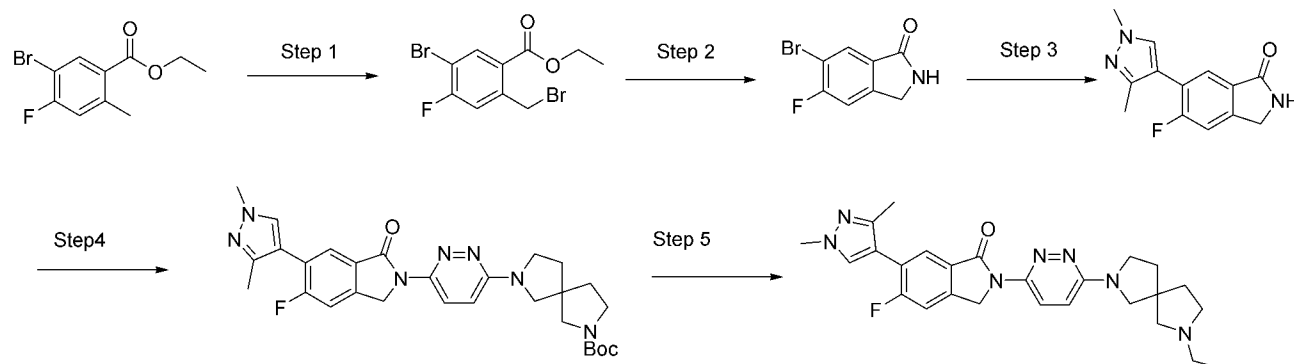
[0460] Step 5: 6-Bromo-4-chloro-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (550 mg, 2.22 mmol), 2,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3-triazole (545.35 mg, 2.44 mmol), K₂CO₃ (921.41 mg, 6.67 mmol) and Pd(dppf)Cl₂ (162.62 mg, 0.22 mmol) were charged into a 100 mL round bottom flask. The flask was placed under nitrogen and anhydrous dioxane (9 mL) and water (1 mL) were added and the mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and washed with EA (50 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated under vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 4-chloro-6-(2,5-dimethyl-1,2,3-triazol-4-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (400 mg, 1.52 mmol, 68.26%) as a brown solid. LC/MS (ESI): 263.1 [M+H]⁺.

[0461] Step 6: To a round bottom flask charged with 4-chloro-6-(1,3-dimethylpyrazol-4-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (120 mg, 0.46 mmol), 2-methylpropan-2-yl(1S,3s,5R)-3-[(6-iodo-1,2-diazin-3-yl)oxy]-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (230.80 mg, 0.50 mmol), Cs₂CO₃ (446.50 mg, 1.37 mmol), and XantPhos Pd G4 (43.96 mg, 0.05 mmol) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and then diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 2-methylpropan-2-yl(1S,3s,5R)-3-[(6-[4-chloro-6-(1,3-dimethylpyrazol-4-yl)-1-oxo-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-2-yl]-1,2-diazin-3-yl)oxy]-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (40 mg), which was dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H₂O as eluent to provide 4-chloro-6-(1,3-dimethylpyrazol-4-yl)-2-(6-[(1S,3s,5R)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl]oxy)-1,2-diazin-3-yl)-2,3-dihydro-1H-pyrrolo[4,3-c]pyridin-1-one (10.3 mg, 0.02 mmol, 4.53%) as a white solid.

[0462] ¹H NMR (DMSO-*d*₆, 400 MHz) δ=8.96 (br d, J = 8.8 Hz, 1H), 8.85 (br d, J = 9.3 Hz, 1H), 8.70 (d, J = 9.6 Hz, 1H), 8.47 (s, 1H), 7.94 (s, 1H), 7.41 (d, J = 9.6 Hz, 1H), 5.61 - 5.47 (m, 1H), 5.16 (s, 2H), 3.82 (s, 3H), 2.48 - 2.42 (m, 5H), 2.16 (br d, J = 8.0 Hz, 2H), 1.95 - 1.75 (m, 4H), 1.45 (s, 6H); LC/MS (ESI): 494.1 [M+H]⁺.

[0463] **Example 30. Synthesis of 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(7-ethyl-2,7-diazaspiro[4.4]nonan-2-yl)pyridazin-3-yl)-5-fluoroisindolin-1-one (Compound No. 414)**

[0464] **Scheme 30.**



[0465] **Step 1:** Ethyl 5-bromo-4-fluoro-2-methylbenzoate (2.60 g, 10.0 mmol, 1.0 eq), *N*-bromosuccinimide (2.49 g, 14.0 mmol, 1.4 eq) and benzoyl peroxide (242. mg, 1.0 mmol, 0.1 eq) were combined with carbon tetrachloride (150 mL). The reaction mixture was heated to 80 °C and stirred for 3 h. The reaction mixture was cooled to RT and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography with PE/EA to afford ethyl 5-bromo-2-(bromomethyl)-4-fluorobenzoate (2.61 g, 77%) as a brown solid. LC/MS (ESI): 338.9, 340.9, 342.9 [M+H]⁺.

[0466] **Step 2:** Ethyl 5-bromo-2-(bromomethyl)-4-fluorobenzoate (2.61 g, 7.7 mmol, 1.0 eq) was suspended in 28 % aqueous ammonium hydroxide and the mixture was stirred at RT for 8 h. Then the mixture was filtered, and the residue was washed with water and methanol. The solid was collected, dried under vacuum and used in the next step without further purification. LC/MS (ESI): 230.0, 232.0 [M+H]⁺.

[0467] **Step 3:** 6-Bromo-5-fluoroisindolin-1-one (456.0 mg, 2.0 mmol, 1.0 eq), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (488 mg, 2.20 mmol, 1.1 eq), aqueous potassium carbonate (2 M, 8 mL) and PdCl₂(dppf).CH₂Cl₂ adduct (146.3 mg, 0.2 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen and anhydrous dioxane (9 mL) was added and the mixture was heated to 85 °C overnight. The mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to afford 6-(1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoroisindolin-1-one (298.9 mg, 61%) as a brown solid. LC/MS (ESI): 246.1 [M+H]⁺.

[0468] **Step 4:** To a round bottom flask charged with 6-(1,3-dimethyl-1H-pyrazol-4-yl)isindolin-1-one (34.2 mg, 0.15 mmol, 1.0 eq), *tert*-butyl 7-(6-bromopyridazin-3-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (57.3 mg, 0.15 mmol, 1.1 eq), Cs₂CO₃ (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to afford *tert*-butyl 7-(6-(6-(1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoro-1-oxoisindolin-2-yl)pyridazin-

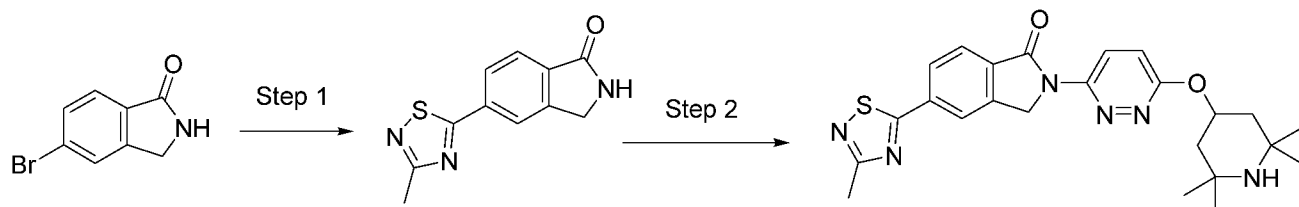
3-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (69 mg, 77%) as a brown solid. LC/MS (ESI): 578.3 [M+H]⁺.

[0469] Step 5: To a round bottom flask charged with *tert*-butyl 7-(6-(6-(1,3-dimethyl-1H-pyrazol-4-yl)-5-fluoro-1-oxoisindolin-2-yl)pyridazin-3-yl)-2,7-diazaspiro[4.4]nonane-2-carboxylate (69 mg, 0.12 mmol, 1.0 eq) and acetaldehyde (0.3 mL, 1.52 mmol, 12.0 eq) was added MeOH (4 mL); and the reaction mixture was stirred at 0 °C for 1h. Then NaBH₃CN (37.24 mg, 0.76 mmol, 6.0 eq) was added and the reaction mixture was stirred at RT for 1 h. The reaction was concentration and the resulting residue was purified by RP-HPLC using MeCN and H₂O as eluent to provide 6-(1,3-dimethyl-1H-pyrazol-4-yl)-2-(6-(7-ethyl-2,7-diazaspiro[4.4]nonan-2-yl)pyridazin-3-yl)-5-fluoroisindolin-1-one (9.02 mg, 0.01 mmol, 12.6%) as a white solid.

[0470] ¹H NMR (400 MHz, METHANOL-*d*₄) δ : 8.58 (d, J = 9.9 Hz, 1H), 7.85 (d, J = 6.9 Hz, 1H), 7.80 (d, J = 1.8 Hz, 1H), 7.51 (d, J = 9.9 Hz, 1H), 7.07 (d, J = 9.9 Hz, 1H), 5.14 (s, 2H), 3.90 (s, 3H), 3.64 - 3.50 (m, 4H), 3.10 (br t, J = 6.8 Hz, 2H), 3.05 - 2.97 (m, 2H), 2.89 (q, J = 7.3 Hz, 2H), 2.33 (s, 3H), 2.20 - 2.10 (m, 2H), 2.04 (dt, J = 2.6, 7.1 Hz, 2H), 1.25 (t, J = 7.3 Hz, 3H); LC/MS (ESI): 476.3 [M+H]⁺.

[0471] Example 31. Synthesis of 5-(3-methyl-1,2,4-thiadiazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isindolin-1-one (Compound No. 451)

[0472] Scheme 31.



[0473] Step 1: 5-Bromoisindolin-1-one (315 mg, 1.5 mmol, 1.5 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (762 mg, 3.0 mmol, 3.0 eq), potassium acetate (300 mg, 3.0 mmol, 3.0 eq) and PdCl₂(dppf).CH₂Cl₂ adduct (109.3 mg, 0.15 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen and anhydrous dioxane (9 mL) was added and the mixture was heated to 90 °C. When full conversion was achieved, the reaction mixture was cooled to room temperature. Then 5-bromo-3-methyl-1,2,4-thiadiazole (177.3 mg, 1.0 mmol, 1.0 eq), aqueous potassium carbonate (2 M, 2 mL) and PdCl₂(dppf).CH₂Cl₂ adduct (109.3 mg, 0.15 mmol, 0.1 eq) were added and the reaction mixture was heated to 90 °C. When full conversion was achieved, the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to afford 5-(3-methyl-1,2,4-thiadiazol-5-yl)isindolin-1-one (71.9 mg, 31%) as a brown solid. LC/MS (ESI): 232.1 [M+H]⁺.

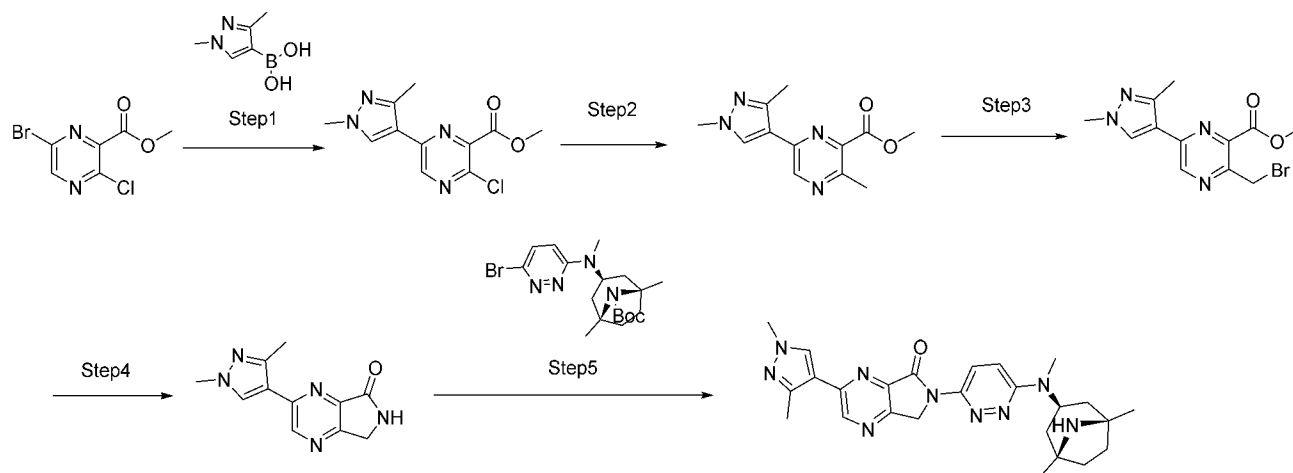
[0474] Step 2: To a round bottom flask charged with 5-(3-methyl-1,2,4-thiadiazol-5-yl)isindolin-1-one (34.8 mg, 0.15 mmol, 1.0 eq), 3-bromo-6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazine (50.0 mg, 0.16 mmol, 1.1 eq), Cs₂CO₃ (148.9 mg, 0.46 mmol, 3.0 eq), and XantPhos Pd G4 (14.2 mg, 0.015 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was

then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v. The resulting residue was further purified by RP HPLC using MeCN and H₂O as eluent to provide 5-(3-methyl-1,2,4-thiadiazol-5-yl)-2-(6-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)pyridazin-3-yl)isoindolin-1-one (20.68 mg, 29.7 %) as a white solid.

[0475] ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.16 (d, *J* = 1.9 Hz, 1H), 8.74 (dd, *J* = 2.6, 9.4 Hz, 1H), 8.71 - 8.67 (m, 1H), 8.47 - 8.44 (m, 1H), 8.42 (d, *J* = 2.0 Hz, 1H), 8.16 (s, 1H), 5.23 (d, *J* = 5.5 Hz, 2H), 4.13 (br s, 1H), 4.06 - 4.03 (m, 1H), 3.90 (s, 3H), 3.54 - 3.44 (m, 1H), 2.76 (br d, *J* = 14.6 Hz, 1H), 2.44 - 2.34 (m, 1H), 2.22 - 2.14 (m, 1H), 2.11 - 2.07 (m, 1H), 2.06 - 1.96 (m, 2H), 1.85 - 1.70 (m, 1H), 1.58 (br d, *J* = 8.0 Hz, 1H); LC/MS (ESI): 402.2 [M+H]⁺.

[0476] **Example 32. Synthesis of 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)(methyl)amino)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one (Compound No. 452)**

[0477] **Scheme 32.**



[0478] **Step 1:** Methyl 6-bromo-3-chloropyrazine-2-carboxylate (400 mg, 1.59 mmol, 1.0 eq), (2,5-dimethylpyrazol-3-yl)boranediol (222.52 mg, 1.59 mmol, 1.0 eq), sodium carbonate (505.57 mg, 4.77 mmol, 3.0 eq) and PdCl₂(dppf).CH₂Cl₂ adduct (116.28 mg, 0.16 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen and anhydrous dioxane (9 mL) and water (1 mL) were added and the reaction mixture was heated to 85 °C overnight. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with PE/EA 5/1, v/v to afford methyl 3-chloro-6-(1,3-dimethylpyrazol-4-yl)pyrazine-2-carboxylate (300 mg, 70.72%) LC/MS (ESI): 267.0 [M+H]⁺.

[0479] **Step 2:** Methyl 3-chloro-6-(1,3-dimethylpyrazol-5-yl)pyrazine-2-carboxylate (500 mg, 1.87 mmol, 1.2 eq), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (1.29 mL, 2.25 mmol, 1.0 eq), potassium

carbonate (777.31 mg, 5.62 mmol, 3.0 eq) and PdCl₂(dppf).CH₂Cl₂ adduct (137.05 mg, 0.19 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (10 mL) was added and the reaction mixture was heated to 110 °C 3 h. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA(100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with PE/EA 5/1, v/v to afford methyl 6-(1,3-dimethylpyrazol-5-yl)-3-methylpyrazine-2-carboxylate (430 mg, 93.13%). LC/MS (ESI): 247.1 [M+H]⁺.

[0480] Step 3: Methyl 6-(1,3-dimethyl-1H-pyrazol-4-yl)-3-methylpyrazine-2-carboxylate (430 mg, 1.75 mmol, 1.0 eq), *N*-bromosuccinimide (371.67 mg, 2.10 mmol, 1.2 eq) and benzoyl peroxide (129.17 mg, 0.79 mmol, 0.45 eq) were combined with carbon tetrachloride (10 mL) and the reaction mixture was heated to 80 °C and stirred for 16 h. The reaction mixture was cooled to RT and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography with PE/EA to afford methyl 3-(bromomethyl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)pyrazine-2-carboxylate (440 mg, 77.32%) as a brown solid. LC/MS (ESI): 325.1, 327.1 [M+H]⁺.

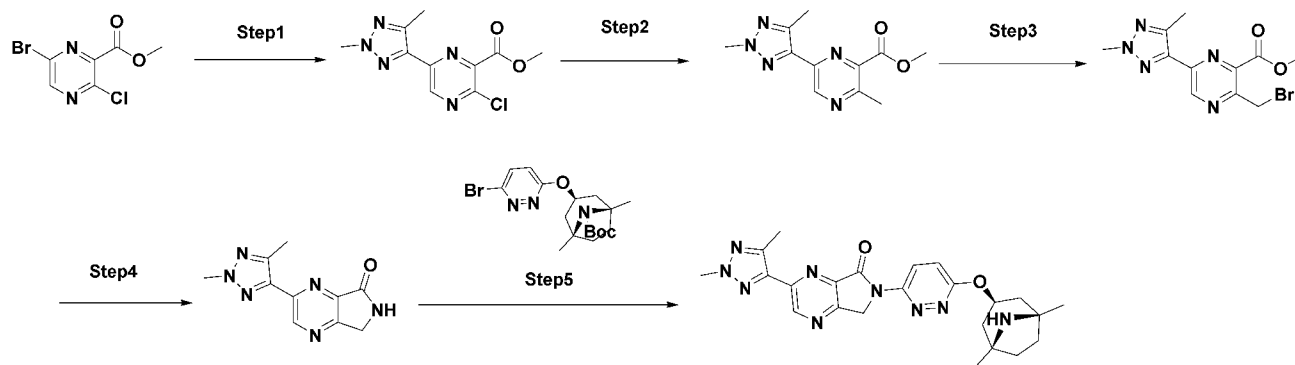
[0481] Step 4: Methyl 3-(bromomethyl)-6-(1,3-dimethylpyrazol-4-yl)pyrazine-2-carboxylate (440 mg, 1.35 mmol, 1.0 eq) was suspended in 28 % aqueous ammonium hydroxide and the mixture was stirred at RT for 8 h. The mixture was filtered, and the residue was washed with water and methanol. The solid was collected, dried under vacuum, and used in the next step without further purification. LC/MS (ESI): 230.1 [M+H]⁺

[0482] Step 5: To a round bottom flask charged with 3-(1,3-dimethylpyrazol-4-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyrazin-5-one (40 mg, 0.17 mmol, 1.0 eq), tert-butyl (1R,3s,5S)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (71.95 mg, 0.17 mmol, 1.0 eq), Cs₂CO₃ (170.13 mg, 0.52 mmol, 3.0 eq), and XantPhos Pd G4 (16.79 mg, 0.02 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated to 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v to obtain 2-methylpropan-2-yl (1R,3s,5S)-3-({6-[2-(1,3-dimethylpyrazol-4-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[4,3-b]pyrazin-6-yl]-1,2-diazin-3-yl}oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (40.2 mg), which was dissolved HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h, and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H₂O as eluent to provide 3-(1,3-dimethylpyrazol-4-yl)-6-(6-{[(1S,3s,5R)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl]oxy}-1,2-diazin-3-yl)-6,7-dihydro-5H-pyrrolo[4,3-b]pyrazin-5-one (25 mg, 30 %) as a white solid.

[0483] ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.10 (s, 1H), 8.49 (s, 2H), 8.30 (s, 1H), 7.35 (d, *J* = 10.0 Hz, 1H), 5.16 (s, 2H), 5.02 (td, *J* = 5.6, 11.3 Hz, 1H), 3.85 (s, 3H), 2.91 (s, 3H), 2.52 (br s, 3H), 1.98 (br d, *J* = 7.6 Hz, 2H), 1.79 (br t, *J* = 10.9 Hz, 2H), 1.74 - 1.68 (m, 2H), 1.66 (br d, *J* = 5.1 Hz, 2H), 1.31 (s, 6H); LC/MS (ESI): 474.3 [M+H]⁺.

[0484] Example 33. Synthesis of 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6-(6-(((1R,3S,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one (Compound No. 453)

[0485] Scheme 33.



[0486] **Step 1:** 4-Bromo-2,5-dimethyl-2H-1,2,3-triazole (262.0 mg, 1.5 mmol, 1.5 eq), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (762 mg, 3.0 mmol, 3.0 eq), potassium acetate (300 mg, 3.0 mmol, 3.0 eq) and $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ adduct (109.3 mg, 0.15 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen and anhydrous dioxane (9 mL) was added and the reaction mixture was heated to 90 °C. When full conversion was achieved, the reaction mixture was cooled to room temperature. Then methyl 6-bromo-3-chloropyrazine-2-carboxylate (249.9 mg, 1.0 mmol, 1.0 eq), aqueous potassium carbonate (2 M, 2 mL) and $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ adduct (109.3 mg, 0.15 mmol, 0.1 eq) were added and the mixture was heated to 90 °C. When full conversion was achieved, the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with DCM/MeOH, 20/1, v/v to obtain methyl 3-chloro-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)pyrazine-2-carboxylate (165.5 mg, 62%) as a brown solid. LC/MS (ESI): 268.1 $[\text{M}+\text{H}]^+$.

[0487] **Step 2:** Methyl 3-chloro-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)pyrazine-2-carboxylate (500 mg, 1.87 mmol, 1.2 eq), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (1.29 mL, 2.25 mmol, 1.0 eq), potassium carbonate (777.31 mg, 5.62 mmol, 3.0 eq) and $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ adduct (137.05 mg, 0.19 mmol, 0.1 eq) were charged to a three-neck 100 mL round bottom flask under nitrogen. Anhydrous dioxane (10 mL) was added and the reaction mixture was heated to 110 °C 3 h. Then the mixture was cooled, filtered through a pad of Celite, and the filter cake was rinsed with EA (100 mL). The filtrate was washed with brine and the organic layer was collected, dried over sodium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography with PE/EA 5/1, v/v to afford methyl 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-3-methylpyrazine-2-carboxylate (430 mg, 93.13%). LC/MS (ESI): 247.1 $[\text{M}+\text{H}]^+$.

[0488] **Step 3:** Methyl 6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-3-methylpyrazine-2-carboxylate (430 mg, 1.75 mmol, 1.0 eq), *N*-bromosuccinimide (371.67 mg, 2.10 mmol, 1.2 eq) and benzoyl peroxide (129.17 mg, 0.79 mmol, 0.45 eq) were combined with carbon tetrachloride (10 mL) and the reaction mixture was

heated to 80 °C and stirred for 16 h. The reaction mixture was cooled to RT and concentrated under vacuum. The resulting residue was purified by silica gel column chromatography with PE/EA to afford methyl 3-(bromomethyl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)pyrazine-2-carboxylate (440 mg, 77.32%) as a brown solid. LC/MS (ESI): 325.1, 327.1 [M+H]⁺.

[0489] Step 4: Methyl 3-(bromomethyl)-6-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)pyrazine-2-carboxylate (440 mg, 1.35 mmol, 1.0 eq) was suspended in 28 % aqueous ammonium hydroxide and the mixture was stirred at RT for 8 h. Then the mixture was filtered, and the residue was washed with water and methanol. The solid was collected, dried under vacuum, and used in the next step without further purification. LC/MS (ESI): 230.1 [M+H]⁺

[0490] Step 5: To a round bottom flask charged with 3-(2,5-dimethyl-2H-1,2,3-triazol-4-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one (40 mg, 0.17 mmol, 1.0 eq), *tert*-butyl (1R,3s,5S)-3-((6-bromopyridazin-3-yl)oxy)-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (71.95 mg, 0.17 mmol, 1.0 eq), Cs₂CO₃ (170.13 mg, 0.52 mmol, 3.0 eq), and XantPhos Pd G4 (16.79 mg, 0.02 mmol, 0.1 eq) was added 1,4-dioxane (4 mL). The reaction mixture was degassed with argon for 5 min and was then heated at 90 °C for 8 h. The reaction mixture was cooled to RT and diluted with EA. The organic phase was washed with brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel column chromatography with DCM/MeOH 20/1, v/v, and was then dissolved in HCl in dioxane (2 mL, 4.0 mol/L). The reaction was stirred at RT for 1 h and was then concentrated. The resulting residue was purified by RP HPLC using MeCN and H₂O as eluent to provide 3-(1,3-dimethyl-1H-pyrazol-4-yl)-6-(6-(((1R,3s,5S)-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl)oxy)pyridazin-3-yl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-one (25 mg, 30 %) as a white solid.

[0491] ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.34 (s, 1H), 8.71 (d, J = 9.6 Hz, 1H), 7.35 (d, J = 9.6 Hz, 1H), 5.52 - 5.42 (m, 1H), 5.25 (s, 2H), 4.23 (s, 3H), 2.62 (s, 3H), 2.17 (br dd, J = 5.8, 11.9 Hz, 2H), 1.80 (br d, J = 6.6 Hz, 2H), 1.53 (br d, J = 6.9 Hz, 2H), 1.46 - 1.37 (m, 2H), 1.21 (s, 6H); LC/MS (ESI): 462.2 [M+H]⁺.

[0492] In some embodiments of the disclosure, the compounds can be made by similar means according to **Examples 1-33**. **Table 7** provides for physical data for the compounds disclosed herein.

Table 7

No.	NMR/MS
1	LC/MS (ESI): 405.2 [M+H] ⁺
2	LC/MS (ESI): 448.2 [M+H] ⁺
3	LC/MS (ESI): 461.2 [M+H] ⁺
4	LC/MS (ESI): 402.20 [M+H] ⁺
5	LC/MS (ESI): 390.2 [M+H] ⁺
6	LC/MS (ESI): 448.2 [M+H] ⁺
7	LC/MS (ESI): 462.2 [M+H] ⁺
8	LC/MS (ESI): 506.3 [M+H] ⁺
9	LC/MS (ESI): 498.2 [M+H] ⁺
10	LC/MS (ESI): 488.2 [M+H] ⁺
11	LC/MS (ESI): 386.17 [M+H] ⁺
12	LC/MS (ESI): 376.1 [M+H] ⁺

No.	NMR/MS
13	LC/MS (ESI): 418.1 [M+H] ⁺
14	LC/MS (ESI): 388.18 [M+H] ⁺
15	LC/MS (ESI): 434.3 [M+H] ⁺
16	LC/MS (ESI): 428.18 [M+H] ⁺
17	¹ H NMR (C ₂ DF ₃ O ₂ , 400MHz) δ 9.94 (d, <i>J</i> = 9.5 Hz, 1H), 9.38 (s, 1H), 9.08 (s, 1H), 9.00 (s, 1H), 8.90 (s, 1H), 8.80 (d, <i>J</i> = 9.5 Hz, 1H), 6.92-6.49 (m, 1H), 5.73 (s, 2H), 4.41 (s, 3H), 3.57 (br d, <i>J</i> = 7.0 Hz, 2H), 2.95 (br d, <i>J</i> = 3.4 Hz, 1H), 2.10 - 2.03 (m, 2H), 2.01-1.91 (m, 2H), 1.73 (s, 6H), 1.67 (s, 6H); LC/MS (ESI): 446.3 [M+H] ⁺
18	LC/MS (ESI): 476.27 [M+H] ⁺
19	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ 8.92 (s, 1H), 8.45-8.40 (m, 2H), 8.13 (s, 1H), 7.99 (s, 1H), 7.26 (d, <i>J</i> = 10.0 Hz, 1H), 5.19 (s, 2H), 4.87-4.76 (m, 1H), 3.90 (s, 3H), 3.58-3.51 (m, 2H), 2.86 (s, 3H), 2.10 (br d, <i>J</i> = 12.9 Hz, 2H), 1.79-1.68 (m, 2H), 1.62 (br d, <i>J</i> = 7.0 Hz, 2H), 1.33 (br t, <i>J</i> = 12.2 Hz, 2H), 1H not observed (NH); LC/MS (ESI): 431.2 [M+H] ⁺
20	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ 8.93 (s, 1H), 8.47 (d, <i>J</i> = 9.9 Hz, 1H), 8.44 (s, 1H), 8.14 (s, 1H), 8.01 (s, 1H), 7.33 (d, <i>J</i> = 10.0 Hz, 1H), 5.21 (s, 2H), 5.07-4.94 (m, 1H), 3.90 (s, 3H), 2.91 (s, 3H), 2.05 - 1.92 (m, 2H), 1.68 (br s, 6H), 1.31 (br s, 6H), 1H not observed (NH); LC/MS (ESI): 459.3 [M+H] ⁺
21	LC/MS (ESI): 506.3 [M+H] ⁺
22	LC/MS (ESI): 417.2 [M+H] ⁺
23	LC/MS (ESI): 490.3 [M+H] ⁺
24	LC/MS (ESI): 474.2 [M+H] ⁺
25	LC/MS (ESI): 430.2 [M+H] ⁺
26	LC/MS (ESI): 492.2 [M+H] ⁺
27	LC/MS (ESI): 429.2 [M+H] ⁺
28	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ 9.02 (d, <i>J</i> = 6.3 Hz, 2H), 8.71 (d, <i>J</i> = 9.6 Hz, 1H), 8.52 (s, 1H), 8.28 (s, 1H), 8.04-7.72 (m, 1H), 7.34 (d, <i>J</i> = 9.5 Hz, 1H), 5.63 (br s, 1H), 5.28 (s, 2H), 2.28-2.07 (m, 2H), 1.58-1.34 (m, 2H), 1.27 (br s, 6H), 1.22-1.03 (m, 6H), 1H not observed (NH); LC/MS (ESI): 484.2 [M+H] ⁺
29	LC/MS (ESI): 484.3 [M+H] ⁺
30	LC/MS (ESI): 516.2 [M+H] ⁺
31	LC/MS (ESI): 490.2 [M+H] ⁺
32	LC/MS (ESI): 445.2 [M+H] ⁺
33	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.58 (s, 2H), 9.30 (s, 1H), 9.21 (s, 1H), 9.17 (br s, 1H), 8.65-8.51 (m, 2H), 7.67-7.52 (m, 1H), 5.32 (s, 2H), 3.93-3.89 (m, 2H), 3.79 (s, 2H), 3.40 (br s, 2H), 1.08-1.00 (m, 2H), 1.00-0.91 (m, 2H); LC/MS (ESI): 400.3 [M+H] ⁺
34	LC/MS (ESI): 433.2 [M+H] ⁺
35	LC/MS (ESI): 497.2 [M+H] ⁺
36	LC/MS (ESI): 417.2 [M+H] ⁺
37	LC/MS (ESI): 453.4 [M+H] ⁺
38	LC/MS (ESI): 403.2 [M+H] ⁺
39	LC/MS (ESI): 417.2 [M+H] ⁺
40	LC/MS (ESI): 431.3 [M+H] ⁺
41	LC/MS (ESI): 419.2 [M+H] ⁺
42	LC/MS (ESI): 434.2 [M+H] ⁺
43	LC/MS (ESI): 475.3 [M+H] ⁺
44	LC/MS (ESI): 403.2 [M+H] ⁺
45	LC/MS (ESI): 422.3 [M+H] ⁺
46	LC/MS (ESI): 419.5 [M+H] ⁺
47	LC/MS (ESI): 475.4 [M+H] ⁺
48	LC/MS (ESI): 431.3 [M+H] ⁺

No.	NMR/MS
49	LC/MS (ESI): 464.3 [M+H] ⁺
50	LC/MS (ESI): 448.2 [M+H] ⁺
51	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.97 - 8.92 (m, 1H), 8.85 - 8.75 (m, 1H), 8.55 - 8.49 (m, 1H), 8.38 - 8.32 (m, 1H), 7.98 - 7.89 (m, 1H), 7.86 - 7.81 (m, 1H), 7.48 - 7.40 (m, 1H), 5.22 - 5.17 (m, 2H), 5.13 - 5.02 (m, 1H), 3.84 - 3.78 (m, 3H), 2.96 - 2.91 (m, 3H), 2.47 (s, 3H), 1.97 - 1.87 (m, 2H), 1.82 - 1.75 (m, 2H), 1.54 - 1.49 (m, 6H), 1.45 - 1.39 (m, 6H); LC/MS (ESI): 475.3 [M+H] ⁺
52	LC/MS (ESI): 417.2 [M+H] ⁺
53	LC/MS (ESI): 431.3 [M+H] ⁺
54	LC/MS (ESI): 476.3 [M+H] ⁺
55	¹ H NMR (DMSO- <i>d</i> ₆ , 400MHz) δ = 9.33 (s, 1H), 8.97 (s, 1H), 8.37 (s, 1H), 7.88 (s, 1H), 5.17 (s, 2H), 5.07 (m, 1H), 3.81 (s, 3H), 3.03 (s, 3H), 2.48 (s, 3H), 1.81 (br d, <i>J</i> = 7.4 Hz, 2H), 1.54-1.69 (m, 6H), 1.23 (s, 6H), 1H not observed (NH); LC/MS (ESI): 474.3 [M+H] ⁺
56	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.06 (s, 1H), 8.72 (s, 1H), 8.71 (d, 2H, <i>J</i> = 9.0 Hz), 8.2-8.3 (m, 1H), 7.99 (s, 1H), 7.35 (dd, 1H, <i>J</i> = 1.4, 9.6 Hz), 5.6-5.7 (m, 1H), 5.29 (s, 2H), 4.28 (d, 2H, <i>J</i> = 7.3 Hz), 2.13 (br dd, 2H, <i>J</i> = 3.9, 15.8 Hz), 1.48 (t, 3H, <i>J</i> = 7.3 Hz), 1.36 (br d, 2H, <i>J</i> = 11.9 Hz), 1.3-1.3 (s, 6H), 1.17 (s, 6H); 1H not observed (NH); LC/MS (ESI): 458.2 [M+H] ⁺
57	LC/MS (ESI): 492.2 [M+H] ⁺
58	LC/MS (ESI): 515.2 [M+H] ⁺
59	¹ H NMR (DMSO- <i>d</i> ₆ , 400MHz) δ = 8.98 (s, 1H), 8.69 (d, <i>J</i> = 9.6 Hz, 1H), 8.37 (s, 1H), 8.19 (br s, 1H), 7.88 (s, 1H), 7.32 (d, <i>J</i> = 9.6 Hz, 1H), 5.63 - 5.53 (m, 1H), 5.24 (s, 2H), 3.81 (s, 3H), 2.48 (s, 3H), 2.11 (br dd, <i>J</i> = 3.6, 12.3 Hz, 1H), 1.88 - 1.80 (m, 1H), 1.63 (br dd, <i>J</i> = 4.3, 11.8 Hz, 1H), 1.37 (t, <i>J</i> = 11.6 Hz, 1H), 1.21 (s, 3H), 1.10 (s, 3H), 0.59 - 0.52 (m, 2H), 0.51 - 0.44 (m, 1H), 0.40 - 0.33 (m, 1H); LC/MS (ESI): 460.1 [M+H] ⁺
60	LC/MS (ESI): 460.2 [M+H] ⁺
61	LC/MS (ESI): 527.2 [M+H] ⁺
62	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.03 (s, 1H), 8.46 (d, <i>J</i> = 9.8 Hz, 1H), 8.31 (s, 1H), 7.89 (s, 1H), 7.34 (d, <i>J</i> = 9.9 Hz, 1H), 5.25 (s, 2H), 5.05 - 4.93 (m, 1H), 2.91 (s, 3H), 2.64 (s, 6H), 1.96 (br d, <i>J</i> = 7.8 Hz, 2H), 1.80 - 1.72 (m, 2H), 1.68 (br d, <i>J</i> = 7.5 Hz, 2H), 1.63 (br dd, <i>J</i> = 5.4, 12.9 Hz, 2H), 1.30 (s, 6H); LC/MS (ESI): 490.2 [M+H] ⁺
63	LC/MS (ESI): 516.2 [M+H] ⁺
64	LC/MS (ESI): 462.3 [M+H] ⁺
65	LC/MS (ESI): 530.2 [M+H] ⁺
66	LC/MS (ESI): 543.2 [M+H] ⁺
67	LC/MS (ESI): 474.2 [M+H] ⁺
68	LC/MS (ESI): 447.2 [M+H] ⁺
69	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.06 (s, 1H), 8.69 (d, <i>J</i> = 9.6 Hz, 1H), 8.24 (s, 1H), 7.92 (s, 1H), 7.35 (d, <i>J</i> = 9.6 Hz, 1H), 5.49 (s, 1H), 5.28 (s, 2H), 2.65 (s, 6H), 2.22 (br dd, <i>J</i> = 5.9, 12.3 Hz, 2H), 1.88 (br d, <i>J</i> = 7.4 Hz, 2H), 1.60 (br d, <i>J</i> = 6.9 Hz, 2H), 1.49 (br t, <i>J</i> = 11.4 Hz, 2H), 1.25 (s, 6H); LC/MS (ESI): 477.2 [M+H] ⁺
70	LC/MS (ESI): 460.2 [M+H] ⁺
71	¹ H NMR (DMSO- <i>d</i> ₆ , 400MHz) δ = 9.03 (s, 1H), 8.63 (s, 1H), 8.47 (d, <i>J</i> = 9.9 Hz, 1H), 8.29 (s, 1H), 7.92 (s, 1H), 7.33 (d, <i>J</i> = 10.0 Hz, 1H), 5.27 (s, 2H), 5.10 - 5.00 (m, 1H), 3.99 (s, 3H), 2.91 (s, 3H), 1.67 - 1.58 (m, 4H), 1.35 (s, 6H), 1.22 (s, 6H); LC/MS (ESI): 529.2 [M+H] ⁺
72	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.98 (s, 1H), 8.71 (d, <i>J</i> = 9.6 Hz, 1H), 8.37 (s, 1H), 8.23 (s, 1H), 7.88 (s, 1H), 7.37 (d, <i>J</i> = 9.6 Hz, 1H), 5.51 (br t, <i>J</i> = 5.7 Hz, 1H), 5.23 (s, 2H), 3.81 (s, 3H), 2.47-2.48 (s, 3H), 2.36 (br dd, <i>J</i> = 13.0, 5.9 Hz, 2H), 2.06 (br d, <i>J</i> = 7.8 Hz, 2H), 1.79 (br d, <i>J</i> = 8.0 Hz, 2H), 1.69 (br t, <i>J</i> = 11.9 Hz, 2H), 1.38 (s, 6H); LC/MS (ESI): 460.2 [M+H] ⁺

No.	NMR/MS
73	LC/MS (ESI): 461.2 [M+H] ⁺
74	¹ H NMR (DMSO- <i>d</i> ₆ , 400MHz) δ : 9.28 (br d, <i>J</i> = 9.8 Hz, 1H), 9.13 (br d, <i>J</i> = 9.0 Hz, 1H), 9.06 (s, 1H), 8.73 (d, <i>J</i> = 9.6 Hz, 1H), 8.64 (s, 1H), 7.96 (s, 1H), 7.40 (d, <i>J</i> = 9.6 Hz, 1H), 5.53 (td, <i>J</i> = 5.2, 10.9 Hz, 1H), 5.27 (s, 2H), 3.99 (s, 3H), 2.43 (br dd, <i>J</i> = 5.9, 13.1 Hz, 2H), 2.15 (br d, <i>J</i> = 8.1 Hz, 2H), 1.95 - 1.82 (m, 4H), 1.47 (s, 6H); LC/MS (ESI): 514.2 [M+H] ⁺
75	LC/MS (ESI): 498.2 [M+H] ⁺
76	¹ H NMR (DMSO- <i>d</i> ₆ , 400MHz) δ = 8.98 (s, 1H), 8.72 (d, <i>J</i> = 9.5 Hz, 1H), 8.38 (s, 1H), 7.89 (s, 1H), 7.38 (br d, <i>J</i> = 9.6 Hz, 1H), 5.74 - 5.58 (m, 1H), 5.25 (s, 2H), 3.82 (s, 3H), 2.48 (s, 3H), 2.30 - 2.13 (m, 2H), 1.53 (br d, <i>J</i> = 6.5 Hz, 2H), 1.45 - 1.16 (m, 12H), ¹ H not observed (NH); LC/MS (ESI): 462.3 [M+H] ⁺
77	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.07 (s, 1H), 8.94 (s, 1H), 8.71 (d, <i>J</i> = 9.6 Hz, 1H), 8.36 - 8.25 (m, 1H), 8.12 (s, 1H), 8.01 - 7.62 (m, 1H), 7.35 (d, <i>J</i> = 9.5 Hz, 1H), 5.57 - 5.45 (m, 1H), 5.28 (s, 2H), 2.57 (s, 3H), 2.22 (dd, <i>J</i> = 5.9, 12.3 Hz, 2H), 1.88 (br d, <i>J</i> = 7.5 Hz, 2H), 1.62 (br d, <i>J</i> = 7.6 Hz, 2H), 1.56 - 1.48 (m, 2H), 1.27 (s, 6H); LC/MS (ESI): 496.2 [M+H] ⁺
78	LC/MS (ESI): 498.2 [M+H] ⁺
79	¹ H NMR (DMSO- <i>d</i> ₆ , 400MHz) δ: 8.87-8.97 (m, 1H), 8.70 (d, <i>J</i> = 9.6 Hz, 1H), 8.31 (s, 1H), 7.83 (d, <i>J</i> = 0.9 Hz, 1H), 7.41 (d, <i>J</i> = 9.6 Hz, 1H), 5.43-5.62 (m, 1H), 5.15 (s, 2H), 4.91-5.12 (m, 1H), 3.75 (s, 3H), 2.41 (s, 3H), 2.17-2.31 (m, 1H), 1.92-2.14 (m, 2H), 1.64-1.91 (m, 3H), 1.25-1.50 (m, 6H), 1H not observed (NH); LC/MS (ESI): 478.2 [M+H] ⁺
80	LC/MS (ESI): 463.2 [M+H] ⁺
81	LC/MS (ESI): 434.2 [M+H] ⁺
82	LC/MS (ESI): 496.2 [M+H] ⁺
83	LC/MS (ESI): 461.2 [M+H] ⁺
84	LC/MS (ESI): 463.3 [M+H] ⁺
85	¹ H NMR (DMSO- <i>d</i> ₆ , 400MHz) δ = 8.97 (s, 1H), 8.48 (d, <i>J</i> = 9.9 Hz, 1H), 8.30 (s, 1H), 7.85 (s, 1H), 7.35 (d, <i>J</i> = 10.0 Hz, 1H), 5.22 (s, 2H), 5.08 (td, <i>J</i> = 5.6, 11.6 Hz, 1H), 3.83 (s, 3H), 2.92 (s, 3H), 2.48 (s, 3H), 2.13 (br d, <i>J</i> = 8.1 Hz, 2H), 2.01 - 1.93 (m, 2H), 1.92 - 1.86 (m, 2H), 1.79 (br dd, <i>J</i> = 5.4, 13.4 Hz, 2H), 1.42 (s, 6H), 1H not observed (NH); LC/MS (ESI): 473.3 [M+H] ⁺
86	LC/MS (ESI): 479.2 [M+H] ⁺
88	LC/MS (ESI): 477.1 [M+H] ⁺
89	LC/MS (ESI): 473.6 [M+H] ⁺
90	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.47 - 8.41 (m, 2H), 8.35 (s, 1H), 7.89 (s, 1H), 7.32 (d, <i>J</i> = 10.0 Hz, 1H), 5.15 (s, 2H), 5.07 - 4.93 (m, 1H), 3.82 (s, 3H), 2.90 (s, 3H), 2.48 (s, 3H), 1.95 - 1.89 (m, 2H), 1.77 - 1.58 (m, 6H), 1.28 (s, 6H); LC/MS (ESI): 507.2 [M+H] ⁺
91	LC/MS (ESI): 466.2 [M+H] ⁺
92	LC/MS (ESI): 476.3 [M+H] ⁺
93	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ , 8.96 (br d, <i>J</i> = 8.8 Hz, 1H), 8.85 (br d, <i>J</i> = 9.3 Hz, 1H), 8.70 (d, <i>J</i> = 9.6 Hz, 1H), 8.47 (s, 1H), 7.94 (s, 1H), 7.41 (d, <i>J</i> = 9.6 Hz, 1H), 5.61 - 5.47 (m, 1H), 5.16 (s, 2H), 3.82 (s, 3H), 2.48 - 2.42 (m, 5H), 2.16 (br d, <i>J</i> = 8.0 Hz, 2H), 1.95 - 1.75 (m, 4H), 1.45 (s, 6H); LC/MS (ESI): 494.1 [M+H] ⁺
94	LC/MS (ESI): 474.2 [M+H] ⁺
95	LC/MS (ESI): 418.2 [M+H] ⁺
96	¹ H NMR (METHANOL- <i>d</i> ₄ , 400 MHz) δ: 9.02 (s, 1H), 8.85 (d, <i>J</i> = 9.6 Hz, 1H), 8.27 (s, 1H), 7.26 (d, <i>J</i> = 9.6 Hz, 1H), 5.69 - 5.57 (m, 1H), 5.29 (s, 2H), 4.19 (s, 3H), 2.61 (s, 3H), 2.61 - 2.56 (m, 2H), 2.38 - 2.29 (m, 2H), 2.08 - 2.00 (m, 2H), 1.86 (dd, <i>J</i> = 11.4, 13.2 Hz, 2H), 1.55 (s, 6H), ¹ H not observed (NH); LC/MS (ESI): 461.2 [M+H] ⁺
97	LC/MS (ESI): 461.3 [M+H] ⁺

No.	NMR/MS
98	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ 8.98 (s, 1H), 8.70 (d, <i>J</i> = 9.6 Hz, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 7.88 (s, 1H), 7.34 (d, <i>J</i> = 9.6 Hz, 1H), 5.51 (s, 1H), 5.24 (s, 2H), 3.81 (s, 3H), 2.48 (s, 3H), 2.26 (br dd, <i>J</i> = 5.6, 12.4 Hz, 2H), 1.90 (br t, <i>J</i> = 7.1 Hz, 2H), 1.71 - 1.48 (m, 6H), 1.30 (s, 3H), 0.91 (t, <i>J</i> = 7.4 Hz, 3H); LC/MS (ESI): 474.2 [M+H] ⁺
99	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.96 (s, 1H), 8.71 (d, <i>J</i> = 9.5 Hz, 1H), 8.45 (s, 1H), 8.27 (s, 1H), 8.15 (s, 1H), 8.05 (s, 1H), 7.35 (d, <i>J</i> = 9.6 Hz, 1H), 5.48 (br d, <i>J</i> = 6.0 Hz, 1H), 5.24 (s, 2H), 3.90 (s, 3H), 2.25 (br dd, <i>J</i> = 6.1, 12.2 Hz, 2H), 1.92 (br d, <i>J</i> = 7.5 Hz, 2H), 1.66 (br d, <i>J</i> = 7.5 Hz, 2H), 1.57 (br t, <i>J</i> = 11.6 Hz, 2H), 1.30 (s, 6H); LC/MS (ESI): 446.2 [M+H] ⁺
100	¹ H NMR (METHANOL- <i>d</i> ₄ , 400 MHz) d : 8.97 (s, 1H), 8.88 (d, <i>J</i> = 9.6 Hz, 1H), 8.13 (s, 1H), 7.95 (s, 1H), 7.28 (d, <i>J</i> = 9.6 Hz, 1H), 5.71 - 5.58 (m, 1H), 5.30 (s, 2H), 3.90 (s, 3H), 2.66 (dd, <i>J</i> = 5.9, 13.9 Hz, 2H), 2.54 (s, 3H), 2.39 - 2.30 (m, 2H), 1.99 (br d, <i>J</i> = 8.5 Hz, 2H), 1.92 - 1.80 (m, 6H), 1.08 (t, <i>J</i> = 7.5 Hz, 6H), ¹ H not observed (NH); LC/MS (ESI): 488.3 [M+H] ⁺
101	LC/MS (ESI): 486.2 [M+H] ⁺
102	LC/MS (ESI): 474.2 [M+H] ⁺
103	LC/MS (ESI): 542.4 [M+H] ⁺
104	LC/MS (ESI): 486.2 [M+H] ⁺
105	LC/MS (ESI): 511.1 [M+H] ⁺
106	LC/MS (ESI): 481.1 [M+H] ⁺
107	LC/MS (ESI): 464.2 [M+H] ⁺
108	LC/MS (ESI): 478.1 [M+H] ⁺
109	LC/MS (ESI): 490.3 [M+H] ⁺
110	LC/MS (ESI): 495.1 [M+H] ⁺
111	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.32 (s, 1H), 8.94 (br s, 1H), 8.86 (br s, 1H), 8.74 (dd, <i>J</i> = 9.6, 0.9 Hz, 1H), 7.43 (d, <i>J</i> = 9.5 Hz, 1H), 5.49-5.60 (m, 1H), 5.21 (s, 2H), 2.84 (s, 3H), 2.67 (s, 3H), 2.42-2.48 (m, 2H), 2.17 (br d, <i>J</i> = 8.1 Hz, 2H), 1.89 (br d, <i>J</i> = 8.3 Hz, 2H), 1.76-1.85 (m, 2H), 1.46 (s, 6H); LC/MS (ESI): 478.3 [M+H] ⁺
112	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.15 (br s, 1H), 9.00 (s, 1H), 8.74 (d, <i>J</i> = 9.6 Hz, 1H), 8.58 (s, 1H), 8.40 (s, 1H), 7.40 (d, <i>J</i> = 9.6 Hz, 1H), 5.58 - 5.48 (m, 1H), 5.26 (s, 2H), 2.72 - 2.68 (m, 3H), 2.48 - 2.38 (m, 2H), 2.21 - 2.08 (m, 2H), 1.94 - 1.77 (m, 4H), 1.46 (s, 6H); LC/MS (ESI): 463.1 [M+H] ⁺
113	LC/MS (ESI): 460.2 [M+H] ⁺
114	LC/MS (ESI): 463.1 [M+H] ⁺
115	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.97 (s, 1H), 8.70 (d, <i>J</i> = 9.6 Hz, 1H), 8.37 (s, 1H), 8.25 (s, 1H), 7.88 (d, <i>J</i> = 1.0 Hz, 1H), 7.35 (d, <i>J</i> = 9.6 Hz, 1H), 5.51 (ddd, <i>J</i> = 4.4, 6.8, 10.9 Hz, 1H), 5.25 (s, 2H), 3.81 (s, 3H), 2.55 - 2.51 (m, 1H), 2.48 (s, 3H), 2.21 - 2.12 (m, 1H), 2.06 (q, <i>J</i> = 10.0 Hz, 3H), 1.91 - 1.83 (m, 1H), 1.79 - 1.63 (m, 2H), 1.51 - 1.37 (m, 2H), 1.19 (s, 3H), 1.13 (s, 3H); LC/MS (ESI): 474.2 [M+H] ⁺
116	LC/MS (ESI): 478.2 [M+H] ⁺
117	LC/MS (ESI): 461.3 [M+H] ⁺
120	LC/MS (ESI): 405.1 [M+H] ⁺
123	LC/MS (ESI): 417.3 [M+H] ⁺
124	LC/MS (ESI): 433.3 [M+H] ⁺
134	LC/MS (ESI): 445.3 [M+H] ⁺
135	LC/MS (ESI): 462.3 [M+H] ⁺
136	LC/MS (ESI): 376.2 [M+H] ⁺
137	LC/MS (ESI): 390.2 [M+H] ⁺
138	LC/MS (ESI): 476.2 [M+H] ⁺
139	LC/MS (ESI): 488.3 [M+H] ⁺
140	LC/MS (ESI): 484.2 [M+H] ⁺

No.	NMR/MS
141	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ 8.95 (d, <i>J</i> = 2.0 Hz, 1H), 8.70 (d, <i>J</i> = 9.6 Hz, 1H), 8.22 - 8.13 (m, 2H), 7.32 (d, <i>J</i> = 9.5 Hz, 1H), 5.62 (ddd, <i>J</i> = 4.1, 7.1, 11.1 Hz, 1H), 5.20 (s, 2H), 3.82 (s, 3H), 2.36 (s, 3H), 2.09 (br d, <i>J</i> = 9.9 Hz, 2H), 1.39 - 1.06 (m, 14H), 1H not observed (NH); LC/MS (ESI): 462.2 [M+H] ⁺
142	LC/MS (ESI): 498.3 [M+H] ⁺
143	LC/MS (ESI): 434.3 [M+H] ⁺
144	LC/MS (ESI): 448.2 [M+H] ⁺
145	LC/MS (ESI): 402.20 [M+H] ⁺
146	LC/MS (ESI): 388.18 [M+H] ⁺
147	LC/MS (ESI): 386.17 [M+H] ⁺
148	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.54 (br d, <i>J</i> = 10.6 Hz, 1H), 9.17 (d, <i>J</i> = 1.9 Hz, 1H), 8.81 (d, <i>J</i> = 10.3 Hz, 1H), 8.68 - 8.57 (m, 1H), 8.47 (s, 1H), 8.43 (d, <i>J</i> = 2.0 Hz, 1H), 8.17 - 8.14 (m, 1H), 8.05 (br s, 1H), 5.09 (s, 2H), 4.85 - 4.77 (m, 1H), 3.90 (s, 3H), 3.08 (s, 3H), 2.21 (br t, <i>J</i> = 12.8 Hz, 2H), 1.81 - 1.72 (m, 2H), 1.56 (s, 6H), 1.53 (s, 6H); LC/MS (ESI): 461.2 [M+H] ⁺
149	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.17 (d, <i>J</i> = 1.9 Hz, 1H), 8.49 (d, <i>J</i> = 10.0 Hz, 1H), 8.42 (d, <i>J</i> = 2.0 Hz, 1H), 8.40 - 8.31 (m, 3H), 7.32 (d, <i>J</i> = 10.0 Hz, 1H), 5.15 (s, 2H), 5.12 - 5.03 (m, 1H), 2.91 (s, 3H), 1.73 (br t, <i>J</i> = 12.4 Hz, 2H), 1.61 (dd, <i>J</i> = 3.1, 12.4 Hz, 2H), 1.39 (s, 6H), 1.28 (s, 6H), 1H not observed (NH); LC/MS (ESI): 447.3 [M+H] ⁺
150	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ 8.95 (d, <i>J</i> = 2.1 Hz, 1H), 8.70 (d, <i>J</i> = 9.6 Hz, 1H), 8.24 (d, <i>J</i> = 2.0 Hz, 1H), 7.34 (d, <i>J</i> = 9.6 Hz, 1H), 5.69 - 5.58 (m, 1H), 5.24 (s, 2H), 2.68 (s, 3H), 2.43 (s, 3H), 2.19 - 2.02 (m, 2H), 1.36 - 1.06 (m, 14H), 1H not observed (NH); LC/MS (ESI): 479.2 [M+H] ⁺
151	LC/MS (ESI): 417.2 [M+H] ⁺
152	LC/MS (ESI): 417.2 [M+H] ⁺
153	LC/MS (ESI): 445.2 [M+H] ⁺
154	LC/MS (ESI): 433.5 [M+H] ⁺
155	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.12 (d, <i>J</i> = 1.6 Hz, 1H), 8.49 (d, <i>J</i> = 9.8 Hz, 1H), 8.44 (s, 1H), 8.36 (d, <i>J</i> = 1.8 Hz, 1H), 8.14 (s, 1H), 7.51 (d, <i>J</i> = 10.0 Hz, 1H), 5.13 (s, 2H), 4.27 (br d, <i>J</i> = 11.1 Hz, 1H), 4.15 (br d, <i>J</i> = 10.8 Hz, 1H), 3.89 (s, 3H), 3.14 - 3.03 (m, 2H), 2.95 (br t, <i>J</i> = 11.5 Hz, 1H), 2.84 - 2.74 (m, 2H), 0.84 (br d, <i>J</i> = 7.1 Hz, 1H), 0.48 (br s, 2H), 0.33 (br s, 2H), 1H not observed (NH); LC/MS (ESI): 417.2 [M+H] ⁺
156	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.93 (d, <i>J</i> = 2.0 Hz, 1H), 8.48 (d, <i>J</i> = 9.9 Hz, 1H), 8.30 (br s, 1H), 8.17 (s, 1H), 8.14 (d, <i>J</i> = 2.0 Hz, 1H), 7.33 (d, <i>J</i> = 10.0 Hz, 1H), 5.17 (s, 2H), 5.06 (br t, <i>J</i> = 11.8 Hz, 1H), 3.82 (s, 3H), 2.91 (s, 3H), 2.37 - 2.34 (m, 5H), 1.69 - 1.52 (m, 3H), 1.35 (s, 6H), 1.22 (s, 6H); LC/MS (ESI): 475.3 [M+H] ⁺
157	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ 9.12 (d, 1H, <i>J</i> = 2.0 Hz), 8.48 (d, 1H, <i>J</i> = 10.0 Hz), 8.44 (s, 1H), 8.37 (d, 1H, <i>J</i> = 2.1 Hz), 8.18 (s, 1H), 8.14 (s, 1H), 7.48 (d, 1H, <i>J</i> = 9.9 Hz), 5.14 (s, 2H), 4.27-4.34 (m, 1H), 4.11-4.19 (m, 1H), 3.90 (s, 3H), 3.02-3.15 (m, 1H), 2.82-2.92 (m, 1H), 2.79-2.86 (m, 1H), 2.62-2.72 (m, 2H), 1.66-1.72 (m, 1H), 0.97 (d, 6H, <i>J</i> = 6.8 Hz); LC/MS (ESI): 419.2 [M+H] ⁺
158	LC/MS (ESI): 431.3 [M+H] ⁺
159	LC/MS (ESI): 431.3 [M+H] ⁺
160	LC/MS (ESI): 497.3 [M+H] ⁺
161	LC/MS (ESI): 464.3 [M+H] ⁺
162	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.41 (s, 1H), 8.95 (d, <i>J</i> = 2.0 Hz, 1H), 8.22 - 8.14 (m, 2H), 5.14 (m, 3H), 3.83 (s, 3H), 3.09 (s, 3H), 2.35 (s, 3H), 1.99 - 1.82 (m, 4H), 1.51 (s, 6H), 1.43 (s, 6H), 1H not observed (NH); LC/MS (ESI): 476.3 [M+H] ⁺
163	LC/MS (ESI): 501.3 [M+H] ⁺

No.	NMR/MS
164	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.94 (s, 1H), 8.85 - 8.66 (m, 2H), 8.53 (d, <i>J</i> = 9.9 Hz, 1H), 8.19 - 8.13 (m, 2H), 7.44 (br d, <i>J</i> = 10.0 Hz, 1H), 5.15 (s, 2H), 5.05 (td, <i>J</i> = 5.7, 11.5 Hz, 1H), 3.82 (s, 3H), 2.94 (s, 3H), 2.36 (s, 3H), 2.18 (br d, <i>J</i> = 8.3 Hz, 2H), 2.03 - 1.93 (m, 2H), 1.90 (br d, <i>J</i> = 8.3 Hz, 2H), 1.83 (br dd, <i>J</i> = 5.4, 13.2 Hz, 2H), 1.44 (s, 6H); LC/MS (ESI): 473.2 [M+H] ⁺
165	LC/MS (ESI): 417.3 [M+H] ⁺
166	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.99 - 8.88 (m, 1H), 8.47 (d, <i>J</i> = 9.9 Hz, 1H), 8.40 - 8.26 (m, 1H), 8.20 (d, <i>J</i> = 2.0 Hz, 1H), 7.33 (d, <i>J</i> = 10.0 Hz, 1H), 5.21 (s, 2H), 5.02 (td, <i>J</i> = 5.7, 11.3 Hz, 1H), 2.90 (s, 3H), 2.68 (s, 3H), 2.43 (s, 3H), 1.98 (br d, <i>J</i> = 7.6 Hz, 2H), 1.85 - 1.74 (m, 2H), 1.73 - 1.59 (m, 4H), 1.31 (s, 6H); LC/MS (ESI): 490.3 [M+H] ⁺
167	LC/MS (ESI): 492.3 [M+H] ⁺
168	LC/MS (ESI): 501.3 [M+H] ⁺
169	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.26 (d, <i>J</i> = 2.1 Hz, 1H), 9.06 (s, 1H), 8.56 (s, 1H), 8.56 (d, <i>J</i> = 3.8 Hz, 2H), 8.48 (d, <i>J</i> = 9.9 Hz, 1H), 8.38 (br s, 1H), 8.07 - 7.70 (m, 1H), 7.31 (d, <i>J</i> = 10.0 Hz, 1H), 5.17 (s, 2H), 5.10 - 4.95 (m, 1H), 2.90 (s, 3H), 1.95 (br d, <i>J</i> = 7.5 Hz, 2H), 1.84 - 1.73 (m, 2H), 1.73 - 1.57 (m, 4H), 1.31 (s, 6H); LC/MS (ESI): 495.3 [M+H] ⁺
170	LC/MS (ESI): 431.2 [M+H] ⁺
171	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.97 - 8.92 (m, 1H), 8.70 (d, <i>J</i> = 9.6 Hz, 1H), 8.40 (s, 1H), 8.19 (d, <i>J</i> = 1.9 Hz, 1H), 8.11 (s, 1H), 7.33 (d, <i>J</i> = 9.6 Hz, 1H), 5.54 - 5.43 (m, 1H), 5.18 (s, 2H), 3.84 (s, 3H), 2.37 (s, 5H), 2.06 (br d, <i>J</i> = 7.8 Hz, 2H), 1.82 (br d, <i>J</i> = 8.1 Hz, 2H), 1.70 (br t, <i>J</i> = 11.8 Hz, 2H), 1.39 (s, 6H); LC/MS (ESI): 460.3 [M+H] ⁺
172	LC/MS (ESI): 530.2 [M+H] ⁺
173	LC/MS (ESI): 543.3 [M+H] ⁺
174	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.95 (d, <i>J</i> = 1.8 Hz, 1H), 8.68 (d, <i>J</i> = 9.6 Hz, 1H), 8.24 (d, <i>J</i> = 1.9 Hz, 1H), 7.32 (d, <i>J</i> = 9.6 Hz, 1H), 5.53 - 5.41 (m, 1H), 5.23 (s, 2H), 2.67 (s, 3H), 2.43 (s, 3H), 2.16 (dd, <i>J</i> = 5.9, 11.9 Hz, 2H), 1.80 (br d, <i>J</i> = 7.0 Hz, 2H), 1.53 (br d, <i>J</i> = 7.4 Hz, 2H), 1.41 (br t, <i>J</i> = 11.3 Hz, 2H), 1.20 (s, 6H), 1H not observed (NH); LC/MS (ESI): 477.2 [M+H] ⁺
175	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.34 (s, 1H), 8.94 (d, <i>J</i> = 1.6 Hz, 1H), 8.18 (s, 2H), 5.13 (s, 2H), 5.01-5.10 (m, 1H), 3.82 (s, 3H), 3.02 (s, 3H), 2.36 (s, 3H), 1.78 (br d, <i>J</i> = 7.4 Hz, 2H), 1.51-1.65 (m, 6H), 1.20 (s, 6H), 1H not observed (NH); LC/MS (ESI): 474.3 [M+H] ⁺
176	LC/MS (ESI): 516.1 [M+H] ⁺
177	LC/MS (ESI): 529.2 [M+H] ⁺
178	LC/MS (ESI): 474.2 [M+H] ⁺
179	LC/MS (ESI): 463.2 [M+H] ⁺
180	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.14 (d, <i>J</i> = 2.0 Hz, 1H), 8.49 (d, <i>J</i> = 10.0 Hz, 1H), 8.33 (d, <i>J</i> = 1.9 Hz, 1H), 8.32 - 8.19 (m, 1H), 7.34 (d, <i>J</i> = 10.0 Hz, 1H), 5.22 (s, 2H), 5.09 (br s, 1H), 4.18 (s, 3H), 2.91 (s, 3H), 2.49 (br s, 3H), 1.75 - 1.59 (m, 4H), 1.39 (s, 6H), 1.27 (s, 6H); LC/MS (ESI): 476.2 [M+H] ⁺
181	LC/MS (ESI): 478.2 [M+H] ⁺
182	LC/MS (ESI): 515.2 [M+H] ⁺
183	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.91 (d, <i>J</i> = 1.8 Hz, 1H), 8.75 - 8.63 (m, 1H), 8.30 (s, 1H), 8.19 (s, 1H), 7.71 (br d, <i>J</i> = 10.3 Hz, 1H), 5.17 (s, 2H), 4.85 (br s, 1H), 4.01 (br s, 3H), 3.00 (s, 3H), 2.23 (br d, <i>J</i> = 8.4 Hz, 2H), 2.06 - 1.84 (m, 6H), 1.46 (s, 6H), 1H not observed (NH); LC/MS (ESI): 527.2 [M+H] ⁺
184	LC/MS (ESI): 498.2 [M+H] ⁺
185	LC/MS (ESI): 474.2 [M+H] ⁺
186	LC/MS (ESI): 460.2 [M+H] ⁺
187	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.98-9.05 (m, 1H), 8.45-8.51 (m, 1H), 8.40-8.44 (m, 1H), 8.31-8.36 (m, 1H), 8.20-8.25 (m, 1H), 7.21-7.41 (m, 1H),

No.	NMR/MS
	5.16 (s, 2H), 5.03-5.09 (m, 1H), 3.80 (s, 3H), 2.91 (s, 3H), 1.55-1.70 (m, 4H), 1.33-1.40 (m, 6H), 1.23 (s, 6H); LC/MS (ESI): 479.6 [M+H] ⁺
188	LC/MS (ESI): 460.2 [M+H] ⁺
189	LC/MS (ESI): 462.3 [M+H] ⁺
190	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.99-9.09 (m, 1H), 8.68 (d, <i>J</i> = 9.6 Hz, 1H), 8.37-8.47 (m, 1H), 8.22-8.31 (m, 1H), 7.24-7.36 (m, 1H), 5.57-5.68 (m, 1H), 5.19 (s, 2H), 3.80 (s, 3H), 2.05-2.07 (m, 2H), 1.24-1.29 (m, 2H), 1.23 (s, 6H), 1.08-1.13 (m, 6H), 1H not observed (NH); LC/MS (ESI): 466.2 [M+H] ⁺
191	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.33 (s, 1H), 8.71 (br d, <i>J</i> = 9.5 Hz, 1H), 8.58 (br s, 1H), 8.53 (s, 1H), 7.35 (br d, <i>J</i> = 9.5 Hz, 1H), 5.64-5.67 (m, 1H), 5.21 (s, 2H), 4.25 (s, 3H), 2.12-2.22 (m, 2H), 1.53-1.57 (m, 2H), 1.41-1.5270m, 6H), 1.23 -1.32(m, 6H), 1H not observed (NH); LC/MS (ESI): 449.2 [M+H] ⁺
193	LC/MS (ESI): 492.3 [M+H] ⁺
194	LC/MS (ESI): 477.2 [M+H] ⁺
195	LC/MS (ESI): 493.2 [M+H] ⁺
196	LC/MS (ESI): 490.2 [M+H] ⁺
197	LC/MS (ESI): 477.2 [M+H] ⁺
198	LC/MS (ESI): 511.2 [M+H] ⁺
199	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.34 (d, <i>J</i> = 1.3 Hz, 1H), 8.70 (d, <i>J</i> = 9.5 Hz, 1H), 8.60 (d, <i>J</i> = 1.3 Hz, 1H), 8.54 (s, 1H), 7.32 (br d, <i>J</i> = 9.6 Hz, 1H), 5.49 (br s, 1H), 5.22 (s, 2H), 4.25 (s, 3H), 2.10 (br d, <i>J</i> = 7.0 Hz, 2H), 1.89-1.99 (m, 2H), 1.74-1.85 (m, 2H), 1.50 (br d, <i>J</i> = 6.6 Hz, 2H), 1.13-1.20 (s, 6H), 1H not observed (NH); LC/MS (ESI): 447.2 [M+H] ⁺
200	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.35 (s, 1H), 8.94 (d, <i>J</i> = 2.1 Hz, 1H), 8.24 (d, <i>J</i> = 2.1 Hz, 1H), 5.18 (s, 2H), 5.01-5.12 (m, 1H), 3.03 (s, 3H), 2.68 (s, 3H), 2.43 (s, 3H), 1.83 (br d, <i>J</i> = 7.4 Hz, 2H), 1.56-1.70 (m, 6H), 1.24 (s, 6H), 1H not observed (NH); LC/MS (ESI): 491.2 [M+H] ⁺
201	LC/MS (ESI): 514.2 [M+H] ⁺
202	LC/MS (ESI): 514.2 [M+H] ⁺
203	LC/MS (ESI): 492.2 [M+H] ⁺
205	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.95 (d, <i>J</i> = 2.1 Hz, 1H), 8.69 (d, <i>J</i> = 9.6 Hz, 1H), 8.19 - 8.15 (m, 2H), 7.31 (d, <i>J</i> = 9.6 Hz, 1H), 5.61 - 5.52 (m, 1H), 5.19 (s, 2H), 3.82 (s, 3H), 2.36 (s, 3H), 2.09 (br dd, <i>J</i> = 3.3, 11.9 Hz, 1H), 2.02 (br s, 1H), 1.80 (t, <i>J</i> = 11.4 Hz, 1H), 1.60 (dd, <i>J</i> = 3.9, 12.0 Hz, 1H), 1.32 (t, <i>J</i> = 11.6 Hz, 1H), 1.19 (s, 3H), 1.07 (s, 3H), 0.55 - 0.48 (m, 2H), 0.46 - 0.39 (m, 1H), 0.36 - 0.27 (m, 1H); LC/MS (ESI): 460.2 [M+H] ⁺
206	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.18 (d, <i>J</i> = 2.0 Hz, 1H), 8.87 (br d, <i>J</i> = 10.6 Hz, 1H), 8.79 (br s, 1H), 8.75 (d, <i>J</i> = 9.6 Hz, 1H), 8.39 (d, <i>J</i> = 2.0 Hz, 1H), 7.41 (d, <i>J</i> = 9.5 Hz, 1H), 5.55 (tt, <i>J</i> = 10.9, 5.6 Hz, 1H), 5.24 (s, 2H), 4.19 (s, 3H), 2.46 (br d, <i>J</i> = 6.1 Hz, 2H), 2.18 (br d, <i>J</i> = 8.0 Hz, 2H), 1.90 (br d, <i>J</i> = 8.3 Hz, 2H), 1.80 (br t, <i>J</i> = 12.1 Hz, 2H), 1.46 (s, 6H), 3H not observed (triazole methyl overlapped with DMSO- <i>d</i> ₆ residue); LC/MS (ESI): 461.2 [M+H] ⁺
207	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.91 (d, <i>J</i> = 2.0 Hz, 1H), 8.39 (d, <i>J</i> = 9.6 Hz, 2H), 8.09-8.16 (m, 2H), 6.99 (d, <i>J</i> = 9.6 Hz, 1H), 5.12 (s, 2H), 4.33-4.45 (m, 1H), 3.82 (s, 3H), 2.35 (s, 3H), 2.07 (br dd, <i>J</i> = 12.9, 2.9 Hz, 2H), 1.34-1.44 (m, 8H), 1.32 (s, 6H), 1H not observed (NH); LC/MS (ESI): 461.3 [M+H] ⁺
208	LC/MS (ESI): 496.2 [M+H] ⁺
209	LC/MS (ESI): 494.2 [M+H] ⁺
210	LC/MS (ESI): 498.2 [M+H] ⁺
211	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.96 (d, <i>J</i> = 2.1 Hz, 1H), 8.75 (d, <i>J</i> = 9.6 Hz, 1H), 8.19 (s, 2H), 7.44 (d, <i>J</i> = 9.6 Hz, 1H), 5.89 - 5.76 (m, 1H), 5.20 (s, 2H), 4.75 (d, <i>J</i> = 52.0 Hz, 1H), 3.83 (s, 3H), 2.37 (s, 3H), 2.00 - 1.88 (m, 1H),

No.	NMR/MS
	1.77 - 1.66 (m, 1H), 1.30 (br s, 6H), 1.19 (br s, 6H), 1H not observed (NH); LC/MS (ESI): 480.2 [M+H] ⁺
212	LC/MS (ESI): 480.2 [M+H] ⁺
213	LC/MS (ESI): 496.2 [M+H] ⁺
214	¹ H NMR (DMSO- <i>d</i> ₆ , 400MHz) δ = 8.94-9.03 (m, 1H), 8.75 (d, <i>J</i> = 9.6 Hz, 1H), 8.19 (s, 2H), 7.43 (d, <i>J</i> = 9.6 Hz, 1H), 5.60 (s, 1H), 5.20 (s, 2H), 4.63-4.87 (m, 1H), 3.83 (s, 3H), 2.37 (s, 3H), 1.98-2.12 (m, 1H), 1.47-1.84 (m, 5H), 1.17-1.35 (s, 6H), 1H not observed (NH); LC/MS (ESI): 478.5 [M+H] ⁺
215	LC/MS (ESI): 478.5 [M+H] ⁺
216	LC/MS (ESI): 492.2 [M+H] ⁺
217	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ : 9.35 (s, 1H), 9.04 (s, 1H), 8.43 (s, 1H), 8.34 (br s, 1H), 8.23-8.31 (m, 1H), 5.12-5.17 (m, 2H), 5.04-5.11 (m, 1H), 3.81 (s, 3H), 3.04 (s, 3H), 1.87 (br d, <i>J</i> =6.9 Hz, 2H), 1.72-1.80 (m, 2H), 1.56-1.67 (m, 4H), 1.27-1.32 (m, 6H); LC/MS (ESI): 478.2 [M+H] ⁺
218	LC/MS (ESI): 499.2 [M+H] ⁺
219	LC/MS (ESI): 461.2 [M+H] ⁺
220	LC/MS (ESI): 443.2 [M+H] ⁺
221	LC/MS (ESI): 475.3 [M+H] ⁺
222	LC/MS (ESI): 448.2 [M+H] ⁺
223	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.41 (s, 1H), 9.05 (d, <i>J</i> = 2.0 Hz, 1H), 8.71 (br d, <i>J</i> = 12.3 Hz, 1H), 8.44 (d, <i>J</i> = 2.1 Hz, 1H), 8.28 (d, <i>J</i> = 2.1 Hz, 1H), 7.70-7.82 (m, 1H), 5.16-5.19 (m, 1H), 5.15 (s, 2H), 3.82 (s, 3H), 3.10 (s, 3H), 1.90-1.98 (m, 2H), 1.81-1.87 (m, 2H), 1.51 (s, 6H), 1.43 (s, 6H); LC/MS (ESI): 480.2 [M+H] ⁺
224	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.70 (s, 1H), 8.94 (d, <i>J</i> = 1.0 Hz, 1H), 8.17-8.17 (m, 1H), 8.07 (s, 1H), 5.48-5.62 (m, 1H), 5.16 (s, 2H), 3.83 (s, 3H), 2.36 (s, 3H), 2.27-2.33 (m, 2H), 1.49 (br s, 8H), 1.39-1.47 (m, 6H), 1H not observed (NH); LC/MS (ESI): 463.3 [M+H] ⁺
225	LC/MS (ESI): 505.2 [M+H] ⁺
226	LC/MS (ESI): 434.2 [M+H] ⁺
227	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.50 (d, <i>J</i> = 1.9 Hz, 1H), 9.36 - 9.25 (m, 1H), 9.16 - 9.07 (m, 1H), 8.77 - 8.73 (m, 2H), 7.41 (d, <i>J</i> = 9.6 Hz, 1H), 5.59 - 5.49 (m, 1H), 5.29 (s, 2H), 2.72 (s, 3H), 2.47 - 2.39 (m, 2H), 2.25 - 2.06 (m, 2H), 1.95 - 1.89 (m, 2H), 1.89 - 1.82 (m, 2H), 1.48 (s, 6H); LC/MS (ESI): 464.2 [M+H] ⁺
228	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.10 (d, <i>J</i> = 2.0 Hz, 2H), 8.68 (d, <i>J</i> = 9.6 Hz, 1H), 8.56 (br d, <i>J</i> = 11.6 Hz, 1H), 8.31 (d, <i>J</i> = 2.0 Hz, 1H), 7.33 (d, <i>J</i> = 9.6 Hz, 1H), 5.51-5.59 (m, 1H), 5.17 (s, 2H), 4.11 (s, 3H), 2.42 (br s, 3H), 2.29 (br dd, <i>J</i> = 13.7, 3.6 Hz, 1H), 2.00-2.12 (m, 1H), 1.94 (br d, <i>J</i> = 3.5 Hz, 1H), 1.68-1.83 (m, 1H), 1.40 (s, 3H), 1.34 (s, 3H), 0.84-1.01 (m, 3H), 0.77 (br d, <i>J</i> = 3.3 Hz, 1H); LC/MS (ESI): 461.2 [M+H] ⁺
230	LC/MS (ESI): 462.3 [M+H] ⁺
231	LC/MS (ESI): 477.2 [M+H] ⁺
232	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.03 (s, 1H), 8.70 (s, 1H), 8.48 (d, 1H, <i>J</i> = 9.9 Hz), 8.3-8.3 (m, 1H), 7.96 (s, 1H), 7.33 (d, 1H, <i>J</i> = 10.0 Hz), 5.27 (s, 2H), 5.0-5.1 (m, 1H), 4.28 (d, 2H, <i>J</i> = 7.4 Hz), 2.91 (s, 3H), 1.59 (br d, 4H, <i>J</i> = 5.5 Hz), 1.47 (t, 3H, <i>J</i> = 7.3 Hz), 1.34 (s, 6H), 1.21 (br s, 6H); 1H not observed (NH); LC/MS (ESI): 458.3 [M+H] ⁺
233	LC/MS (ESI): 464.1 [M+H] ⁺
234	LC/MS (ESI): 448.5 [M+H] ⁺
235	LC/MS (ESI): 476.3 [M+H] ⁺
236	LC/MS (ESI): 418.2 [M+H] ⁺
237	LC/MS (ESI): 463.2 [M+H] ⁺
238	LC/MS (ESI): 474.2 [M+H] ⁺

No.	NMR/MS
239	¹ H NMR (METHANOL- <i>d</i> ₄ , 400 MHz) δ : 8.94 (d, <i>J</i> = 2.0 Hz, 1H), 8.88 (d, <i>J</i> = 9.6 Hz, 1H), 8.29 (d, <i>J</i> = 1.9 Hz, 1H), 7.98 (s, 1H), 7.28 (d, <i>J</i> = 9.6 Hz, 1H), 5.72 - 5.59 (m, 1H), 5.25 (s, 2H), 3.91 (s, 3H), 2.66 (dd, <i>J</i> = 5.9, 13.9 Hz, 2H), 2.44 (s, 3H), 2.39 - 2.31 (m, 2H), 1.99 (br d, <i>J</i> = 8.4 Hz, 2H), 1.92 - 1.86 (m, 4H), 1.82 (br d, <i>J</i> = 13.3 Hz, 2H), 1.08 (t, <i>J</i> = 7.6 Hz, 6H), 1H not observed (NH); LC/MS (ESI): 488.3 [M+H] ⁺
240	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ 8.9-9.0 (m, 1H), 8.7-8.8 (m, 1H), 8.2-8.2 (m, 2H), 7.4-7.4 (m, 1H), 5.5-5.6 (m, 1H), 5.1-5.2 (m, 2H), 3.82 (s, 3H), 2.4-2.5 (m, 2H), 2.3-2.4 (m, 3H), 2.1-2.2 (m, 2H), 1.7-1.9 (m, 6H), 1.4-1.5 (m, 3H), 0.9-1.0 (m, 3H); LC/MS (ESI): 474.2 [M+H] ⁺
241	LC/MS (ESI): 486.2 [M+H] ⁺
242	LC/MS (ESI): 474.2 [M+H] ⁺
243	LC/MS (ESI): 542.4 [M+H] ⁺
244	LC/MS (ESI): 461.2 [M+H] ⁺
245	LC/MS (ESI): 486.2 [M+H] ⁺
246	LC/MS (ESI): 478.2 [M+H] ⁺
247	LC/MS (ESI): 490.2 [M+H] ⁺
248	LC/MS (ESI): 463.2 [M+H] ⁺
249	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.95 (d, <i>J</i> = 2.0 Hz, 1H), 8.71 (d, <i>J</i> = 9.6 Hz, 1H), 8.22 (s, 1H), 8.19 - 8.15 (m, 2H), 7.35 (d, <i>J</i> = 9.6 Hz, 1H), 5.57 - 5.46 (m, 1H), 5.20 (s, 2H), 3.82 (s, 3H), 2.57 - 2.52 (m, 1H), 2.36 (s, 3H), 2.21 - 2.07 (m, 4H), 1.94 - 1.85 (m, 1H), 1.83 - 1.65 (m, 2H), 1.55 - 1.40 (m, 2H), 1.21 (s, 3H), 1.16 (s, 3H); LC/MS (ESI): 474.2 [M+H] ⁺
250	LC/MS (ESI): 463.0 [M+H] ⁺
251	¹ H NMR (C ₂ DF ₃ O ₂ , 400 MHz) δ = 9.90 (s, 1H), 9.64 (s, 1H), 8.89 (br d, <i>J</i> = 9.6 Hz, 1H), 8.70 (s, 1H), 8.24 (br d, <i>J</i> = 9.6 Hz, 1H), 7.72 - 7.49 (m, 1H), 7.39 - 7.14 (m, 1H), 6.07 (br s, 2H), 5.79 (br d, <i>J</i> = 5.1 Hz, 1H), 4.59 (s, 3H), 2.79 (br dd, <i>J</i> = 5.3, 13.8 Hz, 2H), 2.52 - 2.37 (m, 6H), 1.82 (s, 6H); LC/MS (ESI): 447.2 [M+H] ⁺
252	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.14 (d, <i>J</i> = 1.9 Hz, 1H), 8.47 (d, <i>J</i> = 10.0 Hz, 1H), 8.33 (d, <i>J</i> = 1.5 Hz, 1H), 8.18 (br s, 1H), 7.48 (d, <i>J</i> = 10.0 Hz, 1H), 5.20 (s, 2H), 4.37 (br d, <i>J</i> = 12.1 Hz, 1H), 4.18 (s, 3H), 4.12 (br d, <i>J</i> = 12.1 Hz, 1H), 3.09 - 3.05 (m, 1H), 2.87 - 2.80 (m, 1H), 2.78 - 2.70 (m, 1H), 2.60 (br t, <i>J</i> = 11.6 Hz, 1H), 2.49 (br s, 3H), 2.36 (br d, <i>J</i> = 10.4 Hz, 1H), 0.96 (s, 9H); LC/MS (ESI): 448.2 [M+H] ⁺
253	LC/MS (ESI): 461.2 [M+H] ⁺
254	LC/MS (ESI): 433.3 [M+H] ⁺
255	LC/MS (ESI): 422.95 [M+H] ⁺
272	LC/MS (ESI): 434.3 [M+H] ⁺
273	LC/MS (ESI): 476.2 [M+H] ⁺
274	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.51 - 8.33 (m, 2H), 8.04 (s, 1H), 7.64 - 7.60 (m, 1H), 7.55 (d, <i>J</i> = 10.3 Hz, 1H), 7.31 (d, <i>J</i> = 10.0 Hz, 1H), 5.13 (s, 2H), 5.11 - 5.03 (m, 1H), 3.81 (s, 3H), 2.90 (s, 3H), 2.36 (s, 3H), 2.16 (br d, <i>J</i> = 8.1 Hz, 2H), 2.03 - 1.87 (m, 4H), 1.80 (br dd, <i>J</i> = 5.4, 13.6 Hz, 2H), 1.45 (s, 6H); LC/MS (ESI): 490.2 [M+H] ⁺
275	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.48 - 8.39 (m, 1H), 8.36 (d, <i>J</i> = 9.9 Hz, 1H), 7.99 (s, 1H), 7.55 (s, 1H), 7.49 (d, <i>J</i> = 10.4 Hz, 1H), 7.23 (d, <i>J</i> = 10.1 Hz, 1H), 5.14 (br t, <i>J</i> = 11.9 Hz, 1H), 5.02 (s, 2H), 3.79 (s, 3H), 2.89 (s, 3H), 2.33 (s, 3H), 1.95 - 1.82 (m, 2H), 1.75 (br d, <i>J</i> = 11.0 Hz, 2H), 1.54 (s, 6H), 1.43 (s, 6H); LC/MS (ESI): 492.3 [M+H] ⁺
276	¹ H NMR (METHANOL- <i>d</i> ₄ , 400 MHz) δ = 8.84 (d, <i>J</i> = 9.6 Hz, 1H), 8.52 (br s, 1H), 7.90 (s, 1H), 7.75 - 7.72 (m, 1H), 7.53 (dd, <i>J</i> = 0.9, 10.2 Hz, 1H), 7.26 (d, <i>J</i> = 9.6 Hz, 1H), 5.77 (tt, <i>J</i> = 4.1, 10.5 Hz, 1H), 5.22 (s, 2H), 3.89 (s, 3H), 2.47 (dd, <i>J</i> = 4.1, 13.8 Hz, 2H), 2.43 (s, 3H), 1.84 (dd, <i>J</i> = 10.9, 13.3 Hz, 2H), 1.64 (s, 6H), 1.56 (s, 6H); LC/MS (ESI): 479.2 [M+H] ⁺

No.	NMR/MS
277	LC/MS (ESI): 493.3 [M+H] ⁺
278	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.68 (d, <i>J</i> = 9.6 Hz, 1H), 8.36 (s, 1H), 8.09 (s, 1H), 7.65 (s, 1H), 7.60 (d, <i>J</i> = 10.4 Hz, 1H), 7.33 (d, <i>J</i> = 9.8 Hz, 1H), 5.55 - 5.40 (m, 1H), 5.20 (s, 2H), 3.79 (s, 3H), 2.39 - 2.31 (m, 5H), 2.04 (br d, <i>J</i> = 7.9 Hz, 2H), 1.81 (br d, <i>J</i> = 8.0 Hz, 2H), 1.72 (br t, <i>J</i> = 11.9 Hz, 2H), 1.38 (s, 6H); LC/MS (ESI): 477.2 [M+H] ⁺
279	LC/MS (ESI): 497.2 [M+H] ⁺
280	¹ H NMR (CHLOROFORM- <i>d</i> , 400 MHz) δ = 8.92 (d, <i>J</i> = 9.6 Hz, 1H), 8.31 (br s, 1H), 7.75 (d, <i>J</i> = 1.0 Hz, 1H), 7.56 (s, 1H), 7.37 (dd, <i>J</i> = 1.2, 9.8 Hz, 1H), 7.19 (d, <i>J</i> = 9.6 Hz, 1H), 6.02 - 5.86 (m, 1H), 5.28 (s, 2H), 4.87 - 4.67 (m, <i>J</i> = 52.8 Hz, 1H), 3.93 (s, 3H), 2.46 (s, 3H), 2.05 (br d, <i>J</i> = 7.8 Hz, 2H), 1.55 - 1.50 (m, 6H), 1.43 (s, 6H); LC/MS (ESI): 497.2 [M+H] ⁺
281	LC/MS (ESI): 495.2 [M+H] ⁺
282	LC/MS (ESI): 480.2 [M+H] ⁺
283	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ : 9.42 (br d, <i>J</i> = 7.4 Hz, 1H), 9.31 - 9.17 (m, 1H), 8.72 (d, <i>J</i> = 9.6 Hz, 1H), 7.89 (s, 1H), 7.83 (dd, <i>J</i> = 0.8, 9.9 Hz, 1H), 7.39 (d, <i>J</i> = 9.6 Hz, 1H), 5.52 (td, <i>J</i> = 5.3, 10.8 Hz, 1H), 5.27 (s, 2H), 4.16 (s, 3H), 2.48 (s, 3H), 2.41 (br dd, <i>J</i> = 5.8, 13.3 Hz, 2H), 2.13 (br d, <i>J</i> = 8.0 Hz, 2H), 1.95 - 1.81 (m, 4H), 1.48 (s, 6H); LC/MS (ESI): 478.2 [M+H] ⁺
284	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.68 (d, <i>J</i> = 9.6 Hz, 1H), 8.14 (s, 1H), 7.67 (s, 1H), 7.62 (d, <i>J</i> = 10.4 Hz, 1H), 7.31 (d, <i>J</i> = 9.5 Hz, 1H), 5.62 - 5.52 (m, 1H), 5.23 (s, 2H), 3.80 (s, 3H), 2.36 (s, 3H), 2.11 (br dd, <i>J</i> = 3.3, 12.1 Hz, 1H), 1.83 (br t, <i>J</i> = 11.4 Hz, 1H), 1.67 - 1.58 (m, 1H), 1.36 (br t, <i>J</i> = 11.0 Hz, 1H), 1.21 (s, 3H), 1.10 (s, 3H), 0.54 (br d, <i>J</i> = 6.4 Hz, 2H), 0.47 (br d, <i>J</i> = 4.8 Hz, 1H), 0.36 (br s, 1H), 1H not observed (NH); LC/MS (ESI): 477.2 [M+H] ⁺
285	LC/MS (ESI): 515.2 [M+H] ⁺
286	LC/MS (ESI): 494.2 [M+H] ⁺
287	LC/MS (ESI): 496.2 [M+H] ⁺
288	LC/MS (ESI): 497.2 [M+H] ⁺
289	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.45 (d, <i>J</i> = 9.9 Hz, 1H), 8.35 (s, 1H), 7.67 (d, <i>J</i> = 9.8 Hz, 1H), 7.64 (s, 1H), 7.33 (d, <i>J</i> = 10.0 Hz, 1H), 5.25 (s, 2H), 5.06 - 4.95 (m, 1H), 2.91 (s, 3H), 2.66 (s, 3H), 2.45 - 2.42 (m, 3H), 1.96 (br d, <i>J</i> = 7.3 Hz, 2H), 1.77 (br d, <i>J</i> = 12.1 Hz, 2H), 1.69 (br d, <i>J</i> = 7.6 Hz, 2H), 1.63 (br dd, <i>J</i> = 5.7, 12.7 Hz, 2H), 1.31 (s, 6H); LC/MS (ESI): 507.2 [M+H] ⁺
290	LC/MS (ESI): 509.2 [M+H] ⁺
291	¹ H NMR (METHANOL- <i>d</i> ₄ , 400 MHz) δ = 9.57 - 9.47 (m, 1H), 8.60 - 8.48 (m, 1H), 7.90 (s, 1H), 7.76 (s, 1H), 7.53 (d, <i>J</i> = 10.1 Hz, 1H), 5.29 - 5.21 (m, 1H), 5.19 (s, 2H), 3.92 - 3.85 (m, 3H), 3.15 (s, 3H), 2.42 (s, 3H), 2.27 (br d, <i>J</i> = 8.3 Hz, 2H), 2.05 - 1.92 (m, 6H), 1.52 (s, 6H); LC/MS (ESI): 491.3 [M+H] ⁺
292	LC/MS (ESI): 480.2 [M+H] ⁺
293	LC/MS (ESI): 493.2 [M+H] ⁺
294	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.47 (d, <i>J</i> = 10.0 Hz, 1H), 8.27 (s, 1H), 7.88 (s, 1H), 7.81 (d, <i>J</i> = 9.9 Hz, 1H), 7.34 (d, <i>J</i> = 10.0 Hz, 1H), 5.26 (s, 2H), 5.08 - 4.95 (m, 1H), 4.16 (s, 3H), 2.91 (s, 3H), 2.49 (br s, 3H), 1.99 (br d, <i>J</i> = 7.8 Hz, 2H), 1.80 - 1.62 (m, 6H), 1.32 (s, 6H); LC/MS (ESI): 491.2 [M+H] ⁺
295	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.46 (d, <i>J</i> = 9.9 Hz, 1H), 8.13 (s, 1H), 7.64 (s, 1H), 7.61 - 7.56 (m, 1H), 7.47 (d, <i>J</i> = 10.0 Hz, 1H), 5.18 (s, 2H), 4.36 (br d, <i>J</i> = 12.1 Hz, 1H), 4.12 (br d, <i>J</i> = 11.9 Hz, 1H), 3.80 (s, 3H), 3.08 (br d, <i>J</i> = 11.4 Hz, 1H), 2.89 - 2.71 (m, 2H), 2.65 - 2.57 (m, 1H), 2.39 (dd, <i>J</i> = 2.4, 10.8 Hz, 1H), 2.35 (s, 3H), 0.96 (s, 9H), 1H not observed (NH); LC/MS (ESI): 464.2 [M+H] ⁺
296	LC/MS (ESI): 450.2 [M+H] ⁺
297	LC/MS (ESI): 434.1 [M+H] ⁺
298	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.46 (d, <i>J</i> = 9.9 Hz, 1H), 7.88 (s, 1H), 7.81 (d, <i>J</i> = 10.0 Hz, 1H), 7.47 (d, <i>J</i> = 10.0 Hz, 1H), 5.25 (s, 2H), 4.35 (br d, <i>J</i> =

No.	NMR/MS
	11.3 Hz, 1H), 4.16 (s, 3H), 4.11 (br d, $J = 12.0$ Hz, 1H), 3.05 (br d, $J = 11.4$ Hz, 1H), 2.66-2.84 (m, 2H), 2.53-2.61 (m, 1H), 2.49 (br s, 3H), 2.32 (br dd, $J = 10.9, 1.8$ Hz, 1H), 0.96 (s, 9H); 1H not observed (NH); LC/MS (ESI): 465.2 $[M+H]^+$
299	LC/MS (ESI): 467.2 $[M+H]^+$
300	LC/MS (ESI): 451.1 $[M+H]^+$
301	LC/MS (ESI): 437.2 $[M+H]^+$
302	LC/MS (ESI): 451.2 $[M+H]^+$
308	LC/MS (ESI): 447.2 $[M+H]^+$
309	LC/MS (ESI): 433.2 $[M+H]^+$
310	LC/MS (ESI): 434.3 $[M+H]^+$
311	LC/MS (ESI): 475.3 $[M+H]^+$
312	^1H NMR (DMSO- d_6 , 400 MHz) $\delta = 8.72$ (br d, $J = 6.3$ Hz, 2H), 8.51-8.63 (m, 2H), 7.90 (br d, $J = 3.9$ Hz, 2H), 7.30 (br d, $J = 9.6$ Hz, 1H), 5.54-5.69 (m, 1H), 5.26 (s, 2H), 4.03 (s, 3H), 2.07 (br d, $J = 8.3$ Hz, 2H), 1.23 (m, 8H), 1.07-1.14 (s, 6H), 1H not observed (NH); LC/MS (ESI): 475.3 $[M+H]^+$
313	LC/MS (ESI): 447.24 $[M+H]^+$
314	LC/MS (ESI): 483.4 $[M+H]^+$
315	LC/MS (ESI): 515.25 $[M+H]^+$
316	LC/MS (ESI): 444.2 $[M+H]^+$
317	LC/MS (ESI): 444.3 $[M+H]^+$
318	LC/MS (ESI): 447.3 $[M+H]^+$
319	LC/MS (ESI): 474.3 $[M+H]^+$
320	LC/MS (ESI): 451.5 $[M+H]^+$
321	LC/MS (ESI): 465.3 $[M+H]^+$
322	LC/MS (ESI): 474.2 $[M+H]^+$
323	LC/MS (ESI): 484.3 $[M+H]^+$
324	^1H NMR (DMSO- d_6 , 400 MHz) $\delta = 8.77$ (d, $J = 9.6$ Hz, 1H), 8.69 (d, $J = 4.9$ Hz, 2H), 8.17-8.23 (m, 3H), 7.90 (d, $J = 8.0$ Hz, 1H), 7.85 (d, $J = 5.0$ Hz, 2H), 7.38 (d, $J = 9.6$ Hz, 1H), 5.62-5.70 (m, 1H), 5.25 (s, 2H), 2.27 (br dd, $J = 13.0, 3.9$ Hz, 2H), 1.66 (br t, $J = 11.8$ Hz, 2H), 1.46 (s, 6H), 1.37-1.43 (m, 6H); LC/MS (ESI): 444.3 $[M+H]^+$
325	LC/MS (ESI): 512.2 $[M+H]^+$
326	$^1LC/MS$ (ESI): 512.3 $[M+H]^+$
327	LC/MS (ESI): 445.3 $[M+H]^+$
328	LC/MS (ESI): 512.3 $[M+H]^+$
329	LC/MS (ESI): 505.2 $[M+H]^+$
330	LC/MS (ESI): 445.3 $[M+H]^+$
331	LC/MS (ESI): 450.1 $[M+H]^+$
332	LC/MS (ESI): 450.1 $[M+H]^+$
333	LC/MS (ESI): 462.24 $[M+H]^+$
334	LC/MS (ESI): 475.3 $[M+H]^+$
335	LC/MS (ESI): 497.3 $[M+H]^+$
336	LC/MS (ESI): 483.2 $[M+H]^+$
337	LC/MS (ESI): 433.3 $[M+H]^+$
338	LC/MS (ESI): 447.2 $[M+H]^+$
339	LC/MS (ESI): 461.3 $[M+H]^+$
340	LC/MS (ESI): 487.3 $[M+H]^+$
341	LC/MS (ESI): 498.2 $[M+H]^+$
342	LC/MS (ESI): 461.3 $[M+H]^+$
343	LC/MS (ESI): 497.2 $[M+H]^+$
344	LC/MS (ESI): 417.2 $[M+H]^+$
345	LC/MS (ESI): 429.2 $[M+H]^+$
346	LC/MS (ESI): 478.2 $[M+H]^+$

No.	NMR/MS
347	LC/MS (ESI):489.3 [M+H] ⁺
348	LC/MS (ESI):502.3 [M+H] ⁺
349	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.72 (br d, <i>J</i> = 10.9 Hz, 1H), 8.58 (d, <i>J</i> = 9.9 Hz, 1H), 8.31 (s, 1H), 8.01 (s, 1H), 7.96 (s, 1H), 7.92 (dd, <i>J</i> = 1.3, 7.9 Hz, 1H), 7.87 - 7.77 (m, 1H), 7.69 (d, <i>J</i> = 7.9 Hz, 1H), 7.46 (d, <i>J</i> = 10.0 Hz, 1H), 5.12 (s, 2H), 5.11 - 5.02 (m, 1H), 3.88 (s, 3H), 2.94 (s, 3H), 1.95 - 1.85 (m, 2H), 1.83 - 1.76 (m, 2H), 1.52 (s, 6H), 1.42 (s, 6H); LC/MS (ESI): 460.2 [M+H] ⁺
350	LC/MS (ESI):483.2 [M+H] ⁺
351	LC/MS (ESI):486.3 [M+H] ⁺
352	LC/MS (ESI):445.2 [M+H] ⁺
353	LC/MS (ESI):431.1 [M+H] ⁺
354	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.84 - 8.69 (m, 1H), 8.62 - 8.56 (m, 1H), 8.23 (s, 2H), 8.03 (s, 1H), 7.98 (dd, <i>J</i> = 1.4, 7.9 Hz, 1H), 7.93 - 7.84 (m, 1H), 7.69 (d, <i>J</i> = 8.0 Hz, 1H), 7.54 - 7.42 (m, 1H), 5.12 (br d, <i>J</i> = 1.3 Hz, 2H), 5.10 - 5.00 (m, 1H), 2.95 (s, 3H), 1.96 - 1.87 (m, 2H), 1.83 - 1.77 (m, 2H), 1.52 (s, 6H), 1.42 (s, 6H); LC/MS (ESI): 446.2 [M+H] ⁺
355	LC/MS (ESI):475.2 [M+H] ⁺
356	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.74 (d, <i>J</i> = 9.2 Hz, 2H), 8.27 - 8.21 (m, 2H), 7.81 (d, <i>J</i> = 7.8 Hz, 1H), 7.31 (d, <i>J</i> = 9.5 Hz, 1H), 5.67 - 5.59 (m, 1H), 5.21 (s, 2H), 4.12 (s, 3H), 2.16 - 2.07 (m, 2H), 1.35 - 1.30 (m, 2H), 1.28 - 1.24 (m, 6H), 1.15 (br s, 6H), 1H not observed (NH); LC/MS (ESI): 448.2 [M+H] ⁺
357	LC/MS (ESI):473.3 [M+H] ⁺
358	LC/MS (ESI):449.3 [M+H] ⁺
359	LC/MS (ESI):515.2 [M+H] ⁺
360	LC/MS (ESI):489.2 [M+H] ⁺
361	LC/MS (ESI):416.3 [M+H] ⁺
362	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.26 (br d, <i>J</i> = 10.5 Hz, 1H), 8.76 (d, <i>J</i> = 9.6 Hz, 1H), 8.42 (s, 2H), 8.24 (s, 1H), 8.20 (d, <i>J</i> = 7.9 Hz, 1H), 7.82 (d, <i>J</i> = 7.9 Hz, 1H), 7.37 (d, <i>J</i> = 9.6 Hz, 1H), 5.71 - 5.60 (m, 1H), 5.20 (s, 2H), 4.23 (s, 3H), 2.31 (br dd, <i>J</i> = 3.1, 13.1 Hz, 2H), 1.80 (br t, <i>J</i> = 11.9 Hz, 2H), 1.52 (m, 12H); LC/MS (ESI):448.2 [M+H] ⁺
363	LC/MS (ESI):528.2 [M+H] ⁺
364	LC/MS (ESI):504.3 [M+H] ⁺
365	LC/MS (ESI):491.3 [M+H] ⁺
366	LC/MS (ESI):430.2 [M+H] ⁺
367	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 10.02 (br dd, <i>J</i> = 3.4, 2.2 Hz, 1H), 9.07 (br d, <i>J</i> = 9.0 Hz, 1H), 8.71-8.79 (m, 1H), 8.32 (s, 1H), 8.01 (s, 1H), 7.92-8.00 (m, 2H), 7.71 (d, <i>J</i> = 8.0 Hz, 1H), 5.07 (s, 2H), 4.70-4.88 (m, 1H), 3.88 (s, 3H), 3.11 (s, 3H), 2.16-2.33 (m, 4H), 1.76-1.92 (m, 4H), 1.47 (s, 6H); LC/MS (ESI):458.2 [M+H] ⁺
368	LC/MS (ESI):502.3 [M+H] ⁺
369	LC/MS (ESI):448.2 [M+H] ⁺
370	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.50 (d, <i>J</i> = 9.9 Hz, 1H), 8.42 (s, 1H), 8.23 (s, 1H), 8.17 (d, <i>J</i> = 7.5 Hz, 1H), 7.80 (d, <i>J</i> = 8.0 Hz, 1H), 7.30 (d, <i>J</i> = 10.0 Hz, 1H), 5.19 (s, 2H), 5.07 - 4.97 (m, 1H), 4.23 (s, 3H), 2.90 (s, 3H), 1.66 - 1.43 (m, 4H), 1.30 (s, 6H), 1.15 (br s, 6H), 1H not observed (NH); LC/MS (ESI): 461.2 [M+H] ⁺
371	LC/MS (ESI): 505.3 [M+H] ⁺
372	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.55 (d, <i>J</i> = 9.9 Hz, 1H), 8.04 (s, 1H), 8.03 - 8.00 (m, 1H), 7.97 - 7.93 (m, 1H), 7.93 - 7.87 (m, 1H), 7.87 - 7.81 (m, 1H), 7.44 (d, <i>J</i> = 10.0 Hz, 1H), 5.22 (s, 2H), 5.09 (br t, <i>J</i> = 12.2 Hz, 1H), 4.13 (s, 3H), 2.94 (s, 3H), 1.96 - 1.85 (m, 2H), 1.84 - 1.75 (m, 2H), 1.52 (s, 6H), 1.42 (s, 6H); LC/MS (ESI): 461.3 [M+H] ⁺

No.	NMR/MS
373	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ 8.51 (d, <i>J</i> = 9.9 Hz, 1H), 8.41 - 8.32 (m, 2H), 7.92 (d, <i>J</i> = 7.9 Hz, 1H), 7.32 (br d, <i>J</i> = 9.6 Hz, 1H), 5.24 (s, 2H), 5.05 (br d, <i>J</i> = 5.8 Hz, 1H), 4.47 (s, 3H), 2.91 (s, 3H), 1.77 - 1.46 (m, 4H), 1.44 - 1.03 (m, 12H), 1H not observed (NH); LC/MS (ESI): 462.2 [M+H] ⁺
374	LC/MS (ESI): 416.2 [M+H] ⁺
375	LC/MS (ESI): 488.3 [M+H] ⁺
376	LC/MS (ESI): 498.1 [M+H] ⁺
377	LC/MS (ESI): 428.2 [M+H] ⁺
378	LC/MS (ESI): 462.3 [M+H] ⁺
379	LC/MS (ESI): 418.2 [M+H] ⁺
380	LC/MS (ESI): 402.2 [M+H] ⁺
381	LC/MS (ESI): 478.3 [M+H] ⁺
382	LC/MS (ESI): 465.3 [M+H] ⁺
383	LC/MS (ESI): 463.3 [M+H] ⁺
384	LC/MS (ESI): 457.1 [M+H] ⁺
385	LC/MS (ESI): 488.3 [M+H] ⁺
386	LC/MS (ESI): 476.3 [M+H] ⁺
387	LC/MS (ESI): 461.3 [M+H] ⁺
388	LC/MS (ESI): 400.3 [M+H] ⁺
389	LC/MS (ESI): 472.4 [M+H] ⁺
390	LC/MS (ESI): 470.4 [M+H] ⁺
391	LC/MS (ESI): 430.3 [M+H] ⁺
392	LC/MS (ESI): 518.3 [M+H] ⁺
394	LC/MS (ESI): 420.3 [M+H] ⁺
395	LC/MS (ESI): 418.2 [M+H] ⁺
396	LC/MS (ESI): 448.2 [M+H] ⁺
397	LC/MS (ESI): 476.2 [M+H] ⁺
398	LC/MS (ESI): 474.2 [M+H] ⁺
399	LC/MS (ESI): 432.2 [M+H] ⁺
400	LC/MS (ESI): 444.3 [M+H] ⁺
401	LC/MS (ESI): 456.3 [M+H] ⁺
402	LC/MS (ESI): 458.3 [M+H] ⁺
403	LC/MS (ESI): 477.3 [M+H] ⁺
404	LC/MS (ESI): 432.2 [M+H] ⁺
405	LC/MS (ESI): 444.2 [M+H] ⁺
406	LC/MS (ESI): 487.3 [M+H] ⁺
407	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.51 (d, <i>J</i> = 9.9 Hz, 1H), 8.31 (s, 1H), 8.00 (s, 1H), 7.96 - 7.89 (m, 2H), 7.70 (d, <i>J</i> = 7.9 Hz, 1H), 7.49 (d, <i>J</i> = 10.0 Hz, 1H), 5.11 (s, 2H), 4.33 - 4.23 (m, 1H), 4.17 - 4.08 (m, 1H), 3.88 (s, 3H), 3.13 - 3.05 (m, 1H), 2.99 - 2.90 (m, 1H), 2.84 - 2.77 (m, 1H), 2.77 - 2.71 (m, 1H), 2.14 - 1.97 (m, 1H), 0.87 - 0.77 (m, 1H), 0.52 - 0.43 (m, 2H), 0.32 (br s, 2H), 1H not observed (NH); LC/MS (ESI): 416.2 [M+H] ⁺
408	LC/MS (ESI): 448.3 [M+H] ⁺
409	LC/MS (ESI): 446.3 [M+H] ⁺
410	LC/MS (ESI): 490.3 [M+H] ⁺
411	LC/MS (ESI): 476.3 [M+H] ⁺
412	LC/MS (ESI): 416.3 [M+H] ⁺
413	LC/MS (ESI): 477.2 [M+H] ⁺
414	LC/MS (ESI): 476.3 [M+H] ⁺
415	LC/MS (ESI): 476.2 [M+H] ⁺
416	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.73 (d, <i>J</i> = 9.6 Hz, 1H), 8.20 (br d, <i>J</i> = 4.5 Hz, 1H), 8.06 (s, 1H), 7.81 - 7.77 (m, 2H), 7.76 - 7.73 (m, 1H), 7.33 (d, <i>J</i> = 9.5 Hz, 1H), 5.49 (s, 1H), 5.16 (s, 2H), 3.81 (s, 3H), 2.34 (s, 3H), 2.33 - 2.29

No.	NMR/MS
	(m, 2H), 2.03 - 1.93 (m, 2H), 1.72 (br d, $J = 2.5$ Hz, 2H), 1.66 - 1.56 (m, 2H), 1.34 (br s, 6H); LC/MS (ESI): 459.3 [M+H] ⁺
417	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.40 (s, 1H), 8.03 (s, 1H), 7.68-7.81 (m, 3H), 5.11-5.18 (m, 1H), 5.09 (s, 2H), 3.80 (s, 3H), 3.07 (s, 3H), 2.33 (s, 3H), 1.86-1.97 (m, 2H), 1.75-1.85 (m, 2H), 1.49 (s, 6H), 1.41 (s, 6H), 1H not observed (NH); LC/MS (ESI): 475.3 [M+H] ⁺
418	LC/MS (ESI): 445.2 [M+H] ⁺
419	LC/MS (ESI): 445.2 [M+H] ⁺
420	LC/MS (ESI): 462.2 [M+H] ⁺
421	LC/MS (ESI): 461.3 [M+H] ⁺
422	LC/MS (ESI): 477.2 [M+H] ⁺
423	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.48 (d, $J = 9.9$ Hz, 1H), 8.00 (s, 1H), 7.82 - 7.72 (m, 3H), 7.37 - 7.30 (m, 1H), 5.13 (s, 2H), 5.11 - 5.02 (m, 1H), 3.82 (s, 3H), 2.91 (s, 3H), 2.35 (s, 3H), 2.15 (br d, $J = 8.1$ Hz, 2H), 2.00 - 1.87 (m, 4H), 1.79 (br dd, $J = 5.4, 13.4$ Hz, 2H), 1.44 (s, 6H), 1H not observed (NH); LC/MS (ESI): 472.2 [M+H] ⁺
424	LC/MS (ESI): 474.2 [M+H] ⁺
425	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.86 (br s, 1H), 8.72-8.83 (m, 2H), 8.43 (s, 1H), 8.26 (s, 1H), 8.22 (dd, $J = 7.9, 1.3$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.38 (d, $J = 9.6$ Hz, 1H), 5.49-5.58 (m, 1H), 5.20 (s, 2H), 4.23 (s, 3H), 2.45 (br d, $J = 5.9$ Hz, 2H), 2.13-2.21 (m, 2H), 1.89 (br d, $J = 8.3$ Hz, 2H), 1.79 (br t, $J = 12.1$ Hz, 2H), 1.45 (s, 6H), 1H not observed (NH); LC/MS (ESI): 446.2 [M+H] ⁺
426	LC/MS (ESI): 446.2 [M+H] ⁺
427	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.41 (s, 1H), 8.04 (s, 1H), 7.74-7.80 (m, 3H), 5.11-5.17 (m, 1H), 5.10 (s, 2H), 3.81 (s, 3H), 3.06 (s, 3H), 2.34 (s, 3H), 2.08-2.16 (m, 2H), 1.98-2.05 (m, 2H), 1.92 (br d, $J = 8.3$ Hz, 2H), 1.84 (dd, $J = 13.6, 5.6$ Hz, 2H), 1.45 (s, 6H), 1H not observed (NH); LC/MS (ESI): 473.3 [M+H] ⁺
428	LC/MS (ESI): 459.2 [M+H] ⁺
429	LC/MS (ESI): 460.2 [M+H] ⁺
430	LC/MS (ESI): 491.2 [M+H] ⁺
431	LC/MS (ESI): 492.2 [M+H] ⁺
432	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 8.51 (d, $J = 9.9$ Hz, 1H), 7.84 - 7.73 (m, 3H), 7.38 (d, $J = 10.0$ Hz, 1H), 5.17 (s, 2H), 5.12 - 5.00 (m, 1H), 2.92 (s, 3H), 2.65 (s, 3H), 2.44 - 2.39 (m, 3H), 2.25 - 2.12 (m, 2H), 2.01 - 1.87 (m, 4H), 1.80 (br dd, $J = 5.4, 13.3$ Hz, 2H), 1.43 (s, 6H), 1H not observed (NH); LC/MS (ESI): 489.1 [M+H] ⁺
433	LC/MS (ESI): 479.2 [M+H] ⁺
434	LC/MS (ESI): 476.1 [M+H] ⁺
435	LC/MS (ESI): 508.3 [M+H] ⁺
436	LC/MS (ESI): 489.2 [M+H] ⁺
437	LC/MS (ESI): 490.2 [M+H] ⁺
438	LC/MS (ESI): 459.2 [M+H] ⁺
439	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ = 9.26 (br d, $J = 9.3$ Hz, 1H), 9.11 (br d, $J = 8.9$ Hz, 1H), 8.67 (d, $J = 9.6$ Hz, 1H), 7.93-7.99 (m, 2H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.29 (d, $J = 9.5$ Hz, 1H), 5.38-5.48 (m, 1H), 5.12 (s, 2H), 4.07 (s, 3H), 2.38-2.40 (m, 3H), 2.34 (br dd, $J = 13.1, 5.8$ Hz, 2H), 2.06 (br d, $J = 8.0$ Hz, 2H), 1.72-1.89 (m, 4H), 1.39 (s, 6H); LC/MS (ESI): 460.2 [M+H] ⁺
441	LC/MS (ESI): 491.2 [M+H] ⁺
442	LC/MS (ESI): 465.2 [M+H] ⁺
443	LC/MS (ESI): 497.2 [M+H] ⁺
444	LC/MS (ESI): 476.1 [M+H] ⁺

No.	NMR/MS
445	LC/MS (ESI): 506.3 [M+H] ⁺
446	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.70 (d, <i>J</i> = 9.7 Hz, 1H), 8.29 (br d, <i>J</i> = 2.9 Hz, 1H), 8.26 (s, 1H), 8.21 (s, 1H), 8.09 (s, 1H), 7.35 (d, <i>J</i> = 9.6 Hz, 1H), 5.52 - 5.44 (m, 1H), 5.35 (s, 2H), 3.82 (s, 3H), 2.38 (s, 3H), 2.27 - 2.18 (m, 2H), 1.88 (br s, 2H), 1.67 - 1.60 (m, 2H), 1.60 - 1.46 (m, 2H), 1.26 (br s, 6H); LC/MS (ESI): 484.2 [M+H] ⁺
447	LC/MS (ESI): 493.3 [M+H] ⁺
448	LC/MS (ESI): 460.2 [M+H] ⁺
449	LC/MS (ESI): 457.3 [M+H] ⁺
451	LC/MS (ESI): 465.2 [M+H] ⁺
452	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.10 (s, 1H), 8.49 (s, 2H), 8.30 (s, 1H), 7.35 (d, <i>J</i> = 10.0 Hz, 1H), 5.16 (s, 2H), 5.02 (td, <i>J</i> = 5.6, 11.3 Hz, 1H), 3.85 (s, 3H), 2.91 (s, 3H), 2.52 (br s, 3H), 1.98 (br d, <i>J</i> = 7.6 Hz, 2H), 1.79 (br t, <i>J</i> = 10.9 Hz, 2H), 1.74 - 1.68 (m, 2H), 1.66 (br d, <i>J</i> = 5.1 Hz, 2H), 1.31 (s, 6H); LC/MS (ESI): 474.3 [M+H] ⁺
453	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.34 (s, 1H), 8.71 (d, <i>J</i> = 9.6 Hz, 1H), 7.35 (d, <i>J</i> = 9.6 Hz, 1H), 5.52 - 5.42 (m, 1H), 5.25 (s, 2H), 4.23 (s, 3H), 2.62 (s, 3H), 2.17 (br dd, <i>J</i> = 5.8, 11.9 Hz, 2H), 1.80 (br d, <i>J</i> = 6.6 Hz, 2H), 1.53 (br d, <i>J</i> = 6.9 Hz, 2H), 1.46 - 1.37 (m, 2H), 1.21 (s, 6H), 1H not observed (NH); LC/MS (ESI): 462.2 [M+H] ⁺
454	LC/MS (ESI): 431.2 [M+H] ⁺
455	LC/MS (ESI): 461.3 [M+H] ⁺
456	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 13.17 - 12.36 (m, 1H), 8.99 (s, 1H), 8.71 (d, <i>J</i> = 9.5 Hz, 1H), 8.25 (s, 1H), 8.20 (br s, 1H), 7.96 (s, 1H), 7.35 (d, <i>J</i> = 9.6 Hz, 1H), 5.55 - 5.45 (m, 1H), 5.24 (s, 2H), 2.56 (s, 3H), 2.28 (br dd, <i>J</i> = 5.9, 12.5 Hz, 2H), 1.96 (br d, <i>J</i> = 7.8 Hz, 2H), 1.69 (br d, <i>J</i> = 7.5 Hz, 2H), 1.59 (br t, <i>J</i> = 11.6 Hz, 2H), 1.32 (s, 6H); LC/MS (ESI): 446.2 [M+H] ⁺
457	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.02 (s, 1H), 8.70 (d, <i>J</i> = 9.5 Hz, 1H), 8.35 (s, 1H), 7.92 (d, <i>J</i> = 0.8 Hz, 1H), 7.36 (d, <i>J</i> = 9.6 Hz, 1H), 5.48 (td, <i>J</i> = 4.2, 8.1 Hz, 1H), 5.26 (s, 2H), 3.84 (s, 3H), 2.48 (s, 3H), 2.38 - 2.19 (m, 3H), 2.05 - 1.87 (m, 3H), 1.53 (s, 3H), 1.49 (s, 3H), 1.46 - 1.45 (m, 6H), NH not observed; LC/MS (ESI): 238.6 [M+H] ⁺
458	LC/MS (ESI): 481.0 [M+H] ⁺
459	LC/MS (ESI): 462.2 [M+H] ⁺
460	LC/MS (ESI): 481.2 [M+H] ⁺
461	LC/MS (ESI): 247.2 [M+H] ⁺
462	LC/MS (ESI): 434.2 [M+H] ⁺
463	LC/MS (ESI): 448.2 [M+H] ⁺
464	LC/MS (ESI): 489.3 [M+H] ⁺
465	LC/MS (ESI): 463.3 [M+H] ⁺
466	¹ H NMR (400 MHz, C ₂ DF ₃ O ₂) δ = 9.33 (s, 1H), 8.74 (s, 1H), 8.69 (s, 1H), 8.62 (s, 1H), 7.05 - 6.51 (m, 1H), 5.43 (s, 2H), 4.70 - 4.54 (m, 1H), 4.23 (s, 3H), 4.13 (br t, <i>J</i> = 7.6 Hz, 2H), 3.46 (br t, <i>J</i> = 6.8 Hz, 2H), 2.72 (s, 3H), 2.33 - 2.14 (m, 4H), 1.67 (s, 6H), 1.55 (s, 6H); LC/MS (ESI): 487.3 [M+H] ⁺
467	LC/MS (ESI): 477.2 [M+H] ⁺
468	LC/MS (ESI): 503.2 [M+H] ⁺
469	LC/MS (ESI): 231.6 [M+H] ⁺
470	LC/MS (ESI): 476.2 [M+H] ⁺
471	LC/MS (ESI): 248.6 [M+H] ⁺
472	LC/MS (ESI): 240.5 [M+H] ⁺
473	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.98 (s, 1H), 8.73 (d, <i>J</i> = 9.6 Hz, 1H), 8.38 (s, 1H), 8.16 (br s, 2H), 7.89 (s, 1H), 7.37 (d, <i>J</i> = 9.5 Hz, 1H), 5.49 (br s, 1H), 5.24 (s, 2H), 3.82 (s, 3H), 2.48 (s, 3H), 2.29 - 2.16 (m, 3H), 2.03 - 1.86 (m, 3H), 1.52 (s, 3H), 1.49 - 1.37 (m, 9H); LC/MS (ESI): 238.7 [M+2H] ²⁺

No.	NMR/MS
474	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.98 (s, 1H), 8.76 - 8.69 (m, 1H), 8.38 (s, 1H), 8.25 - 8.06 (m, 2H), 7.89 (s, 1H), 7.37 (d, <i>J</i> = 9.6 Hz, 1H), 5.49 (br s, 1H), 5.24 (s, 2H), 3.82 (s, 3H), 2.48 (s, 3H), 2.30 - 2.16 (m, 3H), 2.03 - 1.87 (m, 3H), 1.52 (s, 3H), 1.49 - 1.40 (m, 9H); LC/MS (ESI): 238.7 [M+2H] ²⁺
475	LC/MS (ESI): 499.1 [M+H] ⁺
476	LC/MS (ESI): 485.27 [M+H] ⁺
477	LC/MS (ESI): 480.2 [M+H] ⁺
478	LC/MS (ESI): 431.3 [M+H] ⁺
479	LC/MS (ESI): 238.6 [M+H] ⁺
480	LC/MS (ESI): 481.2 [M+H] ⁺
481	LC/MS (ESI): 462.2 [M+H] ⁺
482	LC/MS (ESI): 247.2 [M+H] ⁺
483	LC/MS (ESI): 489.4 [M+H] ⁺
484	LC/MS (ESI): 526.2 [M+H] ⁺
485	LC/MS (ESI): 463.3 [M+H] ⁺
486	LC/MS (ESI): 448.3 [M+H] ⁺
487	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 8.94 (d, <i>J</i> = 2.1 Hz, 1H), 8.56 (d, <i>J</i> = 9.9 Hz, 1H), 8.17 (d, <i>J</i> = 2.1 Hz, 1H), 8.14 (s, 1H), 7.64 (d, <i>J</i> = 9.9 Hz, 1H), 5.17 (s, 2H), 4.89 - 4.79 (m, 1H), 3.83 (s, 3H), 2.63 - 2.58 (m, 1H), 2.37 (s, 3H), 2.25 (br t, <i>J</i> = 12.9 Hz, 2H), 1.96 (br dd, <i>J</i> = 2.6, 13.1 Hz, 2H), 1.49 (s, 6H), 1.41 (s, 6H), 1.08 - 0.99 (m, 2H), 0.71 - 0.57 (m, 2H), NH not observed; LC/MS (ESI): 501.1 [M+H] ⁺
488	LC/MS (ESI): 249.1 [M+H] ⁺
489	LC/MS (ESI): 231.6 [M+H] ⁺
490	LC/MS (ESI): 476.2 [M+H] ⁺
491	LC/MS (ESI): 480.0 [M+H] ⁺
492	LC/MS (ESI): 248.6 [M+H] ⁺
493	LC/MS (ESI): 483.2 [M+H] ⁺
494	LC/MS (ESI): 487.3 [M+H] ⁺
495	LC/MS (ESI): 449.2 [M+H] ⁺
496	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.10 (s, 1H), 8.49 (s, 2H), 8.30 (s, 1H), 7.35 (d, <i>J</i> = 10.0 Hz, 1H), 5.16 (s, 2H), 5.02 (td, <i>J</i> = 5.6, 11.3 Hz, 1H), 3.85 (s, 3H), 2.91 (s, 3H), 2.52 (br s, 3H), 1.98 (br d, <i>J</i> = 7.6 Hz, 2H), 1.79 (br t, <i>J</i> = 10.9 Hz, 2H), 1.74 - 1.68 (m, 2H), 1.66 (br d, <i>J</i> = 5.1 Hz, 2H), 1.31 (s, 6H); LC/MS (ESI): 474.3 [M+H] ⁺
497	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ = 8.96 (s, 1H), 8.78 (d, <i>J</i> = 9.6 Hz, 1H), 8.45 (s, 1H), 8.21 (s, 1H), 7.17 (d, <i>J</i> = 9.6 Hz, 1H), 5.71 - 5.59 (m, 1H), 5.14 (s, 2H), 3.82 (s, 3H), 2.51 (s, 3H), 2.26 (br dd, <i>J</i> = 2.4, 12.3 Hz, 2H), 1.53 (br t, <i>J</i> = 11.3 Hz, 2H), 1.40 (s, 6H), 1.31 (br s, 6H); LC/MS (ESI): 463.2 [M+H] ⁺
498	¹ H NMR (DMSO- <i>d</i> ₆) δ = 9.38 (br s, 1H), 8.75 (br d, <i>J</i> = 9.3 Hz, 1H), 8.47 (br s, 1H), 7.41 (br d, <i>J</i> = 9.4 Hz, 1H), 5.54 (m, 1H), 5.25 (br s, 2H), 4.31 (br s, 3H), 2.46 (br s, 2H), 2.17 (br d, <i>J</i> = 7.6 Hz, 2H), 1.74-1.99 (m, 4H), 1.46 (br s, 6H), 1H not observed (NH); LC/MS (ESI): 448.3 [M+H] ⁺
499	LC/MS (ESI): 476.3 [M+H] ⁺
500	LC/MS (ESI): 476.2 [M+H] ⁺
501	LC/MS (ESI): 392.1 [M+H] ⁺
502	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.26 (s, 1H), 8.80-8.88 (m, 1H), 8.77 (d, <i>J</i> = 9.6 Hz, 2H), 8.62 (s, 1H), 7.42 (d, <i>J</i> = 9.6 Hz, 1H), 5.48-5.60 (m, 1H), 5.21 (s, 2H), 3.93 (s, 3H), 2.16-2.21 (m, 2H), 1.75-1.94 (m, 6H), 1.45 (s, 6H); LC/MS (ESI): 481.2 [M+H] ⁺
503	¹ H NMR (DMSO- <i>d</i> ₆) δ = 9.35 (s, 1H), 8.91-8.99 (m, 1H), 8.84 (br d, <i>J</i> = 8.8 Hz, 1H), 8.77 (d, <i>J</i> = 9.5 Hz, 1H), 7.44 (d, <i>J</i> = 9.6 Hz, 1H), 5.55 (m, 1H), 5.26 (s, 2H), 4.31 (s, 3H), 2.46 (br d, <i>J</i> = 6.0 Hz, 2H), 2.17 (br d, <i>J</i> = 8.0 Hz, 2H), 1.90 (br d, <i>J</i> = 8.3 Hz, 2H), 1.81 (br t, <i>J</i> = 12.1 Hz, 2H), 1.46 (s, 6H);

No.	NMR/MS
	LC/MS (ESI): 482.2 [M+H] ⁺
504	LC/MS (ESI):239.2 [M+H] ⁺
505	LC/MS (ESI): 249.0 [M+H] ⁺
506	LC/MS (ESI):232.0 [M+H] ⁺
507	LC/MS (ESI):247.5 [M+H] ⁺
508	LC/MS (ESI): 241.1 [M+2H] ²⁺
509	LC/MS (ESI):249.6 [M+H] ⁺
510	LC/MS (ESI): 447.2 [M+H] ⁺
511	LC/MS (ESI): 445.3 [M+H] ⁺
512	LC/MS (ESI): 433.2 [M+H] ⁺
513	LC/MS (ESI): 417.2 [M+H] ⁺
514	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ : 9.02 (s, 1H), 8.47 (d, <i>J</i> = 9.8 Hz, 1H), 8.25 (br s, 1H), 7.87 (s, 1H), 7.22 (br d, <i>J</i> = 9.8 Hz, 1H), 5.23 (s, 2H), 4.87 (br s, 1H), 4.20 (br s, 1H), 3.65 - 3.59 (m, 1H), 3.53 (br s, 1H), 3.16 (br d, <i>J</i> = 10.8 Hz, 1H), 3.06 (br d, <i>J</i> = 10.5 Hz, 1H), 2.63 (s, 6H), 2.04 (br d, <i>J</i> = 10.4 Hz, 1H), 1.89 (br d, <i>J</i> = 10.3 Hz, 1H); LC/MS (ESI): 420.1 [M+H] ⁺
515	LC/MS (ESI): 417.1 [M+H] ⁺
516	LC/MS (ESI): 462.2 [M+H] ⁺
517	LC/MS (ESI): 431.2 [M+H] ⁺
518	LC/MS (ESI): 403.2 [M+H] ⁺
519	LC/MS (ESI): 447.2 [M+H] ⁺
520	LC/MS (ESI):403.1 [M+H] ⁺
521	LC/MS (ESI): 434.1 [M+H] ⁺
522	LC/MS (ESI):431.2 [M+H] ⁺
523	LC/MS (ESI): 420.1 [M+H] ⁺
524	LC/MS (ESI):403.2 [M+H] ⁺
525	LC/MS (ESI):431.2 [M+H] ⁺
526	LC/MS (ESI): 461.2 [M+H] ⁺
527	LC/MS (ESI): 419.2[M+H] ⁺
528	LC/MS (ESI): 433.3[M+H] ⁺
529	LC/MS (ESI): 403.1[M+H] ⁺
530	LC/MS (ESI): 448.2[M+H] ⁺
531	LC/MS (ESI): 405.2 [M+H] ⁺
532	LC/MS (ESI): 431.3[M+H] ⁺
533	LC/MS (ESI): 419.2 [M+H] ⁺
534	LC/MS (ESI): 447.3 [M+H] ⁺
535	LC/MS (ESI): 434.0 [M+H] ⁺
536	LC/MS (ESI): 447.2 [M+H] ⁺
537	LC/MS (ESI): 420.1 [M+H] ⁺
538	LC/MS (ESI): 433.2 [M+H] ⁺
539	LC/MS (ESI):417.2 [M+H] ⁺
540	LC/MS (ESI): 445.3 [M+H] ⁺
541	LC/MS (ESI):448.2 [M+H] ⁺
542	LC/MS (ESI):403.1 [M+H] ⁺
543	LC/MS (ESI): 417.2 [M+H] ⁺
544	LC/MS (ESI): 431.2 [M+H] ⁺
545	LC/MS (ESI): 447.2 [M+H] ⁺
546	LC/MS (ESI): 403.2 [M+H] ⁺
547	LC/MS (ESI):403.1 [M+H] ⁺
548	LC/MS (ESI): 420.2 [M+H] ⁺
549	LC/MS (ESI): 464.2 [M+H] ⁺
550	LC/MS (ESI): 403.1 [M+H] ⁺
551	LC/MS (ESI): 461.3 [M+H] ⁺
552	LC/MS (ESI): 406.2 [M+H] ⁺

No.	NMR/MS
553	LC/MS (ESI): 431.2 [M+H] ⁺
554	LC/MS (ESI): 434.1 [M+H] ⁺
555	LC/MS (ESI): 431.2 [M+H] ⁺
556	LC/MS (ESI): 433.3 [M+H] ⁺
557	LC/MS (ESI): 419.2 [M+H] ⁺
558	LC/MS (ESI): 431.3 [M+H] ⁺
559	LC/MS (ESI): 404.2 [M+H] ⁺
560	LC/MS (ESI): 404.1 [M+H] ⁺
561	LC/MS (ESI): 405.2 [M+H] ⁺
562	LC/MS (ESI): 462.2 [M+H] ⁺
563	LC/MS (ESI): 418.2 [M+H] ⁺
564	LC/MS (ESI): 434.2 [M+H] ⁺
565	LC/MS (ESI): 432.2 [M+H] ⁺
566	LC/MS (ESI): 432.2 [M+H] ⁺
567	LC/MS (ESI): 419.3 [M+H] ⁺
568	LC/MS (ESI): 418.2 [M+H] ⁺
569	LC/MS (ESI): 447.3 [M+H] ⁺
570	LC/MS (ESI): 434.0 [M+H] ⁺
571	LC/MS (ESI): 432.2 [M+H] ⁺
572	LC/MS (ESI):404.1 [M+H] ⁺
573	LC/MS (ESI): 406.2 [M+H] ⁺
574	LC/MS (ESI):404.2 [M+H] ⁺
575	LC/MS (ESI):432.2 [M+H] ⁺
576	LC/MS (ESI): 448.2 [M+H] ⁺
577	LC/MS (ESI): 422.1 [M+H] ⁺
578	LC/MS (ESI): 450.2 [M+H] ⁺
579	LC/MS (ESI): 434.2 [M+H] ⁺
580	LC/MS (ESI): 420.1 [M+H] ⁺
581	LC/MS (ESI): 450.3 [M+H] ⁺
582	LC/MS (ESI): 462.3[M+H] ⁺
583	LC/MS (ESI): 420.2 [M+H] ⁺
584	LC/MS (ESI): 420.1 [M+H] ⁺
585	LC/MS (ESI): 448.3 [M+H] ⁺
586	LC/MS (ESI): 448.2 [M+H] ⁺
587	LC/MS (ESI): 434.2 [M+H] ⁺
588	LC/MS (ESI): 436.2 [M+H] ⁺
589	LC/MS (ESI):494.2 [M+H] ⁺
590	LC/MS (ESI): 475.2 [M+H] ⁺
591	LC/MS (ESI): 471.2 [M+H] ⁺
592	LC/MS (ESI):462.3 [M+H] ⁺
593	LC/MS (ESI):474.2 [M+H] ⁺
594	LC/MS (ESI):504.0 [M+H] ⁺
595	LC/MS (ESI):461.5 [M+H] ⁺
596	LC/MS (ESI):462.2 [M+H] ⁺
597	LC/MS (ESI):474.2 [M+H] ⁺
598	LC/MS (ESI):463.0 [M+H] ⁺
599	LC/MS (ESI):447.2 [M+H] ⁺
600	LC/MS (ESI):448.2 [M+H] ⁺
601	LC/MS (ESI):461.2 [M+H] ⁺
602	LC/MS (ESI):433.3 [M+H] ⁺
603	LC/MS (ESI):446.3 [M+H] ⁺
604	LC/MS (ESI):517.0 [M+H] ⁺
605	LC/MS (ESI):249.1 [M+H] ⁺
606	LC/MS (ESI):463.2 [M+H] ⁺

No.	NMR/MS
607	LC/MS (ESI): [M+H] ⁺
608	LC/MS (ESI):482.2 [M+H] ⁺
609	LC/MS (ESI):493.2 [M+H] ⁺
610	LC/MS (ESI):497.1 [M+H] ⁺
611	LC/MS (ESI):477.2[M+H] ⁺
612	LC/MS (ESI):461.2 [M+H] ⁺
613	LC/MS (ESI):420.2 [M+H] ⁺
614	LC/MS (ESI):440.2 [M+H] ⁺
615	LC/MS (ESI):432.2 [M+H] ⁺
616	LC/MS (ESI):462.3 [M+H] ⁺
617	LC/MS (ESI):482.2 [M+H] ⁺
618	LC/MS (ESI):454.1 [M+H] ⁺
619	LC/MS (ESI):495.2 [M+H] ⁺
620	LC/MS (ESI):452.2 [M+H] ⁺
621	LC/MS (ESI):508.2 [M+H] ⁺
622	LC/MS (ESI):461.2 [M+H] ⁺
623	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.34 (s, 1H), 8.71 (d, J = 9.6 Hz, 1H), 7.35 (d, J = 9.6 Hz, 1H), 5.52 - 5.42 (m, 1H), 5.25 (s, 2H), 4.23 (s, 3H), 2.62 (s, 3H), 2.17 (br dd, J = 5.8, 11.9 Hz, 2H), 1.80 (br d, J = 6.6 Hz, 2H), 1.53 (br d, J = 6.9 Hz, 2H), 1.46 - 1.37 (m, 2H), 1.21 (s, 6H), NH not observed; LC/MS (ESI):462.2 [M+H] ⁺
624	LC/MS (ESI):464.2 [M+H] ⁺
625	LC/MS (ESI):518.2 [M+H] ⁺
626	LC/MS (ESI):509.3 [M+H] ⁺
627	LC/MS (ESI):495.3 [M+H] ⁺
628	LC/MS (ESI):496.1 [M+H] ⁺
629	LC/MS (ESI):437.2 [M+H] ⁺
630	LC/MS (ESI):451.2 [M+H] ⁺
631	LC/MS (ESI):464.2 [M+H] ⁺
632	LC/MS (ESI):534.2 [M+H] ⁺
633	LC/MS (ESI):537.3 [M+H] ⁺
634	LC/MS (ESI):535.2 [M+H] ⁺
635	LC/MS (ESI):524.2 [M+H] ⁺
636	LC/MS (ESI):457.1 [M+H] ⁺
637	LC/MS (ESI):485.1 [M+H] ⁺
638	LC/MS (ESI):471.1[M+H] ⁺
639	LC/MS (ESI):437.2[M+H] ⁺
640	LC/MS (ESI):451.2[M+H] ⁺
641	LC/MS (ESI):437.2 [M+H] ⁺
642	LC/MS (ESI): 457.1[M+H] ⁺
643	LC/MS (ESI):437.2[M+H] ⁺
644	LC/MS (ESI):455.1[M+H] ⁺
645	LC/MS (ESI):469.1[M+H] ⁺
646	LC/MS (ESI):449.2 [M+H] ⁺
647	LC/MS (ESI):443.1 [M+H] ⁺
648	LC/MS (ESI):465.3 [M+H] ⁺
649	LC/MS (ESI):557.2 [M+H] ⁺
650	LC/MS (ESI):435.2[M+H] ⁺
651	LC/MS (ESI):449.3 [M+H] ⁺
652	LC/MS (ESI):469.2 [M+H] ⁺
653	LC/MS (ESI):455.2 [M+H] ⁺
654	LC/MS (ESI):483.2 [M+H] ⁺
655	LC/MS (ESI):441.1 [M+H] ⁺
656	LC/MS (ESI):485.1 [M+H] ⁺

No.	NMR/MS
657	LC/MS (ESI):479.2 [M+H] ⁺
658	LC/MS (ESI):435.2 [M+H] ⁺
659	LC/MS (ESI):469.2 [M+H] ⁺
660	LC/MS (ESI):507.2 [M+H] ⁺
661	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 9.03 (s, 1H), 8.46 (d, J = 9.8 Hz, 1H), 8.31 (s, 1H), 7.89 (s, 1H), 7.34 (d, J = 9.9 Hz, 1H), 5.25 (s, 2H), 5.05 - 4.93 (m, 1H), 2.91 (s, 3H), 2.64 (s, 6H), 1.96 (br d, J = 7.8 Hz, 2H), 1.80 - 1.72 (m, 2H), 1.68 (br d, J = 7.5 Hz, 2H), 1.63 (br dd, J = 5.4, 12.9 Hz, 2H), 1.30 (s, 6H); LC/MS (ESI):495.2 [M+H] ⁺
662	LC/MS (ESI):421.1 [M+H] ⁺
663	LC/MS (ESI):463.2 [M+H] ⁺
664	LC/MS (ESI):496.2 [M+H] ⁺
665	LC/MS (ESI):449.21 [M+H] ⁺
666	LC/MS (ESI):421.2 [M+H] ⁺
667	LC/MS (ESI):471.2 [M+H] ⁺
668	LC/MS (ESI):457.1 [M+H] ⁺
669	LC/MS (ESI):423.2 [M+H] ⁺
670	LC/MS (ESI):441.1 [M+H] ⁺
671	LC/MS (ESI):469.2 [M+H] ⁺
672	LC/MS (ESI):451.3 [M+H] ⁺
673	LC/MS (ESI):463.2 [M+H] ⁺
674	LC/MS (ESI):437.3 [M+H] ⁺
675	LC/MS (ESI):479.3 [M+H] ⁺
676	LC/MS (ESI):498.2 [M+H] ⁺
677	LC/MS (ESI):517.4 [M+H] ⁺
678	LC/MS (ESI):487.2 [M+H] ⁺
679	LC/MS (ESI):527.5 [M+H] ⁺
680	LC/MS (ESI):507.2 [M+H] ⁺
681	LC/MS (ESI):485.2 [M+H] ⁺
682	LC/MS (ESI):520.2 [M+H] ⁺
683	LC/MS (ESI):505.3 [M+H] ⁺
684	LC/MS (ESI):510.2 [M+H] ⁺
685	LC/MS (ESI):518.2 [M+H] ⁺
686	LC/MS (ESI):524.1 [M+H] ⁺
687	LC/MS (ESI): 503.3 [M+H] ⁺
688	LC/MS (ESI):492.2 [M+H] ⁺
689	LC/MS (ESI): 509.3 [M+H] ⁺
690	LC/MS (ESI):464.2 [M+H] ⁺
691	LC/MS (ESI):476.2 [M+H] ⁺
692	LC/MS (ESI):492.2 [M+H] ⁺
693	LC/MS (ESI):485.2 [M+H] ⁺
694	¹ H NMR (DMSO- <i>d</i> ₆ , 400 MHz) δ 9.11 (d, 1H, J=0.8 Hz), 8.83 (d, 1H, J=2.0 Hz), 8.62 (d, 1H, J=1.8 Hz), 8.48 (d, 1H, J=10.0 Hz), 8.35 (s, 1H), 8.08 (d, 1H, J=0.8 Hz), 7.36 (d, 1H, J=10.0 Hz), 5.41 (s, 2H), 5.0-5.1 (m, 1H), 2.93 (s, 3H), 2.00 (br d, 2H, J=7.5 Hz), 1.88 (br t, 2H, J=12.4 Hz), 1.75 (br d, 2H, J=7.8 Hz), 1.67 (br dd, 2H, J=5.4, 12.9 Hz), 1.35 (s, 6H); LC/MS (ESI):470.2 [M+H] ⁺
695	¹ H NMR : (400 MHz, DMSO- <i>d</i> ₆) δ = 8.88 - 8.69 (m, 2H), 8.57 - 8.40 (m, 2H), 7.36 (br d, J = 9.0 Hz, 1H), 5.37 (br s, 2H), 5.08 (br s, 1H), 2.94 (br s, 3H), 2.36 (br s, 3H), 2.14 - 1.97 (m, 4H), 1.91 - 1.80 (m, 2H), 1.77 - 1.66 (m, 2H), 1.42 (br s, 6H); LC/MS (ESI):484.2 [M+H] ⁺
696	LC/MS (ESI):510.3 [M+H] ⁺

[0493] Example 34. Decreasing MSH3 expression

[0494] By decreasing or inhibiting expression of MSH3 gene (e.g., endogenous MSH3 gene in a cell), repair of the nucleotide repeat and the subsequent nucleotide repeat expansion in the cell can be decreased (e.g., as shown in **FIG. 2**), thereby treating the nucleotide repeat expansion disease or condition. As shown in **FIG. 3**, contacting candidate agents with MSH3 pre-mRNA or snRNAs led to decreased MSH3 expression as determined by the decrease of percentage of mRNA of MSH3. **FIG. 4** and **FIG. 5** illustrate exemplary mechanisms of how the candidate agents decreases MSH3 expression. Poison exon is not spliced into the mRNA under endogenous or physiological condition. However, by contacting the poison exon and one of the snRNAs with a candidate agent, the poison exon is spliced into the mRNA, where the poison exon directs the mRNA for degradation.

[0495] Example 35. Identification and screening for poison exon

[0496] Poison exons were identified in endogenous MSH3 genome by employing a proprietary bioinformatics pipeline screening for cryptic exons in combination with examining poison exon candidates that could be regulated by an agent described herein or by nonsense mediated decay (NMD) using cycloheximide. **FIG. 6** and **FIG. 7** illustrate identification of Exon 21A, but not Exon 21B, as a poison exon that could be regulated by the agent described herein. **FIG. 8** and **FIG. 9** illustrate mutations that can be introduced into the poison exon (Exon 21A and Exon 14A_1 or Exon 14A_2, respectively), where the mutated nucleotide bases (e.g., CAG) could further enhance the suppression of the MSH3 expression. Such mutations can be utilized as a method or a system for screening additional candidate agents. **FIG. 8** illustrates splicing and RNA expression changes for targets regulated by an agent described herein. Compound 1 and CHX increased poison exon expression (Exon 21A) and decreased total RNA (e.g., due to NMD). **FIG. 8** also illustrates how mutating a poison exon (e.g., from ATA to CAG) increased percentage of splice inclusion of Exon 21A from 0.13 to 0.98. Such mutations can be useful for designing a method or a system for screening additional agents for modulating splicing in of poison exon into a mRNA (e.g., as shown in **FIG. 10**). **FIG. 9** illustrates splicing and RNA expression changes for targets regulated by an agent described herein. Compound 1 and CHX increased poison exon expression (Exon 14A_1 or Exon 14A_2) and decreased total RNA (e.g., due to NMD). **FIG. 9** also illustrates how mutating the poison exon (e.g., from TGA to CAG) increased percentage of splice inclusion of Exon 14A_1 from 0.00 to 0.59. Such mutations can be useful for designing a method or a system for screening additional agents for modulating splicing in of poison exon into a mRNA (e.g., as shown in **FIG. 10**). As shown in **FIG. 10**, poison exons comprising the CAG mutation were utilized to generate luciferase signal, indicating splicing in of the poison exon into an mRNA (**FIG. 10C**). **FIG. 10A** illustrates engineered minigene donor (e.g., by mutating endogenous trinucleotides to CAG as shown in **FIG. 8** and **FIG. 9**) for driving expression of a luciferase reporter gene. **FIG. 10B** illustrates minigene PCR showing the presence of the poison exon comprising the CAG mutation. The wild-type (WT) mRNA did not have the poison exon as confirmed by the decreased nucleotide length. **FIG. 10C** illustrates increased luciferase signal generated by the presence of the minigene comprising the poison exon comprising the CAG mutation.

[0497] Example 36. Functional validation of MSH3 poison exon 14A (PE5) and poison exon 21A (PE4)

[0498] In this example, MSH3 poison exon 14A (PE5) and poison exon 21A (PE4) were validated. Briefly, HEK293 parental and clonal cells (Synthego) were cultured in DMEM (ThermoFisher Scientific) supplemented with 10% fetal bovine serum (Avantor) and 0.1 µg/mL Primocin (Invivogen). All cell lines were maintained at sub-confluency and grown in a humidified incubator at 37 °C with 5% CO₂. HEK293 clonal cells were generated by Synthego's proprietary CRISPR methods to replace PE14A 5' splice site with a strong donor (TGAGTTG>CAGGTTA) at the endogenous locus. Two clones (C3 and H2) were isolated to express 99-100% of the desired knock-in mutation. Two clones were generated from the parental line HEK293 without any editing (wild-type WT13 and WT7) to be used as controls. WT control and PE14A CAG mutant clones were plated for treatment for 24 hours with an exemplary MSH3 splice modulating agent (Compound 274) as indicated in **FIGS. 11A, 11B, 12A, and 12B** ("Compound A"). RNA, cDNA and qPCR was prepared using TaqMan Cells-to-CT Express kit (ThermoFisher Scientific). Taqman assays (ThermoFisher Scientific) were used for quantification of total MSH3 exons 13/14 (cat# 4351372, ID#: Hs00988993_m1), total MSH3 exons 20/21 (cat# 4351372, ID#: Hs00989000_m1), exon 13/PE14A (Fwd: 5'-CGTAAATTGCCCGACATAGAGA (**SEQ ID NO: 14**); Rev: 5'-AACAGTTACGTAAGTCCTCTTGG (**SEQ ID NO: 15**); Probe: 5'-AGCATTTATCACAAAAAAGTTTAC (**SEQ ID NO: 16**)) and exon 20/PE21A (Fwd: 5'-CTCAGATTGGCTCCTATGTTCC (**SEQ ID NO: 17**); Rev: 5'-GGGCTTCTGTCCCTTCAAAT (**SEQ ID NO: 18**); Probe: 5'-TTCACAAGCATTTTCCTTGCA (**SEQ ID NO: 19**)) mRNA expression. Taqman GAPDH (cat# 4448489, ID#: Hs02758991_g1) was used as a reference for data normalization. Protein lysates were prepared using RIPA buffer (ThermoFisher Scientific) supplemented with Halt protease inhibitor cocktail (ThermoFisher Scientific). Protein concentrations were determined by Rapid Gold BCA (ThermoFisher Scientific). Equal amounts of total proteins were separated on 4-15% SDS-PAGE (Bio-Rad) and blotted to PVDF membranes (Bio-Rad). Antibodies used were MSH3 (Abcam, ab275928) and GAPDH (Cell Signalling, D16H11).

[0499] FIGS. 11A and 11B demonstrate that wild-type clones responded to treatment with Compound A, lowering MSH3 expression and increasing PE5-specific expression. PE5 CAG clones C3 and H2 had a basal level of MSH3 about 90% and 60% reduction relative to wild-type, respectively. PE5 basal expression was higher in clones, as expected. No further decrease was seen with Compound A treatment on total MSH3 13/14 levels. There was ~20-30% further increase of PE5 starting at 0.3-1 µM Compound A.

[0500] FIGS. 12A and 12B demonstrate that wild-type clones responded to treatment with Compound A, lowering MSH3 expression and increasing PE4-specific expression. MSH3 (total, exons 20/21) was about 30-50% lower in the PE5 CAG clones. **FIG. 12C** depicts a Western blot showing that treatment with Compound A led to a decreased in MSH3 levels in both wild-type and PE5 CAG clones.

[0501] To further validate MSH3 poison exon 14A, RT-PCR was used to analyze MSH3 exon 13/poison exon 14A, and poison exon 14A/exon 14 amplicons. Briefly, Cynomolgus monkey primary dermal

fibroblasts (Cellosaurus) and HEK293 cells (ATCC) were cultured in DMEM (ThermoFisher Scientific) supplemented with 10% fetal bovine serum (Avantor) and 0.1 µg/mL Primocin (Invivogen). All cell lines were maintained at sub-confluency and grown in a humidified incubator at 37 °C with 5% CO₂.

Cynomolgus fibroblasts and HEK293 cells were plated for treatment for 24 hours with compound as indicated in **FIG. 13**. RNA was purified using Qiashredder and RNeasy kits (Qiagen), cDNA was prepared with MultiScribe Reverse Transcriptase (ThermoFisher Scientific) and PCR with GoTaq Green Master Mix (Promega). Primers (IDT) used were the following: Fwd-Exon 13 (5'-AAATAAATGCCCGGCTTGATG (**SEQ ID NO: 20**)), Rev-PE14A (5'-GGCTTGTGCATTGTTTTCAAATTTA (**SEQ ID NO: 21**)), Fwd-PE14A (5'-TAAATTTGAAAACAATGCACAAGCC (**SEQ ID NO: 22**)), Rev-Exon 14 (5'-AGCAGGTATTATTGCTTGAAATTCT (**SEQ ID NO: 23**)), Fwd-GAPDH (5'-CCACTAGGCGCTCACTGTTC (**SEQ ID NO: 24**)), Rev-GAPDH (5'-ACCCGTTGACTCCGACCT (**SEQ ID NO: 25**)).

[0502] **FIG. 13** demonstrates that treatment with Compound A in both cynomolgus monkey fibroblasts and HEK293 cells led to an increase in both 13/PE14A and PE14A/14 amplicons, demonstrating that Compound A can modulate splicing of PE14A.

[0503] Example 37. qPCR assay for monitoring levels of MSH3 upon compound treatment

[0504] HEK293T or AD293 cells were treated with Compound 274 at 1 µM and 10 µM. RNA, cDNA and qPCR was prepared using TaqMan Cells-to-CT Express kit (ThermoFisher Scientific). Taqman assays (ThermoFisher Scientific) were used for quantification of total MSH3 exons 13/14 (cat# 4351372, ID#: Hs00988993_m1), total MSH3 exons 20/21 (cat# 4351372, ID#: Hs00989000_m1), exon 13/PE14A (Fwd: 5'-CGTAAATTGCCCGACATAGAGA; Rev: 5'-AACAGTTACGTAAGTCCTCTTGG; Probe: 5'-AGCATTTATCACAAAAAAGTTTTAC) and exon 20/PE21A (Fwd: 5'-CTCAGATTGGCTCCTATGTTCC; Rev: 5'-GGGCTTCTGTCCCTTCAAAT; Probe: 5'-TTCACAAGCATTTTCCTTGCA) mRNA expression. Taqman GAPDH (cat# 4448489, ID#: Hs02758991_g1) was used as a reference for data normalization. The fold-change of the MSH3 transcript at 1 µM and 10 µM of Compound 274, and the EC₅₀ of MSH3 downregulation are shown in **Table 8** below.

Table 8

Compound No.	Fold change (1µM)	Fold change (10 µM)	EC50 nM (XtalPi)
21	0.54	0.58	
51	0.94	0.26	
55	0.56	0.2	
59	1.01	0.29	
61	0.44	0.18	
62	0.18	0.08	689.5

69	0.3	0.11	885
70	1.39	0.56	
73	0.85	0.70	
74	0.96	0.33	
76	0.98	0.2	
79	0.92	0.31	
90	0.38	0.18	
91	0.85	0.74	
93	0.91	0.72	
94	1.06	0.79	
96	0.79	1.19	
98	0.83	0.25	
99	0.9	0.86	
100	0.65	0.11	
106	1.21	1.3	
107	0.97	0.75	
141	0.67	0.06	
148	1.03	0.4	
150	1.16	0.77	
156	0.81	0.19	
161	0.96	0.7	
167	0.47	0.11	
174	1.03	0.62	
175	0.93	0.7	
176	0.94	1.1	
178	0.1	0.05	425.4
179	0.93	0.08	
180	0.5	0.08	1122
181	0.92	1.03	
183	0.99	0.28	
187	0.92	0.25	
188	0.18	0.05	960.3
189	0.73	0.23	
190	1.06	0.45	
191	0.45	0.17	
194	2.24	0.92	
195	0.59	0.42	
200	0.53	0.53	
201	0.9	0.91	
203	0.56	0.62	

205	0.9	0.14	1423
206	0.36	0.13	506.8
207	1.08	0.18	~ 3051
211	0.9	0.55	
214	0.95	0.24	
215	0.97	0.76	
217	0.92	0.78	
226	0.86	0.58	
228	0.58	0.37	792.3
239	0.84	0.19	2035
240	0.87	0.16	2311
261	0.48	0.07	
274	0.17		454.5
275	0.79	0.26	
276	1.03	0.38	
278	0.64	0.14	
280	0.99	0.66	
281	0.85	0.41	
282	0.3	0.59	
283	0.48	0.11	799
284	0.91	0.73	
286	1.17	0.59	
289	0.73	0.22	
291	0.93	0.81	
293	0.54	0.12	~ 1057
294	0.27	0.12	480.4
296	0.54		
298	0.89	0.29	
362	0.65	0.75	
367	0.57	0.27	
370	0.69	0.61	
387	0.96	0.63	
399	0.65	0.43	
416	0.37		
420	0.74	0.73	
423	0.37	0.1	
425	0.82	0.7	
429	1.02	0.52	
438	1.09	0.81	
439	0.87	0.72	

447	0.94		
457	0.85	0.7	
458	0.4	0.11	820.2
460	0.8	0.25	
465	0.93	1.15	
479	1.19	0.56	
480	0.15	0.1	362.7
485	0.88	0.4	
487	1.33	0.31	
488	0.69	0.19	
490	0.9	0.25	
493	0.57	0.13	
496			689.5
498	0.67	0.52	
500	1.01	0.22	
503	0.7	0.18	
509	1.17	0.62	
559	0.93	0.53	
560	0.81	0.29	
563	1.04	0.35	
566	1.33	0.6	
568	0.77	0.46	
589	0.2	0.11	349
590	0.24	0.09	568.8
591	1.09	0.91	634
592	0.9	0.54	
593	1.05	0.34	
594	0.79	1.12	
595	0.91	0.18	
596	0.88	1.06	
597	0.98	0.29	
598	0.62	0.52	
599	0.94	0.24	
600	1.04	0.14	
601	1.17	0.82	
602	0.64	0.29	
603	1.55	0.94	
604	0.63	0.93	
605	0.82	0.56	
606	0.57	0.25	

607	0.72	0.09	
608	0.86	0.2	
609	0.39	0.07	
610	0.93	0.66	
611	0.9	0.79	
612	1.09	0.15	
613	1.3	0.91	
614	1.07	0.79	
615	0.81	0.53	
616	1	0.67	
617	0.93	0.7	
618	0.83	0.68	
619	0.8	0.1	
620	0.93	0.55	
621			229.3
622	0.76	0.30	
623	0.6	0.13	2993
624	0.6	0.12	
625	0.81	1.08	
626	0.98	0.28	
627	0.37	0.11	
628	1.01	0.2	
629	0.74	0.62	
630	1.06	0.72	
631	0.86	0.69	
632	0.72	0.57	
633	1.09	0.89	
634	0.63	0.76	
635	0.54	1.17	
636	0.95	0.41	
637	1.5	0.31	
638	1.12	0.22	
639	1.18	0.55	
640	0.99	0.25	
641	0.96	0.34	
642	0.91	0.21	
643	1.09	0.72	
644	0.87	0.97	
645	0.87	1.04	
646	1.15	0.76	

647	1.19	0.86	
648	1.13	0.87	
649	1.06	0.63	
650	0.97	0.75	
651	0.96	0.6	
652	1.03	0.79	
653	0.93	0.27	
654	0.9	0.61	
655	1.15	0.48	
656	0.7	0.43	
657	0.75	0.26	
658	1.32	0.51	
659	1.42	0.57	
660	1.01	0.5	
661	1.55	0.33	
662	1.91	0.87	
663	2.32	0.62	
664	0.94	0.2	
665	0.92	0.32	
666	0.97	0.59	
667	0.92	0.71	
668	1.03	0.13	
669	0.97	0.42	
670	0.92	0.44	
671	0.94	0.47	
672	0.95	0.74	
673	0.91	0.33	
674	0.98	0.49	
675	0.93	0.67	
676	0.48	0.17	
677	1.2	0.28	
678	1.12	0.19	
679	0.95	0.34	
680	0.94	0.31	
681	0.76	0.08	
682	0.77	0.17	
683	1.38	0.26	
684	1.33	0.24	
685	0.24	0.2	
686	1.09	0.26	

687	1.1	0.19	
688	1.23	0.86	
689	0.88	0.27	
690	0.98	0.65	
691	0.95	0.78	
692	0.97	0.5	
693	0.94	0.4	
694			2482
695			11063

[0505] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A method for modulating splicing of MSH3 pre-mRNA, the method comprising contacting a cell with an agent which modulates splicing of MSH3 pre-mRNA such that an MSH3 mRNA transcript comprising a poison exon is produced, thereby modulating splicing of MSH3 pre-mRNA.
2. A method for treating a disease or condition in a subject, the method comprising administering to the subject an agent which modulates splicing of MSH3 pre-mRNA such that an MSH3 mRNA transcript comprising a poison exon is produced in a cell of the subject, thereby treating the disease or condition.
3. The method of claim 1 or 2, wherein the method results in decreased expression of MSH3 protein in the cell.
4. The method of claim 3, wherein the method results in decreased nucleotide repeat expansion of a target gene in the cell.
5. The method of claim 4, wherein the nucleotide repeat expansion comprises a trinucleotide repeat expansion.
6. The method of claim 4, wherein the nucleotide repeat expansion comprises expansion of a four-nucleotide repeat, a five-nucleotide repeat, a six-nucleotide repeat, a seven-nucleotide repeat, an eight-nucleotide repeat, a nine-nucleotide repeat, a ten-nucleotide repeat, an eleven-nucleotide repeat, or a twelve-nucleotide repeat.
7. The method of any one of claims 4-6, wherein the nucleotide repeat expansion is in an exon of the target gene.
8. The method of any one of claims 4-6, wherein the nucleotide repeat expansion is in an intron of the target gene.
9. The method of any one of claims 4-6, wherein the nucleotide repeat expansion is in a UTR of the target gene.
10. The method of any one of claims 4-6, wherein the nucleotide repeat expansion is in a promoter of the target gene.
11. The method of any one of claims 7-10, wherein the gene is selected from the group consisting of: ATN1, HTT, AR, ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7, PPP2R2B, TBP, TCF4, JPH3, DMPK, ATXN8, ZNF713, FMR1, AFF/FMR2, FXN, ZFN9, ATXN10, NOP56, C9orf72, CSTB, and any combination thereof.
12. The method of any one of claim 4-11, wherein the nucleotide repeat expansion in the cell comprises at least 20 repeats, at least 30 repeats, at least 40 repeats, at least 50 repeats, at least 60 repeats, at least 70 repeats, at least 80 repeats, at least 90 repeats, at least 100 repeats, at least 200 repeats, at least 500 repeats, at least 1000 repeats, at least 2000 repeats, at least 5000 repeats, at least 10,000 repeats, or at least 20,000 repeats.
13. The method of claim 4, wherein the nucleotide repeat expansion in the target gene is decreased by at least about 0.1 fold, at least about 0.2 fold, at least about 0.5 fold, at least about 1.0 fold, at least

about 2.0 fold, at least about 5.0 fold, at least about 10.0 fold, or at least about 100.0 fold, as compared to a level of nucleotide repeat expansion in the target gene in the absence of the agent.

14. The method of any one of claims 1-13, wherein the poison exon comprises a nucleic acid sequence that has at least about 80% sequence identity to the nucleic acid sequence of SEQ ID NO: 1.
15. The method of any one of claims 1-14, wherein the poison exon is or comprises exon 21A, or a portion thereof, of MSH3.
16. The method of any one of claims 1-15, wherein the poison exon is located at or within position chr5:80832901-80832994 of Human Genome Assembly hg38 of December 2013.
17. The method of any one of claims 1-16, wherein the poison exon comprises a nucleic acid sequence that has at least about 80% sequence identity to the nucleic acid sequence of SEQ ID NO: 2 or SEQ ID NO: 3.
18. The method of any one of claims 1-17, wherein the poison exon is or comprises exon 14A_1, or a portion thereof, of MSH3.
19. The method of any one of claims 1-18, wherein the poison exon is or comprises exon 14A_2, or a portion thereof, of MSH3.
20. The method of any one of claims 1-19, wherein the poison exon is located at or within position chr5:80763222-80763369 or position chr5:80763222-80767932 of Human Genome Assembly hg38 of December 2013.
21. The method of any one of claims 1-20, wherein the poison exon is selected from the group consisting of any one of the poison exons listed in **Table 1** or **Table 2**.
22. The method of any one of claims 1-21, wherein the poison exon introduces a premature termination codon (PTC) into the MSH3 mRNA transcript.
23. The method of any one of claims 1-22, wherein the agent forms a complex with the MSH3 pre-mRNA and a spliceosomal RNA.
24. The method of any one of claims 1-23, wherein the agent increases binding of a spliceosomal RNA to the MSH3 pre-mRNA.
25. The method of claim 23 or 24, wherein the spliceosomal RNA comprises a small nuclear RNA (snRNA).
26. The method of claim 25, wherein the snRNA is selected from the group consisting of: U1 snRNA, U2 snRNA, U4 snRNA, U5 snRNA, U6 snRNA, and any combination thereof.
27. The method of claim 26, wherein the snRNA comprises U1 snRNA.
28. The method of any one of claims 1-27, wherein the agent is selected from the group consisting of: a small molecule, a polypeptide, an oligosaccharide, a polysaccharide, an oligonucleotide, an aptamer, a ribonucleoprotein (RNP), an enzyme, a nuclease, and any combination thereof.
29. The method of any one of claims 1-28, wherein the agent is a small molecule.
30. The method of any one of claims 2-29, wherein the disease or condition is a nucleotide repeat disorder.

31. The method of claim 30, wherein the disease or condition is selected from the group consisting of: dentatorubropallidolusian atrophy (DRPLA), Huntington's disease (HD), spinal and bulbar muscular atrophy (SBMA), spinocerebellar ataxia (SCA) type 1, spinocerebellar ataxia (SCA) type 2, spinocerebellar ataxia (SCA) type 3, spinocerebellar ataxia (SCA) type 6, spinocerebellar ataxia (SCA) type 7, spinocerebellar ataxia (SCA) type 8, spinocerebellar ataxia (SCA) type 10, spinocerebellar ataxia (SCA) type 12, spinocerebellar ataxia (SCA) type 17, spinocerebellar ataxia (SCA) type 31, spinocerebellar ataxia (SCA) type 36, spinocerebellar ataxia (SCA) type 37, spinocerebellar ataxia (SCA) type 50, Friedreich ataxia, fragile X syndrome (FRAXA), fragile X-associated tremor/ataxia syndrome (FXTAS), Baratela-Scott syndrome (BSS), myotonic dystrophy (DM) type 1, myotonic dystrophy (DM) type 2, amyotrophic lateral sclerosis (ALS), Kennedy's disease, fragile X E mild mental retardation (FRAXE), progressive myoclonus epilepsy (EPM1), oculopharyngodistal myopathy (OPDM) type 1, oculopharyngodistal myopathy (OPDM) type 2, oculopharyngeal myopathy with leukoencephalopathy (OPML), frontotemporal dementia (FTD), Neuronal intranuclear inclusion disease (NIID), essential tremor, global developmental delay, progressive ataxia, and elevated glutamine (GDPAG), familial myoclonic epilepsy (FAME) type 1, familial myoclonic epilepsy (FAME) type 2, familial myoclonic epilepsy (FAME) type 3, familial myoclonic epilepsy (FAME) type 4, familial myoclonic epilepsy (FAME) type 6, familial myoclonic epilepsy (FAME) type 7, premature ovarian failure (FXPOF), cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS), multiple system atrophy (MSA), refractory chronic cough, Fuchs endothelial corneal dystrophy (FECD), X-linked dystonia-parkinsonism (XDP), intellectual disability (FRA12A type), Jacobsen syndrome (CBL2), and any combination thereof.
32. The method of any one of claims 1-31, wherein the MSH3 mRNA comprising the poison exon undergoes nonsense mediated decay (NMD).
33. A system comprising:
- (a) an MSH3 pre-mRNA;
 - (b) a spliceosomal RNA; and
 - (c) an agent which modulates splicing of the MSH3 pre-mRNA such that an MSH3 mRNA transcript comprising the poison exon is produced.
34. The system of claim 33, further comprising the MSH3 mRNA transcript comprising the poison exon.
35. The system of claim 33 or 34, wherein the agent, the MSH3 pre-mRNA, and the spliceosomal RNA are in a complex.
36. The system of any one of claims 33-35, wherein the agent is an agent that induces binding of the spliceosomal RNA to the MSH3 pre-mRNA.
37. The system of any one of claims 33-36, wherein the poison exon introduces a premature termination codon into the MSH3 mRNA.
38. The system of any one of claims 33-37, wherein the poison exon comprises a nucleic acid sequence that has at least 80% sequence identity to the nucleic acid sequence of SEQ ID NO: 1.

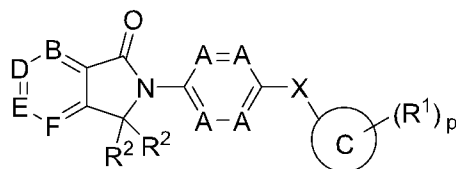
39. The system of any one of claims 33-38, wherein the poison exon is or comprises exon 21A, or a portion thereof, of MSH3.
40. The system of any one of claims 33-39, wherein the poison exon is located at or within position chr5:80832901-80832994 of Human Genome Assembly hg38 of December 2013.
41. The system of any one of claims 33-40, wherein the poison exon comprises a nucleic acid sequence that has at least 80% sequence identity to the nucleic acid sequence of SEQ ID NO: 2 or SEQ ID NO: 3.
42. The system of any one of claims 33-41, wherein the poison exon is or comprises exon 14A_1, or a portion thereof, of MSH3.
43. The system of any one of claims 33-42, wherein the poison exon is or comprises exon 14A_2, or a portion thereof, of MSH3.
44. The system of any one of claims 33-43, wherein the poison exon is located at or within position chr5:80763222-80763369 or position chr5:80763222-80767932 of Human Genome Assembly hg38 of December 2013.
45. The system of any one of claims 33-44, wherein the poison exon is selected from the group consisting of any one of the poison exons listed in **Table 1** or **Table 2**.
46. The system of any one of claims 33-45, wherein the MSH3 pre-mRNA and the spliceosomal RNA are partially complementary.
47. The system of any one of claims 33-46, wherein the spliceosomal RNA comprises a small nuclear RNA (snRNA).
48. The system of claim 47, wherein the snRNA is selected from the group consisting of: U1 snRNA, U2 snRNA, U4 snRNA, U5 snRNA, U6 snRNA, and any combination thereof.
49. The system of claim 47 or 48, wherein the snRNA comprises U1 snRNA.
50. The system of any one of claims 33-49, wherein the agent is selected from the group consisting of: a small molecule, a polypeptide, a carbohydrate, a monosaccharide, a oligosaccharide, a polysaccharide, an oligonucleotide, an aptamer, a biologic, a ribonucleoprotein (RNP), and any combination thereof.
51. The system of any one of claims 33-50, wherein the agent comprises a small molecule.
52. A vessel containing the system of any one of claims 33-51.
53. The vessel of claim 52, wherein the vessel is selected from the group consisting of: a vial, a tube, a plate, and a dish.
54. A cell containing the system of any one of claims 33-51.
55. An mRNA transcript comprising an MSH3 mRNA and at least one poison exon.
56. The mRNA transcript of claim 55, wherein the at least one poison exon comprises a nucleic acid sequence that has at least about 80% sequence identity to the nucleic acid sequence of SEQ ID NO: 1.
57. The mRNA transcript of claim 55 or 56, wherein the at least one poison exon is or comprises exon 21A, or a portion thereof, of MSH3.

58. The mRNA transcript of any one of claims 55-57, wherein the at least one poison exon is located at or within position chr5:80832901-80832994 of Human Genome Assembly hg38 of December 2013.
59. The mRNA transcript of any one of claims 55-58, wherein the at least one poison exon comprises a nucleic acid sequence that has at least about 80% sequence identity to the nucleic acid sequence of SEQ ID NO: 2 or SEQ ID NO: 3.
60. The mRNA transcript of any one of claims 55-59, wherein the at least one poison exon is or comprises exon 14A_1, or a portion thereof, of MSH3.
61. The mRNA transcript of any one of claims 55-60, wherein the at least one poison exon is or comprises exon 14A_2, or a portion thereof, of MSH3.
62. The mRNA transcript of any one of claims 55-61, wherein the poison exon is located at or within position chr5:80763222-80763369 or position chr5:80763222-80767932 of Human Genome Assembly hg38 of December 2013.
63. The mRNA transcript of any one of claims 55-62, wherein the at least one poison exon is selected from the group consisting of any one of the poison exons listed in **Table 1** or **Table 2**.
64. The mRNA transcript of any one of claims 55-63, wherein the at least one poison exon introduces a premature termination codon (PTC) into the MSH3 mRNA.
65. A cell comprising the mRNA transcript of any one of claims 55-64.
66. A method of screening for an agent that modulates splicing of an MSH3 pre-mRNA, the method comprising:
- (a) contacting a cell with a candidate agent;
 - (b) detecting presence or absence of a poison exon in an MSH3 mRNA transcript; and
 - (c) identifying the candidate agent as an agent that modulates splicing of the MSH3 pre-mRNA when the poison exon is detected in the MSH3 mRNA transcript.
67. The method of claim 66, wherein the detecting comprises sequencing the MSH3 mRNA transcript.
68. The method of claim 66 or 67, wherein the detecting comprises detecting an amount of the MSH3 mRNA transcript comprising the poison exon.
69. The method of any one of claims 66-68, wherein the detecting comprises determining a level of MSH3 protein expression.
70. The method of claim 69, wherein the identifying comprises identifying the candidate agent as an agent that modulates splicing of the MSH3 pre-mRNA when the level of MSH3 protein expression is decreased as compared to a level of MSH3 protein expression in the absence of the candidate agent.
71. The method of any one of claims 66-70, wherein the detecting comprises determining or measuring a level of MSH3 mRNA transcript.
72. The method of claim 71, wherein the identifying comprises identifying the candidate agent as an agent that modulates splicing of the MSH3 pre-mRNA when the level of MSH3 mRNA transcript is decreased as compared to a level of MSH3 mRNA transcript in the absence of the candidate agent.

73. The method of any one of claims 66-72, wherein the detecting comprises detecting viability of the cell.
74. The method of claim 73, wherein the identifying comprises identifying the candidate agent as an agent that modulates splicing of the MSH3 pre-mRNA when viability is decreased as compared to in the absence of the candidate agent.
75. The method of any one of claims 66-74, further comprising contacting the cell with an inhibitor of nonsense-mediated decay (NMD).
76. The method of claim 75, wherein the inhibitor of NMD is cycloheximide.
77. The method of claim 75 or 76, further comprising determining that the poison exon leads to NMD of the MSH3 mRNA transcript when a level of the MSH3 mRNA transcript is decreased in the absence of the inhibitor of NMD, and a level of the MSH3 mRNA transcript is increased in the presence of the inhibitor of NMD.
78. The method of any one of claims 66-77, further comprising contacting a plurality of cells with a library of candidate agents, wherein each cell of the plurality of cells is contacted with a different candidate agent.
79. An agent that modulates splicing of MSH3 pre-mRNA such that an MSH3 mRNA transcript comprising a poison exon is produced, for use in a method of treatment of the human or animal body by therapy.
80. An agent that modulates splicing of MSH3 pre-mRNA such that an MSH3 mRNA transcript comprising a poison exon is produced, for use in a method of treatment of an expansion repeat disorder.
81. The agent for use of claim 80, wherein the expansion repeat disorder is selected from the group consisting of: wherein the disease or condition is selected from the group consisting of: dentatorubropallidoluysian atrophy (DRPLA), Huntington's disease (HD), spinal and bulbar muscular atrophy (SBMA), spinocerebellar ataxia (SCA) type 1, spinocerebellar ataxia (SCA) type 2, spinocerebellar ataxia (SCA) type 3, spinocerebellar ataxia (SCA) type 6, spinocerebellar ataxia (SCA) type 7, spinocerebellar ataxia (SCA) type 8, spinocerebellar ataxia (SCA) type 10, spinocerebellar ataxia (SCA) type 12, spinocerebellar ataxia (SCA) type 17, spinocerebellar ataxia (SCA) type 31, spinocerebellar ataxia (SCA) type 36, spinocerebellar ataxia (SCA) type 37, spinocerebellar ataxia (SCA) type 50, Friedreich ataxia, fragile X syndrome (FRAXA), fragile X-associated tremor/ataxia syndrome (FXTAS), Baratela-Scott syndrome (BSS), myotonic dystrophy (DM) type 1, myotonic dystrophy (DM) type 2, amyotrophic lateral sclerosis (ALS), Kennedy's disease, fragile X E mild mental retardation (FRAXE), progressive myoclonus epilepsy (EPM1), oculopharyngodistal myopathy (OPDM) type 1, oculopharyngodistal myopathy (OPDM) type 2, oculopharyngeal myopathy with leukoencephalopathy (OPML), frontotemporal dementia (FTD), Neuronal intranuclear inclusion disease (NIID), essential tremor, global developmental delay, progressive ataxia, and elevated glutamine (GDPAG), familial myoclonic epilepsy (FAME) type 1, familial myoclonic epilepsy (FAME) type 2, familial myoclonic epilepsy (FAME) type 3, familial myoclonic epilepsy (FAME) type 4, familial myoclonic epilepsy (FAME) type 6, familial myoclonic epilepsy (FAME) type 7, premature ovarian failure (FXPOF),

cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS), multiple system atrophy (MSA), refractory chronic cough, Fuchs endothelial corneal dystrophy (FECD), X-linked dystonia-parkinsonism (XDP), intellectual disability (FRA12A type), Jacobsen syndrome (CBL2), and any combination thereof.

82. The method of any one of claims 1-32, the system of any one of claims 33-51, or the agent of any one of claims 79-81, wherein the agent is a compound having the structure of Formula (I''), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I''),

wherein,

ring C is 4 to 10-membered heterocycloalkyl or 4 to 10-membered heterocycloalkenylene;

each R¹ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R¹ are taken together to form an oxo; or

two R¹ are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R¹ are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R² is independently hydrogen, halogen, -OH, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; or

X is absent, -CH₂-, -O-, -OCH₂-, -S-, or -NR³-;

R³ is hydrogen, C₁-C₃alkyl, C₁-C₃hydroxyalkyl, C₁-C₃haloalkyl, or C₃-C₆cycloalkyl;

each A is independently N or CR⁴, wherein at least two of A are N;

each R⁴ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl;

or R³ and one of R⁴ are taken together to form a 5 or 6-membered heterocycloalkylene or 5 or 6-membered heteroarylene;

B is N or CR⁵;

D is N or CR⁶;

E is N or CR⁷;

F is N or CR⁸;

R^5 , R^6 , R^7 or R^8 are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -OCH₂R^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, 4 to 6 membered heterocycloalkyl, 5 to 10-membered heteroaryl, or -O-(C₁-C₆alkylene)-5 to 10-membered heteroaryl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, heterocycloalkyl, or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

wherein at least one of R^5 , R^6 , R^7 or R^8 is C₂-C₆alkene, C₃-C₆cycloalkyl, 4 to 6 membered heterocycloalkyl, 5 to 10-membered heteroaryl, or -O-(C₁-C₆alkylene)-5 to 10-membered heteroaryl, wherein the alkene, cycloalkyl, heterocycloalkyl and heteroaryl is optionally substituted with 1 to 4 substituents selected from R^e;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

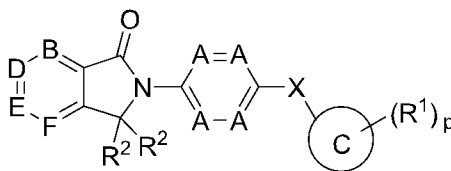
each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

p is an integer from 1-9.

83. The method of any one of claims 1-32, the system of any one of claims 33-51, or the agent of any one of claims 79-81, wherein the agent is a compound having the structure of Formula (I'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I'),

wherein,

ring C is 4 to 10-membered heterocycloalkyl or 4 to 10-membered heterocycloalkenylene;

each R¹ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c; or

two R¹ are taken together to form an oxo; or

two R¹ are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^c; or

two R¹ are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^c;

each R² is independently hydrogen, halogen, -OH, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; or

X is absent, -CH₂-, -O-, -S-, or -NR³-;

R³ is hydrogen, C₁-C₃alkyl, C₁-C₃hydroxyalkyl, C₁-C₃haloalkyl, or C₃-C₆cycloalkyl;

each A is independently N or CR⁴, wherein at least two of A are N;

each R⁴ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl;

B is N or CR⁵;

D is N or CR⁶;

E is N or CR⁷;

F is N or CR⁸;

R⁵ and R⁸ are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c;

one of R⁶ or R⁷ is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R¹⁰; and the other of R⁶ or R⁷ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the

alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, and heterocycloalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; wherein R⁷ is not pyridyl substituted with two methoxy groups;

each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e; or

two R¹⁰ are taken together to form an oxo;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

p is an integer from 1-9.

84. The method, the system, or the agent of claim 82 or 83, or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently hydrogen.

85. The method, the system, or the agent of any one of claims 82-84, or a pharmaceutically acceptable salt or solvate thereof, wherein D is CR⁶ or E is CR⁷.

86. The method, the system, or the agent of any one of claims 83-85, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R⁶ is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R¹⁰; and

R^7 is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6 membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e.

87. The method, the system, or the agent of claim 86, or a pharmaceutically acceptable salt or solvate thereof, wherein R⁷ is hydrogen, halogen, -OH, -OR^a, C₁-C₆alkyl, or C₁-C₆haloalkyl.

88. The method, the system, or the agent of claim 87, or a pharmaceutically acceptable salt or solvate thereof, wherein R⁷ is hydrogen.

89. The method, the system, or the agent of any one of claims 83-85, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R⁶ is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6 membered heterocycloalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl, and heterocycloalkyl, wherein each of the alkyl, alkene, alkyne, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e; and R⁷ is a 5 to 10-membered heteroaryl optionally substituted with 1 to 4 substituents independently selected from R¹⁰.

90. The method, the system, or the agent of claim 89, or a pharmaceutically acceptable salt or solvate thereof, wherein R⁶ is hydrogen, halogen, -OH, -OR^a, C₁-C₆alkyl, or C₁-C₆haloalkyl.

91. The method, the system, or the agent of claim 90, or a pharmaceutically acceptable salt or solvate thereof, wherein R⁶ is hydrogen.

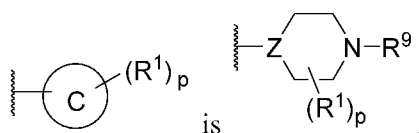
92. The method, the system, or the agent of any one of claims 82-91, or a pharmaceutically acceptable salt or solvate thereof, wherein ring C is a 6-membered heterocycloalkyl.

93. The method, the system, or the agent of any one of claims 82-92, or a pharmaceutically acceptable salt or solvate thereof, wherein ring C is piperidine, piperazine, or morpholine.

94. The method, the system, or the agent of claim 93, or a pharmaceutically acceptable salt or solvate thereof, wherein ring C is piperazine.

95. The method, the system, or the agent of claim 93, or a pharmaceutically acceptable salt or solvate thereof, wherein ring C is piperidine.

96. The method, the system, or the agent of any one of claims 82-95, or a pharmaceutically acceptable salt or solvate thereof, wherein



wherein,

Z is N or CH;

each R^1 is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R^1 are taken together to form an oxo; or

two R^1 are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R^1 are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^e;

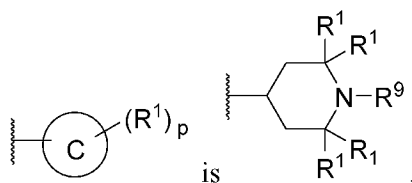
R⁹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R^e;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e; and

each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heteroaryl.

97. The method, the system, or the agent of claim 95, or a pharmaceutically acceptable salt or solvate thereof, wherein



wherein,

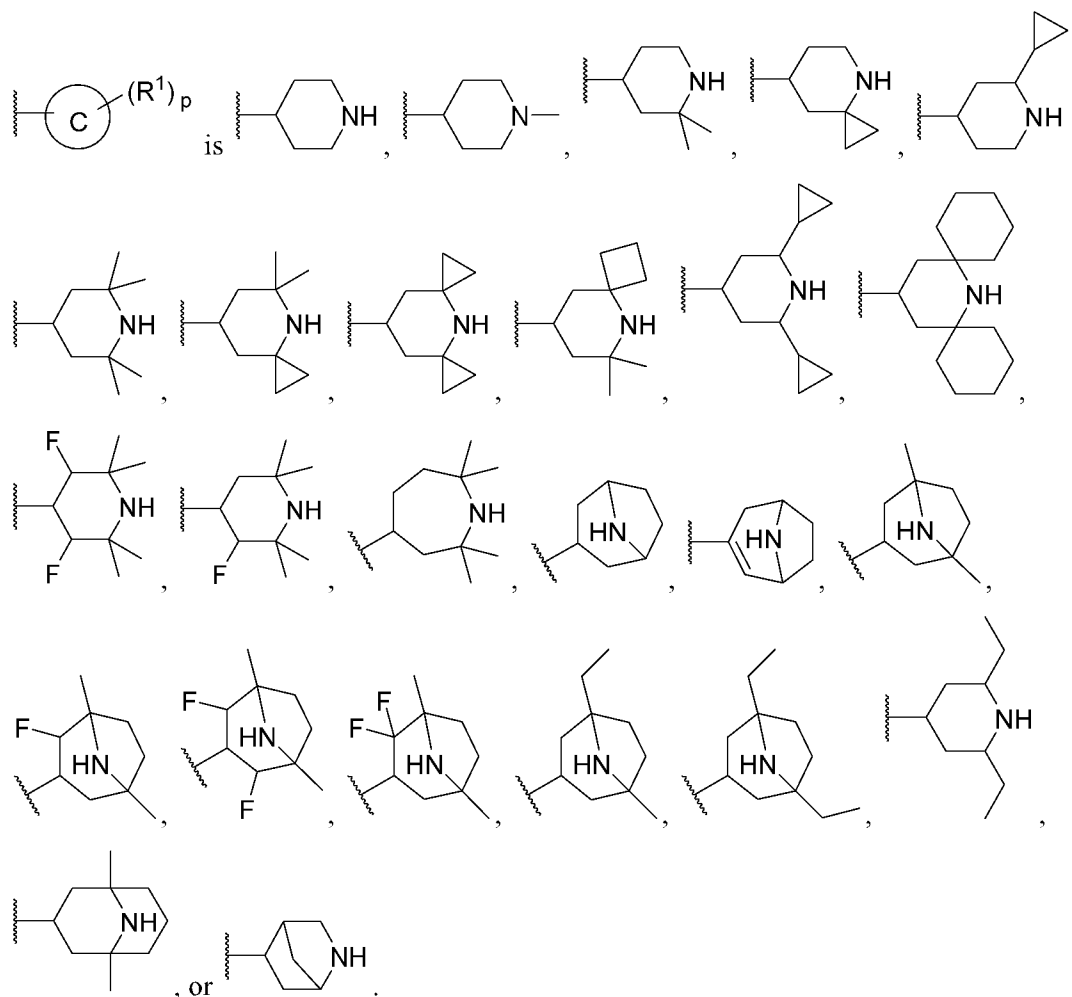
each R¹ is independently hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c; or

two R¹ are taken together to form a C₁-C₃alkylene or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e; or

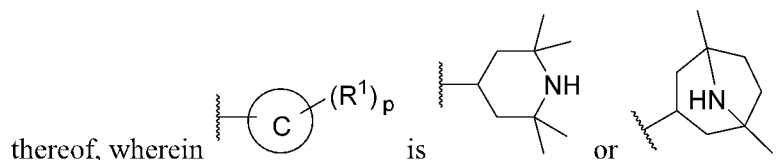
two R¹ are taken together to form a C₃-C₆cycloalkyl; and

R⁹ is hydrogen.

98. The method, the system, or the agent of any one of claims 82-93 or 95-97, or a pharmaceutically acceptable salt or solvate thereof, wherein

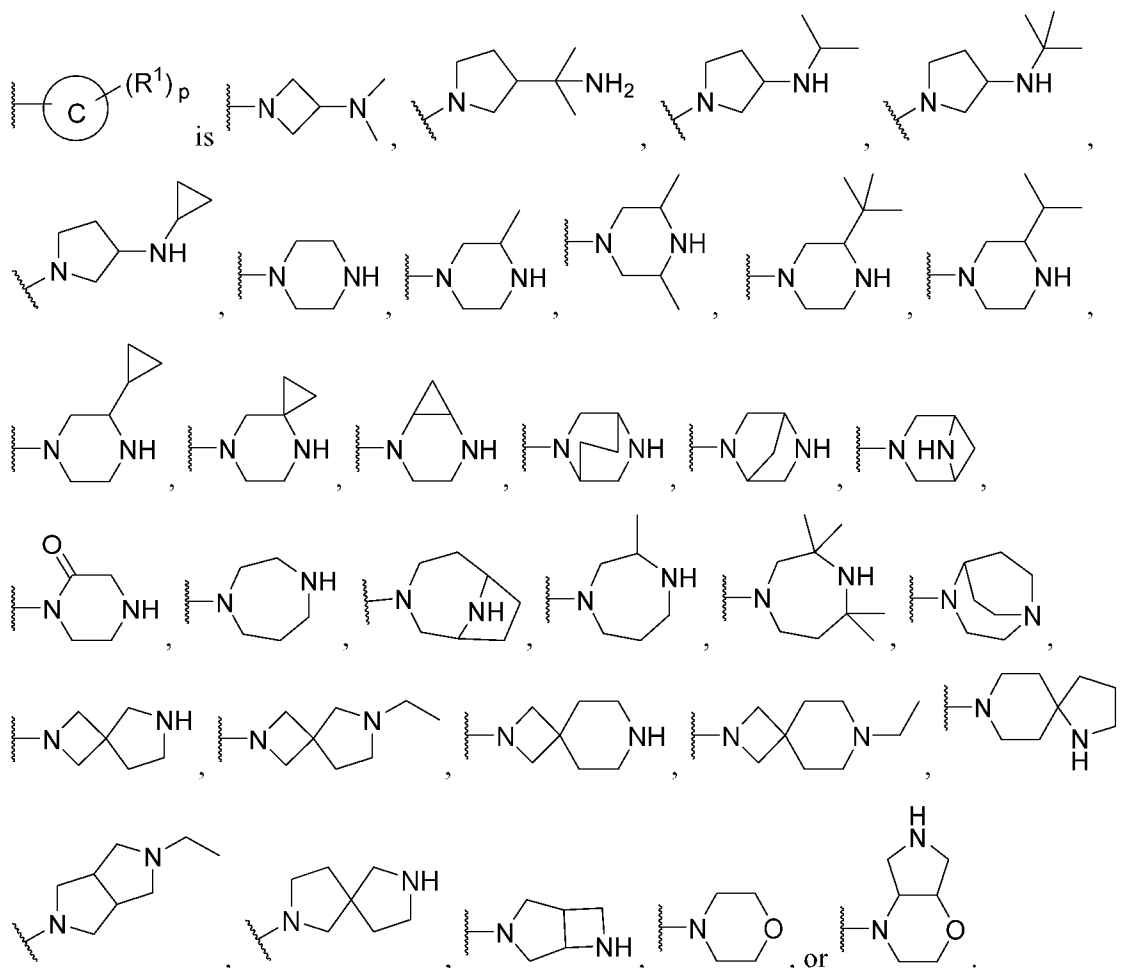


99. The method, the system, or the agent of claim 98, or a pharmaceutically acceptable salt or solvate

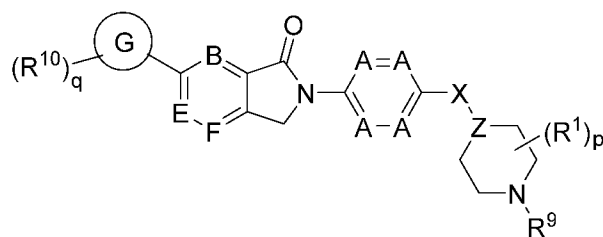


100. The method, the system, or the agent of any one of claims 82-99, or a pharmaceutically acceptable salt or solvate thereof, wherein X is -O- or -NR³-.

101. The method, the system, or the agent of any one of claims 82-93, or a pharmaceutically acceptable salt thereof, wherein X is absent; and



102. The method, the system, or the agent of claim 82 or 83, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (II'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each R¹ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^eR^d,

C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R¹ are taken together to form an oxo; or

two R¹ are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R¹ are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^e;

X is bond, -CH₂-, -O-, -S-, or -NR³-;

Z is CH or N, wherein when X is -O-, -S-, or -NR³-, then Z is CH;

R³ is hydrogen, C₁-C₃alkyl, C₁-C₃hydroxyalkyl, C₁-C₃haloalkyl, or C₃-C₆ cycloalkyl;

each A is independently N or CR⁴, wherein at least two of A are N;

each R⁴ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl;

B is N or CR⁵;

E is N or CR⁷;

F is N or CR⁸;

R⁵, R⁷, and R⁸ are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d, C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, haloalkyl, alkene, alkyne, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R⁹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R^e;

each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e; or

two R¹⁰ are taken together to form an oxo;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl,

heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^c;

each R^c is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heteroaryl; and

p is 8;

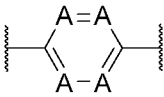
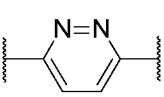
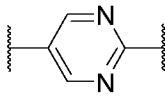
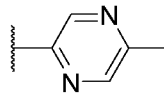
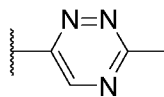
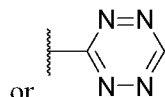
q is 0, 1, 2, or 3.

103. The method, the system, or the agent of claim 102, or a pharmaceutically acceptable salt or solvate thereof, wherein X is -CH₂-, -O-, -S-, or -NR³-; and Z is CH.

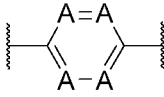
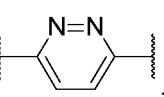
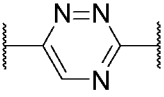
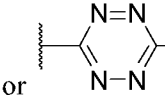
104. The method, the system, or the agent of claim 102, or a pharmaceutically acceptable salt or solvate thereof, wherein X is bond and Z is N.

105. The method, the system, or the agent of any one of claims 82-104, or a pharmaceutically acceptable salt or solvate thereof, wherein each A is independently N or CH, wherein two of A are N.

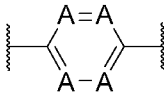
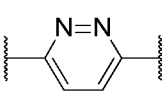
106. The method, the system, or the agent of any one of claims 82-104, or a pharmaceutically

acceptable salt or solvate thereof, wherein  is , , , , or .

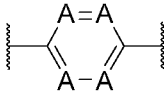
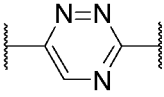
107. The method, the system, or the agent of claim 106, or a pharmaceutically acceptable salt or

solvate thereof, wherein  is , , or .

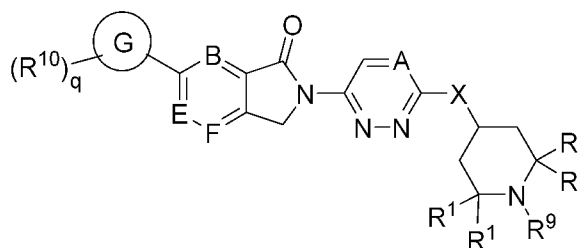
108. The method, the system, or the agent of claim 106, or a pharmaceutically acceptable salt or

solvate thereof, wherein  is .

109. The method, the system, or the agent of claim 106, or a pharmaceutically acceptable salt or

solvate thereof, wherein  is .

110. The method, the system, or the agent of claim 102, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (III'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each R¹ is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d,

C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R¹ are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R¹ are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^e;

X is -CH₂-, -O-, -S-, or -NR³-;

R³ is hydrogen, C₁-C₃alkyl, C₁-C₃hydroxyalkyl, C₁-C₃haloalkyl, or C₃-C₆cycloalkyl;

A is N or CH;

B is N or CR⁵;

E is N or CR⁷;

F is N or CR⁸;

R⁵, R⁷, and R⁸ are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -

S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d,

C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or

C₁-C₆aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R⁹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R^e;

each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e; or

two R¹⁰ are taken together to form an oxo;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

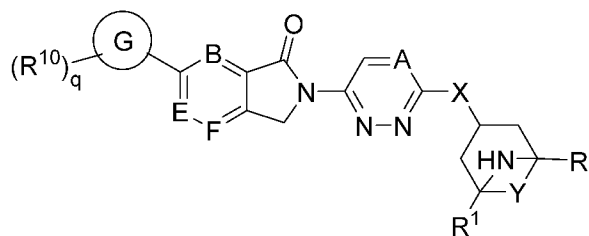
each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

q is 0, 1, 2, or 3.

111. The method, the system, or the agent of any one of claims 102-110, or a pharmaceutically acceptable salt or solvate thereof, wherein two R¹ are taken together to form a C₁-C₃alkylene or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e.

112. The method, the system, or the agent of claim 111, or a pharmaceutically acceptable salt or solvate thereof, wherein two R¹ are taken together to form a C₁-C₃alkylene.

113. The method, the system, or the agent of claim 110, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound of Formula (III') has the structure of Formula (IIIa'), or a pharmaceutically acceptable salt or solvate thereof:

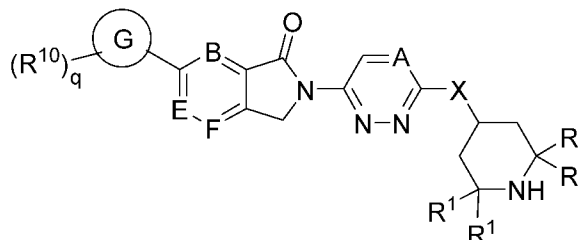


Formula (IIIa'),

wherein Y is C₁-C₃alkylene.

114. The method, the system, or the agent of claim 113, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is $-\text{CH}_2\text{CH}_2-$.

115. The method, the system, or the agent of claim 110, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound of Formula (III') has the structure of Formula (IIIb'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIb').

116. The method, the system, or the agent of claim 115, or a pharmaceutically acceptable salt or solvate thereof, wherein two R^1 are taken together to form a C_3 - C_6 cycloalkyl.

117. The method, the system, or the agent of claim 116, or a pharmaceutically acceptable salt or solvate thereof, wherein two R^1 are taken together to form a cyclopropyl.

118. The method, the system, or the agent of any one of claims 102-117, or a pharmaceutically acceptable salt or solvate thereof, each R^1 is independently hydrogen, halogen, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c .

119. The method, the system, or the agent of claim 118, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^1 is independently hydrogen, halogen, or C_1 - C_6 alkyl.

120. The method, the system, or the agent of claim 118, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^1 is independently hydrogen or methyl.

121. The method, the system, or the agent of any one of claims 102-120, or a pharmaceutically acceptable salt or solvate thereof, wherein X is $-\text{O}-$ or $-\text{NR}^3-$.

122. The method, the system, or the agent of claim 121, or a pharmaceutically acceptable salt or solvate thereof, wherein X is $-\text{O}-$.

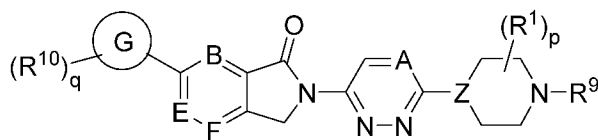
123. The method, the system, or the agent of claim 121, or a pharmaceutically acceptable salt or solvate thereof, wherein X is $-\text{NR}^3-$.

124. The method, the system, or the agent of claim 123, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen, C_1 - C_3 alkyl or C_3 - C_6 cycloalkyl.

125. The method, the system, or the agent of claim 124, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen, methyl, ethyl, or cyclopropyl.

126. The method, the system, or the agent of claim 124, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen or methyl.

127. The method, the system, or the agent of claim 102, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the structure of Formula (IV'), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV'),

wherein,

ring G is a 5 to 10-membered heteroaryl;

each R^1 is independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -NR^cR^d,

C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, or aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R^1 are taken together to form an oxo; or

two R^1 are taken together to form a bond, C₁-C₃alkylene, or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e; or

two R^1 are taken together to form a C₃-C₆cycloalkyl or 4 to 6-membered heterocycloalkyl, each of which is optionally substituted with 1 to 4 substituents independently selected from R^e;

Z is CH or N;

A is N or CH;

B is N or CR⁵;

E is N or CR⁷;

F is N or CR⁸;

R⁵, R⁷, and R⁸ are each independently hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, -SH, -SR^a, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂NR^cR^d, -NR^cR^d, -C(=O)R^a, -C(=O)OR^b, -C(=O)NR^cR^d,

C₁-C₆alkyl, C₂-C₆alkene, C₂-C₆alkyne, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or

C₁-C₆aminoalkyl; wherein each of the alkyl, alkene, alkyne, haloalkyl, and hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R⁹ is hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered

heterocycloalkyl, wherein each alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is independently substituted with 1 to 4 substituents selected from R^e;

each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e; or

two R¹⁰ are taken together to form an oxo;

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl,

cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^e is independently halogen, oxo, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -S(=O)₂NH₂, -S(=O)₂NHCH₃, -S(=O)₂N(CH₃)₂, -C(=O)NH₂, -C(=O)NHCH₃, -C(=O)N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl;

p is 8; and

q is 0, 1, 2, or 3.

128. The method, the system, or the agent of claim 127, or a pharmaceutically acceptable salt or solvate thereof, wherein Z is CH.

129. The method, the system, or the agent of claim 127, or a pharmaceutically acceptable salt or solvate thereof, wherein Z is N.

130. The method, the system, or the agent of any one of claims 127-129, or a pharmaceutically acceptable salt or solvate thereof, wherein two R¹ are taken together to form a C₁-C₃alkylene or C₁-C₃heteroalkylene, wherein the alkylene or heteroalkylene is optionally substituted with 1 to 4 substituents independently selected from R^e.

131. The method, the system, or the agent of claim 130, or a pharmaceutically acceptable salt or solvate thereof, wherein two R¹ are taken together to form a C₁-C₃alkylene.

132. The method, the system, or the agent of any one of claims 127-129, or a pharmaceutically acceptable salt or solvate thereof, wherein two R¹ are taken together to form a C₃-C₆cycloalkyl.

133. The method, the system, or the agent of any one of claims 127-129, or a pharmaceutically acceptable salt or solvate thereof, each R¹ is independently hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl, wherein each of the alkyl, haloalkyl, or hydroxyalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e.

134. The method, the system, or the agent of claim 133, or a pharmaceutically acceptable salt or solvate thereof, wherein each R¹ is independently hydrogen, halogen, or C₁-C₆alkyl.

135. The method, the system, or the agent of claim 133, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^1 is independently hydrogen or methyl.
136. The method, the system, or the agent of any one of claims 102-135, or a pharmaceutically acceptable salt or solvate thereof, wherein A is N.
137. The method, the system, or the agent of any one of claims 102-135, or a pharmaceutically acceptable salt or solvate thereof, wherein A is CH.
138. The method, the system, or the agent of any one of claims 82-137, or a pharmaceutically acceptable salt or solvate thereof, wherein B is CR^5 .
139. The method, the system, or the agent of any one of claims 82-137, or a pharmaceutically acceptable salt or solvate thereof, wherein B is N.
140. The method, the system, or the agent of any one of claims 82-138, or a pharmaceutically acceptable salt or solvate thereof, wherein R^5 is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c.
141. The method, the system, or the agent of claim 140, or a pharmaceutically acceptable salt or solvate thereof, wherein R^5 is hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl.
142. The method, the system, or the agent of any one of claims 82-137, or a pharmaceutically acceptable salt or solvate thereof wherein B is CH.
143. The method, the system, or the agent of any one of claims 82-142, or a pharmaceutically acceptable salt or solvate thereof, wherein F is CR^8 .
144. The method, the system, or the agent of any one of claims 82-142, or a pharmaceutically acceptable salt or solvate thereof, wherein F is N.
145. The method, the system, or the agent of any one of claims 82-143, or a pharmaceutically acceptable salt or solvate thereof, wherein R^8 is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, haloalkyl, hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^c.
146. The method, the system, or the agent of claim 145, or a pharmaceutically acceptable salt or solvate thereof, wherein R^8 is hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl.
147. The method, the system, or the agent of any one of claims 82-146, or a pharmaceutically acceptable salt or solvate thereof, wherein E is CR^7 .
148. The method, the system, or the agent of any one of claims 82-146, or a pharmaceutically acceptable salt or solvate thereof, wherein E is N.
149. The method, the system, or the agent of any one of claims 82-147, or a pharmaceutically acceptable salt or solvate thereof, wherein R^7 is hydrogen, halogen, -CN, -NO₂, -OH, -OR^a, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, or C₁-C₆aminoalkyl; wherein each of the alkyl, haloalkyl,

hydroxyalkyl, and aminoalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e.

150. The method, the system, or the agent of claim 149, or a pharmaceutically acceptable salt or solvate thereof, wherein R⁷ is hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl.

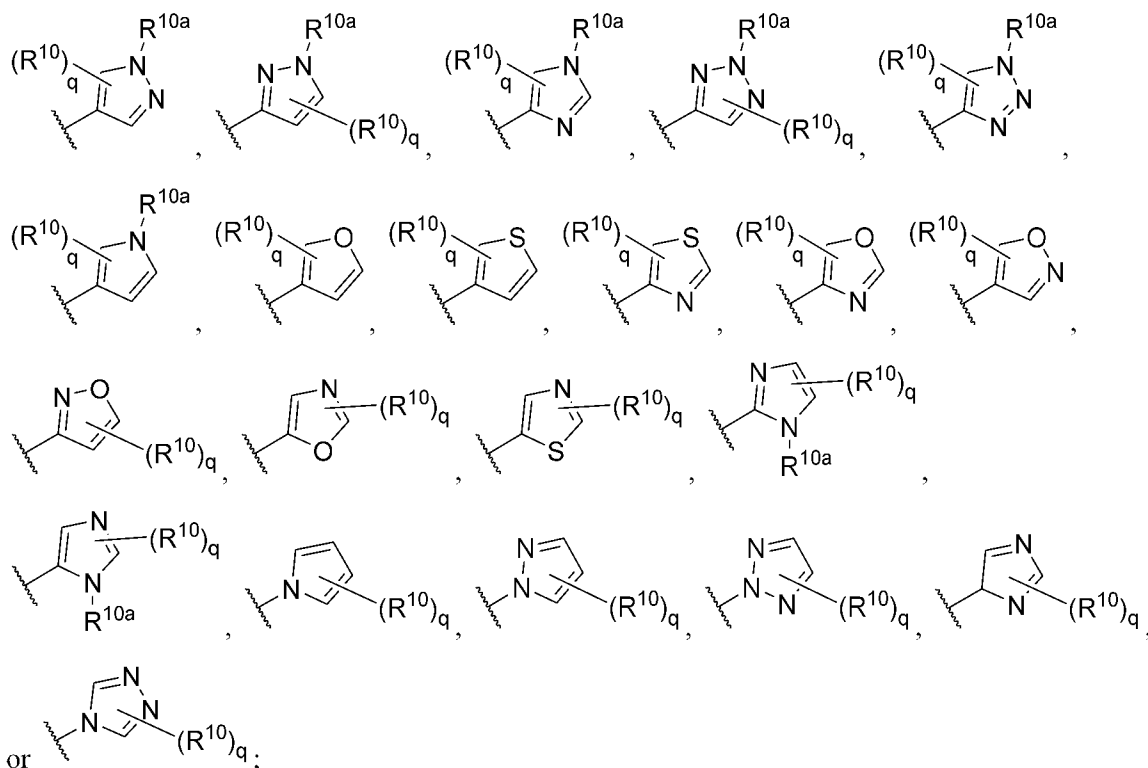
151. The method, the system, or the agent of any one of claims 82-147, or a pharmaceutically acceptable salt or solvate thereof, wherein E is CH.

152. The method, the system, or the agent of any one of claims 102-151, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G a 5 to 6-membered heteroaryl optional substituted with 1 or 4 substituents selected from R^e.

153. The method, the system, or the agent of claim 152, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is a 5-membered heteroaryl optional substituted with 1 or 2 substituents selected from R^e.

154. The method, the system, or the agent of claim 153, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is pyrrole, imidazole, triazole, tetrazole, thiophene, oxazole, thiazole, or thiadiazole.

155. The method, the system, or the agent of any one of claims 102-151, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is:



wherein,

each R¹⁰ is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^e;

each R^{10a} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^c ; and

q is 0, 1, 2, or 3.

156. The method, the system, or the agent of claim 155, or a pharmaceutically acceptable salt or solvate thereof, wherein

each R^{10} is independently halogen, $-CN$, $-NO_2$, $-OH$, $-OR^a$, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, or 4 to 6-membered heterocycloalkyl;

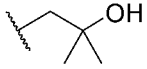
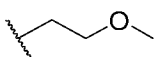
each R^{10a} is independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, or 4 to 6-membered heterocycloalkyl; and

q is 0, 1, or 2.

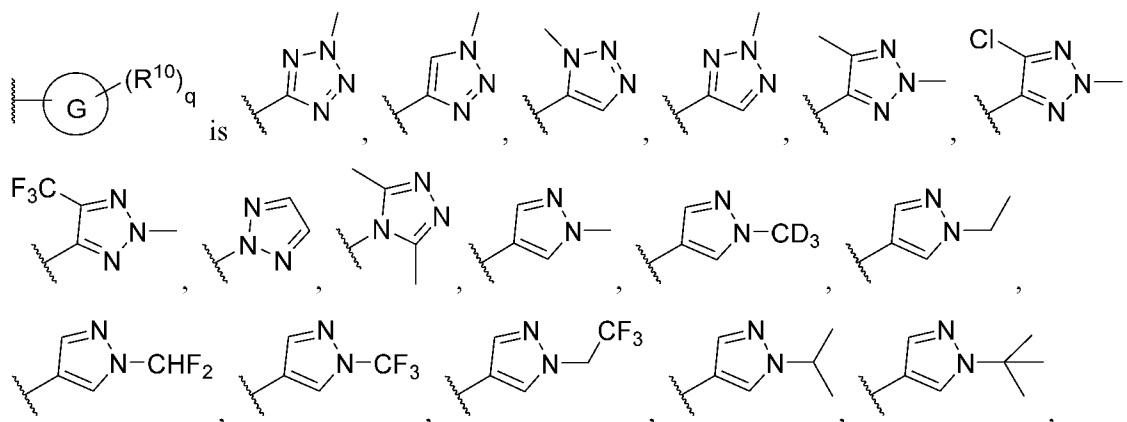
157. The method, the system, or the agent of claim 155 or 156, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{10} is independently $-F$, $-Cl$, methyl, ethyl, $-OCH_3$, $-CF_3$, $-CHF_2$, or $-CH_2F$.

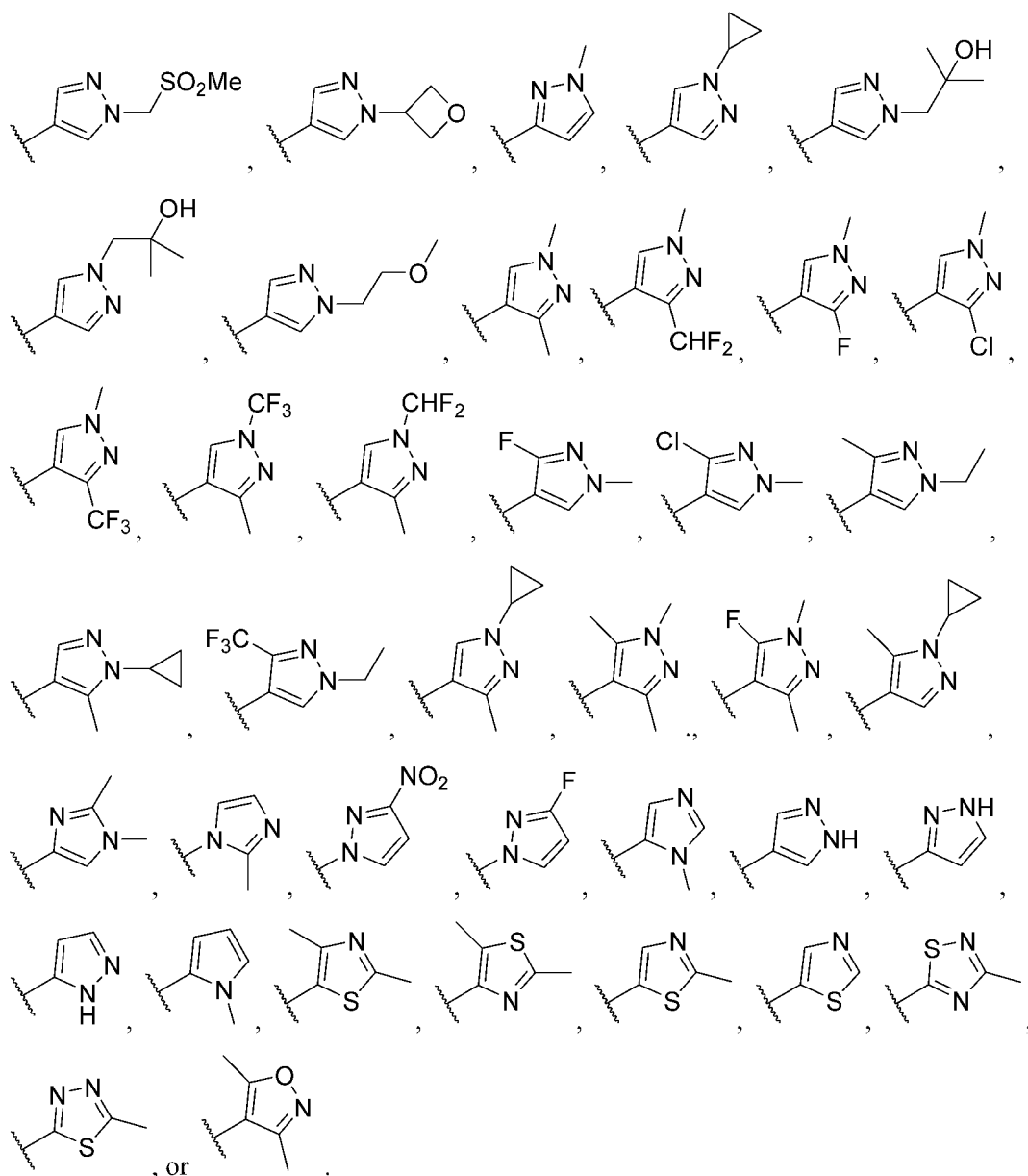
158. The method, the system, or the agent of any one of claims 155-157, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{10a} is independently C_1 - C_6 alkyl which is optionally substituted with 1 to 4-substituents independently selected from halogen, $-OH$, $-CH_2S(=O)_2CH_3$, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, and C_1 - C_6 hydroxyalkyl.

159. The method, the system, or the agent of any one of claims 155-158, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{10a} is independently hydrogen, methyl, ethyl, isopropyl,

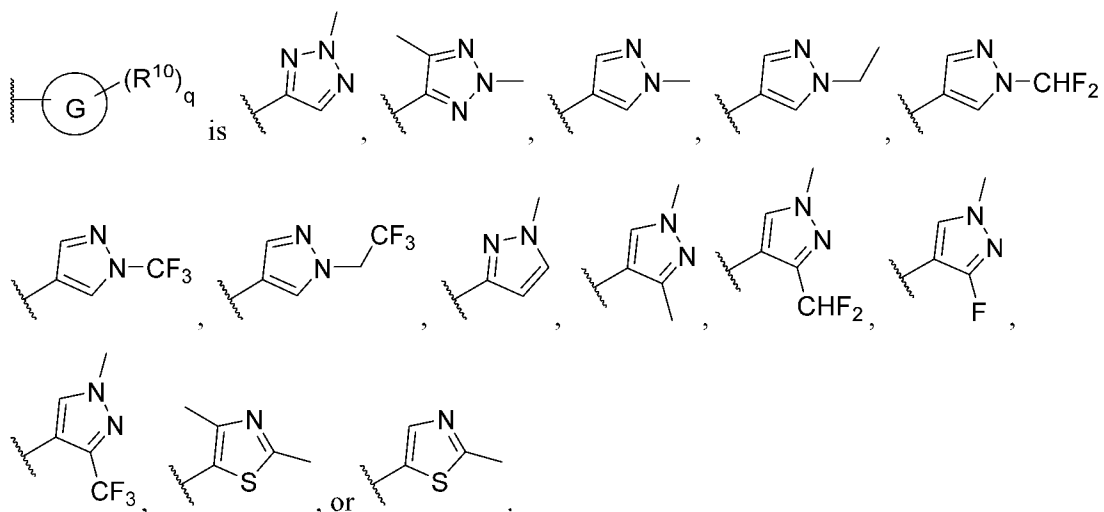
tert-butyl, $-CD_3$, $-CF_3$, CHF_2 , CH_2F , $-CH_2CF_3$, $-CH_2SO_2CH_3$, cyclopropyl, oxetanyl, , , or .

160. The method, the system, or the agent of any one of claims 102-151, or a pharmaceutically acceptable salt or solvate thereof, wherein:





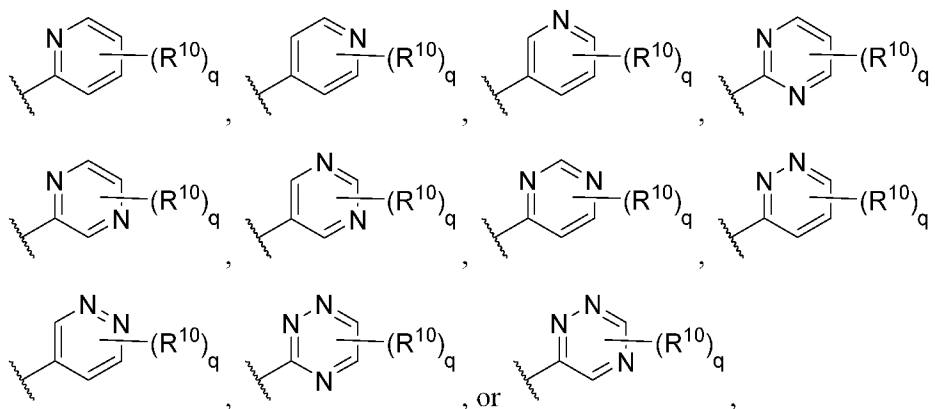
161. The method, the system, or the agent of claim 160, or a pharmaceutically acceptable salt or solvate thereof, wherein



162. The method, the system, or the agent of claim 152, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is a 6-membered heteroaryl optional substituted with 1 to 4 substituents selected from R^c .

163. The method, the system, or the agent of claim 162, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is pyridine, pyrimidine, or triazine.

164. The method, the system, or the agent of any one of claims 102-151, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is:



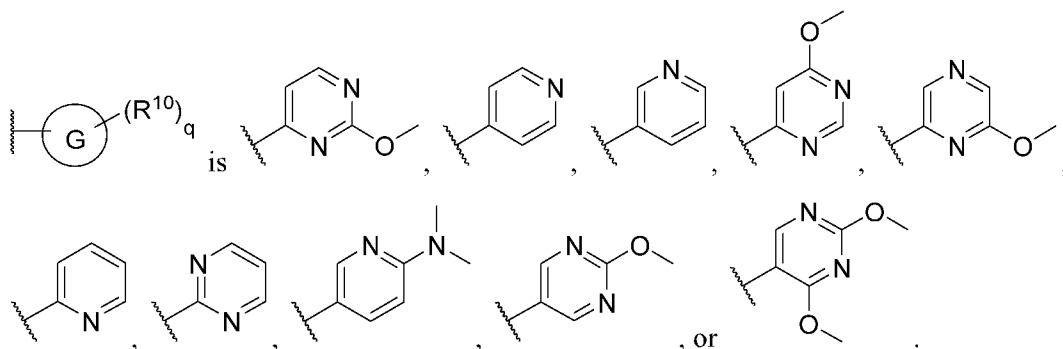
wherein,

each R^{10} is independently halogen, -CN, -NO₂, -OH, -OR^a, -NR^cR^d, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₁-C₆aminoalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl, wherein each of the alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, cycloalkyl and heterocycloalkyl is optionally substituted with 1 to 4-substituents independently selected from R^c ; and

q is 0, 1, 2, or 3.

165. The method, the system, or the agent of claim 164, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{10} is independently -OCH₃ or -N(CH₃)₂; and q is 0, 1, or 2.

166. The method, the system, or the agent of claim 160, or a pharmaceutically acceptable salt thereof, wherein



167. The method, the system, or the agent of any one of claims 102-151, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is a 9 or 10-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S; and optional substituted with 1 to 4 substituents selected from R^c .

168. The method, the system, or the agent of claim 167, or a pharmaceutically acceptable salt or solvate thereof, wherein ring G is a 9-membered bicyclic heteroaryl comprising 1 to 3 heteroatoms selected from N; and optional substituted with 1 to 4 substituents selected from R^c.

169. The method, the system, or the agent of any one of claims 82-168, or a pharmaceutically acceptable salt or solvate thereof, wherein:

each R^a is independently C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆hydroxyalkyl, wherein each of the alkyl, haloalkyl, and hydroxyalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e;

each R^b is independently hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, or C₁-C₆hydroxyalkyl, wherein each of the alkyl, haloalkyl, and hydroxyalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e; and

R^c and R^d are each independently hydrogen, C₁-C₆alkyl, or C₁-C₆haloalkyl, wherein each of the alkyl, and haloalkyl is optionally substituted with 1 to 4 substituents independently selected from R^e.

170. The method, the system, or the agent of claim 169, or a pharmaceutically acceptable salt or solvate thereof, wherein:

each R^a is independently C₁-C₆alkyl;

each R^b is independently hydrogen or C₁-C₆alkyl; and

R^c and R^d are each independently hydrogen or C₁-C₆alkyl.

171. The method, the system, or the agent of claim 170, or a pharmaceutically acceptable salt or solvate thereof, wherein:

each R^a is independently methyl, ethyl, isopropyl, or tert-butyl;

each R^b is independently hydrogen, methyl or ethyl; and

R^c and R^d are each independently hydrogen, methyl, or ethyl.

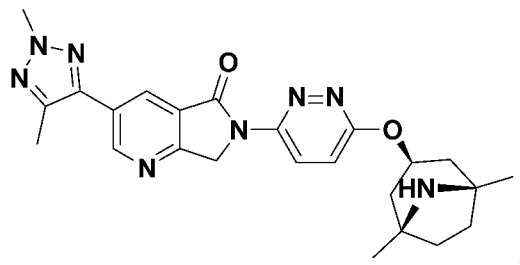
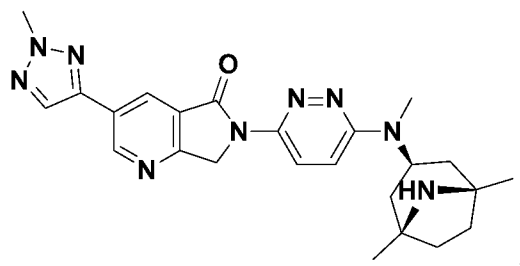
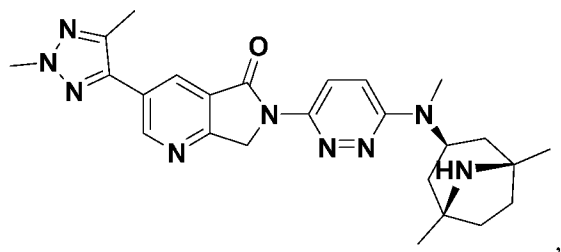
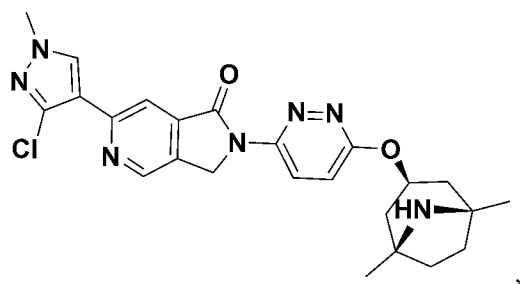
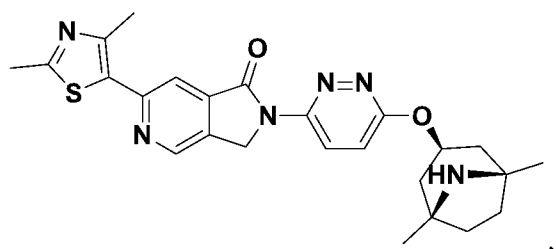
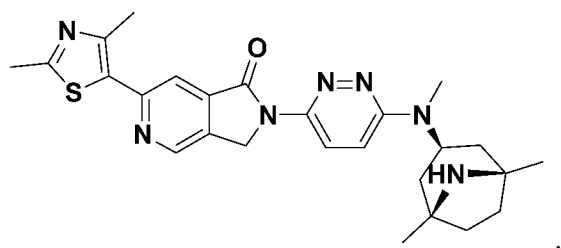
172. The method, the system, or the agent of any one of claims 82-171, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^e is independently halogen, -CN, -OH, -S(=O)CH₃, -S(=O)₂CH₃, -CH₂S(=O)₂CH₃, -NH₂, -NHCH₃, -N(CH₃)₂, -C(=O)CH₃, -C(=O)OH, -C(=O)OCH₃, C₁-C₆alkyl, C₁-C₆alkoxy, C₁-C₆haloalkyl, C₁-C₆hydroxyalkyl, C₃-C₆cycloalkyl, or 4 to 6-membered heterocycloalkyl.

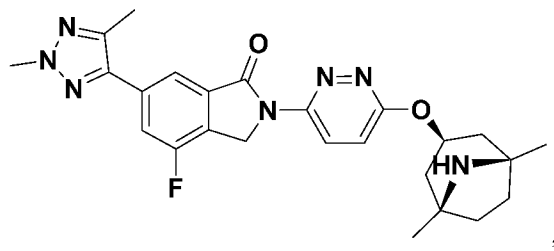
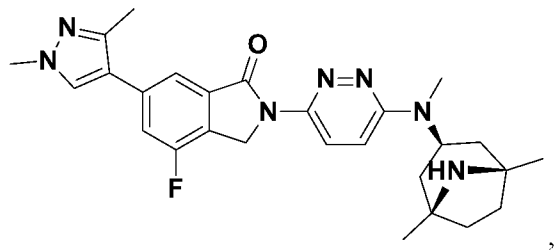
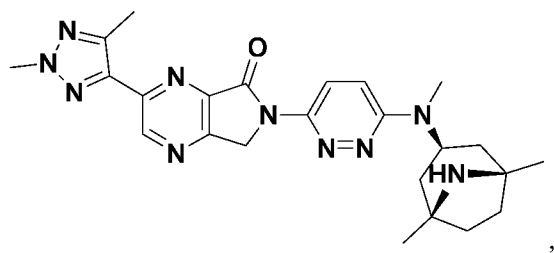
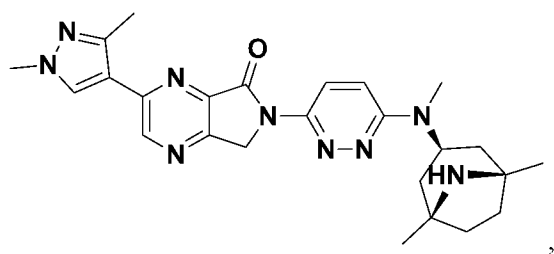
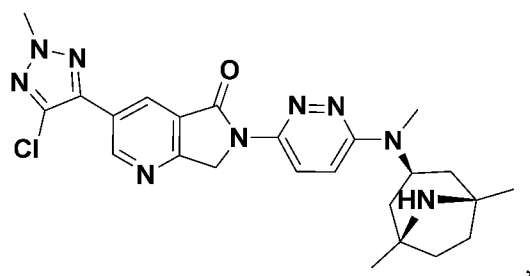
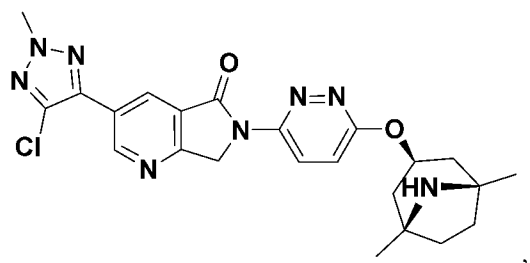
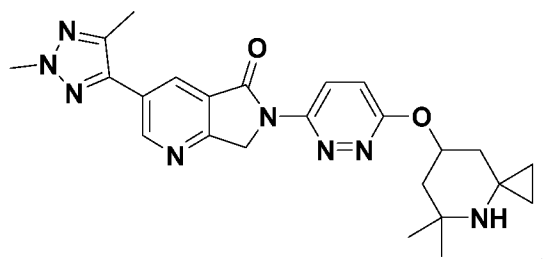
173. The method, the system, or the agent of claim 172, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^e is independently -F, -Cl, -OH, -CH₂S(=O)₂CH₃, methyl, ethyl, isopropyl, tertbutyl, -OCH₃, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or azetidine, oxytane, piperidine, piperazine, or morpholine.

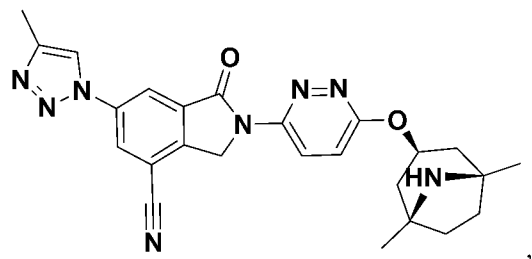
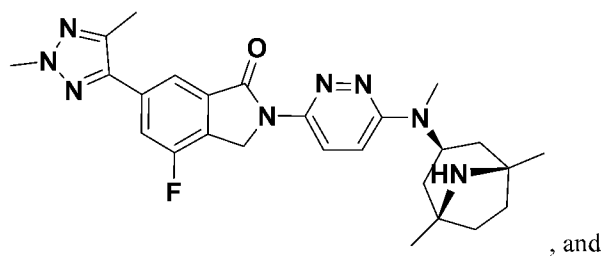
174. The method, the system, or the agent of claim 171, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^e is independently -F, -OH, -CF₃, -CHF₂, -OCH₃, or methyl.

175. The method, the system, or the agent of any one of claims 82-174, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is selected from a compound of **Table 3A**, **Table 3B**, **Table 3C**, **Table 4**, or **Table 5**, or a pharmaceutically acceptable salt or solvate thereof.

176. The method, the system, or the agent of any one of claims 82-175, wherein the compound is selected from the group consisting of:







or a pharmaceutically acceptable salt or solvate thereof.

177. The method, the system, or the agent of any one of claims 82-175, wherein the compound is provided in a pharmaceutical composition comprising a compound of any one of claims 82-175, or a pharmaceutically acceptable salt or solvate thereof; and a pharmaceutically acceptable excipient.

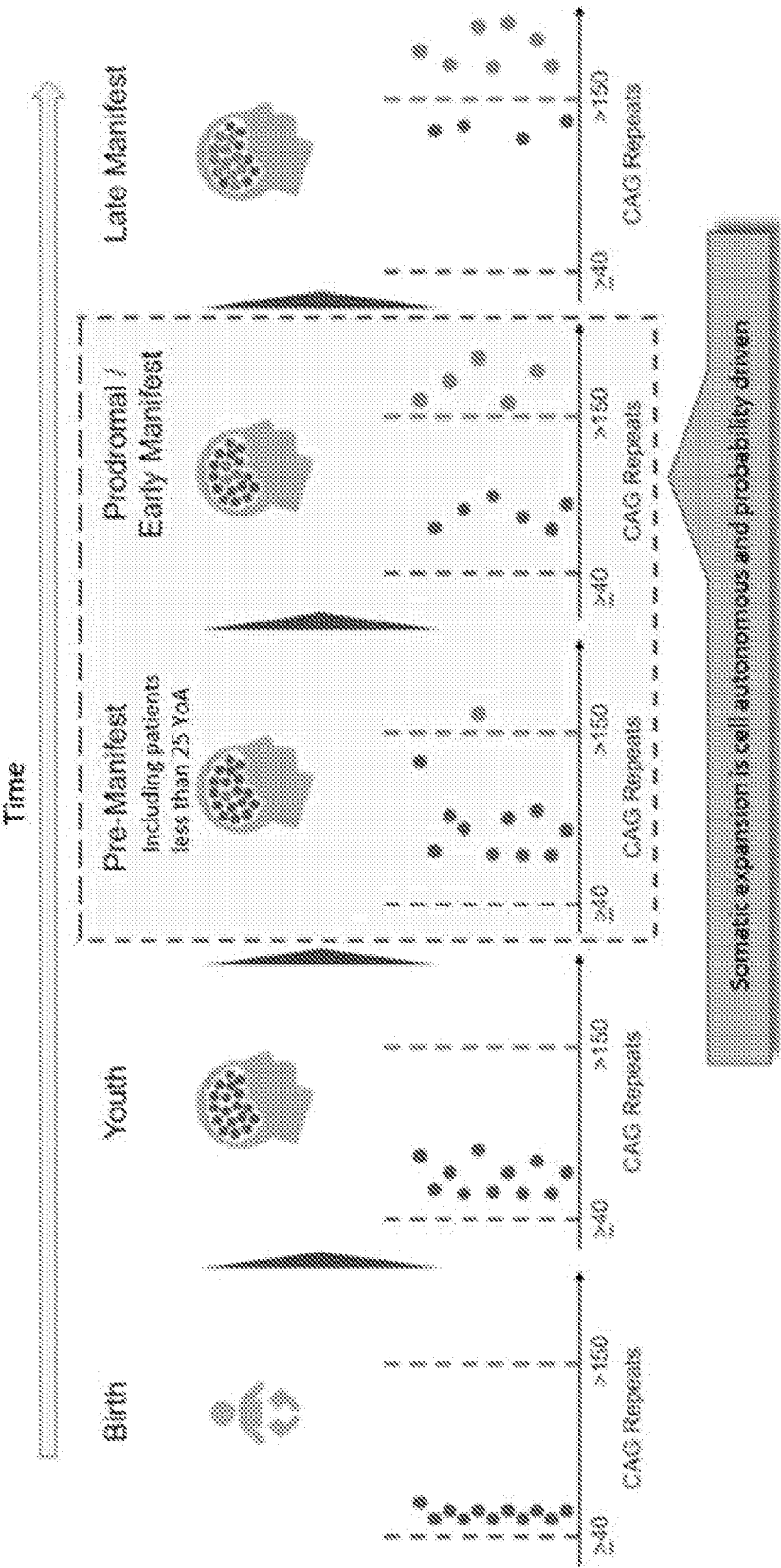


FIG. 1A

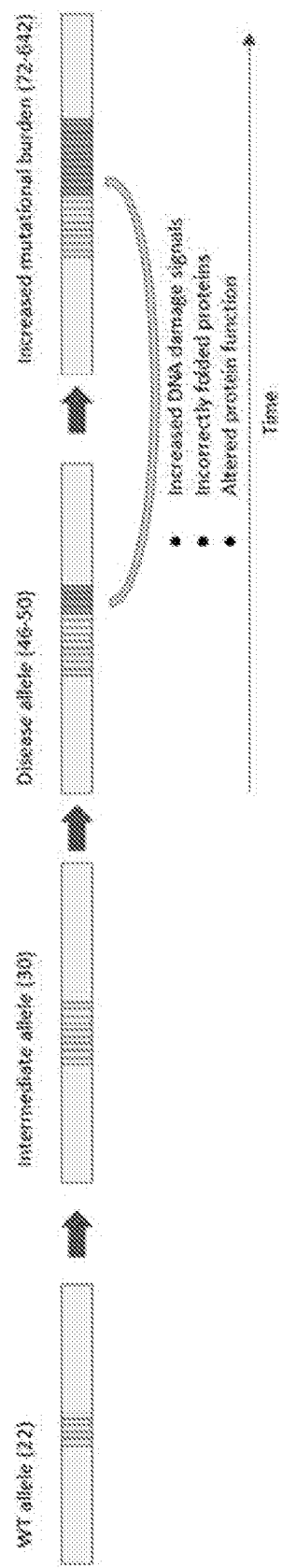


FIG. 1B

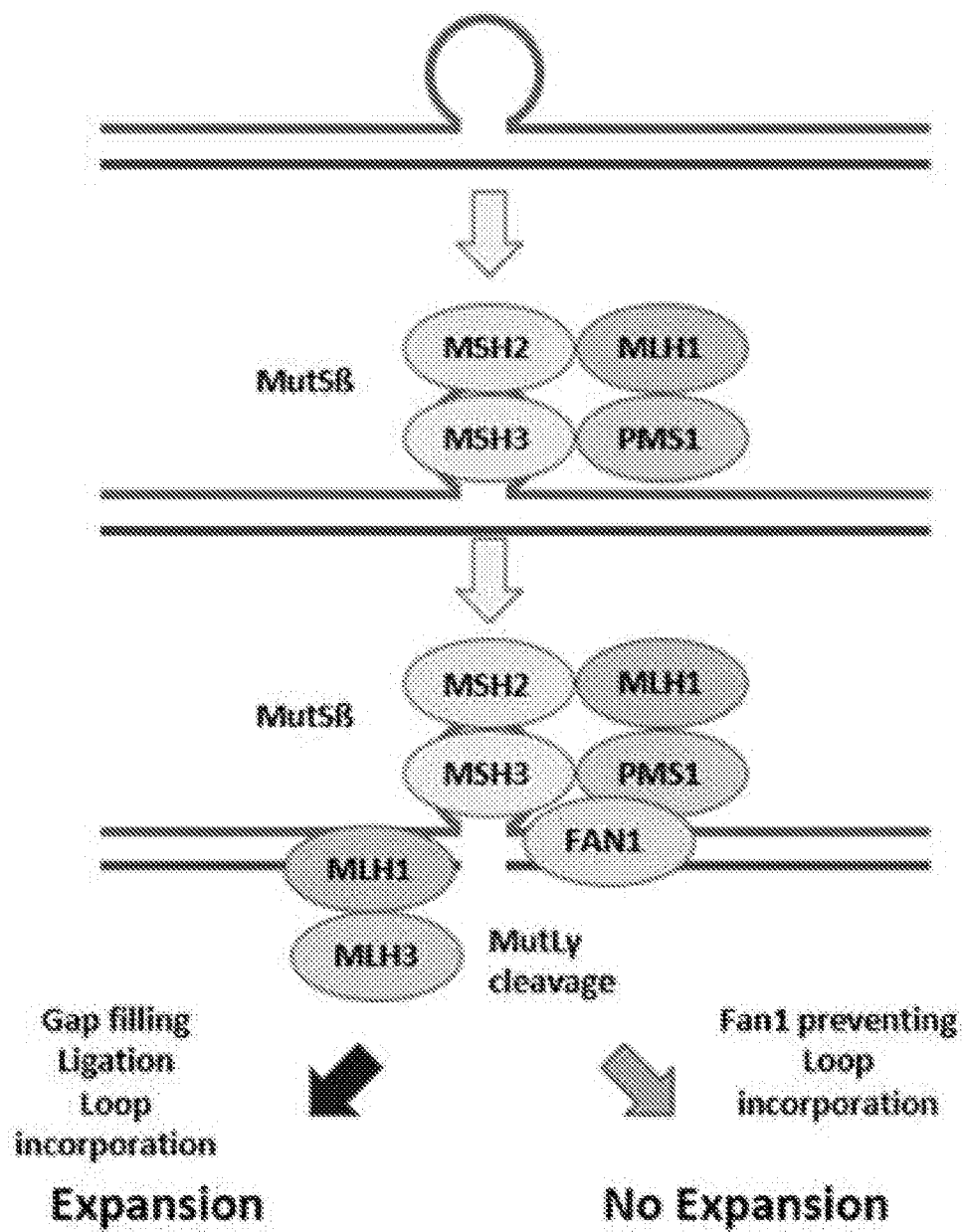


FIG. 2

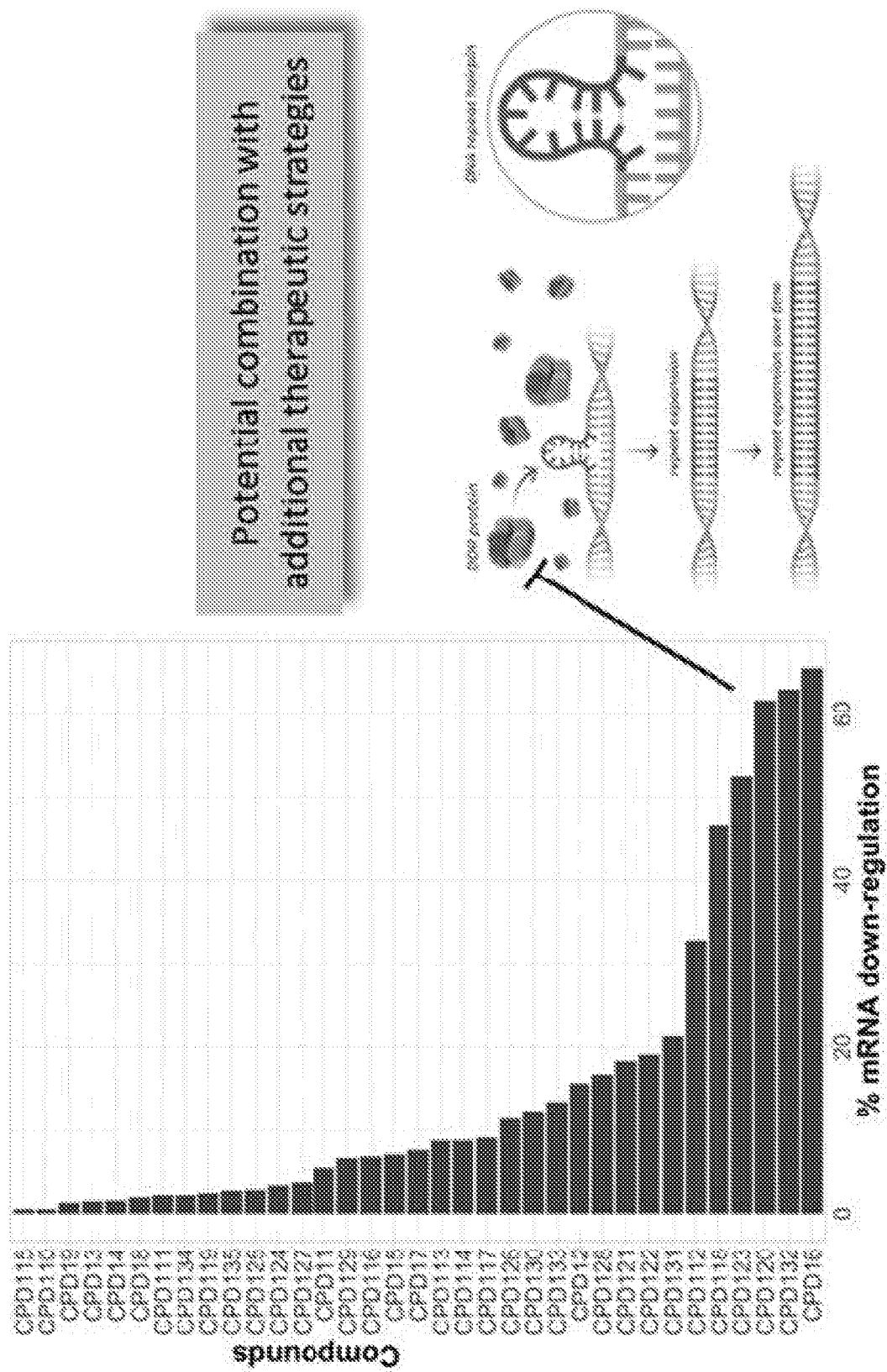


FIG. 3

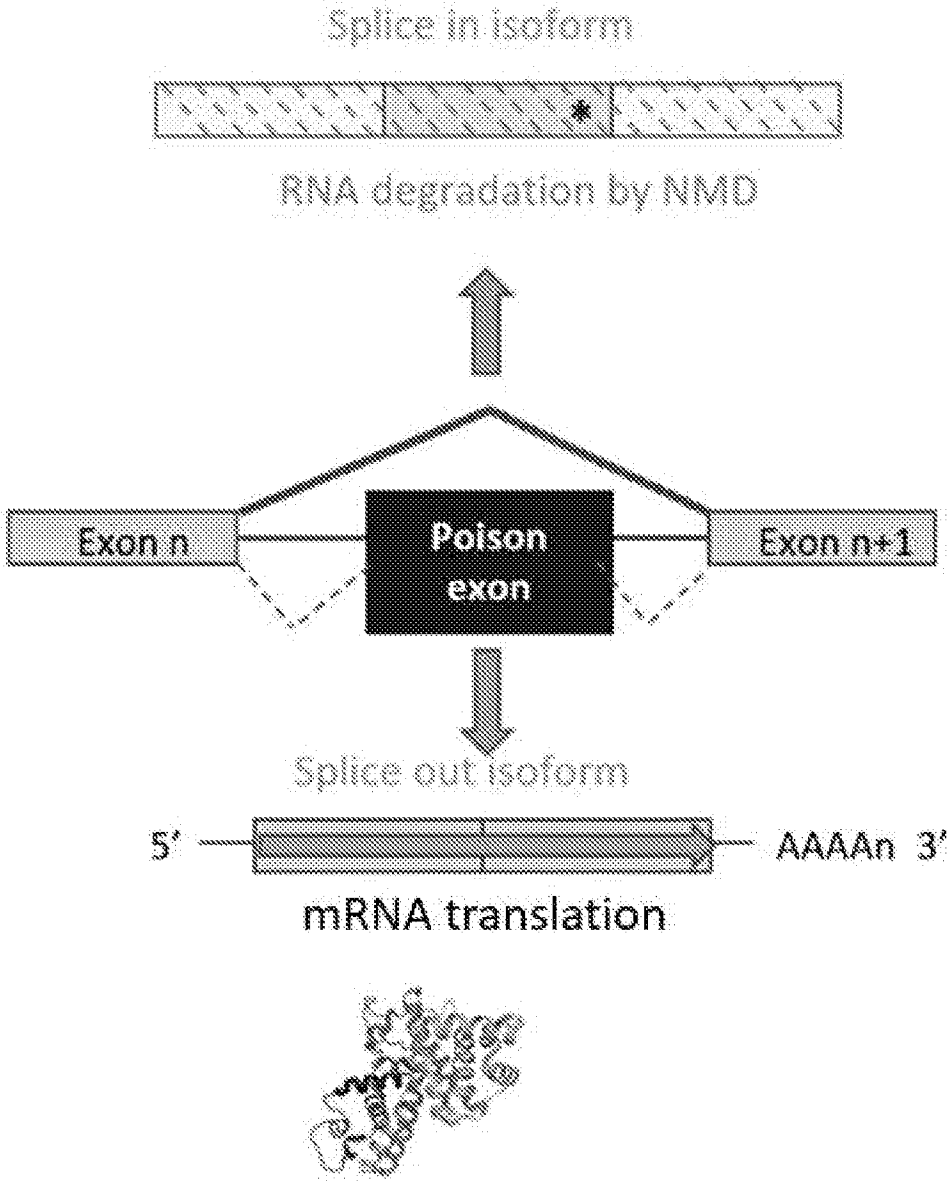
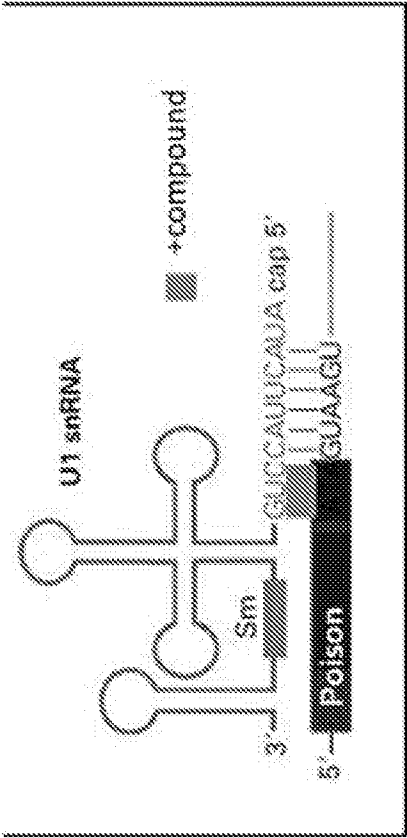


FIG. 4

Compound enhances U1 binding, increases splicing of poison exon and leads to RNA degradation by NMD



Expected splicing and RNA expression changes for targets regulated by compound
Cpd increases poison exon exp and decreases total RNA due to e.g. NMD, addition of CHX* rescues NMD

Activity	Effective Cmpd vs DMSO	Effective Cmpd + CHX vs Effective Cmpd
Poison exon expression (log2FC)	↑	↑↑
Target RNA expression	↓	↑

*CHX: translation inhibitor to rescue NMD (nonsense mediated decay)

FIG. 5

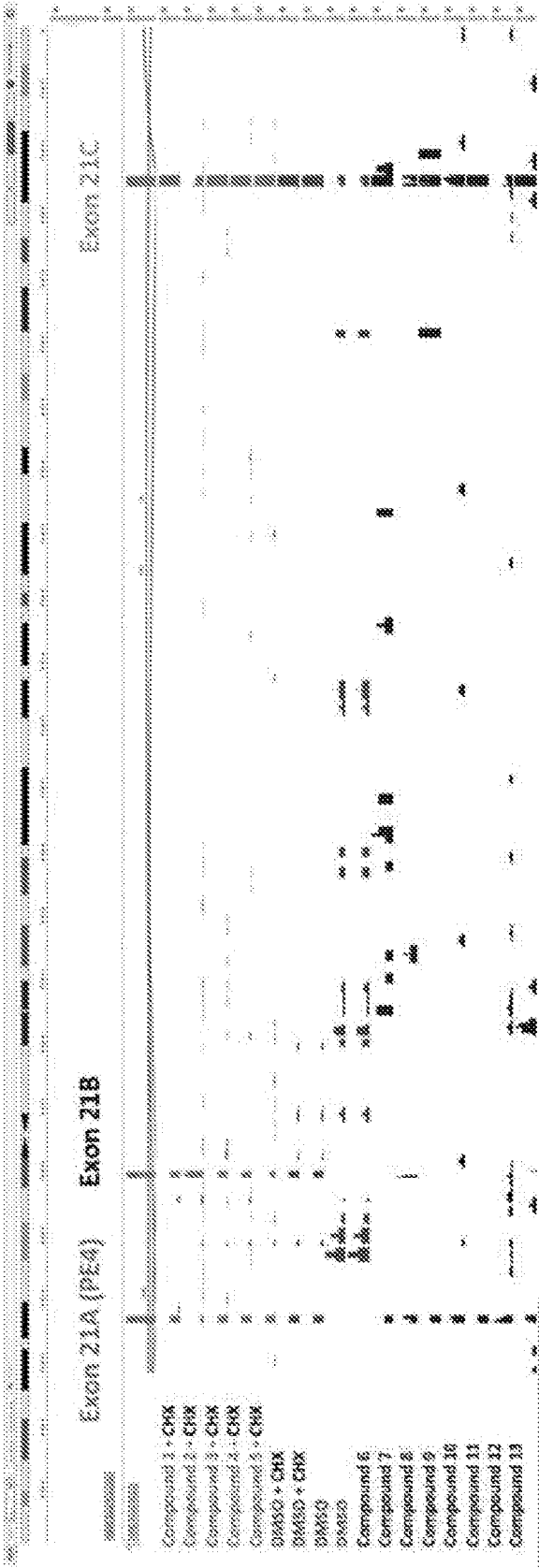


FIG. 6

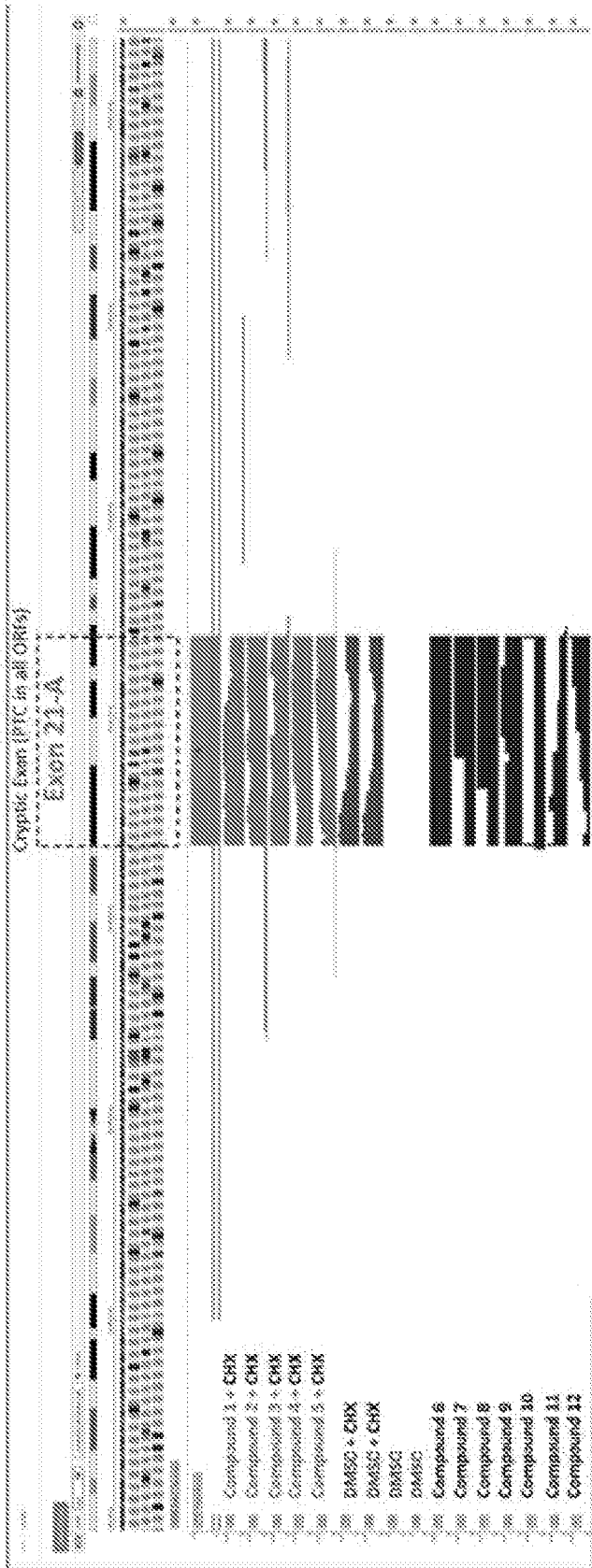


FIG. 7

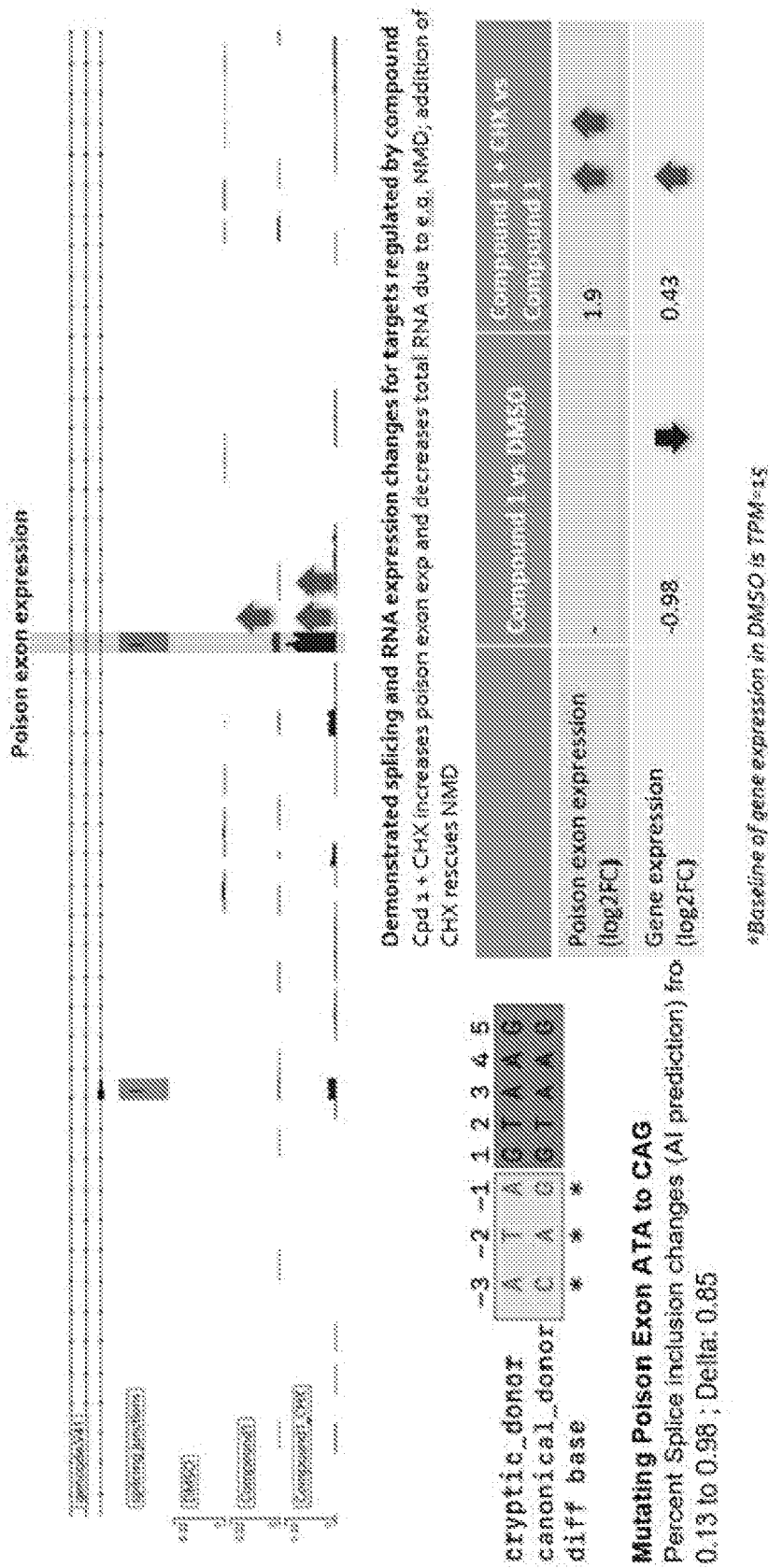


FIG. 8

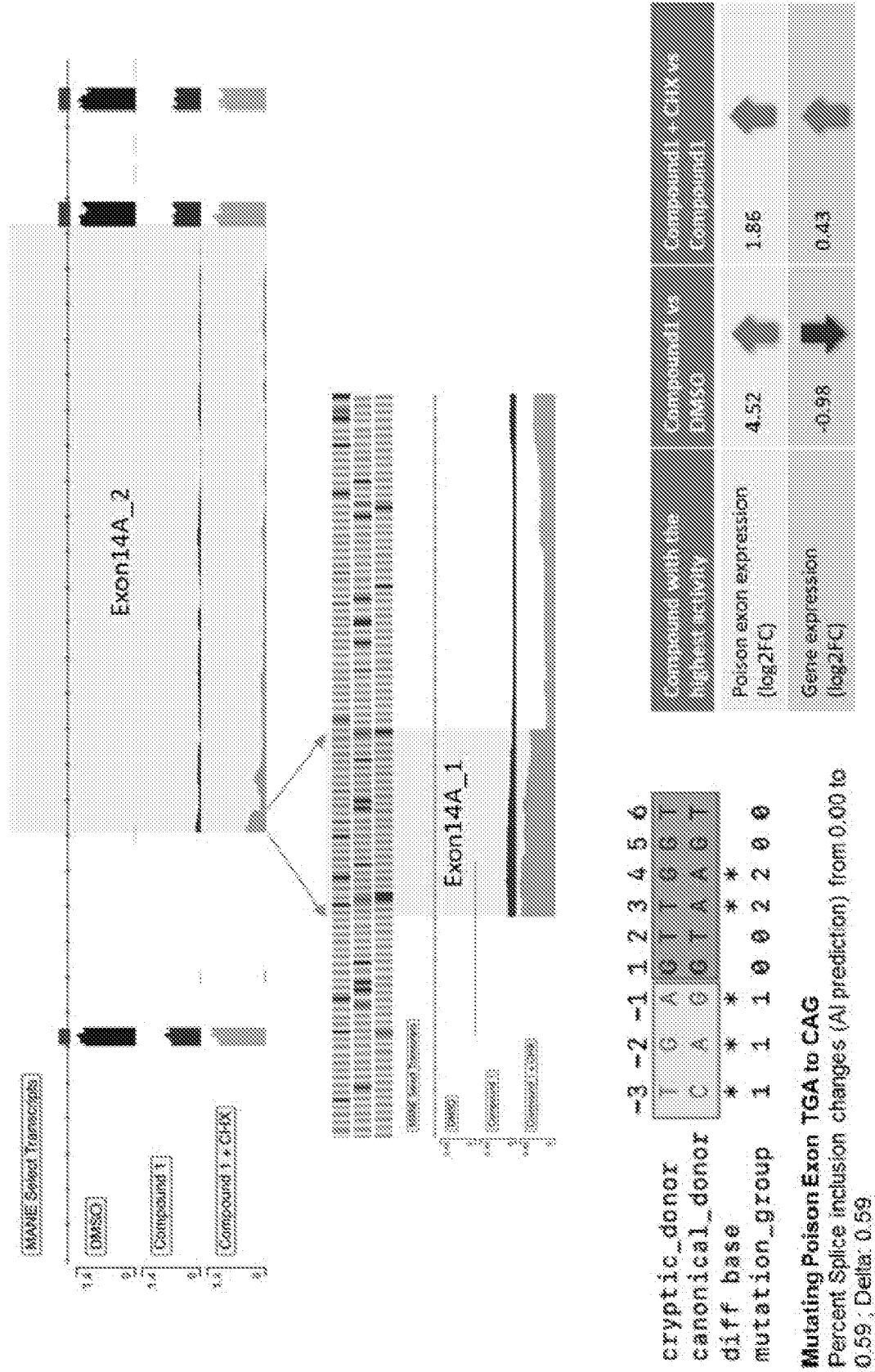


FIG. 9

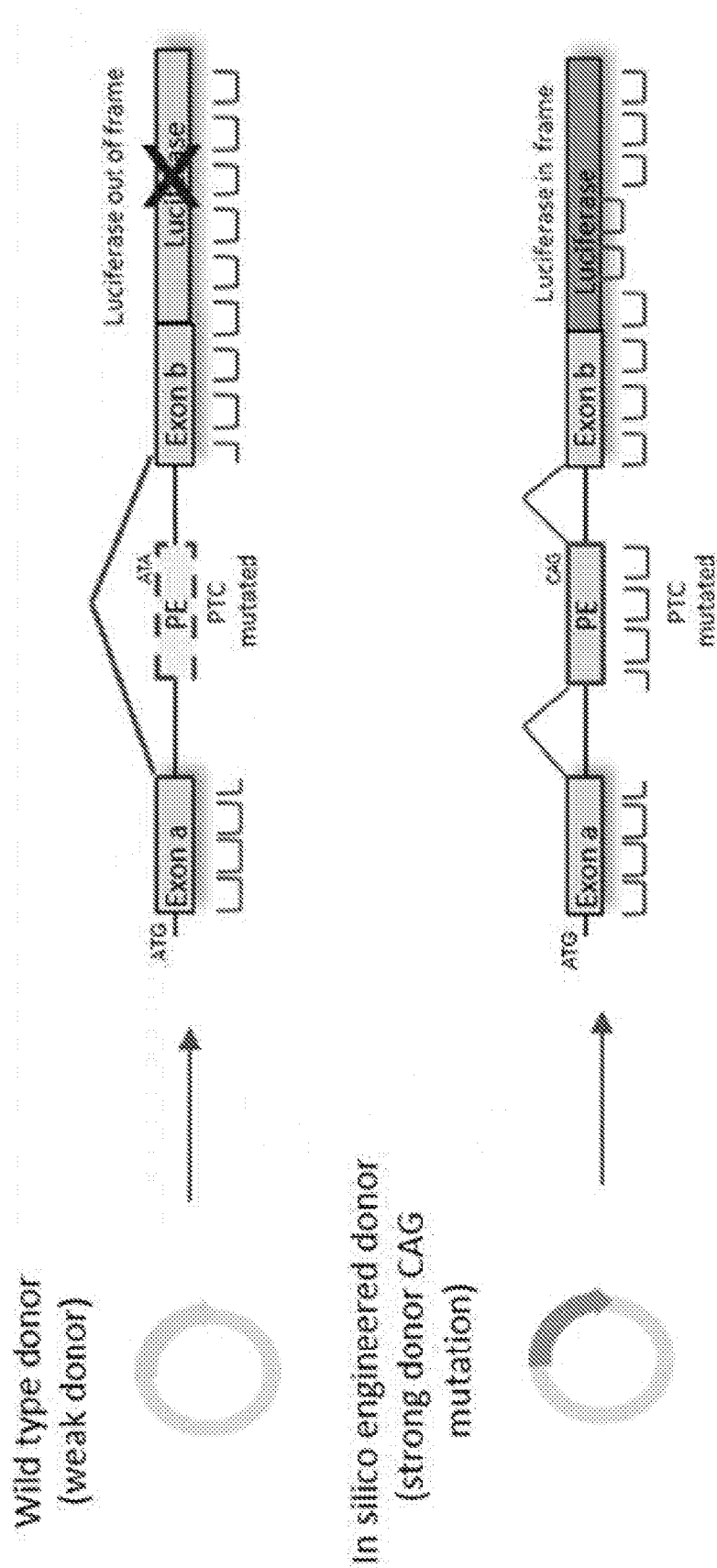


FIG. 10A

Minigene PCR

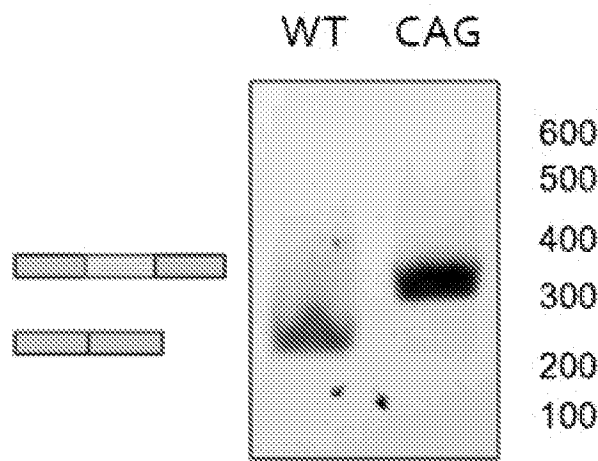


FIG. 10B

Minigene luciferase assay

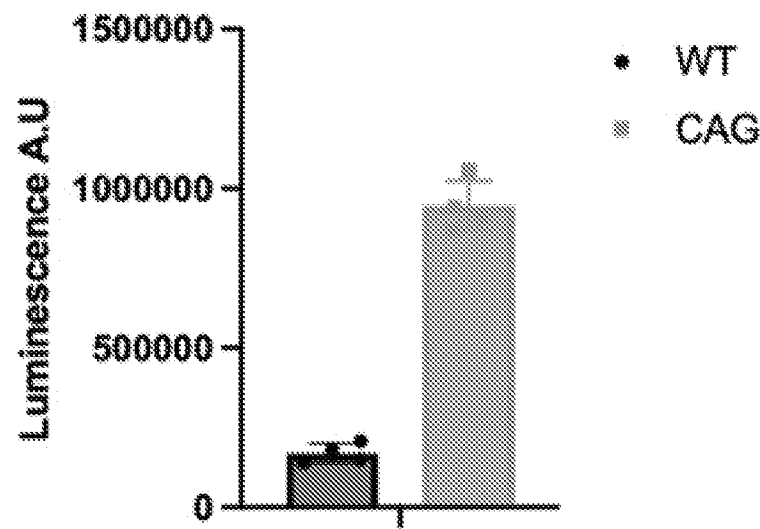


FIG. 10C

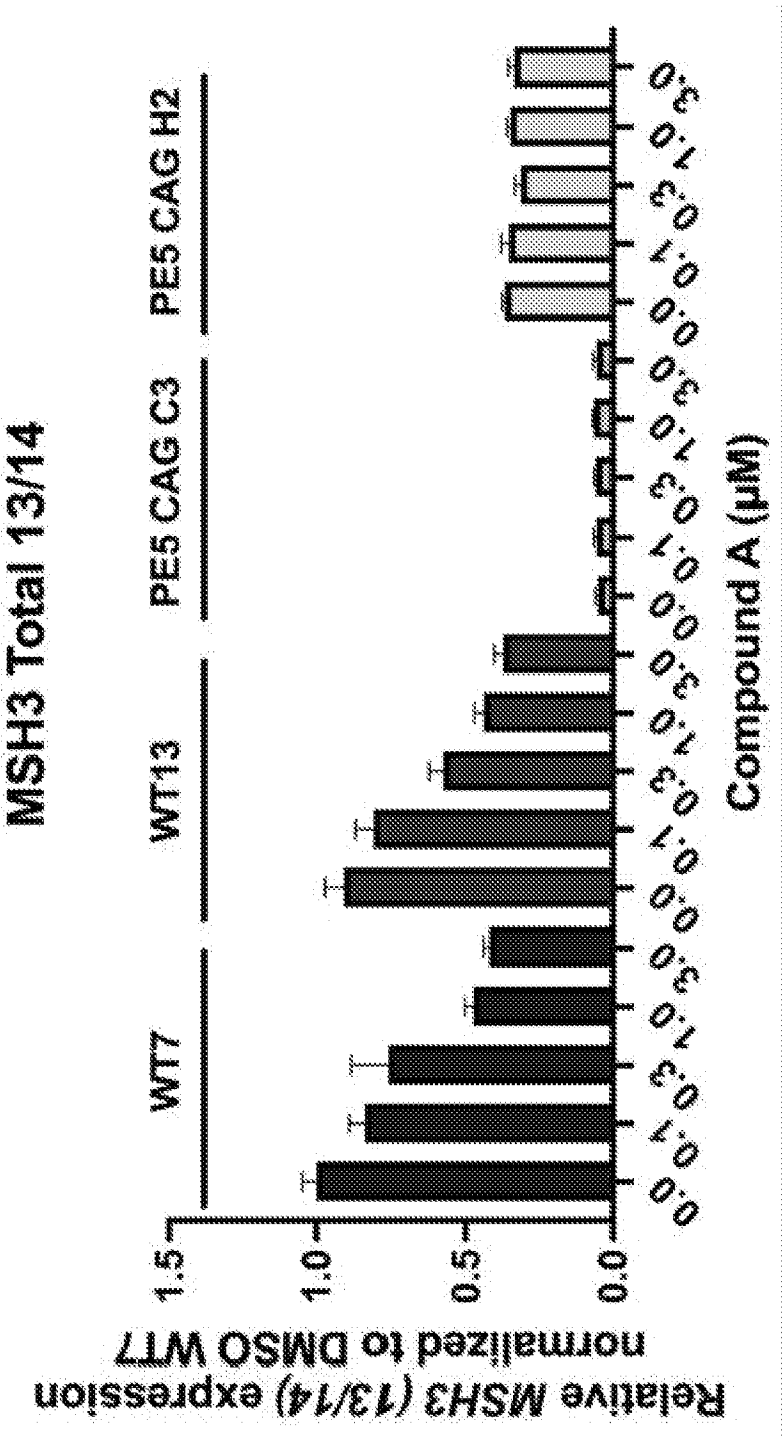


FIG. 11A

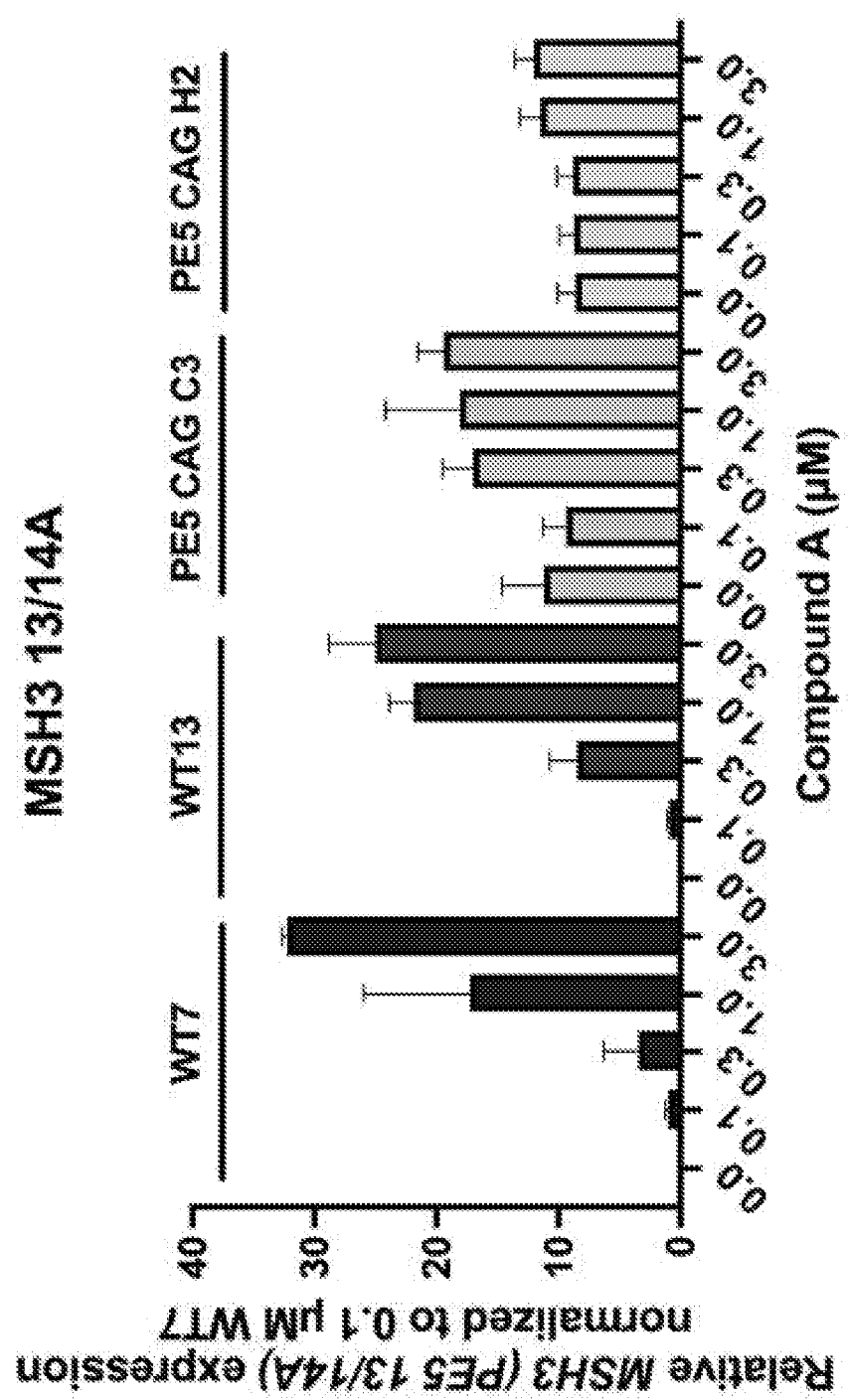


FIG. 11B

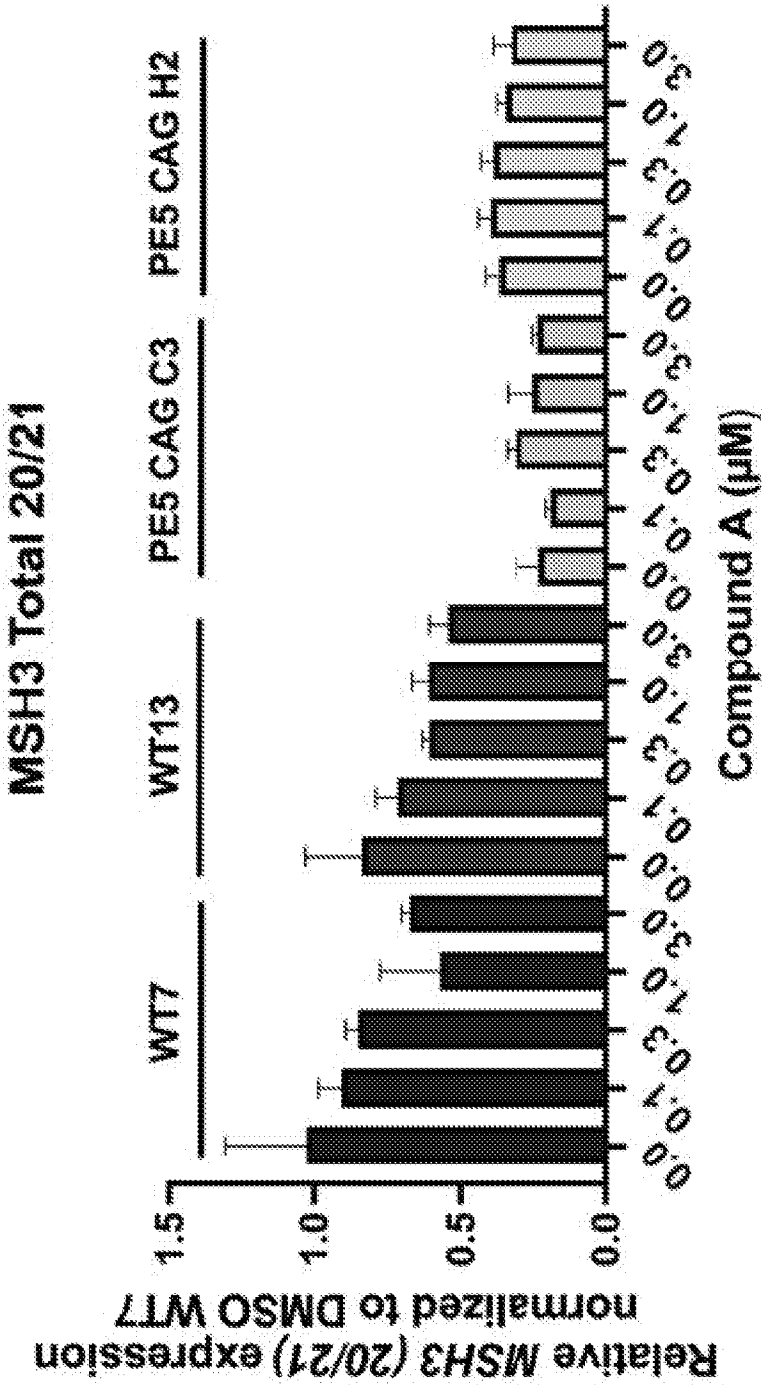


FIG. 12A

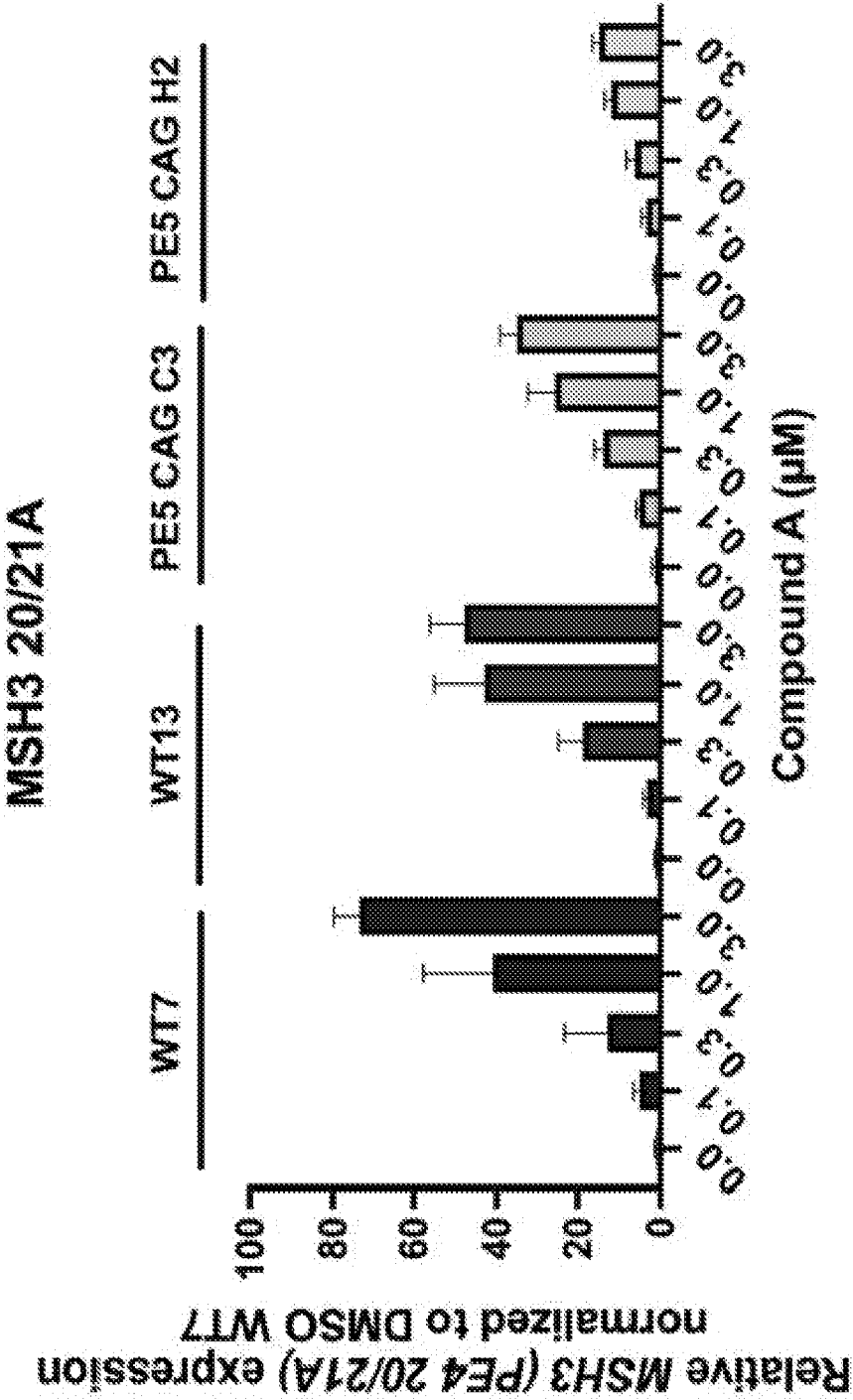


FIG. 12B

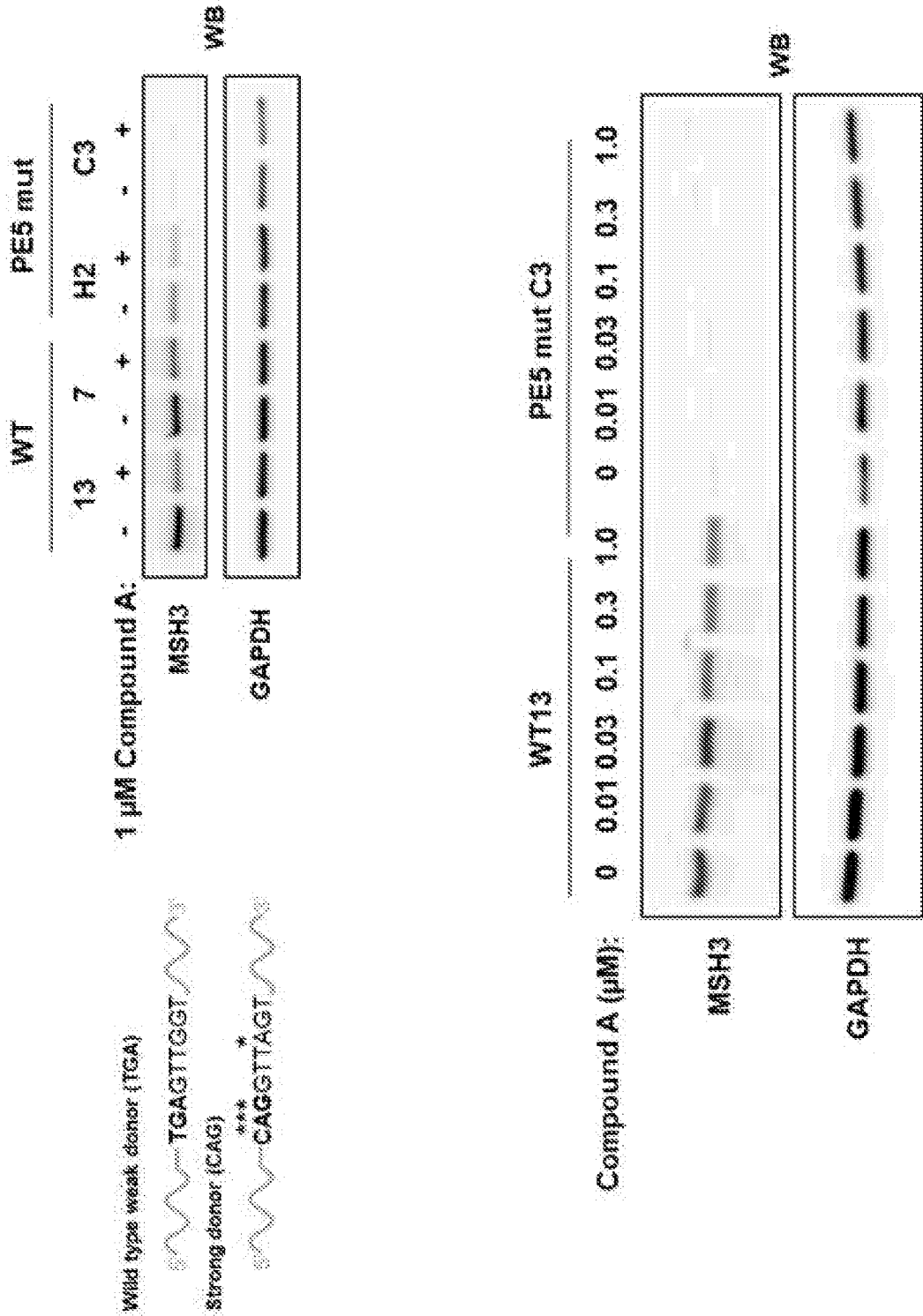


FIG. 12C

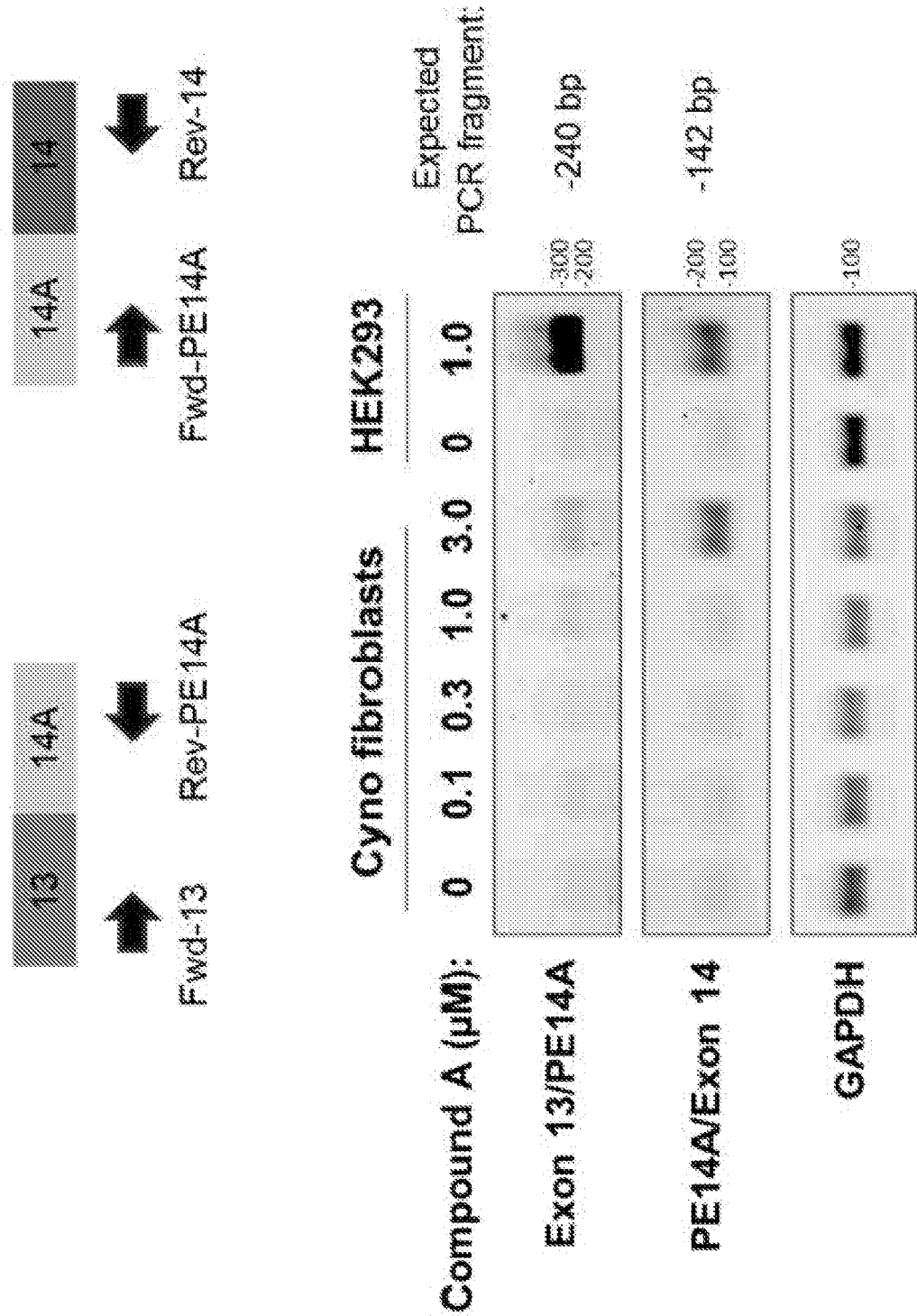


FIG. 13

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2024/097830

A. CLASSIFICATION OF SUBJECT MATTER

A61K31/501(2006.01)i; C12N15/113(2010.01)i; C12N5/071(2010.01)i; C07D 237/04(2006.01)i; A61P25/00(2006.01)i; A61P25/14(2006.01)i

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)

IPC: A61K; C12N; C07D; A61P

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)

CNABS, CNTXT, DWPI, WPABS, ENTXT, VCN, ISI Web of Science, PubMed, STNext, splicing, poison exon, repeat expansion, transcript, mRNA, pre-mRNA, Huntington's disease, MSH, inhibitor, decrease

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 20230054781 A1 (SKYHAWK THERAPEUTICS, INC.) 23 February 2023 (2023-02-23) description, paragraphs [0007]-[0024], [0880]-[0881], [0887], [0909] tables 2A-2B	1-81
A	US 20230054781 A1 (SKYHAWK THERAPEUTICS, INC.) 23 February 2023 (2023-02-23) description, paragraphs [0007]-[0024], [0880]-[0881], [0887], [0909] tables 2A-2B	82-177
X	WO 2020190793 A1 (SKYHAWK THERAPEUTICS, INC.) 24 September 2020 (2020-09-24) description, paragraphs [0006], [0598]-[0600], [0644]-[0656]	1-81
A	WO 2020190793 A1 (SKYHAWK THERAPEUTICS, INC.) 24 September 2020 (2020-09-24) description, paragraphs [0006], [0598]-[0600], [0644]-[0656]	82-177
X	WO 2007124171 A2 (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) 01 November 2007 (2007-11-01) claims 43, 45	2-32, 79-81



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance
 “D” document cited by the applicant in the international application
 “E” earlier application or patent but published on or after the international filing date
 “L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 “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

23 September 2024

Date of mailing of the international search report

27 September 2024

Name and mailing address of the ISA/CN

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2024/097830

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2024/097830

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **2-32, 82-177 (in part)**
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 2-32 and claims (in part) 82-177 relate to a method for treating diseases. Such subject-matter is not capable of performing international searches according to criteria specified by PCT Rule 39.1 (iv) . The search report is based on the subject-matter of the manufacture of a medicament correspondingly.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 20230047208 A1 (THE GENERAL HOSPITAL CORPORATION, ET AL) 16 February 2023 (2023-02-16) description, paragraphs [0009], [0905], [0950]	2-32, 79-81
X	WO 2022006550 A1 (REMIX THERAPEUTICS INC.) 06 January 2022 (2022-01-06) claims 108-112; page 139	2-32, 79-81
X	US 20220072028 A1 (TRIPLET THERAPEUTICS, INC.) 10 March 2022 (2022-03-10) claims 53-67	2-32, 79-81
X	US 20170183655 A1 (BOARD OF SUPERVISORS OF LOUISIANA STATE UNIVERSITY AND AGRICULTURAL AND MECHANICAL COLLEGE) 29 June 2017 (2017-06-29) description, paragraphs [0007]-[0008]	2-32, 79-81

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2024/097830

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
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				EP	3921311	A4	09 November 2022
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				EP	3937942	A1	19 January 2022
				EP	3937942	A4	16 November 2022
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				WO	2021138678	A1	08 July 2021
WO	2022006550	A1	06 January 2022	BR	112022027107	A2	14 March 2023
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				KR	20230051168	A	17 April 2023
				US	2024002375	A1	04 January 2024
				EP	4175956	A1	10 May 2023
				AU	2021299515	A1	02 February 2023
				CA	3183321	A1	06 February 2022
				MX	2023000168	A	20 April 2023
				TW	202216710	A	01 May 2022
				JP	2023532332	A	27 July 2023
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				CA	3121779	A1	11 June 2020
				WO	2020117703	A1	11 June 2020
				WO	2020117702	A1	11 June 2020
				MX	2021006463	A	28 September 2021
				KR	20210099090	A	11 August 2021
				JP	2022510041	A	25 January 2022
US	20170183655	A1	29 June 2017	US	10669542	B2	02 June 2020
				US	2021062188	A1	04 March 2021
				WO	2015171918	A2	12 November 2015
				WO	2015171918	A3	07 January 2016